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WATCHMAN®

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Left Atrial Appendage Closure Device with Delivery System

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(Table of Contents omitted from this draft.)

℞ ONLY

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

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.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

DEVICE DESCRIPTION

The WATCHMAN Left Atrial Appendage Closure (LAAC) Technology is intended for percutaneous, transcatheter closure of the left atrial appendage and consists of the WATCHMAN Access System (Access Sheath and Dilator) and WATCHMAN Delivery System (Delivery Catheter and WATCHMAN Device). The Access System and Delivery System permit device placement in the left atrial appendage (LAA) via femoral venous access and inter-atrial septum crossing into the left atrium. The WATCHMAN Device is a self-expanding nitinol structure with a polyethylene terephthalate (PET) porous membrane on the proximal face. The device is constrained within the Delivery System until deployment in the LAA. The device is available in 5 sizes from 21 to 33 mm. Appropriate device sizing is determined by LAA measurements using fluoroscopy (fluoro) and transesophageal echocardiography (TEE).

The WATCHMAN Device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to close the appendage to inflow. The placement procedure can be done under local or general anesthesia in a hospital cardiac catheterization or electrophysiology laboratory setting.

User Information

Intended users of the WATCHMAN Device are physicians who are trained in percutaneous and transseptal procedures and who have completed the WATCHMAN Physician Training program. Implantation of the WATCHMAN Device should only be performed by these Intended Users.

Contents

Quantity	**Description**

1 WATCHMAN Left Atrial Appendage Closure Device with Delivery System

INTENDED USE / INDICATIONS FOR USE

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

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc[1] scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

CONTRAINDICATIONS

Do not use the WATCHMAN Device if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- 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 device. See **Table 46**.
- Any of the customary contraindications for other percutaneous catheterization procedures (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 warfarin, aspirin, or clopidogrel.
- 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 Device is contraindicated.

WARNINGS

- Device selection should be based on accurate LAA measurements obtained using fluoro and ultrasound guidance (TEE recommended) in multiple angles (e.g., 0º, 45º, 90º, 135º).
- Do not release the WATCHMAN Device from the core wire if the device does not meet all release criteria (see step 14).
- If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.
- The potential for device embolization exists with cardioversion <30 days following device implantation. Verify device position post-cardioversion during this period.
- Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.
- 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

[1] January CT, Wann LS, Alpert JS, et. al., 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, Circulation, 2014; 130: e199-e267.

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.

PRECAUTIONS

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying the device.
- Use caution when introducing the 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 device, do not allow the WATCHMAN 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 100 psi.
- In view of the concerns that were raised by the RE-ALIGN[2] study of dabigatran in the presence of prosthetic mechanical heart valves, caution should be used when prescribing oral anticoagulants other than warfarin in patients treated with the WATCHMAN Device. The WATCHMAN Device has only been evaluated with the use of warfarin post-device implantation.

PATIENT SELECTION FOR TREATMENT

In considering the use of the WATCHMAN Device, the rationale for seeking an alternative to long-term warfarin therapy and the safety and effectiveness of the device compared to warfarin should be taken into account. See "Patient Counseling Information," "Summary of Primary Clinical Studies," and "Clinical Studies" sections for additional information.

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 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 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).

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

Selection among available treatment options must first take into account whether anticoagulation is indicated to reduce the risk of stroke based on $CHADS_2$ or CHA_2DS_2-VASc scores. Next, in a patient who is deemed by their physicians to be suitable for anticoagulation with warfarin, physicians and patients should consider the rationale for implantation of the WATCHMAN Device as an alternative to long-term warfarin therapy. Specific factors may include one or more of the following:

- a history of major bleeding while taking therapeutic anticoagulation therapy

[2] Eikelboom JW, Connolly SJ, Brueckmann M, et al. N Engl J Med 2013;369:1206-14.

- the patient's prior experience with oral anticoagulation (if applicable), which may include an inability to maintain a stable therapeutic International Normalized Ratio (INR) or inability to comply with regular INR monitoring AND unavailability of an approved alternative anticoagulation agent
- 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.[3,4,5]
- the presence of indication(s) for long-term warfarin use, other than non-valvular atrial fibrillation (e.g. mechanical heart valve, hypercoagulable states, recurrent deep venous thrombosis)

Details regarding the indications, contraindications, warnings and precautions for warfarin and other 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 Device has been compared to warfarin and not to other oral anticoagulants that have been approved for patients with non-valvular atrial fibrillation.
- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.

Specific factors that need to be considered for the WATCHMAN 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, trans-septal 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 Device implant pharmacologic regimen, especially for patients at high risk for bleeding, i.e., the need for warfarin plus aspirin for at least 45 days post-device implantation, clopidogrel and aspirin through 6 months post-procedure, and aspirin indefinitely.

PATIENT COUNSELING INFORMATION

Physicians should review the following information when counseling patients about the WATCHMAN

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

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

[5] 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.

Device and implant procedure:

- The safety and effectiveness of systemic anticoagulation and localized percutaneous, LAA closure with the WATCHMAN 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 WATCHMAN Device implantation. **Table 4** details the major clinical events related to the device or procedure as observed in the WATCHMAN clinical trial program.
- The need for adherence to a defined pharmacologic regimen of warfarin and antiplatelet therapy following WATCHMAN Device implant
- Clinical conditions may arise that require continuation or resumption of warfarin therapy following WATCHMAN Device implantation
- The risk of the device implantation procedure plus post-procedure related bleeding weighed against the risk of bleeding on long-term warfarin therapy

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

MAGNETIC RESONANCE IMAGING

Non-clinical testing demonstrated that the WATCHMAN Device is MR Conditional. A patient with the device can be scanned safely, immediately after placement of this implant, under the following conditions:

- Static magnetic fields of 3.0 Tesla or 1.5 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- The maximum whole body averaged specific absorption rate (SAR) shall be limited to 2.0 W/kg (normal operating mode only) for 15 minutes of scanning
- Normal operating mode of the MRI scanner

The WATCHMAN Device should not migrate in this MRI environment. This device has not been evaluated to determine if it is MR Conditional beyond these parameters.

3.0 Tesla Temperature Information

In non-clinical testing, the WATCHMAN Device produced a temperature rise of <1.1°C at a maximum MR system-reported SAR of 2.0 W/kg as measured by calorimetry for 15 minutes of continuous MR scanning in a 3.0 Tesla MR system (Excite, Software G3.0-052B, GE Healthcare, Milwaukee, WI).

These calculations do not take into consideration the cooling effects of blood flow.

1.5 Tesla Temperature Information

Non-clinical testing of RF-induced heating in the WATCHMAN Device was performed at 64 MHz in a 1.5 Tesla whole body coil MR scanner (Intera, Software Release 10.6.2.4, 2006-03-10, Philips Medical Systems, Andover, MA) and produced a temperature rise of <1.5°C at an MR extrapolated SAR of 2.0 W/kg for 15 minutes of continuous MR scanning.

These calculations do not take into consideration the cooling effects of blood flow.

Image Artifact Information

In non-clinical testing, the image artifact cause by the device extends less than 3 mm from the WATCHMAN Device when imaged with a spin echo pulse sequence and a 3-Tesla MRI system. The image artifact caused by the device extends less than 5mm from the WATCHMAN Device when imaged with a gradient echo pulse sequence and a 3-Tesla MRI system. MR image quality may be compromised if the area of interest is relatively close to the WATCHMAN Device. Optimization of MR imaging parameters is recommended.

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. These four studies enrolled subjects that were deemed by their physicians to be suitable for warfarin, and warfarin was used in the post-procedure during the period of tissue coverage of the device. **Table 1** shows a summary of study designs, number of study subjects enrolled, and planned follow-up for each study.

Table 1: Summary of WATCHMAN® Clinical Studies

Patient Population	Subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for warfarin therapy to reduce the risk of ischemic stroke and systemic embolism			
Study	**PROTECT AF**	**CAP**	**PREVAIL**	**CAP2**
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
Study Design	2:1 Randomized, non-inferiority	Non-randomized	2:1 Randomized, non-inferiority	Non-randomized
Primary Endpoints	1. Effectiveness: Stroke, cardiovascular death, and systemic embolism 2. Safety: Life-threatening events which include device embolization requiring retrieval and bleeding events		1. Effectiveness: Stroke, systemic embolism, and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after seven days post-randomization or WATCHMAN implant procedure 3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications within seven-days of the implantation procedure	
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	579 WATCHMAN subjects
Status of Subject Follow-Up	Study Complete 2717 patient-years	Study Ongoing 2022 patient-years	Study Ongoing 860 patient-years	Study Ongoing 332 patient-years
Scheduled Follow-Up Duration	5 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. Key eligibility criteria are provided in **Table 2**.

Table 2: PROTECT AF Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 1 or greater
Key Exclusion Criteria
The subject requires long-term warfarin therapy
The subject is contraindicated for warfarin therapy
The subject is contraindicated for aspirin
The subject has a history of atrial septal repair or has an atrial septal defect (ASD)/patent foramen ovale (PFO) closure device
Key Echo Exclusion Criteria
The subject has Left Ventricular Ejection Fraction (LVEF) <30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
The subject has a high risk PFO defined as a PFO with an atrial septal aneurysm (total excursion >15 mm or length ≥15 mm) or a large shunt (early, within 3 beats, substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque of the descending aorta and/or aortic arch
The subject has a cardiac tumor

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

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

PREVAIL Study

The PREVAIL study is 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. Key eligibility criteria are provided in **Table 3**.

Table 3: PREVAIL Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply: • The subject is a female age 75 or older • The subject has a baseline LVEF ≥30% and <35% • The subject is age 65-74 and has diabetes or coronary artery disease • The subject is age 65 or greater and has documented congestive heart failure
Key Exclusion Criteria
The subject requires long-term warfarin
The subject is contraindicated for warfarin therapy
The subject is contraindicated or allergic to aspirin
The subject has a history of atrial septal repair or has an ASD/PFO closure device
Key Echo Exclusion Criteria
The subject has LVEF <30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
The subject has a high risk PFO defined as an atrial septal aneurysm (excursion >15 mm or length >15 mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque of the descending aorta and/or aortic arch
The subject has a cardiac tumor

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

CAP Registry

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

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

CAP2 Registry

The CAP2 registry is a multi-center prospective non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Entry criteria were the same as the PREVAIL study. A total of 579 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.

ADVERSE EVENTS

Observed Adverse Events

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 4**.

Table 4: PROTECT AF, CAP, PREVAIL, and CAP2 Major Clinical Events Related to the WATCHMAN Device or Implant Procedure

Event	PROTECT AF n (%) N=463	CAP n (%) N=566	PREVAIL n (%) N=269	CAP2 n (%) N=579
Pericardial effusion with cardiac tamponade	13 (2.8)	7 (1.2)	4 (1.5)	8 (1.2)
Pseudoaneurysm	3 (0.6)	5 (0.9)	0 (0.0)	1 (0.2)
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)	1 (0.2)	2 (0.7)	5 (0.9)
Ischemic stroke related to device thrombus	2 (0.4)	1 (0.2)	1 (0.4)	3 (0.5)
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)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
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)	2 (0.7)	4 (0.7)
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)	2 (0.3)

Infection	2 (0.4)	0 (0.0)	3 (1.1)	1 (0.2)
Device thrombus	2 (0.4)	1 (0.2)	1 (0.4)	5 (0.9)
Arrhythmias	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)
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 **Tables 8**, **Table 19**, **Table 32**, and **Table 39**.

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 contrast media/medications or device materials
- Altered mental status
- Anemia requiring transfusion
- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- AV fistula
- Bruising, hematoma or seroma
- Cardiac perforation
- Chest pain/discomfort
- Confusion post procedure
- Congestive heart failure
- Contrast related nephropathy
- Cranial bleed
- Decreased hemoglobin
- Deep vein thrombosis
- Death
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Excessive bleeding
- Fever
- 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
- Nausea
- Oral bleeding
- Pericardial effusion / tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Renal failure
- Respiratory insufficiency / failure
- Surgical removal of the device
- Stroke – Ischemic
- Stroke – Hemorrhagic
- Systemic embolism
- TEE complications (throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular damage
- Vasovagal reactions

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

CLINICAL STUDIES

PROTECT AF Study

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

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

Main entry criteria included, but were not limited to, at least 18 years of age, non-valvular atrial fibrillation, a $CHADS_2$ score of 1 or greater, and eligibility for long-term warfarin therapy. Following

randomization, subjects were assessed at 45 days, 6, 9, 12 months 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 months after successful implantation. Subjects randomized to the Control group were to remain on warfarin with INR monitored every other week through 6 months and monthly thereafter.

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

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

Enrollment: The study enrolled 800 subjects with 707 randomized and the remaining 93 participating in the WATCHMAN Roll-in group. Of the 707 randomized subjects, 463 were assigned to the WATCHMAN group and 244 assigned to the warfarin control group as shown in **Table 5**.

Table 5: PROTECT AF Enrollment Summary

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

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

Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.2±1.2, the mean CHA_2DS_2-VASc score was 3.2±1.4, the mean age was 72 years, 70% were male, and 92% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.3±1.2, the mean CHA_2DS_2-VASc score was 3.5±1.6, the mean age was 73 years, 70% were male, and 91% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Tables 6** and **7**.

Table 6: PROTECT AF Baseline Demographics

Characteristic	WATCHMAN N=463	Control N=244	P-value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	72.7 ± 9.2 (244) (41.0, 95.0)	0.179
Sex			0.928
Female	137/463 (29.6%)	73/244 (29.9%)	
Male	326/463 (70.4%)	171/244 (70.1%)	
Race/Ethnicity			0.779
Asian	4/463 (0.9%)	1/244 (0.4%)	
Black/African American	6/463 (1.3%)	5/244 (2.0%)	
Caucasian	425/463 (91.8%)	222/244 (91.0%)	
Hispanic/Latino	25/463 (5.4%)	15/244 (6.1%)	
Hawaiian/Pacific Islander	1/463 (0.2%)	1/244 (0.4%)	
Other	2/463 (0.4%)	0/244 (0.0%)	

Table 7: PROTECT AF Baseline Risk Factors

Characteristic	WATCHMAN N=463	Control N=244	P-value
$CHADS_2$ Score			0.411
1	156/463 (33.7%)	66/244 (27.0%)	
2	158/463 (34.1%)	88/244 (36.1%)	
3	89/463 (19.2%)	51/244 (20.9%)	
4	37/463 (8.0%)	24/244 (9.8%)	
5	19/463 (4.1%)	10/244 (4.1%)	
6	4/463 (0.9%)	5/244 (2.0%)	
$CHADS_2$ Score (Continuous)	2.2±1.2 (463) (1.0, 6.0)	2.3±1.2 (244) (1.0, 6.0)	0.072
$CHADS_2$ Risk Factors			
Congestive Heart Failure (CHF)	124/463 (26.8%)	66/244 (27.0%)	0.9392
Hypertension	415/463 (89.6%)	220/244 (90.2%)	0.8243
Age ≥ 75	190/463 (41.0%)	115/244 (47.1%)	0.1198
Diabetes	113/463 (24.4%)	72/244 (29.5%)	0.1423
Previous TIA/Ischemic Stroke	82/463 (17.7%)	49/244 (20.1%)	0.4404
CHA_2DS_2-VASc Score			0.469
1	44/460 (9.6%)	16/239 (6.7%)	
2	105/460 (22.8%)	54/239 (22.6%)	
3	139/460 (30.2%)	64/239 (26.8%)	
4	91/460 (19.8%)	47/239 (19.7%)	
5	45/460 (9.8%)	32/239 (13.4%)	
6	27/460 (5.9%)	19/239 (7.9%)	
7	5/460 (1.1%)	5/239 (2.1%)	
8	2/460 (0.4%)	2/239 (0.8%)	
9	0/460 (0.0%)	0/239 (0.0%)	
CHA_2DS_2-VASc Score (Continuous)	3.2±1.4 (460)	3.5±1.5 (239)	0.022

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 8**. 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 8: PROTECT AF Primary Effectiveness Results (Intent-to-Treat) and % of subjects who experienced 1 or more events (2717 patient years)

Randomization Allocation (2 Device: 1 Control)

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

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

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

CrI = credible interval

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

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

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

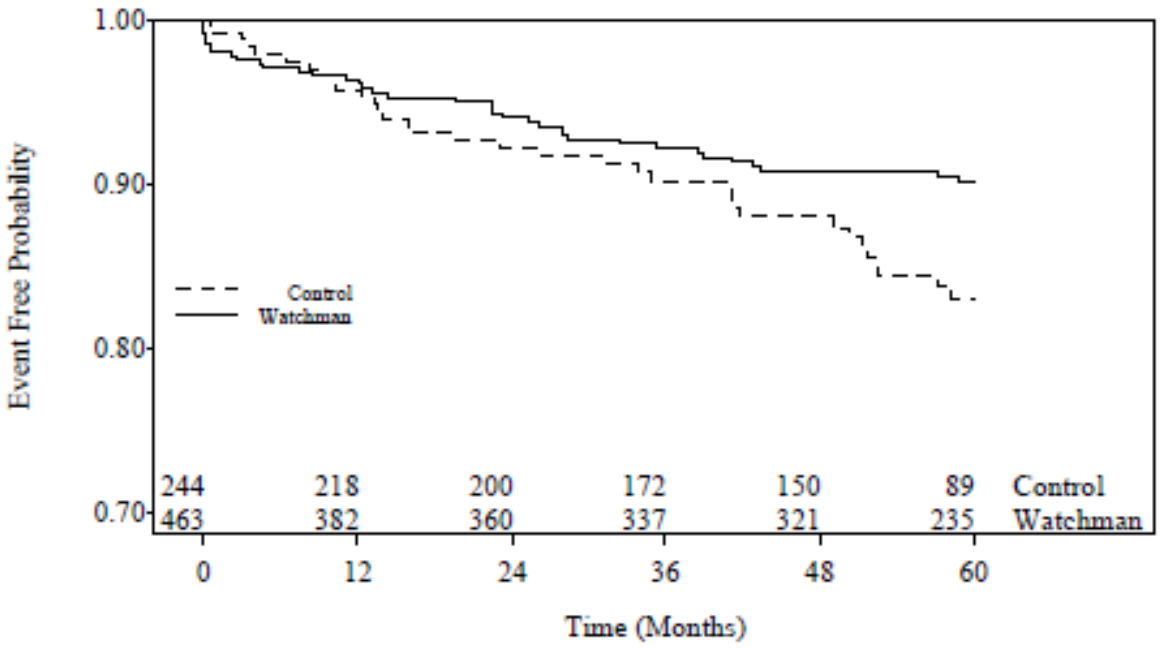

Figure 1: PROTECT AF Primary Effectiveness (2717 patient-years)

Safety: The primary safety rate was 3.5 events per 100 patient years for the Device group and 3.2 events per 100 patient years for the Control group resulting in a relative risk ratio of 1.08. These results are summarized in **Table 9**.

Table 9: 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 10**. 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 10: PROTECT AF Major Bleeding

	WATCHMAN		Control	
Major Bleeding	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)	N Events/ Subjects (%)	Rate (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 11**. Serious adverse events related to the WATCHMAN Device or implant procedure are shown in **Table 4**.

Table 11: 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
Death	59	59	12.7%	44	44	18.0%
Gastrointestinal Bleeding	32	26	5.6%	27	22	9.0%
Stroke - Ischemic	26	24	5.2%	11	10	4.1%
Stroke - Hemorrhagic	3	3	0.6%	10	10	4.1%
Systemic Embolization	3	3	0.6%	0	0	0
Other Study Related	18	17	3.7%	2	2	0.8%
Cranial Bleed	4	4	0.9%	1	1	0.4%
Major Bleed Requiring Transfusion	2	2	0.4%	1	1	0.4%
Rectal Bleeding	1	1	0.2%	1	1	0.4%
AV Fistula	1	1	0.2%	0	0	0
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
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
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
Hematuria	4	4	0.9%	0	0	0
Infection	2	2	0.4%	0	0	0
Oral Bleeding	0	0	0	1	1	0.4%
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
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 12**.

Table 12: PROTECT AF Device-related Thrombus

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

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

PREVAIL Study

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

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

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

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

This study had three primary endpoints:

- First primary endpoint: The 18-month rates of the composite of stroke (including hemorrhagic or ischemic), systemic embolism, and cardiovascular or unexplained death. The non-inferiority success criterion for the WATCHMAN group vs. the control group was a rate ratio of less than 1.75 with posterior probability of at least 97.5% (or equivalently that the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 1.75).
- Second primary endpoint: The 18-month rates of ischemic stroke or systemic embolism excluding the first 7 days post-randomization. The non-inferiority success criterion for the WATCHMAN group vs. the control group was either: (1) a rate ratio of less than 2.0, or (2) a

rate difference of less than 0.0275, each with a posterior probability of at least 97.5% (or equivalently that (1) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 2.0 or (2) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate difference would be less than 0.0275).

- Third primary endpoint: The percentage of WATCHMAN subjects that experienced one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later: all-cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. The following events were not included in the assessment of this endpoint: percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat a femoral pseudoaneurysm, and non-surgical treatments of access site complications. The third primary endpoint event rate was compared to a performance goal of 2.67%.

A Bayesian approach based on a piecewise exponential model was used to evaluate the first and second primary endpoints based on time to first event. In addition, this approach included prior PROTECT AF historical data from subjects with the same $CHADS_2$ enrollment criteria as the PREVAIL subjects (see **Table 3**, PREVAIL Key Eligibility Criteria) with a discounting weight of 50%. For the third primary endpoint, a Bayesian approach based on a beta-binomial model was used to incorporate historical data from the PROTECT AF study and CAP registry through a prior distribution (without discounting) from subjects with the same $CHADS_2$ score enrollment criteria as the PREVAIL subjects.
Enrollment: The study enrolled 461 subjects with 407 randomized and the remaining 54 participating in the WATCHMAN Roll-in group. Of the 407 randomized subjects, 269 were assigned to the WATCHMAN group and 138 assigned to the warfarin control group as shown in **Table 13**.

Table 13: PREVAIL Enrollment Summary

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

*Implant attempt is defined as venous access.

Subject Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.6±1.0, the mean CHA_2DS_2-VASc score was 3.8±1.2, the mean age was 74 years, 68% were male, and 94% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.6±1.0, the mean CHA_2DS_2-VASc score was 3.9±1.2, the mean age was 75 years, 75% were male, and 95% were Caucasian. The two treatment groups

had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Tables 14** and **15**.

Table 14: PREVAIL Baseline Demographics

Characteristic	WATCHMAN N=269	Control N=138	P-value
Age (years)	74.0 ± 7.4 (269) (50.0 ,94.0)	74.9 ± 7.2 (138) (53.0 ,90.0)	0.260
Sex			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/Ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
Caucasian	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	

Table 15: PREVAIL Baseline Risk Factors

Characteristic	WATCHMAN N=269	Control N=138	P-value
$CHADS_2$ Score (Categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
$CHADS_2$ Score (Continuous)	2.6 ± 1.0 (269) (1.0 ,6.0)	2.6 ± 1.0 (138) (1.0 ,5.0)	0.838
$CHADS_2$ Risk Factors			
CHF	63/269 (23.4%)	32/138 (23.2%)	0.958
History of Hypertension	238/269 (88.5%)	134/138 (97.1%)	0.003
Age ≥ 75	140/269 (52.0%)	78/138 (56.5%)	0.391
Diabetes	91/269 (33.8%)	41/138 (29.7%)	0.401
Previous TIA/Ischemic Stroke	74/269 (27.5%)	39/138 (28.3%)	0.873
CHA_2DS_2 VASc Score (Categorical)			0.300
2	19/269 (7.1%)	7/138 (5.1%)	
3	78/269 (29.0%)	44/138 (31.9%)	
4	95/269 (35.3%)	35/138 (25.4%)	
5	50/269 (18.6%)	37/138 (26.8%)	
6	20/269 (7.4%)	12/138 (8.7%)	
7	6/269 (2.2%)	3/138 (2.2%)	
8	1/269 (0.4%)	0/138 (0.0%)	
CHA_2DS_2 VASc Score (Continuous)	4.0 ± 1.1 (269) (2.0 ,8.0)	4.1 ± 1.2 (138) (2.0 ,7.0)	0.399

The PREVAIL study is ongoing. Current follow-up of the 407 randomized subjects is 860 patient-years. PREVAIL follow-up visit attendance is shown in **Table 16**.

Table 16: PREVAIL Only Follow-Up Visit Attendance

Visit	WATCHMAN Attended/Expected (%)	Control Attended/Expected (%)
1 Year	234/236 (99%)	119/124 (96%)
2 Years	208/211 (99%)	96/99 (97%)
3 Years	61/62 (98%)	26/26 (100%)
4 Years	0/0 (NA)	0/0 (NA)
5 Years	0/0 (NA)	0/0 (NA)

Results:

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

There were two analyses of the PREVAIL trial results: (1) a pre-specified dataset lock in January 2013 and (2) an updated dataset lock in June 2014.

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. As shown in **Table 17**, this dataset included 396.2 PREVAIL Only patient-years, whereas the discounted prior data borrowed from PROTECT AF included 618.8 patient-years. In the updated June 2014 dataset, the mean follow-up duration for PREVAIL Only subjects was 25.9±9.7 months, and all randomized subjects reached or passed the window for their 18-month follow-up visit [and 310 randomized subjects (76%) reached or passed the window for their 24-month follow-up visit]. The updated dataset follow-up duration for PREVAIL Only subjects increased to 860.3 patient-years.

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
January 2013	256.2	140.0	396.2	395.3	223.5	618.8
June 2014	562.6	297.7	860.3	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%)
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
Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL Only June 2014 Dataset (860.3 pt-yrs)	0.065	0.057	1.21 (0.69, 2.05)	92.60%	No

CrI = credible interval, NI = non-inferiority

In the January 2013 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%).

In the June 2014 Bayesian analysis, the 18-month rate was 0.065 for the Device group and 0.057 for the Control group. The Bayesian estimate for the 18-month rate ratio was 1.21 with a 95% credible interval of 0.69 to 2.05. Since the upper bound of 2.05 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 92.6%).

The primary effectiveness endpoint analysis from the June 2014 dataset for the PREVAIL Only subjects is shown as time to event in a Kaplan-Meier curve in **Figure 2**.

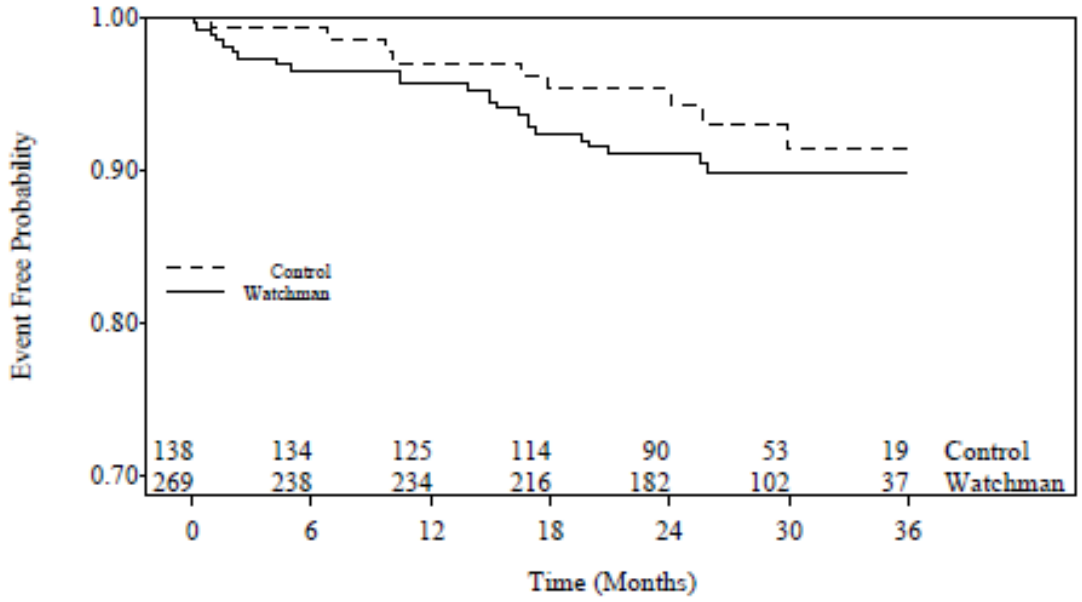

Figure 2: PREVAIL Only Subjects – First Primary Endpoint Event

Table 19 shows the individual event rates of the composite endpoint for PREVAIL Only subjects. The ischemic stroke rate (2.3 vs. 0.3 per 100 pt-years) favored to the Control group, while the hemorrhagic stroke rate (0.4 vs. 0.7 per 100 pt-years) and death (cardiovascular or unexplained) rate (1.4 vs. 2.3 per 100 pt-years) favored the WATCHMAN group.

Table 19: PREVAIL Effectiveness Results and % of subjects who experienced 1 or more events – June 2014 Dataset (PREVAIL Only Subjects)

Randomization Allocation (2 Device: 1 Control)

	WATCHMAN		Control	
Component of First Primary Endpoint	**Event Rate (per 100 Pt-yrs)**	**Event Rate / Subject**	**Event Rate (per 100 Pt-yrs)**	**Event Rate / Subject**
Stroke - Ischemic	2.3 (13/565)	4.8% (13/269)	0.3 (1/298)	0.7% (1/138)
Stroke - Hemorrhagic	0.4 (2/577)	0.7% (2/269)	0.7 (2/300)	1.4% (2/138)
Systemic Embolism	0.2 (1/577)	0.4% (1/269)	0.0 (0/300)	0.0% (0/138)
Death (Cardiovascular or Unexplained)	1.4 (8/578)	3.0% (8/269)	2.3 (7/300)	5.1% (7/138)
Ischemic Stroke and Systemic Embolism	2.5 (14/563)	5.2% (14/269)	0.3 (1/298)	0.7% (1/138)
All stroke	2.7 (15/564)	5.6% (15/269)	1.0 (3/298)	2.2% (3/138)

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
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
Prior PROTECT AF information (618.8 pt-yrs) +PREVAIL Only June 2014 Dataset (860.3 pt-yrs)	0.0294	0.0131	2.8 (0.9,7.3) 37.3%	0.0163 (-0.0023, 0.0342) 89.5%	No

CrI = credible interval

In the January 2013 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 June 2014 Bayesian analysis, the 18-month rate was 0.0294 for the WATCHMAN group and 0.0131 for the control group. The non-inferiority criterion was not met for either the rate difference (0.0163 with an upper bound of 0.0342, which exceeded the allowable 95% credible interval upper bound of 0.0275) or the rate ratio (2.8 with an upper bound of 7.3, which exceeded the allowable 95% credible interval upper bound of 2.0). The posterior probability of non-inferiority was 37.3% for the rate ratio and 89.5% for the rate difference, neither probability meeting the criterion of 97.5%.

The second effectiveness endpoint for the PREVAIL Only subjects (June 2014 dataset) is shown as time to event analysis in a Kaplan Meier curve in **Figure 3**.

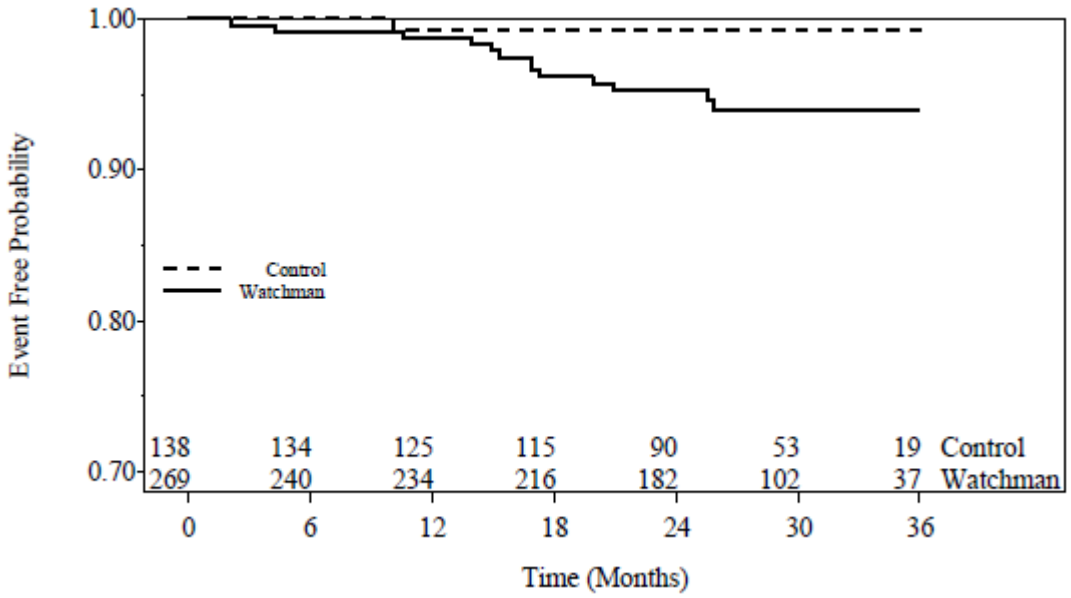

Figure 3: PREVAIL Only Subjects – Second Primary Endpoint Event

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 with are shown in **Table 22**.

Table 22: 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 6 months with a lower rate of new bleeding events beyond 6 months. The overall major bleeding rates were similar between the WATCHMAN group and the Control group.

Table 23: PREVAIL Only Major Bleeding

	WATCHMAN		Control	
Major Bleeding	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)
Procedure-related	12/269 (4.5%)	NA	NA	NA
Non-procedure related	20/269 (7.4%)	3.6 (20/550.1)	14/138 (10.1%)	5.0 (14/282.1)
0-45 days	8/269 (3.0%)	25.0 (8/31.9)	0/138 (0.0%)	0.0 (0/16.9)
46 days – 6 months	7/269 (2.6%)	7.9 (7/88.6)	3/138 (2.2%)	6.0 (3/50.4)
>6 months	5/269 (1.9%)	1.2 (5/429.6)	11/138 (8.0%)	5.1 (11/214.8)
Total major bleeding	29/269 (10.8%)	5.5 (29/531.1)	14/138 (10.1%)	5.0 (14/282.1)

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 4**.

Table 24: PREVAIL Only Serious Adverse Events

	WATCHMAN N=269				Control N=138			
Event Type	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**
AV Fistula	1	1.0	1	0.4	0	0.0	0	0.0
Anemia Requiring Transfu-sion	3	3.1	3	1.1	0	0.0	0	0.0
Bleeding, Other	0	0.0	0	0.0	2	6.1	2	1.4
Cardiac Perforation	1	1.0	1	0.4	0	0.0	0	0.0
Cranial Bleed	1	1.0	1	0.4	0	0.0	0	0.0
Death	22	22.7	22	8.2	13	39.4	13	9.4
Device Embolization	2	2.1	2	0.7	0	0.0	0	0.0
Device Thrombus	1	1.0	1	0.4	0	0.0	0	0.0
Epistaxis	2	2.1	1	0.4	2	6.1	2	1.4
Gastrointestinal Bleeding	14	14.4	14	5.2	7	21.2	7	5.1
Hematoma	2	2.1	2	0.7	0	0.0	0	0.0
Hematuria	1	1.0	1	0.4	2	6.1	2	1.4
Infection	3	3.1	3	1.1	0	0.0	0	0.0
Major Bleed Requiring Transfusion	4	4.1	4	1.5	1	3.0	1	0.7
Other Study Related	7	7.2	6	2.2	1	3.0	1	0.7
Pericardial Effusion with Cardiac Tamponade	4	4.1	4	1.5	0	0.0	0	0.0

	WATCHMAN N=269				Control N=138			
Event Type	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**
Pseudoaneurysm	1	1.0	1	0.4	0	0.0	0	0.0
Rectal Bleeding	1	1.0	1	0.4	0	0.0	0	0.0
Respiratory Failure	2	2.1	2	0.7	0	0.0	0	0.0
Respiratory Insufficiency	1	1.0	1	0.4	0	0.0	0	0.0
Stroke - Hemorrhagic	2	2.1	2	0.7	2	6.1	2	1.4
Stroke - Ischemic	14	14.4	13	4.8	1	3.0	1	0.7
Subdural Hematoma	2	2.1	2	0.7	0	0.0	0	0.0
Systemic Embolism	1	1.0	1	0.4	0	0.0	0	0.0
Transient Ischemic Attack (TIA)	5	5.2	4	1.5	2	6.1	2	1.4

PREVAIL Only Device Thrombus Rates

The device thrombus-related stroke rate was 0.2 events per 100 patient-years as shown in **Table 25**.

Table 25: PREVAIL Only Device-related Thrombus

	N=252
Thrombus Subjects	15 (6.0%)
Thrombus Events	16
Experienced Ischemic Stroke	1
Experienced Serious Adverse Event	1
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, 92% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

Other Procedural and Secondary Outcomes of Interest from the Randomized Studies

PROTECT AF Subgroup Analysis

The PROTECT AF and PREVAIL study effectiveness results were analyzed for selected subgroups as shown in **Table 26**. These studies were not prospectively powered for subgroup analyses, and these analyses should be considered to be exploratory.

No statistically significant interactions were detected by sex, age, or baseline $CHADS_2$ score. Results by race were not performed due to the small sample sizes.

Table 26: Subgroup Analysis for the PROTECT AF and PREVAIL Primary Effectiveness Endpoints

	PROTECT AF		PREVAIL	
Subgroup	**WATCHMAN % (n/N)**	**Control % (n/N)**	**WATCHMAN % (n/N)**	**Control % (n/N)**
Sex				
Female	13.1 (18/137)	13.7 (10/73)	3.4% (3/87)	5.7% (2/35)
Male	6.7 (22/326)	14.0 (24/171)	11.5% (21/182)	6.8% (7/103)
Age				
≤72 years	6.4 (15/235)	8.5 (9/106)	6.4% (7/109)	6.1% (3/49)
>72 years	11.0 (25/228)	18.1 (25/138)	10.6% (17/160)	6.7% (6/89)
$CHADS_2$				
1-3	7.2 (29/403)	11.2 (23/205)	7.6% (17/223)	3.6% (4/110)
4-6	18.3 (11/60)	28.2 (11/39)	15.2% (7/46)	17.9% (5/28)

Table 27 summarizes the relationship between a prior history of ischemic stroke and the incidence of new ischemic stroke observed post-randomization. The data demonstrate that patients in both PROTECT AF and PREVAIL with a prior ischemic stroke are at a higher risk of recurrent ischemic strokes.

Table 27: PROTECT AF and PREVAIL Incidence of Ischemic Stroke or SE by Study and History of Ischemic Stroke

	WATCHMAN % (n/N)	Control % (n/N)
PROTECT AF no prior ischemic stroke	4.5 (19/418)	2.8 (6/212)
PROTECT AF prior ischemic stroke	15.6 (7/45)	12.5 (4/32)
PREVAIL- no prior ischemic stroke	4.1 (9/217)	0.0 (0/112)
PREVAIL- prior ischemic stroke	9.6 (5/52)	3.8 (1/26)

CAP Registry

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

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

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

Enrollment: A total of 26 centers (24 U.S., 2 European) participated by enrolling at least one subject. A total of 566 subjects were enrolled. The average $CHADS_2$ score was 2.5±1.2, the mean CHA_2DS_2-VASc score was 3.9±1.5, the mean age was 74 years, and 66% of subjects were male as shown in **Table 28** and **29**.

Table 28: CAP Registry Baseline Demographics

Characteristic	Mean±SD (N) Min,Max or N/Total (%)
Age (years)	74.0 ± 8.3 (566) 44.0, 94.0
Sex	
Female	195/566 (34.5%)
Male	371/566 (65.5%)
Race/Ethnicity	
Asian	9/566 (1.6%)
Black/African American	11/566 (1.9%)
Caucasian	520/566 (91.9%)
Hispanic/Latino	20/566 (3.5%)
Hawaiian/Pacific Islander	1/566 (0.2%)
Other	5/566 (0.9%)

Table 29: CAP Registry Baseline Risk Factors

Characteristic	Mean±SD (N) Min,Max or N/Total (%)
$CHADS_2$ Score (Categorical)	
1	131/566 (23.1%)
2	200/566 (35.3%)
3	122/566 (21.6%)
4	77/566 (13.6%)
5	32/566 (5.7%)
6	4/566 (0.7%)
$CHADS_2$ Score (Continuous)	2.5 ± 1.2 (566) 1.0, 6.0
CHA_2DS_2-VASc Score (Categorical)	
1	23/564 (4.1%)
2	71/564 (12.6%)
3	152/564 (27.0%)
4	149/564 (26.4%)
5	83/564 (14.7%)
6	53/564 (9.4%)
7	28/564 (5.0%)
8	4/564 (0.7%)
9	1/564 (0.2%)
CHA_2DS_2-VASc Score (Continuous)	3.9 ± 1.5 (564) 1.0, 9.0
Risk Factors	
CHF	108/566 (19.1%)
Hypertension	503/565 (89.0%)
Diabetes	141/566 (24.9%)
Stroke/TIA	172/566 (30.4%)
Previous MI	79/566 (14.0%)
LVEF 40% or Less	43/565 (7.6%)
Age <65	61/566 (10.8%)
Age 65-75	212/566 (37.5%)
Age >75	293/566 (51.8%)

The CAP Registry is ongoing. Current follow-up of the 566 subjects is 2022 patient-years. The CAP Registry follow-up visit attendance is shown in **Table 30**.

Table 30: CAP Registry Follow-Up Visit Attendance

Visit	Attended/Expected (%)
1 Year	490/508 (96.5%)
2 Years	466/480 (97.1%)
3 Years	437/449 (97.3%)
4 Years	353/374 (94.4%)
5 Years	90/93 (96.8%)

Results: The WATCHMAN Device was successfully implanted in 534/566 (94%) subjects. For the primary effectiveness endpoint, a rate of 2.6 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 44 months as shown in **Tables 31** and **32**.

Table 31: CAP Primary Effectiveness Endpoint (2022 Patient Years)

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	(95% CI)
Primary Effec-tiveness	2.6 (53/2021.8)	2.0,3.4

Table 32: CAP Events Contributing to Primary Effectiveness Endpoint

Type	N Events	% of Subjects N=566
Death (Cardiovascular or Unexplained)	25	4.4%
Stroke - Ischemic	24	4.2%
Stroke - Hemorrhagic	2	0.4%
Systemic Embolism	1	0.2%

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN is presented in **Table 33**. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in **Table 4**.

Table 33: CAP Registry Serious Adverse Events

Event	Number of Events	Number of Subjects	% of Subjects N=566
Death	80	80	14.1%
Stroke - Ischemic	28	24	4.2%
Stroke - Hemorrhagic	3	2	0.4%
Systemic Embolization	1	1	0.2%
Gastrointestinal Bleeding	66	42	7.4%
Other Study Related	22	20	3.5%
Transient Ischemic Attack (TIA)	13	11	1.9%
Major Bleed Requiring Transfusion	9	8	1.4%
Pericardial Effusion with Cardiac Tamponade	7	7	1.2%
Anemia Requiring Transfusion	5	4	0.7%
Pericardial Effusion	5	5	0.9%
Pseudoaneurysm	5	5	0.9%
Prolonged Bleeding from a Laceration	3	3	0.5%
Cranial Bleed	2	2	0.4%
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 0.05 events per 100 patients as shown in **Table 34.**

Table 34: CAP Device-related Thrombus

	N=534
Thrombus Subjects	12 (2.2%)
Thrombus Events	19
Experienced Ischemic Stroke	1
Experienced Serious Adverse Event	1
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.05

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

CAP2 Registry

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

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

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

Following baseline evaluation and device implantation, subjects were seen at 45 days, 6 and 12 months, 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 579 subjects were enrolled. The average $CHADS_2$ score was 2.7±1.1, the mean CHA_2DS_2-VASc score was 4.5±1.3, the mean age was 75 years, and 61% of subjects were male as shown in **Tables 35** and **36**.

Table 35: CAP2 Registry Baseline Demographics

Characteristic	
Age at Enrollment (years)	75.3±8.0 (576) (33.0, 94.0)
Sex	
Female	39.4% (227/576)
Male	60.6% (349/576)
Race	
American Indian or Alaskan	0.3% (2/576)
Asian	0.7% (4/576)
Black/African American	1.2% (7/576)
Caucasian	94.1% (542/576)
Hispanic/Latino	2.1% (12/576)
Hawaiian/Pacific Islander	0.0% (0/576)
Other	0.7% (4/576)

Table 36: CAP2 Registry Baseline Risk Factors

Characteristic	
$CHADS_2$ Score (Categorical)	
1	6.8% (39/576)
2	46.2% (266/576)
3	24.3% (140/576)
4	15.8% (91/576)
5	5.9% (34/576)
6	1.0% (6/576)
$CHADS_2$ Score (Continuous)	2.7±1.1 (576) (1.0, 6.0)
$CHADS_2$ Risk Factors	
CHF	27.1% (156/576)
History of Hypertension	92.5% (533/576)
Age ≥ 75	59.7% (344/576)
Diabetes	33.7% (194/576)
History of TIA / Ischemic Stroke	29.0% (167/576)
CHA_2DS_2-VASc Score (Categorical)	
1	0.0% (0/576)
2	1.7% (10/576)
3	21.9% (126/576)
4	32.5% (187/576)
5	22.2% (128/576)
6	13.9% (80/576)
7	5.2% (30/576)
8	2.3% (13/576)
9	0.3% (2/576)
CHA_2DS_2-VASc Score (Continuous)	4.5±1.3 (576) (2.0, 9.0)

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

The CAP2 Registry is ongoing. Current follow-up of the 579 subjects is 332 patient-years. The CAP Registry follow-up visit attendance is shown in **Table 37**.

Table 37: CAP2 Registry Follow-Up Visit Attendance

Visit	Attended/Expected (%)
1 Year	97.2% (172/177)
2 Years	100.0% (13/13)
3 Years	0/0 (NA)
4 Years	0/0 (NA)
5 Years	0/0 (NA)

Results: The WATCHMAN Device was successfully implanted in 545/575 (95%) subjects (no implant attempt in 4 subjects).

First Primary Endpoint: A rate of 3.3 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 7 months as shown in **Tables 38** and **39**.

Table 38: CAP2 First Primary Endpoint (322 Patient Years)

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
3.3 (11/329.5)	(1.9, 5.6)

Table 39: CAP2 Events Contributing to First Primary Endpoint

Endpoint Event Type	N Events	% of Subjects N=579
Stroke - Ischemic	9	1.6%
Stroke - Hemorrhagic	0	0.0%
Systemic Embolism	2	0.3%
Death (Cardiovascular or Unexplained)	0	0.0%

Second Primary Endpoint: A rate of 2.7 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 7 months as shown in **Tables 40** and **41**.

Table 40: CAP2 Second Primary Endpoint (322 Patient Years)

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
2.7 (9/329.7)	(1.5, 4.8)

Table 41: CAP2 Events Contributing to Second Primary Endpoint

Endpoint Event Type	N Events	% of Subjects N=579
Stroke - Ischemic	7	1.2%
Systemic Embolism	2	0.3%

Third Primary Endpoint: Five 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 0.9% as shown in **Tables 42** and **43**.

Table 42: CAP2 Third Primary Endpoint

% (n/N)	95% CI
0.9% (5/579)	[0.3%, 2.0%]

Table 43: CAP2 Events Contributing to Third Primary Endpoint

Type	N Events	% of Subjects N=579
Cardiac Perforation	3	0.5%
Stroke (Ischemic)	1	0.2%
Death	1	0.2%

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN is presented in **Table 44**. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in **Table 4**.

Table 44: CAP2 Registry Serious Adverse Events

Type	N Events	% (N Pats with Event /579) N=579
Death - Non-cardiovascular	2	0.3% (2/579)
Stroke (Ischemic)	6	1.0% (6/579)
Systemic Embolism	2	0.3% (2/579)
Gastrointestinal Bleeding	3	0.5% (3/579)
Other (Study Related)	11	1.7% (10/579)
Transient Ischemic Attack (TIA)	2	0.3% (2/579)
Major Bleed Requiring Transfusion	13	2.2% (13/579)
Pericardial Effusion with Cardiac Tamponade	8	1.2% (7/579)

Type	N Events	% (N Pats with Event /579) N=579
Anemia Requiring Transfusion	1	0.2% (1/579)
Pericardial Effusion	3	0.5% (3/579)
Pseudoaneurysm	1	0.2% (1/579)
Hematuria	3	0.5% (3/579)
Arrhythmias	1	0.2% (1/579)
Hematoma	2	0.3% (2/579)
Subdural Hematoma	3	0.5% (3/579)
Cardiac Perforation	3	0.5% (3/579)
Device Thrombus (thrombus on the atrial facing side of the device)	5	0.9% (5/579)
Respiratory Failure	2	0.3% (2/579)
Oral Bleeding	2	0.3% (2/579)
Bleeding from Varicose Veins	1	0.2% (1/579)
Bleeding, Other	1	0.2% (1/579)
Respiratory Insufficiency	1	0.2% (1/579)
Valvular Damage	1	0.2% (1/579)
Infection	1	0.2% (1/579)

CAP2 Device Thrombus Rates
The device thrombus-related stroke rate was 0.9 events per 100 patients as shown in **Table 45.**

Table 45: CAP2 Device-related Thrombus

	N=545
Thrombus Subjects	10 (2.2%)
Thrombus Events	10
Experienced Ischemic Stroke	3
Experienced Serious Adverse Event	5
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.9

Discontinuation of warfarin among WATCHMAN subjects: The CAP2 Registry is ongoing and data collection is ongoing. Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 98% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

HOW SUPPLIED

- The WATCHMAN Left Atrial Appendage Closure Device is pre-loaded in the Delivery System.

- The WATCHMAN Access System is packaged separately.
- The WATCHMAN products are supplied STERILE using an ethylene oxide (EO) process.
- Do not use if package is opened or damaged.
- Do not use if labeling is incomplete or illegible.

Note: Contents of inner package are STERILE.

Handling and Storage

Store in a cool, dry, dark place.

OPERATIONAL INSTRUCTIONS

Pre-Procedural Instructions

A baseline TEE should be performed to verify that a patient's anatomy is appropriate for a WATCHMAN Device to be implanted.

1. Assess the following through multiple imaging planes (0°, 45°, 90° and 135° sweep):
   - LAA size /shape, number of lobes in LAA, and location of lobes relative to the ostium.
   - Confirm the absence of thrombus (use Color Doppler and echo contrast as necessary).
2. Record LAA ostium and LAA length measurements (0°, 45°, 90° and 135° sweep). Measure the LAA ostium at approximately these angles:
   - at 0° measure from coronary artery marker to a point 2 cm from tip of the "limbus"
   - at 45° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"
   - at 90° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"
   - at 135° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"

Measured maximum LAA ostium width must be ≥17 mm or ≤31 mm to accommodate available device sizes.

Note: The maximum LAA ostium and LAA depth measurements determine device size selection.

PROCEDURAL INSTRUCTIONS

Equipment Needed for Implantation Procedure

- Venous Introducer (optional)
- Standard transseptal access system
- 0.035 in guidewire (exchange length extra support)
- 5F or 6F Angiographic Pigtail Catheter
- WATCHMAN Access System (which includes the Access Sheath and Dilator)

Implantation Procedure

NOTE: Aspirin should be started one day prior to scheduled procedure and continued daily.

NOTE: Use of fluoroscopy and echocardiographic imaging should be used when implanting the device (TEE is recommended as an aid in placing the WATCHMAN Device).

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

1. Use standard percutaneous techniques to puncture femoral vein and insert 0.035 in guidewire and vessel dilator. Use a standard, commercially available transseptal access system to cross inter-atrial septum.
2. Exchange crossing sheath with exchange length extra support 0.035 in guidewire. Position guidewire in left

upper pulmonary vein (LUPV) or loop in left atrium.

3. Prepare 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 sterile saline prior to use.

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

4. Advance WATCHMAN Access System over guidewire into left atrium (LA). As Access Sheath nears center of LA, unsnap the Access Sheath from the Dilator, hold 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.

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5. Remove Dilator and guidewire, leaving Access Sheath in LA or LUPV. Allow back bleed to minimize potential for introducing air before tightening valve. Flush the Access Sheath with saline.
6. Confirm LAA size and select appropriate WATCHMAN Device.

A. Using ultrasound guidance (TEE recommended), measure LAA ostium width and LAA depth in 4 views (0°, 45°, 90°, 135°).

B. Choose a device based on **maximum** LAA ostium width recorded. The LAA depth must be at least as long as the LAA ostium width. Use **Table 46** as a guide.

NOTE: LAA anatomy should accommodate a WATCHMAN Device as described in **Table 46**.

Table 46: WATCHMAN Device Selection

Max LAA Ostium (mm)	Device Size (mm)
17 – 19	21
20 – 22	24
23 – 25	27
26 – 28	30
29 – 31	33

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.

C. Carefully advance pigtail catheter through Access Sheath into distal portion of the LAA under fluoro guidance. Carefully advance Access Sheath over pigtail catheter until Access Sheath radiopaque (RO) marker band corresponding to device size (see **Figure 4**) is at or just distal to LAA ostium. Slowly remove pigtail catheter.

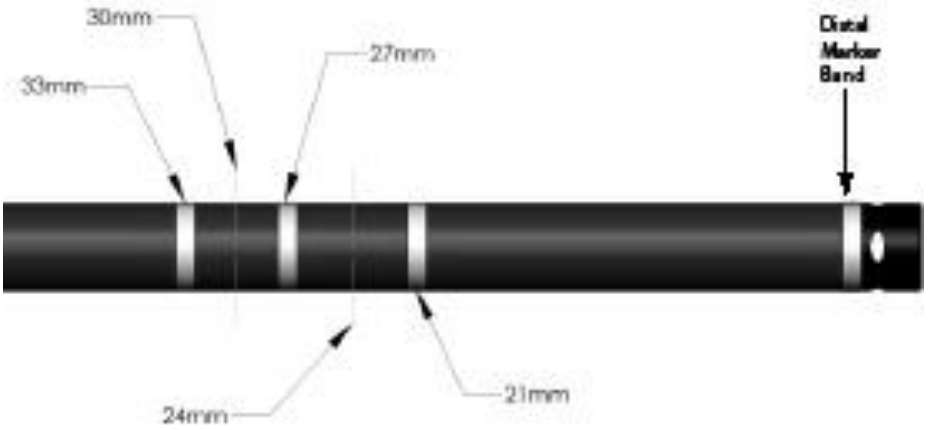

Figure 4: WATCHMAN Device Size Relative to Access Sheath Marker Bands

7. Prepare WATCHMAN Delivery System
   A. Remove Delivery System under sterile conditions.
   B. Inspect prior to use to ensure no damage to handle, catheter connections and device (through Delivery System).

NOTE: If sterile barrier, labeling, packaging, or device have been compromised in any way, or Delivery System appears damaged DO NOT USE.

   C. Confirm that the distal tip of the device is aligned with the RO marker band on Delivery System.
   D. Flush Delivery System with saline removing all air and maintaining fluid throughout system. Open and flush proximal valve.

NOTE: To avoid introducing air, apply pressurized saline bag to the side port of the 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.

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8. Loosen hemostasis valve of Access Sheath allowing bleed back before inserting Delivery System. Note: Hemostasis valve should spin freely (fully open).
9. 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.

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10. Under fluoroscopic guidance, align the most distal marker band on the Delivery System with most distal marker band on Access Sheath. Once marker bands are aligned, stabilize Delivery System, retract Access Sheath and snap together as Access Sheath/Delivery System assembly.
11. Using fluoro and ultrasound imaging (TEE recommended) confirm position of Delivery System tip before deploying the device.

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 100 psi.

---

12. If repositioning is required, unsnap the Delivery System from the Access Sheath and slowly remove Delivery System from Access Sheath. If necessary reinsert pigtail catheter to reposition Access Sheath. Reinsert Delivery System as described in Steps 9 and 10.
13. Deploy WATCHMAN Device by loosening valve on Delivery System and holding deployment knob stationary while retracting the Access Sheath/Delivery System assembly to completely deploy Device. Leave core wire

attached.

14. Device release criteria:

A. **Position:** Plane of maximum diameter is at or just distal to and spans the entire LAA ostium (See **Figure 5**).

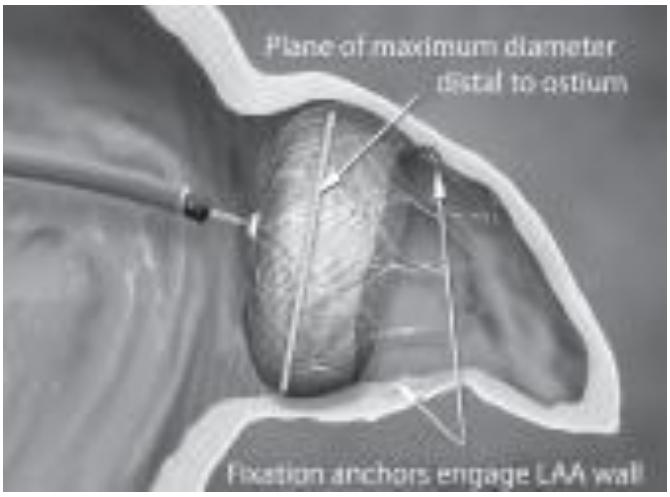

Figure 5: WATCHMAN Device Position and Size

B. **Anchor:** Gently pull back then release deployment knob to visualize movement of device and LAA together.

C. **Size (compression):** Measure plane of maximum diameter of device (See **Figure 5**). Use **Table 47** as a guide.

D. **Seal:** Ensure all lobes are distal to device and sealed, i.e., ≤5 mm jet.

Table 47: WATCHMAN Device Diameter

Original Diameter (mm)	Deployed Diameter (80-92% of original) (mm)
21	16.8-19.3
24	19.2-22.1
27	21.6-24.8
30	24.0-27.6
33	26.4-30.4

15. Partial device recapture, if necessary

NOTE: Partially recapture and redeploy WATCHMAN Device if too distal to LAA ostium

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A. Advance the tip of the Access/Delivery System assembly up to device (do not unsnap). Fix deployment knob position with right hand and gently advance Access/Delivery System assembly over shoulders of device. Position right thumb against Delivery System hub for stability. Resistance will be felt as device shoulders collapse. Continue to advance assembly up to but not past fixation anchors. When resistance is felt a second time (anchor contact), stop, tighten hemostasis valve.

NOTE: If device is retrieved past fixation anchors, recapture fully and replace Delivery System with a new system. Refer to Step 16. The WATCHMAN Device and Delivery System are for single use only. Do not reuse or resterilize.

B. Reposition Access Delivery/System assembly proximally and re-deploy by holding deployment knob and retracting Access Sheath until device is completely deployed. Leave core wire attached.

WARNING: Do not release the WATCHMAN Device from the core wire if the device does not meet release criteria (Step 14).

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16. Full device recapture.

NOTE: The WATCHMAN Device should be fully recaptured into the delivery system, removed and discarded if the device is deployed too proximal or does not meet the release criteria test. The WATCHMAN Device and Delivery System are for single use only. Do not reuse or resterilize the fully recaptured device.

A. Advance tip of Access/Delivery System assembly up to face of device (do not unsnap).

B. Fix deployment knob with right hand and gently advance Access/Delivery System assembly over shoulders of device. Position right thumb against Delivery System for stability. Resistance will be felt as device shoulders collapse. Continue to advance assembly until device is completely collapsed and fully recaptured (past anchors).

C. Withdraw the device until distal anchors are proximal to the RO marker band, then tighten hemostasis valve.

D. Unsnap Delivery System from Access Sheath while maintaining position. Slowly remove the entire Delivery System.

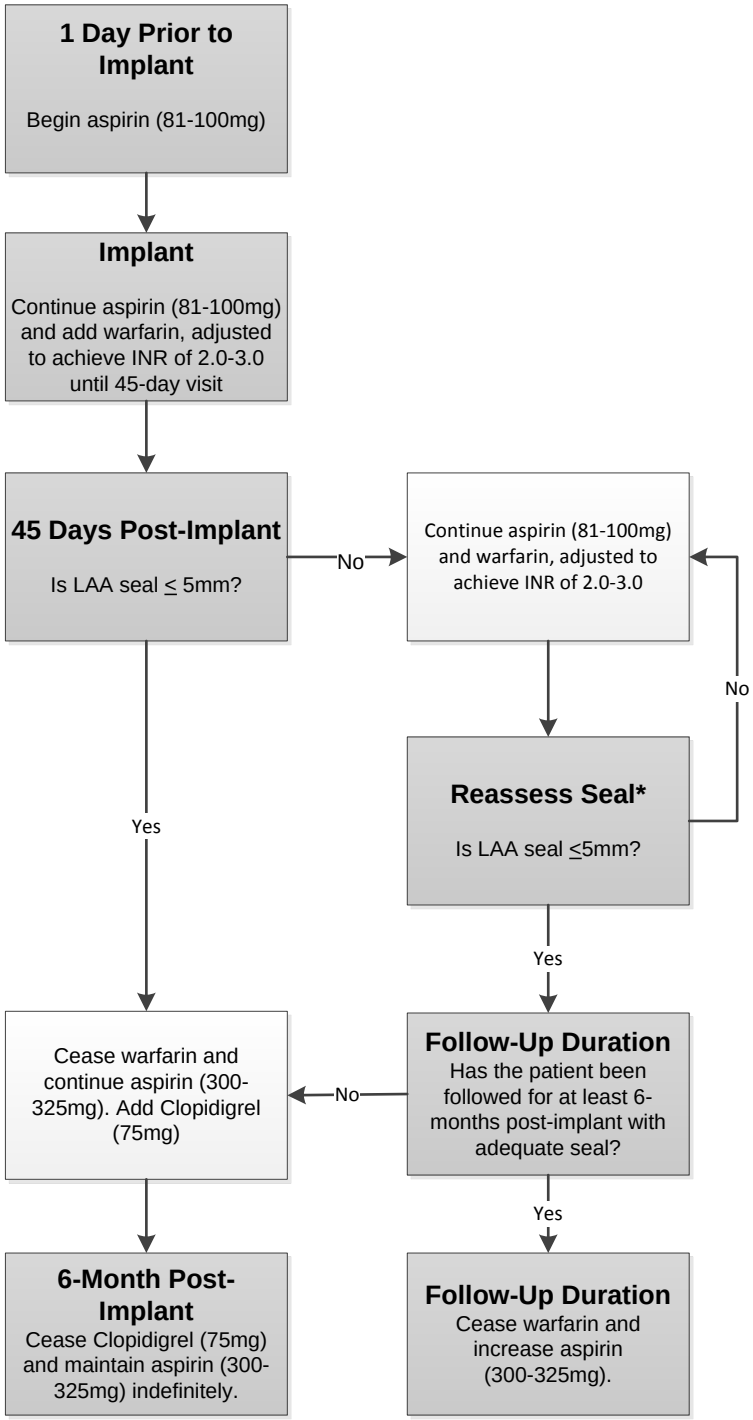
E. Insert pigtail catheter to reposition Access Sheath in LAA if necessary.

F. Repeat Steps 7-14 with new Delivery System.

17. WATCHMAN Device release criteria: Confirm proper position, anchor, size, and seal (PASS criteria), and then advance assembly to face of device. Rotate deployment knob counter clockwise 3-5 full turns. Confirm core wire is disconnected.
18. Remove Access Sheath and Delivery System based on parameters for hemostasis.
19. Use standard of care for post-procedure bleeding at access site.

Post Procedure Information

A. Post-procedure warfarin therapy is required in ALL patients receiving a WATCHMAN Device. Patients should remain on 81-100 mg of aspirin and warfarin should be taken post-implant (INR 2.0-3.0). At 45 days (±15 days) post-implant, perform WATCHMAN Device assessment with TEE. Cessation of warfarin is at physician discretion provided that any peri-device flow demonstrated by TEE is ≤5 mm. If adequate seal is not demonstrated, subsequent warfarin cessation decisions are contingent on demonstrating flow ≤5 mm. At the time the patient ceases warfarin, the patient should begin clopidogrel 75 mg daily and increase aspirin dosage to 300-325 mg daily. This regimen should continue until 6 months have elapsed after implantation. Patients should then remain on aspirin 300-325 mg indefinitely. If a patient remains on warfarin and aspirin 81-100 mg for at least 6 months after implantation, and then ceases warfarin, the patient should not require clopidogrel, but should increase to aspirin 300-325 mg daily, which should be taken indefinitely.



*The performance and timing of TEE to re-evaluate the LAA seal is left to physician discretion.

Figure 6: WATCHMAN Device Implant Pharmacologic Regimen

B. At 45 days and 12 months: assess WATCHMAN 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 if necessary.
- If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.

C. Prescribe appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to

continue endocarditis prophylaxis beyond 6 months is at physician discretion.

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