The WATCHMAN® PROTECT AF PIVOTAL CLINICAL REPORT

Title of Investigation: WATCHMAN LAA Closure Device for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF Pivotal Clinical Study)

Device Name and Models: WATCHMAN® LAA Closure Technology

consisting of the following components:

WATCHMAN LAA Closure Device (Implant)

WATCHMAN Delivery System

WATCHMAN Access System

WATCHMAN Obturator

Name of Sponsor: Atritech, Inc.

Protocol Number:

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1 Introduction

This report details the clinical data collected under Atritech Clinical Protocol [redacted] for the study entitled WATCHMAN® LAA Closure Technology for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF). The study was conducted under IDE [redacted] at approved investigational centers in both the United States and Europe with the active enrollment phase from February 2005 through June 2008.

1.1 Background and Clinical Need

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, currently affecting more than 3 million Americans. This population is projected to increase to 16 million by the year 2050.[25,29]

AF patients have a five-fold increased risk of stroke, compared to patients in normal sinus rhythm, due to blood stasis from the improperly beating atrium that results in thrombus formation. Over 87% of strokes are thromboembolic with >90% of the thrombus accumulation originating in the Left Atrial Appendage (LAA).[13,17,74]

Thromboembolic stroke is a costly and debilitating complication associated with AF, as shown by the following facts:

- Stroke is the third leading cause of death and the number one cause of long-term disability. [17,106, 22]
- Patients with permanent AF constitute approximately 51% of the AF population. However, even patients with paroxysmal AF are at risk for stroke. For patients with AF, the risk of stroke increases with age (particularly > 75 years), previous TIA or stroke, hypertension, diabetes, impaired left ventricular function, or a large left atrium.
- Non-valvular AF increases the risk of stroke five-fold, with ischemic stroke comprising 87% of all strokes.[17]
- AF patients not treated with warfarin therapy incur a risk of thromboembolic events as high as 12%, with the percentage of patients with major functional disability after AF related ischemic stroke as high as 59%.[128]
- The U.S. will pay $2.2 trillion over the next 45 years to care for people who suffer the most common form of stroke.[22] Hospital admissions associated with AF have increased 66% in the last 20 years.[26,129] Average hospital stay for an acute stroke is 5.2 days with a cost of $140,048 per patient for the duration of their lifetime.[17] There is considerable evidence that AF patients who suffer a stroke have a higher mortality, severity and impairment/dependency rate.[131]

The most common treatment for stroke prevention in AF patients has been long-term warfarin therapy. Despite its proven efficacy, warfarin therapy is not well-tolerated by patients, has a very narrow therapeutic range and carries a high risk for bleeding complications. Furthermore, the effectiveness of anticoagulation varies because of interactions with certain foods and medications, thus requiring frequent monitoring and dose adjustments, which can be inconvenient. Even with dose adjustments, patients are outside the therapeutic range up to half the time.[108]

The problems associated with warfarin therapy are particularly significant in the elderly population, which has a greater risk of falling and greater challenges with maintaining the therapeutic range. This is of importance since individuals over the age of 75 constitute approximately half of AF-associated stroke patients.[129] In multiple studies, warfarin treatment has been shown to produce severe and costly consequences, including major bleeding complications. In fact, a "black box" warning about bleeding risks associated with warfarin was incorporated into U.S. product labeling in 2006.[113]

When prescribing warfarin therapy in patients with AF, the physician must weigh the risks of significant bleeding complications, and non-compliance issues, against the risk of ischemic stroke without warfarin. Fewer than 50% of the patients eligible for long-term warfarin are currently being treated either due to noncompliance or tolerance issues.[110]

Current facts regarding long-term warfarin therapy:

- Preliminary results of a Medicare-based projection measuring the national economic burden of stroke associated with AF in the U.S. in 2003 indicated that only one-tenth of the potential anticoagulation benefit is currently attained because of the substantial under-prescription of warfarin.[27] Use of warfarin has leveled to approximately 50-60% of eligible patients with AF.[103]
- The SPORTIF trials suggest that only 60% of patients receiving warfarin are within a therapeutic INR (International Normalized Ratio) range (INR between 2.0 and 3.0), while 29% have INR levels below the therapeutic range (INR < 2.0) and 13% have INR levels above the therapeutic range (11% between INR of 3.1 - 4.0, and 2% with INR >4.0).[106]
- Among patients admitted with AF-related stroke, nearly two-thirds had an INR less than 2, which almost doubled the odds of a severe stroke and increased 30-day mortality by 3-4 fold.[27]
- The FDA Adverse Event Reporting System counted warfarin among the top ten drugs with the largest number of serious adverse event reports from 1990-2000.[113] In 2003-2004, anticoagulants ranked first in the number of total deaths for drugs causing "adverse effects in therapeutic use" from US death certificates.[113]
- Major bleeding with warfarin use is estimated to occur at a frequency as high as 16%.[113]
- Approximately 12% to 24% of intra-cerebral bleeds are warfarin-related and as many as 10,000 anticoagulant-related intracerebral hemorrhages occur annually in the U.S.[21]

1.2 Risk Factors and Stroke

The most widely recognized tool for assessing the risk of stroke in patients with AF is the $CHADS_2$ risk stratification scheme published in 2001. A $CHADS_2$ score is obtained based on a patient's medical history utilizing a point system that assigns one point each for Congestive heart failure, Hypertension, Age >75, and Diabetes, and assigns 2 points for a previous Stroke or TIA. The higher the $CHADS_2$ score, the greater the risk of stroke. Specifically, with a $CHADS_2$ score of 0 the risk is 2% per year, and it rises to 18% per year with a $CHADS_2$ score of 6.[129]

The cumulative $CHADS_2$ score is commonly used to guide therapy, by targeting the use of anticoagulation or other therapeutic options toward those patients who have the greatest risk.

1.3 Warfarin Therapy as Standard of Care

The current standard of care for stroke prevention in AF patients with at least one moderate risk factor ($CHADS_2$ score of 1) is long term warfarin therapy.[129] Long term warfarin has been extensively studied both for its therapeutic benefit and long term sequela, and has demonstrated significant complications affecting lifestyle and long term care.

There is a wealth of published literature from controlled trials on stroke prevention in AF. The Stroke Prevention in Atrial Fibrillation (SPAF) studies examined treatment strategies for patients with non-valvular AF and provided evidence that forms the backbone of today's standard stroke prevention modalities. SPAF I showed a reduction in stroke events of 67% at one year, confirming that antithrombotic therapy with aspirin or warfarin was effective in ischemic stroke prevention. SPAF III confirmed that if the risk of thromboembolism justified antithrombotic therapy, warfarin adjusted for a target INR of 2.0 to 3.0 was most effective.

The SPAF studies documented a stroke rate of 2.2% per year in patients treated with warfarin. In a meta-analysis of randomized trials on antithrombotic therapy for stroke prevention in AF patients, thromboembolic/ischemic stroke risk with warfarin therapy ranged from 2.2% with no known risk factors to >10% with multiple risk factors. [11]

Warfarin as a clinical treatment is not without its risks. The frequency of major bleeding while on warfarin has been estimated to be as high as 16%.[113] The decision guidelines for AF patients at risk of ischemic stroke without warfarin therapy must be weighed against the risk of intracranial hemorrhage with warfarin therapy. AF-related ischemic stroke is associated with a significant risk of death and major disability. If a stroke occurs while the patient is not taking warfarin, the outcomes are worse. This risk must be considered in the context of the mortality or long term disability rate of approximately 90% from warfarin-associated hemorrhage.

The ACC/AHA/ESC 2006 practice guidelines outline the therapeutic INR range of 2.0-3.0 for prevention of ischemic stroke and the avoidance of hemorrhagic complications. Although chronic warfarin therapy has been proven to reduce the risk of clinical thromboembolism among those with non-valvular AF, there are several difficulties in administering it. Frequent blood tests to monitor INR are required at some cost and patient inconvenience. In addition, because warfarin is affected by a large number of drug and dietary interactions; it can be unpredictable and difficult to manage.

If INR values fall below 1.8, there is an increased risk of thromboembolism and if they rise above 3.0, there is an increased risk of hemorrhagic complications. Even an INR within the range of 2.0 to 3.0 is associated with an increased risk for major and minor hemorrhagic events. Thus the potential for hemorrhagic events combined with the narrow therapeutic range limits the desirability of warfarin for patients and health care providers alike.

Furthermore, chronic anticoagulation presents problems of safety and tolerability in many patients, especially those older than 75, the age group encompassing perhaps half of AF-associated strokes [10]. The efficacy of aspirin for stroke prevention in AF patients is less clear and remains controversial. Aspirin is somewhat effective in AF-related stroke prevention, but it is clearly less effective than warfarin.[134]

1.4 Investigational Antithrombotic Agents and Combination Therapies

Although chronic warfarin therapy has been proven to reduce the risk of clinical thromboembolism, its substantial risk of hemorrhage, variability in dose response among individuals and its interaction with food and drugs has prompted intensive efforts to find a safer, more convenient alternative. Several randomized trials, e.g., Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W), Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with Non-valvular Atrial Fibrillation (SPORTIF III and V), Randomized Evaluation of Long Term Anticoagulant Therapy (RELY) and ROCKET AF, have encountered multiple challenges including major and minor bleeding complications, liver toxicity, etc.[103] Presently, new pharmacological approaches continue to be evaluated by medical professionals.

Additionally, multiple anticoagulation regimens in combination, raises confounding questions. For example, AF patients who have drug-eluting stents (DES) are required to take aspirin and clopidogrel in addition to warfarin according to standard treatment therapies. This combination potentially leads to an increased risk of bleeding over a patients' lifetime.[129] Aspirin resistance, warfarin resistance and combinations of other cardiac medications multiply the challenges of treatment within this population.

1.5 LAA Closure Techniques

Removal of the left atrial appendage (LAA) to prevent stroke was first described during mitral valvulotomy procedures for rheumatic mitral stenosis in the 1930s.[13] It was known at that time that nearly 50% of all atrial thrombi occurred in the LAA.[87] Recent data show that up to 90% of cardiac emboli appear to originate from the LAA with a high prevalence especially in non-rheumatic atrial fibrillation (AF) patients.[13, 74, 90]

Today, many procedures to close off or remove the LAA are routinely performed surgically with suture or staples, as an adjunct during open chest surgery or during minimally invasive procedures. Recent advancements have allowed LAA exclusion to be performed less invasively. A number of different methods for LAA closure have been described in the literature with variable success.

1.5.1 Surgical Closure

Surgical closure or ligation of the LAA with suture has shown to be feasible, and has been performed during cardiac surgery, especially mitral valve surgery. In several investigations it was reported that surgical closure of the LAA may not completely seal the LAA from the LA circulation. One study in particular showed that incomplete surgical LAA closure was common, as investigators found patent flow into the LAA during follow-up evaluation by transesophageal echocardiogram (TEE). In that study 18 of 50 (36%) patients had incomplete LAA closure on subsequent TEE follow-up. Furthermore, spontaneous echo contrast (SEC) or thrombus was detected within the appendages in 9 of 18 (50%) patients with incomplete closure. Most importantly, 4 of 18 (22%) patients had some type of thromboembolic event after the procedure [92] indicating that the residual communication between the incompletely ligated LAA and the LA body might be a potential source of the increased embolic events.

Stapling the LAA with a device during open chest surgery has been another approach to close the LAA. The LAAOS study compared a stapling device to suture ligation during coronary artery bypass grafting (CABG) in 77 patients. Using the surgical stapler, 24 of 33 (72%) patients demonstrated complete occlusion while only 5 of 11 (45%) patients using sutures had a similar result.[88] Appendage tears were reported in 9 of 77 (12%) patients during surgery and all were repaired with sutures. In the experience of those surgeons who performed at least 4 cases with the stapling device, the rate of complete LAA occlusion increased from 9 of 21 (43%) to 20 of 23 (87%) over that period.[88] A learning curve may play a role in achieving greater success rates with this method.

1.5.2 Percutaneous Closure

Percutaneous closure of the LAA has been studied in human clinical trials since August 2001. Over time the procedure has become more widely attempted and accepted as the design of LAA closure devices has improved and the implantation techniques and imaging methods have been refined. In addition, the understanding of the complex nature of the anatomy of the LAA has increased.

The PLAATO device (Appriva Medical/ev3) was the first percutaneous LAA closure device implanted in humans. Its structure is a nitinol frame closed at both ends with three rows of anchors along the frame struts to stabilize the device in the LAA. An expanded polytetrafluoroethylene (ePTFE) membrane covers the frame and is designed to seal the LAA and allow for endothelialization.

Two concurrent multi-center feasibility trials on the PLAATO device were conducted, one in Europe and one in North America from August 2001 until November 2003. The primary population included non-rheumatic AF patients at high risk for ischemic stroke who were not candidates for long-term warfarin therapy. The primary study endpoint was the occurrence of major adverse event (MAE) related to the PLAATO procedure within one month of the index procedure. MAE was defined as new major or minor stroke, cardiac or neurologic death, myocardial infarction or the requirement for cardiovascular surgery. LAA occlusion was attempted in 111 patients with successful implant in 108 patients (97.3%). Average follow-up was 9.8 months. Of the 108 implanted patients, 100 patients (92.6%) received aspirin and 82 patients (75.9%) received Clopidogrel after the procedure. The annual stroke rate reported in December 2003, one month following closure of the trial, was 2.2% (two events during 90.7 documented implant years) in the 108 patients who underwent successful occlusion of the LAA.[75] After completing

feasibility studies, the PLAATO device clinical study program stalled, and a pivotal investigation of the device was never initiated.

The Amplatzer septal occluder has also been used for LAA closure, however its use was off label and not in an approved clinical study. The Amplatzer device is a double-disc of a nitinol braid and when used in LAA closure relies only on radial force for stability rather than an anchoring system or fixation barbs. The device was designed for closing atrial septal defects rather than the LAA.

The WATCHMAN LAA Closure Technology, specifically the WATCHMAN LAA Closure Device (Atritech) was first implanted in humans in August 2002. Atritech successfully completed feasibility studies in both Europe and the US and has concluded enrollment in a randomized pivotal study (PROTECT AF) to assess safety and long term efficacy of the WATCHMAN Device. Additional details on the WATCHMAN Technology and the WATCHMAN Device are provided in the next section.

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2 Investigational Device Description - WATCHMAN LAA Closure Technology

The WATCHMAN LAA Closure Technology used in the clinical study consists of three required components, the WATCHMAN LAA Closure Device (WATCHMAN Device), the WATCHMAN Delivery System and the WATCHMAN Access System and one optional component, the WATCHMAN Obturator.

The implant procedure is performed percutaneously under conscious sedation or general anesthesia in either a cardiac catheterization or electrophysiology laboratory setting. The device is a permanent implant positioned distal to the ostium of the left atrial appendage (LAA) using both angiography, echocardiography and standard transseptal techniques. Each component of the system is described in additional detail below.

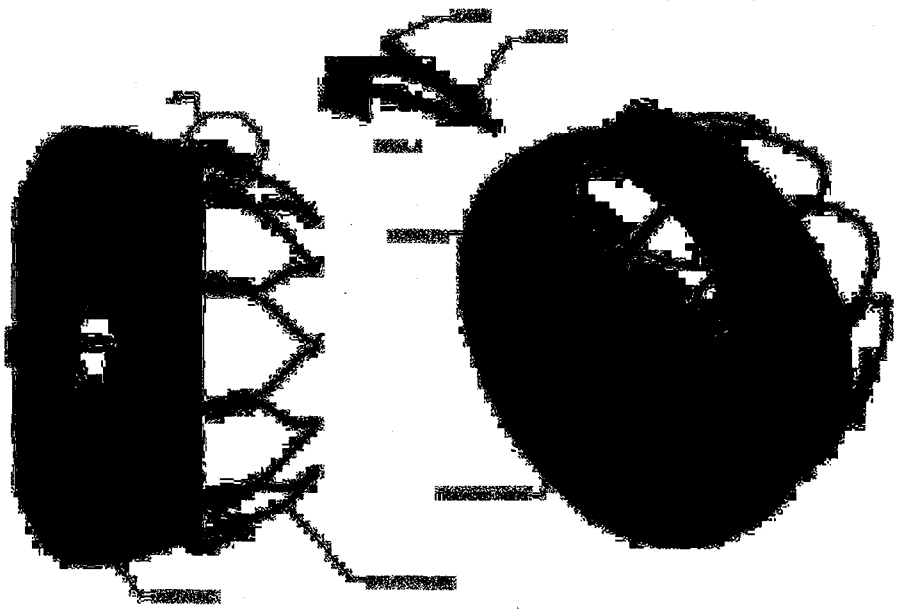
2.1 WATCHMAN LAA Closure Device

The WATCHMAN Device is a self-expanding nitinol frame structure, designed to be permanently implanted in the LAA. The frame is closed and covered only at its proximal end by permeable polyester polyethylene terephthalate (PET) fabric, and the frame tapers to an open distal end. A row of fixation barbs designed into the frame structure are located around the perimeter of the frame and aid in the stabilization of the device *in situ*. Refer to **Figure 2-1** for an image of the Device.

The PET fabric is secured to the frame structure above the fixation barbs using braided polyester suture. The fabric is also secured at the top of the device by means of a titanium threaded insert assembly. The threaded insert is attached to the nitinol frame by a welded dowel pin and provides the mechanism for attachment of the implant to the core wire on a delivery catheter. The WATCHMAN Device is constrained and pre-loaded into a delivery catheter during the manufacturing process.

The WATCHMAN Device is available in five sizes to accommodate a range of LAA ostial diameters. The device size, measured in mm, is the diameter of the device at its maximum dimension in an uncompressed (fully expanded) state. The five available sizes are: 21 mm, 24 mm, 27 mm, 30 mm and 33 mm.

Figure 2-1. WATCHMAN LAA Closure Device

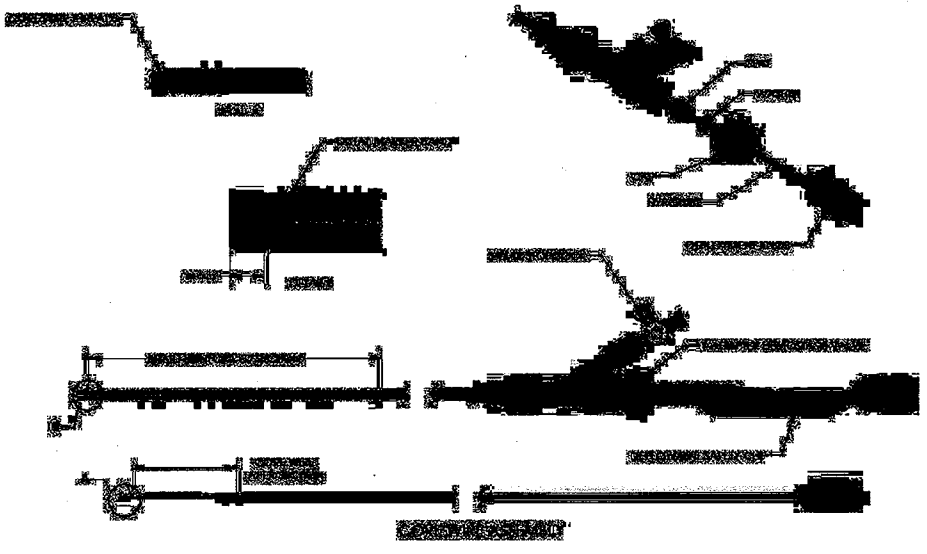


2.2 WATCHMAN Delivery System

The WATCHMAN Delivery System used in the clinical study consists of 12 Fr OD delivery catheter constructed of wire-braid reinforced tubing with a handle assembly at the proximal end and the constrained, pre-loaded WATCHMAN Device at the distal end of the catheter. The Device is pre-loaded into the delivery catheter during the manufacturing process. Each of the five available device sizes can be constrained within the 12 Fr delivery catheter.

The distal end of the Delivery Catheter contains a marker band for *in situ* visualization. The handle assembly of the delivery catheter consists of a Y-adapter with attached stopcock and a stiffener hypo tube with deployment knob. A core wire with a reinforced braided jacket runs the length of the delivery catheter. This core wire attaches to the deployment knob at the proximal end and a screw wire assembly at the distal end. The screw is mated to the threaded insert component of the device and provides the mechanism for attachment and release of the implant. The core wire provides both the rigidity necessary to deploy the device and the flexibility necessary to not bias the device in the LAA until the device is evaluated and released. Refer to **Figure 2-2** for an image of the Delivery System.

Figure 2-2. WATCHMAN Delivery System



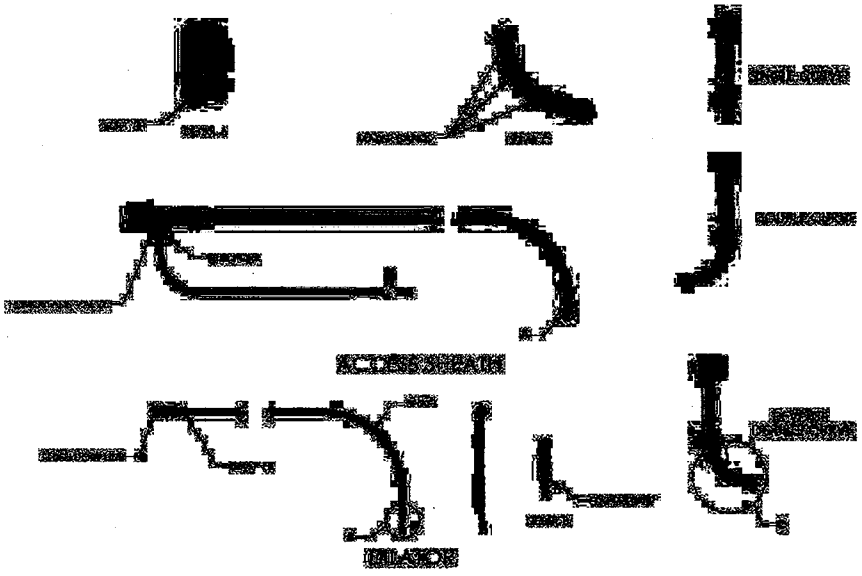
2.3 WATCHMAN Access System

The WATCHMAN Access System consists of a 14 Fr OD (12 Fr ID) access sheath and 12 Fr dilator. The distal end of the Access Sheath is available in three curve styles to assist with placement of the sheath into the LAA. Various curve styles allow for coaxial placement of the sheath into the LAA. The distal tip contains a marker band for *in situ* visualization as well as sizing marker bands used to gauge if the access sheath is positioned at the appropriate depth in the LAA based on the device size selected. The marker bands also serve to prevent procedure complications or damage to the LAA. The proximal end of the Access Sheath is comprised of a Touhy-borst style hemostasis valve with an attached sideport. Refer to **Figure 2-3** for an image of the Access System.

The 12 Fr dilator is tapered at the distal tip and curved to an approximate 90° angle to aid in septal crossing. The proximal end of the dilator contains a flush port hub with standard luer taper and threads. The hub is designed for snap fit connection to the access sheath hemostasis valve. The Access Sheath and dilator are utilized to gain access to the LAA after initial transseptal access into the left atrium has been established. Once the access sheath is positioned into the left atrium and the dilator has been removed, the Access Sheath then serves as a conduit for the delivery catheter and placement of the device.

The Delivery System is introduced into the Access Sheath and the components snap together to act as one during device implantation. Together, the Access Sheath and Delivery System are designed to facilitate device placement into the LAA by way of femoral venous access and transseptal crossing. The device is deployed by retracting the access sheath and Delivery System delivery catheter together along the proximal handle. The device is released by turning the deployment knob on the delivery catheter handle assembly counterclockwise until the core wire and screw mechanism are completely disconnected from the device.

Figure 2-3. WATCHMAN Access System



2.4 WATCHMAN Obturator

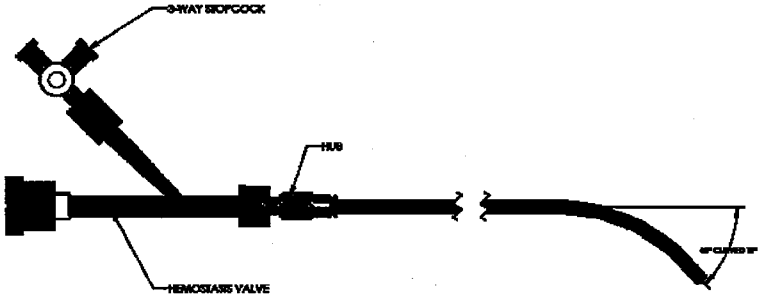
The WATCHMAN Obturator is a 12 Fr OD (6 Fr ID) optional adjunctive device that may be used to assist with placement and guidance of the access sheath into the LAA. The Obturator first became available to investigational sites January 2008 and has been used in a limited number of procedures.

The Obturator is designed to provide a smooth transition from the Access Sheath to a pigtail catheter (if utilized) for increased specific and directed placement in the desired location of the LAA. The Obturator fits within the Access Sheath, extends 5cm past the sheath tip (when fully extended), and will accommodate up to a 6F pigtail catheter. Refer to **Figure 2-4** for an image of the Obturator.

The proximal end of the Obturator has a luer fitting with an attached Y adapter hemostasis valve and 3-way stopcock and has a snap fit hub for connection to the Access Sheath hemostasis valve. The distal end of the Obturator is rounded and curved to a 45 degree angle. The Obturator shaft is an extruded

catheter with a decreasing durometer (hardness) at the distal section to increase the flexibility. The Obturator also contains a radiopaque marker band 5mm from distal tip to aid in visualization during advancement into the LAA.

Figure 2-4. WATCHMAN Obturator



2.4.1 Investigational Device Modifications

During the clinical study, the WATCHMAN LAA Closure Technology included several model numbers and iterations for both the WATCHMAN LAA Closure Device and WATCHMAN Access System. No product changes were made to the WATCHMAN Delivery System during the PROTECT AF study.

The original or "Long" WATCHMAN Device was available to investigators throughout the entire study duration, (model numbers WS-2101 through WS-3301). A "Short" version of the WATCHMAN Device was introduced in October 2006, (model numbers WS-2102 through WS-3302), following IDE supplement approval to minimize length requirements necessary to implant a device. The "Short" WATCHMAN was a device whose only difference is a decreased length of 20% for each of the existing five "Long" device diameter sizes. The Short device was used with the existing Delivery Catheter and Access System and used the same principles of implant sizing relative to the maximum size of the measured LAA ostium. Atritech intends to commercialize only the Short version of the WATCHMAN LAA Closure Device.

See **Table 2-1** for WATCHMAN Device size and model numbers.

Table 2-1. WATCHMAN Device Sizes and Model Numbers

21mm	WS-2101	WS-2102
24mm	WS-2401	WS-2402
27mm	WS-2701	WS-2702
30mm	WS-3001	WS-3002
33mm	WS-3301	WS-3302

The WATCHMAN Access System iterations consisted of various enhancements to the Access Sheath, including minor material changes, marker band additions and distal side holes for contrast dispersion to optimize safe device deployment. Enhancements to the distal tip of the Access Sheath, including durometer changes, were made in an effort to address some of the procedural adverse events reported in the study. This enhancement called the soft-tip (model numbers TS 1001 through TS 1004, TS 2001 through TS 2004 and TS 3003) replaced the original Access Sheath design versions (TS 1000 and TS 2000) and was released to clinical sites beginning in August 2006. See **Table 2-2** for WATCHMAN Access System model numbers. FDA approved these modifications to the Access System in various IDE supplements.

Table 2-2. WATCHMAN Access System Model Numbers

Model #'s	Single	TS 1000	TS 1001/1004	TS 1002/1003
Model #'s	Double	TS 2000	TS 2001/2004	TS 2002/2003
Model #'s	Reverse	N/A	N/A	TS 3003

The modifications implemented during the pivotal trial were intended to address procedural issues and handling characteristics during the implant procedure itself. The modifications to the WATCHMAN product family did not materially affect the way the implant was placed or deployed, its long-term position in the body nor its effect in occluding the LAA. An analysis comparing the data from patients with Long and Short devices is provided in **Section 12.3.7.3**. Therefore, the data collected in this study, in aggregate, can be used to demonstrate the safety and effectiveness of the WATCHMAN LAA Closure Technology.

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3 Control Description – Warfarin or Warfarin Derivative

Anticoagulation with warfarin therapy is the accepted standard of care for patients with an increased tendency for thrombosis, specifically patients with atrial fibrillation and other risk factors that increase the chance of stroke. Therefore, warfarin was selected as the treatment of choice for the Control group of the PROTECT AF study.

In the PROTECT AF study, all patients were required to be eligible to receive warfarin at the time of enrollment. Patients were also required to agree to remain on warfarin for the duration of the study if they were randomized to the Control group of the study (i.e., long-term warfarin therapy.)

The use of warfarin was mandated in the PROTECT AF study at actively participating centers however a variety of generic and trade name formulations were used particularly in Europe (specifically Germany).

Coumarin is a chemical compound (benzopyrone) and has clinical / medical value as the precursor for several anticoagulants, notably warfarin. Warfarin (also known under the brand names of Coumadin, Jantoven, Marevan, and Waran) is a synthetic derivative of coumarin. Phenprocoumon (marketed under the brand names Marcoumar, Marcumar and Falithrom) is also a derivative of coumarin. Since all the coumarin derivative compounds are Vitamin K antagonists, their pharmacological mechanism of action is the same and therefore no differences in the effects or effectiveness would be expected.

The dosing requirements of warfarin derivatives can vary widely. In order to optimize the therapy, the anticoagulation level for patients in the Control group was measured against the universally accepted therapeutic INR rather than a specific warfarin dose. All patients regardless of the anticoagulation therapy prescribed were monitored through frequent blood tests with the goal of maintaining a therapeutic INR of 2.0-3.0.[129]

At the time of study enrollment, a baseline INR was required for each patient. Furthermore, Control patients were required to have their INR monitored every other week through 6 months and then monthly during study participation. An INR monitoring worksheet was to be completed for all patients to record and provide this information to the investigator, and for data collection purposes to ensure monitoring against the therapeutic INR level was consistent across centers.

As monitoring of the INR was the method to confirm effective Control group anticoagulation rather than mandating a specific warfarin derivative or dose, the opportunity for variations in patient outcomes in the Control group was minimized.

4 Study Objectives and Endpoints

The purpose of the PROTECT AF study was to determine whether the WATCHMAN LAA Closure Device is a safe and effective alternative to long term warfarin therapy.

4.1 Study Objective

The objective of the PROTECT AF study was to demonstrate that the WATCHMAN LAA Closure Technology and specifically the WATCHMAN LAA Closure Device is safe and effective in patients with non-valvular atrial fibrillation who require anticoagulation therapy for potential thrombus formation. This objective was assessed with the following study primary and secondary endpoints as adjudicated by the Clinical Events Committee.

4.2 Primary Endpoints

Primary endpoints of safety and effectiveness were established.

4.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was defined as the successful treatment of the randomized patient without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism.

4.2.2 Primary Safety Endpoint

The primary safety endpoint was defined as the treatment of the patient without the occurrence of life-threatening events as determined by the Clinical Events Committee, 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.

4.3 Secondary Endpoints

Secondary endpoints were established by treatment group.

4.3.1 Device Group

The secondary endpoints specific for the Device group included:

- Technical Success defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary;
- Procedure Success defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay;
- 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer);
- Individual complication rates including, but not limited to hematomas, pseudoaneurysms, myocardial infarction and death.

- TIA [defined as an acute focal neurological event lasting at least 5 minutes and up to 24 hours that is MR imaging negative].

4.3.2 Control Group

The secondary endpoints specific for the Control group included:

- Non-therapeutic INR > 3.0 or < 2.0, and stopped therapy (Interruption of Therapy (IOT))
- Excessive anticoagulation INR > 4.0
- Bleeding complications such as: hematuria, rectal bleeding, epistaxis, bleeding from varicose veins, oral bleeding, prolonged bleeding from a laceration, bruising-hematoma, hemathorax, red eye, or thrombosis.
- Individual complication rates including, but not limited to myocardial infarction and death.
- TIA [defined as an acute focal neurological event lasting at least 5 minutes and up to 24 hours that is MR imaging negative].

4.4 Study Hypotheses

The criterion for establishing non-inferiority and superiority in the PROTECT AF pivotal clinical study is described below:

4.4.1 Criterion for Non-inferiority

- The posterior probability that the event rate for the Device group is less than 2 times the event rate for the Control group is at least
- The posterior probability that the event rate for the Device group is less than the event rate for the Control group must be at least

4.4.2 Criterion for Superiority

- The posterior probability that the event rate for the Device group is less than the event rate for the Control group must be at least

4.5 Event Definitions

Definitions related to endpoint events are provided below:

- **Death** – Patient deaths were recorded on a patient data form with a detailed description of the circumstances surrounding the patient's death documented. Autopsy results and explanation of the device were obtained when possible.
- **Device Embolization** - An obstruction or occlusion by a device that has been dislodged from the LAA and is introduced into the circulatory system potentially occluding vessels and / or organs by occluding its blood supply.
- **Serious Adverse Event (SAE)** - Any untoward medical occurrence or any Adverse Event that:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
- **Ischemic Stroke** - Sudden onset of a focal neurological deficit with symptoms and/or signs persisting more than 24 hours or symptoms less than 24 hours confirmed by CT or MRI, including a full neurological exam by a Neurologist.
- **Hemorrhagic Stroke** - Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage, including full neurological exam by a Neurologist.
- **Systemic Embolism** - Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.
- **Thromboembolism** - The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation.
- **Thrombosis** - The formation or presence of a blood clot within a blood vessel.
- **Transient Ischemic Attack (TIA)** - Acute focal neurological event (including focal motor deficit aphasia, difficulty walking, hemi sensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes and up to 24 hours that is MR imaging negative, including full neurologic exam by Neurologist.
- **Unanticipated Adverse Device Effect (UADE)** - Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, the WATCHMAN Device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with the WATCHMAN Device that relates to the rights, safety, or welfare of subjects.

5 Investigational Plan and Methods

The investigation of the WATCHMAN LAA Closure Technology was a multi-center prospective randomized design comparing the WATCHMAN Device to a Control group of long-term warfarin therapy. A 2:1 randomization allocation ratio (two Device to one Control) was used with stratification by center.

5.1 Study Design

The PROTECT AF pivotal study was designed to demonstrate that the WATCHMAN LAA Closure Technology and specifically the WATCHMAN LAA Closure Device can be used safely and effectively in patients with non-valvular atrial fibrillation who require anticoagulation therapy for potential thrombus formation. A documented history of paroxysmal, persistent or permanent atrial fibrillation was required for every patient.

5.2 Study Scope and Duration

The study was conducted under an approved Investigational Device Exemption (IDE) [redacted] Enrollment commenced in February 2005 and randomized enrollment ended in June 2008.

The PROTECT AF study was approved for up to 60 investigative centers and a maximum enrollment of 1500 patients. A total of 59 centers (55 U.S., 4 European) actively participated by enrolling at least one patient in the study. A total of 785 patients (including 93 roll-in patients) were enrolled at the time of the database lock and subsequent analysis of the data that is contained in this report.

The protocol allowed sequential evaluations of the statistical objectives under a Bayesian Model. [redacted]

Since the minimum required follow-up data requirements have been satisfied, an application for pre-market approval (PMA) for the WATCHMAN LAA Closure Technology is being submitted to the FDA. Following submission of the PMA application, patients will continue to be followed until the WATCHMAN Technology is approved for market release and all FDA requirements have been satisfied, or until the investigation is otherwise terminated.

5.3 Enrollment Methodology

The enrolled population consisted of adult patients, without regard to race or gender, with non-valvular atrial fibrillation who were eligible for warfarin therapy. Patients were screened as candidates for the PROTECT AF study across all participating investigational centers.

In accordance with the investigational plan, all patients were to receive warfarin for a minimum of 30-60 days; therefore, all patients were required to be warfarin eligible at the time of enrollment. Patients also were required to agree to remain on warfarin for the duration of their study participation if they were randomized to the Control group of the study.

Prospective patients who met the basic study entrance criteria were informed about the study and invited to participate. Patients were fully informed by the study investigator and/or assigned study coordinator

about the investigation and the potential benefits and risks of the WATCHMAN Device prior to any study related testing. Patients were presented with the current, site specific IRB-approved version of the consent form for signature and study enrollment.

A sample informed consent document suitable for use in this study, including the elements of informed consent in conformance with 21 CFR Part 50, is included in the study protocol attachments. Only those patients (or legal guardians, if applicable) who voluntarily provided written consent to participate were enrolled in this investigation.

Centers also recorded the following information on a site specific Enrollment Log for any patient who signed a consent form and were enrolled into the study:

- Patient initials
- Date Consent signed
- Study status (enrolled or screen failed)
- Patient study #
- Randomization date.

Patients were allowed to withdraw their participation at any time during the course of the investigation without sacrificing their rights as a patient or compromising their quality of medical care.

After providing written consent to participate, history and baseline data, blood work and a baseline neurologic exam by a neurologist were obtained to ensure that all patient selection criteria were met. For those patients who had experienced a prior embolic stroke or TIA, brain imaging (CT or MRI) was performed prior to randomization.

Patients who met all the Clinical Inclusion and Exclusion Criteria subsequently underwent an echocardiographic examination (via transthoracic TTE and transesophageal TEE) to evaluate the Echocardiographic Exclusion Criteria prior to randomization.

If the baseline echocardiographic examination confirmed the patient met no Echocardiographic Exclusion Criteria, the patient was eligible for study enrollment.

All echocardiographic examinations were performed in accordance with an Imaging Protocol.

Consenting patients who fulfilled all entrance criteria were eligible for study enrollment and only then proceeded to study randomization.

Baseline study requirements for patients enrolled in the PROTECT AF study are listed in **Table 5-1**.

Table 5-1. Baseline Study Requirements

Blood Work	√ [a]
TTE	√ [b]
TEE	√ [b]
INR	√
Neurological Assessment by Neurologist	√ [c]
Blood Pressure (Systolic / diastolic)	√
Resting Heart Rate	√
NIH Stroke Scale	√
Barthel Index (BI)	√
Modified Rankin Scale (MRS)	√
SF-12v2 Health Survey	√
Brain Imaging (CT/MRI)	√ [d]

[a] Obtain serum creatinine, platelet count and hemoglobin level at baseline or within 7 days prior to study enrollment.
[b] Obtain within 2 days of potential implant procedure.
[c] Obtain within 30 days prior to randomization
[d] Required for enrolled patients with prior embolic stroke or TIA. Obtain 30±15 days prior to enrollment

5.4 Randomization Methods

A patient was randomized only after meeting all requirements for study enrollment outlined in the investigational plan.

A 2:1 randomization allocation ratio (two Device patients for one Control patient) was used. The randomization schedule at each site was formed by randomly permuting blocks of treatment assignments. Study randomization occurred electronically via a web based database at each given site, except in rare instances where technical difficulties necessitated randomization to occur by phone from the Atritech clinical department.

In order to randomize a patient, a study center was required to access the electronic randomization program and enter the center number and initials for an enrolled patient. The randomization program electronically assigned the patient to either the Device group or the Control group in a 2:1 allocation ratio. The randomization assignment was printed for documentation. The assigned study group was recorded on the appropriate study Case Report Forms (CRFs).

5.5 This section intentionally left blank

5.6 Device Group

Patients randomized to the Device group underwent an implant procedure to receive a WATCHMAN Device. At the investigator's discretion, patients were administered prophylactic antibiotics during the implant procedure. Patients were fully heparinized throughout the procedure with a recommended minimum active clotting time (ACT) of 200-250 seconds before or after transseptal puncture. ACT levels were obtained throughout the procedure, per standard practice at each investigative center, to ensure an appropriate ACT is maintained for the duration of the procedure. Prior to hospital discharge, the patient's recovery status was evaluated.

Patients in the Device group who were successfully implanted with a device underwent a TEE to assess device performance at 45 days, 6 months and 12 months. Evaluations of residual flow into the LAA, device stability, device position, residual atrial septal shunt and intracardiac thrombus were made during the echocardiographic examinations.

If warfarin was discontinued at the 45-day follow-up visit, Clopidogrel (75 mg) daily and aspirin (81-325 mg) were prescribed until completion of the 6-month follow-up visit and continuing with aspirin daily through the duration of the study.

Patients in the Device group continued on warfarin therapy if the 45-day TEE demonstrated a residual jet flow of $> 3 \pm 2$ mm around the WATCHMAN Device into the LAA. If the 6-month TEE continued to demonstrate flow around the WATCHMAN Device (i.e., jet $> 3 \pm 2$ mm), Device patients continued on warfarin therapy until the flow noted was $\leq 3 \pm 2$ mm on a subsequent follow-up TEE. Additional TEE

examinations were at the discretion of the investigator. Device patients were followed long term to re-assess their medical status and the occurrence of adverse events.

5.7 Control Group

Patients randomized to the Control group initiated warfarin therapy (if applicable) or remained on their current long-term warfarin therapy per standard medical practice, with the goal of maintaining a therapeutic INR of 2.0 - 3.0.[129] A baseline INR was required to be recorded for each patient at the time of study enrollment.

Control patients were required to have their INR monitored every other week through 6 months and then monthly during study participation. An INR monitoring worksheet was completed for all patients to record and provide this information to the investigator and for data collection purposes. Control patients were followed long-term to re-assess their medical status and the occurrence of adverse events.

5.8 Follow-up Testing

All enrolled patients in both groups were required to receive follow-up assessments to re-assess their medical status and evaluate for the occurrence of adverse events. Assessments occurred at 45-days, 6-months, 9-months, 12-months and semi-annually thereafter from either the date of randomization for Control patients or the date of the implant procedure for Device patients.

Annual office visits and semi-annual telephone visits were required for all patients for up to five years, or until the study is either terminated or sufficient information for regulatory authorities has been obtained (whichever comes first). Interim follow-up visits were also recorded and reported as needed for all patients. During each follow-up visit (scheduled or interim), patients were evaluated for any adverse events.

Follow-up requirements for patients enrolled in the PROTECT AF study are listed in **Table 5-2**.

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Table 5-2. Follow-up Study Requirements

WATCHMAN Group:					
TEE	√	√		√[c]	
INR[b]	√	Monthly if required	Monthly if required	Monthly if required	Monthly if required
All Enrolled Patients:					
Resting Heart Rate SBP and DBP	√			√	
Neurological Assessment[a]				√[g]	
NIH Stroke Scale[e]	√	√		√	
Barthel Index (BI)[f]	√	√	√	√	√
Modified Rankin Scale (MRS)[f]	√	√	√	√	√
SF-12v2 Health Survey[c]				√[c]	
Brain Imaging (CT/MRI) and Stroke Scales[d]	As needed	As needed	As needed	As needed	As needed

[a] Neurological assessment by neurologist.
[b] For WATCHMAN patients, INR checks required every other week through 45-Day Follow-up Visit. If WATCHMAN patients continue warfarin beyond 45-Day visit, INR checks should be done every other week through 6 months and monthly thereafter if required. For Control patients, INR should be obtained every other week from randomization until 6 months and monthly thereafter.
[c] At 12 months only.
[d] Required following a stroke or TIA event including neurological assessment by a Neurologist.
[e] Neurological consult required if the NIHSS score increases ≥ 2 points from previous visit.
[f] Neurological consult required if the BI decreases ≥ 15 points or the MRS increases ≥1 point from the previous assessment, and the increase/decrease is NOT attributed to a non-neurological cause
[g] At 12 and 24 months only.

Follow-up windows allowed for patients enrolled in the study are listed in **Table 5-3**.

Table 5-3. Follow-up Windows

45-day	45 days	30 - 60 days
6-month	182 days	152 - 242 days
9-month	273 days	243 - 333 days
12-month	365 days	335 - 425 days
18-month	547 days	517 - 607 days
24-month	730 days	700 - 790 days
Semi-Annual	Based on randomization date or procedure date	-30 days of target to +60 days of target

Control patient - visit window calculated from date of randomization. WATCHMAN patient - visit window calculated from date of implant.

5.9 Study Modifications (including Protocol Amendments)

Four major revisions, requiring IRB notification, were made to the PROTECT AF investigational plan during the enrollment phase.

Patient enrollment in the PROTECT AF study commenced in and randomized enrollment ended in Additional centers were added until The majority of study patients were enrolled during a period when the last two protocol revisions were in effect.

5.10 Blinding

It was not ethically or practically possible to blind subjects or physicians to the treatment in the PROTECT AF study due to the invasiveness of the procedure. Randomization to treatment groups was used to control any potential enrollment bias.

The Clinical Events Committee, an independent but not blinded group, adjudicated all study endpoints. Aggregate results of clinical data and the clinical decisions of the Clinical Events Committee were not released to Atritech field personnel, study investigators or site personnel at any participating investigative center.

5.11 Confounding Variables

The PROTECT AF study was designed with the best available knowledge and advice at the time, with FDA review and agreement. A randomized study is the gold-standard for protection against bias induced by confounding variables. Randomization tends to create groups that are statistically similar on all confounding variables, both measured and unmeasured.

$CHADS_2$ score is a well-established predictor of stroke. For the PROTECT AF trial, in addition to the balance in $CHADS_2$ scores between the Device and Control groups created by randomization, the primary analysis model was stratified on $CHADS_2$ score. This provides additional protection against confounding because small and statistically insignificant imbalances between groups in this important predictor are handled in the statistical analysis.

5.12 Limitations of Study Design

There are several limitations of randomized clinical trials. First, since treatment assignments are not determined by clinical judgment, the randomization process can create an artificial situation that may not reflect what would happen in real-world clinical practice. Randomized trials may also be of smaller size than non-randomized studies due to their logistical difficulties and thus suffer from a lack of power. Results from randomized trials may be of limited generalizability if patients recruited into the trial are not representative of those patients that will be treated with the device. To assess these limitations, comparisons can be made between experiences and results from a randomized clinical trial with those from published reports of non-randomized studies such as large cohort studies and population surveys.

Under a traditional intent-to-treat analysis, a non-inferiority trial may result in biased estimates if a substantial number of patients randomly assigned to the experimental treatment do not receive their assigned treatment. This would tend to produce two groups with equal outcomes and may result in a finding of non-inferiority for an experimental treatment that is in actuality inferior.

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6 Investigators and Training

Investigators and research staff participating in the PROTECT AF study were evaluated thoroughly and formally trained to ensure, at a minimum, that the following responsibilities were understood and met:

The Principal Investigator (PI) designated at a site was responsible for the overall clinical management of patients enrolled in the study at their institution. The PI was charged with overall responsibility and accountability for the clinical team and for the data obtained from each patient participating in the trial. The PI was expected to ensure compliance with the investigational plan, ensure the informed consent process was followed, and review and sign case report forms. A signature by the PI indicated that documentation was accurate and complete.

Any co-investigator at a site (if applicable) was responsible for the clinical study activities in coordination with the site PI and in accordance with the investigational plan. Study Coordinators or research personnel assigned to the study were responsible for tracking patients and study devices and maintaining all records defined in the investigational plan. Roles and responsibilities for other site personnel were assigned and documented in site records

Echocardiographers utilized in the study were responsible for the management of all imaging requirements. This individual assumed overall responsibility and accountability for the TTE and TEE images obtained at baseline, and if applicable, at the procedure and appropriate follow-up time points. Echocardiographers were expected to ensure compliance with the imaging protocol and ensure the required imaging was recorded as required.

A complete list of the principal investigators / investigative centers that actively enrolled in the PROTECT AF study is provided in **Attachment 2.**

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7 Ethics

Atritech, as the study sponsor, was responsible for the conduct of the study including assurance that the regulatory requirements of the Food and Drug Administration (FDA) were met. Atritech ensured compliance to these responsibilities directly or by delegation to designated CROs and consultants. Atritech ensured adherence to FDA Title 21 Code of Federal Regulations Part 812, 50.54 and 56 and Good Clinical Practice Standards. A brief summary of some of those responsibilities are described below.

7.1 Selection of Investigators

Atritech selected qualified investigators as required by FDA regulations and Atritech internal standard operating procedures. A prospective center was evaluated to ensure that it had an adequate patient base and could provide sufficient staff and documentation support to conduct the study properly. Meetings were conducted with each potential center in order to inform the prospective investigator and staff of the study elements, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for patient enrollment, patient selection, informed consent, required clinical data and record keeping, etc.

7.2 Control of Investigational Devices

Investigational devices were shipped to participating investigators only after the following documents were received by Atritech:

- Written IRB approval for conduct of the study
- Approved site specific patient informed consent
- Signed Investigator Agreement
- Investigator's and Co-investigators' current curriculum vitae
- Signed financial disclosure statement

7.3 Compliance to Regulations

Atritech obtained FDA approval of the original study protocol and ensured that each study center received appropriate IRB approvals prior to any patient enrollment. Documentation of IRB approval for all enrolling sites in the PROTECT AF study is on file at Atritech.

As appropriate, Atritech submitted changes in the Investigational Plan to the FDA and investigators to obtain IRB re-approval. Atritech followed the requirements for submitting FDA reports including unanticipated adverse device effects, withdrawal of IRB or FDA approval, updated investigators lists, periodic and annual progress reports.

7.4 Record Retention

Atritech maintained copies of correspondence, subject data, shipment of devices, details of adverse device effects and other records related to the clinical trial or to the signed Investigator Agreements. All investigational clinical sites and the core laboratory agreed to maintain study records for two years after pre-market approval (PMA) is obtained or two years after the FDA is notified that research under the

IDE has been terminated by Atritech. At study completion, Atritech will provide specific record retention dates to all those affected by this requirement.

7.5 Informed Consent

Informed consent was obtained in accordance with the FDA regulation 21 CFR, Part 50 and Atritech internal operating procedures. Each IRB reviewed and approved the site-specific consent document. Any site requested modifications to the Atritech Patient Informed Consent Form were approved by Atritech, and as necessary by the FDA. A copy of the local IRB approved Patient Informed Consent Form along with a copy of each patient's signed consent form was maintained by each investigational site. A signed copy of the consent form was given to each patient. For patients enrolled in the roll-in phase, a separate Informed Consent was designed to specifically indicate that the investigator may be using the investigational device for the first time.

7.6 Confidentiality

All information and data sent to Atritech concerning patients or their participation in this trial is treated as confidential. Only authorized Atritech personnel have access to these confidential files. Authorized FDA personnel have the right to inspect all records pertinent to this trial. All data used in the analysis and reporting of this evaluation is without identifiable reference to the patient.

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8 Selection of Study Population

Study site personnel (i.e., primary investigator, co-investigator and/or study coordinator(s)) evaluated patients to determine whether they met appropriate study entrance criteria. Specifically, patients were evaluated to ensure they met all inclusion criteria and did not meet any exclusion criteria in the investigational protocol.

During the PROTECT AF study, revisions to the investigational protocol and patient selection criteria were introduced. Protocol revisions were reviewed and approved by the study site IRB prior to implementation. A summary of the patient selection criteria modifications utilized in the PROTECT AF study and their relationship to each protocol version are detailed in **Attachment 3**. These modifications affected only exclusion criteria and either clarified criteria already listed or added additional exclusions to refine the patient population. Overall, these modifications to the entrance criteria did not affect the scientific soundness of the clinical study nor do they affect the safety and effectiveness assessment of the device. Investigational centers commenced enrollment at different times during the PROTECT AF study; therefore, some centers may not have enrolled study patients under all protocol versions.

8.1 Number of Subjects Enrolled and Duration of Follow-up

Patients who were enrolled and whose data were entered into the database as of [redacted] are included in this report. On this date, the database underwent a "soft" lock after which existing data were reviewed and cleaned, and outstanding issues were resolved to create a final data set for analysis as of [redacted] A total of 785 patients were enrolled in the trial. This total included 93 roll-in patients, 454 patients randomized to the Device group, and 238 patients randomized to the Control group.

While follow-up is ongoing, at database closure there were a total of 633 patient-years of follow-up for the primary efficacy endpoint aggregated across the 692 randomized patients. In the roll-in cohort there were a total of 94 patient-years of follow-up for the primary efficacy endpoint aggregated across the 93 patients.

8.2 Inclusion Criteria

A patient was enrolled in the study if all of the following inclusion criteria were met:

- The patient is 18 years of age or older
- The patient has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease)
- The patient is eligible for long-term warfarin therapy
- The patient is eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice)
- The patient has a calculated $CHADS_2$ score of 1 or greater
- The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial
- The patient is able and willing to return for required follow-up visits and examinations

8.3 Clinical Exclusion Criteria

A patient was excluded from the study if any of the following clinical exclusion criteria were met:

- The patient suffers from New York Heart Association Class IV Congestive Heart Failure
- The patient has had a recent MI (within 3 months)
- The patient has an ASD and/or atrial septal repair or closure device
- The patient had a single occurrence of AF
- The patient has an ablation procedure planned within 30 days of potential WATCHMAN Device implant
- The patient has a planned cardioversion 30 days post implant of the WATCHMAN Device
- The patient has a resting heart rate > 110 bpm
- The patient had a transient case of AF (i.e., secondary to recent CABG (within 3 months), etc.)
- The patient has an implanted mechanical valve prosthesis
- The patient's left atrial appendage is obliterated
- The patient has undergone heart transplantation
- The patient has symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
- The patient had a prior embolic stroke or TIA within the last 30 days
- The patient requires long-term warfarin therapy (refer to protocol for additional details)
- The patient is contraindicated for warfarin therapy (refer to approved labeling for additional details)
- The patient has thrombocytopenia (< 100,000 platelets/mm3) or anemia with hemoglobin concentration of < 10 g/dl
- The patient is contraindicated for aspirin
- The patient is actively enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug (post-market study participation is acceptable)
- The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential
- The patient has an active infection of any kind
- The patient has a terminal illness with life expectancy less than two years
- The patient has a life expectancy of less than two years

8.4 Echocardiographic Exclusion Criteria

A patient was excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) were met:

- The patient has LVEF < 30%
- The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
- The patient has a high risk patent foramen ovale (PFO) (refer to protocol for additional details):
- The patient has significant mitral valve stenosis (i.e., MV <1.5 cm2)
- The patient has an existing pericardial effusion of > 2 ± 1 mm
- The patient has complex atheroma with mobile plaque of the descending aorta and/or aortic arch
- The patient has a cardiac tumor

8.5 Justification for Use of Foreign Investigational Sites (21 CFR 814.15)

All sites involved in the study, regardless of geographic location, followed the same study protocol and collected the same data. The demographic profile and the risk factors associated with non-valvular atrial fibrillation in the population of patients evaluated in this study are the same throughout the investigational centers used in the study. In addition, the standard of care in the treatment of this patient population is the same throughout Europe, including the usage of warfarin and the challenges of monitoring and maintaining compliance with a warfarin regimen. Lastly, Atritech has performed an analysis to assess poolability across sites, to further verify the appropriateness of including foreign patients in the study sample, which is located at the end of **Section 12.3.7.2**.

8.6 Removal of Patients from Therapy or Assessment

Patients who withdrew from the study for any reason, and patients' lost-to-follow-up during the investigation were documented on an End of Study CRF. If a patient death occurred, the investigator was asked to describe the circumstances and the suspected cause of death. Autopsy and device retrieval were requested whenever possible.

Patients randomized to the Device group but who did not receive a device for reasons such as an aborted procedure due to inability to implant or a procedural complication were followed at a minimum until the 45 day follow-up visit to record any adverse events.

9 WATCHMAN Device Treatment

9.1 Device Distribution

Atritech provided IRB approved centers with an adequate supply of investigational devices for use in the PROTECT AF study. All investigational products were labeled "For Investigational Use Only." Device accountability logs were maintained at investigational centers and at Atritech.

The WATCHMAN LAA Closure Technology consisted of three required components, the WATCHMAN LAA Closure Device, the WATCHMAN Delivery System and the WATCHMAN Access System and one optional component, the WATCHMAN Obturator, which became available for use at sites beginning

In order to prevent unauthorized use, Atritech shipped investigational product only to investigators, or their designated study coordinators for storage in a designated locked and secure location with limited access. Atritech maintained shipping records of all investigational products released; however, investigational inventory at the investigational site was the responsibility of designated site personnel.

Investigational product was returned from centers directly to Atritech if the center did not maintain storage for inventory, if product expired during the course of the study, or occasionally if it was necessary to replenish inventory demands at another center. Any unused investigational devices were to be returned to Atritech upon site close out.

9.2 Treatments Administered - Implantation of the WATCHMAN LAA Closure Device

9.2.1 Procedure Steps, Description and Summary

Refer to the Device Description section and Instructions for Use for additional details regarding the WATCHMAN LAA Closure Technology components.

The implant procedure was performed percutaneously under conscious sedation or general anesthesia in either a cardiac catheterization or electrophysiology laboratory setting. The device was a permanent implant positioned distal to the ostium of the LAA using a standard transseptal technique.

A procedure utilizing the WATCHMAN LAA Closure Technology was performed with a recommended INR < 2.0. Aspirin was begun at least one day before procedure and continued daily. Per current protocol guidelines, warfarin was required for at least 45 $\pm$ 15 days following implant and then discontinued following demonstration of sufficient LAA closure by TEE. Clopidogrel (75 mg) and aspirin (81-325 mg) was then used for several months to prevent thrombosis around the device.

Conventional transseptal catheterization was performed using angiography and/or echocardiography. If present, a patent foramen ovale could be used for access. A heparin bolus was administered after transseptal puncture, and the ACT generally was maintained at $\geq$200 seconds during the procedure. Hand injections of contrast medium were performed in multiple views to provide LAA angiograms and assist with catheter manipulation.

Since the LAA is a complex structure, TEE was utilized to accurately size the LAA orifice diameter and length in numerous angles. TEE was also used to assess the number and orientation of LAA lobes, the anatomic relationship between the pulmonary veins and criteria for device release including proper

device positioning and flow around the device after implantation. Subacute bacterial endocarditis prophylaxis was recommended during follow-up.

Generic procedure steps for Left Atrial Appendage Closure using the WATCHMAN LAA Closure Technology are described in **Table 9-1** below.

Table 9-1. WATCHMAN LAA Closure Technology Procedure Steps

Obtain venous access	Femoral vein access using standard percutaneous technique is performed.
Cross intra-atrial septum	Intra-atrial septum is crossed using a standard technique and equipment. Transesophageal and/or intracardiac echocardiographic guidance may be used.
Obtain left atrium access	Left atrium access with standard sheath and guidewire after transseptal crossing is performed
Prepare and introduce WATCHMAN Access Sheath and Dilator	After standard preparation, the WATCHMAN Access Sheath and Dilator are exchanged into the left atrium using standard percutaneous technique.
Remove WATCHMAN Dilator	WATCHMAN Dilator is removed using standard percutaneous technique.
Advance WATCHMAN Access Sheath into the left atrial appendage	The WATCHMAN Access Sheath is advanced into the left atrial appendage using standard percutaneous technique. A guidewire, pigtail catheter and WATCHMAN Obturator may be utilized to aid in advancing the Access Sheath into the LAA.
Position WATCHMAN Access Sheath for device deployment	The WATCHMAN Access Sheath is positioned for device deployment to the proper orientation and depth into the left atrial appendage with standard angiographic and echocardiographic imaging.
Remove all components from the WATCHMAN Access Sheath	Components utilized to position the access sheath including a guidewire, pigtail catheter and WATCHMAN Obturator are removed using standard percutaneous technique.
Prepare and introduce WATCHMAN Delivery System	After standard preparation, the WATCHMAN Delivery System is introduced into the access sheath and advanced using standard percutaneous technique.
Connect WATCHMAN Delivery System to WATCHMAN Access Sheath	Forward advancement of the WATCHMAN Delivery System is stopped when the distal marker band of the WATCHMAN Delivery System aligns with the distal marker band of the WATCHMAN Access Sheath. The WATCHMAN Access Sheath is then retracted and snapped into the hub of the WATCHMAN Delivery System.
Deploy the WATCHMAN LAA Closure Device	The valve on the WATCHMAN Delivery System proximal handle is opened. While maintaining a stable proximal handle position, the WATCHMAN Delivery Catheter and WATCHMAN Access Sheath are retracted along the proximal handle until deployment (unsheathing) of the WATCHMAN Device occurs.

Assess WATCHMAN Device release criteria	WATCHMAN Device position, Device stability, Device size (*in situ* compression) and Device sealing of the LAA are assessed. The determination of acceptable or not acceptable for each criterion is performed. All release criteria must be met for an acceptable device release. If one or more of the release criteria are not acceptable, a partial or full device recapture may be performed.
Perform partial recapture of WATCHMAN Device (if applicable)	Advance the WATCHMAN Delivery Catheter and WATCHMAN Access Sheath together to the device. Continue advancement until the device begins to collapse and retract back into the WATCHMAN Delivery Catheter. Stop recapture process after the device initially collapses and before the fixation barbs on the WATCHMAN Device are recaptured. A partial recapture allows the device to be moved more proximal and redeployed.
Perform full recapture of WATCHMAN Device (if applicable)	Advance the WATCHMAN Delivery Catheter and WATCHMAN Access Sheath together to the device. Continue advancement until the device begins to collapse and retract back into the WATCHMAN Delivery Catheter. Continue recapture process after the device initially collapses and the fixation barbs and the WATCHMAN Device are fully recaptured. Remove WATCHMAN Delivery System and replace. A full recapture does not allow the device to be moved more proximal and redeployed.
Release WATCHMAN Device	If release criteria are met, rotate the Delivery Catheter deployment knob counter clockwise three to four full turns to disconnect the core wire from the WATCHMAN Device.
Remove WATCHMAN Delivery System and WATCHMAN Access Sheath	Components utilized to deploy and release (if applicable) the WATCHMAN Device including the WATCHMAN Delivery System and WATCHMAN Access Sheath are removed using standard percutaneous technique.
Maintain hemostasis	Venous closure using standard technique is performed.

10 Data Requirements

The critical processes and procedures by which clinical data was collected, recorded and reported in the PROTECT AF study are briefly described in the following sections.

10.1 This section intentionally left blank

10.2 Data Collected and Methods of Collection

10.2.1 This section intentionally left blank

10.2.2 Case Report Forms (CRFs)

Case Report Forms (CRFs) were designed following an internal operating procedure to ensure appropriate information was collected during the course of the study. Completed CRFs were maintained in patient files in a locked storage room at Atritech.

Atritech provided investigators with patient data collection binders and CRFs during the study. CRFs were completed and signed by clinical site personnel who had been authorized by the principal investigator and whose names were documented on a study *Signature Log*, with the exception of Adverse Event and Protocol Deviation CRFs. All Adverse Event and Protocol Deviation CRFs were to be signed by the investigator.

CRFs were required to be completed and submitted to Atritech within 2 weeks of a study visit, except for serious adverse events, which were to be submitted within 48 hours. Completed CRFs were inspected by Atritech for accuracy and completeness. Errors, data discrepancies or incomplete entries were resolved through data queries and/or monitoring visits.

All data used in the analysis and reporting of this evaluation was provided to Atritech without identifiable reference to the patient.

10.2.3 This section intentionally left blank

10.3 Adverse Event Handling

Adverse events reported by a center were adjudicated by the Clinical Events Committee as described in **Section 10.5**. Events were assessed for causality including study relatedness, seriousness, device and procedure relationship and primary safety and efficacy endpoint contribution. The CEC adjudicated events with the medical source documentation as required.

Adverse events and/or symptoms reported by investigational sites were individually adjudicated. Each AE form was reviewed and those which were considered a symptom of, treatment of or a follow-up report to a primary event were identified.

10.4 Description of Core Laboratory

A central echocardiography core laboratory (Core Lab) worked collaboratively with Atritech and the investigators in the PROTECT AF trial. The Core Lab and Atritech designed the imaging protocol, provided training in both imaging and interpretation of the echo images and consulted on some echocardiograms obtained throughout the trial. Review of echocardiogram images was performed at baseline, and intra-procedurally to measure anatomical characteristics and then again at 45 days, 6 months and 12 months as designated in the protocol.

All clinical decisions regarding patient care, such as echocardiographic entrance criteria, clinical outcomes and cessation of warfarin related to imaging interpretations were made by the participating investigators in the study. No study endpoints were collected by the Core Lab.

10.5 Independent Committees

Three independent committees were utilized in the PROTECT AF study to ensure the trial was conducted with proper oversight and regulation. Additional information on the formation, members and responsibilities of the Data Safety Monitoring Board, Clinical Events Committee and Steering Committee are described in the following sections below.

10.5.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) was assembled by Atritech in December 2005 with input from the previous PILOT study DSMB members. An internal Atritech Standard Operating Procedure as well as the DSMB Charter governed the activities of the committee.

Members of the DSMB included an interventional cardiologist, a clinical cardiologist, an electrophysiologist, a cardiovascular surgeon and a statistician. See **Table 10-1** for Data Safety Monitoring Board members and their affiliation. Past DSMB members are also included in the table.

DSMB members did not control or own stock in Atritech, nor did they serve on the Steering Committee or Data Safety Monitoring Board of a competing device study. Members did not have any affiliation with the core laboratory utilized in the study, or the principal investigator of the study.

DSMB meetings were convened at regular intervals throughout the trial. Each meeting included an update on study progress, a review of summarized data and an evaluation of the results against the pre-approved stopping guidelines. Any trends [redacted] were extensively discussed with the DSMB and augmented with real-time communication from Atritech to the Chairman of the DSMB as necessary. At the conclusion of each DSMB meeting a vote was taken to continue the trial as currently designed, continue the trial with specific conditions, or suspend the trial.

10.5.2 Clinical Events Committee

A Clinical Events Committee (CEC) was assembled for the PROTECT AF study in October 2005. The CEC's charter was to review and adjudicate all adverse events in the PROTECT AF study for causality including study relatedness, seriousness, device and procedure relationship and primary safety and efficacy endpoint contribution. The CEC adjudicated events with the medical source documentation as required. An internal Atritech Standard Operating Procedure as well as the CEC Charter governed the activities of the committee.

CEC members did not control or own stock in Atritech, nor did they serve on the Steering Committee or Clinical Events Committee of a competing device study. Members did not have any affiliation with the core laboratory utilized in the study, or the principal investigator of the study.

During a meeting, adverse events were discussed, the committee voted on the adjudication and the CEC adjudication form was signed. Adjudication of each event was required to be unanimous. Data from the adjudication form was then entered into the clinical trial database. A copy of the signed adjudication form was placed in each patient file with the corresponding event.

All serious adverse events adjudicated were summarized, and the summary reviewed and signed by the Chairman of the CEC. Additionally, all strokes designated as endpoint events by the CEC were summarized and associated imaging was reviewed by an independent Neuroradiologist) for confirmation of the findings. Any discrepancies in findings were to be returned to the full CEC for further review.

10.5.3 Steering Committee

A Steering Committee for the PROTECT AF study was assembled in October 2005. The charter of the committee included a review of strategic issues related to the clinical study and publication in collaboration with Atritech personnel.

The Steering Committee was comprised of employees of Atritech as well as implanting physicians from different geographic and practice environments. The committee included both electrophysiologists and interventional cardiologists. The PROTECT AF National Principal Investigator , was designated chairperson of the Steering Committee. See **Table 10-4** for Steering Committee members and their affiliation. Past committee members are also included in the table.

10.6 Data Quality Assurance

10.6.1 Investigator Training on Data Collection

Investigators and site staff were trained during the site initiation visits on the data required to be collected during the clinical trial. In addition, data required by protocol and their location on specific CRFs was documented in specific CRF completion guidelines. Training records were maintained by Atritech. If additional training was required due to significant non-compliance, Atritech required re-training.

10.6.2 Clinical Trial Monitoring

Study site monitoring in the PROTECT AF study was performed by Atritech clinical personnel and designated contract monitors. Monitoring was done according to a standard operating procedure designed to ensure data integrity and continued protocol compliance. Each site was monitored according to the pre-specified monitoring plan to ensure that the study was conducted in compliance with all applicable regulations, and with the study protocol. The monitor was required to complete and file an observation report after each visit.

Completed CRFs were reviewed at the investigational site by authorized monitoring personnel at regular intervals throughout the trial. Missing or unclear data was requested as necessary. Additionally, source documentation records were reviewed to confirm data collected and to capture any unreported adverse events.

Investigators were required to permit inspection of the patient files and patient CRFs by monitoring representatives and/or responsible government agencies.

10.6.3 Protocol Deviation Handling

Protocol deviations in the PROTECT AF study were reported by investigational sites on a protocol deviation CRF. Major protocol deviations that required IRB notification included the following:

- Informed consent not properly obtained
- Study entrance criteria not met
- Device used outside randomized assigned treatment

Sites were required to notify Atritech within 24 hours if a protocol deviation occurred and whether IRB notification was required. Planned corrective action was also recorded on the protocol deviation CRF.

Deviations to Informed Consent were addressed immediately at the site level with reporting to the IRB and corrective action. Study entrance criteria deviations were evaluated throughout the trial and addressed both at the site level and by subsequent protocol revisions.

No protocol deviation due to treatment outside randomized assigned treatment was reported throughout the trial. Specifically, no Control group patient received a device.

Medication modifications due to changes in medical practice were reviewed with the Steering Committee and modified using the FDA 5 day notification followed by a memo to all investigational sites.

10.6.4 Financial Disclosure of Clinical Investigators

Financial disclosure forms were collected at the start of a center's participation in the trial and again at the time of data analysis and submission. Financial Disclosure Forms for each clinical center participating in the PROTECT AF study are on file at Atritech.

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11 Statistical Methodology

11.1 Statistical Design

The PROTECT AF study was a randomized, prospective, multi-center, group-sequential study to determine the safety and effectiveness of the WATCHMAN LAA Closure Technology. The Device group consisted of patients receiving the WATCHMAN Device. The Control group consisted of patients receiving warfarin drug therapy. Patients were allocated randomly in a 2:1 Device:Control ratio.

The primary efficacy endpoint consisted of the occurrence of all stroke (including ischemic and hemorrhagic), cardiovascular death (limited to any cardiovascular and unexplained), and systemic embolism. 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 efficacy endpoint. Event rate was defined as the expected number of events per 100 patient years of follow-up. A Bayesian Model stratified on $CHADS_2$ score was used for evaluation of the statistical objective. Sequential evaluation of the statistical objective allowed for early stopping for futility or non-inferiority if the study data gave clear indications for the decision.

11.1.1 Sequential Analysis Plan

The first sequential interim analysis was performed after collection of [redacted] Subsequent analyses are allowed after each additional [redacted] years of follow-up. At each interim analysis, posterior distributions for the event rates for the Device group and the Control group were calculated and the following criteria were assessed in order.

11.1.2 Criterion for Futility (Not Non-inferiority)

The criterion for establishing futility (not non-inferiority) at an interim analysis was a posterior probability that the event rate for the Device group was greater than or equal to the event rate for the Control group [redacted] If futility was declared, no assessment of non-inferiority or superiority was made. [redacted]

11.1.3 Criterion for Non-inferiority

The criterion for establishing non-inferiority at an interim analysis was a posterior probability that the event rate for the Device group was less than [redacted] and that the preceding criterion for futility was not met.

11.1.4 Criterion for Superiority

The criterion for establishing superiority was a posterior probability that the event rate for the Device group was less than the event rate for the Control group [redacted] The superiority test was only performed if non-inferiority had been established.

If neither "Futility" nor "Non-inferiority" (nor "Superiority") were declared, the decision for the interim analysis was "Undecided," and an additional [redacted] years of follow-up was to be collected before the next evaluation time, up to a limit of [redacted] patient years of follow-up. If after the maximum of [redacted]

patient years of follow-up the Device group was not established as "Non-inferior", the device was to be considered "Not Non-inferior."

11.2 Determination of Sample Size

The design parameters of the sequential analysis plan were chosen to provide adequate probability of success (Frequentist "power") in situations where the device is truly non-inferior and to ensure an acceptable false-positive rate (Frequentist "Type I" error rate) in situations where the device is not non-inferior. These parameters provide for acceptable operating characteristics across a range of Device and Control group event rates.

11.2.1 Historical Basis for Assumed Control Event Rates

The SPAF studies database is a compilation of data from three clinical trials concerning the effects of warfarin and aspirin for patients with atrial fibrillation. In cooperation with Carl van Walraven, M.D., event rates for the composite event of all stroke, cardiovascular death or systemic embolism were computed for patients assigned to receive full dose warfarin among clinical trials included in the SPAF database. This data was used to provide rates for evaluation of the Sequential Bayesian Analysis Plan in determining the sample size. **Table 11-1** provides results for SPAF patients assigned to full dose warfarin for each $CHADS_2$ score of 1 or greater.

Table 11-1. Historical Events Rates from SPAF Trials*

1	22	673.45	3.27
2	29	508.82	5.70
3	26	288.65	9.01
4	15	112.64	13.32
5	6	35.55	16.88
6	2	6.44	31.06

* Originally provided to FDA in IDE G020312/S012, Dec 17, 2004.

Forming a weighted average of the event rates for the different $CHADS_2$ scores from **Table 11-1**, the overall event rate was expected to be 6.15 events per 100 patient years. This rate formed the basis for the sample size for the PROTECT AF trial.

To evaluate the performance of the Bayesian Model, simulations were carried out for several event rate patterns. **Table 11-2** provides results of the simulations for the sixteen patterns of event rates used. The Control and Device primary efficacy event rates per 100 patient-years are given in the second and third column respectively. The simulations include patterns where the Control group rate is equal to, higher than, and lower than the SPAF database. Similarly, patterns are included where the Device rate is equal to, higher than, and lower than the Control group rate. The probability that the trial would meet Criteria of Futility (Prob Fut), Non-inferiority (Prob NI), and Superiority (Prob Sup) are provided in the last three columns.

11.3 Statistical Methods

Statistical analyses were performed in an "intent-to-treat" approach unless otherwise noted, with each patient analyzed as being part of their randomly assigned treatment regardless of the actual treatment received. All patients not having an event or lost to follow-up were censored at the time of the last documented follow-up visit or last known status. Patient years was calculated for each patient from the date of randomization to the appropriate event or censoring date (for patients without an event) and aggregated over analysis groups. Event rates were calculated as the number of events per 100 patient years of follow-up. In addition to the set of intent-to-treat analyses, other analyses were performed to provide additional information on the safety and efficacy of the WATCHMAN Device as described below. Descriptive statistics were generated for the data collected at baseline, the procedure and at follow-up.

Detailed descriptions are included in the Statistical Analysis Plan, which is on file at Atritech.

11.3.1 Primary Analysis Dataset: Intent-to-Treat (Pre-specified)

The intent-to-treat cohort consisted of all randomized patients, analyzed according to their randomly assigned treatment group. Event status and censoring was determined regardless of the treatment actually received.

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11.3.3 This section intentionally left blank

11.3.4 Additional Analyses

Additional analyses were performed to further explore the robustness of the primary analysis, to explore the sensitivity of the results to statistical assumptions, and to answer clinically relevant questions that arose during the course of the study. These analyses followed standard statistical practice and the relevant methods are described along with the results.

11.4 Treatment of Missing Data

Extensive efforts were made in the planning and execution of the study in order to minimize the amount of missing data. Methods of survival analysis (i.e., the calculation of patient-years with appropriate censoring) were used to analyze all available data. These methods have the advantage of using the maximal amount of information for patients that have not yet experienced an event. Where the methods of survival analysis were not appropriate, all available data are included for analysis.

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12 Results

12.1 Demographics

12.1.1 Enrollment Accountability/Subject Disposition

Table 12-1 summarizes patient enrollment across treatment groups, including non-randomized roll-in patients. A total of 785 patients were enrolled in the trial at 59 centers. This total included 454 patients randomized to the Device group, 238 patients randomized to the Control group and 93 roll-in patients. A 2:1 randomization allocation ratio was implemented across investigational centers in the randomized cohort.

Table 12-1. Enrollment Summary

Randomized	454
Implant Attempted	440
Implanted	400
Randomized	238
Warfarin Administered	236
Warfarin Never Administered	2
Enrolled	93
Implant Attempted	93
Implanted	77

Of the 454 Device group patients, 440 had an implant attempted and 14 were randomized but not attempted due to the following reasons:

- (10) Patients in whom a procedure did not occur within protocol required window or patients in whom insurance was denied.
- (2) Patients withdrew consent prior to procedure.
- (1) Patient died between randomization and procedure.
- (1) Patient diagnosed with cardiac tumor prior to procedure.

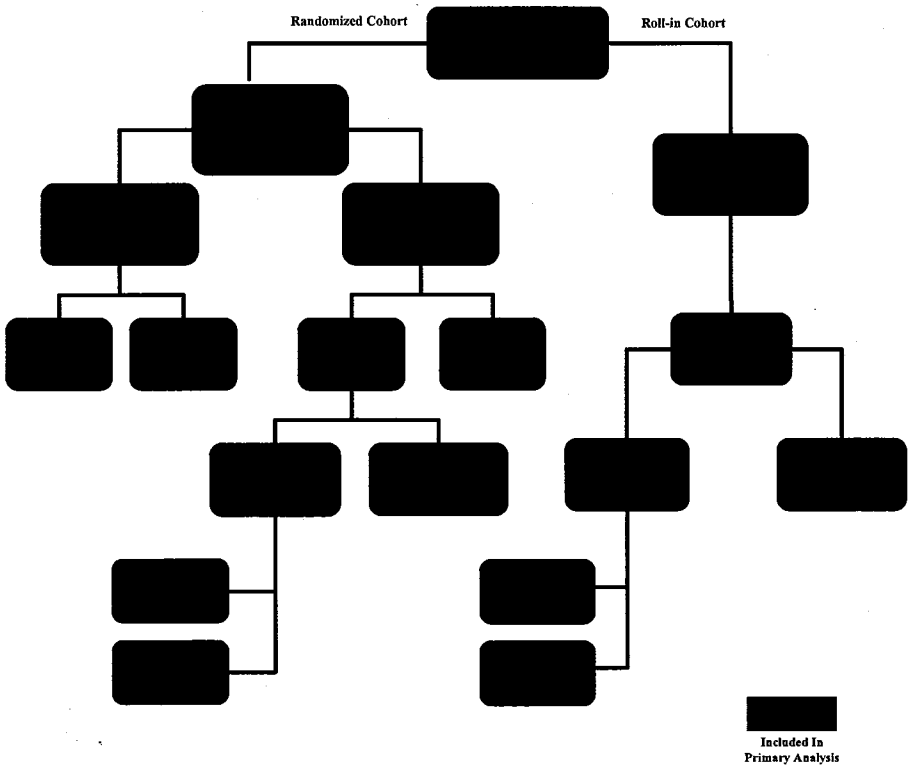
A successful implant occurred in 90.9% (400/440) of patients for whom an implant procedure was attempted. The unsuccessful (discontinued) patients are accounted for in the enrollment flowchart **Figure 12-1**.

A total of 93 patients were enrolled as roll-in (non-randomized) patients at 33 centers. The roll-in phase was implemented in [redacted] and therefore not all centers participated in this phase. A successful implant occurred in 82.7% (77/93) of roll-in patients for whom an implant procedure was attempted. The unsuccessful roll-in procedures are accounted for in the enrollment flowchart **Figure 12-1**. The

procedural success rate in the roll-in group was lower than the randomized group; likely reflecting the presence of a learning curve for implanting the device.

Two patients in the Control group did not receive warfarin therapy following randomization for unknown reasons.

Figure 12-1. PROTECT AF Enrollment Flowchart



* One or more of the release criteria of acceptable device position, *in-situ* size (compression), stability and LAA seal were not met for device release.

Table 12-2 provides a listing of the 59 centers (55 in the U.S. and 4 in Europe) that enrolled at least one patient in the PROTECT AF study. The number of patients enrolled in each treatment group or roll-in group (if applicable) is listed. An acceptable enrollment distribution across centers occurred in the randomized cohort in that 20 centers randomized at least 10 or more patients in the study and 33 centers randomized at least 5 patients. The top three enrolling centers separately accounted for between 7 to 9% of the total study enrollment each.

Atritech implemented a roll-in phase of the study beginning in [redacted] whereby new investigational centers were allowed three (3) cases before initiating the randomization phase of the study. The roll-in phase was intended to allow new investigators to gain experience in implanting the device prior to proceeding with the enrollment of randomized subjects. [redacted]

Analysis of the data from the roll-in cohort and a comparison to the randomized population is provided in **Section 12.3.8** (Roll-in Cohort Analysis) of this report.

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Table 12-2. PROTECT AF Enrollment Summary

1		44	22		3
2		33	17		3
3		34	16		0
4		26	13		3
5		24	12		0
6		23	12		0
7		23	11		0
8		19	10		3
9		19	9		3
10		20	9		0
11		18	9		0
12		15	8		0
13		13	7		0
14		13	7		0
15		10	6		0
16		9	5		0
17		7	4		3
18		6	4		3
19		8	4		0
20		4	4		4
21		5	3		3
22		5	3		3
23		5	3		3
24		6	4		0
25		4	2		4
26		6	2		0
27		5	3		0
28		5	3		0
29		4	4		0
30		3	2		3
31		3	1		3
32		2	2		3
33		2	0		5
34		4	2		0
35		3	1		2
36		3	2		0
37		4	1		0
38		2	1		2
39		1	1		3
40		2	0		3
41		2	0		3
42		1	1		3
43		2	0		3
44		1	0		3
45		1	2		0
46		1	2		0
47		1	1		1
48		0	0		3
49		0	0		3
50		0	0		3
51		0	0		2
52		0	0		2
53		0	0		2
54		0	0		2
55		1	1		0
56		2	0		0
57		0	0		1
58		0	1		0
59		0	1		0

12.1.2 Population/Subject Demographics

Table 12-3 summarizes the patient baseline demographic information of the randomized cohort. Baseline demographics demonstrate that patients in the two treatment groups are comparable.

Table 12-3. Baseline Demographics

Age (years)	71.7 ± 8.8 454 (46.0, 95.0)	72.6 ± 9.3 238 (41.0, 95.0)	0.1919
Height (inches)	68.3 ± 4.2 453 (54.0, 82.0)	68.4 ± 4.2 238 (59.0, 78.0)	0.6259
Weight (lbs)	195.1 ± 44.7 454 (85.0, 376.0)	194.9 ± 43.0 238 (105.0, 312.0)	0.9514
Gender			0.9310
Female	134/454 (29.5)	71/238 (29.8)	
Male	320/454 (70.5)	167/238 (70.2)	
Race/Ethnicity			0.7573
Asian	4/454 (0.9)	1/238 (0.4)	
Black/African American	6/454 (1.3)	5/238 (2.1)	
Caucasian	417/454 (91.9)	216/238 (90.8)	
Hispanic/Latino	24/454 (5.3)	15/238 (6.3)	
Hawaiian/Pacific Islander	1/454 (0.2)	1/238 (0.4)	
Other	2/454 (0.4)	0/238 (0.0)	

Values presented are mean±standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

In the PROTECT AF study all patients with atrial fibrillation presenting to the participating investigator were screened and randomized based on their characteristics and willingness to participate regardless of their gender or race. However, both treatment groups enrolled significantly more males in the study. This trend is consistent with the major trials for warfarin and other drug and device therapies being evaluated for atrial fibrillation. SPORTIF III, SPORTIF V and the ACTIVE W trials had enrollments of significantly larger male populations of 69%, 69% and 67% respectively. In the LAAOS surgical trial, 72.8% were male and 27.2% were female. The elective nature of the implant procedure and the statistics seen in other interventional treatments for atrial fibrillation is comparable to the PROTECT AF study.[88]

Baseline risk factors for enrolled patients are summarized in **Table 12-4**. There was no statistically significant difference in risk factors between groups.

Table 12-4. Baseline Risk Factors

$CHADS_2$ score			0.2218
1	155/454 (34.1)	63/238 (26.5)	
2	157/454 (34.6)	87/238 (36.6)	
3	87/454 (19.2)	50/238 (21.0)	
4	32/454 (7.0)	24/238 (10.1)	
5	19/454 (4.2)	9/238 (3.8)	
6	4/454 (0.9)	5/238 (2.1)	
CHF	121/454 (26.7)	64/238 (26.9)	0.9463
History of hypertension	402/454 (88.5)	216/238 (90.8)	0.3715
Age ≥ 75	185/454 (40.7)	113/238 (47.5)	0.0894
Diabetes	111/454 (24.4)	71/238 (29.8)	0.1266
Previous TIA/Ischemic Stroke	79/454 (17.4)	47/238 (19.7)	0.4473
AF Pattern			0.7316
Paroxysmal	198/454 (43.6)	96/238 (40.3)	
Persistent	93/454 (20.5)	49/238 (20.6)	
Permanent	157/454 (34.6)	91/238 (38.2)	
Unknown	6/454 (1.3)	2/238 (0.8)	
LVEF %	57.4 ± 9.7 451 (30.0, 82.0)	56.7 ± 10.2 233 (30.0, 86.0)	0.4175

Values presented are mean±standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

Over 80% of patients in both treatment groups were enrolled with a $CHADS_2$ score of 3 or lower out of a possible score of 6. The mean (standard deviation) of the $CHADS_2$ score was 2.2 (1.1) and 2.3 (1.2) for the Device and Control groups respectively.

To calculate a patient's $CHADS_2$ score, one point is assigned each for the presence of congestive heart failure, history of hypertension, age 75 years or older, and diabetes, and two points assigned for prior stroke or TIA.[129] The two most common risk factors in the study based on the $CHADS_2$ criteria were history of hypertension and age ≥ 75 years which occurred approximately 88.5-90.8% and 40.7-47.5% respectively. Previous cerebral ischemia, the least common risk factor, nonetheless was reported in 17.4-19.7% of patients.

Paroxysmal AF, defined as an intermittent form of atrial fibrillation that is characterized by a sudden onset and abrupt cessation of this rhythm, was the presenting rhythm in 40.3-43.6% of subjects in both groups. The second most common AF pattern reported was permanent AF, defined as ongoing atrial fibrillation that fails to terminate using cardioversion, or is terminated but reoccurs, which accounted for 34.6-38.2% of patients in the study.

Baseline LAA characteristics recorded and reported by the site for enrolled patients are summarized in **Table 12-5**. There was no statistically significant difference in characteristics between groups.

Table 12-5. Baseline LAA Characteristics - Site Reported

No. of LAA lobes			0.4032
One	218/451 (48.3)	122/236 (51.7)	
More than one	233/451 (51.7)	114/236 (48.3)	
LAA length, mm	30.5 ± 6.8 448 (2.2, 52.0)	30.4 ± 7.2 233 (2.6, 61.5)	0.9255
LAA ostium diameter, mm	21.5 ± 3.9 448 (1.6, 37.1)	21.8 ± 3.9 233 (1.5, 34.0)	0.3354

Values presented are mean±standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

There were no appreciable differences noted in the baseline morphology or anatomical dimensions of the left atrial appendage measured at baseline between treatment groups. An echocardiographic imaging protocol was utilized to measure LAA length and ostium measurements appropriately. Patients whose LAA length or ostium measurements fell outside the range of available device sizes were excluded from study participation.

Both groups were similar in that the average length of the LAA was approximately 30mm while the average ostium size was approximately 21mm as measured during the baseline exam. It was also noted that an almost equal number of patients in both groups were noted to have had one major LAA lobe compared to those patients where more than one lobe was identified.

12.1.3 Follow-up Compliance

Table 12-6 provides an accounting of follow-up compliance achieved in the PROTECT AF study. Expected visits are based on visit windows defined in the protocol. Visit windows closed prior to May 30, 2008, are considered expected.

Due to enrollment occurring continually over time and the ongoing follow-up of patients, the number of expected visits declines with each subsequent visit. Patients who die or are withdrawn are not counted as having expected visits after that date.

Due to the cumulative patient-year design of the statistical plan, achieving maximum follow-up compliance for all required visits was of significant importance. All attempts were made to ensure patients attended scheduled follow-up visits within their windows. This process was facilitated through diligent communication efforts with the study coordinator, reminders through company newsletters and tools to track upcoming patient visits where necessary. As a result, very few patients were lost to follow-up in the study and approximately 98% follow-up was achieved in both groups.

Table 12-6. Follow-up Visit Attendance

45 day	404/413 (97.8)	217/221 (98.2)
6 month	311/312 (99.7)	170/172 (98.8)
9 month	249/255 (97.6)	134/136 (98.5)
12 month	202/205 (98.5)	101/103 (98.1)
18 month	107/109 (98.2)	68/68 (100.0)
24 month	65/66 (98.5)	35/36 (97.2)
30 month	28/28 (100.0)	13/14 (92.9)
36 month	3/3 (100.0)	0/0 (NA)

A summary of reasons for completion of an end-of-study form is provided in **Table 12-7**.

Table 12-7. End of Study Summary

No Device Implanted	38*/454 (8.4)	N/A
Death	14/454 (3.1)	11/238 (4.6)
Patient Consent Withdrawn	6/454 (1.3)	16/238 (6.7)
Outside Implant Window	10/454 (2.2)	0/238 (0.0)
Lost to Follow-up	1/454 (0.2)	2/238 (0.8)
Other	7/454 (1.5)	6/238 (2.5)

* Two of the 40 patients in the Device group who were not successfully implanted did not have an end of study forms at the time of data lock.

The most frequent reason for study termination for the Device group was that a device was unable to be successfully implanted. These patients were followed at least until the 45 day visit to review for acute adverse events. For the Control group, the most frequent reason was "Patient Consent Withdrawn." The second most frequent reason for both groups was "Death." "Outside Implant Window" was given as the reason for 10 of the 14 patients for whom no implant was attempted. As discussed in **Section 12.1.1**, of the remaining 4 patients for whom no implant was attempted, 2 were "Patient Consent Withdrawn," 1 was "Death" and 1 was "Other." The patients with "Other" reasons for end-of-study are provided in **Table 12-8**.

Table 12-8. Discontinuation Reason "Other" Category Details

	Device	Other	WATCHMAN Device was explanted due to pericarditis/endocarditis at approximately 30 days.
	Device	Other	Patient was found to have an atheroma on TEE prior to implant and the patient was deemed ineligible for implant. No WATCHMAN Device was implanted.
	Device	Other	WATCHMAN Device embolized and was explanted the day after implant.
	Device	Other	Subject was unable to return for follow-up visits.
	Device	Other	Perforation of the LAA during WATCHMAN Device delivery required surgery. No WATCHMAN Device was placed.
	Device	Other	Patient was diagnosed with amyloidosis and deemed ineligible for study.
	Device	Other	WATCHMAN Device embolized and was explanted at approximately 50 days post-implant.
	Control	Other	Patient experienced a cardiovascular accident with expressive aphasia and withdrew participation from the study.
	Control	Other	Patient underwent ligation of left atrial appendage.
	Control	Other	Patient discontinued warfarin due to urological bleeding and never reinitiated.
	Control	Other	Subject relocated to Italy with no forwarding address – was lost-to-follow-up.
	Control	Other	Patient discontinued warfarin therapy as recommended by the family physician.
	Control	Other	Patient discontinued warfarin therapy.

Results from Kaplan-Meier analyses for the time to end of study are provided in **Figure 12-2** and **Table 12-9**.

Figure 12-2. Kaplan Meier Curve: Time to End of Study

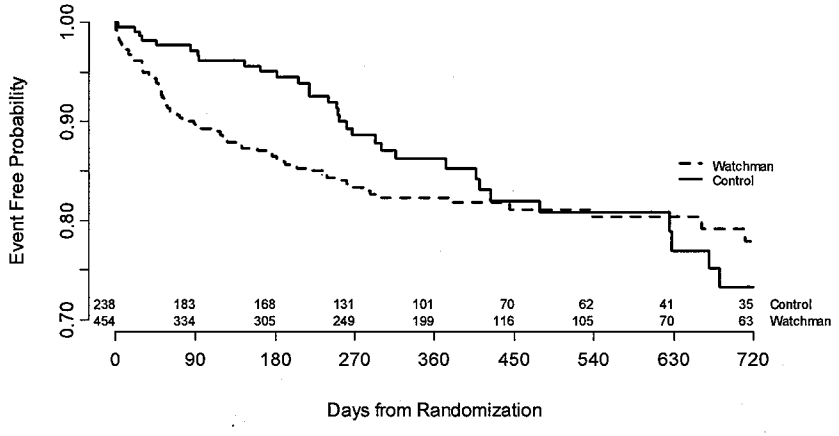

Table 12-9. Kaplan-Meier Estimates: End of Study

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	10	10	97.7	1	1	99.6
45-days	15	25	94.3	3	4	98.2
6-months	30	55	86.5	6	10	95.0
1-year	13	68	82.3	13	23	86.3
2-year	5	73*	78.0	11	34*	68.9

*Three Device group patients had end of study forms post two years: patient [redacted], 784 days due to death; [redacted], 856 days due to "No Device Implanted"; [redacted], 785 days due to "Outside Implant Window". One Control patient had an end of study form post two years: patient [redacted], 846 days due to "Patient Consent Withdrawn."

The largest fraction of end-of-study patients in the Device group was observed between 45-days and 6-months; 16/30 (53%) discontinued due to no device implanted. Twenty-five patients completed an end-of-study form prior to 45-days; 14/25 (56%) were due to no device implanted.

The largest fraction of end-of-study patients in the Control group was observed between 6-months and 1-year; 6/13 (46%) discontinued due to consent withdrawn. Four patients (31%) discontinued due to death.

The primary concern with differential withdrawal rates is the potential for bias. Concerns about this form of bias are mitigated in this trial by the use of survival analysis methods and the calculation of event rates based on patient years of follow-up. With these methods, all randomized patients contribute to the endpoint regardless of the amount of time followed.

For example, the most common reason for end-of-study in the Device group was no device implanted. Among these 40 patients, there were 2 primary efficacy events and 14 primary safety events; included in the primary intent-to-treat analysis.

For the Control group, the most common reason for end-of-study was withdrawal of consent. There were no primary efficacy or safety events among these patients. If these patients were likely to discontinue warfarin therapy post-end of study, it is likely that a bias would be created in that the Control group event rate would be underestimated. If the Control group event rate is underestimated, correcting for it would result in an increased chance of a finding of non-inferiority or superiority for the Device.

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12.2 Procedural Data

The procedural data contained in the following section is an analysis of the data from the **Randomized Cohort Only**. A comparison of the roll-in cohort to the randomized population is provided in **Section 12.3.8** (Roll-in Cohort Analysis) of this report.

12.2.1 Implant Procedure Success

Implant Procedure Success was defined as the successful delivery and release of a WATCHMAN Device into the LAA. Implant procedure success rates for the randomized cohort is presented in **Table 12-10**. A successful implant occurred in 90.9% (400/440) of patients for whom an implant procedure was attempted. As noted in **Section 12.1.1**, 14 patients did not have an implant attempted.

Table 12-10. Implant Procedure Success

[redacted]
400/440 (90.9)

12.2.2 Final Device Size Implanted

Table 12-11 provides an accounting of the various WATCHMAN Device sizes released and implanted in the PROTECT AF study for the randomized cohort. A total of 400 devices in the randomized group were implanted during the study. No patient was implanted with more than one WATCHMAN Device.

The five device sizes available in the study are listed along with the number of those devices implanted and its corresponding percentage. The 24mm device was the most commonly implanted device size in the study. Device usage demonstrated a prevalence to implant the smaller device sizes, however all five available device sizes have been implanted successfully in the study. Slightly less than 90% of devices implanted were 21, 24 or 27mm devices.

Table 12-11. Final Device Size Implanted

[redacted]	
21 mm	100/400 (25.0)
24 mm	145/400 (36.3)
27 mm	112/400 (28.0)
30 mm	29/400 (7.2)
33 mm	14/400 (3.5)

12.2.3 Full Device Recaptures / Device Malfunctions

During an implant procedure, release criteria of device position, compression, stability and seal were assessed. If one or more release criteria were deemed not-acceptable, the device may undergo full or partial device recapture as described in Table 9-1 - WATCHMAN LAA Closure Technology Procedure Steps.

Fully recaptured devices were completely removed and replaced, as required by the protocol and instructions for use. The incidence of full device recaptures that occurred in the PROTECT AF study is presented in **Table 12-12**.

Table 12-12. Full Device Recaptures

0	255/440 (58.0)
1	107/440 (24.3)
2	44/440 (10.0)
3	18/440 (4.1)
4 +	16/440 (3.6)

The average number of devices used per case decreased from 1.8 devices in the first half of the study to 1.5 devices in the second half of the study.

In the randomized cohort, 82.3% of all implant procedures used either one device or required only one full device recapture. The 4+ category contained procedures where four or more recaptures were performed. There was no evidence that patients experiencing procedure or device related adverse events were associated with the number of full recaptures (p=0.16 from a chi-square test).

Device malfunctions were recorded on the Implant Procedure CRF if a "packaging issue, breakage or failure to perform as intended" occurred. Twenty eight device malfunctions were reported during the trial.

During the initial Short device evaluation period, two device failures were discovered with Short devices that were fully recaptured. Following full recapture into the delivery sheath, the devices were returned to Atritech for inspection. Upon inspection, both devices were missing 2 of the 10 anchoring barbs. The patients in whom Short devices were used did not experience any adverse event related to the device. This failure mode was reported to FDA on [redacted] at which time the Short device evaluation was stopped and the device was redesigned. None of the reported malfunctions resulted in patient injury or recall.

12.3 Pivotal Study Results

12.3.1 Introduction

Current standard stroke prevention modalities are based in large part on the Stroke Prevention in Atrial Fibrillation (SPAF) studies, which examined treatment strategies for patients with non-valvular AF. SPAF I showed a reduction in stroke events of 67% at one year, confirming that antithrombotic therapy with aspirin or warfarin was effective in ischemic stroke prevention. SPAF III confirmed that if the risk of thromboembolism justified antithrombotic therapy, warfarin adjusted for a target INR of 2.0 to 3.0 was most effective.

Chronic anticoagulation however presents problems of safety and tolerability in many patients, especially those older than 75, the age group encompassing perhaps half of AF-associated strokes.[10] The efficacy of aspirin for stroke prevention in AF patients is less clear and remains controversial. Aspirin is somewhat effective in AF-related stroke prevention, but it is clearly less effective than warfarin.[11] Warfarin also remains more effective than aspirin and Plavix combined.

Although chronic warfarin therapy has been proven to reduce the risk of clinical thromboembolism, its substantial risk of hemorrhage, variability in dose response among individuals and its interaction with food and drugs has prompted intensive efforts to find a safer, more convenient alternative. Several randomized trials, e.g., Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W), Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with Non-valvular Atrial Fibrillation (SPORTIF III and V), Randomized Evaluation of Long Term Anticoagulant Therapy (RELY) and ROCKET AF, have encountered multiple challenges including major and minor bleeding complications, liver toxicity, etc.[103] Presently, new pharmacological approaches continue to be evaluated by medical professionals.

Additionally, multiple anticoagulation regimens in combination, raises confounding questions. For example, AF patients who have drug-eluting stents (DES) are required to take aspirin and clopidogrel in addition to warfarin according to standard treatment therapies. This combination leads to an increased risk of bleeding.[129] Aspirin and clopidogrel resistance and combinations of other cardiac medications multiply the challenges of treatment within this population.

With the known disutility of warfarin, the PROTECT AF study was conducted to determine if added protection against thromboembolism in certain patients with AF could be achieved. Furthermore, the elimination of warfarin therapy in those patients may reduce bleeding complications associated with long-term anticoagulation including catastrophic hemorrhagic stroke which will be examined in the primary safety section.

12.3.2 Primary Analysis (Intent-to-Treat)

12.3.2.1 Description of Cohort

The pre-specified intent-to-treat cohort includes all randomized patients in the group to which they were assigned and all primary events. Rates are calculated per 100 patient-years of follow-up. Calculations of credible intervals and posterior probabilities are from the primary Bayesian model stratified by $CHADS_2$ score as described in the Statistical Analysis Plan.

12.3.2.2 Primary Efficacy Endpoint (Intent-to-Treat)

Results for the primary efficacy endpoints of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 12-13**.

Table 12-13. Primary Efficacy Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

[redacted]								
N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
454	18/409.3	4.4 (2.6, 6.7)	238	13/223.6	5.8 (3.0, 9.1)	0.76 (0.39, 1.67)	0.992	0.734

N = number Pts = patients Pt-yrs = patient-years CI = 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 efficacy event rate was 4.4 events per 100 patient years for the Device group and 5.8 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.76, a 24% lower rate of efficacy events in the Device group than in the Control group.
- The 95% credible interval for the rate ratio was (0.39, 1.67). The value of the upper bound for the rate ratio (1.67) is 0.33 lower than the non-inferiority margin of 2.0.

The criterion for establishing futility was that the probability that the event rate for the Device group was greater than the Control group was [redacted] or greater. The probability that the event rate for the Device group was greater than the Control group was 0.266 (equal to one minus the probability of superiority, or 1-0.734). The criterion for futility was not met as this probability was less than [redacted] This indicates the trial should not be stopped for futility.

The posterior probability of non-inferiority was defined as the probability that the event rate for the Device group was less than twice that for the Control group. The probability of non-inferiority at the first interim analysis was [redacted] This probability was required to be greater than [redacted] for a finding of non-inferiority. The criterion for non-inferiority was met.

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority at the first interim analysis was [redacted] This probability was required to be at least [redacted] for a finding of superiority. The criterion for superiority was not met.

The primary efficacy event rate for the Control group of 5.8 events per 100 patient years was comparable to the weighted average of 6.15 events per 100 patient years from the SPAF studies, the rate that formed the basis of the sample size justification of this study.

Table 12-14 summarizes the specific primary efficacy events by randomized group.

Table 12-14. Primary Efficacy Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Stroke - Ischemic	13	2.9	4	1.7
Death (Cardiovascular or Unexplained)	2	0.4	5	2.1
Stroke - Hemorrhagic	1	0.2	4	1.7
Systemic Embolism	2	0.4	0	0.0

The ischemic stroke rate was higher in the Device group; however it is important to note that the events in this group included 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with procedural events including air embolism and excessive sedation. Without these events, the Device ischemic stroke rate (7/454, 1.5%,) becomes comparable to the Control rate.

The rate of death and hemorrhagic stroke is lower in the Device group. However, the rate of systemic embolism is slightly higher in the Device group compared to the Control group.

Additional details regarding the timing of primary efficacy events are included in the following sections.

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Primary efficacy events used in the primary analysis are listed in **Table 12-15**. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events. Multiple events are summarized in **Section 12.3.6** (Adverse Events) of this report.

Table 12-15. Primary Efficacy Events - Initial Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

1		Device	14FEB2006	15FEB2006	15FEB2006	Stroke - Ischemic
2		Device	25APR2007	26APR2007	26APR2007	Stroke - Ischemic
3		Device	26SEP2005	03OCT2005	05DEC2005	Stroke - Ischemic
4		Device	05JUN2006	06JUN2006	15MAY2008	Death*
5		Device	31JUL2006	01AUG2006	16AUG2006	Stroke - Hemorrhagic
6		Device	20FEB2006	21FEB2006	09MAR2006	Stroke - Ischemic
7		Device	05DEC2005	07DEC2005	15JAN2008	Systemic Embolism
8		Device	09MAR2005	10MAR2005	30JUL2005	Death*
9		Device	01AUG2006	01AUG2006	04AUG2006	Systemic Embolism
10		Device	29JAN2007	30JAN2007	14SEP2007	Stroke - Ischemic
11		Device	25JAN2008	29JAN2008	29JAN2008	Stroke - Ischemic
12		Device	11NOV2005	11NOV2005	11NOV2005	Stroke - Ischemic
13		Device	13FEB2007	15FEB2007	19FEB2008	Stroke - Ischemic
14		Device	10JUL2007	19JUL2007	28SEP2007	Stroke - Ischemic
15		Device	17JUL2006	18JUL2006	18JUL2006	Stroke - Ischemic
16		Device	19SEP2006	21SEP2006	06MAY2008	Stroke - Ischemic
17		Device	21FEB2007	21FEB2007	07JUL2007	Stroke - Ischemic
18		Device	21MAY2007	NA**	24MAY2007	Stroke - Ischemic
1		Control	31OCT2005	NA	12NOV2006	Stroke - Ischemic
2		Control	11MAR2008	NA	29MAR2008	Stroke - Ischemic
3		Control	09AUG2005	NA	31AUG2005	Stroke - Hemorrhagic
4		Control	03APR2007	NA	10DEC2007	Death*
5		Control	23JAN2006	NA	10MAR2007	Death*
6		Control	06JUN2006	NA	03AUG2007	Death*
7		Control	23APR2007	NA	03MAR2008	Stroke - Hemorrhagic
8		Control	21MAR2007	NA	19JUN2007	Death*
9		Control	04MAY2007	NA	15MAR2008	Death*
10		Control	10AUG2007	NA	11DEC2007	Stroke - Hemorrhagic
11		Control	31OCT2007	NA	17MAY2008	Stroke - Ischemic
12		Control	15AUG2006	NA	03APR2008	Stroke - Hemorrhagic
13		Control	10NOV2006	NA	22DEC2007	Stroke - Ischemic

* Cause of death located in **Table 12-24**.

** Patient experienced their primary efficacy events prior to an attempted implant so a value of "NA" (not applicable) is shown for the implant date.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are provided in **Figure 12-3** and **Table 12-16**.

Figure 12-3. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Intent-to-Treat)

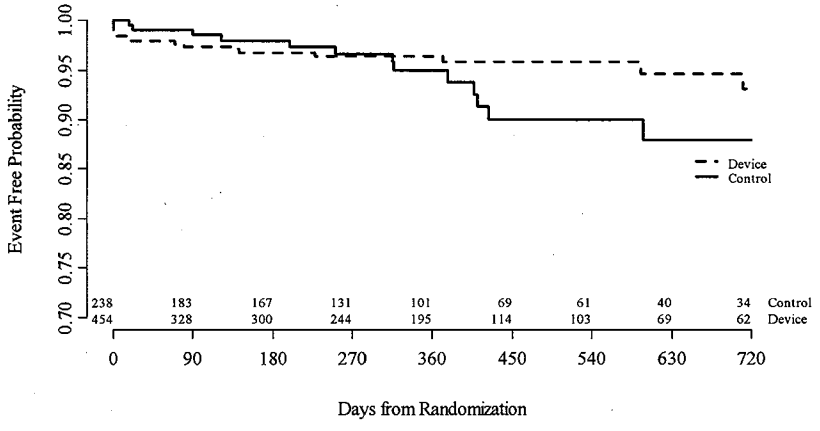

Table 12-16. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	7	7	98.4	0	0	100.0
45-days	2	9	98.0	2	2	99.1
6-months	4	13	96.8	2	4	98.0
1-year	1	14	96.4	4	8	94.9
2-year	3	17*	93.1	5	13	88.0

*One additional efficacy event occurred post two years in the Device arm at 771 days post-randomization and is not reflected in the above table as number of follow-up years becomes small. This event was a systemic embolism in patient

The largest portion of the primary efficacy events for the Device group (7/18*, 39%) occurred within 7-days of randomization. The largest portion of the primary efficacy events for the Control group (5/13, 38%) occurred between 1-year and 2-years post-randomization. At 2 years, the Device group had a Kaplan Meier estimated event rate of 6.9% compared to a 12.0% event rate in the Control group, a 43% lower relative rate for the Device group.

Two Year Success Rates

In the Device group, the estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on an unadjusted Kaplan-Meier estimate was 93.1% (88.8%-97.4%). In the Control group, the estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on an unadjusted Kaplan-Meier estimate was 88.0% (81.0%-94.9%).

Based on suggestions from the FDA, several additional analyses of two year rates were performed.

For one additional analysis, data on the 50 implanted patients from the PILOT study was combined with the PROTECT AF randomized cohort to produce two-year estimates. From this analysis, the Device group estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on a Kaplan-Meier estimate was 94.8% (91.9%-97.7%).

Additional analyses incorporated covariates to allow for the calculation of adjusted Kaplan-Meier rates. This analysis included the following covariates as in a proportional hazards regression model: gender, age, and $CHADS_2$ score, AF category, left ventricular ejection fraction, LA length, and LA width. Data on LA size (length and width) was not collected on case report forms but was available from the core lab on 58% of patients in the randomized cohort. As the purpose of the covariate adjusted analysis was to increase the precision of the two-year rate estimates, a covariate with such a high percentage of missing data would be counterproductive. Therefore, imputation of missing LA size was performed to allow inclusion of the maximal number of patients in the covariate adjusted analysis of two-year rates.

To examine the sensitivity of the first covariate adjusted model, a second covariate adjusted analysis was performed using site reported LAA size (length and ostium diameter) in place of LA size. LAA size was used in this analysis as there was a modest but statistically significant correlation between LAA and available LA size, and LAA size was available on nearly all randomized patients. This second covariate adjusted analysis did not involve the use of imputation. All other covariates used in the first covariate adjusted model were included.

For each covariate adjusted analysis, separate estimates were formed for each treatment group as shown in **Table 12-17**. The average value was used for continuous covariates and the most frequent value was used for categorical covariates to produce a hypothetical cohort for which the survival distribution was estimated. The specific values of these covariates used in the model were as follows: male gender, age of 72 years, $CHADS_2$ score of 2, Paroxysmal AF, LVEF of 57%, LA length of 5.9cm, LA width of 4.5cm, LAA length of 30.5mm, and LAA ostium diameter of 21.6mm.

The first covariate adjusted model (using LA size) produced estimates (95% confidence bounds) for freedom from the primary efficacy event at 2 years for the device of 96.1% (92.4% - 100%) and corresponding estimates (95% confidence bounds) for the Control group of 95.6% (91.0% - 100%). The second covariate adjusted model (using LAA size) produced corresponding Device group estimates of 96.7% (93.4%, 100%) and Control group estimates of 95.9% (91.4%, 100%).

Table 12-17. Two Year Success Rate Estimates

Unadjusted, PROTECT AF Alone	93.1 (88.8, 97.4)	88.0 (81.0, 94.9)
Unadjusted, PROTECT AF Plus PILOT	94.8 (91.9, 97.7)	88.0 (81.0, 94.9)
Adjusted Model 1, PROTECT AF Alone	96.1 (92.4, 100.0)	95.6 (91.0, 100.0)
Adjusted Model 2, PROTECT AF Alone	96.7 (93.4, 100.0)	95.9 (91.4, 100.0)

In all analyses of two year rates, the two year event-free rate for the Device group was higher the corresponding Control group rate. These findings were consistent with the overall primary analysis finding of non-inferiority.

Assessment of Proportional Hazards Assumption

The potential for non-constant hazard function across time exists; therefore, a test for equality of event rates across time was made separately for each treatment group using six month intervals as shown in **Table 12-18**.

Table 12-18. Homogeneity of Event Rates Over 6 Month Intervals Primary Efficacy Endpoint (Intent-to-Treat)

	Events/ Patient-years	Event Rate	Events/ Patient-years	Event Rate
0-6 Months	13/174.0	7.47	4/94.2	4.25
6-12 Months	1/118.9	0.84	4/64.0	6.25
12-18 Months	1/60.4	1.65	4/35.5	11.27
18-24 Months	2/35.9	5.58	1/20.5	4.87
24-30 Months	1/17.5	5.72	0/8.7	0.00
P-value	0.0786		0.5732	

Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization. P-values were calculated via Monte Carlo estimates for a test of homogeneity of Poisson rates across strata separately for each treatment group.

For the Device group, the p-value of 0.0786, while not significant at a 0.05 level provides some evidence that the rate of primary efficacy events for the Device group varies by time. This is consistent with the short term procedure risk (e.g., strokes from air embolisms). For the Control group, the p-value of 0.5732 is consistent with the assumption that the primary efficacy event rate is constant over time.

To explore the sensitivity of inferences to this assumption, and more generally to explore model sensitivity, a series of models for the primary efficacy endpoint were fit. This included Bayesian proportional hazards models, both unstratified and stratified by $CHADS_2$ score, and Bayesian piecewise constant hazards models, both unadjusted and adjusted for $CHADS_2$ score as represented in **Table 12-19**.

Table 12-19. Protection Against Non-Constant Hazard Primary Efficacy Endpoint (Intent-to-Treat)

Bayesian Proportional Hazards Model	0.81	0.37, 1.60
Bayesian Proportional Hazards Model, Stratified By $CHADS_2$	0.83	0.37, 1.64
Bayesian Piecewise Hazards Model	0.83	0.38, 1.65
Bayesian Piecewise Hazards Model With $CHADS_2$ Adjustment	0.88	0.40, 1.73

HR = hazard ratio

All models were consistent with the finding of non-inferiority of the device from the primary efficacy model; the relative risk estimate was less than 1 and the upper bound of the 95% credible interval was less than 2 for each model.

Components of Primary Efficacy

The most common primary efficacy events were strokes and deaths (cardiovascular and unexplained). Analyses of these endpoints, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates for these components are displayed in **Table 12-20** through **Table 12-23** and **Figure 12-4** and **Figure 12-5**.

Table 12-20. Bayesian Model Results: Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
454	13/409.3	3.2 (1.7, 5.2)	238	8/223.6	3.6 (1.5, 6.3)	0.89 (0.39, 2.42)

N = number Pts = patients Pt-yrs = patient-years CI = 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 stroke rate was 3.2 events per 100 patient years for the Device group and 3.6 events per 100 patient years for the Control group.
- This yielded a relative risk, or rate ratio, of 0.89, an 11% lower rate of stroke in the Device group than in the Control group. The 95% credible interval for the rate ratio was (0.39, 2.42).

Figure 12-4. Kaplan-Meier Curve: Freedom from Stroke (Intent-to-Treat)

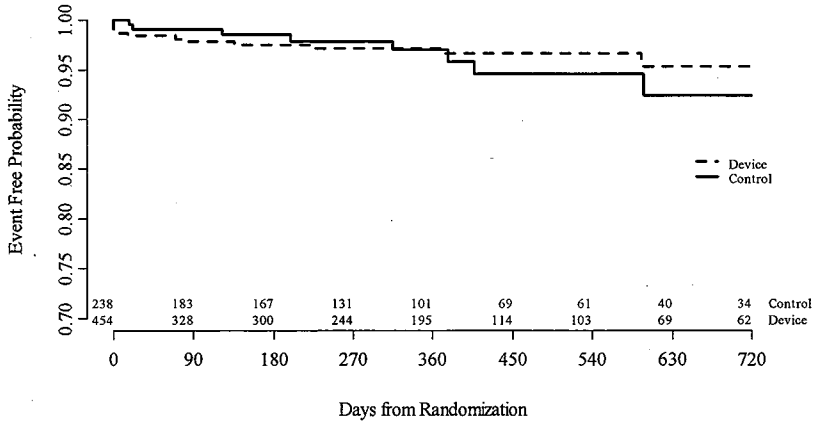

Table 12-21. Kaplan-Meier Estimates: Freedom from Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	6	6	98.7	0	0	100.0
45-days	1	7	98.4	2	2	99.1
6-months	3	10	97.5	1	3	98.5
1-year	1	11	97.2	2	5	97.0
2-year	2	13	95.3	3	8	92.4

The largest portion of the stroke events for the Device group (6/13, 46%) occurred within 7-days of randomization. Moreover, of these six events, one event occurred pre-procedure and five were procedural events. The largest portion of the stroke events for the Control group (3/8, 38%) occurred between 1-year and 2-years post-randomization. At 2 years, the Device group had a Kaplan-Meier estimated stroke event rate of 4.7% compared to a 7.6% stroke event rate in the Control group, a 38% lower relative rate for the Device group.

Table 12-22. Bayesian Model Results: All-Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
454	14/416.7	3.4 (1.8, 5.4)	238	11/225.1	4.9 (2.3, 7.8)	0.69 (0.33, 1.66)

- The mortality rate was 3.4 events per 100 patient years for the Device group and 4.9 events per 100 patient years for the Control group.
- This yielded a relative risk, or rate ratio, of 0.69, a 31% lower rate of death in the Device group than in the Control group. The 95% credible interval for the rate ratio was (0.33, 1.66).

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Figure 12-5. Kaplan-Meier Curve: Freedom from All Cause Mortality (Intent-to-Treat)

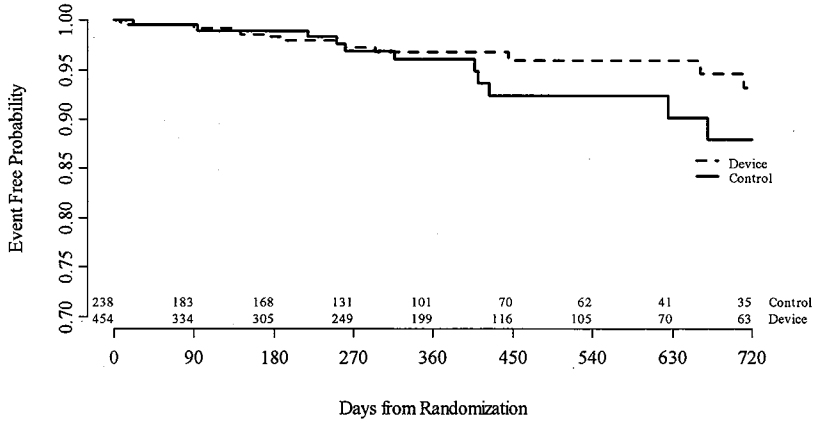

Table 12-23. Kaplan-Meier Estimates: Freedom from All Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.5	1	1	99.5
6-months	4	6	98.3	1	2	99.0
1-year	4	10	96.8	4	6	96.0
2-year	3	13*	93.1	5	11	87.9

*One additional death occurred post two years in the Device arm at 784 days post-randomization and is not reflected in the above table. This event was in patient

The largest portion of the deaths for the Device group (8/14*, 57%) occurred between 45-days and 1-year post-randomization. The largest portion of the deaths for the Control group (5/11, 45%) occurred between 1-year and 2-years post-randomization. At 2 years, the Device group had a Kaplan Meier estimated all cause mortality event rate of 6.9% compared to a 12.1% all cause mortality event rate in the Control group. This represents a 43% lower relative rate of all cause mortality for the Device group at 2 years.

Table 12-24 summarizes the patient deaths by randomized group.

Table 12-24. Patient Deaths by Group

	Device	13APR2005	14APR2005	06JUN2007	Ongoing respiratory issues while in hospice.
	Device	25APR2007	26APR2007	30DEC2007	Complications from unresolved urosepsis.
	Device	05JUN2006	06JUN2006	15MAY2008	Unknown – patient died during sleep.
	Device	31JUL2006	01AUG2006	16AUG2006	Spontaneous subarachnoid hemorrhage.
	Device	21SEP2005	21SEP2005	14JUL2007	Complications from gastric carcinoma.
	Device	08NOV2006	08NOV2006	06FEB2007	Complications from colitis in hospice care.
	Device	09MAR2005	10MAR2005	30JUL2005	Unknown – patient found dead.
	Device	10APR2006	11APR2006	26DEC2006	Endocarditis of aortic and mitral valves.
	Device	11NOV2005	11NOV2005	31MAR2006	Renal failure.
	Device	16JAN2007	17JAN2007	04APR2008	Complications secondary to lung carcinoma.
	Device	27AUG2007	30AUG2007	20FEB2008	Complications secondary to lung carcinoma.
	Device	14FEB2007	15FEB2007	25AUG2007	Cardiopulmonary arrest secondary to pneumonia, renal failure and leukemia.
	Device	18MAY2007	30MAY2007	08MAR2008	Urosepsis and catabolism secondary to diabetes.
	Device	21MAY2007	NA	29MAY2007	Secondary to ischemic stroke.
	Control	09AUG2005	NA	31AUG2005	Secondary to hemorrhagic stroke.
	Control	03APR2007	NA	10DEC2007	Complications secondary to myocardial infarction.
	Control	23JAN2006	NA	10MAR2007	Myocardial infarction.
	Control	06JUN2006	NA	03AUG2007	Acute coronary insufficiency.
	Control	09SEP2005	NA	10JUL2007	Secondary to adenocarcinoma of lung.
	Control	21MAR2007	NA	23JUN2007	Cardiogenic arrest secondary to coronary artery lesions.
	Control	01JUN2007	NA	16FEB2008	Bilateral pulmonary fibrosis, bronchopneumonia.
	Control	04MAY2007	NA	15MAR2008	Ventricular arrhythmia secondary to cardiovascular disease.
	Control	10AUG2007	NA	15MAR2008	Unknown cause secondary to fall.
	Control	15AUG2006	NA	30APR2008	Failure to thrive and pneumonia after stroke.
	Control	10NOV2006	NA	22DEC2007	Secondary to stroke.

[1] – Death is the initial efficacy event and included in **Table 12-14**.
[2] – Death is linked to a primary efficacy event.

Two strokes in the Device group were fatal compared to three strokes in the Control group Neither of the fatal strokes in the Device group were attributed to the device as one occurred before device implant and the other stroke was adjudicated as a hemorrhagic stroke while the patient was still on warfarin (see adverse event narratives located in **Attachment 5** for additional information). Two of the three fatal strokes in the Control group were hemorrhagic strokes while the patient was receiving warfarin therapy and one stroke was ischemic.

12.3.2.3 Primary Safety Endpoint (Intent-to-Treat)

Warfarin therapy has been shown to be successful in terms of reducing the incidence of the most serious and frequent sequela of non-valvular atrial fibrillation; specifically, stroke, death, and systemic embolism. However, use of warfarin places patients at risk for other safety events, primarily major and minor bleeding complications. These risks are ongoing in nature as AF is a chronic condition requiring long-term therapy during which events occur, while device events are primarily procedure-related.

Both stroke and cardiovascular death were the largest contributors to the primary efficacy endpoint of the PROTECT AF study and were seen at a reduced rate in the Device group compared to the Control group. While these events are critical safety events, other types of safety events were defined as a separate primary safety endpoint.

The primary safety endpoint was defined as the occurrence of life-threatening events as determined by the Clinical Events Committee, 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 primary safety results experienced are either early self limited procedural safety issues or ongoing chronic safety issues related to long-term warfarin. With device implantation, potential early safety issues were mitigated through operator experience, additional training and device modifications. However, chronic ongoing safety issues related to warfarin therapy, use, and administration cannot be mitigated.

In contrast to the primary efficacy endpoint, there was no pre-specified hypothesis for the primary safety endpoint.

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Results for the primary safety endpoint are displayed in **Table 12-25**. Credible intervals are calculated from the same Bayesian model used for the primary efficacy endpoint.

Table 12-25. Primary Safety Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
454	45/386.4	11.6 (8.5, 15.3)	238	9/220.4	4.1 (1.9, 7.2)	2.85 (1.48, 6.43)

N = number, Pts = patients, Pt-yrs = patient-years, CI = 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 safety rate was 11.6 events per 100 patient years for the Device group and 4.1 events per 100 patient years for the Control group.
- This yielded a rate ratio, or relative risk, of 2.85. The 95% credible interval for the rate ratio based on the Bayesian model was (1.48, 6.43).

Table 12-26 summarizes the types of primary safety events by randomized group

Table 12-26. Primary Safety Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Pericardial Effusion - Serious*	23	5.1	0	0.0
Gastrointestinal Bleeding	9	2.0	4	1.7
Stroke - Ischemic	5	1.1	0	0.0
Stroke - Hemorrhagic	1	0.2	4	1.7
Device Embolization	3	0.7	0	0.0
Esophageal Tear	1	0.2	0	0.0
Cranial Bleed	1	0.2	0	0.0
Major Bleed Requiring Transfusion	1	0.2	0	0.0
Arrhythmias	1	0.2	0	0.0
Anemia Requiring Transfusion	0	0.0	1	0.4

* Serious pericardial effusion was defined as one that required either pericardiocentesis or surgery.

Table 12-26 is based upon event type for the first event noted in a patient. If multiple events share the same event date, then the primary event as established in the AE linking process was used.

A higher rate of early primary safety events in the Device group compared to the Control group is not unexpected due to the invasive nature of the implant procedure.. The majority of primary safety events in the Device group (28/45, 62%) occurred on the day of the procedure. Ischemic and hemorrhagic stroke events can be independently categorized as both a safety and efficacy event. Further explanation is provided regarding the safety events of both treatment groups below:

- Of the 454 randomized Device group patients there were 23 pericardial effusions considered to be serious (5.1%). Of these, 7 effusions required surgical intervention with a median hospitalization of 6 days. The remaining 16 effusions were treated percutaneously with fluid drainage with a median hospitalization of 4 days; however, none of the effusions resulted in death.
- The rate of gastrointestinal bleeds in the Device group versus the Control group was essentially the same at 1.8% and 1.7%, respectively. However, 4 of 9 gastrointestinal bleeds in the Device group occurred while the patients were still taking warfarin per the 45-day post procedure requirement. The remaining 5 gastrointestinal bleeds in the Device group occurred post warfarin cessation as a result of combination clopidogrel and/or aspirin therapy. Patients who experienced a gastrointestinal bleed spent a median of 4 days in the hospital.
- There were five (1.1%) ischemic strokes in the Device group considered to be safety endpoint related. All five were noted following the implant procedure and 3 of the 5 were related to air embolism, a common occurrence in transseptal procedures, as reported by the sites. Device patients who experienced an ischemic stroke spent a median of 7 days in the hospital and none of these events resulted in death.
- There was one (0.2%) hemorrhagic stroke in the Device group versus four (1.7%) hemorrhagic strokes in the Control group. The stroke in the Device group was a spontaneous bleed which occurred 15 days post implant while the patient was still on warfarin therapy. Of the 4 hemorrhagic strokes in the Control group, 2 resulted in death. The median number of days spent in the hospital was 10.
- Of the 454 randomized Device group patients, three (0.7%) embolizations occurred. Two of the three were surgically removed. One patient who experienced a device embolization refused surgical removal and has been followed for ongoing evaluation. Information on this patient has been previously reported to the FDA.

Primary safety events used in the primary analysis are listed in **Table 12-27**. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events. Multiple events are summarized in **Section 12.3.6** (Adverse Events) of this report.

Table 12-27. Primary Safety Events - Initial Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

1		Device	14FEB2006	15FEB2006	15FEB2006	Stroke - Ischemic
2		Device	08MAY2006	09MAY2006	09MAY2006	Pericardial Effusion-Serious
3		Device	31JAN2007	31JAN2007	25JUL2007	Gastrointestinal Bleeding
4		Device	19MAR2007	25MAR2007	25MAR2007	Pericardial Effusion-Serious
5		Device	23FEB2005	24FEB2005	25FEB2005	Pericardial Effusion-Serious
6		Device	13APR2005	14APR2005	14APR2005	Major Bleed Requiring Transfusion
7		Device	25APR2007	26APR2007	26APR2007	Stroke - Ischemic
8		Device	26SEP2005	27SEP2005	27SEP2005	Pericardial Effusion-Serious
9		Device	29NOV2007	29NOV2007	29NOV2007	Pericardial Effusion-Serious
10		Device	22FEB2006	23FEB2006	09APR2006	Gastrointestinal Bleeding
11		Device	17OCT2006	18OCT2006	18OCT2006	Pericardial Effusion-Serious
12		Device	31JUL2006	01AUG2006	16AUG2006	Stroke - Hemorrhagic
13		Device	19FEB2008	20FEB2008	25FEB2008	Gastrointestinal Bleeding
14		Device	20OCT2005	20OCT2005	03JAN2008	Gastrointestinal Bleeding
15		Device	18JUL2005	19JUL2005	24JUL2005	Gastrointestinal Bleeding
16		Device	12JUL2005	12JUL2005	12JUL2005	Gastrointestinal Bleeding
17		Device	20FEB2006	21FEB2006	25FEB2006	Pericardial Effusion-Serious
18		Device	07APR2006	07APR2006	07APR2006	Arrhythmias
19		Device	15FEB2008	15FEB2008	15FEB2008	Pericardial Effusion-Serious
20		Device	11DEC2007	11DEC2007	11DEC2007	Esophageal Tear from TEE
21		Device	19OCT2005	19OCT2005	19OCT2005	Pericardial Effusion-Serious
22		Device	29MAR2005	30MAR2005	30MAR2005	Pericardial Effusion-Serious
23		Device	30MAR2006	31MAR2006	31MAR2006	Pericardial Effusion-Serious
24		Device	27NOV2006	28NOV2006	15JAN2007	Device Embolization
25		Device	14MAR2007	15MAR2007	15MAR2007	Pericardial Effusion-Serious
26		Device	13DEC2007	14DEC2007	14DEC2007	Pericardial Effusion-Serious
27		Device	25JAN2008	29JAN2008	29JAN2008	Stroke - Ischemic
28		Device	27JUL2006	28JUL2006	28JUL2006	Pericardial Effusion-Serious
29		Device	28NOV2005	29NOV2005	29NOV2005	Device Embolization
30		Device	11NOV2005	11NOV2005	11NOV2005	Stroke - Ischemic
31		Device	11JUN2007	13JUN2007	02JUL2007	Cranial Bleed

32		Device	09JUL2007	17JUL2007	05FEB2008	Gastrointestinal Bleeding
33		Device	21AUG2007	23AUG2007	24AUG2007	Pericardial Effusion-Serious
34		Device	22OCT2007	07NOV2007	08NOV2007	Pericardial Effusion-Serious
35		Device	13NOV2007	03DEC2007	03DEC2007	Pericardial Effusion-Serious
36		Device	13MAR2007	16MAR2007	16MAR2007	Pericardial Effusion-Serious
37		Device	10AUG2007	21AUG2007	28JAN2008	Gastrointestinal Bleeding
38		Device	11FEB2008	25FEB2008	25FEB2008	Pericardial Effusion-Serious
39		Device	23JAN2007	23JAN2007	23JAN2007	Pericardial Effusion-Serious
40		Device	17JUL2006	18JUL2006	18JUL2006	Stroke - Ischemic
41		Device	18OCT2006	20OCT2006	20OCT2006	Pericardial Effusion-Serious
42		Device	22APR2008	24APR2008	24APR2008	Pericardial Effusion-Serious
43		Device	02JUN2006	02JUN2006	16JUN2006	Pericardial Effusion-Serious
44		Device	04APR2007	11APR2007	05JUN2007	Device Embolization
45		Device	18SEP2007	19SEP2007	03DEC2007	Gastrointestinal Bleeding
1		Control	13JUN2006	NA	19FEB2007	Gastrointestinal Bleeding
2		Control	09AUG2005	NA	31AUG2005	Stroke - Hemorrhagic
3		Control	13JUL2005	NA	01MAY2006	Anemia Requiring Transfusion
4		Control	23APR2007	NA	03MAR2008	Stroke - Hemorrhagic
5		Control	27NOV2006	NA	24DEC2006	Gastrointestinal Bleeding
6		Control	10AUG2007	NA	11DEC2007	Stroke - Hemorrhagic
7		Control	15AUG2006	NA	03APR2008	Stroke - Hemorrhagic
8		Control	27FEB2007	NA	11MAR2008	Gastrointestinal Bleeding
9		Control	10JAN2007	NA	06SEP2007	Gastrointestinal Bleeding

Figure 12-6 and **Table 12-28** display results from a Kaplan-Meier analysis of the primary safety events.

Figure 12-6. Kaplan-Meier Curve: Freedom from Primary Safety Event (Intent-to-Treat)

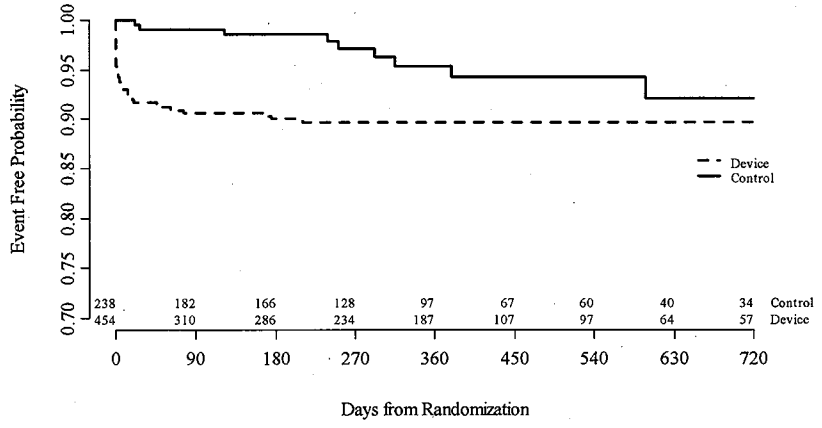

Table 12-28. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	31	31	93.1	0	0	100.0
45-days	6	37	91.7	2	2	99.1
6-months	6	43	90.0	1	3	98.5
1-year	1	44	89.6	4	7	95.4
2-year	0	44*	89.6	2	9	92.0

*One additional safety event occurred post two years in the Device arm at 805 days post-randomization and is not reflected in the above table. This event was a gastrointestinal bleed in patient

The largest portion of the primary safety events for the Device group (31/45*, 68.9%) occurred within 7-days of randomization. Furthermore, (28/45*, 62.2%) of the primary safety events occurred on the day of implant. The largest portion of the primary safety events for the Control group (4/9, 44%) occurred between 6-months and 1-year post-randomization. After the 7 day time point and through 2 years, the change in the Kaplan-Meier event free rate in the Device group was 3.5% compared to 8.0% in the Control group. This trend in long term warfarin events would be expected to continue beyond 2 years as data for 3-5 year event rates in the SPAF trials has previously demonstrated an increase in events over time. Additional consideration regarding time to events is further discussed in **Section 12.3.3 Post Procedure Analysis** and **Section 12.3.4 Per-Protocol Analysis**.

To assess the variation in primary safety event rates over the course of follow-up, an analysis of rates by six month intervals was performed as shown in **Table 12-29**. Additionally, a statistical test was performed separately by treatment group to examine whether or not rates varied over time.

Table 12-29. Homogeneity of Event Rates Over 6 Month Intervals Primary Safety Endpoint (Intent-to-Treat)

	Events/ Patient-years	Event Rate	Events/ Patient-years	Event Rate
0-6 Months	43/164.9	26.08	3/93.8	3.20
6-12 Months	1/113.9	0.88	4/62.6	6.39
12-18 Months	0/56.6	0.00	1/34.5	2.90
18-24 Months	0/33.3	0.00	1/20.5	4.87
24-30 Months	1/15.7	6.37	0/8.3	0.00
P-value	<0.01		0.9032	

Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization. P-values were calculated via Monte Carlo estimates for a test of homogeneity of Poisson rates across strata separately for each treatment group.

For the Device group, the p-value of <0.01 provides evidence that the rate of primary safety events for the Device group varies by time. This is consistent with procedural complications experienced in the study. For the Control group, the p-value of 0.9032 is consistent with the assumption that the primary safety event rate is consistent over time.

To explore the sensitivity of inferences to this assumption, and more generally to explore model sensitivity, a series of models for the primary safety endpoint were fit as shown in **Table 12-30**. This included Bayesian proportional hazards models, both unstratified and stratified by $CHADS_2$ score, and Bayesian piecewise constant hazards models, both unadjusted and adjusted for $CHADS_2$ score.

Table 12-30. Protection Against Non-constant Hazard Primary Safety Endpoint (Intent-to-Treat)

Bayesian Proportional Hazards Model	3.06	1.43, 6.29
Bayesian Proportional Hazards Model, Stratified By $CHADS_2$	3.07	1.42, 6.29
Bayesian Piecewise Hazards Model	3.23	1.51, 6.75
Bayesian Piecewise Hazards Model With $CHADS_2$ Adjustment	3.36	1.59, 6.87

The increased risk for Device patients was similar in magnitude in each of the above models. However, further analyses exploring the variation in the primary efficacy and safety event rates over time are presented in the post-procedure and per-protocol analyses.

12.3.2.4 Exploratory Safety Analysis: Effusions

Pericardial effusion events were noted early in the PROTECT AF trial and were the primary safety event associated with the WATCHMAN LAA closure procedure.

The Statistical Analysis Plan pre-specified that the first three patients (either roll-in or randomized) receiving a device at a site were to be treated as "early" patients in an analysis comparing "early" and "late" patient groups. This analysis captures learning at a site level.

All pericardial effusions were reported and adjudicated by the Clinical Events Committee (CEC) as either:

- "Serious" as defined as any effusion requiring either pericardiocentesis or surgery.
- "Not Serious" as defined as any effusion that did not cause hemodynamic change and required no treatment.

In addition, each effusion was adjudicated based upon its relation to the procedure or device.

In **Table 12-31**, the following three categories of events were analyzed:

- "Any," which includes both serious and not serious effusions.
- "Any procedure/device-related," which includes only effusions caused by the procedure or device. This category includes both serious and not serious effusions.
- "Any serious," which includes only effusions requiring pericardiocentesis or surgery.

Table 12-31. Pericardial Effusions by Site Experience

Early Patients (1-3)	18/153 (11.8)	13/153 (8.5)	11/153 (7.2)
Late Patients (4+)	31/380 (8.2)	25/380 (6.6)	18/380 (4.7)
Total:	49/533 (9.2)	38/533 (7.1)	29/533 (5.4)

The overall effusion rate for any procedure/device related and any serious effusion categories decreased between early and late patient groups from 8.5% to 6.6% and 7.2% to 4.7%, respectively. Late patients implanted experienced a relative reduction of 22.4% and 34.7% in any procedure/device related and any serious effusions. As expected a site level learning curve related to a new procedure occurred.

All adverse event reports of effusions, excluding events adjudicated by the CEC as non-events, are listed in **Attachment 4**.

To capture learning throughout the trial, an additional analysis was performed based upon the date a site began implanting patients. Based on this date, sites were divided into two groups; those that began implanting before July 1, 2006 (first half) and those sites that began after (second half). Patients were additionally stratified into the early/late patient groups. Rates of effusions for each group are shown in **Table 12-32**.

Table 12-32. Pericardial Effusions by Site and Trial Experience

Early Patients (1-3)	10/75 (13.3)	7/75 (9.3)	7/75 (9.3)
Late Patients (4+)	24/253 (9.5)	18/253 (7.1)	12/253 (4.7)
Early Patients (1-3)	8/78 (10.3)	6/78 (7.7)	4/78 (5.1)
Late Patients (4+)	7/127 (5.5)	7/127 (5.5)	6/127 (4.7)

Rates of effusions in all categories were higher in the first half of implanting sites as compared with the second half. This was seen for both early and late patients. The differences in rates of serious effusion between early vs. late patients were smaller in the second half of the trial as compared to the first.

For example, in the first half of the trial, the difference in incidence of any serious effusion between early and late patients was (9.3-4.7 = 4.6%) while this same difference in the second half of the trial was (5.1-4.7 = 0.4%).

This implies that trial-level learning was a larger influence on the effusions than the site-level learning in the second half of the trial. Based upon site and trial experience, serious effusions rates decreased over time for the early patients (first three) and then plateaued in late patients with a rate of 4.7%.

Pericardial effusions as a general complication of intracardiac procedures have been well documented. In some situations, these effusions are asymptomatic and do not require treatment, while in others, the effusion results in hemodynamic changes such as tamponade and require drainage. Factors associated with pericardial effusions include anticoagulant therapy, placement of multiple catheters, and excessive catheter manipulation.

These have been reported as a complication of AF ablation, permanent pacemaker implantation, myocardial biopsy, placement of ICD's, and transseptal procedures.

The June 2007, HRS Consensus Statement, cited cardiac tamponade occurring in up to 6% in AF ablation cases.[96] Current literature for other intracardiac modalities report rates of cardiac perforation and tamponade of 1.2-2.9%.[96,99,100] Cardiac tamponade and perforation cited in the literature are equivalent to the definition of any serious effusion in the PROTECT trial.

Pericardial effusion was recognized early in the PROTECT AF trial and was addressed through a variety of activities including:

- a reduction in the intensity of anticoagulant therapy
- the addition of a roll-in phase
- new improved technical approaches to engage the left atrial appendage
- enhanced recognition of the need for careful catheter manipulation
- additional case review
- modifications of the Device and Access Sheath

These activities were initiated between January and November 2006 and overlap the break in first half/second half sites analyzed in **Table 12-32**. The result of these efforts and enhanced operator experience led to an overall decline of effusion rates during the course of the trial. It must be kept in mind that while this complication is serious, it did not result in any mortality.

To explore statistical predictors of effusions, multivariate logistic regression models were fit for the risk of each event category. Predictors (covariates) included the implant date and a variable discriminating between early and late implants. Results of these models are displayed in **Table 12-33**.

Table 12-33. Analysis of Pericardial Effusion Risk Factors

	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value
Early Vs. Late Implant	1.03	0.9407	1.04	0.9157	0.83	0.6830
Implant Date (Per 6 Months)	0.74	0.0071	0.80	0.07592	0.83	0.1971

Later implant date was significantly associated with a decreased odds of experiencing any effusion (odds ratio = 0.74, p-value = 0.0071). No other models were found to contain statistically significant predictors at the 0.05 level, though the p-values for later implant date for both any procedure/device-related effusion and any serious effusion approached the 0.05 level.

12.3.3 Post Procedure Analysis (Pre-Specified)

12.3.3.1 Description of Cohort

While an intent-to-treat cohort includes all randomized patients in the group to which they were assigned, other analyses may be performed to exclude certain enrolled patients that were not able to benefit from the treatment. One such analysis is a post procedure analysis to examine the long term treatment effect following implant of the device. Understanding that any catheter intervention has its inherent risks, from a clinician perspective it is important to answer the following questions: 1) What happens after the patient leaves the table? and 2) More importantly, are there any adverse events that the clinician needs to be aware of to educate the patient before leaving the hospital? For this analysis, patients were analyzed according to their randomized group. Follow-up time for Device patients is calculated from the date of implant as opposed to the date of randomization. The median (inter-quartile range) number of days from randomization to implant was 1 (0-4 days).

12.3.3.2 Primary Efficacy Endpoint – Post Procedure

Six patients with primary efficacy events that either occurred prior to or on the date of the implant were excluded from the post-procedure analysis as listed in **Table 12-34**. In total, 19 patients were excluded from this analysis; 14 patients for whom no implant was attempted as discussed in Section 12.1.1 (one of which was who experienced an ischemic stroke and died prior to an attempted device implant) and 5 patients who experienced events on the date of implant.

Table 12-34. Post Procedure Analysis - Excluded Patients with Efficacy Events

Device		No	15FEB2006	Stroke - Ischemic
Device		Yes	26APR2007	Stroke - Ischemic
Device		Yes	29JAN2008	Stroke - Ischemic
Device		Yes	11NOV2005	Stroke - Ischemic
Device		Yes	18JUL2006	Stroke – Ischemic
Device		No	29MAY2007	Stroke – Ischemic

* Treatment received = Device implanted

Table 12-35. Primary Efficacy Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-Inferiority	Superiority
435	12/399.3	3.0 (1.6, 5.1)	238	13/223.6	5.8 (3.0, 9.1)	0.52 (0.24, 1.22)	0.999	0.932

N = number Pts = patients Pt-yrs = patient-years CI = 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 efficacy rate for the post-procedure analysis was 3.0 events per 100 patient years for the Device group and 5.8 events per 100 patient years for the Control group as shown in **Table 12-35**.
- This yielded a rate ratio, or relative risk, of 0.52. The 95% credible interval for the rate ratio based on the Bayesian model was (0.24, 1.22).
- Following the implant procedure, Device group patients experienced a 48% reduction in strokes, death or systemic embolism.

The posterior probability of non-inferiority was defined as the probability that the event rate for the Device group was less than twice that for the Control group. The probability of non-inferiority for the post-procedure analysis was 0.999.

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority for the post-procedure analysis was 0.932.

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Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 12-7** and **Table 12-36**.

Figure 12-7. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Post Procedure)

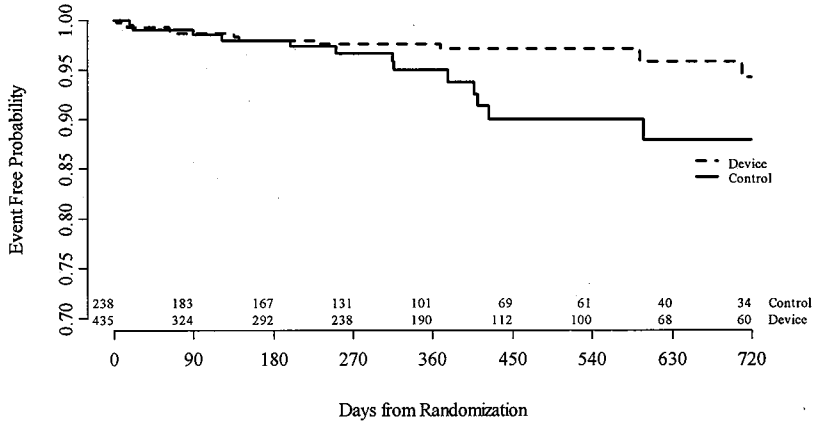

Table 12-36. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.8	0	0	100.0
45-days	2	3	99.3	2	2	99.1
6-months	4	7	98.0	2	4	98.0
1-year	1	8	97.7	4	8	94.9
2-year	3	11*	94.2	5	13	88.0

*One additional efficacy event occurred post two years in the Device arm at 771 days post-randomization and is not reflected in the above table as number of follow-up years becomes small. This event was a systemic embolism in patient

The largest portion of post procedure primary efficacy events in the Device group (4/12*, 33%) occurred between 45-days and 6-months post-implant. The largest portion of the post procedure efficacy events for the Control group (5/13, 38%) occurred between 1-year and 2-years post-randomization. At 2 years, the Device group had a Kaplan Meier estimated post procedure efficacy event rate of 5.8% compared to a 12.0% post procedure efficacy event rate in the Control group, a 52% lower relative rate for the Device group.

12.3.3.3 Primary Safety Endpoint – Post Procedure

Twenty eight patients with primary safety events on the date of implant were excluded from the post-procedure analysis as listed in **Table 12-37**. In 13 of these 28 patients a device was not successfully implanted, in 15 of these 28, a device was successfully implanted. Fourteen additional patients who did not have an attempted implant (as discussed in **Section 12.1.1**) and without primary safety events were excluded.

Table 12-37. Post Procedure Analysis - Excluded Patients with Safety Events

Device		No	15FEB2006	Stroke - Ischemic
Device		No	09MAY2006	Pericardial Effusion-Serious
Device		Yes	25MAR2007	Pericardial Effusion-Serious
Device		Yes	14APR2005	Major Bleed Requiring Transfusion
Device		Yes	26APR2007	Stroke - Ischemic
Device		No	27SEP2005	Pericardial Effusion-Serious
Device		Yes	29NOV2007	Pericardial Effusion-Serious
Device		No	18OCT2006	Pericardial Effusion-Serious
Device		Yes	12JUL2005	Gastrointestinal Bleeding
Device		No	07APR2006	Arrhythmias
Device		No	15FEB2008	Pericardial Effusion-Serious
Device		Yes	11DEC2007	Esophageal Tear from TEE
Device		Yes	19OCT2005	Pericardial Effusion-Serious
Device		No	30MAR2005	Pericardial Effusion-Serious
Device		Yes	31MAR2006	Pericardial Effusion-Serious
Device		No	15MAR2007	Pericardial Effusion-Serious
Device		No	14DEC2007	Pericardial Effusion-Serious
Device		Yes	29JAN2008	Stroke - Ischemic
Device		No	28JUL2006	Pericardial Effusion-Serious
Device		Yes	29NOV2005	Device Embolization
Device		Yes	11NOV2005	Stroke - Ischemic
Device		Yes	03DEC2007	Pericardial Effusion-Serious
Device		Yes	16MAR2007	Pericardial Effusion-Serious
Device		No	25FEB2008	Pericardial Effusion-Serious
Device		No	23JAN2007	Pericardial Effusion-Serious
Device		Yes	18JUL2006	Stroke - Ischemic
Device		Yes	20OCT2006	Pericardial Effusion-Serious
Device		No	24APR2008	Pericardial Effusion-Serious

* Treatment received = Device implanted

Table 12-38. Primary Safety Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
412	17/376.4	4.5 (2.7, 7.0)	238	9/220.4	4.1 (1.9, 7.2)	1.11 (0.51, 2.68)

- The primary safety rate was 4.5 events per 100 patient years for the Device group and 4.1 events per 100 patient years for the Control group as shown in **Table 12-38**.
- This yielded a rate ratio, or relative risk, of 1.11. The 95% credible interval for the rate ratio based on the Bayesian model was (0.51, 2.68). Twelve of the 17 device events occurred while patients were on warfarin.

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Figure 12-8 and **Table 12-39** display results from a Kaplan-Meier analysis of the primary safety events.

Figure 12-8. Kaplan-Meier Curve: Freedom from Primary Safety Event (Post Procedure)

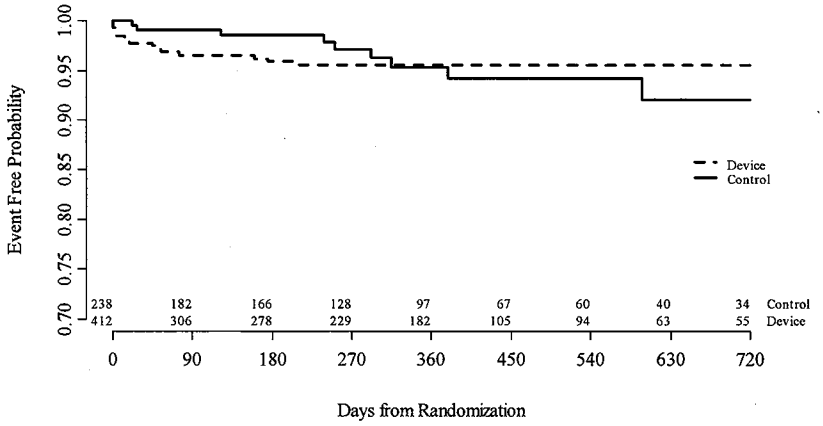

Table 12-39. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	6	6	98.5	0	0	100.0
45-days	4	10	97.5	2	2	99.1
6-months	5	15	95.9	1	3	98.5
1-year	1	16	95.5	4	7	95.4
2-year	0	16*	95.5	2	9	92.0

*One additional safety event occurred post two years in the Device arm at 805 days post-randomization and is not reflected in the above table. This event was a gastrointestinal bleed in patient

The largest portion of post procedure primary safety events in the Device group (6/17*, 35%) occurred within 7-days post-implant. The majority of these events were gastrointestinal bleeds and pericardial effusions. The largest portion of the post procedure primary safety events for the Control group (4/9, 44%) occurred between 6-months and 1-year post-randomization. Two of these were gastrointestinal bleeds, and the other two events were hemorrhagic stroke and anemia requiring transfusion. At 2 years, the Device group had a Kaplan Meier estimated post procedure primary safety event rate of 4.5% compared to a 8.0% post procedure efficacy event rate in the Control group, a 44% relatively lower rate for the Device group.

12.3.4 Per-Protocol Analysis (Pre-Specified)

12.3.4.1 Description of Cohort

An intent-to-treat analysis forms the cornerstone of randomized trials and was the primary analysis for the PROTECT AF trial. However, there are other considerations from the patient standpoint. Specifically in the PROTECT AF trial, one problem was the time lag between the implantation of the device and the time at which warfarin therapy could be discontinued. During this time, the patients were exposed to both the risks of the implantation procedure and the risks of warfarin therapy, without the potential benefit of being off warfarin. Important questions from the patient perspective are: 1) Will I be able to stop warfarin? and 2) What are the outcomes after being taken off warfarin therapy?

To quantify this potential benefit of the device, a per-protocol analysis was performed that only included randomized Device patients who were successfully implanted with the device that were then able to discontinue warfarin therapy and only included Control patients that were taking warfarin therapy at baseline or 45-days. This analysis was performed to support the primary intent-to-treat analysis. Such a secondary per-protocol analysis also attempts to avoid the potential that treatment estimates from an intent-to-treat analysis in a non-inferiority trial can be biased when patients in the investigational treatment group do not receive the new device.

In the per-protocol analysis, time to event was calculated from the date of first warfarin cessation for Device patients. Primary efficacy and safety results for the per-protocol analysis are provided below.

12.3.4.2 Primary Efficacy Endpoint- Per-Protocol Analysis

Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. This included 10 Device patients with primary efficacy events and an additional 82 patients without primary efficacy events. Of the 440 patients in the Device group for whom an implant was attempted, 423 had 45-day visit windows that closed prior to the closure of the database. Thus, the 362 patients in the Device group in the per-protocol efficacy analysis represent approximately 86% (362/423) of the patients in the Device group for whom treatment was successful (defined as successfully implanted and able to discontinue warfarin therapy). In the Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. This included a total of two Control group patients, one of whom experienced a primary efficacy event.

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Patients with primary efficacy events that were excluded are listed in the **Table 12-40**.

Table 12-40. Per-Protocol Analysis - Excluded Patients with Efficacy Events

Device		No	15FEB2006	Stroke - Ischemic
Device		No	26APR2007	Stroke - Ischemic
Device		No	05DEC2005	Stroke - Ischemic
Device		No	16AUG2006	Stroke - Hemorrhagic
Device		No	09MAR2006	Stroke - Ischemic
Device		No	04AUG2006	Systemic Embolism
Device		No	29JAN2008	Stroke - Ischemic
Device		No	11NOV2005	Stroke - Ischemic
Device		No	18JUL2006	Stroke - Ischemic
Device		No	24MAY2007	Stroke - Ischemic
Control		No	19JUN2007	Death

* Treatment received = Device implanted and cessation of warfarin (Device group) or warfarin taken at baseline and/or 45 days (Control group).

Table 12-41. Primary Efficacy Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-Inferiority	Superiority
PP	362	8/318.5	2.5 (1.1, 4.8)	236	12/223.1	5.4 (2.7, 8.6)	0.47 (0.19, 1.21)	0.999	0.938

N = number, Pts = patients, Pt-yrs = patient-years, CI = 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 efficacy rate was 2.5 events per 100 patient years for the Device group and 5.4 events per 100 patient years for the Control group as shown in **Table 12-41**.
- This yielded a rate ratio, or relative risk, of 0.47. The 95% credible interval for the rate ratio based on the Bayesian model was (0.19, 1.21).
- 86% (362/423) of Device group patients were treated successfully (defined as successfully implanted and able to discontinue warfarin therapy).

The posterior probability of non-inferiority was defined as the probability that the event rate for the Device group was less than twice that for the Control group. The probability of non-inferiority at the first interim analysis was 0.999.

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority at the first interim analysis was 0.938.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 12-9** and **Table 12-42**.

Figure 12-9. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Per-Protocol)

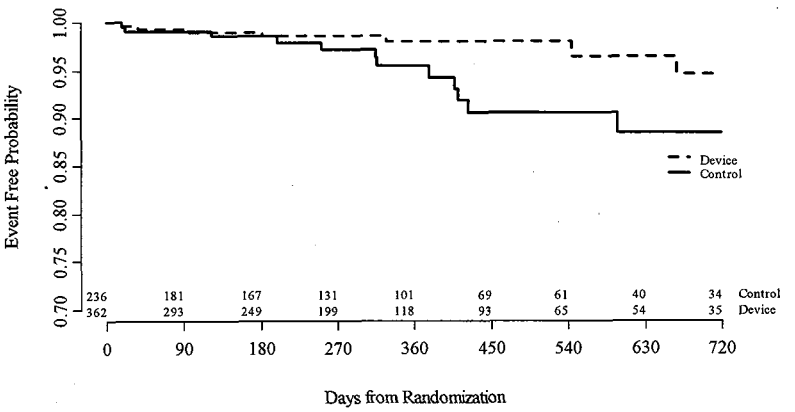

Table 12-42. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.3	2	2	99.1
6-months	1	3	99.0	1	3	98.5
1-year	2	5	97.9	4	7	95.4
2-year	3	8	91.8	5	12	88.4

The largest portion of per-protocol primary efficacy events in the Device group (3/8, 38%) occurred between 1-year and 2-years post-warfarin cessation. The largest portion of the per-protocol primary efficacy events for the Control group (5/12, 42%) occurred between 1-year and 2-years post-randomization. At 2 years, the Device group had a Kaplan Meier estimated per-protocol primary efficacy event rate of 8.2% compared to a 11.6% per-protocol efficacy event rate in the Control group, a 29% relatively lower rate for the Device group.

12.3.4.3 Primary Safety Endpoint - Per-Protocol Analysis

The per-protocol analysis excluded 39 patients who experienced primary safety events from the Device group. As in the efficacy analysis, patients in the Device group were excluded when either no implant was attempted, when the device was not successfully implanted, or when patients did not discontinue warfarin therapy, and from the Control group when there was no evidence that warfarin was taken at baseline or at the 45-day visit. The patients with primary safety events that were excluded are listed in **Table 12-43**.

Table 12-43. Per-Protocol Analysis - Excluded Patients with Safety Events

Device		No	15FEB2006	Stroke - Ischemic
Device		No	09MAY2006	Pericardial Effusion-Serious
Device		No	25MAR2007	Pericardial Effusion-Serious
Device		No	25FEB2005	Pericardial Effusion-Serious
Device		No	14APR2005	Major Bleed Requiring Transfusion
Device		No	26APR2007	Stroke - Ischemic
Device		No	27SEP2005	Pericardial Effusion-Serious
Device		No	29NOV2007	Pericardial Effusion-Serious
Device		No	09APR2006	Gastrointestinal Bleeding
Device		No	18OCT2006	Pericardial Effusion-Serious
Device		No	16AUG2006	Stroke - Hemorrhagic
Device		No	25FEB2008	Gastrointestinal Bleeding
Device		No	24JUL2005	Gastrointestinal Bleeding
Device		No	12JUL2005	Gastrointestinal Bleeding
Device		No	25FEB2006	Pericardial Effusion-Serious
Device		No	07APR2006	Arrhythmias
Device		No	15FEB2008	Pericardial Effusion-Serious
Device		No	11DEC2007	Other Study Related
Device		No	19OCT2005	Pericardial Effusion-Serious
Device		No	30MAR2005	Pericardial Effusion-Serious
Device		No	31MAR2006	Pericardial Effusion-Serious
Device		No	15JAN2007	Device Embolization
Device		No	15MAR2007	Pericardial Effusion-Serious
Device		No	14DEC2007	Pericardial Effusion-Serious
Device		No	29JAN2008	Stroke - Ischemic
Device		No	28JUL2006	Pericardial Effusion-Serious

Device	[redacted]	No	29NOV2005	Device Embolization
Device		No	11NOV2005	Stroke - Ischemic
Device		No	02JUL2007	Cranial Bleed
Device		No	24AUG2007	Pericardial Effusion-Serious
Device		No	08NOV2007	Pericardial Effusion-Serious
Device		No	03DEC2007	Pericardial Effusion-Serious
Device		No	16MAR2007	Pericardial Effusion-Serious
Device		No	25FEB2008	Pericardial Effusion-Serious
Device		No	23JAN2007	Pericardial Effusion-Serious
Device		No	18JUL2006	Stroke - Ischemic
Device		No	20OCT2006	Pericardial Effusion-Serious
Device		No	24APR2008	Pericardial Effusion-Serious
Device		No	05JUN2007	Device Embolization

* Treatment received = Device implanted and cessation of warfarin (Device group) or warfarin taken at baselin and/or 45 days (Control group).

Table 12-44. Primary Safety Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
PP	362	6/317.0	1.9 (0.7, 3.7)	236	9/219.9	4.1 (1.9, 7.2)	0.46 (0.15, 1.30)

N = number Pts = patients Pt-yrs = patient-years CI = 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 safety rate was 1.9 events per 100 patient years for the Device group and 4.1 events per 100 patient years for the Control group as shown in **Table 12-44**.
- This yielded a rate ratio, or relative risk, of 0.46. The 95% credible interval for the rate ratio based on the Bayesian model was (0.15, 1.30).

Results from Kaplan-Meier analyses for the primary safety endpoint are given in **Figure 12-10** and **Table 12-45**.

Figure 12-10. Kaplan-Meier Curve: Freedom from Primary Safety Event (Per-Protocol)

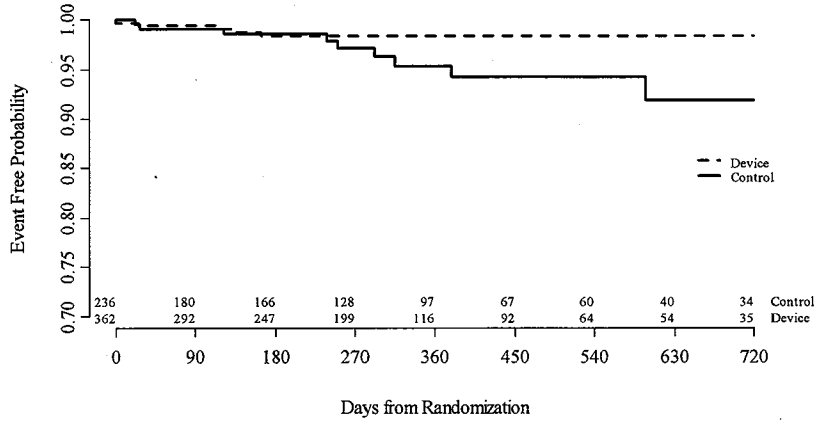

Table 12-45. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.7	0	0	100.0
45-days	1	2	99.4	2	2	99.1
6-months	3	5	98.3	1	3	98.5
1-year	0	5	98.3	4	7	95.4
2-year	0	5	98.3	2	9	92.0

The largest portion of per-protocol safety events in the Device group (3/5, 60%) occurred between 45-days and 6-months post-warfarin cessation. In addition, the Device group had no per-protocol safety events between 1-year and 2-years. The largest portion of the per-protocol safety events for the Control group (4/9, 44%) occurred between 6-months and 1-year post-randomization. At 2 years, the Device group had a Kaplan Meier estimated per-protocol safety event rate of 1.7% compared to an 8.0% per-protocol safety event rate in the Control group, a 79% relatively lower rate for the Device group.

12.3.4.4 Additional Per-Protocol Analysis

An additional per-protocol analysis was performed that excluded patients who for any reason did not receive the treatment to which they were assigned. This included Device patients who did not receive a successful implant and Control patients for whom there was not evidence that warfarin was taken at baseline or at the 45-day visit.

Under this analysis, the primary efficacy rate was 3.8 events per 100 patient years (15 events / 394.7 patient-years) for the Device group and 5.4 events per 100 patient years (12 events / 223.1 patient-years) for the Control group. This yielded a rate ratio, or relative risk, of 0.71. The 95% credible interval for the rate ratio based on the Bayesian model was (0.35, 1.65). The probability of non-inferiority for this analysis was 0.992.

The primary safety rate was 8.2 events per 100 patient years (31 events / 376.5 patient-years) for the Device group and 4.1 events per 100 patient years (9 events / 219.9 patient-years) for the Control group. This yielded a rate ratio, or relative risk, of 2.01. The 95% credible interval for the rate ratio based on the Bayesian model was (1.01, 4.61).

These results also support the finding of non-inferiority for the Device group relative to the Control group for the primary efficacy endpoint.

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12.3.4.5 Risk / Benefit Analysis

The risk / benefit analysis was evaluated with three analysis cohorts: intent-to-treat, post procedure and per-protocol. Each analysis is summarized below assessing the safety and efficacy of implanting a device.

Intent-to-Treat	Provide the analysis that includes all randomized patients
Post Procedure	Evaluate the safety and efficacy of the device following the acute procedure
Per-Protocol	Evaluate the safety and efficacy of the device for patients who received their assigned therapy: Device patients were able to discontinue warfarin therapy, Control patients took warfarin therapy at baseline or 45-days

Intent-to-Treat Analysis

- Statistically significant finding of non-inferiority for the primary efficacy event rate.
- 24% lower rate of primary efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- 11% lower rate of stroke in the Device group than in the Control group.
- 31% lower rate of death in the Device group than in the Control group.
- Statistically significant 2.85 fold higher rate of primary safety events for the Device group relative to the Control group. Most of the events in the Device group were procedural effusions that decreased over the course of the study.

Post Procedure Analysis

- The post procedure primary efficacy event rate yielded a 48% lower rate of efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- Rates of primary safety events were similar for the Device and Control group, 4.5% and 4.1% respectively.

Per-Protocol Analysis

- The per-protocol primary efficacy event rate yielded a 53% lower rate of efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- The per-protocol primary safety event rate yielded a 54% lower rate of primary safety events in the Device group than in the Control group.
- Approximately 86% of patients in the Device group were able to be successfully implanted and discontinue warfarin therapy.

The primary efficacy and safety results for these cohorts are summarized in **Table 12-46**.

Table 12-46. Summary of Primary Efficacy and Safety Results by Analysis Cohort

Intent-to-Treat	0.76 (0.39, 1.67)	2.85 (1.48, 6.43)
Post-Procedure	0.52 (0.24, 1.22)	1.11 (0.51, 2.68)
Per-Protocol	0.47 (0.19, 1.21)	0.46 (0.15, 1.30)

Additionally, **Table 12-47** displays the rates of stroke (all stroke, ischemic, and hemorrhagic) by randomized group for the primary intent-to-treat analysis and the per-protocol analysis.

Table 12-47. Stroke Rates by Type

	Events	Rate	Fatal	Rate	Events	Rate	Fatal	Rate
All stroke	14	3.4	2	0.5	8	3.6	3	1.3
Ischemic stroke	13	3.2	1	0.2	4	1.8	1	0.4
Hemorrhagic stroke	1	0.2	1	0.2	4	1.8	2	0.9
	Events	Rate	Fatal	Rate	Events	Rate	Fatal	Rate
All stroke	5	1.6	0	0.0	8	3.6	3	1.3
Ischemic stroke	5	1.6	0	0.0	4	1.8	1	0.4
Hemorrhagic stroke	0	0.0	0	0.0	4	1.8	2	0.9

In total, these results demonstrate that while there were procedural risks in the treatment, the risks were reduced as physicians became more familiar with the implant procedure. Furthermore, the procedural risks experienced in the trial increased the number of days in the hospital, but did not cause procedure related death. These results also demonstrate that once a device was successfully implanted, the rate of late complications in the Device patients was substantially lower than the Control patients. Lastly, the late complications in the Control patients were more severe than the early complications of the Device group.

In conclusion, these analyses demonstrate an overall favorable risk/benefit profile for Device patients even with the risk of procedural complications. Clinicians associated with the PROTECT AF trial believe this study provides quantitative evidence to represent the risk/benefit of the WATCHMAN procedure as a compelling alternative to warfarin therapy.

12.3.5 Secondary Endpoints and Warfarin Analyses

12.3.5.1 Secondary Endpoints - Both Randomized Groups

The protocol listed the following secondary endpoints to be investigated for both randomized groups

- TIA
- Other individual complication rates including, but not limited to MI and death.

TIA and other individual complications rates were too infrequent to perform formal statistical analysis that would lead to reliable conclusions. Analyses of mortality rates are presented in **Table 12-22** and **Table 12-23**. Analyses of pericardial effusion are presented in **Section 12.3.2.4**. All adverse events (i.e., individual complication rates) are summarized by treatment group in **Section 12.3.6**, by individual complication type, seriousness, and device/procedure relatedness.

12.3.5.2 Secondary Endpoints - Device Group

The following secondary endpoints for the Device group were defined in the protocol:

- Technical Success defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary
- Procedure Success defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay
- 30-Day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer)
- Individual complication rates including, but not limited to hematomas and pseudoaneurysms.

Results for the first three Device group secondary endpoints are presented in the following table. Refer to **Section 12.3.6 (Adverse Events)** for analysis of individual complications for the Device group.

Results for secondary endpoints in the Device group are displayed in **Table 12-48**.

Table 12-48. Device Group Secondary Endpoints

Technical Success	400/440 (90.9)
Procedure Success	369/440 (83.9)
30-Day Major Complications	51/415 (12.3)

The device was successfully implanted in 90.9% (400/440) of Device group patients for whom an implant was attempted. Procedure success was achieved in 83.9% (369/440) of Device group patients for whom an implant was attempted. The percentage of patients experiencing a 30-Day Major Complication was 12.3% (51/415).

Twenty-five Device group patients for whom an implant was attempted were not included in the calculation of 30-Day Major Complications as the patients were not followed for at least 30 days and had not yet experienced a major complication related to the treatment or procedure; this yields a denominator of 415 patients instead of 440 for this endpoint.

12.3.5.3 Secondary Endpoints - Control Group

The following Secondary Endpoints were defined for the Control group in the protocol:

- Non-therapeutic INR > 3.0 or < 2.0, and stopped therapy (Interruption of Therapy (IOT))
- Excessive anticoagulation INR > 4.0
- Bleeding complications such as: hematuria, rectal bleeding, epistaxis, bleeding from varicose veins, oral bleeding, prolonged bleeding from a laceration, bruising-hematoma, hemathorax, re eye, or thrombosis.

Results for secondary endpoints in the Control group are provided in **Table 12-49** and **Table 12-50**. Values of INR from the INR monitoring form collected following randomization were used to assess the frequency of patients ever having a non-therapeutic INR or excessive anti-coagulation. Patients may have had INR values both below and above the therapeutic levels during the course of follow-up and so the percentages for "Patients Ever Having" INR values at each category add up to more than 100%.

Table 12-49. Control Group Secondary Endpoints – INR Related Endpoints

INR < 2.0	150/170 (88.2)
INR ≥2.0 to < 3.0	161/170 (94.7)
INR ≥3.0 to < 4.0	129/170 (75.9)
INR ≥ 4.0	68/170 (40.0)
INR < 2.0	836/2747 (30.4)
INR ≥2.0 to < 3.0	1404/2747 (51.1)
INR ≥3.0 to < 4.0	380/2747 (13.8)
INR ≥ 4.0	127/2747 (4.6)

Enrollment was ongoing through [redacted] therefore, not all Control group patients had a follow-up INR monitoring form in the database at the time of analysis. There were 170 Control group patients that had one or more INR draws documented; this is comparable to the 217 and 170 Control group patients that had a 45-day and 6-month study visit, respectively, at the time of this analysis.

The majority of patients had a non-therapeutic/excessive INR value (88.2% less than 2.0, 75.9% between 3.0 and 4.0, and 40% above 4.0) at least once during follow-up.

The percent of the measurements that represented non-therapeutic INR or excessive anti-coagulation was also calculated. Based on these measurements, patients remained in the therapeutic range (INR 2.0 - 3.0) only 51.1% of the time.

Table 12-50. Control Group Secondary Endpoints – Bleeding Complications

	N Events	Patient Years	Event Rate
Any Bleeding Event	9	215.44	4.18
Any Serious Bleeding Event	1	224.72	0.44

Bleeding complications were defined in the protocol as hematuria, rectal bleeding, epistaxis, bleeding from varicose veins, oral bleeding, prolonged bleeding from a laceration, bruising-hematoma, hemathorax, red eye, or thrombosis and were based on the classification of the Clinical Event Committee. Serious bleeding complications were defined as bleeding complications that were adjudicated as serious by the Clinical Event Committee.

12.3.5.4 Interruption of Therapy

Of the 238 randomized Control patients, 50 (21.0%) interrupted or discontinued warfarin therapy at least once during the trial according to their office follow-up visit forms.

Warfarin discontinuation rates for patients implanted with the device are displayed in **Table 12-51**. According to the protocol, patients randomized to the Device group were to discontinue warfarin therapy at the 45-day visit if TEE indicated there was complete occlusion of the LAA or a residual jet flow of $\leq 3 \pm 2$ mm around the margins of the device.

A majority of patients (87.3%) were able to discontinue warfarin therapy at 45 days. Subsequent follow-ups demonstrated an increase in the percent of patients discontinuing warfarin over the 45-day visit.

Table 12-51. Warfarin Discontinuation – Successfully Implanted Patients Only

45 day	329/377 (87.3)
6 month	276/299 (92.3)
12 month	178/196 (90.8)
24 month	60/64 (93.8)

Among successfully implanted Device patients, the most frequent reason for the 48 patients remaining on warfarin therapy at the 45-day visit was the observation of flow in the left atrial appendage (n=28). The second most frequent reason was physician order (n=11). The remaining reasons in descending order were as follows: explant or embolization (n=4), TEE not done or pending review (n=3), and thrombus (n=2).

Figure 12-11 and **Table 12-52** display results from a Kaplan-Meier analysis for the time-to-warfarin discontinuation for Device patients who received a device. Time to event is calculated from the date of randomization. The majority of patients discontinued warfarin at their 45-day visit.

Figure 12-11. Time to Warfarin Discontinuation - Successfully Implanted Patients Only

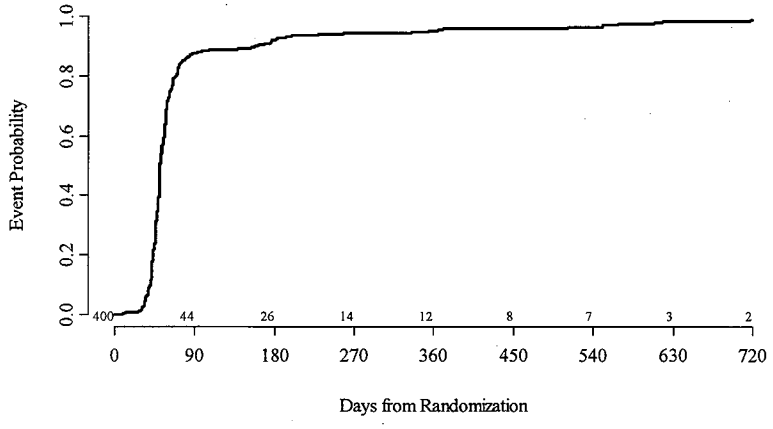

Table 12-52. Kaplan-Meier Estimates: Time to Warfarin Discontinuation

	N Events	N Cumulative Events	Event Rate (%)
7-days	0	0	0.0
45-days	91	91	23.8
6-months	253	344	91.9
1-year	11	355	95.7
2-year	7	362	99.0

Over 90% of implanted patients discontinued warfarin therapy by six months. As can be seen in **Figure 12-11**, many patients discontinued warfarin between approximately 30 and 60 days post-randomization. This degree of variation in timing is expected as the 45-day visit window was as 30 to 60 days post-implant. The Kaplan-Meier estimated rate of discontinuation by 2-years post-randomization was 99%.

12.3.6 Adverse Events

Additional summaries of all adverse events reported in the trial are contained in the following section.

Line listings and related individual narratives of the serious adverse events by patient experienced in the PROTECT AF study are provided in **Attachment 5.** Line listings of the non-serious adverse events by patient experiencd in the PROTECT AF study are provided in **Attachment 6.**

Adverse event results are provided by randomized treatment group. Classification into event types is based on CEC adjudication unless otherwise noted. Multiple reports of an event that were determined by the CEC to be symptoms/follow-up to an initial event are not included in the total number of events. The percent of patients experiencing each event type is based on the number of randomized patients in each treatment group. The percent of events is calculated as the percent of events of that type over of the total number of events.

Serious adverse events are summarized in **Table 12-53** and **Table 12-54**. **Table 12-53** presents events adjudicated by the Clinical Event Committee as serious. **Table 12-54** presents events that were not adjudicated by the Clinical Event Committee as serious, but were reported by the site to have resulted in death, were life-threatening, prolonged hospitalization, resulted in significant disability, or were unanticipated as defined in the protocol. In **Table 12-54**, events are classified by the event category originally provided by the site.

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Table 12-53. Summary of Serious Adverse Events

	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Pericardial Effusion-Serious	24*	24.0	24	5.3	0	0	0	0
Gastrointestinal Bleeding	12	12.0	12	2.6	7	26.9	6	2.5
Death	10	10.0	10	2.2	7	26.9	7	2.9
Stroke - Ischemic	12	12.0	12	2.6	4	15.4	4	1.7
Other Study Related	13	13.0	13	2.9	1	3.8	1	0.4
Stroke - Hemorrhagic	1	1.0	1	0.2	4	15.4	4	1.7
Bruising - Hematoma	3	3.0	3	0.7	0	0	0	0
Device Embolization	3	3.0	3	0.7	0	0	0	0
Pseudoaneurysm	3	3.0	3	0.7	0	0	0	0
Adjudicated As Non-Event	1	1.0	1	0.2	1	3.8	1	0.4
Rectal Bleeding	1	1.0	1	0.2	1	3.8	1	0.4
Systemic Embolism	2	2.0	2	0.4	0	0	0	0
Arrhythmias	2	2.0	2	0.4	0	0	0	0
Anemia Requiring Transfusion	2	2.0	2	0.4	0	0	0	0
Major Bleed Requiring Transfusion	1	1.0	1	0.2	1	3.8	1	0.4
Infection	2	2.0	2	0.4	0	0	0	0
Bleeding from Varicose Veins	1	1.0	1	0.2	0	0	0	0
Thrombosis	1	1.0	1	0.2	0	0	0	0
Device Thrombus	1	1.0	1	0.2	0	0	0	0
Pleural Effusion	1	1.0	1	0.2	0	0	0	0
Pulmonary Edema	1	1.0	1	0.2	0	0	0	0
AV Fistula	1	1.0	1	0.2	0	0	0	0
Cranial Bleed	1	1.0	1	0.2	0	0	0	0
Transient Ischemic Attack TIA	1	1.0	1	0.2	0	0	0	0
Totals:	**100**	**100.0**	**82**	**18.1**	**26**	**100.0**	**22**	**9.2**

* Patient [redacted] had a serious pericardial effusion. This event was not adjudicated by CEC as a primary safety event; therefore, it is not listed in **Table 12-26**.

Table 12-54. Summary of Serious Adverse Events as Reported by Site

	CEC Adjudicated Non-Events							
	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Other Non-Study Related	125	58.7	82	18.1	55	57.9	33	13.9
Chest Pain/Discomfort	21	9.9	16	3.5	8	8.4	7	2.9
Arrhythmias	9	4.2	9	2.0	8	8.4	6	2.5
Other Study Related	7	3.3	6	1.3	2	2.1	2	0.8
Pleural Effusion	6	2.8	5	1.1	2	2.1	2	0.8
Pulmonary Embolism	5	2.3	4	0.9	1	1.1	1	0.4
Myocardial Infarction	4	1.9	4	0.9	2	2.1	2	0.8
Infection	4	1.9	4	0.9	2	2.1	2	0.8
Dyspnea	4	1.9	4	0.9	1	1.1	1	0.4
INR>4.0	1	0.5	1	0.2	4	4.2	4	1.7
Gastrointestinal Bleeding	3	1.4	3	0.7	1	1.1	1	0.4
Ventricular Tachyarrhythmia	3	1.4	3	0.7	1	1.1	1	0.4
Bruising - Hematoma	2	0.9	2	0.4	1	1.1	1	0.4
Pulmonary Edema	2	0.9	2	0.4	1	1.1	1	0.4
Pneumonia	2	0.9	2	0.4	1	1.1	1	0.4
Complete Heart Block	2	0.9	2	0.4	1	1.1	1	0.4
Warfarin Therapy Stopped	1	0.5	1	0.2	2	2.1	2	0.8
Epistaxis	2	0.9	2	0.4	0	0	0	0
Hematuria	1	0.5	1	0.2	1	1.1	1	0.4
Pericardial Effusion	2	0.9	2	0.4	0	0	0	0
Cranial Bleed	2	0.9	2	0.4	0	0	0	0
Prolonged Bleeding from a Laceration	1	0.5	1	0.2	0	0	0	0
Coronary Artery Thrombosis	0	0	0	0	1	1.1	1	0.4
Stroke - Ischemic	1	0.5	1	0.2	0	0	0	0
Anemia Requiring Transfusion	1	0.5	1	0.2	0	0	0	0
Ventricular Fibrillation	1	0.5	1	0.2	0	0	0	0
Thromboembolism	1	0.5	1	0.2	0	0	0	0
Totals:	**213**	**100.0**	**114**	**25.1**	**95**	**100.0**	**51**	**21.4**

Device or Procedure Related Events are summarized in **Table 12-55**. Events are divided into serious and non-serious events as determined by the Clinical Event Committee. For this table, classification into event types is based on CEC adjudication.

Table 12-55. Summary of Device or Procedure Related Events

CEC Adjudicated Serious Events				
[redacted]				
Pericardial Effusion-Serious	24	36.9	24	5.3
Other Study Related	13	20.0	13	2.9
Stroke - Ischemic	6	9.2	6	1.3
Bruising - Hematoma	3	4.6	3	0.7
Device Embolization	3	4.6	3	0.7
Pseudoaneurysm	3	4.6	3	0.7
Arrhythmias	2	3.1	2	0.4
Anemia Requiring Transfusion	2	3.1	2	0.4
Infection	2	3.1	2	0.4
Thrombosis	1	1.5	1	0.2
Device Thrombus	1	1.5	1	0.2
Pleural Effusion	1	1.5	1	0.2
Pulmonary Edema	1	1.5	1	0.2
AV Fistula	1	1.5	1	0.2
Transient Ischemic Attack TIA	1	1.5	1	0.2
Major Bleed Requiring Transfusion	1	1.5	1	0.2
Totals:	**65**	**100.0**	**56**	**12.3**
CEC Adjudicated Non-Serious				
[redacted]				
Other Study Related	11	30.6	11	2.4
Device Thrombus	8	22.2	8	1.8
Pericardial Effusion	7	19.4	7	1.5
Adjudicated As Non-Event	1	2.8	1	0.2
Bruising - Hematoma	1	2.8	1	0.2
Oral Bleeding	1	2.8	1	0.2
Inability to Move or Retrieve Device	1	2.8	1	0.2
Pleural Effusion	1	2.8	1	0.2
AV Fistula	1	2.8	1	0.2
Vasovagal Reactions	1	2.8	1	0.2
Anemia Requiring Transfusion	1	2.8	1	0.2
Air Embolism	1	2.8	1	0.2
Allergic Reaction to Contrast Media	1	2.8	1	0.2
Totals:	**36**	**100.0**	**32**	**7.0**

Table 12-56 summarizes the number of events and number of patients experiencing adverse events by type of event.

Table 12-56. Summary of Adverse Events

	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Adjudicated As Non-Event	790	83.2	260	57.3	354	90.5	127	53.4
Other Study Related	26	2.7	26	5.7	2	0.5	2	0.8
Pericardial Effusion-Serious	24	2.5	24	5.3	0	0	0	0
Gastrointestinal Bleeding	15	1.6	15	3.3	7	1.8	6	2.5
Stroke - Ischemic	13	1.4	13	2.9	4	1.0	4	1.7
Death	10	1.1	10	2.2	7	1.8	7	2.9
Epistaxis	10	1.1	7	1.5	2	0.5	2	0.8
Rectal Bleeding	4	0.4	4	0.9	5	1.3	5	2.1
Device Thrombus	9	0.9	9	2.0	0	0	0	0
Bruising - Hematoma	6	0.6	6	1.3	2	0.5	2	0.8
Pericardial Effusion	7	0.7	7	1.5	0	0	0	0
Stroke - Hemorrhagic	1	0.1	1	0.2	4	1.0	4	1.7
Hematuria	2	0.2	2	0.4	2	0.5	2	0.8
Oral Bleeding	2	0.2	2	0.4	1	0.3	1	0.4
Device Embolization	3	0.3	3	0.7	0	0	0	0
Pseudoaneurysm	3	0.3	3	0.7	0	0	0	0
Anemia Requiring Transfusion	3	0.3	3	0.7	0	0	0	0
Infection	3	0.3	3	0.7	0	0	0	0
Systemic Embolism	2	0.2	2	0.4	0	0	0	0
Pleural Effusion	2	0.2	2	0.4	0	0	0	0
AV Fistula	2	0.2	2	0.4	0	0	0	0
Transient Ischemic Attack TIA	2	0.2	2	0.4	0	0	0	0
Arrhythmias	2	0.2	2	0.4	0	0	0	0
Major Bleed Requiring Transfusion	1	0.1	1	0.2	1	0.3	1	0.4
Bleeding from Varicose Veins	1	0.1	1	0.2	0	0	0	0
Thrombosis	1	0.1	1	0.2	0	0	0	0
Inability to Move or Retrieve Device	1	0.1	1	0.2	0	0	0	0
Pulmonary Edema	1	0.1	1	0.2	0	0	0	0
Vasovagal Reactions	1	0.1	1	0.2	0	0	0	0
Cranial Bleed	1	0.1	1	0.2	0	0	0	0
Air Embolism	1	0.1	1	0.2	0	0	0	0
Allergic Reaction to Contrast Media	1	0.1	1	0.2	0	0	0	0
Total:	**950**	**100.0**	**304**	**66.7**	**391**	**100.0**	**134**	**56.3**

The Core Lab played an important role in the identification and/or confirmation of thrombus during the study and provided training and consultation to physicians as requested.

The majority of the reported events were determined by the CEC to be "non-events". Non-event was defined as any event that the CEC determined was not study related, or of minor or not lasting clinical significance or non-specific symptom.

These events are classified by event category originally provided by the site in **Table 12-57**.

Table 12-57. Summary of Non-Events

	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Other Non-Study Related	428	54.2	185	40.7	198	55.9	87	36.6
Other Study Related	83	10.5	43	9.5	10	2.8	10	4.2
Bruising - Hematoma	52	6.6	47	10.4	18	5.1	16	6.7
Arrhythmias	45	5.7	36	7.9	16	4.5	13	5.5
Chest Pain/Discomfort	40	5.1	32	7.0	15	4.2	13	5.5
Warfarin Therapy Stopped	7	0.9	5	1.1	37	10.5	32	13.4
Epistaxis	16	2.0	13	2.9	7	2.0	7	2.9
INR<2.0	11	1.4	8	1.8	9	2.5	5	2.1
Pleural Effusion	15	1.9	13	2.9	4	1.1	4	1.7
Infection	10	1.3	8	1.8	5	1.4	5	2.1
Dyspnea	11	1.4	11	2.4	2	0.6	2	0.8
Hematuria	6	0.8	6	1.3	5	1.4	5	2.1
INR>4.0	5	0.6	4	0.9	6	1.7	6	2.5
Ventricular Tachyarrhythmia	7	0.9	7	1.5	2	0.6	2	0.8
Pericardial Effusion	8	1.0	8	1.8	0	0	0	0
Prolonged Bleeding from a Laceration	5	0.6	5	1.1	2	0.6	2	0.8
Rectal Bleeding	4	0.5	4	0.9	3	0.8	3	1.3
Pulmonary Embolism	5	0.6	4	0.9	1	0.3	1	0.4
Myocardial Infarction	4	0.5	4	0.9	2	0.6	2	0.8
Complete Heart Block	5	0.6	5	1.1	1	0.3	1	0.4
Gastrointestinal Bleeding	3	0.4	3	0.7	1	0.3	1	0.4
Pneumonia	2	0.3	2	0.4	2	0.6	2	0.8
Oral Bleeding	2	0.3	2	0.4	1	0.3	1	0.4
Pulmonary Edema	2	0.3	2	0.4	1	0.3	1	0.4
Coronary Artery Thrombosis	1	0.1	1	0.2	2	0.6	2	0.8
Transient Ischemic Attack TIA	1	0.1	1	0.2	2	0.6	2	0.8
Red Eye	1	0.1	1	0.2	1	0.3	1	0.4
Stroke - Ischemic	1	0.1	1	0.2	1	0.3	1	0.4
Cranial Bleed	2	0.3	2	0.4	0	0	0	0
Anemia Requiring Transfusion	2	0.3	2	0.4	0	0	0	0
Ventricular Fibrillation	2	0.3	2	0.4	0	0	0	0
Thromboembolism	2	0.3	2	0.4	0	0	0	0
Device Thrombus	1	0.1	1	0.2	0	0	0	0
Vasovagal Reactions	1	0.1	1	0.2	0	0	0	0
Totals:	**790**	**100.0**	**260**	**57.3**	**354**	**100.0**	**127**	**53.4**

12.3.7 Subgroup and Other Analyses

12.3.7.1 Events by $CHADS_2$ Score

As $CHADS_2$ is an established predictor of risk of stroke. **Table 12-58**, **Table 12-59** and **Table 12-60** present rates of events by randomized group stratified by $CHADS_2$ score. It is important to note that while the pre-specified primary analysis was stratified by $CHADS_2$ the trial was not designed with adequate power to generate conclusions regarding subgroups defined by $CHADS_2$ scores and there were no specific hypotheses, neither for non-inferiority nor for superiority, defined for $CHADS_2$ score groups.

Table 12-58. Primary Efficacy Endpoints By $CHADS_2$ Score

	N Patients	N Events	Total Patient-Years	Event Rate	N Patients	N Events	Total Patient-Years	Event Rate
1	155	2	130.0	1.54	63	2	65.3	3.06
2	157	4	150.9	2.65	87	4	83.2	4.81
3	87	10	74.3	13.46	50	2	40.3	4.96
4	32	0	34.2	0.00	24	3	19.5	15.37
5+6	23	2	20.0	10.02	14	2	15.4	13.03

The primary efficacy rate is generally lower in the Device group than in the Control group across $CHADS_2$ strata. The exception is for patients with a $CHADS_2$ score of 3. For these patients, the 95% confidence interval for the efficacy rate is (6.5-24.8) and (0.6-17.9) for the Device and Control groups respectively. This yields a rate ratio, Device to Control, of 2.71 (95% CI = 0.6 - 25.5) and p=0.30 from an exact rate ratio test. There is no statistical evidence that the Device group event rate differs from than that of the Control group for patients with a $CHADS_2$ score of 3.

The rate of primary efficacy events from the SPAF studies database among patients with a $CHADS_2$ score of 3 was 9.01 events per 100 patient-years. In the PROTECT AF study, the corresponding observed rate among Control group patients was approximately half this (4.96 events per 100 patient-years).

The largest portion of the primary efficacy events (70%, 7/10) among the 87 Device patients with a $CHADS_2$ score of 3 occurred prior to warfarin discontinuation; the three remaining events in this group occurred following warfarin discontinuation.

Table 12-59. Strokes By $CHADS_2$ Score

	N Patients	N Events	Total Patient-Years	Event Rate	N Patients	N Events	Total Patient-Years	Event Rate
1	155	2	130.0	1.54	63	1	65.3	1.53
2	157	3	150.9	1.99	87	3	83.2	3.61
3	87	6	74.3	8.07	50	1	40.3	2.48
4	32	0	34.2	0.00	24	2	19.5	10.25
5+6	23	2	20.0	10.02	14	1	15.4	6.51

The small number of strokes and small number of patient years within each $CHADS_2$ score make formal statistical comparisons difficult. The rates of stroke in the Device group are approximately equal to or lower than that for the Control group for $CHADS_2$ scores of 1, 2, and 4. Rates for the Device group are higher for patients with $CHADS_2$ scores of 3 and 5 or 6. As with the primary efficacy endpoint, the confidence intervals for the rates are very wide. For the Device group, the 95% confidence interval for the stroke rate is (3.0-17.6), and (1.2-36.1) for patients with $CHADS_2$ scores of 3 and 5 or 6 respectively. For the Control group, the corresponding 95% confidence intervals are (0.1-13.8) and (0.2-36.2).

Table 12-60. Deaths By $CHADS_2$ Score

	N Patients	N Events	Total Patient-Years	Event Rate	N Patients	N Events	Total Patient-Years	Event Rate
1	155	2	130.3	1.53	63	1	65.3	1.53
2	157	6	151.4	3.96	87	4	83.5	4.79
3	87	4	80.0	5.00	50	1	40.3	2.48
4	32	1	34.2	2.92	24	3	20.6	14.58
5+6	23	1	20.7	4.84	14	2	15.4	13.03

Table 12-60 shows that mortality rates were generally lower in the Device group than in the Control group, the exception being among patients with a $CHADS_2$ score of 3. However, there is substantial uncertainty in these estimates due to the small number of events and patient-years for this subgroup of patients. Among patients with a $CHADS_2$ score equal to 3, the 95% confidence bounds for the mortality rate for the Device and Control groups were (1.4-12.8) and (0.6-13.8), respectively.

Results from proportional hazards regression models for mortality are displayed in the **Table 12-61**.

Table 12-61. Proportional Hazards Models For Mortality

Unadjusted	0.71	0.32, 1.56
Stratified By $CHADS_2$	0.74	0.34, 1.64

In both unadjusted and stratified models, the Device group had lower risk than the Control group (i.e., the hazards ratios were less than 1). This was a 29% and 26% relative reduction in hazards respectively. The upper bounds of the 95% confidence intervals are both less than 2, further supporting the finding of non-inferiority.

12.3.7.2 Events by Investigative Center

The number of enrolled patients and number of patients experiencing a primary efficacy or safety event by site are given in **Table 12-62** and **Table 12-63**. Rates on a site-level were not calculated as the number of patient-years and events at each site is too small to produce reliable estimates. Both tables are sorted in descending order by the total number of enrolled patients.

Table 12-62. Primary Efficacy Events By Sites

	N Patients	N Events	N Patients	N Events
	44	2	22	1
	33	2	17	3
	34	0	16	0
	26	0	13	0
	24	0	12	1
	23	4	12	1
	23	1	11	1
	20	1	9	1
	19	2	10	1
	19	0	9	1
	18	2	9	0
	15	0	8	1
	13	1	7	0
	13	0	7	0
	10	1	6	0
	9	0	5	0
	8	1	4	0
	7	0	4	0
	6	0	4	0
	6	0	4	0
	6	1	2	0
	5	0	3	0
	5	0	3	0
	5	0	3	0
	5	0	3	0
	4	0	4	0
	5	0	3	0
	4	0	4	0
	4	0	2	1
	4	0	2	0
	3	0	2	0
	4	0	1	0
	3	0	2	1
	3	0	1	0
	2	0	2	0
	3	0	1	0
	1	0	2	0
	2	0	1	0
	1	0	2	0
	1	0	1	0
	2	0	0	0
	1	0	1	0
	2	0	0	0
	2	0	0	0
	2	0	0	0
	2	0	0	0
	1	0	1	0
	1	0	1	0
	1	0	0	0
	0	0	1	0
	0	0	1	0

Table 12-63. Primary Safety Events By Sites

	N Patients	N Events	N Patients	N Events
	44	3	22	2
	33	3	17	1
	34	1	16	0
	26	4	13	0
	24	2	12	0
	23	2	12	0
	23	2	11	1
	20	3	9	0
	19	1	10	0
	19	0	9	0
	18	2	9	0
	15	2	8	1
	13	4	7	0
	13	1	7	1
	10	1	6	0
	9	0	5	0
	8	2	4	1
	7	0	4	0
	6	1	4	0
	6	0	4	0
	6	3	2	0
	5	1	3	0
	5	0	3	0
	5	0	3	0
	5	0	3	0
	4	1	4	0
	5	0	3	0
	4	0	4	1
	4	1	2	0
	4	0	2	0
	3	0	2	0
	4	1	1	0
	3	0	2	1
	3	0	1	0
	2	0	2	0
	3	1	1	0
	1	1	2	0
	2	0	1	0
	1	0	2	0
	1	1	1	0
	2	1	0	0
	1	0	1	0
	2	0	0	0
	2	0	0	0
	2	0	0	0
	2	0	0	0
	1	0	1	0
	1	0	1	0
	1	0	0	0
	0	0	1	0
	0	0	1	0

To statistically assess the consistency of the treatment effect and the appropriateness of pooling data across sites, sites were grouped as US or OUS sites as shown in **Table 12-64** for primary efficacy and in **Table 12-65** for primary safety. The rate of events per 100 patient-years was calculated for site group and treatment group combination.

Table 12-64. Primary Efficacy Events by US/OUS Sites

[redacted]				
US Sites	12/334.5	3.6 (1.9, 6.3)	11/182.1	6.0 (3.0, 10.8)
OUS Sites	6/74.8	8.1 (3.0, 17.6)	2/41.5	4.8 (0.6, 17.4)

Table 12-65. Primary Safety Events by US/OUS Sites

[redacted]				
US Sites	41/312.2	13.1 (9.4, 17.8)	8/179.2	4.5 (1.9, 8.8)
OUS Sites	4/74.2	5.4 (1.5, 13.8)	1/41.2	2.4 (0.1, 13.5)

Confidence bounds are based on exact intervals for Poisson rates. The confidence intervals for the OUS sites are extremely wide due to the small number of total patient-years of follow-up. Within each treatment group, there is substantial overlap in the confidence bounds for the rates between the site groupings.

Additional analyses were performed to understand the potential for site variability to impact the primary analysis as shown in **Table 12-66** for the primary efficacy endpoint and in **Table 12-67** for the primary safety endpoint. A series of regression models were fit that included adjustment for clinical site. Models without adjustment are provided as a reference to understand the effect of the adjustment.

Table 12-66. Primary Efficacy Endpoint – Consistency Across US/OUS Sites

Poisson regression, no adjustment	-0.2791	0.3640
Poisson regression, with US/OUS fixed effect	-0.2775	0.3640
Poisson regression, with US/OUS clusters	-0.2826	0.3667

Table 12-67. Primary Safety Endpoint – Consistency Across US/OUS Sites

Poisson regression, no adjustment	1.0479	0.3651
Poisson regression, with US/OUS fixed effect	1.0511	0.3652
Poisson regression, with US/OUS clusters	Did not converge	NA

For each model, a 0/1 indicator variable (0=Control group, 1 = Device group) was used as a covariate to produce a treatment group regression coefficient and associated standard error. Under this parameterization, regression coefficients less than zero indicate a decreased risk of events for the Device group.

The differences between these models are small. In total, these results support the conclusion that the potential for variability between sites does not impact the primary efficacy or safety analyses and the finding of non-inferiority.

12.3.7.3 [redacted]

The Statistical Analysis Plan specified that 90% intervals would be used to compare rates of the treatment groups by device types.

Table 12-68 provides an accounting of the 400 devices implanted in the PROTECT AF study for the randomized cohort. That total included 194 Long devices and 206 Short devices. The usage across device sizes in comparable between the long and short types.

A "Short" version of the WATCHMAN Device was introduced in October 2006 to minimize length requirements necessary to implant a device. The "Short" WATCHMAN was a device whose only difference is a decreased length of 20% for each of the existing five "Long" device diameter sizes. The Short device was used with the existing Delivery Catheter and Access System and used the same principles of implant sizing relative to the maximum size of the measured LAA ostium.

Table 12-68. Final Device Size Implanted (Long vs. Short)

[redacted]		
21 mm	60/194 (30.9)	40/206 (19.4)
24 mm	62/194 (32.0)	83/206 (40.3)
27 mm	51/194 (26.3)	61/206 (29.6)
30 mm	12/194 (6.2)	17/206 (8.3)
33 mm	9/194 (4.6)	5/206 (2.4)
Totals	400	

As the device was not successfully implanted in 40 of the patients in the Device group for whom an implant was attempted, an analysis was performed based on whether or not a patient was exposed to the Short device during the procedure as shown in **Table 12-69** and **Table 12-70**. All confidence intervals above are exact Poisson 90% intervals. For each analysis the confidence bounds for the event rates overlap considerably.

Table 12-69. Primary Efficacy by Device Type Used

[redacted]				
Long Only	214	13	275.5	4.7 (2.8, 7.5)
Short Used	226	4	130.2	3.1 (1.0, 7.0)

Table 12-70. Primary Safety by Device Type Used

[redacted]				
Long Only	214	27	258.6	10.4 (7.4, 14.4)
Short Used	226	18	124.4	14.5 (9.4, 21.5)

As the Short device was introduced mid-trial, there were a lower total number of patient-years for this version of the device; this inflated the primary safety event rate as compared to the Long device in calculations based on patient-years. When the rate of primary safety events is calculated on a per-patient basis, as opposed to a patient-years basis, patients in whom only the Long device was used had an incidence of 12.6% (27 events /214 patients) and patients in whom a Short device was used had an incidence of 8.0% (18 events / 226 patients). This calculation may be considered more appropriate considering the acute nature of the majority of the primary safety events for the Device group.

Additional analyses were performed to understand the potential for the versions of the device to impact the primary analysis. A series of regression models were fit to compare each version of the device with the Control group as shown in **Table 12-71** for the primary efficacy endpoint and in **Table 12-72** for the primary safety endpoint. Device type was parameterized based on type of devices used. Regression coefficients less than zero indicate a decreased risk for the Device group compared to the Control group, while coefficients greater than zero indicate an increased risk for the Device group as compared to the Control group.

Table 12-71. Primary Efficacy Consistency Across Devices Used (Long or Short vs. Control)

Poisson Regression Model, Only Long Device vs. Control	-0.2088	0.3922
Poisson Regression Model, Any Short Device vs. Control	-0.6381	0.5718

Table 12-72. Primary Safety Consistency Across Devices Used (Long or Short vs. Control)

Poisson Regression Model, Only Long Device vs. Control	0.9389	0.3849
Poisson Regression Model, Any Short Device vs. Control	1.2653	0.4082

All results are generally consistent with the primary analysis; there is a lower risk of efficacy events for the Device group (all coefficients for efficacy analyses are less than zero) and an increased risk of safety events (all coefficients for safety analyses are greater than zero). Results by device type were similar to each other considering the standard error of the associated coefficients.

To explore possible variation in the timing of primary efficacy and safety events by device type, Kaplan-Meier figures are presented for both the primary efficacy and safety endpoints stratified by device type as shown in **Figure 12-12** and **Figure 12-13**. This was done for patient groups defined by device type used.

Figure 12-12. Kaplan-Meier Curve: Primary Efficacy by Device Type Used

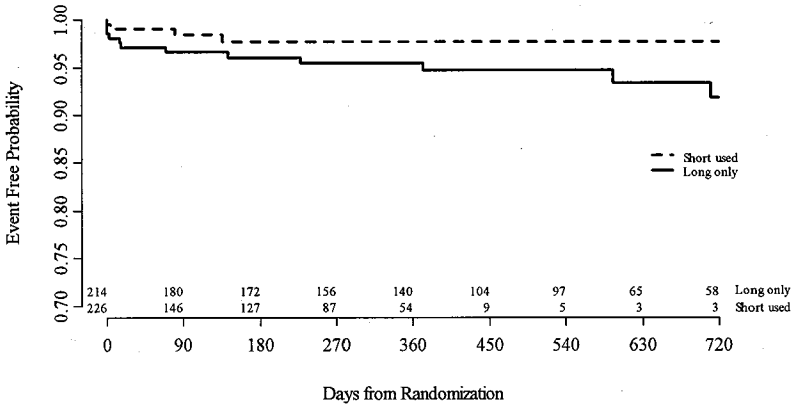
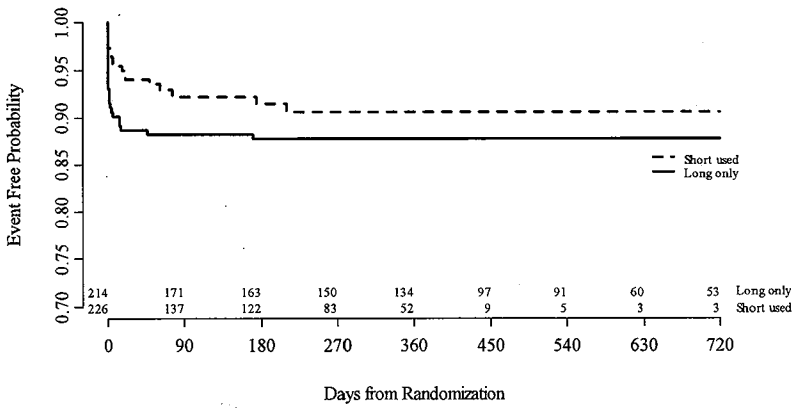


Figure 12-13. Kaplan-Meier Curve: Primary Safety by Device Type Used



As can be seen in the above two figures, the efficacy and safety profile of the Short device is generally similar or better than the Long device.

12.3.7.4 Effects of Preoperative Characteristics

To assess the consistency of the treatment effect by subgroups of patients, proportional hazards regression models were fit to test for an interaction of treatment group and patient subgroup as shown in **Table 12-73** and **Table 12-74**. These analyses were performed for both the primary efficacy and primary safety events on the intent-to-treat cohort.

The number and percent of patients experiencing events in each subgroup is displayed under each randomized group. Results from a test for interactions are given in the far right column; small p-values (e.g., <0.05 or <0.10) would indicate variation in the treatment difference by subgroup. Additional proportional hazards models were fit to compare the treatment groups within patient subgroups; these results are displayed as the Subgroup Hazard Ratio. NA (not applicable) is displayed in cases where statistical analysis could not be performed due to a lack of events.

Subgroups in the **Table 12-73** and **Table 12-74** below were either defined based on covariates pre-specified in the Statistical Analysis Plan or were suggested for exploration by the DSMB. The later include "warfarin experience" and "enrollment quartile".

"Warfarin experience" was defined based on the first date of warfarin use prior to randomization that was listed on a patient's medication form. Some patients had no date available and so the total number of patients for these subgroups does no add up to the total number of randomized patients.

Enrollment quartiles are approximately equal sized groups based on the date of randomization; this covariate separates patients that were enrolled earliest in the trial from those that were enrolled later.

The p-value from a test of an interaction between randomized treatment assignment and racial group for the primary efficacy endpoint was 0.97. This indicates there was no evidence that the treatment effect varied by racial group. The p-value from a test of interaction randomized treatment assignment and racial group for the primary safety endpoint was 0.99. This indicates there was no evidence that the treatment effect varied by racial group.

There was no evidence that the treatment effect varied by subgroups of patients; all interaction p-values were greater than 0.10. This was true for both the primary efficacy and safety endpoints.

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Table 12-73. Primary Efficacy Events by Patient Subgroups

	Events/Total (%)	Events/Total (%)		
Gender				
Females	11/134 (8.2%)	5/71 (7.0%)	1.2 (0.4, 3.6)	0.18
Male	7/320 (2.2%)	8/167 (4.8%)	0.5 (0.2, 1.3)	
Age				
≥ 75	8/185 (4.3%)	9/113 (8.0%)	0.6 (0.2, 1.5)	0.34
< 75	10/269 (3.7%)	4/125 (3.2%)	1.2 (0.4, 3.9)	
$CHADS_2$ score				
= 1	2/155 (1.3%)	2/63 (3.2%)	0.5 (0.1, 3.6)	0.61
≥ 2	16/299 (5.4%)	11/175 (6.3%)	0.8 (0.4, 1.8)	
Warfarin experience				
< 1 year	13/248 (5.2%)	7/140 (5.0%)	1.0 (0.4, 2.6)	0.39
≥ 1 year	5/197 (2.5%)	5/96 (5.2%)	0.5 (0.2, 1.8)	
Enrollment quartile				
I	10/113 (8.8%)	5/60 (8.3%)	1.2 (0.4, 3.4)	
II	4/119 (3.4%)	3/56 (5.4%)	0.5 (0.1, 2.5)	0.65
III	3/112 (2.7%)	3/59 (5.1%)	0.5 (0.1, 2.5)	
IV	1/110 (0.9%)	2/63 (3.2%)	0.2 (0.0, 2.3)	
AF pattern				
Paroxysmal	8/198 (4.0%)	4/96 (4.2%)	1.0 (0.3, 3.3)	
Persistent	1/93 (1.1%)	5/49 (10.2%)	0.1 (0.0, 0.7)	0.16
Permanent	9/157 (5.7%)	4/91 (4.4%)	1.5 (0.5, 4.8)	
Unknown	0/6 (0.0%)	0/2 (0.0%)	NA	
AF initial onset				
< 1 year	4/69 (5.8%)	2/47 (4.3%)	1.4 (0.3, 7.6)	0.69
≥ 1 year	12/351 (3.4%)	9/179 (5.0%)	0.7 (0.3, 1.6)	
No estimate	2/34 (5.9%)	2/12 (16.7%)	0.5 (0.1, 3.4)	
No. of LAA lobes*				
One	11/218 (5.0%)	6/122 (4.9%)	1.1 (0.4, 2.9)	0.29
More than one	7/233 (3.0%)	7/114 (6.1%)	0.5 (0.2, 1.4)	
LAA length*				
Above median	5/226 (2.2%)	6/118 (5.1%)	0.5 (0.1, 1.5)	0.34
Below median	12/222 (5.4%)	7/115 (6.1%)	0.9 (0.4, 2.4)	
LAA ostium diameter*				
Above median	7/242 (2.9%)	9/123 (7.3%)	0.4 (0.2, 1.1)	0.13
Below median	10/206 (4.9%)	4/110 (3.6%)	1.3 (0.4, 4.3)	
LVEF				
Above median	10/231 (4.3%)	5/121 (4.1%)	1.0 (0.3, 2.9)	0.44
Below median	8/220 (3.6%)	8/112 (7.1%)	0.6 (0.2, 1.5)	

* Site reported

Table 12-74. Primary Safety Events by Patient Subgroups

	Events/Total (%)	Events/Total (%)		
Gender				
Females	21/134 (15.7%)	3/71 (4.2%)	4.0 (1.2, 13.3)	0.42
Male	24/320 (7.5%)	6/167 (3.6%)	2.1 (0.9, 5.2)	
Age				
≥ 75	22/185 (11.9%)	7/113 (6.2%)	2.0 (0.9, 4.8)	0.25
< 75	23/269 (8.6%)	2/125 (1.6%)	5.4 (1.3, 22.9)	
$CHADS_2$ score				
= 1	14/155 (9.0%)	0/63 (0.0%)	NA	0.99
≥ 2	31/299 (10.4%)	9/175 (5.1%)	2.0 (1.0, 4.3)	
Warfarin experience				
< 1 year	26/248 (10.5%)	5/140 (3.6%)	3.0 (1.2, 7.8)	0.64
≥ 1 year	17/197 (8.6%)	4/96 (4.2%)	2.2 (0.7, 6.4)	
Enrollment quartile				
I	20/113 (17.7%)	4/60 (6.7%)	2.9 (1.0, 8.5)	
II	9/119 (7.6%)	3/56 (5.4%)	1.4 (0.4, 5.3)	0.83
III	6/112 (5.4%)	2/59 (3.4%)	1.6 (0.3, 8.0)	
IV	10/110 (9.1%)	0/63 (0.0%)	NA	
AF pattern				
Paroxysmal	24/198 (12.1%)	4/96 (4.2%)	3.0 (1.0, 8.7)	
Persistent	11/93 (11.8%)	1/49 (2.0%)	5.8 (0.7, 44.9)	0.70
Permanent	10/157 (6.4%)	4/91 (4.4%)	1.6 (0.5, 5.0)	
Unknown	0/6 (0.0%)	0/2 (0.0%)	NA	
AF initial onset				
< 1 year	9/69 (13.0%)	0/47 (0.0%)	NA	0.92
≥ 1 year	33/351 (9.4%)	8/179 (4.5%)	2.1 (1.0, 4.6)	
No estimate	3/34 (8.8%)	1/12 (8.3%)	1.2 (0.1, 12.0)	
No. of LAA lobes*				
One	19/218 (8.7%)	6/122 (4.9%)	1.8 (0.7, 4.6)	0.25
More than one	26/233 (11.2%)	3/114 (2.6%)	4.4 (1.3, 14.5)	
LAA length*				
Above median	18/226 (8.0%)	5/118 (4.2%)	1.9 (0.7, 5.2)	0.37
Below median	27/222 (12.2%)	4/115 (3.5%)	3.7 (1.3, 10.6)	
LAA ostium diameter*				
Above median	27/242 (11.2%)	5/123 (4.1%)	2.9 (1.1, 7.5)	0.83
Below median	18/206 (8.7%)	4/110 (3.6%)	2.4 (0.8, 7.2)	
LVEF				
Above median	23/231 (10.0%)	4/121 (3.3%)	3.0 (1.0, 8.6)	0.79
Below median	22/220 (10.0%)	5/112 (4.5%)	2.4 (0.9, 6.4)	

* Site reported

12.3.7.5 Poolability

Based on the above results, no issues were found with regards to pooling of data. Primary efficacy and safety results are consistent across subgroups.

12.3.7.6 Protocol Deviations

Protocol deviations by group are summarized in **Table 12-75**.

Table 12-75. Protocol Deviations by Randomized Group-

Follow-up Outside Window*	96/83	83/66
Follow-up Testing Not Performed	82/63	85/52
Aspirin Not Administered	51/46	5/5
Baseline Testing Not Done	19/17	29/26
Inclusion/Exclusion	27/23	13/13
Follow-up Visit Missed	16/15	16/15
Non-Compliant Medication Regimen	29/26	1/1
Warfarin Discontinued Outside Protocol Requirements	3/3	22/19
Neurological Assessment Not Completed	14/14	9/8
Non-Compliant Warfarin Regimen	13/12	10/9
INR Non -Compliance / Out of Range	12/10	8/8
Non-Compliant ACT	19/17	0/0
Non-Compliant ASA Regimen	12/11	2/2
Informed Consent	9/9	2/2
Other	38/34	31/28

* "Follow-up Outside Window" is a combination of "Follow-up Outside Window" and "Follow-up Testing Outside Window."

Protocol deviations fall into five major categories related to the following:

- timing or completeness of data collection at study visits (59%, 449/756)
- medication usage (25%, 187/756)
- inclusion/exclusion criteria (5%, 40/756)
- informed consent (1%, 11/756)
- other (9%, 69/756)

The 11 informed consent deviations between both groups were due to the following:

- (6) patients - baseline testing was completed prior to consent signed
- (2) patients - date and/or time not recorded on consent
- (1) patient - wrong version of consent used
- (1) patient - PI signature not obtained on consent
- (1) patient - release of medical record not obtained

The primary efficacy and safety endpoints of the study are based on reported adverse events and the calculation of patient-years used in the calculation of rates is based on the onset date of the occurrence of adverse events. The primary efficacy and safety results therefore are not affected by the timing or completeness of data collection at study visits.

Deviations related to medications are independent of the efficacy and safety of the device. Their affect on the efficacy and safety of the Control group is representative of real-world experience with these medications. Well known difficulties of warfarin therapy include failure to maintain adequate INR levels and difficulty in maintaining patient adherence. More generally, the medications used as part of the protocol of this study are associated with bleeding risks and other complications. In certain cases, this may have required adjustment or discontinuation of therapy in order to provide for the medical needs of individual patients.

Protocol deviations related to inclusion/exclusion criteria or informed consent were related to activities that occurred prior to randomization and device implant and therefore do not affect the efficacy or safety of the device. Following the protocol and standard scientific practice, the primary analysis was performed according to the principle of intent-to-treat and included patients with protocol deviations related to informed consent or inclusion/exclusion criteria.

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Patient listings of the "other" protocol deviations by group (38 Device / 31 Control) are provided in **Table 12-76** and **Table 12-77**.

Table 12-76. Device Group – Listing of "Other" Protocol Deviations

Device		Baseline	Inclusion/Exclusion Deviation: ASA 23 mm.
Device		Procedure/Discharge	Patient was implanted outside the required timeline between randomization and procedure
Device		Baseline	Not a deviation - Historical values not exclusionary therefore proceeded with randomization
Device		Baseline	Not a deviation - Labs not exclusionary (creatinine) therefore proceeded with randomization
Device		Baseline	Testing done outside of window
Device		Baseline	Neurological testing not done
Device		Baseline	Incorrect consent form used.
Device		Baseline	Baseline assessment performed before consent.
Device		Baseline	Baseline assessment performed before consent
Device		Baseline	Used previously collected testing for baseline – therefore baseline testing was prior to consent date
Device		Baseline	Inclusion/Exclusion Deviation: LAA length in less than diameter in 135 degree measurement
Device		Procedure/Discharge	Testing not done per-protocol
Device		6-Month	Noncompliance with medication.
Device		Baseline	Inclusion/Exclusion Deviation - Cardioversion 28 days prior to procedure.
Device		Baseline	Inclusion/Exclusion Deviation : Cardioversion within 30 days of procedure
Device		Inclusion/Exclusion	Patient provided written informed consent prior to enrollment. Document misplaced/lost.
Device		45-Day	Follow-up testing not performed
Device		45-Day	Follow-up testing outside of window
Device		45-Day	Follow-up testing outside of window
Device		45-Day	Follow-up testing not done
Device		Baseline	Baseline testing done outside of window.
Device		Baseline	Used previously collected testing for baseline – therefore baseline testing was prior to consent date
Device		45-Day	Non-compliance with medication (Plavix)
Device		Baseline	Baseline testing was prior to consent date
Device		Baseline	Baseline testing done outside of window
Device		Baseline	Patient was randomized prior to obtaining a TEE
Device		Baseline	Baseline testing was done outside of window
Device		Baseline	Patient was not properly obtained

Device		Baseline	Baseline testing performed outside of window
Device		Baseline	Baseline testing performed outside of window
Device		Inclusion/Exclusion	Not a deviation - TEE was reviewed again by principal investigator and it was determined that there was no thrombus
Device		Baseline	Inclusion/Exclusion Deviation: ASA length
Device		Procedure/Discharge	Baseline testing done outside of window
Device		Baseline	Patient was implanted outside the required timeline between randomization and procedure
Device		Baseline	Inclusion/Exclusion Deviation: hemodynamically stable pericardial effusion
Device		Baseline	Inclusion/Exclusion Deviation: Resting heart rate
Device		Inclusion/Exclusion	Patient using incorrect IC version
Device		Baseline	Patient was implanted outside the required timeline between randomization and procedure

Table 12-77. Control Group – Listing of "Other" Protocol Deviations

Control		Baseline	Electronic TEE images were lost. Report is available.
Control		Baseline	Inclusion/Exclusion Deviation: LAA length is less than the ostium diameter
Control		6-Month	Follow-up testing was not done
Control		Baseline	Baseline testing done after randomization
Control		Baseline	Baseline testing performed outside of window.
Control		Baseline	Baseline testing performed outside of window.
Control		Baseline	Patient signed consent after the baseline assessments were done, but before randomization.
Control		Inclusion/Exclusion	Patient provided written informed consent prior to enrollment. Document misplaced/lost.
Control		Baseline	Baseline neurological assessments performed prior to patient consent.
Control		Baseline	Baseline testing performed after randomization.
Control		Baseline	Baseline testing performed after randomization
Control		Baseline	Unable to confirm deviation - No neurologist had an appointment available to do a baseline consultation.
Control		45-Day	Non-compliance with medications
Control		Baseline	Baseline testing performed prior to subject consent
Control		45-Day	Unable to confirm deviation – Patient withdrew from study
Control		Baseline	Baseline testing done outside of window.

Control		Inclusion/Exclusion	Baseline testing done outside of window.
Control		Inclusion/Exclusion	Testing done outside of window
Control		Baseline	Baseline assessment done prior to patient consent.
Control		Baseline	Baseline testing done outside of window
Control		Baseline	Baseline testing performed prior to subject consent
Control		Baseline	Baseline assessment was conducted prior to signed informed consent
Control		Baseline	Baseline testing performed prior to formal patient consent
Control		Baseline	Baseline testing outside of window
Control		Baseline	Inclusion/Exclusion Deviation: Question of plaque (mobile or not) on aorta.
Control		Other Visit	Proper consent was performed, but no time was recorded on form
Control		Baseline	Inclusion/Exclusion Deviation: ASA length > 14mm
Control		Baseline	Baseline testing done outside of window
Control		Baseline	Baseline testing done outside of window
Control		45-Day	Non-compliance with Warfarin requirement
Control		Baseline	Baseline testing done outside of window

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12.3.7.7 Inclusion/Exclusion Violations

A total of eight Device group patients and three Control group patients had inclusion/exclusion violations. **Table 12-78** lists these patients.

Table 12-78. Patients with Inclusion/Exclusion Violations

Device		Patient has had a prior stroke or TIA within the last 30 days.
Device		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
Device		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
Device		Patient has complex atheroma with mobile plaque in the descending aorta and/or aortic arch.
Device		Patient has an active infection of any kind.
Device		Patient has a planned cardioversion or ablation procedure within 30 days of potential WATCHMAN device implant.
Device		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
Device		Patient has thrombocytopenia (<100,000 platelets/mm^3) or anemia with hemoglobin < 10 g/dl.
Control		Patient has thrombocytopenia (<100,000 platelets/mm^3) or anemia with hemoglobin < 10 g/dl.
		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
Control		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
Control		Patient was found to have existing pericardial effusion during ECHO assessment of > 2 ± 1mm
		Patient has a planned cardioversion or ablation procedure within 30 days of potential WATCHMAN device implant.

As shown in **Table 12-75**, a total of 36 patients in the randomized groups had protocol deviations related to inclusion/exclusion criteria, while 11 patients had inclusion/exclusion violations on their inclusion/exclusion case report form. Data queries are currently outstanding to resolve the number of patients with inclusion/exclusion protocol deviations and inclusion/exclusion criteria violations. At most, a total of 40 patients had either a protocol deviation related to inclusion/exclusion criteria or inclusion/exclusion violations on their inclusion/exclusion case report form.

There were three primary efficacy events and three primary safety events among the Device group patients with possible inclusion/exclusion violations. There was one primary efficacy and one primary safety event among the Control group patients with possible inclusion/exclusion violations.

Removing the patients with possible inclusion/exclusion violations from the analysis would not change the conclusion regarding non-inferiority for the primary efficacy rate. Among the cohort without any possible inclusion/exclusion violations the primary efficacy rate was 3.9 events per 100 patient-years (15 events/385.6 patient-years) among the Device group and 5.8 vents per 100 patient-years (12 events/208.4 patient-years) among the Control group, yielding a relative risk of 0.68. This compares with rates of 4.4 and 5.8 and a relative risk of 0.76 from the intent-to-treat analysis.

12.3.8 Roll-in Cohort Analysis

Data on Roll-in patients is presented in the next section. Corresponding results for randomized Device group patients were presented alongside the roll-in cohort to allow for informal comparisons. Formal statistical analysis was not done as no attempt was made to draw conclusions from the roll-in patient (such a comparison was not pre-specified, was not powered, and would not be a randomized comparison.) Informally, the characteristics and outcomes of roll-in patients are qualitatively similar to randomized Device patients, although as would be expected, events rates were slightly higher in the roll-in population.

Data on roll-in patients compared to the randomized cohort, where applicable, are shown in **Table 12-79** through **Table 12-92**. A summary of the roll-in population follows:

- Most patients were male with a $CHADS_2$ score of 1 or 2.
- The mean age was 72.2 years.
- The device was successfully implanted in 83% (77/93) of patients.
- The rate of primary efficacy events was 2.1 events per 100 patient-yrs (2 events/93.7 patient-yrs).
- The rate of primary safety events was 10.3 events per 100 patient-yrs (9 events/87.2 patient-yrs).
- Both primary efficacy events were ischemic strokes. The most frequent primary safety event was pericardial effusion.
- Follow-up compliance was comparable in both groups.

The first roll-in patient was implanted on February 10, 2006, and the last roll-in patient was implanted on January 16, 2008. Summaries of baseline demographics and risk factors for roll-in patients compared to the randomized cohort are provided in **Table 12-79**, **Table 12-80**, and **Table 12-81**.

Table 12-79. Baseline Demographics

Age (years)	72.2 ± 8.9 93 (37.0, 88.0)	71.7 ± 8.8 454 (46.0, 95.0)
Height (inches)	67.7 ± 4.1 93 (58.0, 77.0)	68.3 ± 4.2 453 (54.0, 82.0)
Weight (lbs)	201.4 ± 44.6 93 (113.0, 333.0)	195.1 ± 44.7 454 (85.0, 376.0)
Gender		
Female	28/93 (30.1)	134/454 (29.5)
Male	65/93 (69.9)	320/454 (70.5)
Race/Ethnicity		
Asian	0/93 (0.0)	4/454 (0.9)
Black/African American	3/93 (3.2)	6/454 (1.3)
Caucasian	87/93 (93.5)	417/454 (91.9)
Hispanic/Latino	3/93 (3.2)	24/454 (5.3)
Hawaiian/Pacific Islander	0/93 (0.0)	1/454 (0.2)
Other	0/93 (0.0)	2/454 (0.4)

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

Table 12-80. Baseline Risk Factors

$CHADS_2$ score		
1	29/93 (31.2)	155/454 (34.1)
2	31/93 (33.3)	157/454 (34.6)
3	20/93 (21.5)	87/454 (19.2)
4	8/93 (8.6)	32/454 (7.0)
5	5/93 (5.4)	19/454 (4.2)
6	0/93 (0.0)	4/454 (0.9)
CHF	17/93 (18.3)	121/454 (26.7)
History of hypertension	83/93 (89.2)	402/454 (88.5)
Age ≥ 75	43/93 (46.2)	185/454 (40.7)
Diabetes	21/93 (22.6)	111/454 (24.4)
Previous TIA/Ischemic Stroke	22/93 (23.7)	79/454 (17.4)
AF Pattern		
Paroxysmal	42/93 (45.2)	198/454 (43.6)
Persistent	16/93 (17.2)	93/454 (20.5)
Permanent	35/93 (37.6)	157/454 (34.6)
Unknown	0/93 (0.0)	6/454 (1.3)
LVEF %	54.6 ± 9.9 90 (30.0, 78.0)	57.4 ± 9.7 451 (30.0, 82.0)

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

Table 12-81. Baseline LAA Characteristics – Site Reported

No. of LAA lobes		
One	43/92 (46.7)	218/451 (48.3)
More than one	49/92 (53.3)	233/451 (51.7)
LAA length, mm	29.2 ± 6.6 92 (3.5, 56.0)	30.5 ± 6.8 448 (2.2, 52.0)
LAA ostium diameter, mm	21.5 ± 4.1 91 (2.1, 35.0)	21.5 ± 3.9 448 (1.6, 37.1)

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

Table 12-82 provides an accounting of follow-up compliance achieved among roll-in patients and randomized Device group patients. Expected visits are based on visit windows defined in the protocol. Visit windows closed prior to May 30, 2008, are considered expected.

Table 12-82. Follow-up Visit Attendance

	Attended/ Expected (%)	Attended/ Expected (%)
45 day	90/91 (98.9)	404/413 (97.8)
6 month	81/81 (100.0)	311/312 (99.7)
9 month	76/76 (100.0)	249/255 (97.6)
12 month	61/61 (100.0)	202/205 (98.5)
18 month	25/25 (100.0)	107/109 (98.2)
24 month	2/4 (50.0)	65/66 (98.5)
30 month	0/0 (NA)	28/28 (100.0)
36 month	0/0 (NA)	3/3 (100.0)

A summary of reasons for completion of an end-of-study form is provided in Table 12-83

Table 12-83. End of Study Summary

No Device Implanted	16/93 (17.2)	38/454 (8.4)
Death	0/93 (0.0)	14/454 (3.1)
Patient Consent Withdrawn	0/93 (0.0)	6/454 (1.3)
Outside Implant Window	0/93 (0.0)	10/454 (2.2)
Lost to Follow-up	0/93 (0.0)	1/454 (0.2)
Other	0/93 (0.0)	7/454 (1.5)

Implant procedure success (successful implant of the device) comparing roll-in patients to the randomized cohort is displayed in **Table 12-84**.

Table 12-84. Implant Procedure Success

77/93 (82.7)	400/440 (90.9)

As expected in a learning situation, implant procedure success was lower in the roll-in cohort.

Table 12-85 displays the final implanted device size for roll-in patients compared to the randomized cohort.

Table 12-85. Final Device Size Implanted

	N/Total (%)	N/Total (%)
21 mm	23/77 (29.9)	100/400 (25.0)
24 mm	34/77 (44.1)	145/400 (36.3)
27 mm	13/77 (16.9)	112/400 (28.0)
30 mm	3/77 (3.9)	29/400 (7.2)
33 mm	4/77 (5.2)	14/400 (3.5)

The incidence of full device recaptures is presented in **Table 12-86**.

Table 12-86. Full Device Recaptures

0	52/93 (55.9)	255/440 (58.0)
1	21/93 (22.6)	107/440 (24.3)
2	11/93 (11.8)	44/440 (10.0)
3	2/93 (2.2)	18/440 (4.1)
4+	7/93 (7.5)	16/440 (3.6)

Warfarin discontinuation rates for patients implanted with the device are displayed in **Table 12-87**.

Table 12-87. Warfarin Discontinuation – Both Device Groups

45 day	65/77 (84.4)	329/377 (87.3)
6 month	73/75 (97.3)	276/299 (92.3)
12 month	54/58 (93.1)	178/196 (90.8)
24 month	2/2 (100.0)	60/64 (93.8)

Primary efficacy and safety events in roll-in patients are summarized in **Table 12-88**. Those roll-in patients and the type of event they experienced are listed in **Table 12-89** and **Table 12-90**.

Table 12-88. Primary Safety and Efficacy Events (Roll-in Phase)

Primary Efficacy	2	93.7	2.1	0.3 – 7.7
Primary Safety	9	87.2	10.3	4.7 - 19.6

Table 12-89. Primary Efficacy Events

	Roll In Patient	16MAR2006	27AUG2007	Stroke - ischemic
	Roll In Patient	07SEP2006	21APR2008	Stroke - ischemic

Table 12-90. Primary Safety Events

	Roll In Patient	29DEC2006	29DEC2006	Bruising - Hematoma
	Roll In Patient	29DEC2006	30DEC2006	Gastrointestinal bleeding
	Roll In Patient	17JAN2007	20JAN2007	Pericardial effusion with cardiac tamponade
	Roll In Patient	12SEP2006	15SEP2006	Pericardial effusion with cardiac tamponade
	Roll In Patient	16JAN2007	22JAN2007	Gastrointestinal bleeding
	Roll In Patient	10FEB2006	10FEB2006	Pericardial effusion with cardiac tamponade
	Roll In Patient	07MAY2007	07MAY2007	Cardiac perforation
	Roll In Patient	08DEC2006	29DEC2006	AV fistula
	Roll In Patient	30MAY2007	30MAY2007	Pericardial effusion with cardiac tamponade
	Roll In Patient	15MAY2007	21MAY2007	Major Bleed Requiring Transfusion

Protocol deviations are summarized in **Table 12-91**.

Table 12-91. Protocol Deviation Summary

Follow-up Outside Window	22/19
Follow-up Testing Not Performed	19/15
Aspirin Not Administered	14/14
Non-Compliant Medication Regimen	8/8
Inclusion/Exclusion	4/4
Baseline Testing Not Done	3/3
Follow-up Visit Missed	3/3
Warfarin Discontinued Outside Protocol Requirements	3/3
INR Non -Compliance / Out of Range	2/2
Non-Compliant ACT	2/2
Informed Consent	2/2
Non-Compliant ASA Regimen	2/1
Neurological Assessment Not Completed	1/1
Non-Compliant Warfarin Regimen	1/1
Other	11/10

Patient listings of the "other" protocol deviations are provided in **Table 12-92**.

Table 12-92. Listing of "Other" Protocol Deviations (Roll-in Phase)

Roll In Patient		Baseline	Baseline testing done outside of window
Roll In Patient		Other Visit	Assessment was not clinically indicated
Roll In Patient		Baseline	Baseline testing done outside of window
Roll In Patient		45-Day	Follow-up testing not done or done outside of window
Roll In Patient		Baseline	Baseline testing performed before informed consent signed
Roll In Patient		9-Month	SAE not reported in required window
Roll In Patient		Baseline	Baseline testing performed before informed consent signed
Roll In Patient		Baseline	Baseline testing done outside of window
Roll In Patient		Baseline	Baseline testing done outside of window
Roll In Patient		Baseline	Baseline testing done outside of window
Roll In Patient		Baseline	Baseline testing done outside of window

13 Summary and Conclusions

The WATCHMAN PROTECT AF study, involving 785 patients treated with either the WATCHMAN Device or standard warfarin therapy in a 2:1 randomized ratio, was performed to evaluate the safety and effectiveness of the WATCHMAN LAA Closure Technology. The primary analyses support a statistically significant finding of non-inferiority for the Device group relative to the Control group for the primary efficacy endpoint, and this finding was consistent across a wide range of secondary analyses. Data from the Control group demonstrate both the difficulties associated with the use of and complications due to warfarin therapy, including difficulty in maintaining therapeutic levels of anti-coagulation (only 50% of the time).

The WATCHMAN PROTECT AF study results support the following statements:

- The WATCHMAN Device was associated with a 24% reduction in endpoint events (stroke, cardiovascular death, and systemic embolism) compared to patients on a standard warfarin regimen.
- The WATCHMAN Device was successfully implanted in a significant majority (91%) of patie in whom an implant was attempted.
- After successful implant of the WATCHMAN Device, 87% of patients were able to discontinu warfarin therapy after 45 days. This percentage increased as follow-up continued.
- While there was risk associated with the WATCHMAN implant procedure, these risks declined over the course of the trial as investigators gained experience with the procedure and the device If an effusion occurred, the event prolonged hospital stay but did not result in mortality.
- In patients who were successfully implanted and in whom warfarin was discontinued, the rate o stroke was reduced by 56%. Furthermore, the rate of hemorrhagic stroke was reduced by 100% compared to patients on long-term warfarin therapy.

These data demonstrate that the WATCHMAN LAA Closure Technology is a safe and effective alternative to warfarin therapy for use in preventing the embolization of thrombi, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation.

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