WATCHMAN

WATCHMAN®LAA Closure Device
Instructions for Use

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Key of Symbols

	Use Before Date	STERILE EO	Contents Sterile: Ethylene Oxide Gas
REF	Model Number		Refer to accompanying instructions for use
LOT	Lot Number		Use only if Package is Unopened or Undamaged
	Single Use only		MR Conditional

2009-4434/b1-06

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

Device Description
The WATCHMAN LAA Closure Technology consists of the Access System, Delivery System and LAA Closure Device. The Access System and Delivery System permit Device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium. The WATCHMAN Device is a self-expanding nitinol structure with membrane on the proximal face. The Device is constrained within the Delivery Catheter until deployment in the LAA. The Device is available in 5 sizes from 21 to 33 mm. Device selection is determined by LAA measurements using Fluoroscopy (Fluoro) and Transesophageal Echocardiography (TEE).

The WATCHMAN LAA Closure Device is designed to be permanently implanted at or slightly distal to the ostium of the LAA to trap potential emboli before they exit the LAA. The placement procedure can be done under local or general anesthesia in a catheterization laboratory setting.

Contraindications
Do not use the WATCHMAN LAA Closure Device if:

1. Intracardiac thrombus is visualized by TEE.

NOTE: If thrombus is identified in the LAA, dissolve with anticoagulation therapy before attempting to implant the WATCHMAN Device.

2. An atrial septal repair or closure device is present.
3. The LAA anatomy will not accommodate a Device. See Table 1.
4. All the customary contraindications for other percutaneous, catheterization interventions e.g., patient size (i.e., too small for TEE probe, catheter size, etc.) or condition (i.e., active infection, bleeding disorder, untreated ulcer or any other contraindication to anticoagulation therapy etc.).

Warnings and Precautions
Implantation of the WATCHMAN LAA Closure Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN training program.

- **The LAA is a thin walled structure. Use caution when accessing the LAA and deploying the Device.**
- The WATCHMAN Access and Delivery Systems are sterile and intended for single use only. Do not reuse or resterilize.
- If sterile barrier has been compromised in any way, or WATCHMAN Access System, Obturator or Delivery System appear damaged DO NOT USE.
- Careful consideration should be given to use of the Device in pregnant and/or breastfeeding women due to the risk of significant exposure to x-rays and the use of strong anticoagulation medication.
- Device selection should be based on accurate LAA measurements obtained using fluoroscopy and TEE in multiple angles (e.g. 0°, 45°, 90°, 135°).
- Aspirin should be started one day prior to scheduled procedure and continued daily.
- Patients should be fully heparinized throughout the procedure with an active clotting time (ACT) of 200 - 300 seconds after transseptal puncture.
- Fluoro and TEE should be used when implanting the Device.
- Do not release (unscrew) the Device unless release criteria (implantation procedure step 15) are satisfied.
- Potential for Device embolization exists with cardioversion < 30 days following Device implantation. Verify Device position post cardioversion.
- Post- procedure warfarin therapy is <u>required</u> in <u>ALL</u> patients receiving a Device per each institution's protocol. Patients should remain on warfarin for a minimum of 45 days post implant (INR 2.0-3.0). At 45 days post implant perform Device assessment with TEE. Cessation of warfarin is at physician discretion. Patients ceasing warfarin should begin clopidogrel 75mg daily for 6 months post-implant and remain on one adult aspirin indefinitely.
- Prescribe appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

Magnetic Resonance Imaging
The WATCHMAN LAA Closure Device was determined to be MR-conditional (International, Designation: F2503-05. Standard Practice for Marking Medical Devices and Other Items for Safety in the MR Environment. ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, Pennsylvania, 19428, 2005).
A patient with the Device can be scanned safely, immediately after placement and thereafter under the following conditions: Static magnetic field of 3-Tesla or less Spatial gradient field of 720-Gauss/cm or less Max MR system reported SAR of 3-W/kg for 15min of scanning.
In non-clinical testing, the Device produced a temperature rise of < 0.5°C at a max MR system-reported SAR of 3-W/kg as assessed by calorimetry for 15min of MR scanning in a 3-Tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare, Milwaukee, WI).
MR image quality may be compromised if the area of interest is relatively close to the Device. Optimization of MR imaging parameters is recommended.

Adverse Events
Atritech conducted a clinical study evaluating 707 randomized patients (463 to the WATCHMAN Device group and 244 to the Control group) using a 2:1 randomization allocation ratio. The randomized cohort was followed for a total of 900 patient-years for the primary efficacy endpoint at the time of the analysis.
Adverse events reported in the WATCHMAN group during the clinical study were adjudicated by the Clinical Events Committee. A total of seventeen deaths were reported, five of which were related to efficacy endpoints (stroke, cardiovascular causes or systemic embolism). No deaths were due to device or procedure-related causes. Those events adjudicated as "study-related" (serious and non-serious) were as follows in descending order of frequency:

- Pericardial Effusion-Serious
- Stroke - Ischemic
- Device Thrombus
- Bruising - Hematoma
- Rectal Bleeding
- Hematuria
- Pseudoaneurysm
- Arrhythmia
- Bleeding From Varicose Veins
- Major Bleed Requiring Transfusion
- Pleural Effusion
- Transient Ischemic Attack (TIA)
- Allergic Reaction To Contrast Media
- Pulmonary Edema
- Thrombosis
- Gastrointestinal Bleeding
- Death
- Pericardial Effusion
- Epistaxis
- Device Embolization
- Infection
- Anemia Requiring Transfusion
- AV Fistula
- Cranial Bleed
- Oral Bleeding
- Systemic Embolization
- Air Embolism
- Inability To Move Or Retrieve Device
- Stroke - Hemorrhagic
- Vasovagal Reactions

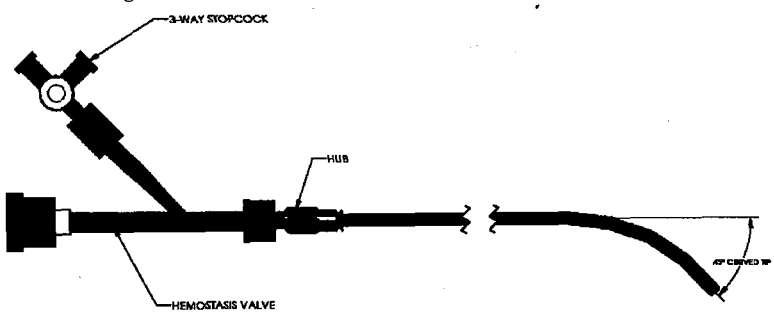
Some additional events that may be expected in catheterization procedures include:
- Pneumothorax
- Pulmonary Vein Obstruction
- Valvular or vascular damage

Pre-Procedural Instructions
A baseline TEE should be performed to confirm the absence of intracardiac thrombus and measure LAA to verify that a WATCHMAN LAA Closure Device may be implanted.

Procedural Instructions
Equipment Needed for Implantation Procedure
- Venous Introducer (optional)
- Standard transseptal access system
- 0.035" guidewire (exchange length extra support)
- 6Fr Pigtail Catheter

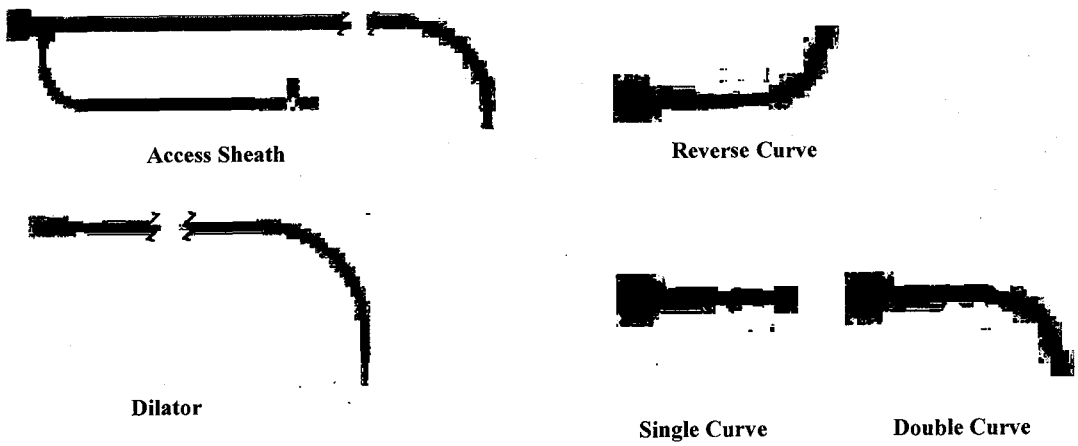
- WATCHMAN® Obturator (Optional Accessory)

Figure 1: WATCHMAN® Obturator (Optional Accessory)



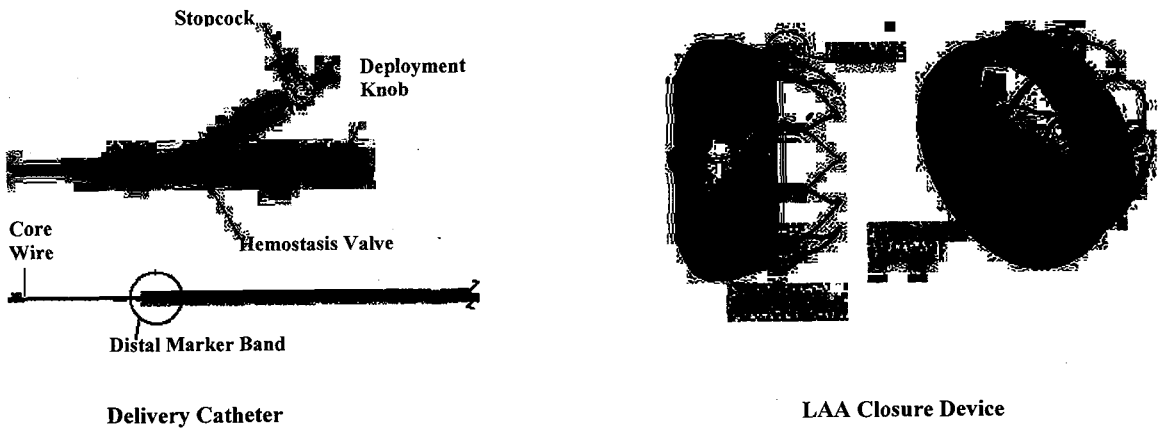
- WATCHMAN® Access System (Access Sheath/ Dilator)

Figure 2: WATCHMAN® Access System



- WATCHMAN Delivery System (Delivery Catheter and Device)

Figure 3: WATCHMAN® Delivery System (Delivery Catheter and Device)



Implantation Procedure

WARNING: The use of echocardiographic imaging is required (Transesophageal echocardiography is recommended as an aid in placing the WATCHMAN Device).

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

Use standard practice to puncture vessel and insert 0.035" guidewire and vessel dilator.

1. Use a standard transseptal access system to cross inter-atrial septum.
2. Exchange crossing sheath with exchange length extra support 0.035 " guidewire. Position guidewire in left upper pulmonary vein (LUPV) or loop in left atrium.
3. Prepare WATCHMAN Access System
   a. Remove Access Sheath and Dilator under sterile conditions.
   b. Inspect prior to use to ensure no damage.

NOTE: If sterile barrier has been compromised in any way, or WATCHMAN Access System appears damaged DO NOT USE.

   c. Flush Access Sheath and Dilator with saline prior to use.
   d. Insert Dilator into hemostasis valve/Access Sheath.
4. Advance WATCHMAN Access System over guidewire into left atrium (LA). As Access Sheath nears center of LA, hold Dilator and advance Access Sheath into initial position in LA or ostium of LUPV.

NOTE: Use caution when introducing WATCHMAN Access System to prevent damage to cardiac structures.

5. Remove Dilator and guidewire, leaving Access Sheath. Allow back bleed to minimize potential for introducing air before tightening valve. Flush with saline.
6. Confirm LAA size and select appropriate WATCHMAN LAA Closure Device.
   a. Using TEE, measure LAA ostium width and LAA length in 3-4 views (0°, 45°, 90°, 135°).
   b. Choose a device based on **maximum** LAA ostium width recorded. Use Table 1 as a guide.

NOTE: LAA anatomy should accommodate a Device as described in Table 1.

Table 1: WATCHMAN® LAA Closure Device Selection

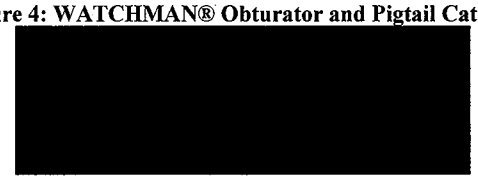
17 – 19.9	21
20 – 22.9	24
23 – 25.9	27
26 – 28.9	30
29 – 31.9	33

7. The use of the WATCHMAN Obturator (packaged separately) is optional. If Obturator is used, remove from sterile packaging and ensure hemostasis valve and stopcock are securely attached. Flush with saline prior to use.

NOTE: If sterile barrier has been compromised in any way, or Obturator appears damaged DO NOT USE.

Insert pigtail catheter through Obturator and flush to ensure all air is removed. Position distal tip of Obturator just proximal to distal marker band on Access Sheath. Carefully advance pigtail catheter into distal LAA. Advance Obturator over pigtail catheter up to initial curve of pigtail catheter tip -See Figure 4.

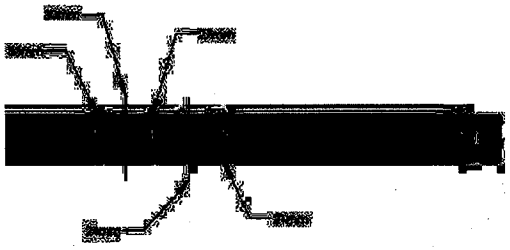
Figure 4: WATCHMAN® Obturator and Pigtail Catheter



NOTE: Record multiple angles on cine with contrast prior to advancing Access Sheath into LAA. Use fluoro guidance while advancing pigtail catheter, Obturator and/or Access Sheath. Stop if resistance is felt.

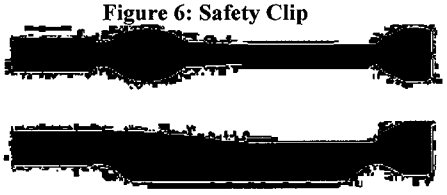
If Obturator is not used, carefully advance pigtail catheter through Access Sheath into distal LAA under flouro guidance. Carefully advance Access Sheath over pigtail catheter until Access Sheath marker band corresponding to Device size-see Figure 5 is at or just distal to LAA ostium. Slowly remove pigtail catheter .

Figure 5: WATCHMAN® Access Sheath Marker Bands



8. Prepare WATCHMAN Delivery System
   a . Remove Delivery System under sterile conditions.
   b. Remove and discard deployment Safety Clip by pressing on Clip's thumb pad -See Figure 6.

Figure 6: Safety Clip



   c. Inspect prior to use to ensure no damage to handle, catheter connections and Device (through Delivery Catheter)

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

   d. Confirm that the distal tip of the Device is aligned with marker band on Delivery Catheter.

CAUTION: Do not allow WATCHMAN Device to protrude to prevent damage to Delivery Catheter.

   e. Flush system with saline removing all air and maintaining fluid throughout Delivery Catheter. Open and flush proximal valve.

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

9. Loosen proximal valve of Access Sheath allowing bleed back before inserting Delivery Catheter.
10. To avoid introduction of air, slowly advance Delivery Catheter into Access Sheath under fluoro guidance.

NOTE: Use caution when introducing Delivery Catheter to prevent damage to cardiac structures.

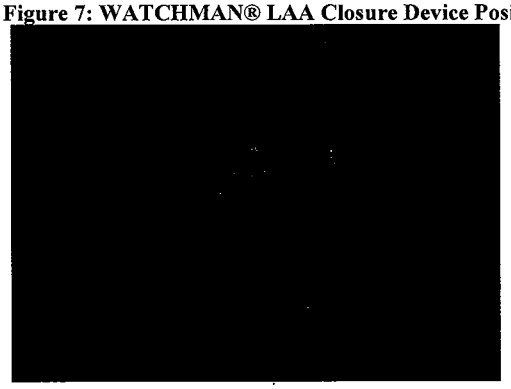
11. On fluoro, align most distal marker band on Access Sheath with marker band on Delivery Catheter. Once bands are aligned, stabilize Delivery Catheter, retract Access Sheath and snap together as Access Sheath/Delivery Catheter (AS/DC) Assembly.
12. Using fluoro and TEE confirm position of Delivery Catheter tip before deploying the Device.

NOTE: To inject contrast, flush catheter or measure pressure while inserting Delivery Catheter into Access Sheath. Contrast syringe or manifold must be attached to flush port of Delivery Catheter.

13. If repositioning is required, unsnap and slowly remove Delivery Catheter from Access Sheath. If necessary reinsert pigtail catheter and/or Obturator to reposition Access Sheath. Reinsert Delivery Catheter as described in Step 11.
14. Deploy WATCHMAN Device by loosening valve on Delivery System and holding deployment knob stationary while retracting Assembly to completely deploy Device. Leave core wire attached.
15. Device release criteria:

a. **Position:** Plane of maximum diameter is at or just distal to and spans entire LAA Ostium.-See Figure 7.

Figure 7: WATCHMAN® LAA Closure Device Position



b. **Stability:** Gently pull back then release deployment knob to visualize movement of Device and LAA together.
c. **Size (compression)**: Measure plane of maximum diameter of Device -See Figure 7. Use Table 2 as a guide.
d. **Seal:** Ensure all lobes are distal to Device and sealed.

Table 2: WATCHMAN® LAA Closure Device Diameter

Original Diameter (mm)	[redacted]
21	
24	
27	
30	
33	

16. Partial Device Recapture

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

a. Advance tip of AS/DC Assembly up to Device (do not unsnap). Fix deployment knob with right hand and gently advance AS/DC Assembly over shoulders of Device. Position right thumb against Delivery Catheter hub for stability. Resistance will be felt as Device shoulders collapse. Continue to advance Assembly up to but not past fixation barbs. When resistance is felt a second time (barb contact), stop, tighten hemostasis valve.

NOTE: If Device is retrieved past fixation barbs, recapture fully and replace Delivery System. Refer to Step 17. The WATCHMAN Device and Delivery System are for single use only. Do not reuse or resterilize.

b. Reposition AS/DC Assembly proximally and re-deploy by holding deployment knob and retracting Access Sheath until Device is completely deployed. Leave core wire attached.

WARNING: Do not release the WATCHMAN Device from the core wire if the Device does not meet release criteria (Step 15).

17. Full Device recapture.

NOTE: Fully recapture the Device if too proximal or does not meet release criteria.

a. Advance tip of AS/DC Assembly up to face of Device (do not unsnap).
b. Fix deployment knob with right hand and gently advance AS/DC Assembly over shoulders of Device. Position right thumb against Delivery Catheter for stability. Resistance will be felt as Device shoulders collapse. Continue to advance Assembly until Device is completely collapsed and recaptured.
c. Withdraw Device until distal tines are proximal to marker band then tighten hemostasis valve.
d. Unsnap Delivery System from Access Sheath while maintaining position. Slowly remove Delivery System.
e. Insert pigtail catheter and/or Obturator to reposition Access Sheath in LAA if necessary.
f. Repeat Steps 8- 15 with new Delivery System.

18. WATCHMAN Device Release: Confirm proper position, stability, size, and seal, and then advance Assembly to face of Device. Rotate deployment knob counter clockwise 3-5 full turns. Confirm core wire is disconnected.
19. Use standard of care for post procedure bleeding at access site.
20. Post Procedure Information
    a. Patients should remain on warfarin and 81mg aspirin for a minimum of 45 days post implant (INR 2.0-3.0). At 45 days assess WATCHMAN Device with TEE. Cessation of warfarin is at physician discretion. Patients ceasing warfarin should begin clopidogrel 75mg and adult aspirin daily through 6 months post-implant and remain on one adult aspirin per day indefinitely.
    b. Prescribe appropriate endocarditis prophylaxis for 6 months following Device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

CLINICAL SUMMARY

The WATCHMAN LAA Closure Technology was evaluated in a multicenter, prospective randomized study, comparing the WATCHMAN device to long-term warfarin therapy, demonstrating the treatment arm is non-inferior to the control arm. A 2:1 randomization allocation ratio (two device to one control) was used with stratification by center.
A total of 59 centers (55 U.S., 4 European) actively participated by enrolling at least one patient in the study. A total of 800 patients were enrolled in the trial. This total included 707 randomized patients (463 to the Device group, 244 to the Control group) and 93 roll-in patients.

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

- LVEF <30%
- intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
- a high risk patent foramen ovale (PFO)
- significant mitral valve stenosis (MV <1.5 cm^2)
- an existing pericardial effusion of >2 ±1 mm
- complex atheroma with mobile plaque of the descending aorta and/or aortic arch
- a cardiac tumor

Population/Subject Demographics
Table 3 summarizes the patient baseline demographic information of the randomized cohort.

Table 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.

Baseline Risk Factors
Table 4 summarizes baseline risk factors for the randomized cohort.

Table 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.

The mean (standard deviation) of the CHADs score was 2.2 (1.1) and 2.3 (1.2) for the Device and Control groups respectively.

Enrollment Summary
Table 5 summarizes patient enrollment across treatment groups, including non-randomized roll-in patients.

Table 5 - 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 was diagnosed with cardiac tumor prior to procedure.

A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted.
A total of 93 patients were enrolled as roll-in (non-randomized) patients at 33 centers. The roll-in phase was implemented in January 2006 and therefore not all centers participated in this phase. A successful implant occurred in 82.7% (77/93) of roll-in patients for whom an implant procedure was attempted. The procedural success rate in the roll-in group was lower than the randomized group; likely reflecting the presence of a learning curve for implanting the device.

Adverse Events – Device Group

Table 6 - Summary of Serious Device or Procedure Related Adverse Events

Pericardial Effusion-Serious	23	23	5.0
Other Study Related	14	14	3.0
Stroke - Ischemic	6	6	1.3
Bruising - Hematoma	4	4	0.9
Device Embolization	3	3	0.6
Pseudoaneurysm	3	3	0.6
Arrhythmias	2	2	0.4
Infection	2	2	0.4
Gastrointestinal Bleeding	1	1	0.2
Thrombosis	1	1	0.2
Device Rhrombus	1	1	0.2
Pleural Effusion	1	1	0.2
Pulmonary Edema	1	1	0.2
AV Fistula	1	1	0.2
Transient Ischemic Attack TIA	1	1	0.2
Anemia Requiring Transfusion	1	1	0.2
Major Bleed Requiring Transfusion	1	1	0.2
Totals:	**66**	**57**	**12.3**

The total number of events does not equal the total number of patients with events as patients may have experienced multiple events.

Primary Efficacy Analysis

Intent-to-Treat

The pre-specified intent-to-treat cohort includes all randomized patients in the group to which they were assigned. Results for the primary efficacy endpoint comprised of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in Table 7.

Table 7. 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 pre-specified non-inferiority margin of 2.0.. The posterior probability of non-inferiority of 0.998 exceeds the pre-specified non-inferiority criterion.

Table 8. Freedom from Primary Efficacy Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	7	7	98.5	0	0	100.0
45-days	2	9	98.0	2	2	99.2
6-months	4	13	97.1	3	5	97.9
1-year	2	15	96.4	4	9	95.7
2-year	4	19	93.5	6	15	90.3
3-year	1	20	92.1	1	16	87.7

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

Post Procedure

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed including 1 patient who experienced a stroke before a device was implanted and 13 patients who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events. As these 5 events occurred on the date of the implant and were primarily safety related, they were removed from the post procedure analysis (in part, to avoid double counting of the events as both efficacy and safety). Results of the primary efficacy endpoint once these 19 patients were removed are displayed in **Table 9**.

Table 9. 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

The primary efficacy event rate was 2.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group. These rates yielded a relative risk, or rate ratio, of 0.49, a 51% lower rate of efficacy events in the Device group. The 95% credible interval for the rate ratio was (0.24, 1.06). The probability of superiority of 0.965 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

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

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.8	0	0	100.0
45-days	2	3	99.3	2	2	99.2
6-months	4	7	98.3	3	5	97.9
1-year	2	9	97.7	4	9	95.7
2-year	4	13	94.6	6	15	90.3
3-year	1	14	93.2	1	16	87.7

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

Per Protocol

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare effectiveness in patients who successfully received their assigned treatment. Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for Device patients. Results for the primary efficacy endpoint for this analysis population are displayed in **Table 11**.

Table 11. 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

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. This yielded a rate ratio, or relative risk, of 0.44, a 56% lower rate of efficacy events in the Device group. The 95% credible interval for the rate ratio based on the Bayesian model was (0.20, 1.03). The probability of superiority of 0.971 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

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

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.5	2	2	99.2
6-months	1	3	99.2	2	4	98.3
1-year	3	6	98.1	4	8	96.1
2-year	4	10	93.4	6	14	90.7
3-year	0	10	93.4	1	15	88.0

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

Primary Safety Analysis

Intent-to-Treat

Results for the primary safety endpoint are displayed in **Table 13**. In contrast to the primary efficacy endpoint, there was no pre-specified hypothesis for the primary safety endpoint.

Table 13. 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)

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

Randomization Allocation (2 Device: 1 Control)

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

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

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. Ischemic and hemorrhagic stroke events have been categorized as both a safety and efficacy event as described above. The 5 ischemic strokes in the Device group were due to procedure complications including air embolism and excessive sedation which resulted in extended median hospitalization of 7 days and no deaths. The 22 pericardial effusions required physician intervention (15 were treated percutaneously with fluid drainage with a median hospitalization of 4 days and 7 required surgical intervention with a median hospitalization of 6 days).

Post Procedure

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events and 22 patients were removed who experienced procedural events including pericardial effusions. This analysis is intended to provide an alternate way to assess post procedural, long term safety which is an issue with warfarin by evaluating the risk/benefit after the acute procedure risks with the device. As such, these 27 patients with procedure events were removed from this analysis. Results of the primary safety endpoint results are displayed in **Table 15**.

Table 15. 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. 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).

Table 16. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

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

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

Per Protocol

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare safety in patients who successfully received their assigned treatment. Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for Device patients. Results for the primary safety endpoint for this analysis population are displayed in **Table 17**.

Table 17. 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, 0.96)

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. 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, 0.96).

Table 18. Kaplan-Meier Estimates: Freedom from Primary Safety (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.7	0	0	100.0
45-days	1	2	99.5	2	2	99.2
6-months	3	5	98.6	4	6	97.4
1-year	1	6	98.3	4	10	95.2
2-year	0	6	98.3	2	12	93.0
3-year	2	8	92.9	1	13	90.1

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

Additional Analyses – Device Group

Additional analyses were performed for the Device group to evaluate procedure success.

- Technical Success was defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary
- Procedure Success was defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay

Table 19 –Technical/Procedure Success

Technical Success	408/449 (90.9)
Procedure Success	375/449 (83.5)

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.

Additional Analyses – Control Group
Additional analyses were performed for the Control group to evaluate warfarin use.

- Non-therapeutic INR > 3.0 or < 2.0, and stopped therapy (Interruption of Therapy (IOT))
- Excessive anticoagulation INR > 4.0

The frequency of patients ever having a non-therapeutic INR or excessive anti-coagulation was assessed. 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 20 -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)

The percent of the measurements that represented non-therapeutic INR or excessive anticoagulation was also calculated. Based on these measurements, patients remained in the therapeutic range (INR 2.0 - 3.0) only 55% of the time.

Warfarin Discontinuation – Device Group
Warfarin discontinuation rates for patients implanted with the device are displayed in **Table 21**. 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 ≤3 ± 2 mm around the margins of the device. A majority of patients (87%) were able to discontinue warfarin therapy at 45 days.

Table 21 -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)

Event Definitions
Definitions related to endpoint events are provided below:

- **Device Embolization** - An obstruction or occlusion by a device that has been dislodged from the LAA and is introduced into the circulatory system potentially occluding vessels and / or organs by occluding its blood supply.
- **Serious Adverse Event (SAE)** - Any untoward medical occurrence or any Adverse Event that:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
- **Ischemic Stroke** - Sudden onset of a focal neurological deficit with symptoms and/or signs persisting more than 24 hours or symptoms less than 24 hours confirmed by CT or MRI, including a full neurological exam by a Neurologist.
- **Hemorrhagic Stroke** - Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage, including full neurological exam by a Neurologist.

- **Pericardial Effusion (non serious)** – Increased fluid within the pericardial sac that did not cause circulatory compromise and did not require drainage.
- **Pericardial Effusion (serious)** –
    - Cardiac Tamponade - any pericardial effusion requiring percutaneous treatment.
    - Cardiac Perforation - any pericardial effusion requiring surgical intervention.
- **Systemic Embolism** - Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.
- **Thromboembolism** - The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation.
- **Thrombosis** - The formation or presence of a blood clot within a blood vessel.
- **Transient Ischemic Attack (TIA)** - Acute focal neurological event (including focal motor deficit aphasia, difficulty walking, hemi sensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes and up to 24 hours that is MR imaging negative, including full neurologic exam by Neurologist.
- **Unanticipated Adverse Device Effect (UADE)** - Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, the WATCHMAN Device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with the WATCHMAN Device that relates to the rights, safety, or welfare of subjects.

How Supplied
The WATCHMAN LAA Closure Device is provided pre-loaded in the Delivery Catheter. The WATCHMAN Access System and Obturator are packaged separately.

NOTE: Contents of inner package are STERILE.

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