The WATCHMAN®
PROTECT AF PIVOTAL CLINICAL REPORT
900 Patient-Year Results
Supplement to [redacted]

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

Device Name and Models: WATCHMAN® LAA Closure Technology

consisting of the following components:

WATCHMAN LAA Closure Device (Implant)

WATCHMAN Delivery System

WATCHMAN Access System

WATCHMAN Obturator

Name of Sponsor: Atritech, Inc.

Protocol Number: [redacted]

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1 Introduction

This report represents an update to the 600 patient year data presented in the Pre-Market Approval Application for the study entitled WATCHMAN Left Atrial Appendage System for Embolic PROTECTion of Patients with Atrial Fibrillation (PROTECT AF), [redacted]. The study was conducted under IDE #[redacted]at investigational centers in both the United States and Europe. This report includes 900 patient year data as collected through December 22, 2008.

2 Results

2.1 Demographics

2.1.1 Enrollment Accountability/Subject Disposition

Table 2-1 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 463 patients randomized to the Device group, 244 patients randomized to the Control group and 93 roll-in patients. A 2:1 randomization allocation ratio was implemented across investigational centers in the randomized cohort.

Table 2-1. 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:

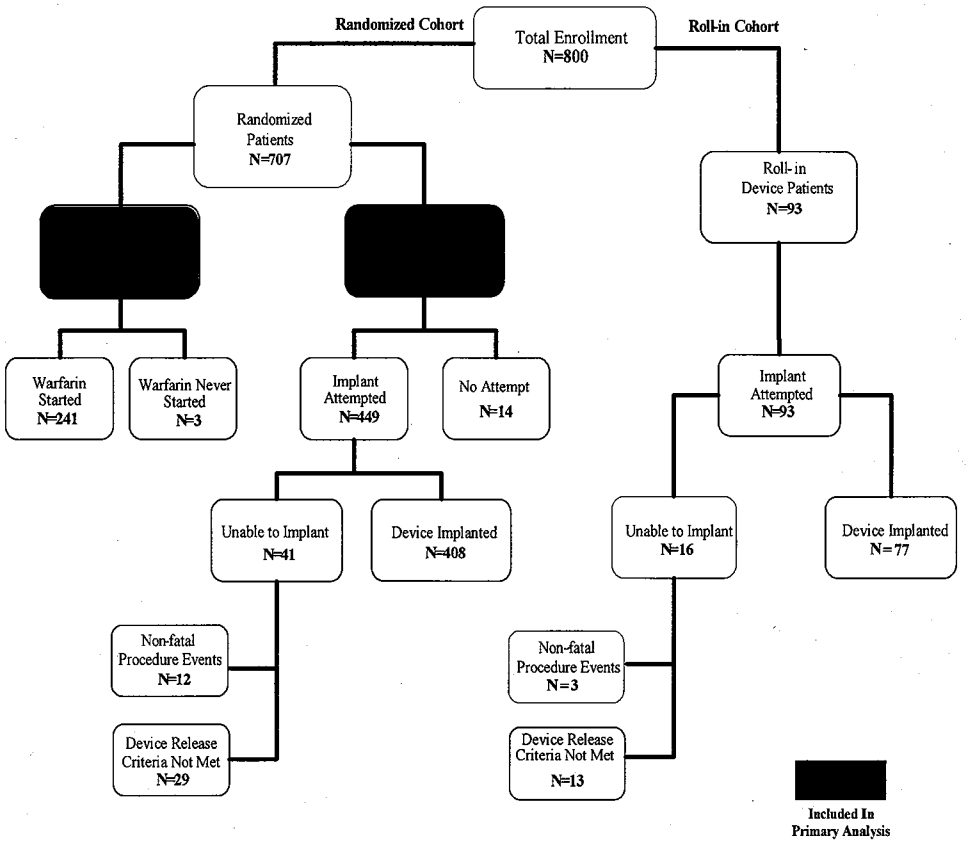
- (10) Patients in whom a procedure did not occur within protocol required window or patients in whom insurance was denied.
- (2) Patients withdrew consent prior to procedure.
- (1) Patient died between randomization and procedure.
- (1) Patient diagnosed with cardiac tumor prior to procedure.

A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted. The unsuccessful (discontinued) patients are accounted for in the enrollment flowchart **Figure 2-1**.

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 unsuccessful roll-in procedures are accounted for in the enrollment flowchart **Figure 2-1**. The procedural success rate in the roll-in group was lower than the randomized group; likely reflecting the presence of a learning curve for implanting the device.

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

Figure 2-1. 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 2-2 provides a listing of the 59 centers (55 in the U.S. and 4 in Europe) that enrolled at least one patient in the PROTECT AF study. The number of patients enrolled in each treatment group or roll-in group (if applicable) is listed. An acceptable enrollment distribution across centers occurred in the randomized cohort in that 20 centers randomized at least 10 or more patients in the study and 33 centers randomized at least 5 patients. The top three enrolling centers separately accounted for between 7 to 9% of the total study enrollment each.

One enrolling center utilized two implanting hospitals under one common IRB approval. Both hospitals are located in [redacted]. A primary implanting physician was assigned for each center. In August 2005, one IRB ([redacted]) withdrew approval for the study at its center after the occurrence of an adverse event, specifically a serious pericardial effusion requiring surgical intervention. All other participating centers and FDA were notified of this withdrawal as required.

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. Three roll-in centers (sites numbers 322, 364 and 377) requested and were granted more than 3 roll-in patients as a result of aborted procedures that occurred during the phase.

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Table 2-2. 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

2.1.2 Population/Subject Demographics

Table 2-3 summarizes the patient baseline demographic information of the randomized cohort. Baseline demographics demonstrate that patients in the two treatment groups are comparable.

Table 2-3. 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 atrial fibrillation presenting to the participating investigator were screened and randomized based on their characteristics and willingness to participate regardless of their gender or race. However, both treatment groups enrolled significantly more males in the study. This trend is consistent with the major trials for warfarin and other drug and device therapies being evaluated for atrial fibrillation. SPORTIF III, SPORTIF V and the ACTIVE W trials had enrollments of significantly larger male populations of 69%, 69% and 67% respectively. In the LAAOS surgical trial, 72.8% were male and 27.2% were female. The elective nature of the implant procedure and the statistics seen in other interventional treatments for atrial fibrillation is comparable to the PROTECT AF study.[88]

Baseline risk factors for enrolled patients are summarized in **Table 2-4**. There was no statistically significant difference in risk factors between groups.

Table 2-4. 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.

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.

To calculate a patient's $CHADS_2$ score, one point is assigned each for the presence of congestive heart failure, history of hypertension, age 75 years or older, and diabetes, and two points assigned for prior stroke or TIA.[129] The two most common risk factors in the study based on the $CHADS_2$ criteria were history of hypertension and age ≥ 75 years which occurred approximately 89.0-90.2% and 41.0-47.1% respectively. Previous cerebral ischemia, the least common risk factor, nonetheless was reported in 17.7-20.1% of patients.

Paroxysmal AF, defined as an intermittent form of atrial fibrillation that is characterized by a sudden onset and abrupt cessation of this rhythm, was the presenting rhythm in 40.6-43.2% of subjects in both groups. The second most common AF pattern reported was permanent AF, defined as ongoing atrial fibrillation that fails to terminate using cardioversion, or is terminated but reoccurs, which accounted for 34.6-38.1% of patients in the study.

Baseline LAA characteristics recorded and reported by the site for enrolled patients are summarized in **Table 2-5**. There was no statistically significant difference in characteristics between groups.

Table 2-5. Baseline LAA Characteristics - Site Reported

No. of LAA lobes			0.4208
One	221/460 (48.0)	124/242 (51.2)	
More than one	239/460 (52.0)	118/242 (48.8)	
LAA length, mm	30.5 ± 6.8 457 (2.2, 52.0)	30.6 ± 7.3 239 (2.6, 61.5)	0.8642
LAA ostium diameter, mm	21.5 ± 3.9 457 (1.6, 37.1)	21.9 ± 3.9 239 (1.5, 34.0)	0.2338

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

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

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

2.1.3 Follow-up Compliance

Table 2-6 provides an accounting of follow-up compliance achieved in the PROTECT AF study. Expected visits are based on visit windows defined in the protocol. Visit windows closed prior to December 1, 2008, are considered expected.

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

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

Table 2-6. 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 in **Table 2-7**.

Table 2-7. 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)

* Two patients in the Device group did not have an end of study forms at the time of data lock: patient 331-003 died 974 days post-implant and patient 354-004 died 765 days post-implant.

The most frequent reason for study termination for the Device group was that a device was unable to be successfully implanted. These patients were followed at least until the 45 day visit to review for acute adverse events. For the Control group, the most frequent reason was "Patient Consent Withdrawn." The second most frequent reason for both groups was "Death." "Outside Implant Window" was given as the reason for 10 of the 14 patients for whom no implant was attempted. As discussed in **Section 2.1.1**, of the remaining 4 patients for whom no implant was attempted, 2 were "Patient Consent Withdrawn," 1 was "Death" and 1 was "Other." The patients with "Other" reasons for end-of-study are provided in **Table 2-8**.

Table 2-8. Discontinuation Reason "Other" Category Details

	Device	Other	WATCHMAN Device was explanted due to pericarditis/endocarditis at approximately 30 days.
	Device	Other	Patient was found to have an atheroma on TEE prior to implant and the patient was deemed ineligible for implant. No WATCHMAN Device was implanted.
	Device	Other	WATCHMAN Device embolized and was explanted the day after implant.
	Device	Other	Subject was unable to return for follow-up visits.
	Device	Other	Investigator withdrew patient from study follow-up due to deteriorating health.
	Device	Other	Perforation of the LAA during WATCHMAN Device delivery required surgery. No WATCHMAN Device was placed.
	Device	Other	Patient was diagnosed with amyloidosis and deemed ineligible for study.
	Device	Other	WATCHMAN Device embolized and was explanted at approximately 50 days post-implant.
	Device	Other	Plastic reconstruction of mitral and tricuspidal valve, MAZE-Cryo procedure, resection of left atrial appendage with Watchman device
	Control	Other	Patient experienced a cardiovascular accident with expressive aphasia and withdrew participation from the study.
	Control	Other	Patient underwent ligation of left atrial appendage.
	Control	Other	Discontinued on 15 November 2007. Control patient - Warfarin discontinued due to urological bleeding in 2006 (previously reported as adverse event) - Warfarin never reinitiated.
	Control	Other	Subject relocated to Italy with no forwarding address – was lost-to-follow-up.
	Control	Other	Patient discontinued warfarin therapy.
	Control	Other	Patient discontinued warfarin therapy as recommended by the family physician.
	Control	Other	Patient discontinued warfarin therapy.

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

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

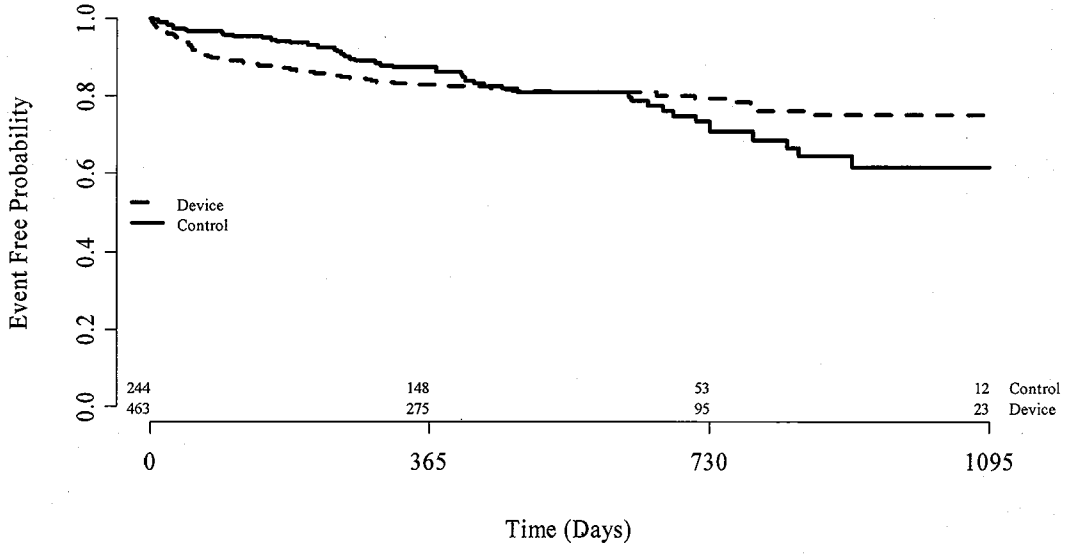

Table 2-9. Kaplan-Meier Estimates: End of Study

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	10	10	97.8	1	1	99.6
45-days	17	27	94.2	6	7	97.1
6-months	32	59	87.1	7	14	94.2
1-year	16	75	83.2	14	28	87.5
2-year	8	83	79.4	17	45	70.8
3-year	4	87	75.0	4	49*	61.8

* One Control patient had an end of study form post three years: patient [redacted], 1109 days due to "Patient Consent Withdrawn."

The largest fraction of end-of-study patients in the Device group was observed between 45-days and 6-months; 18/32 (56%) discontinued due to no device implanted. Twenty-seven patients completed an end-of-study form prior to 45-days; 15/27 (56%) were due to no device implanted.

The largest fraction of end-of-study patients in the Control group was observed between 1-year and 2-years; 6/17 (35%) discontinued due to consent withdrawn. Seven patients (41%) discontinued due to death.

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

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

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2.2 Procedural Data

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

2.2.1 Implant Procedure Success

Implant Procedure Success was defined as the successful delivery and release of a WATCHMAN Device into the LAA. Implant procedure success rates for the randomized cohort is presented in **Table 2-10**. A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted. As noted in **Section 2.1.1**, 14 patients did not have an implant attempted.

Table 2-10. Implant Procedure Success

[redacted]
408/449 (90.9)

2.2.2 Final Device Size Implanted

Table 2-11 provides an accounting of the various WATCHMAN Device sizes released and implanted in the PROTECT AF study for the randomized cohort. A total of 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. Device usage demonstrated a prevalence to implant the smaller device sizes, however all five available device sizes have been implanted successfully in the study. Slightly less than 90% of devices implanted were 21, 24 or 27mm devices.

Table 2-11. Final Device Size Implanted

[redacted]	
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)

2.2.3 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 2-12**.

Table 2-12. 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. The 4+ category contained procedures where four or more recaptures were performed. There was no evidence that patients experiencing procedure or device related adverse events were associated with the number of full recaptures (p=0.48 from a chi-square test).

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

During the initial Short device evaluation period, two device failures were discovered with Short devices that were fully recaptured. Following full recapture into the delivery sheath, the devices were returned to Atritech for inspection. Upon inspection, both devices were missing 2 of the 10 anchoring barbs. The patients in whom Short devices were used did not experience any adverse event related to the device. This failure mode was reported to FDA on May 16, 2006, S034, at which time the Short device evaluation was stopped and the device was redesigned. None of the reported malfunctions resulted in patient injury or recall.

2.3 Pivotal Study Results

2.3.1 Introduction

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

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

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

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

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

2.3.2 Primary Analysis (Intent-to-Treat)

2.3.2.1 Description of Cohort

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

2.3.2.2 Primary Efficacy Endpoint (Intent-to-Treat)

Results for the primary efficacy endpoints of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 2-13**.

Table 2-13. Primary Efficacy Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**		**Non-inferiority**	**Superiority**
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.

- 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.
- 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 criterion for establishing futility was that the probability that the event rate for the Device group was greater than the Control group was 0.95 or greater. The probability that the event rate for the Device group was greater than the Control group was 0.163 (equal to one minus the probability of superiority, or 1-0.837). The criterion for futility was not met as this probability was less than 0.95. This indicates the trial should not be stopped for futility.

The posterior probability of non-inferiority was defined as the probability that the event rate for the Device group was less than twice that for the Control group. The probability of non-inferiority at the first interim analysis was 0.992. This probability was required to be greater than 0.975 for a finding of non-inferiority. The criterion for non-inferiority was met.

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority at the first interim analysis was 0.734. This probability was required to be at least 0.95 for a finding of superiority. The criterion for superiority was not met.

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 2-14 summarizes the specific primary efficacy events by randomized group.

Table 2-14. Primary Efficacy Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Stroke - Ischemic	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

The ischemic stroke rate was higher in the Device group; however it is important to note that the events in this group included 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with procedural events including air embolism and excessive sedation. Without these events, the Device ischemic stroke rate (8/463, 1.7%,) becomes comparable to the Control rate.

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

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

Primary efficacy events used in the primary analysis are listed in

Table 2-15. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events. Multiple events are summarized in **Section 2.3.7** (Adverse Events) of this report.

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Table 2-15. Primary Efficacy Events - Initial Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

1		Device	14FEB2006	15FEB2006	15FEB2006	Stroke - Ischemic
2		Device	25APR2007	26APR2007	26APR2007	Stroke - Ischemic
3		Device	26SEP2005	03OCT2005	05DEC2005	Stroke - Ischemic
4		Device	05JUN2006	06JUN2006	15MAY2008	Death*
5		Device	31JUL2006	01AUG2006	16AUG2006	Stroke - Hemorrhagic
6		Device	20FEB2006	21FEB2006	09MAR2006	Stroke - Ischemic
7		Device	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
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 2-24**.

** 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 2-3** and **Table 2-16.**

Figure 2-3. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Intent-to-Treat)

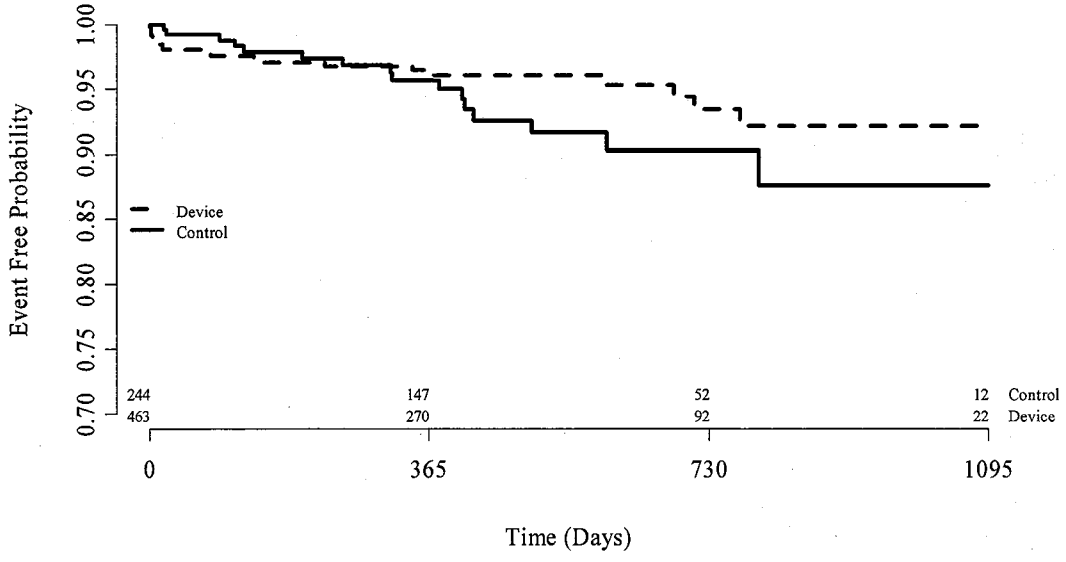

Table 2-16. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	7	7	98.5	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. The largest portion of the primary efficacy events for the Control group (6/16, 38%) occurred between 1-year and 2-years post-randomization. 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.

Two Year Success Rates

In the Device group, the estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on an unadjusted Kaplan-Meier estimate was 93.5% (90.0%-96.9%). In the Control group, the estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on an unadjusted Kaplan-Meier estimate was 90.3% (85.2%-95.4%).

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

For one additional analysis, data on the 50 implanted patients from the PILOT study was combined with the PROTECT AF randomized cohort to produce two-year estimates. From this analysis, the Device group estimate (95% confidence bounds) for freedom from the primary efficacy event at two years based on a Kaplan-Meier estimate was 94.7% (92.1%-97.3%).

Additional analyses incorporated covariates to allow for the calculation of adjusted Kaplan-Meier rates. This analysis included the following covariates as in a proportional hazards regression model: gender, age, and $CHADS_2$ score, AF category, left ventricular ejection fraction, LA length, and LA width. Data on LA size (length and width) was not collected on case report forms but was available from the core lab on 57% of patients in the randomized cohort. As the purpose of the covariate adjusted analysis was to increase the precision of the two-year rate estimates, a covariate with such a high percentage of missing data would be counterproductive. Therefore, imputation of missing LA size was performed to allow inclusion of the maximal number of patients in the covariate adjusted analysis of two-year rates.

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

For each covariate adjusted analysis, separate estimates were formed for each treatment group as shown in **Table 2-17**. The average value was used for continuous covariates and the most frequent value was used for categorical covariates to produce a hypothetical cohort for which the survival distribution was estimated. The specific values of these covariates used in the model were as follows: male gender, age of 72 years, $CHADS_2$ score of 2, Paroxysmal AF, LVEF of 57%, LA length of 5.9cm, LA width of 4.5cm, LAA length of 30.5mm, and LAA ostium diameter of 21.7 mm.

The first covariate adjusted model (using LA size) produced estimates (95% confidence bounds) for freedom from the primary efficacy event at 2 years for the device of 96.1% (92.7% - 99.5%) and corresponding estimates (95% confidence bounds) for the Control group of 94.8% (90.2% - 99.7%). The second covariate adjusted model (using LAA size) produced corresponding Device group estimates of 96.5% (93.4%, 99.7%) and Control group estimates of 95.1% (90.6%, 99.9%).

Table 2-17. Two Year Success Rate Estimates

Unadjusted, PROTECT AF Alone	93.5 (90.0, 96.9)	90.3 (85.2, 95.4)
Unadjusted, PROTECT AF Plus PILOT	94.7 (92.1, 97.3)	90.3 (85.2, 95.4)
Adjusted Model 1, PROTECT AF Alone	96.1 (92.7, 99.5)	94.8 (90.2, 99.7)
Adjusted Model 2, PROTECT AF Alone	96.5 (93.4, 99.7)	95.1 (90.6, 99.9)

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

Assessment of Proportional Hazards Assumption

The potential for non-constant hazard function across time exists; therefore, a test for equality of event rates across time was made separately for each treatment group using six month intervals as shown in **Table 2-18**.

Table 2-18. Homogeneity of Event Rates Over 6 Month Intervals Primary Efficacy Endpoint (Intent-to-Treat)

	Events/ Patient-years	Event Rate	Events/ Patient-years	Event Rate
0-6 Months	13/204.1	6.37	5/114.8	4.36
6-12 Months	2/164.2	1.22	4/91.0	4.40
12-18 Months	1/107.2	0.93	5/55.1	9.07
18-24 Months	3/57.6	5.21	1/31.5	3.17
24-30 Months	1/31.9	3.13	1/16.9	5.92
P-value	0.0691		0.7667	

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

For the Device group, the p-value of 0.0691, while not significant at a 0.05 level provides some evidence that the rate of primary efficacy events for the Device group varies by time. This is consistent with the short term procedure risk (e.g., strokes from air embolisms). For the Control group, the p-value of 0.7667 is consistent with the assumption that the primary efficacy event rate is constant over time.

To explore the sensitivity of inferences to this assumption, and more generally to explore model sensitivity, a series of models for the primary efficacy endpoint were fit. This included Bayesian proportional hazards models, both unstratified and stratified by $CHADS_2$ score, and Bayesian piecewise constant hazards models, both unadjusted and adjusted for $CHADS_2$ score as represented in **Table 2-19**.

Table 2-19. Protection Against Non-Constant Hazard Primary Efficacy Endpoint (Intent-to-Treat)

Bayesian Proportional Hazards Model	0.73	0.35, 1.37
Bayesian Proportional Hazards Model, Stratified By $CHADS_2$	0.80	0.39, 1.50
Bayesian Piecewise Hazards Model	0.74	0.35, 1.40
Bayesian Piecewise Hazards Model With $CHADS_2$ Adjustment	0.78	0.38, 1.46

HR = hazard ratio

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

Components of Primary Efficacy

The most common primary efficacy events were strokes and deaths (cardiovascular and unexplained). Analyses of these endpoints, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates for these components are displayed in **Table 2-20** through **Table 2-23** and **Figure 2-4** and **Figure 2-5**.

Table 2-20. Bayesian Model Results: Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
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)

N = number Pts = patients Pt-yrs = patient-years CI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

- The stroke rate was 2.6 events per 100 patient years for the Device group and 3.5 events per 100 patient years for the Control group.
- This yielded a relative risk, or rate ratio, of 0.74, a 26% lower rate of stroke in the Device group than in the Control group. The 95% credible interval for the rate ratio was (0.36, 1.76).

Figure 2-4. Kaplan-Meier Curve: Freedom from Stroke (Intent-to-Treat)

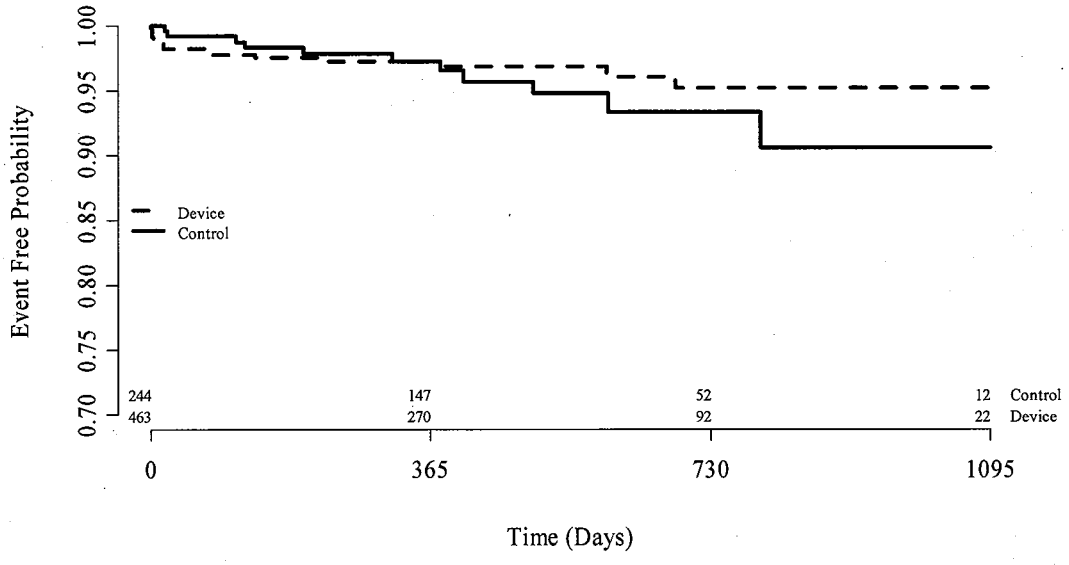

Table 2-21. Kaplan-Meier Estimates: Freedom from Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	6	6	98.7	0	0	100.0
45-days	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 stroke events for the Device group (6/15, 40%) occurred within 7-days of randomization. Moreover, of these six events, one event occurred pre-procedure and five were procedural events. The largest portion of the stroke events for the Control group (4/11, 36%) occurred between 1-year and 2-years post-randomization. At 3 years, the Device group had a Kaplan-Meier estimated stroke event rate of 4.8% compared to a 9.4% stroke event rate in the Control group, a 49% lower relative rate for the Device group.

Table 2-22. Bayesian Model Results: All-Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	
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)

- 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.
- This yielded a relative risk, or rate ratio, of 0.61, a 39% lower rate of death in the Device group than in the Control group. The 95% credible interval for the rate ratio was (0.32, 1.32).

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Figure 2-5. Kaplan-Meier Curve: Freedom from All Cause Mortality (Intent-to-Treat)

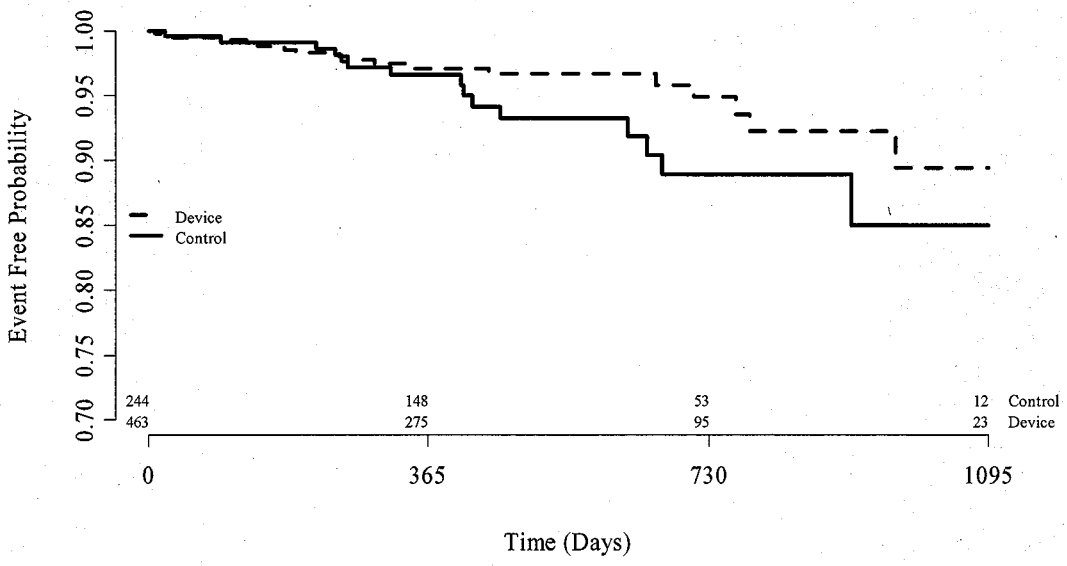

Table 2-23. Kaplan-Meier Estimates: Freedom from All Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.6	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 largest portion of the deaths for the Device group (5/17, 29%) occurred between 6-months and 1-year post-randomization. The largest portion of the deaths for the Control group (7/15, 47%) occurred between 1-year and 2-years post-randomization. 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 event rate in the Control group. This represents a 29% lower relative rate of all cause mortality for the Device group at 3 years.

Table 2-24 summarizes the patient deaths by randomized group.

Table 2-24. Patient Deaths by Group

	Device	13APR2005	14APR2005	06JUN2007	Ongoing respiratory issues while in hospice.
	Device	25APR2007	26APR2007	30DEC2007	Complications from unresolved urosepsis.
	Device	05JUN2006	06JUN2006	15MAY2008	Unknown – patient died during sleep.
	Device	31JUL2006	01AUG2006	16AUG2006	Spontaneous subarachnoid hemorrhage.
	Device	21SEP2005	21SEP2005	14JUL2007	Complications from gastric carcinoma.
	Device	08NOV2006	08NOV2006	06FEB2007	Complications from colitis in hospice care.
	Device	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 2-14**.
[2] – Death is linked to a primary efficacy event.

Two strokes in the Device group ([redacted]) were fatal compared to five strokes in the Control group ([redacted]) 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.

2.3.2.3 Primary Safety Endpoint (Intent-to-Treat)

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

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

The primary safety endpoint was defined as the occurrence of life-threatening events as determined by the Clinical Events Committee, which included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitates an operation.

The primary safety results experienced are either early self limited procedural safety issues or ongoing chronic safety issues related to long-term warfarin. With device implantation, potential early safety issues were mitigated through operator experience, additional training and device modifications. However, chronic ongoing safety issues related to warfarin therapy, use, and administration cannot be mitigated.

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

Results for the primary safety endpoint are displayed in **Table 2-25**. Credible intervals are calculated from the same Bayesian model used for the primary efficacy endpoint.

Table 2-25. Primary Safety Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
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)

N = number, Pts = patients, Pt-yrs = patient-years, CI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

- The primary safety rate was 8.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group.
- This yielded a rate ratio, or relative risk, of 2.08. The 95% credible interval for the rate ratio based on the Bayesian model was (1.18, 4.13).

Table 2-26 summarizes the types of primary safety events by randomized group.

Table 2-26. Primary Safety Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Pericardial Effusion - Serious*	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.

Table 2-26 is based upon event type for the first event noted in a patient. If multiple events share the same event date, then the primary event as established in the AE linking process was used.

A higher rate of early primary safety events in the Device group compared to the Control group is not unexpected due to the 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. Ischemic and hemorrhagic stroke events can be independently categorized as both a safety and efficacy event. Further explanation is provided regarding the safety events of both treatment groups below:

- Of the 463 randomized Device group patients there were 22 pericardial effusions considered to be serious (4.8%). Of these, 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.
- 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 as a result of combination clopidogrel and/or aspirin therapy. Patients who experienced a gastrointestinal bleed spent a median of 4 days in the hospital.
- There were five (1.1%) ischemic strokes in the Device group considered to be safety endpoint related. All five were noted following the implant procedure and 3 of the 5 were related to air embolism, a common occurrence in transseptal procedures, as reported by the sites. Device patients who experienced an ischemic stroke spent a median of 7 days in the hospital and none of these events resulted in death.
- There was one (0.2%) hemorrhagic stroke in the Device group versus 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.

Primary safety events used in the primary analysis are listed in **Table 2-27**. The primary analysis is based on the initial event per-patient even if a patient experiences multiple events. Multiple events are summarized in **Section 2.3.7** (Adverse Events) of this report.

Table 2-27. Primary Safety Events - Initial Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

1		Device	14FEB2006	15FEB2006	15FEB2006	Stroke - Ischemic
2		Device	08MAY2006	09MAY2006	09MAY2006	Pericardial Effusion-Serious
3		Device	31JAN2007	31JAN2007	25JUL2007	Gastrointestinal Bleeding
4		Device	19MAR2007	25MAR2007	25MAR2007	Pericardial Effusion-Serious
5		Device	23FEB2005	24FEB2005	25FEB2005	Pericardial Effusion-Serious
6		Device	13APR2005	14APR2005	14APR2005	Major Bleed Requiring Transfusion
7		Device	25APR2007	26APR2007	26APR2007	Stroke - Ischemic
8		Device	26SEP2005	27SEP2005	27SEP2005	Pericardial Effusion-Serious
9		Device	29NOV2007	29NOV2007	29NOV2007	Pericardial Effusion-Serious
10		Device	22FEB2006	23FEB2006	09APR2006	Gastrointestinal Bleeding
11		Device	17OCT2006	18OCT2006	18OCT2006	Pericardial Effusion-Serious
12		Device	31JUL2006	01AUG2006	16AUG2006	Stroke - Hemorrhagic
13		Device	19FEB2008	20FEB2008	25FEB2008	Gastrointestinal Bleeding
14		Device	20OCT2005	20OCT2005	03JAN2008	Gastrointestinal Bleeding
15		Device	18JUL2005	19JUL2005	24JUL2005	Gastrointestinal Bleeding
16		Device	12JUL2005	12JUL2005	12JUL2005	Gastrointestinal Bleeding
17		Device	20FEB2006	21FEB2006	25FEB2006	Pericardial Effusion-Serious
18		Device	07APR2006	07APR2006	07APR2006	Arrhythmias
19		Device	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
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 2-6 and **Table 2-28** display results from a Kaplan-Meier analysis of the primary safety events.

Figure 2-6. Kaplan-Meier Curve: Freedom from Primary Safety Event (Intent-to-Treat)

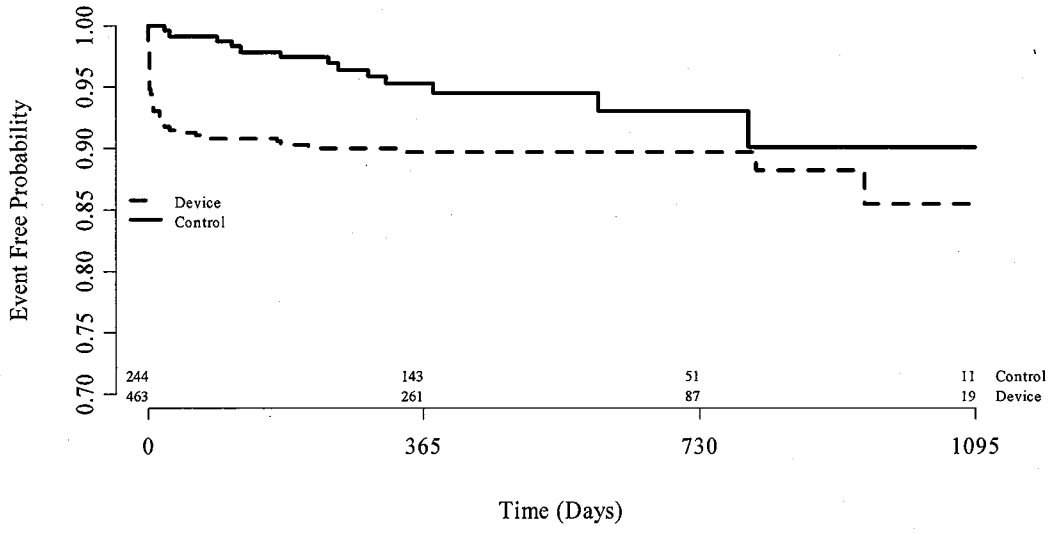

Table 2-28. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	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 largest portion of the primary safety events for the Device group (32/48, 67%) occurred within 7-days of randomization. Furthermore, (27/48, 56%) of the primary safety events occurred on the day of implant. The largest portion of the primary safety events for the Control group (8/13, 62%) occurred between 45-days and 1-year post-randomization. After the 7 day time point and through 3 years, the change in the Kaplan-Meier event free rate in the Device group was 7.6% compared to 9.9% in the Control group. This trend in long term warfarin events 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. Additional consideration regarding time to events is further discussed in **Section 2.3.3 Post Procedure Analysis** and **Section 2.3.4 Per-Protocol Analysis**.

To assess the variation in primary safety event rates over the course of follow-up, an analysis of rates by six month intervals was performed as shown in **Table 2-29**. Additionally, a statistical test was performed separately by treatment group to examine whether or not rates varied over time.

Table 2-29. Homogeneity of Event Rates Over 6 Month Intervals Primary Safety Endpoint (Intent-to-Treat)

	Events/ Patient-years	Event Rate	Events/ Patient-years	Event Rate
0-6 Months	44/193.2	22.77	6/114.1	5.26
6-12 Months	2/157.1	1.27	4/89.6	4.46
12-18 Months	0/103.6	0.00	1/53.2	1.87
18-24 Months	0/54.8	0.00	1/30.6	3.27
24-30 Months	1/30.2	3.31	1/16.2	6.17
30-36 Months	1/12.7	7.87	0/7.2	0.00
P-value	<0.001		0.9177	

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

For the Device group, the p-value of <0.001 provides evidence that the rate of primary safety events for the Device group varies by time. This is consistent with procedural complications experienced in the study. For the Control group, the p-value of 0.9177 is consistent with the assumption that the primary safety event rate is consistent over time.

To explore the sensitivity of inferences to this assumption, and more generally to explore model sensitivity, a series of models for the primary safety endpoint were fit as shown in **Table 2-30**. This included Bayesian proportional hazards models, both unstratified and stratified by $CHADS_2$ score, and Bayesian piecewise constant hazards models, both unadjusted and adjusted for $CHADS_2$ score.

Table 2-30. Protection Against Non-constant Hazard Primary Safety Endpoint (Intent-to-Treat)

Bayesian Proportional Hazards Model	2.22	1.17, 4.05
Bayesian Proportional Hazards Model, Stratified By $CHADS_2$	2.23	1.17, 4.08
Bayesian Piecewise Hazards Model	2.35	1.23, 4.21
Bayesian Piecewise Hazards Model With $CHADS_2$ Adjustment	2.37	1.26, 4.18

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

2.3.3 Post Procedure Analysis (Pre-Specified)

2.3.3.1 Description of Cohort

While an intent-to-treat cohort includes all randomized patients in the group to which they were assigned, other analyses may be performed to exclude certain enrolled patients that were not able to benefit from the treatment. One such analysis is a post procedure analysis to examine the long term treatment effect following implant of the device. Understanding that any catheter intervention has its inherent risks, from a clinician perspective it is important to answer the following questions: 1) What happens after the patient leaves the table? and 2) are there any adverse events that the clinician needs to be aware of to educate the patient before leaving the hospital? For this analysis, patients were analyzed according to their randomized group. Follow-up time for Device patients is calculated from the date of implant as opposed to the date of randomization. The median (inter-quartile range) number of days from randomization to implant was 1 (0-3 days).

2.3.3.2 Primary Efficacy Endpoint – Post Procedure

Six patients with primary efficacy events that either occurred prior to or on the date of the implant were excluded from the post-procedure analysis as listed in **Table 2-31**. In total, 19 patients were excluded from this analysis; 14 patients for whom no implant was attempted as discussed in Section 12.1.1 (one of which was [redacted] who experienced an ischemic stroke and died prior to an attempted device implant) and 5 patients who experienced events on the date of implant.

Table 2-31. Post Procedure Analysis - Excluded Patients with Efficacy Events

[redacted]				
Device	301-009	No	15FEB2006	Stroke - Ischemic
Device	302-008	Yes	26APR2007	Stroke - Ischemic
Device	336-035	Yes	29JAN2008	Stroke - Ischemic
Device	344-002	Yes	11NOV2005	Stroke - Ischemic
Device	370-002	Yes	18JUL2006	Stroke – Ischemic
Device	378-018	No	24MAY2007	Stroke – Ischemic

* Treatment received = Device implanted

Table 2-32. Primary Efficacy Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**		**Non-Inferiority**	**Superiority**
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

N = number Pts = patients Pt-yrs = patient-years CI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

- The primary efficacy rate for the post-procedure analysis was 2.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group as shown in **Table 2-32.**
- This yielded a rate ratio, or relative risk, of 0.49. The 95% credible interval for the rate ratio based on the Bayesian model was (0.24, 1.06).
- Following the implant procedure, Device group patients experienced a 51% reduction in strokes, death or systemic embolism.

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

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority for the post-procedure analysis was 0.965.

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Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 2-7** and **Table 2-33**.

Figure 2-7. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Post Procedure)

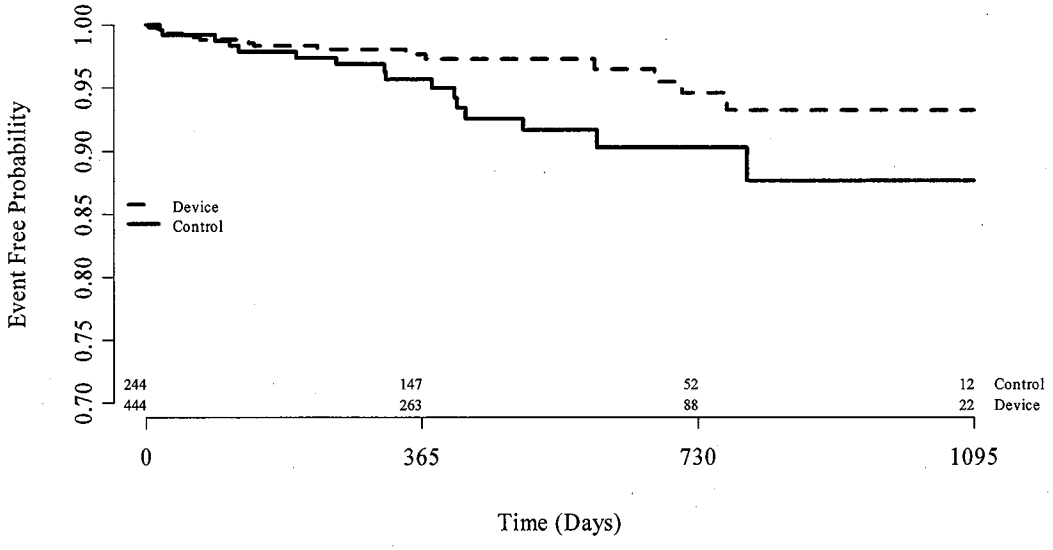

Table 2-33. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Post Procedure)

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

The largest portion of post procedure primary efficacy events in the Device group (8/14, 57%) occurred between 45-days and 6-months or between 1-year and 2-years post-implant. The largest portion of the post procedure efficacy events for the Control group (6/16, 38%) occurred between 1-year and 2-years post-randomization. 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.

2.3.3.3 Primary Safety Endpoint – Post Procedure

Twenty seven patients with primary safety events on the date of implant were excluded from the post-procedure analysis as listed in **Table 2-34**. In 12 of these 27 patients a device was not successfully implanted, in 15 of these 27, a device was successfully implanted. Fourteen additional patients who did not have an attempted implant (as discussed in **Section 2.1.1**) and without primary safety events were excluded.

Table 2-34. Post Procedure Analysis - Excluded Patients with Safety Events

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

* Treatment received = Device implanted

Table 2-35. Primary Safety Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
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)

- 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 as shown in **Table 2-35**.
- This yielded a rate ratio, or relative risk, of 0.93. 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 2-8 and **Table 2-36** display results from a Kaplan-Meier analysis of the primary safety events.

Figure 2-8. Kaplan-Meier Curve: Freedom from Primary Safety Event (Post Procedure)

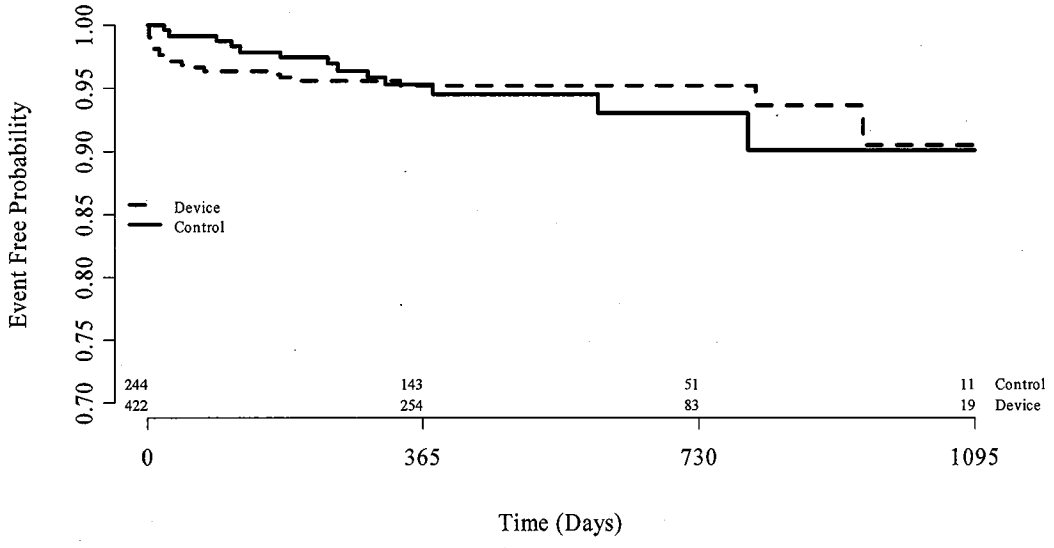

Table 2-36. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Post Procedure)

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

The largest portion of post procedure primary safety events in the Device group (8/21, 38%) occurred within 7-days post-implant. The majority of these events were gastrointestinal bleeds and pericardial effusions. The largest portion of the post procedure primary safety events for the Control group (8/13, 62%) occurred between 45-days and 1-year post-randomization. Four of these were gastrointestinal bleeds, three were hemorrhagic stroke, and one was anemia requiring transfusion. 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 efficacy event rate in the Control group, a 4% relatively lower rate for the Device group.

2.3.4 Per-Protocol Analysis (Pre-Specified)

2.3.4.1 Description of Cohort

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

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

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

2.3.4.2 Primary Efficacy Endpoint- Per-Protocol Analysis

Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. This included 10 Device patients with primary efficacy events and an additional 66 patients without primary efficacy events. Of the 449 patients in the Device group for whom an implant was attempted, all had 45-day visit windows that closed prior to the closure of the database. Thus, the 387 patients in the Device group in the per-protocol efficacy analysis represent approximately 86% (387/449) of the patients in the Device group for whom treatment was successful (defined as successfully implanted and able to discontinue warfarin therapy). In the Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. This included a total of three Control group patients, one of whom experienced a primary efficacy event.

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Patients with primary efficacy events that were excluded are listed in the **Table 2-37**.

Table 2-37. Per-Protocol Analysis - Excluded Patients with Efficacy Events

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

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

Table 2-38. Primary Efficacy Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-Inferiority	Superiority
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

N = number, Pts = patients, Pt-yrs = patient-years, CI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate

- The primary efficacy rate was 2.1 events per 100 patient years for the Device group and 4.7 events per 100 patient years for the Control group as shown in **Table 2-38**.
- This yielded a rate ratio, or relative risk, of 0.44. 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 posterior probability of non-inferiority was defined as the probability that the event rate for the Device group was less than twice that for the Control group. The probability of non-inferiority was >0.999.

The posterior probability of superiority was defined as the probability that the event rate for the Device group was less than that for the Control group. The probability of superiority was 0.971.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 2-9** and **Table 2-39**.

Figure 2-9. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Per-Protocol)

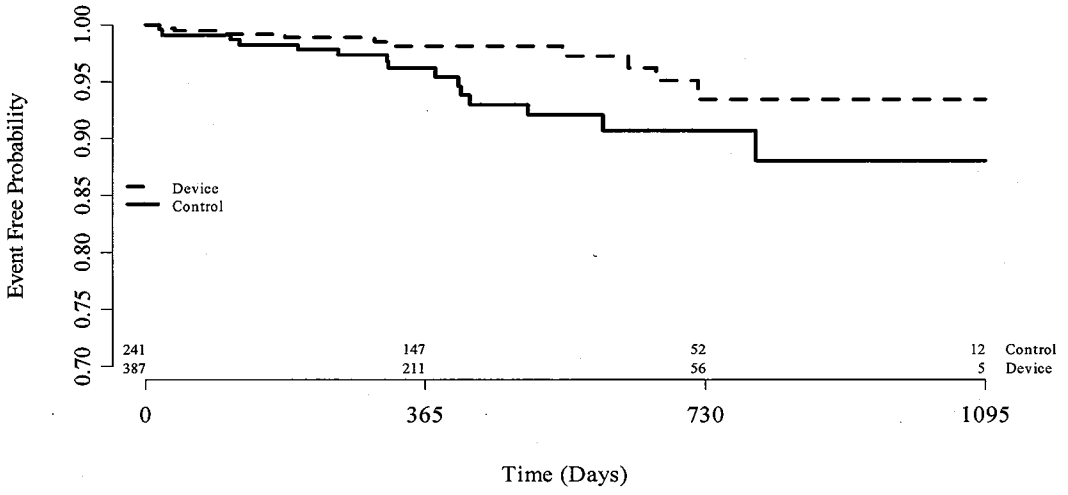

Table 2-39. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Per-Protocol)

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

The largest portion of per-protocol primary efficacy events in the Device group (4/10, 40%) occurred between 1-year and 2-years post-warfarin cessation. The largest portion of the per-protocol primary efficacy events for the Control group (6/15, 40%) occurred between 1-year and 2-years post-randomization. At 3 years, the Device group had a Kaplan Meier estimated per-protocol primary efficacy event rate of 6.6% compared to a 12.0% per-protocol efficacy event rate in the Control group, a 45% relatively lower rate for the Device group.

2.3.4.3 Primary Safety Endpoint - Per-Protocol Analysis

The per-protocol analysis excluded 40 patients who experienced primary safety events from the Device group. As in the efficacy analysis, patients in the Device group were excluded when either no implant was attempted, when the device was not successfully implanted, or when patients did not discontinue warfarin therapy, and from the Control group when there was no evidence that warfarin was taken at baseline or at the 45-day visit. The patients with primary safety events that were excluded are listed in **Table 2-40**.

Table 2-40. Per-Protocol Analysis - Excluded Patients with Safety Events

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

Device		No	29NOV2005	Device Embolization
Device		No	11NOV2005	Stroke - Ischemic
Device		No	02JUL2007	Cranial Bleed
Device		No	24AUG2007	Pericardial Effusion-Serious
Device		No	08NOV2007	Pericardial Effusion-Serious
Device		No	03DEC2007	Pericardial Effusion-Serious
Device		No	16MAR2007	Pericardial Effusion-Serious
Device		No	25FEB2008	Pericardial Effusion-Serious
Device		No	23JAN2007	Pericardial Effusion-Serious
Device		No	18JUL2006	Stroke - Ischemic
Device		No	20OCT2006	Pericardial Effusion-Serious
Device		No	06JUN2008	Major Bleed Requiring Transfusion
Device		No	05JUN2007	Device Embolization
Device		No	04JUN2008	Bruising-Hematoma

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

Table 2-41. Primary Safety Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
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)

N = number Pts = patients Pt-yrs = patient-years CI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

- The primary safety rate was 1.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group as shown in **Table 2-41**.
- This yielded a rate ratio, or relative risk, of 0.40. The 95% credible interval for the rate ratio based on the Bayesian model was (0.16, 0.97).

Results from Kaplan-Meier analyses for the primary safety endpoint are given in **Figure 2-10** and **Table 2-42**.

Figure 2-10. Kaplan-Meier Curve: Freedom from Primary Safety Event (Per-Protocol)

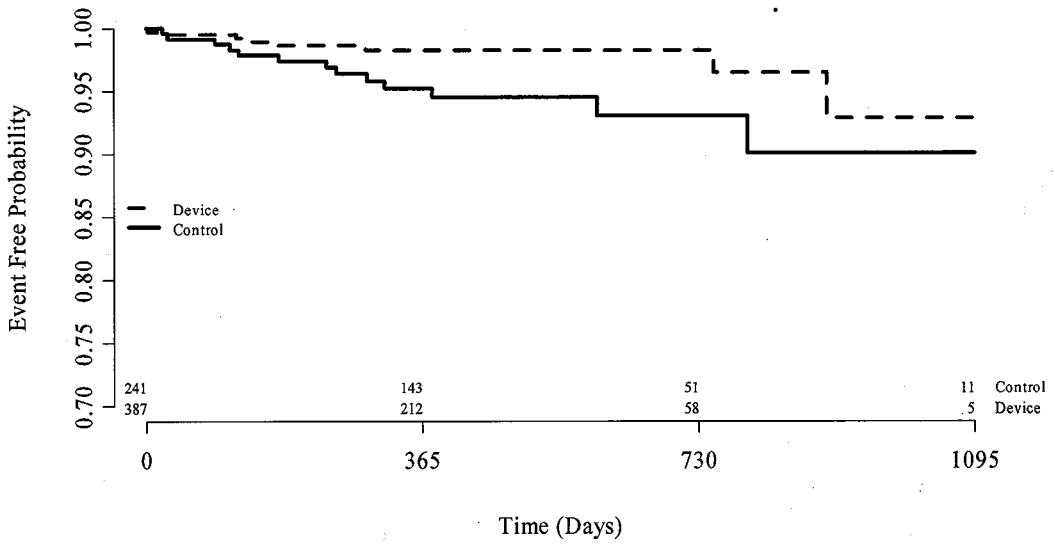

Table 2-42. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Per-Protocol)

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

The largest portion of per-protocol safety events in the Device group (3/8, 38%) occurred between 45-days and 6-months post-warfarin cessation. In addition, the Device group had no per-protocol safety events between 1-year and 2-years. The largest portion of the per-protocol safety events for the Control group (8/13, 62%) occurred between 45-days and 1-year post-randomization. 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% relatively lower rate for the Device group.

2.3.4.4 Additional Per-Protocol Analysis

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

Under this analysis, the primary efficacy rate was 3.0 events per 100 patient years (17 events / 567.3 patient-years) for the Device group and 4.7 events per 100 patient years (15 events / 317.5 patient-years) for the Control group. This yielded a rate ratio, or relative risk, of 0.63. The 95% credible interval for the rate ratio based on the Bayesian model was (0.33, 1.36). The probability of non-inferiority for this analysis was 0.998.

The primary safety rate was 6.4 events per 100 patient years (35 events / 543.8 patient-years) for the Device group and 4.2 events per 100 patient years (13 events / 311.4 patient-years) for the Control group. This yielded a rate ratio, or relative risk, of 1.54. The 95% credible interval for the rate ratio based on the Bayesian model was (0.85, 3.11).

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

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2.3.5 Risk / Benefit Analysis

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

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

Intent-to-Treat Analysis

- Statistically significant finding of non-inferiority for the primary efficacy event rate.
- 32% lower rate of primary efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- 26% lower rate of stroke in the Device group than in the Control group.
- 39% lower rate of death in the Device group than in the Control group.
- Statistically significant 2.08 fold higher rate of primary safety events for the Device group relative to the Control group. Most of the events in the Device group were procedural pericardial effusions that decreased over the course of the study.

Post Procedure Analysis

- The post procedure primary efficacy event rate yielded a 51% lower rate of efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- Rates of primary safety events were similar for the Device and Control group, 3.9% and 4.2% respectively.

Per-Protocol Analysis

- The per-protocol primary efficacy event rate yielded a 56% lower rate of efficacy events (stroke, cardiovascular or unexplained death and systemic embolism) in the Device group than in the Control group.
- The per-protocol primary safety event rate yielded a 60% lower rate of primary safety events in the Device group than in the Control group.
- Approximately 86% of patients in the Device group were able to be successfully implanted and discontinue warfarin therapy.

The primary efficacy and safety results for these cohorts are summarized in **Table 2-43**.

Table 2-43. 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)

Additionally, **Table 2-44** displays the rates of stroke (all stroke, ischemic, and hemorrhagic) by randomized group for the primary intent-to-treat analysis and the per-protocol analysis.

Table 2-44. Stroke Rates by Type

	Events	Rate	Fatal	Rate	Events	Rate	Fatal	Rate
All stroke	15	2.6	2	0.3	11	3.5	5	1.6
Ischemic stroke	14	2.4	1	0.2	5	1.6	1	0.3
Hemorrhagic stroke	1	0.2	1	0.2	6	1.9	4	1.3
	Events	Rate	Fatal	Rate	Events	Rate	Fatal	Rate
All stroke	6	1.2	0	0.0	11	3.5	5	1.6
Ischemic stroke	6	1.2	0	0.0	5	1.6	1	0.3
Hemorrhagic stroke	0	0.0	0	0.0	6	1.9	4	1.3

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

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

2.3.6 Secondary Endpoints and Warfarin Analyses

2.3.6.1 Secondary Endpoints - Both Randomized Groups

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

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

TIA and other individual complications rates were too infrequent to perform formal statistical analysis that would lead to reliable conclusions. Analyses of mortality rates are presented in **Table 2-22** and **Table 2-23**. All adverse events (i.e., individual complication rates) are summarized by treatment group in **Section 2.3.7**, by individual complication type, seriousness, and device/procedure relatedness.

2.3.6.2 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 2.3.7 (Adverse Events)** for analysis of individual complications for the Device group.

Results for secondary endpoints in the Device group are displayed in **Table 2-45**.

Table 2-45. 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).

Eight Device group patients for whom an implant was attempted were not included in the calculation of 30-Day Major Complications as the patients were not followed for at least 30 days and had not yet experienced a major complication related to the treatment or procedure; this yields a denominator of 441 patients instead of 449 for this endpoint.

2.3.6.3 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 2-46** and **Table 2-47**. Values of INR from the INR monitoring form collected following randomization were used to assess the frequency of patients ever having a non-therapeutic INR or excessive anti-coagulation. Patients may have had INR values both below and above the therapeutic levels during the course of follow-up and so the percentages for "Patients Ever Having" INR values at each category add up to more than 100%.

Table 2-46. 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 study 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 anti-coagulation 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 2-47. 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.

2.3.6.4 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 2-48.** 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 2-48. 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)

Among successfully implanted Device patients, the most frequent reason for the 52 patients remaining on warfarin therapy at the 45-day visit was the observation of flow in the left atrial appendage (n=28). The second most frequent reason was physician order (n=13). The remaining reasons in descending order were as follows: explant or embolization (n=4), TEE not done or pending review (n=5), and thrombus (n=2).

Figure 2-11 and **Table 2-49** display results from a Kaplan-Meier analysis for the time-to-warfarin discontinuation for Device patients who received a device. Time to event is calculated from the date of randomization. The majority of patients discontinued warfarin at their 45-day visit.

Figure 2-11. Time to Warfarin Discontinuation - Successfully Implanted Patients Only

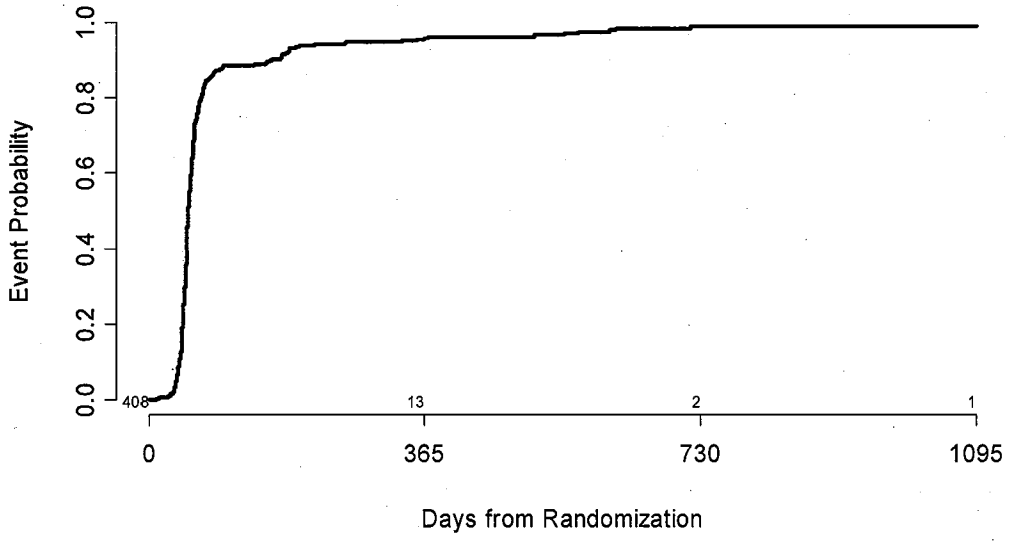

Table 2-49. Kaplan-Meier Estimates: Time to Warfarin Discontinuation

	N Events	N Cumulative Events	Event Rate (%)
7-days	0	0	100.0
45-days	102	102	74.7
6-months	263	365	8.6
1-year	15	380	4.1
2-year	7	387	1.0
3-year	0	387	1.0

Over 90% of implanted patients discontinued warfarin therapy by six months. As can be seen in **Figure 2-11**, many patients discontinued warfarin between approximately 30 and 60 days post-randomization. This degree of variation in timing is expected as the 45-day visit window was as 30 to 60 days post-implant. The Kaplan-Meier estimated rate of discontinuation by 3-years post-randomization was 99%.

2.3.7 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. The percent of events is calculated as the percent of events of that type over of the total number of events.

Serious adverse events are summarized in **Table 2-50** and **Table 2-51**. **Table 2-50** presents events adjudicated by the Clinical Event Committee as serious. **Table 2-51** presents events that were not adjudicated by the Clinical Event Committee as serious, but were reported by the site to have resulted in death, were life-threatening, prolonged hospitalization, resulted in significant disability, or were unanticipated as defined in the protocol. In **Table 12-54**, events are classified by the event category originally provided by the site.

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Table 2-50. Summary of Serious Adverse Events

	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Gastrointestinal bleeding	16	14.0	15	3.2	10	27.8	9	3.7
Death	13	11.4	13	2.8	10	27.8	10	4.1
Pericardial Effusion-Serious	23*	20.2	23	5.0	0	0	0	0
Stroke - ischemic	13	11.4	13	2.8	5	13.9	5	2.0
Other Study Related	15	13.2	15	3.2	2	5.6	2	0.8
Stroke - hemorrhagic	1	0.9	1	0.2	6	16.7	6	2.5
Bruising - Hematoma	4	3.5	4	0.9	0	0	0	0
Adjudicated as Non-Event	2	1.8	2	0.4	1	2.8	1	0.4
Device embolization	3	2.6	3	0.6	0	0	0	0
Pseudoaneurysm	3	2.6	3	0.6	0	0	0	0
Major Bleed Requiring Transfusion	2	1.8	2	0.4	1	2.8	1	0.4
Rectal bleeding	1	0.9	1	0.2	1	2.8	1	0.4
Systemic embolization	2	1.8	2	0.4	0	0	0	0
Cranial bleed	2	1.8	2	0.4	0	0	0	0
Arrhythmias	2	1.8	2	0.4	0	0	0	0
Infection	2	1.8	2	0.4	0	0	0	0
Bleeding from varicose veins	1	0.9	1	0.2	0	0	0	0
Epistaxis	1	0.9	1	0.2	0	0	0	0
Hematuria	1	0.9	1	0.2	0	0	0	0
Thrombosis	1	0.9	1	0.2	0	0	0	0
Device thrombus	1	0.9	1	0.2	0	0	0	0
Pleural effusion	1	0.9	1	0.2	0	0	0	0
Pulmonary edema	1	0.9	1	0.2	0	0	0	0
AV fistula	1	0.9	1	0.2	0	0	0	0
Transient ischemic attack TIA	1	0.9	1	0.2	0	0	0	0
Anemia Requiring Transfusion	1	0.9	1	0.2	0	0	0	0
Totals:	**114**	**100.0**	**90**	**19.4**	**36**	**100.0**	**32**	**13.1**

* Patient 319-001 had a serious pericardial effusion. This event was not adjudicated by CEC as a primary safety event; therefore, it is not listed in **Table 2-26**.

Table 2-51. Summary of Serious Adverse Events as Reported by Site

CEC Adjudicated Non-Events								
	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Other Non-Study Related	179	58.3	106	22.9	86	60.6	50	20.5
Arrhythmias	23	7.5	18	3.9	17	12.0	13	5.3
Chest pain/discomfort	26	8.5	20	4.3	9	6.3	8	3.3
Other Study Related	10	3.3	9	1.9	2	1.4	2	0.8
Dyspnea	9	2.9	7	1.5	1	0.7	1	0.4
Pleural effusion	7	2.3	5	1.1	2	1.4	2	0.8
Pulmonary embolism	7	2.3	6	1.3	1	0.7	1	0.4
Myocardial infarction	6	2.0	6	1.3	2	1.4	2	0.8
Gastrointestinal bleeding	3	1.0	3	0.6	3	2.1	3	1.2
Infection	4	1.3	4	0.9	2	1.4	2	0.8
Bruising - Hematoma	4	1.3	4	0.9	1	0.7	1	0.4
Ventricular tachyarrhythmia	4	1.3	4	0.9	1	0.7	1	0.4
INR>4.0	1	0.3	1	0.2	4	2.8	4	1.6
Coumadin therapy stopped	2	0.7	2	0.4	3	2.1	3	1.2
Hematuria	2	0.7	2	0.4	2	1.4	2	0.8
Pneumonia	3	1.0	3	0.6	1	0.7	1	0.4
Pulmonary edema	2	0.7	2	0.4	1	0.7	1	0.4
Complete heart block	2	0.7	2	0.4	1	0.7	1	0.4
Epistaxis	2	0.7	2	0.4	0	0	0	0
Pericardial effusion	2	0.7	2	0.4	0	0	0	0
Stroke - ischemic	1	0.3	1	0.2	1	0.7	1	0.4
Cranial bleed	2	0.7	2	0.4	0	0	0	0
Anemia Requiring Transfusion	1	0.3	1	0.2	1	0.7	1	0.4
Prolonged bleeding from a laceration	1	0.3	1	0.2	0	0	0	0
Thrombosis	1	0.3	1	0.2	0	0	0	0
Coronary artery thrombosis	0	0	0	0	1	0.7	1	0.4
Vasovagal reactions	1	0.3	1	0.2	0	0	0	0
Ventricular fibrillation	1	0.3	1	0.2	0	0	0	0
Thromboembolism	1	0.3	1	0.2	0	0	0	0
Totals:	**307**	**100.0**	**147**	**31.7**	**142**	**100.0**	**69**	**28.3**

Device or Procedure Related Events are summarized in **Table 2-52.** Events are divided into serious and non-serious events as determined by the Clinical Event Committee. For this table, classification into event types is based on CEC adjudication.

Table 2-52. Summary of Device or Procedure Related Events

CEC Adjudicated Serious Events				
[redacted]				
Pericardial Effusion-Serious	23	34.8	23	5.0
Other Study Related	14	21.2	14	3.0
Stroke - ischemic	6	9.1	6	1.3
Bruising - Hematoma	4	6.1	4	0.9
Device embolization	3	4.5	3	0.6
Pseudoaneurysm	3	4.5	3	0.6
Arrhythmias	2	3.0	2	0.4
Infection	2	3.0	2	0.4
Gastrointestinal bleeding	1	1.5	1	0.2
Thrombosis	1	1.5	1	0.2
Device thrombus	1	1.5	1	0.2
Pleural effusion	1	1.5	1	0.2
Pulmonary edema	1	1.5	1	0.2
AV fistula	1	1.5	1	0.2
Transient ischemic attack TIA	1	1.5	1	0.2
Anemia Requiring Transfusion	1	1.5	1	0.2
Major Bleed Requiring Transfusion	1	1.5	1	0.2
Totals:	**66**	**100.0**	**57**	**12.3**
CEC Adjudicated Non-Serious				
[redacted]				
Other Study Related	13	31.7	13	2.8
Device thrombus	10	24.4	10	2.2
Pericardial effusion	8	19.5	8	1.7
Adjudicated as Non-Event	1	2.4	1	0.2
Bruising - Hematoma	1	2.4	1	0.2
Oral bleeding	1	2.4	1	0.2
Inability to move or retrieve device	1	2.4	1	0.2
Pleural effusion	1	2.4	1	0.2
AV fistula	1	2.4	1	0.2
Vasovagal reactions	1	2.4	1	0.2
Anemia Requiring Transfusion	1	2.4	1	0.2
Air embolism	1	2.4	1	0.2
Allergic reaction to contrast media	1	2.4	1	0.2
Totals:	**41**	**100.0**	**37**	**8.0**

Table 2-53 summarizes the number of events and number of patients experiencing adverse events by type of event.

Table 2-53. 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**

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

These events are classified by event category originally provided by the site in **Table 2-54**.

Table 2-54. Summary of Non-Events

	N Events	% of Events	N Pts With Events	% of Patients	N Events	% of Events	N Pts With Events	% of Patients
Other Non-Study Related	654	58.6	241	52.1	305	56.2	120	49.2
Other Study Related	93	8.3	49	10.6	12	2.2	12	4.9
Arrhythmias	70	6.3	48	10.4	31	5.7	24	9.8
Bruising - Hematoma	66	5.9	59	12.7	31	5.7	26	10.7
Coumadin therapy stopped	11	1.0	8	1.7	65	12.0	44	18.0
Chest pain/discomfort	52	4.7	41	8.9	19	3.5	16	6.6
Epistaxis	19	1.7	15	3.2	11	2.0	10	4.1
Dyspnea	22	2.0	20	4.3	4	0.7	4	1.6
Pleural effusion	19	1.7	16	3.5	5	0.9	5	2.0
INR<2.0	11	1.0	8	1.7	9	1.7	5	2.0
Hematuria	9	0.8	8	1.7	7	1.3	7	2.9
Infection	10	0.9	8	1.7	6	1.1	6	2.5
Ventricular tachyarrhythmia	8	0.7	8	1.7	3	0.6	3	1.2
INR>4.0	5	0.4	4	0.9	6	1.1	6	2.5
Prolonged bleeding from a laceration	6	0.5	6	1.3	4	0.7	4	1.6
Pericardial effusion	10	0.9	10	2.2	0	0	0	0
Gastrointestinal bleeding	5	0.4	5	1.1	3	0.6	3	1.2
Pulmonary embolism	7	0.6	6	1.3	1	0.2	1	0.4
Myocardial infarction	6	0.5	6	1.3	2	0.4	2	0.8
Rectal bleeding	4	0.4	4	0.9	3	0.6	3	1.2
Complete heart block	5	0.4	5	1.1	1	0.2	1	0.4
Red eye	1	0.1	1	0.2	4	0.7	4	1.6
Pneumonia	3	0.3	3	0.6	2	0.4	2	0.8
Oral bleeding	2	0.2	2	0.4	1	0.2	1	0.4
Pulmonary edema	2	0.2	2	0.4	1	0.2	1	0.4
Coronary artery thrombosis	1	0.1	1	0.2	2	0.4	2	0.8
Stroke - ischemic	1	0.1	1	0.2	2	0.4	2	0.8
Transient ischemic attack TIA	1	0.1	1	0.2	2	0.4	2	0.8
Anemia Requiring Transfusion	2	0.2	2	0.4	1	0.2	1	0.4
Ventricular fibrillation	3	0.3	3	0.6	0	0	0	0
Vasovagal reactions	2	0.2	2	0.4	0	0	0	0
Cranial bleed	2	0.2	2	0.4	0	0	0	0
Thromboembolism	2	0.2	2	0.4	0	0	0	0
Thrombosis	1	0.1	1	0.2	0	0	0	0
Device thrombus	1	0.1	1	0.2	0	0	0	0
Totals:	**1117**	**100.0**	**311**	**67.2**	**543**	**100.0**	**158**	**64.8**

3 Summary and Conclusion

Results from the 900 patient year analysis are consistent or better than the initial analysis (600 patient years). These data demonstrate that the WATCHMAN LAA Closure Technology is a safe and effective alternative to warfarin therapy for use in preventing the embolization of thrombi, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation.