Atritech, Inc.
WATCHMAN® LAA Closure Technology

Sponsor Executive Summary

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Sponsor Executive Summary
Brief Synopsis

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, currently affecting more than 3 million Americans. AF patients have a five-fold increased risk of stroke 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). 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.

Indications for Use

The WATCHMAN® Left Atrial Appendage (LAA) Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation. The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism.

Device Description

The WATCHMAN LAA Closure Device is a self-expanding nitinol structure with a membrane on the proximal face, with the following components: LAA Closure Device, Delivery System (Delivery Catheter and loaded Device), Access System (Access Sheath and Dilator), and the Obturator (Optional Accessory). The Access System and Delivery Catheter provide femoral venous access and a means to cross into the left atrium via the intra-atrial septum. The Obturator, an optional accessory, provides transition from the Access Sheath to a pigtail catheter, facilitating atraumatic entry into the distal segment of the LAA. The device is positioned distal to the ostium of the LAA using angiography, echocardiography and standard transseptal techniques. The implant procedure is performed percutaneously under conscious sedation or general anesthesia in either a cardiac catheterization or electrophysiology laboratory setting.

Nonclinical Studies

- **Bench Testing**

The company has conducted bench testing to address key performance characteristics of the Closure Device, Delivery System, Access System, and the Obturator. All tests met the specified performance criteria. Biocompatibility testing was performed to evaluate all patient contacting materials and all applicable requirements of ISO 10993 were met.

- **Animal Testing**

Atritech conducted several canine studies to evaluate procedural and device effects. These studies indicated that the WATCHMAN LAA Closure Device can be safely and effectively implanted into the LAA. The studies demonstrated that the device promotes endothelial overgrowth and completely seals the LAA from the left atrium within 45 days. There were no visible strut fractures and implantation of

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the device did not result in clinically significant effects on adjacent tissues. An acceptable healing response, with no evidence of risk associated with thrombus formation, was also shown. Procedural methods and retrievability of the device were shown to be simple, repeatable, and safe.

Pivotal Trial

The objective of the PROTECT AF study was to demonstrate that the WATCHMAN LAA Closure Device provides reasonable assurance of safety and effectiveness in patients with non-valvular AF who require anticoagulation therapy for potential thrombus formation.

o Study Design

The investigation was a multi-center prospective randomized design comparing the WATCHMAN Device to long-term warfarin therapy. A 2:1 randomization allocation ratio was used. Enrollment commenced in February 2005 and randomized enrollment ended in June 2008. The protocol allowed sequential evaluations of the statistical objectives under a Bayesian Model. For the first sequential analysis (at 600 patient-years), a minimum of 300 subjects must have reached one year of follow-up and 100 subjects must have reached 2 years of follow-up.

o Study Endpoints

The primary effectiveness endpoint was successful treatment of the patient without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The criterion for establishing non-inferiority was a posterior probability of at least 0.975 that the event rate for the Device group was less than 2 times the event rate for the Control group.

The primary safety endpoint was treatment without the occurrence of life-threatening events as determined by the Clinical Events Committee, including 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. No hypothesis was associated with the primary safety endpoint.

o Study Results

The PMA was initially submitted based on the first sequential analysis at 600 patient years and was recently updated based on an analysis of the 900 patient year dataset. A total of 800 patients were enrolled at 59 centers in the trial at the time of the later database lock. This included 707 randomized patients (463 Device and 244 Control) and 93 roll-in patients. The Device was not implanted in 14/463 patients principally because the procedure could not occur within the specified time window. A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted; the device was unable to be implanted in 41 patients (12 non-fatal procedural events and 29 device-related criteria not met).

▪ Primary Efficacy Analysis

<u>Intent-to-Treat Analysis</u>

Results for the primary efficacy endpoint are displayed in Table 1.

Table 1. Primary Efficacy Results (Intent-to-Treat)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	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
900	463	20/582.3	3.4 (2.1, 5.2)	244	16/318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837

At 900 patient years, the primary efficacy event rate was 3.4 events/100 patient years for the Device group and 5.0 events/100 patient years for the Control group, yielding a relative risk of 0.68 or a 32% lower rate of efficacy events in the Device group than in the Control group. The 900 patient year analysis shows stronger efficacy results than the 600 pt year analysis (24% lower event rate than Control), due to the longer follow-up of most patients. Non-inferiority of the Device compared to the Control is demonstrated at both 600 and 900 patient years.

Table 2 summarizes the specific efficacy events which comprise the primary efficacy endpoint.

Table 2. Primary Efficacy Events by Type at 900 Patient Years (Intent-to-Treat)

	N Events	% Patients	N Events	% Patients
Stroke – Ischemic	14	3.0	5	2.0
Death (Cardiovascular or Unexplained)	3	0.6	5	2.0
Stroke - Hemorrhagic	1	0.2	6	2.5
Systemic Embolism	2	0.4	0	0.0

Importantly, these results show that the rate of cardiovascular or unexplained death is lower in the Device group (0.6% vs. 2.0%) and the rate of often debilitating hemorrhagic stroke was also lower in the Device group (0.2% vs. 2.5%). There were no device or procedure related deaths in the Device group. Of the 14 patients in the Device group who experienced ischemic stroke, 1 experienced a stroke after randomization but before a device was implanted and 5 had ischemic stroke on the day of the procedure due to air embolism and excessive sedation.

Post Procedure Analysis

A pre-specified analysis was performed excluding 14 patients who were randomized to the device but for whom no implant was attempted and 5 patients who experienced events (ischemic strokes) on the day of the procedure (counted as both primary efficacy and safety events). Results of the primary efficacy endpoint once these 19 patients were removed are displayed in Table 3.

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Table 3. Primary Efficacy Results (Post Procedure)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	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
900	444	14/572.3	2.4 (1.4, 4.0)	244	16/318.0	5.0 (2.8, 7.6)	0.49 (0.24, 1.06)	>0.999	0.965

The primary efficacy event rate was 2.4 events/100 patient years for the Device group and 5.0 events/100 patient years for the Control group, reflecting a 51% lower rate of efficacy events in the Device group. The probability of superiority of 0.965 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group under this post-procedure analysis.

Per Protocol Analysis

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. At 900 patient years, the primary efficacy rate was 2.1 events/100 patient years for the Device group and 4.7 events/100 patient years for the Control group, reflecting a 56% lower rate of efficacy events in the Device group. The probability of superiority of 0.971 was greater than the pre-specified superiority criterion.

- **Primary Safety Analysis**

Intent-to-Treat Analysis

Results for the primary safety endpoint are displayed in Table 4. There was no pre-specified hypothesis for the primary safety endpoint.

Table 4. Primary Safety Results (Intent-to-Treat)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
600	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)
900	463	48/554.2	8.7 (6.4, 11.3)	244	13/312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)

At 900 patient years, the primary safety rate was 8.7 events/100 patient years for the Device group and 4.2 events/100 patient years for the Control group, yielding a relative risk of 2.08, which was lower than the relative risk of 2.85 at 600 patient years. This 27% reduction in risk reflects higher continuing safety events with warfarin in the Control Group. The majority of primary safety events in the Device group (27/48; 56%) occurred on the day of implant of which 22 were serious pericardial effusions or ischemic

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strokes. Safety events in the Control group tended to occur later and on a continuing basis. Moreover, data from the SPAF trials have shown long term warfarin events continue beyond 3 years. Thus, the company believes the initial device safety events are offset by the longer term drug effects and clinical events associated with ongoing, possibly life-time, warfarin therapy.

Of the 463 randomized Device group patients there were 22 pericardial effusions considered to be serious (4.8%); 7 required surgical intervention with a median hospitalization of 6 days, and the remaining 15 were treated percutaneously with fluid drainage with a median hospitalization of 4 days. None of the effusions resulted in death, nor resulted in permanent complications. Based on investigator experience with the device, the rate of pericardial effusions decreased in the second half of the study.

Five (1.1%) ischemic strokes in the Device group occurred on the day of the procedure; 3/5 were related to air embolism, a potential occurrence in any left heart procedure. None of these events resulted in death. With the exception of 1 patient who experienced continuing mild neurological deficit on the right side, all symptoms associated with the ischemic strokes experienced during the procedure fully resolved.

The rate of hemorrhagic stroke was lower in the Device group compared to the Control group (0.2% vs. 2.5%, respectively). The 1 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 6 hemorrhagic strokes in the Control group, 4 resulted in death.

Of the 463 randomized Device group patients, 3 (0.6%) embolizations occurred. Two of the 3 were surgically removed and 1 was removed percutaneously.

Further information from the company's ongoing continued access registry shows only 1 safety event (gastrointestinal bleed) in 88 patients.

Post Procedure Analysis

Patients who were randomized to the Device group but for whom no implant was attempted or who experienced events during the procedure were excluded from this analysis. This analysis provides an alternate way to assess post procedural, long term safety which is a known issue with warfarin therapy. Excluded were 14 patients who were unable to be implanted during the allotted time window following randomization, 5 patients who experienced procedural ischemic strokes, and 22 patients who experienced other procedural events including pericardial effusions. At 900 patient years, the primary safety rate was 3.9 events/100 patient years for the Device group and 4.2 events/100 patient years for the Control group, reflecting comparable rates between groups.

Per Protocol Analysis

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis compares effectiveness in patients who successfully received their assigned treatment. At 900 patient years, the primary safety event rate was 1.7 events/100 patient years for the Device group and 4.2 events/100 patient years for the Control group.

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Conclusion

The clinical study results demonstrate a positive overall risk/benefit profile for Device patients even with the risk of procedural complications.

- The WATCHMAN LAA Device was associated with a 32% reduction in primary endpoint events (stroke, cardiovascular death, and systemic embolism) at 900 patient years compared to patients on a standard warfarin regimen under the ITT analysis, meeting the non-inferiority criterion for the primary efficacy endpoint at both 600 and 900 patient years. The 900 patient year analysis shows stronger efficacy results than the 600 patient year analysis, given the longer follow-up of most patients. Under a post procedure analysis, the efficacy of the WATCHMAN Device was superior to the Control.
- After successful implantation of the WATCHMAN Device, 87% of patients were able to discontinue warfarin therapy after 45 days. This percentage increased as follow-up continued.
- Device patients experienced a higher rate of safety events than the Control group; however, once the initial procedural risk passed, the safety profile of the Device was comparable to the Control. The principal procedural related safety events in the Device group were pericardial effusions which are a known complication of intracardiac procedures. The rate of pericardial effusions decreased over the course of the study attributable to investigator experience; none had lasting clinical complications.
- In the continued access registry, only one serious effusion has occurred in 88 enrolled patients for a rate of 1.1%, reflective of the effects of continued training and experience.
- Device patients experienced 15 strokes (14 ischemic and 1 hemorrhagic) (event rate of 2.6% per 100 pt yrs) compared to Control patients with 11 strokes (5 ischemic and 6 hemorrhagic) (event rate of 3.5% per 100 pt yrs). 6/15 Device strokes were either pre-procedure or were due to air embolism or excessive sedation during the procedure. No hemorrhagic strokes occurred in the Device group once patients discontinued warfarin.
- The rate of hemorrhagic stroke was lower in the Device group compared to the Control group (0.2% vs. 2.5%, respectively). 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 6 patients with hemorrhagic strokes in the Control group, 4 died.
- None of the patient deaths in the Device group were adjudicated to be either device or procedure related.
- The substantial efficacy benefit of the WATCHMAN device in reduced mortality and hemorrhagic stroke outweighs the risk of procedural complications (including pericardial effusions and ischemic stroke), especially where the risks associated with ongoing warfarin therapy are well-known.
- The study established that the WATCHMAN Device provides a reasonable assurance of safety and effectiveness for patients with non-valvular AF who require anticoagulation therapy for potential thrombus formation.

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1 Introduction

This Executive Summary details the clinical data collected in the study entitled WATCHMAN® Left Atrial Appendage (LAA) Closure Technology for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) as well as a brief discussion of the preclinical testing performed and submitted as part of the PMA. The clinical study was conducted under IDE #G[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 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]

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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 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 required for 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 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 **C**ongestive heart failure, **H**ypertension, **A**ge >75, and **D**iabetes, and assigns 2 points for a previous **S**troke 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 **S**troke **P**revention in **A**trial **F**ibrillation (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.

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If INR values fall below 2.0, 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 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 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.

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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 with two concurrent multi-center feasibility trials 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. 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 one month following closure of the trial, was 2.2% (two events during 90.7 documented implant years). [75]

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 LAA using 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.

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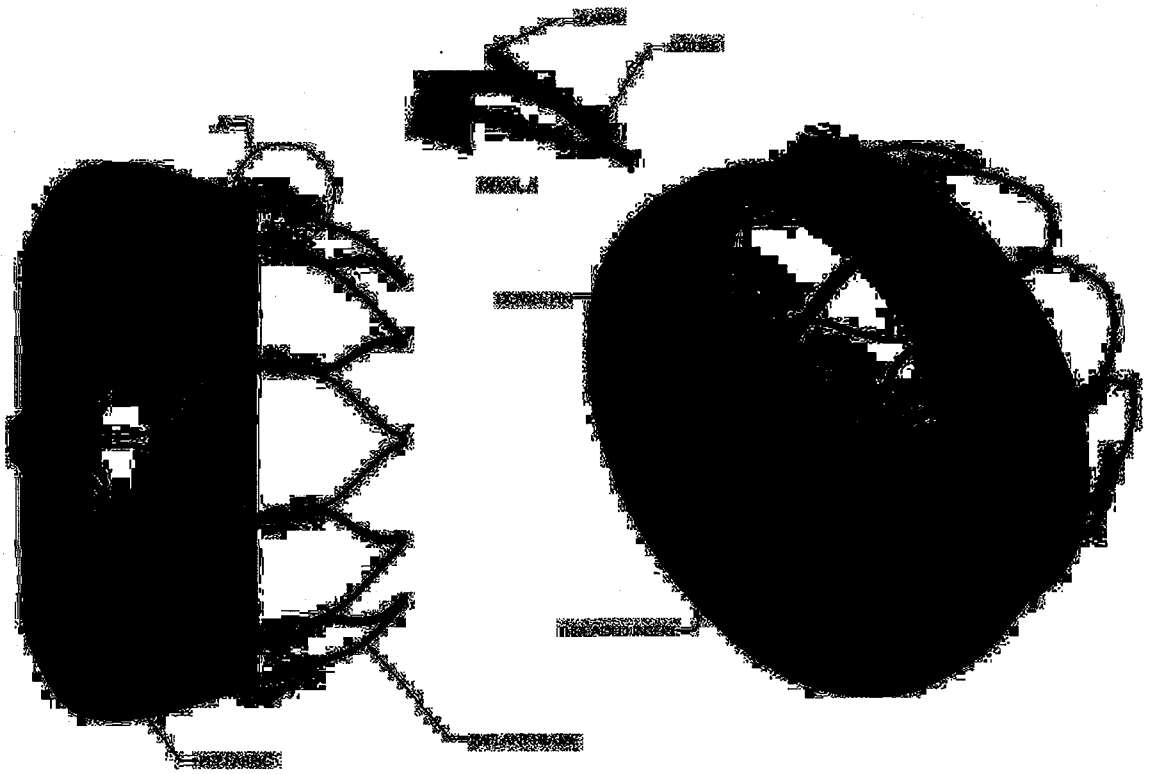
Figure 2-1. WATCHMAN LAA Closure Device

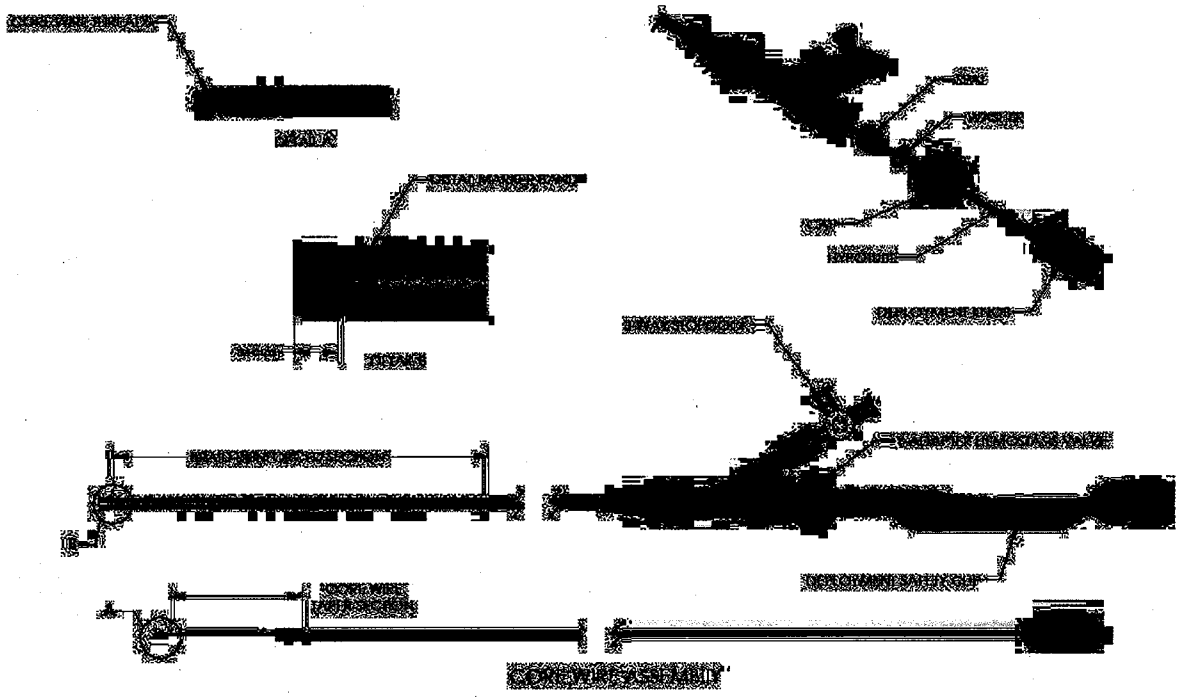


2.2 WATCHMAN Delivery System

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



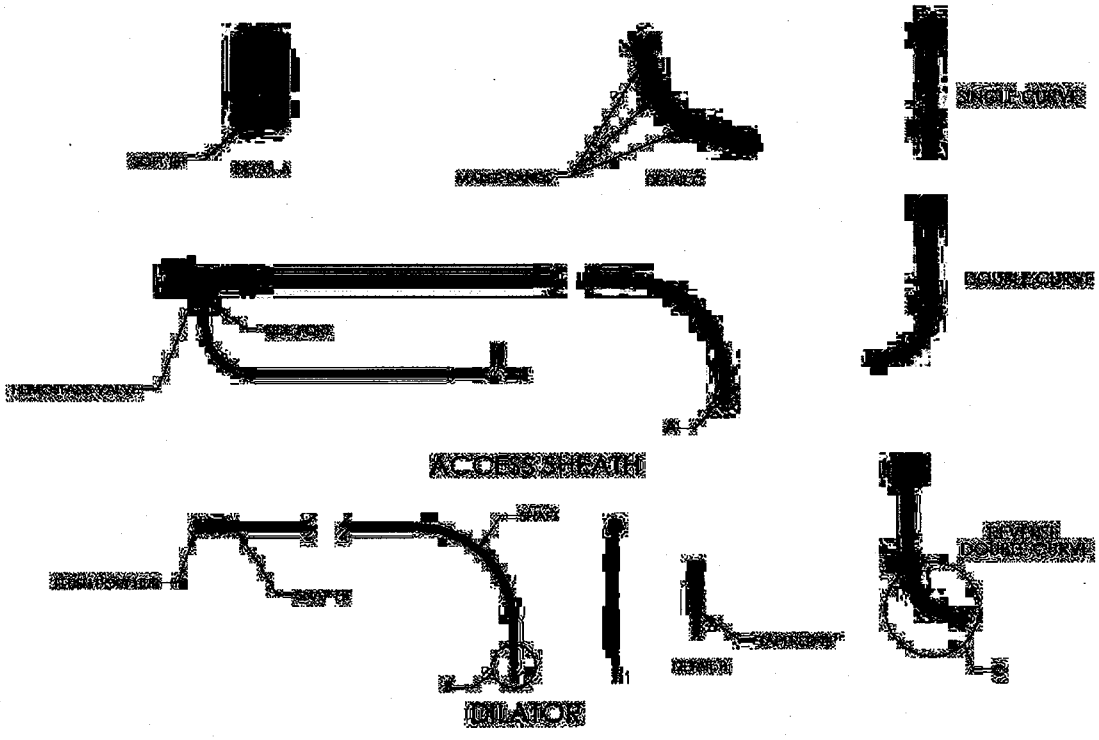
2.3 WATCHMAN Access System

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 (Optional Accessory)

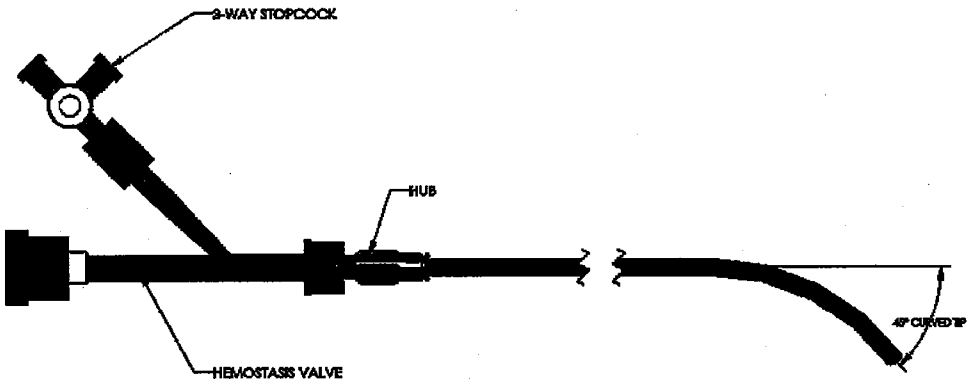
The WATCHMAN Obturator is a 12 Fr OD (6 Fr ID) optional adjunctive device that may be used to assist with placement and guidance of the Access Sheath into the LAA. The Obturator first became available to investigational sites January 2008 and has been used in a limited number of procedures.

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

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.

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 replaced the original Access Sheath design.

2.5 Summary of Preclinical Studies

2.5.1 Bench Testing

Atritech performed an extensive series of mechanical and functional testing to demonstrate that the WATCHMAN LAA Closure Device, Delivery System, Access System, and Obturator met design input requirements and engineering specifications. The results show that all requirements were met, thus supporting the integrity and reliability of the WATCHMAN LAA Closure Technology.

A summary of the WATCHMAN bench testing is provided in Table 2-1.

Table 2-1. Summary of WATCHMAN Bench Testing

Implant Threaded Insert to NiTi Tube Joint	Pass
Core Wire Assembly Wire through Threaded Insert Tensile Strength	Pass
Implant Filtration	Pass
Implant Deployment and Recapture Force	Pass
Implant Mechanical Integrity	Pass
Individual Barb Mechanical Integrity	Pass
Implant Radial Force	Pass
Implant Diameter Recovery	Pass
Implant Dislodgement Force	Pass
MRI Field Interactions	Pass
Implant Corrosion Resistance	Pass
Implant Durability/Fatigue (Test articles were cycled up to the equivalent of 10 years of use or 400,000,000 cycles corresponding to 76 heartbeats per minute for ten years)	Pass
Finite Element Analysis (for characterization)	N/A
Delivery System Tensile Strength	Pass
Snap Fit Luer Connection Compressive and Tensile Properties	Pass
Core Wire Torque Properties	Pass
Core Wire Assembly Torquer Bond Strength	Pass
Kink Resistance – Delivery System	Pass
Contrast Flow Rate – Delivery System	Pass
Leak Free Conduits - Delivery System	Pass
Corrosion Resistance – Delivery System	Pass
WATCHMAN Access System – Tensile Testing	Pass
Kink Resistance – Access System	Pass
Contrast Flow Rate	Pass
Leak Free Conduits – Access System	Pass
Access System Distal Tip Deflection	Pass
Dilator Tensile Strength	Pass
Leak Free Conduits – Obturator	Pass
Obturator Tensile Strength	Pass

2.5.2 Biocompatibility Tests

The safety of the WATCHMAN LAA Closure Technology has been evaluated in a series of biocompatibility/toxicity studies on the WATCHMAN LAA Closure Device, Delivery System, Access System, and Obturator. According to ISO 10993, the WATCHMAN Delivery System, Access System, and Obturator are classified as blood contacting, externally communicating device with limited, less than 24 hour exposure. The WATCHMAN LAA Closure Device is classified as a blood contacting, permanent duration implant.

All studies were conducted in compliance with U.S. Food and Drug Administration regulations set forth in 21 CFR Part 58 - *Good Laboratory Practice for Non Clinical Laboratory Studies.*

These test results in accordance with ISO 10993 demonstrate that the WATCHMAN LAA Closure Technology including the WATCHMAN LAA Closure Device, Delivery Catheter, Access System and Obturator are biocompatible for its intended use. A summary of the biocompatibility testing is provided in Table 2-2.

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Table 2-2. Summary of Biocompatibility Testing

Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Pass
Sensitization (ISO 10993-10)	Pass
Acute Systemic Toxicity (ISO 10993-11)	Pass
Pyrogenicity (ISO 10993-11)	Pass
Genotoxicity (ISO 10993-3)	Pass
Implant / Chronic Toxicity	Pass
Hemocompatibility (ISO 10993-4)	Pass
USP Physico-Chemical Test (USP<25>)	Pass
Lee & White	Pass
UPTT	Pass
Carcinogenicity	Assessed
Cytotoxicity (ISO 10993-5) L-929 MEM Elution	Pass
Irritation (ISO 10993-10) Intracutaneous Injection	Pass
Sensitization (ISO 10993-10) Murine Local Lymph Node Assay	Pass
Acute Systemic Toxicity (ISO 10993-11) Systemic Injection	Pass
Pyrogenicity (ISO 10993-11) Material Mediated/Rabbit Pyrogen	Pass
In-vitro Hemocompatibility (ISO 10993-4) Direct and Indirect Methods	Pass
Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Pass
Sensitization (ISO 10993-10)	Pass
Acute Systemic Toxicity (ISO 10993-11)	Pass
Pyrogenicity (ISO 10993-11)	Pass
Hemocompatibility (ISO 10993-4)	Pass
Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Assessed
Sensitization (ISO 10993-10)	Assessed
Acute Systemic Toxicity (ISO 10993-11)	Assessed
Pyrogenicity (ISO 10993-11)	Assessed
Hemocompatibility (ISO 10993-4)	Pass

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2.5.3 Packaging, Sterilization & Shelf Life Testing

The WATCHMAN LAA Closure Technology packaging was evaluated to demonstrate that the package design adequately protects the product during storage and distribution. Based upon these results, the WATCHMAN Delivery System and Access System are labeled with a 3 year shelf life and the WATCHMAN Obturator is labeled with a 2 year shelf life.

The WATCHMAN LAA Closure Technology products are single-use devices that are provided sterile (via ethylene oxide) to the user. WATCHMAN LAA Closure Technology products are sterilized using a validated 100% gaseous ethylene oxide (EO) mixed load sterilization process that provides a Sterility Assurance Level (SAL) of $\leq 10^{-6}$.

2.5.4 Animal Testing

Atritech conducted several animal studies in canines to evaluate the procedural and device effects associated with various device designs and implant variables. A total of 96 animals were tested as part of Atritech development, design and safety testing processes. Four GLP studies were conducted to assess the safety of the device, and for design verification.

The study results indicate that the WATCHMAN LAA Closure Technology intended for commercialization can be safely and effectively implanted into the LAA. The results indicate that the device promotes endothelial overgrowth and completely seals the LAA from the left atrium within 45 days. The studies have also shown that there are no visible strut fractures, and that the device has caused no clinically significant effects on adjacent tissues. The results also show an acceptable healing response, with no evidence of risk associated with thrombus formation. Procedural methods and retrievability of the device were shown to be simple, repeatable and safe.

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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 risk for thrombosis, specifically patients with AF 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).

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.

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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 Device is safe and effective in patients with non-valvular AF who require anticoagulation therapy for potential thrombus formation.

4.2 Primary Endpoints

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

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].

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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 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 0.975.
- 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 0.05.

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 0.95.

5 Investigational Plan and Methods

5.1 Study Design

The PROTECT AF 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 AF who require anticoagulation therapy for potential thrombus formation. A documented history of paroxysmal, persistent or permanent AF was required for every patient.

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.

5.2 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 for 600 patient years and subsequent analysis of the data that was contained the PROTECT AF Clinical Report [redacted] submitted to the FDA.

The protocol allowed sequential evaluations of the statistical objectives under a Bayesian Model. For the first sequential analysis (i.e., at 600 patient-years), a minimum of 300 subjects must have reached one year of follow-up and 100 subjects must have reached 2 years of follow-up. A total of 800 patients (including 93 roll-in patients) were enrolled at the time of the database lock for 900 patient years and subsequent analysis of the data that was contained in the PROTECT AF 900 Patient Year Update (A005) submitted to the FDA.

Patients will continue to be followed until the WATCHMAN LAA Closure 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 AF 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.

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 This section intentionally left blank

5.5 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.

Patients in the Device group discontinued warfarin therapy if the 45-day TEE demonstrated complete LAA occlusion, or a residual jet flow of ≤ 3 mm around the margins of the WATCHMAN Device, in either a retrograde or antegrade fashion. To account for interpretation variability in the operator and imaging equipment, a tolerance of ± 2 mm was included when evaluating the residual flow around the margins of the device.

If warfarin was discontinued at the 45-day follow-up visit, clopidogrel and aspirin were recommended until completion of the 6-month follow-up visit and patients continued 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.

5.6 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.

5.7 Follow-up Testing

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

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.

5.8 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.

5.9 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.

5.10 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

A Principal Investigator (PI) was designated for each site and was responsible for the overall clinical management of patients enrolled in the study at their institution. The PI was expected to ensure compliance with the investigational plan, the clinical trial agreement, and regulations set forth by the institution's Institutional Review Board.

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 Table 6-1.

Table 6-1. Investigator / Institution List: Intentionally removed for privacy

6.1 Investigational Device Training

Successful completion of each investigator's training was documented in training records. At a minimum, implanting investigators in the PROTECT AF study received the following training, unless otherwise noted in site specific training records:

- Investigational Study Protocol review
- WATCHMAN Technology training including:
  - Device preparation, use and handling
  - Device deployment, recapture and release
  - Device release criteria
- Implantation procedure steps and training
- Animal lab experience or SimSuite (simulation program) procedure training
- Case review
- Imaging review / echocardiography imaging protocol

7 Selection of Study Population

7.1 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

7.2 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)

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- 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

7.3 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

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8 Data Oversight

8.1 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 sections below.

8.1.1 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.

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, such as the analysis of pericardial effusion rates in the study, 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 or continue the trial with specific conditions.

8.1.2 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.

Specific definitions were established by the CEC as follows:

- 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. Upon adjudication as a non-event, further classification by the CEC was stopped. For any event that was determined to be a non-event or not study related, no further review was necessary.
- Pericardial Effusion definitions were determined by the clinical therapy associated with the effusion. The following definitions of pericardial effusion were written and approved by the CEC, then submitted to and approved by the FDA.

- Pericardial Effusion (Non-Serious) - increased fluid within the pericardial sac that did not cause circulatory compromise and did not require drainage.
- Pericardial Effusion (Serious)
  - Cardiac Tamponade - any pericardial effusion requiring percutaneous treatment.
  - Cardiac Perforation - any pericardial effusion requiring surgical intervention.

The CEC was comprised of two Interventional Cardiologists and a Neurologist.

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.

8.1.3 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, including both electrophysiologists and interventional cardiologists. The PROTECT AF National Principal Investigator [redacted], was designated chairperson of the Steering Committee.

8.2 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.

9 Statistical Methodology

9.1 Statistical Design

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.

9.1.1 Sequential Analysis Plan

The first sequential interim analysis was performed after collection of 600 patient years of follow-up which included 300 subjects with one year of follow-up and 100 subjects with two years of follow-up. Subsequent analyses are allowed after each additional 150 patient years up to a maximum of 1500 patient 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.

9.1.2 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 2 times the event rate for the Control group of at least 0.975 and that the preceding criterion for futility was not met.

9.1.3 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 of at least 0.95. 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 150 patient years of follow-up was to be collected before the next evaluation time, up to a limit of 1500 patient years of follow-up. If after the maximum of 1500 patient years of follow-up the Device group was not established as "Non-inferior", the device was to be considered "Not Non-inferior."

9.2 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.

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9.2.1 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 AF. 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.

Forming a weighted average of the event rates for the different $CHADS_2$ scores, 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 study.

9.3 Statistical Methods

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.

9.3.1 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.

9.3.2 Secondary Analysis Dataset: Post Procedure (Pre-specified)

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) Are there any adverse events that the clinician needs to be aware of to educate the patient before leaving the hospital?

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9.3.3 Secondary Analysis Dataset: Per-Protocol (Pre-specified)

In the PROTECT AF study, one potential bias was the possible 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 if so, what are the chances? and 2) What are the outcomes after being taken off warfarin therapy?

To quantify the 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.

A summary of the primary and secondary analysis cohorts are provided in Table 9-1.

Table 9-1. Summary of Analysis Cohorts (Pre-Specified)

Intent-to-Treat	None	None
Post Procedure	Patients with events that occurred before or on the date of device implant	None
Per-Protocol	Patients without an implanted device or who did not discontinue warfarin therapy	Patients for whom there was no evidence of warfarin use at baseline or the 45-day visit

9.4 PMA Data Analyses

Patients whose data were entered into the database as of May 31, 2008, are included in the 600 Patient Year Report (SR1062). The data entered by this date were reviewed and outstanding issues were resolved which led to a final, locked data set for analysis as of June 17, 2008. As of this date, 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.

This data set includes a total of 633 patient-years of follow-up for the primary efficacy endpoint. The average follow-up per patient was 11 months.

9.4.1 Post PMA Data Analyses

As described in section 5.2, the protocol allows for sequential evaluations of the statistical objectives under a Bayesian Model. A sequential evaluation was completed using the 900 patient-year data collected through December 22, 2008. As of this date, a total of 800 patients were enrolled in the trial; a difference of only 15 patients from the first analysis. This total included 93 roll-in patients, 463 patients randomized to the Device group, and 244 patients randomized to the Control group.

This data set includes a total of 900 patient-years of follow-up for the primary efficacy endpoint. The average follow-up per patient was 16 months (an increase of 5 months or 45% from the 600 patient year results). An analysis was performed on the 900 patient-year data and the report is included in CR1062, as a supplement to SR1062 and is included under Tab 7.

9.4.2 Additional Patient Data

Upon completion of enrollment in the PROTECT AF study, continued access to the WATCHMAN device was allowed to a subset of the PROTECT AF investigators through a study entitled Continued Access PROTECT AF Registry (CAP Registry) under IDE #[redacted] Participating sites were allowed to enroll new patients in this non-randomized trial to collect additional data to further characterize the performance of the WATCHMAN device. Preliminary safety data from the CAP Registry, [redacted] is presented in Tab 7.

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10 Results

Results from the most contemporary dataset, 900 patient years, are provided below. In the analysis of the primary efficacy and safety endpoints (sections 10.2-10.6), both 600 and 900 patient-year results are presented.

10.1 Demographics

10.1.1 Enrollment Accountability/Subject Disposition

Table 10-1 summarizes patient enrollment across treatment groups, including non-randomized roll-in patients. A total of 800 patients were enrolled in the trial at 59 centers. This total included 707 randomized patients (463 patients to the Device group and 244 patients 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 10-1. Enrollment Summary

Randomized	463
Implant Attempted	449
Implanted	408
Randomized	244
Warfarin Administered	241
Warfarin Never Administered	3
Enrolled	93
Implant Attempted	93
Implanted	77

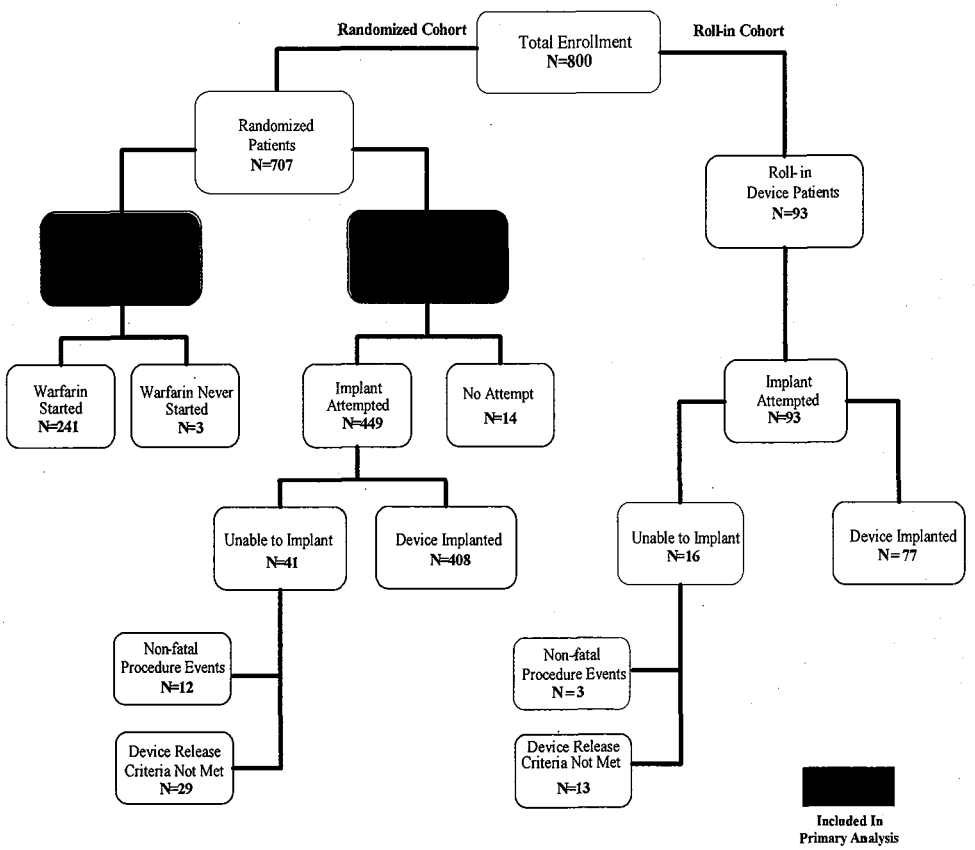
Of the 463 Device group patients, 449 had an implant attempted and 14 were randomized but not attempted due to the following reasons:

- (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% (408/449) of patients for whom an implant procedure was attempted.

A total of 93 patients were enrolled as roll-in (non-randomized) patients at 33 centers. The roll-in phase was implemented in January 2006 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 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.

Figure 10-1. 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 10-2 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.

Atritech implemented a roll-in phase of the study beginning in January 2006 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.

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Table 10-2. PROTECT AF Enrollment Summary

1		44	22	66	3	69
2		35	17	52	0	52
3		33	17	50	3	53
4		29	14	43	3	46
5		25	13	38	0	38
6		23	12	35	0	35
7		23	11	34	0	34
8		19	10	29	0	29
9		20	9	29	0	29
10		19	10	29	3	32
11		19	9	28	3	31
12		15	8	23	0	23
13		13	7	20	0	20
14		13	7	20	0	20
15		11	6	17	0	17
16		9	5	14	0	14
17		8	5	13	3	16
18		8	4	12	0	12
19		6	4	10	0	10
20		6	4	10	3	13
21		6	2	8	0	8
22		5	3	8	0	8
23		5	3	8	0	8
24		5	3	8	3	11
25		5	3	8	3	11
26		4	4	8	4	12
27		5	3	8	3	11
28		4	4	8	0	8
29		4	2	6	0	6
30		4	2	6	4	10
31		3	2	5	0	5
32		4	1	5	0	5
33		3	2	5	3	8
34		3	1	4	3	7
35		2	2	4	2	6
36		2	2	4	3	7
37		3	1	4	2	6
38		2	2	4	0	4
39		1	2	3	0	3
40		1	1	2	0	2
41		2	0	2	0	2
42		1	1	2	3	5
43		2	0	2	3	5
44		2	0	2	3	5
45		2	0	2	3	5
46		2	0	2	5	7
47		1	1	2	1	3
48		1	1	2	3	5
49		1	0	1	3	4
50		0	1	1	0	1
51		0	1	1	0	1
52		0	0	0	2	2
53		0	0	0	3	3
54		0	0	0	2	2
55		0	0	0	1	1
56		0	0	0	3	3
57		0	0	0	2	2
58		0	0	0	3	3
59		0	0	0	2	2

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10.1.2 Population/Subject Demographics

Table 10-3 summarizes the patient baseline demographic information of the randomized cohort. Baseline demographics demonstrate that patients in the two treatment groups are comparable.

Table 10-3. Baseline Demographics

Age (years)	71.7 ± 8.8 463 (46.0, 95.0)	72.7 ± 9.2 244 (41.0, 95.0)	0.1800
Height (inches)	68.2 ± 4.2 462 (54.0, 82.0)	68.4 ± 4.2 244 (59.0, 78.0)	0.6067
Weight (lbs)	195.3 ± 44.4 463 (85.0, 376.0)	194.6 ± 43.1 244 (105.0, 312.0)	0.8339
Gender			0.9276
Female	137/463 (29.6)	73/244 (29.9)	
Male	326/463 (70.4)	171/244 (70.1)	
Race/Ethnicity			0.7788
Asian	4/463 (0.9)	1/244 (0.4)	
Black/African American	6/463 (1.3)	5/244 (2.0)	
Caucasian	425/463 (91.8)	222/244 (91.0)	
Hispanic/Latino	25/463 (5.4)	15/244 (6.1)	
Hawaiian/Pacific Islander	1/463 (0.2)	1/244 (0.4)	
Other	2/463 (0.4)	0/244 (0.0)	

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 AF 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 AF. 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 AF is comparable to the PROTECT AF study.[88]

Baseline risk factors for enrolled patients are summarized in Table 10-4. There was no statistically significant difference in risk factors between groups.

Table 10-4. Baseline Risk Factors

$CHADS_2$ score			0.3662
1	158/463 (34.1)	66/244 (27.0)	
2	157/463 (33.9)	88/244 (36.1)	
3	88/463 (19.0)	51/244 (20.9)	
4	37/463 (8.0)	24/244 (9.8)	
5	19/463 (4.1)	10/244 (4.1)	
6	4/463 (0.9)	5/244 (2.0)	
CHF	124/463 (26.8)	66/244 (27.0)	0.9392
History of hypertension	412/463 (89.0)	220/244 (90.2)	0.6284
Age ≥ 75	190/463 (41.0)	115/244 (47.1)	0.1198
Diabetes	113/463 (24.4)	72/244 (29.5)	0.1423
Previous TIA/Ischemic Stroke	82/463 (17.7)	49/244 (20.1)	0.4404
AF Pattern			0.7623
Paroxysmal	200/463 (43.2)	99/244 (40.6)	
Persistent	97/463 (21.0)	50/244 (20.5)	
Permanent	160/463 (34.6)	93/244 (38.1)	
Unknown	6/463 (1.3)	2/244 (0.8)	
LVEF %	57.3 ± 9.7 460 (30.0, 82.0)	56.7 ± 10.1 239 (30.0, 86.0)	0.4246

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.

Inclusion in the PROTECT AF study required a $CHADS_2$ score of ≥ 1. 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]

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 (1.2) and 2.3 (1.2) for the Device and Control groups respectively.

Paroxysmal AF, defined as an intermittent form of AF that is characterized by a sudden onset and abrupt cessation of this rhythm, was the presenting rhythm in 42% of subjects. The second most common AF pattern reported was permanent AF, defined as ongoing AF that fails to terminate using cardioversion, or is terminated but reoccurs, which accounted for 36% of patients in the study.

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

10.1.3 Follow-up Compliance

Table 10-5 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 December 1, 2008, are considered expected.

Very few patients were lost to follow-up in the study and approximately 98% follow-up was achieved in both groups.

Table 10-5. Follow-up Visit Attendance

45 day	432/438 (98.6)	235/239 (98.3)
6 month	389/391 (99.5)	220/221 (99.5)
9 month	336/344 (97.7)	190/192 (99.0)
12 month	288/295 (97.6)	151/154 (98.1)
18 month	203/205 (99.0)	104/104 (100.0)
24 month	103/106 (97.2)	53/56 (94.6)
30 month	59/61 (96.7)	32/32 (100.0)
36 month	25/26 (96.2)	12/13 (92.3)

A summary of reasons for completion of an end-of-study form is provided Table 10-6.

Table 10-6. End of Study Summary

No Device Implanted	41/463 (8.9)	0/244 (0.0)
Patient Consent Withdrawn	10/463 (2.2)	25/244 (10.2)
Death	15/463 (3.2)	15/244 (6.1)
Outside Implant Window	10/463 (2.2)	0/244 (0.0)
Lost to Follow-up	2/463 (0.4)	3/244 (1.2)
Other	9/463 (1.9)	7/244 (2.9)

The most common reason for end-of-study in the Device group was no device implanted. Among these 41 patients, there were 2 primary efficacy events and 13 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 events and 1 primary safety event among these patients.

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10.2 Procedural Data

The procedural data contained in the following section is an analysis of the data from the **Randomized Cohort Only**.

10.2.1 Implant Procedure Success

Implant Procedure Success was defined as the successful delivery and release of a WATCHMAN Device into the LAA. A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted.

10.2.2 Final Device Size Implanted

Table 10-7 provides an accounting of the various WATCHMAN Device sizes released and implanted in the PROTECT AF study for the randomized cohort. A total of 408 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.

Table 10-7. Final Device Size Implanted

21 mm	102/408 (25.0)
24 mm	144/408 (35.3)
27 mm	115/408 (28.2)
30 mm	32/408 (7.8)
33 mm	15/408 (3.7)

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10.2.3 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.

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 10-8.

Table 10-8. Full Device Recaptures

0	261/449 (58.1)
1	108/449 (24.1)
2	45/449(10.0)
3	18/449 (4.0)
4 +	17/449 (3.8)

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, 82.2% of all implant procedures used either one device or required only one full device recapture. There was no evidence that patients experiencing procedure or device related adverse events were associated with the number of full recaptures (p=0.48 from a chi-square test).

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10.3 Pivotal Study Results

10.3.1 Primary Efficacy Analysis

10.3.1.1 Intent-to-Treat

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.

Results for the primary efficacy endpoint comprised of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in Table 10-9.

Table 10-9. Primary Efficacy Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**		**Non-inferiority**	**Superiority**
600	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
900	463	20/582.3	3.4 (2.1, 5.2)	244	16/318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837

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.

- At 900 patient years, the primary efficacy event rate was 3.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.68, a 32% lower rate of efficacy events in the Device group than in the Control group. This compares to a relative risk of 0.76 at 600 patient years, an improvement of 10%
- The 95% credible interval for the rate ratio was (0.37, 1.41). The value of the upper bound for the rate ratio (1.41) is 0.59 lower than the non-inferiority margin of 2.0.
- The 900 patient year analysis shows stronger efficacy results than the 600 patient year analysis (24% lower event rate than Control), due to the longer follow-up of most patients.

The posterior probability of non-inferiority of 0.998 exceeds the pre-specified non-inferiority criterion meeting the statistical objective in the PROTECT AF study. Non-inferiority of the Device compared to the Control is demonstrated at both 600 and 900 patient years.

The primary efficacy event rate for the Control group of 5.0 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 10-10 summarizes the specific primary efficacy events by randomized group.

Table 10-10. 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	14	3.0	5	2.0
Death (Cardiovascular or Unexplained)	3	0.6	5	2.0
Stroke - Hemorrhagic	1	0.2	6	2.5
Systemic Embolism	2	0.4	0	0.0

While 14 patients in the Device group experienced ischemic stroke, it is important to note that these events include 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with ischemic stroke occurring on the day of the procedure due to air embolism and excessive sedation. With exception of 1 patient who experienced continuing mild neurological deficit on the right side, all symptoms associated with ischemic strokes experienced on the day of the procedure fully resolved in the patients. Without these 6 events, the Device ischemic stroke rate (8/463, 1.7%) is comparable to the Control rate.

The rate of cardiovascular or unexplained death and hemorrhagic stroke is lower in the Device group; notably, there were no device or procedure related deaths in the Device group. The rate of systemic embolism is comparable between groups.

Primary efficacy events used in the primary analysis are listed in Table 10-11. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events.

Table 10-11. Primary Efficacy Events - Initial Event (Intent-to-Treat)

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	29AUG2007	29AUG2007	05AUG2008	Death*
8		Device	05DEC2005	07DEC2005	15JAN2008	Systemic Embolism
9		Device	09MAR2005	10MAR2005	30JUL2005	Death*
10		Device	01AUG2006	01AUG2006	04AUG2006	Systemic Embolism
11		Device	29JAN2007	30JAN2007	14SEP2007	Stroke - Ischemic
12		Device	25JAN2008	29JAN2008	29JAN2008	Stroke - Ischemic

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13		Device	11NOV2005	11NOV2005	11NOV2005	Stroke - Ischemic
14		Device	13FEB2007	15FEB2007	19FEB2008	Stroke - Ischemic
15		Device	10JUL2007	19JUL2007	28SEP2007	Stroke - Ischemic
16		Device	17JUL2006	18JUL2006	18JUL2006	Stroke - Ischemic
17		Device	19SEP2006	21SEP2006	06MAY2008	Stroke - Ischemic
18		Device	30AUG2006	11SEP2006	15JUL2008	Stroke - Ischemic
19		Device	21FEB2007	21FEB2007	07JUL2007	Stroke - Ischemic
20		Device	21MAY2007	NA**	24MAY2007	Stroke - Ischemic
1		Control	25JUL2006	NA	28SEP2008	Stroke - Hemorrhagic
2		Control	31OCT2005	NA	12NOV2006	Stroke - Ischemic
3		Control	11MAR2008	NA	29MAR2008	Stroke - Ischemic
4		Control	09AUG2005	NA	31AUG2005	Stroke - Hemorrhagic
5		Control	25MAY2007	NA	04OCT2008	Stroke - Ischemic
6		Control	03APR2007	NA	10DEC2007	Death*
7		Control	23JAN2006	NA	10MAR2007	Death*
8		Control	06JUN2006	NA	03AUG2007	Death*
9		Control	23JAN2008	NA	12MAY2008	Stroke – Hemorrhagic
10		Control	23APR2007	NA	03MAR2008	Stroke - Hemorrhagic
11		Control	21MAR2007	NA	19JUN2007	Death*
12		Control	04MAY2007	NA	15MAR2008	Death*
13		Control	10AUG2007	NA	11DEC2007	Stroke - Hemorrhagic
14		Control	31OCT2007	NA	17MAY2008	Stroke - Ischemic
15		Control	15AUG2006	NA	03APR2008	Stroke - Hemorrhagic
16		Control	10NOV2006	NA	22DEC2007	Stroke - Ischemic

* Cause of death located in Table 10-21.

** Patient [redacted] 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 10-2** and Table 10-12.

Figure 10-2. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Intent-to-Treat)

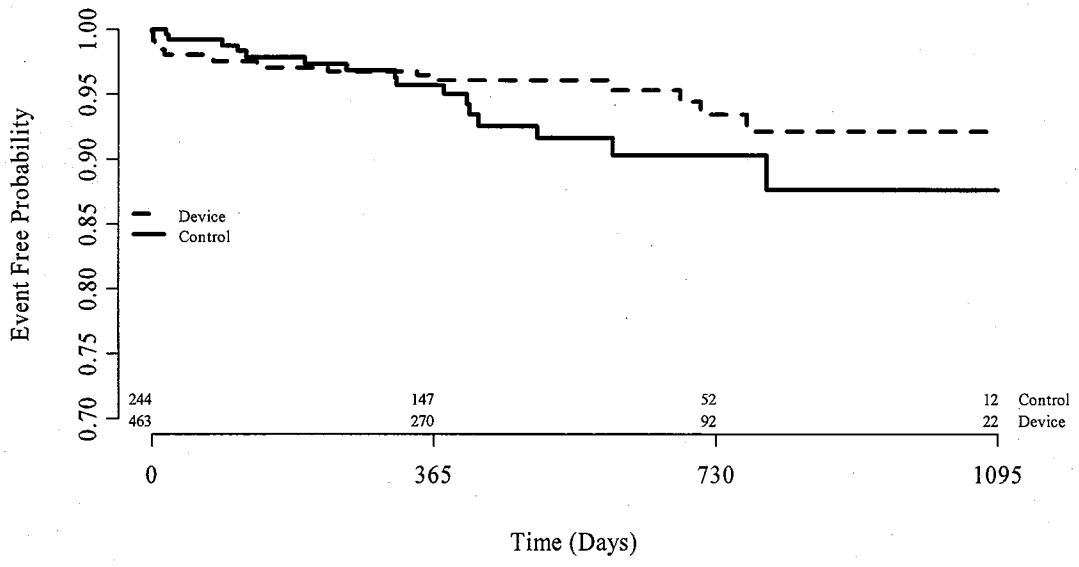

Table 10-12. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Intent-to-Treat)

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	98.5	0	0	100.0
45-days	2	9	98.0	2	2	99.2
6-months	4	13	97.1	3	5	97.9
1-year	2	15	96.4	4	9	95.7
2-year	4	19	93.5	6	15	90.3
3-year	1	20	92.1	1	16	87.7

The largest portion of the primary efficacy events for the Device group (7/20, 35%) occurred within 7-days of randomization, with 1 of these events (a stroke) occurring after randomization but prior to implant and 5 other events (also strokes) occurring on the day of implant procedure. For the reasons described below, these 5 procedural events were also, and more appropriately, characterized as safety events. At 3 years, the Device group had a Kaplan Meier estimated event rate of 7.9% compared to a 12.3% event rate in the Control group, a 36% lower relative rate for the Device group.

10.3.1.2 Post Procedure Analysis (Pre-Specified)

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) Are there any adverse events that the clinician needs to be aware of to educate the patient before leaving the hospital?

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed including 1 patient who experienced a stroke before a device was implanted and 13 patients who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events. As these 5 events occurred on the date of the implant and were primarily safety related, they were removed from the post procedure analysis (in part, to avoid double counting of the events as both efficacy and safety). Results of the primary efficacy endpoint once these 19 patients were removed are displayed in Table 10-13.

Table 10-13. Primary Efficacy Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	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
900	444	14/572.3	2.4 (1.4, 4.0)	244	16/318.0	5.0 (2.8, 7.6)	0.49 (0.24, 1.06)	>0.999	0.965

- At 900 patient years, the primary efficacy rate was 2.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group.
- This yielded a rate ratio, or relative risk, of 0.49, a 51% lower rate of efficacy events in the Device group. This compares to a relative risk of 0.52 at 600 patient years.
- The 95% credible interval for the rate ratio based on the Bayesian model was (0.24, 1.06).

The probability of superiority of 0.965 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 10-3** and Table 10-14.

Figure 10-3. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Post Procedure)

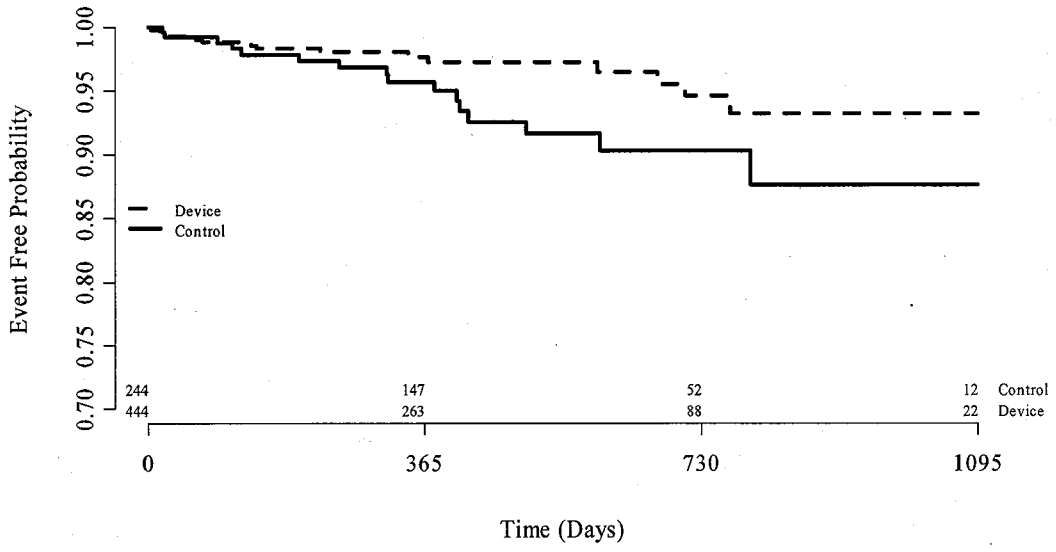

Table 10-14. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Post Procedure)

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	99.2
6-months	4	7	98.3	3	5	97.9
1-year	2	9	97.7	4	9	95.7
2-year	4	13	94.6	6	15	90.3
3-year	1	14	93.2	1	16	87.7

At 3 years, the Device group had a Kaplan Meier estimated post procedure efficacy event rate of 6.8% compared to a 12.3% post procedure efficacy event rate in the Control group, a 45% lower relative rate for the Device group.

10.3.1.3 Per-Protocol Analysis (Pre-Specified)

In the PROTECT AF study, one potential bias 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 if so, what are my chances? and 2) What are the outcomes after being taken off warfarin therapy?

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare effectiveness in patients who successfully received their assigned treatment. 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. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for Device patients. Results for the primary efficacy endpoint for this analysis population are displayed in Table 10-15.

Table 10-15. Primary Efficacy Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	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
900	387	10/484.4	2.1 (1.0, 3.7)	241	15/317.5	4.7 (2.6, 7.2)	0.44 (0.20, 1.03)	>0.999	0.971

- At 900 patient years, the primary efficacy rate was 2.1 events per 100 patient years for the Device group and 4.7 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.44, a 56% lower rate of efficacy events in the Device group. This compares to a relative risk of 0.47 at 600 patient years.
- The 95% credible interval for the rate ratio based on the Bayesian model was (0.20, 1.03).
- 86% (387/449) of Device group patients were treated successfully (defined as successfully implanted and able to discontinue warfarin therapy).

The probability of superiority of 0.971 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in Figure 10-4 and Table 10-16.

Figure 10-4. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Per-Protocol)

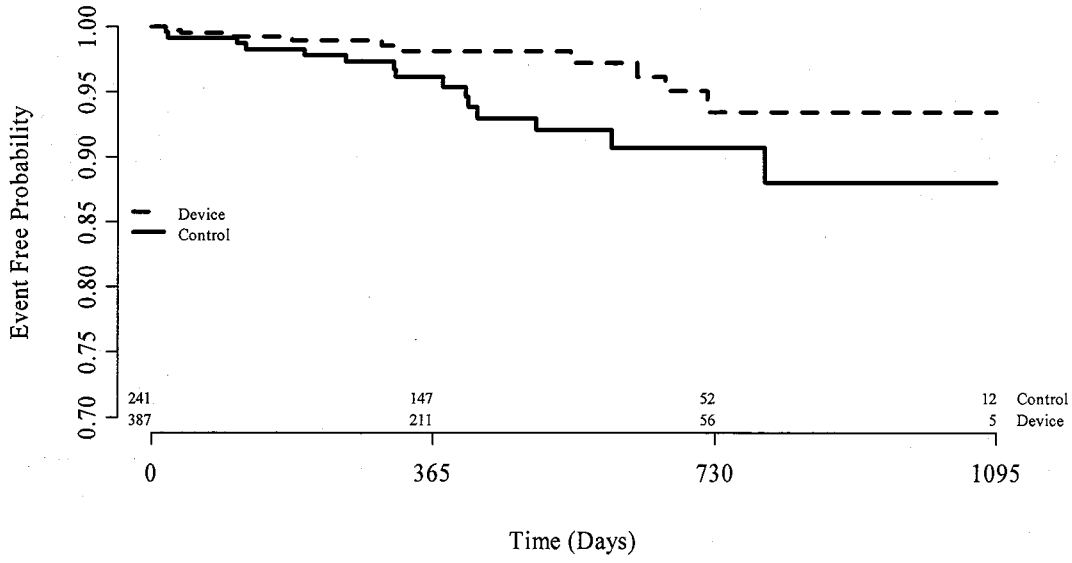

Table 10-16. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Per-Protocol)

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	99.5	2	2	99.2
6-months	1	3	99.2	2	4	98.3
1-year	3	6	98.1	4	8	96.1
2-year	4	10	93.4	6	14	90.7
3-year	0	10	93.4	1	15	88.0

At 3 years, the Device group had a Kaplan Meier estimated per-protocol efficacy event rate of 6.6% compared to an 12.0% per-protocol efficacy event rate in the Control group, a 45% lower relative rate for the Device group.

10.3.1.4 Stroke (Intent-to-Treat)

As the largest contributor to the primary efficacy endpoint, an analysis of stroke under Intent-to-Treat was completed. This analysis, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates, is provided in Table 10-17, Figure 10-5. Kaplan-Meier Curve: Freedom from Stroke (Intent-to-Treat)and Table 10-18.

Table 10-17. Bayesian Model Results: Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	454	14/409.3	3.4 (1.9, 5.5)	238	8/223.6	3.6 (1.5, 6.3)	0.96 (0.43, 2.57)	0.927	0.488
900	463	15/582.9	2.6 (1.5, 4.1)	244	11/318.1	3.5 (1.7, 5.7)	0.74 (0.36, 1.76)	0.988	0.731

- At 900 patient years, the stroke rate was 2.6 events per 100 patient years for the Device group and 3.5 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.74, a 26% lower rate of stroke in the Device group. This compares to a relative risk of 0.89 at 600 patient years, an improvement of 15%.
- The 95% credible interval for the rate ratio was (0.36, 1.76).

The posterior probability of non-inferiority of 0.988 exceeds the pre-specified non-inferiority.

Figure 10-5. Kaplan-Meier Curve: Freedom from Stroke (Intent-to-Treat)

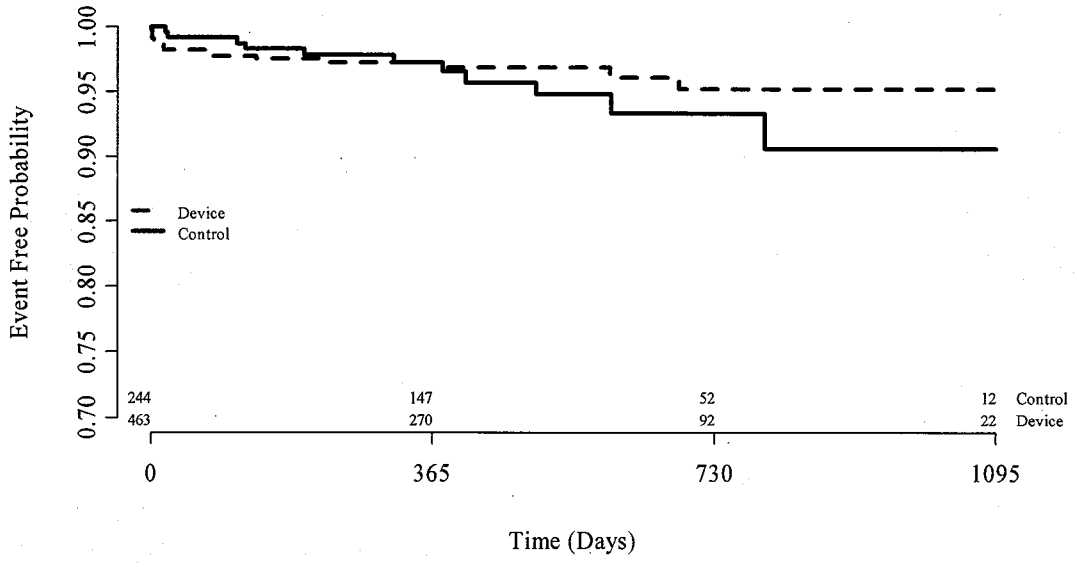

Table 10-18. Kaplan-Meier Estimates: Freedom from Stroke (Intent-to-Treat)

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	2	8	98.3	2	2	99.2
6-months	3	11	97.5	2	4	98.3
1-year	1	12	97.2	2	6	97.2
2-year	3	15	95.2	4	10	93.4
3-year	0	15	95.2	1	11	90.6

The largest portion of the strokes for the Device group (6/15, 40%) occurred within 7 days of randomization; however these strokes occurred on or before the day of the procedure and are not reflective of the long term efficacy of the device. At 3 years, the Device group had a Kaplan Meier estimated stroke event rate of 4.8% compared to a 9.4% stroke rate in the Control group, a 49% lower relative rate for the Device group.

Under a post procedure analysis of the stroke endpoint, the stroke rate was 1.6 events per 100 patient years for the Device group and 3.5 events per 100 patient years for the Control group. As described above, 6 strokes occurred either after randomization but before a device was implanted (1 patient) or on

the day of the procedure due to the safety complications of air embolism and excessive sedation (5 patients). The post procedure analysis yielded a relative risk, or rate ratio, of 0.45, a 55% lower stroke rate in the Device group. The 95% credible interval for the rate ratio was (0.19, 1.17).

10.3.2 All Cause Mortality (Intent-to-Treat)

Analysis of all cause mortality, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates, is provided in Table 10-19, Figure 10-6 and Table 10-20, respectively.

Table 10-19. Bayesian Model Results: All-Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
600	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)	0.991	0.779
900	463	17/593.6	2.9 (1.7, 4.4)	244	15/320.3	4.7 (2.5, 7.1)	0.61 (0.32, 1.32)	0.999	0.889

- At 900 patient years, the mortality rate was 2.9 events per 100 patient years for the Device group and 4.7 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.61, a 39% lower rate of death in the Device group. This compares to a relative risk of 0.69 at 600 patient years, an improvement of 12%.
- The 95% credible interval for the rate ratio was (0.32, 1.32).

The posterior probability of non-inferiority of 0.999 exceeds the pre-specified non-inferiority criterion.

Figure 10-6. Kaplan-Meier Curve: Freedom from All Cause Mortality (Intent-to-Treat)

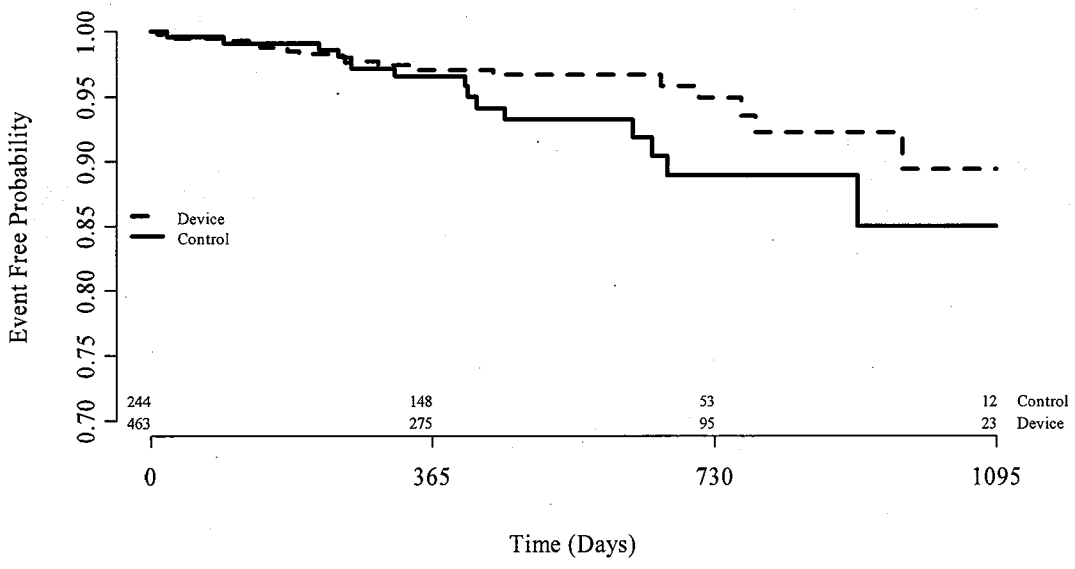

Table 10-20. Kaplan-Meier Estimates: Freedom from All Cause Mortality (Intent-to-Treat)

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	99.6	1	1	99.6
6-months	4	6	98.6	1	2	99.2
1-year	5	11	97.1	5	7	96.6
2-year	3	14	94.9	7	14	88.9
3-year	3	17	89.4	1	15	85.0

The estimated all cause mortality rates were similar between groups through 1 year, and thereafter mortality in the Device group tended to be lower than that in the Control group. At 3 years, the Device group had a Kaplan Meier estimated all cause mortality event rate of 10.6% compared to a 15.0% all cause mortality rate in the Control group, a 29% lower relative rate for the Device group.

No deaths in the Device group were adjudicated as device or procedure-related causes.

Table 10-21summarizes the patient deaths by randomized group.

Table 10-21. 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	29AUG2007	29AUG2007	05AUG2008	Complications from subdural hematoma
	Device	05DEC2005	07DEC2005	05AUG2008	Colitis
	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	11OCT2006	11OCT2006	14NOV2008	Degenerative neurologic
	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	21AUG2006	NA	01JUN2008	Renal failure
	Control	09AUG2005	NA	31AUG2005	Secondary to hemorrhagic stroke.
	Control	13MAR2006	NA	15SEP2008	Cancer
	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	23APR2007	NA	24JUL2008	Secondary to hemorrhagic stroke
	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	Secondary to hemorrhagic stroke.
	Control	21DEC2007	NA	20AUG2008	Renal failure
	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 10-11.
[2] – Death is linked to a primary efficacy event.
[3] – Patients had a primary efficacy event and were included in Table 10-11; CEC adjudicated the deaths as neither device or procedure related

Two strokes in the Device group were fatal compared to five strokes in the Control group Neither of the fatal strokes in the Device group was 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. Four of the five fatal strokes in the Control group were hemorrhagic strokes while the patient was receiving warfarin therapy and one stroke was ischemic.

10.3.3 Primary Safety Analysis

10.3.3.1 Intent-to-Treat

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.

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

Results for the primary safety endpoint are displayed in Table 10-22. Credible intervals are calculated from the same Bayesian model used for the primary efficacy endpoint.

Table 10-22. Primary Safety Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
600	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)
900	463	48/554.2	8.7 (6.4, 11.3)	244	13/312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)

- At 900 patient years, the primary safety rate was 8.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 2.08. This compares to a relative risk of 2.85 at 600 patient years, an improvement of 27%.
- The 95% credible interval for the rate ratio based on the Bayesian model was (1.18, 4.13).

Table 10-23 summarizes the types of primary safety events by randomized group

Table 10-23. 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*	22	4.8	0	0.0
Gastrointestinal Bleeding	10	2.2	6	2.5
Stroke – Ischemic	5	1.1	0	0.0
Stroke – Hemorrhagic	1	0.2	6	2.5
Device Embolization	3	0.6	0	0.0
Esophageal Tear	1	0.2	0	0.0
Cranial Bleed	2	0.4	0	0.0
Major Bleed Requiring Transfusion	2	0.4	0	0.0
Arrhythmias	1	0.2	0	0.0
Bruising - Hematoma	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.

A higher rate of early primary safety events in the Device group compared to the Control group is not unexpected due to the nature of the implant procedure. The majority of primary safety events in the Device group (27/48, 56%) occurred on the day of the procedure. These 27 events consisted of 17 serious effusions, 5 ischemic strokes, 1 device embolization and 4 other events. Nine of the 48 safety events in the Device group occurred within 7 days of the procedure; therefore only 12/48 safety events in the Device group occurred more than 7 days post procedure. Safety events in the Control group occurred later and on a continuing basis. Ischemic and hemorrhagic stroke events have been categorized as both a safety and efficacy event as described above. Further explanation is provided regarding the safety events of both treatment groups below:

- Of the 463 randomized Device group patients there were 22 pericardial effusions considered to be serious (4.8%). Seventeen of the effusions occurred on the day of the procedures and 5 occurred post procedure. Of the 22 total effusions, 7 effusions required surgical intervention with a median hospitalization of 6 days. The remaining 15 effusions were treated percutaneously with fluid drainage with a median hospitalization of 4 days; however, none of the effusions resulted in death, nor did any of the patients experience permanent complications. Based on investigator experience with the device, the rate of pericardial effusions decreased in the second half of the study.
- The rate of gastrointestinal bleeds in the Device group versus the Control group was essentially the same at 2.2% and 2.5%, respectively. However, 4 of 10 gastrointestinal bleeds in the Device group occurred while the patients were still taking warfarin per the 45-day post procedure requirement. The remaining 6 gastrointestinal bleeds in the Device group occurred post warfarin cessation while the patients were on a 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 reported occurrence in left heart 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. With the exception of 1 patient experiencing continuing mild neurological deficit on the right side, symptoms of the other patients experiencing ischemic stroke during the procedure completely resolved.
- There was one (0.2%) hemorrhagic stroke in the Device group versus six (2.5%) 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 6 hemorrhagic strokes in the Control group, 4 resulted in death. The median number of days spent in the hospital was 15.
- Of the 463 randomized Device group patients, three (0.6%) embolizations occurred. Two of the three were surgically removed and one removed percutaneously.

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Primary safety events used in the primary analysis are listed in Table 10-24. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events.

Table 10-24. 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	29AUG2007	29AUG2007	28JUL2008	Cranial Bleed
20		Device	15FEB2008	15FEB2008	15FEB2008	Pericardial Effusion-Serious
21		Device	11DEC2007	11DEC2007	11DEC2007	Esophageal Tear from TEE
22		Device	19OCT2005	19OCT2005	19OCT2005	Pericardial Effusion-Serious
23		Device	29MAR2005	30MAR2005	30MAR2005	Pericardial Effusion-Serious
24		Device	05DEC2005	07DEC2005	12JUL2008	Gastrointestinal Bleeding
25		Device	30MAR2006	31MAR2006	31MAR2006	Pericardial Effusion-Serious
26		Device	27NOV2006	28NOV2006	15JAN2007	Device Embolization
27		Device	14MAR2007	15MAR2007	15MAR2007	Pericardial Effusion-Serious
28		Device	13DEC2007	14DEC2007	14DEC2007	Pericardial Effusion-Serious
29		Device	25JAN2008	29JAN2008	29JAN2008	Stroke - Ischemic
30		Device	27JUL2006	28JUL2006	28JUL2006	Pericardial Effusion-Serious
31		Device	28NOV2005	29NOV2005	29NOV2005	Device Embolization
32		Device	11NOV2005	11NOV2005	11NOV2005	Stroke - Ischemic

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33		Device	11JUN2007	13JUN2007	02JUL2007	Cranial Bleed
34		Device	09JUL2007	17JUL2007	05FEB2008	Gastrointestinal Bleeding
35		Device	21AUG2007	23AUG2007	24AUG2007	Pericardial Effusion-Serious
36		Device	22OCT2007	07NOV2007	08NOV2007	Pericardial Effusion-Serious
37		Device	13NOV2007	03DEC2007	03DEC2007	Pericardial Effusion-Serious
38		Device	13MAR2007	16MAR2007	16MAR2007	Pericardial Effusion-Serious
39		Device	10AUG2007	21AUG2007	28JAN2008	Gastrointestinal Bleeding
40		Device	11FEB2008	25FEB2008	25FEB2008	Pericardial Effusion-Serious
41		Device	23JAN2007	23JAN2007	23JAN2007	Pericardial Effusion-Serious
42		Device	17JUL2006	18JUL2006	18JUL2006	Stroke - Ischemic
43		Device	18OCT2006	20OCT2006	20OCT2006	Pericardial Effusion-Serious
44		Device	02JUN2006	02JUN2006	16JUN2006	Pericardial Effusion-Serious
45		Device	09MAY2008	09MAY2008	06JUN2008	Major Bleed Requiring Transfusion
46		Device	04APR2007	11APR2007	05JUN2007	Device Embolization
47		Device	18SEP2007	19SEP2007	03DEC2007	Gastrointestinal Bleeding
48		Device	03JUN2008	03JUN2008	04JUN2008	Bruising - Hematoma
1		Control	25JUL2006	NA	28SEP2008	Stroke - Hemorrhagic
2		Control	13JUN2006	NA	19FEB2007	Gastrointestinal Bleeding
3		Control	09AUG2005	NA	31AUG2005	Stroke - Hemorrhagic
4		Control	18MAR2008	NA	10SEP2008	Gastrointestinal Bleeding
5		Control	23JAN2008	NA	12MAY2008	Stroke - Hemorrhagic
6		Control	09APR2008	NA	08JUL2008	Gastrointestinal Bleeding
7		Control	13JUL2005	NA	01MAY2006	Anemia Requiring Transfusion
8		Control	23APR2007	NA	03MAR2008	Stroke - Hemorrhagic
9		Control	27NOV2006	NA	24DEC2006	Gastrointestinal Bleeding
10		Control	10AUG2007	NA	11DEC2007	Stroke - Hemorrhagic
11		Control	15AUG2006	NA	03APR2008	Stroke - Hemorrhagic
12		Control	27FEB2007	NA	11MAR2008	Gastrointestinal Bleeding
13		Control	10JAN2007	NA	06SEP2007	Gastrointestinal Bleeding

Figure 10-7 and Table 10-25 display results from a Kaplan-Meier analysis of the primary safety events.

Figure 10-7. Kaplan-Meier Curve: Freedom from Primary Safety Event (Intent-to-Treat)

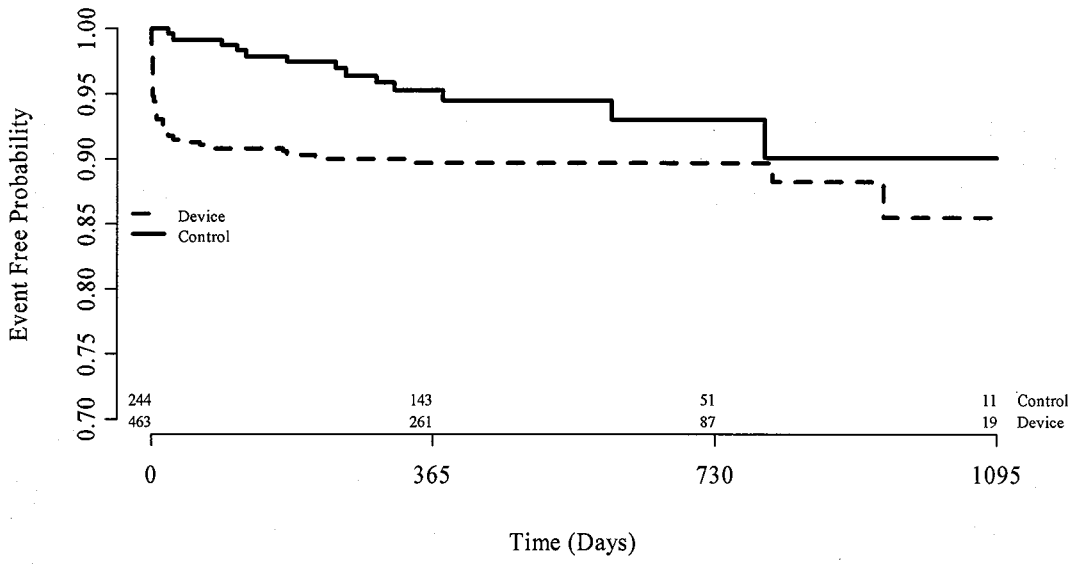

Table 10-25. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	32	32	93.1	0	0	100.0
45-days	7	39	91.5	2	2	99.2
6-months	5	44	90.3	4	6	97.4
1-year	2	46	89.7	4	10	95.2
2-year	0	46	89.7	2	12	93.0
3-year	2	48	85.5	1	13	90.1

The majority of primary safety events in the Device group (27/48, 56%) occurred on the day of implant. The observed trend in long term warfarin events in the Control group would be expected to continue beyond 3 years as data for 3-5 year event rates in the SPAF trials has previously demonstrated an increase in events over time.

10.3.3.2 Primary Safety Endpoint – Post Procedure

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced procedural strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events and 22 patients were removed who experienced procedural events including pericardial effusions. This analysis is intended to provide an alternate way to assess post procedural, long term safety which is an issue with warfarin, by evaluating the risk/benefit profile after the acute procedure risks with the device. As such, these 27 patients with procedure events were removed from this analysis. Results of the primary safety endpoint results are displayed in Table 10-26.

Table 10-26. Primary Safety Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
600	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)
900	422	21/544.1	3.9 (2.4, 5.8)	244	13/312.0	4.2 (2.2, 6.7)	0.93 (0.48, 1.97)

- At 900 patient years, the primary safety rate was 3.9 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.93, a 7% lower rate of safety events in the Device group. This compares to a relative risk of 1.11 at 600 patient years, an improvement of 16%.
- The 95% credible interval for the rate ratio based on the Bayesian model was (0.48, 1.97). Twelve of the 21 device events occurred while patients were on warfarin.

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Figure 10-8 and Table 10-27 display results from a Kaplan-Meier analysis of the primary safety events.

Figure 10-8. Kaplan-Meier Curve: Freedom from Primary Safety Event (Post Procedure)

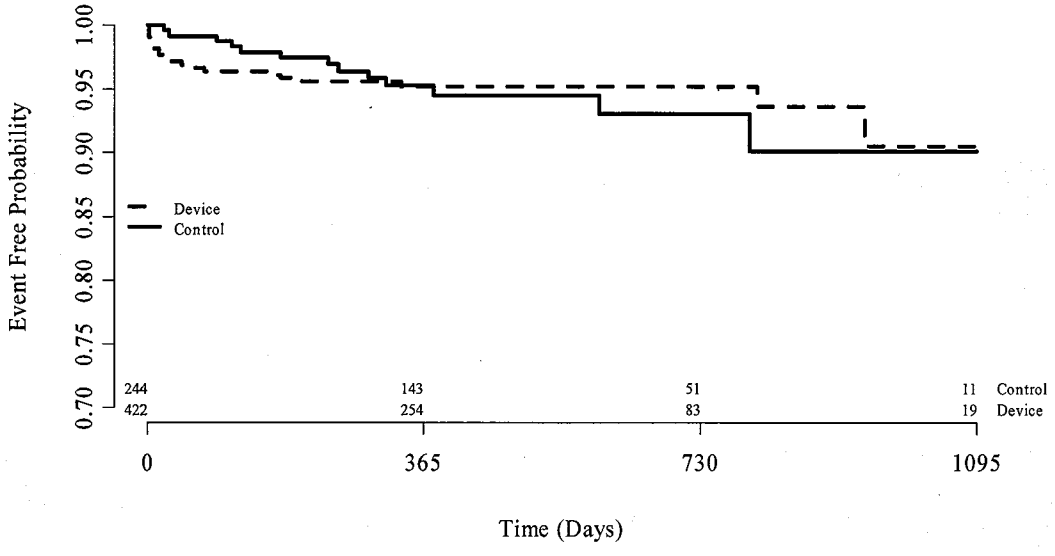

Table 10-27. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	8	8	98.1	0	0	100.0
45-days	5	13	96.9	2	2	99.2
6-months	4	17	95.8	4	6	97.4
1-year	2	19	95.2	4	10	95.2
2-year	0	19	95.2	2	12	93.0
3-year	2	21	90.5	1	13	90.1

Under the post procedure analysis, at 3 years, the Device group had a Kaplan Meier estimated post procedure primary safety event rate of 9.5% compared to a 9.9% post procedure safety event rate in the Control group. After the first 7 days, the safety profile of the Device group with a primary safety event rate of 7.6% is slightly better than the 9.9% rate in the Control group.

10.3.3.3 Per-Protocol Analysis (Pre-Specified)

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare effectiveness in patients who successfully received their assigned treatment. 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. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for Device patients. Results for the primary safety endpoint for this analysis population are displayed in Table 10-28.

Table 10-28. Primary Safety Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

Patient-Year Dataset	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
600	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)
900	387	8/483.9	1.7 (0.7, 3.1)	241	13/311.4	4.2 (2.2, 6.7)	0.40 (0.16, 0.97)

- At 900 patient years, the primary safety event rate was 1.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group.
- These rates yielded a relative risk, or rate ratio, of 0.40, a 60% lower rate of safety events in the Device group than in the Control group. This compares to a relative risk of 0.46 at 600 patient years, an improvement of 13%.
- The 95% credible interval for the rate ratio based on the Bayesian model was (0.16, 0.97).

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Results from Kaplan-Meier analyses for the primary safety endpoint are given in Figure 10-9 and Table 10-29.

Figure 10-9. Kaplan-Meier Curve: Freedom from Primary Safety Event (Per-Protocol)

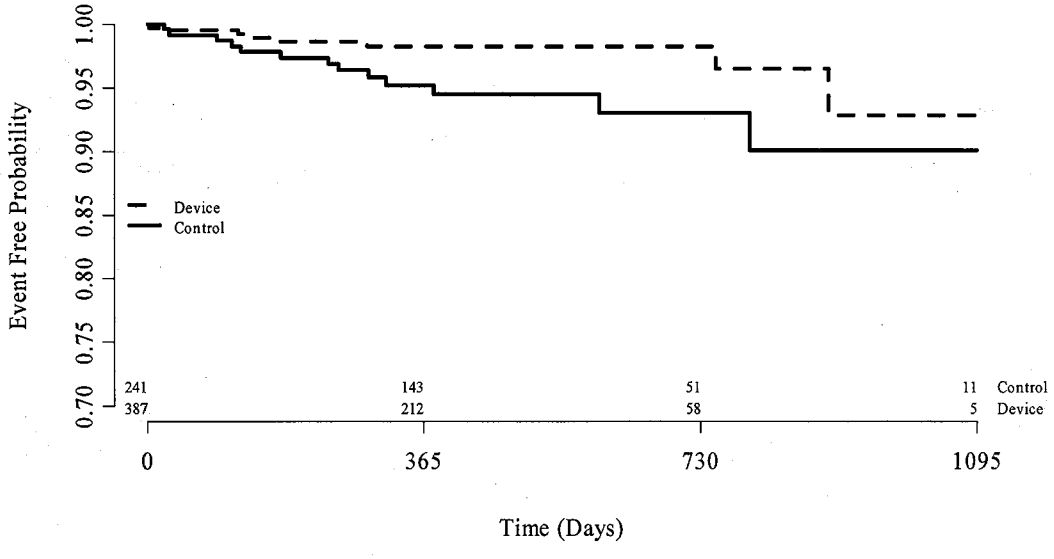

Table 10-29. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Per-Protocol)

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	99.5	2	2	99.2
6-months	3	5	98.6	4	6	97.4
1-year	1	6	98.3	4	10	95.2
2-year	0	6	98.3	2	12	93.0
3-year	2	8	92.9	1	13	90.1

At 3 years, the Device group had a Kaplan Meier estimated per-protocol safety event rate of 7.1% compared to an 9.9% per-protocol safety event rate in the Control group, a 28% lower relative rate for the Device group.

10.3.3.4 Exploratory Safety Analysis: Pericardial 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.

All pericardial effusions were reported and adjudicated by the Clinical Events Committee (CEC).

In Table 10-30, 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 10-30. Pericardial Effusions by Site Experience

[redacted]			
Early Patients (1-3)	19/154 (12.3)	13/154 (8.4)	11/154 (7.1)
Late Patients (4+)	34/388 (8.8)	25/388 (6.4)	17/388 (4.4)
Total:	53/542 (9.8)	38/542 (7.0)	28/542 (5.2)

The overall effusion rate for any procedure/device related and any serious effusion categories decreased between early and late patient groups from 8.4% to 6.4% and 7.1% to 4.4%, respectively. Late patients implanted experienced a relative reduction of 23.8% and 38.0% in any procedure/device related and any serious effusions. As expected a site level learning curve related to a new procedure occurred.

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 10-31.

Table 10-31. 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+)	27/257 (10.5)	18/257 (7.0)	11/257 (4.3)
Early Patients (1-3)	9/79 (11.4)	6/79 (7.6)	4/79 (5.1)
Late Patients (4+)	7/131 (5.3)	7/131 (5.3)	6/131 (4.6)

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 (9.3-4.3 = 5.0%) while this same difference in the second half of the trial was (5.1-4.6 = 0.5%).

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 effusion rates decreased over time for the early patients (first three) and then plateaued in late patients with a rate of 4.6%.

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 ("Any Serious" in the above table). 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.

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
- introduction of short device
- modifications of the Access Sheath

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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.

In the continued access registry, only one serious effusion has occurred in 88 enrolled patients for a rate of 1.1%, reflective of the effects of continued training and experience.

11 Secondary Endpoints and Warfarin Analyses

11.1.1.1 Secondary Endpoints - Both Randomized Groups

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 **Section 10.3.2**. Analyses of pericardial effusions are presented in **Section 10.3.3.4**. All adverse events (i.e., individual complication rates) are summarized by treatment group in **Section 11.1.2**, by individual complication type, seriousness, and device/procedure relatedness.

11.1.1.2 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 11.1.2 (Adverse Events)** for analysis of individual complications for the Device group.

Results for secondary endpoints in the Device group are displayed in Table 11-1.

Table 11-1. Device Group Secondary Endpoints

Technical Success	408/449 (90.9)
Procedure Success	375/449 (83.5)
30-Day Major Complications	53/441 (12.0)

The device was successfully implanted in 90.9% (408/449) of Device group patients for whom an implant was attempted. Procedure success was achieved in 83.5% (375/449) of Device group patients for whom an implant was attempted. The percentage of patients experiencing a 30-Day Major Complication was 12.0% (53/441).

11.1.1.3 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, red eye, or thrombosis.

Results for secondary endpoints in the Control group are provided in Table 11-2and Table 11-3. 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 anticoagulation. 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 11-2. Control Group Secondary Endpoints – INR Related Endpoints

INR < 2.0	189/202 (93.6)
INR ≥2.0 to ≤ 3.0	197/202 (97.5)
INR >3.0 to < 4.0	149/202 (73.8)
INR ≥ 4.0	86/202 (42.6)
INR < 2.0	1170/3948 (29.6)
INR ≥2.0 to ≤ 3.0	2170/3948 (55.0)
INR >3.0 to < 4.0	446/3948 (11.3)
INR ≥ 4.0	162/3948 (4.1)

There were 202 Control group patients that had one or more INR draws documented; this is comparable to the 235 and 220 Control group patients that had a 45-day and 6-month follow-up visit, respectively, at the time of this analysis.

The majority of patients had a non-therapeutic/excessive INR value (93.6% less than 2.0, 73.8% between 3.0 and 4.0, and 42.6% above 4.0) at least once during follow-up.

The percent of the measurements that represented non-therapeutic INR or excessive anticoagulation was also calculated. Based on these measurements, patients remained in the therapeutic range (INR 2.0 - 3.0) only 55.0% of the time.

Table 11-3. Control Group Secondary Endpoints – Bleeding Complications

	N Events	Patient Years	Event Rate
Any Bleeding Event	9	307.79	2.92
Any Serious Bleeding Event	1	319.90	0.31

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.

11.1.1.4 Interruption of Therapy

Of the 244 randomized Control patients, 66 (27.0%) 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 11-4. 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.

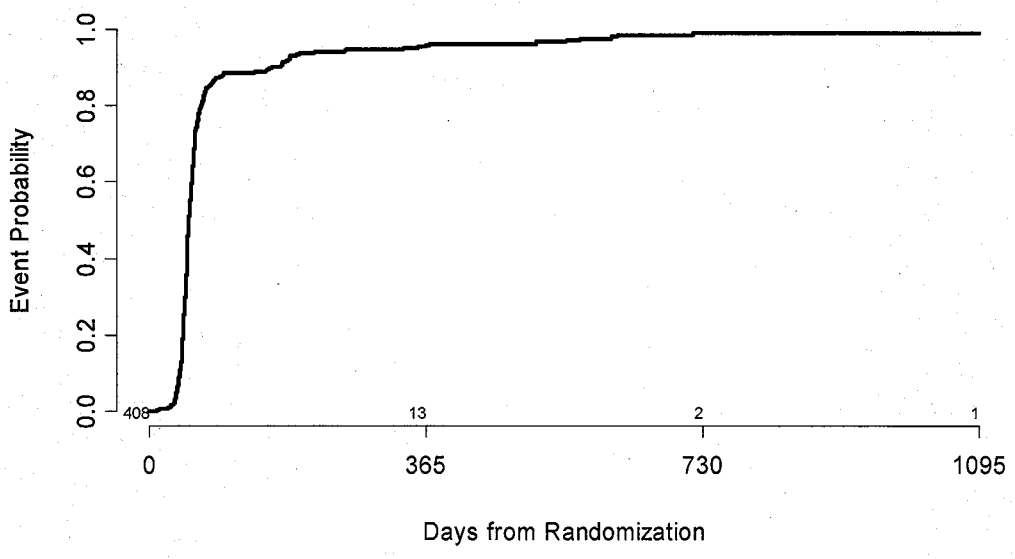
A majority of patients (87.0%) were able to discontinue warfarin therapy at 45 days. Subsequent follow-ups demonstrated an increase in the percent of patients discontinuing warfarin over the 45-day visit.

Table 11-4. Warfarin Discontinuation – Successfully Implanted Patients Only

45 day	349/401 (87.0)
6 month	347/375 (92.5)
12 month	261/280 (93.2)
24 month	95/101 (94.1)
36 month	22/25 (88.0)

Figure 11-1 displays 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 11-1. Time to Warfarin Discontinuation - Successfully Implanted Patients Only



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11.1.2 Adverse Events

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

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.

Table 11-5. Summary of Serious Adverse Events

	N Pts With Events	% of Patients	N Pts With Events	% of Patients
Gastrointestinal Bleeding	15	3.2	9	3.7
Death	13	2.8	10	4.1
Pericardial Effusion-Serious	23	5.0	0	0
Stroke - Ischemic	13	2.8	5	2.0
Other Study Related	15	3.2	2	0.8
Stroke - Hemorrhagic	1	0.2	6	2.5
Bruising - Hematoma	4	0.9	0	0
Adjudicated as Non-Event	2	0.4	1	0.4
Device Embolization	3	0.6	0	0
Pseudoaneurysm	3	0.6	0	0
Major Bleed Requiring Transfusion	2	0.4	1	0.4
Rectal Bleeding	1	0.2	1	0.4
Systemic Embolization	2	0.4	0	0
Cranial Bleed	2	0.4	0	0
Arrhythmias	2	0.4	0	0
Infection	2	0.4	0	0
Bleeding from Varicose Veins	1	0.2	0	0
Epistaxis	1	0.2	0	0
Hematuria	1	0.2	0	0
Thrombosis	1	0.2	0	0
Device Thrombus	1	0.2	0	0
Pleural Effusion	1	0.2	0	0
Pulmonary Edema	1	0.2	0	0
AV Fistula	1	0.2	0	0
Transient Ischemic Attack TIA	1	0.2	0	0
Anemia Requiring Transfusion	1	0.2	0	0
Totals:	**90**	**19.4**	**32**	**13.1**

Device or Procedure Related Events are summarized in Table 11-6. Events are divided into serious and non-serious events as determined by the CEC. For this table, classification into event types is based on CEC adjudication.

Table 11-6. Summary of Device or Procedure Related Events

CEC Adjudicated Serious Events		
[redacted]		
Pericardial Effusion-Serious	23	5.0
Other Study Related	14	3.0
Stroke - Ischemic	6	1.3
Bruising - Hematoma	4	0.9
Device Embolization	3	0.6
Pseudoaneurysm	3	0.6
Arrhythmias	2	0.4
Infection	2	0.4
Gastrointestinal Bleeding	1	0.2
Thrombosis	1	0.2
Device Thrombus	1	0.2
Pleural Effusion	1	0.2
Pulmonary Edema	1	0.2
AV Fistula	1	0.2
Transient Ischemic Attack TIA	1	0.2
Anemia Requiring Transfusion	1	0.2
Major Bleed Requiring Transfusion	1	0.2
Totals:	**57**	**12.3**
CEC Adjudicated Non-Serious		
[redacted]		
Other Study Related	13	2.8
Device Thrombus	10	2.2
Pericardial Effusion	8	1.7
Adjudicated as Non-Event	1	0.2
Bruising - Hematoma	1	0.2
Oral Bleeding	1	0.2
Inability to Move or Retrieve Device	1	0.2
Pleural Effusion	1	0.2
AV Fistula	1	0.2
Vasovagal Reactions	1	0.2
Anemia Requiring Transfusion	1	0.2
Air Embolism	1	0.2
Allergic Reaction to Contrast Media	1	0.2
Totals:	**37**	**8.0**

Table 11-7 summarizes the number of events and number of patients experiencing adverse events by type of event.

Table 11-7. 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	1117	85.9	311	67.2	543	92.0	158	64.8
Other Study Related	31	2.4	31	6.7	3	0.5	3	1.2
Gastrointestinal bleeding	19	1.5	17	3.7	10	1.7	9	3.7
Death	13	1.0	13	2.8	10	1.7	10	4.1
Pericardial Effusion-Serious	23	1.8	23	5.0	0	0	0	0
Stroke - ischemic	14	1.1	14	3.0	5	0.8	5	2.0
Epistaxis	10	0.8	7	1.5	2	0.3	2	0.8
Device thrombus	12	0.9	12	2.6	0	0	0	0
Bruising - Hematoma	7	0.5	7	1.5	2	0.3	2	0.8
Rectal bleeding	4	0.3	4	0.9	5	0.8	5	2.0
Pericardial effusion	9	0.7	9	1.9	0	0	0	0
Stroke - hemorrhagic	1	0.1	1	0.2	6	1.0	6	2.5
Hematuria	3	0.2	3	0.6	2	0.3	2	0.8
Bleeding from varicose veins	3	0.2	2	0.4	0	0	0	0
Oral bleeding	2	0.2	2	0.4	1	0.2	1	0.4
Device embolization	3	0.2	3	0.6	0	0	0	0
Pseudoaneurysm	3	0.2	3	0.6	0	0	0	0
Major Bleed Requiring Transfusion	2	0.2	2	0.4	1	0.2	1	0.4
Infection	3	0.2	3	0.6	0	0	0	0
Systemic embolization	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
Cranial bleed	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
Anemia Requiring Transfusion	2	0.2	2	0.4	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
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
Other Non-Study Related	1	0.1	1	0.2	0	0	0	0
Totals:	**1300**	**100.0**	**349**	**75.4**	**590**	**100.0**	**164**	**67.2**

12 Conclusion

The PROTECT AF study, involving 707 randomized 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.

The primary efficacy and safety results for these cohorts are summarized in Table 12-1.

Table 12-1. Summary of Primary Efficacy and Safety Results by Analysis Cohort

Intent-to-Treat	0.68 (0.37, 1.41)	2.08 (1.18, 4.13)
Post-Procedure	0.49 (0.24, 1.06)	0.93 (0.48, 1.97)
Per-Protocol	0.44 (0.20, 1.03)	0.40 (0.16, 0.97)

The PROTECT AF study results support the following statements:

- The WATCHMAN LAA Device was associated with a 32% reduction in primary endpoint events (stroke, cardiovascular death, and systemic embolism) at 900 patient years compared to patients on a standard warfarin regimen under the ITT analysis, meeting the non-inferiority criterion for the primary efficacy endpoint at both 600 and 900 patient years. The 900 patient year analysis shows stronger efficacy results than the 600 patient year analysis, due to the longer follow-up of most patients. Under a post procedure analysis, the efficacy of the WATCHMAN Device was superior to the Control.
- The WATCHMAN LAA Device was successfully implanted in a significant majority (91%) of patients in whom an implant was attempted.
- After successful implant of the WATCHMAN Device, 87% of patients were able to discontinue warfarin therapy after 45 days. This percentage increased as follow-up continued (e.g. 93% after 6 months).
- In a modified intent-to-treat analysis (post procedure), the efficacy of the WATCHMAN device was statistically superior to warfarin therapy. This analysis removed 6 patients with events which are not reflective of the long term efficacy of the device, namely: 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with ischemic stroke occurring on the day of the procedure due to air embolism and excessive sedation. These events are not reflective of the long term efficacy of the device.
- When comparing the effectiveness in patients who successfully received their assigned treatment (per protocol), the WATCHMAN device was statistically superior with a 56% lower relative rate of primary efficacy events in the Device group.

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- In analyzing the stroke endpoint, the Device group experienced 15 strokes (14 ischemic and 1 hemorrhagic) for an event rate of 2.6% per 100 years and the Control group had 11 strokes (5 ischemic and 6 hemorrhagic) for an event rate of 3.5% per 100 years.
- As described above, 6 of the 14 Device group ischemic strokes were either pre-procedure or were due to air embolism or excessive sedation during the procedure. Excluding these 6 events, the ischemic stroke rate was 1.4% per 100 years (8 ischemic strokes) in the Device group compared 1.6% in the Control group (5 ischemic strokes).
- The rate of hemorrhagic stroke was lower in the Device group compared to the Control group (0.2% vs. 2.5%, respectively). The stroke in the Device group was a spontaneous bleed which occurred 15 days post implant while the patient was still on warfarin therapy. No hemorrhagic strokes occurred in the Device group once patients discontinued warfarin. Of the 6 patients with hemorrhagic strokes in the Control group, 4 died.
- Device patients experienced a higher rate of safety events than the Control group; however, once the initial procedural risk passed, the safety profile of the Device was comparable to the Control. The principal procedural related safety events in the Device group were pericardial effusions which are a known complication of intracardiac procedures. The rate of pericardial effusions decreased over the course of the study attributable to investigator experience; none had lasting clinical complications.
- In the continued access registry, only one serious effusion has occurred in 88 enrolled patients for a rate of 1.1%, reflective of the effects of continued training and experience.
- None of the patient deaths in the Device group were adjudicated to be either device or procedure related.
- The substantial efficacy benefit of the WATCHMAN device in reduced mortality and hemorrhagic stroke outweighs the risk of procedural complications (including pericardial effusions and ischemic stroke), especially where the risks associated with ongoing warfarin therapy are well-known.
- The study established that the WATCHMAN Device provides a reasonable assurance of safety and effectiveness for patients with non-valvular AF who require anticoagulation therapy for potential thrombus formation.

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.

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The collaboration between FDA and Atritech achieved a rigorous randomized controlled study that provides valid scientific evidence needed for a determination of safety and effectiveness. The clinical study results demonstrate an overall positive risk/benefit profile for Device patients even with the risk of procedural complications.

Effective treatment for the prevention of stroke in AF patients represents a significant unmet clinical need. Current medical therapy is considered the primary therapeutic option, despite evidence of variable compliance and lifestyle challenges; however, no technology has been market-approved for stroke prevention in AF patients in the US. Clinicians who served on the Steering Committee during the PROTECT AF study believe this study provides quantitative evidence to represent the risk/benefit of the WATCHMAN procedure as a compelling alternative to warfarin therapy.

These data demonstrate that the WATCHMAN LAA Closure Technology is a safe and effective alternative to warfarin therapy in patients with non-valvular atrial fibrillation, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism and reducing the occurrence of warfarin complications of hemorrhagic stroke and major bleeding events.

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