Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients with Atrial Fibrillation: 2.3 Year Follow-Up of the PROTECT AF Trial

Running title: Reddy et al.; 2.3 Year Follow-Up of PROTECT AF

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This work was presented in part at the 59th Annual Scientific Sessions of the American College of Cardiology, March 28, 2010; and at the 30th Annual Scientific Sessions of the Heart Rhythm Society, May 15, 2009.

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Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs; [27] Other Treatment; [53] Embolic stroke; [74] Other Stroke Treatment - Medical; [184] Coumarins
Abstract:

**Background**—The multicenter PROTECT AF study was conducted to determine whether percutaneous left atrial appendage (LAA) closure with a filter device (Watchman) was noninferior to warfarin for stroke prevention in atrial fibrillation (AF).

**Methods and Results**—Patients (n = 707) with nonvalvular AF and at least one risk factor (age > 75, hypertension, heart failure, diabetes or prior stroke/TIA) were randomized to either the Watchman device (n = 463) or continued warfarin (n = 244) in a 2:1 ratio. After device implantation, warfarin was continued for ~45 days, followed by clopidogrel for 4.5 months and lifelong aspirin. Study discontinuation rates were 15.3% (71/463) and 22.5% (55/244) for the Watchman and warfarin groups respectively. The time in therapeutic range for the warfarin group was 66%. The composite primary efficacy endpoint included stroke, systemic embolism and cardiovascular death, and the primary analysis was by intention-to-treat. After 1,588 patient-years of follow-up (mean 2.3±1.1 years), the primary efficacy event rates were 3.0% and 4.3% (percent per 100-patient years) in the Watchman and warfarin groups, respectively (RR = 0.71, 95% CI 0.44–1.30%/y), meeting the criteria for non-inferiority (probability of non-inferiority > 0.999). There were more primary safety events in the Watchman group (5.5%/y, 95% CI 4.2–7.1%/y) than in the control group (3.6%/y; 95% CI 2.2–5.3%/y; RR 1.53, 95% CI 0.95–2.70).

**Conclusions**—The “local” strategy of LAA closure is noninferior to “systemic” anticoagulation with Warfarin. PROTECT AF has, for the first time, implicated the LAA in the pathogenesis of stroke in AF.

**Clinical Trial Registration Information**—Clinicaltrials.gov; Unique Identifier: NCT00129545.

**Key words**: atrial fibrillation, stroke, left atrial appendage, anticoagulation, pericardial effusion, Watchman device, clopidogrel
Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, affects millions of people around the world, with vast sociomedical consequences because of its association with ischemic stroke.\textsuperscript{1-3} Systemic anticoagulant drug therapy is highly effective but difficult for many patients to sustain over time, leading to an intensive quest for alternative strategies, especially for patients at highest risk.\textsuperscript{4,5} Non-pharmacological approaches are under development to isolate the left atrial appendage (LAA) from the systemic circulation, based on evidence suggesting this to be the main site of thrombus formation, and subsequent cardioembolic stroke in AF patients.\textsuperscript{6-10} The PROTECT AF trial was designed to evaluate whether systemic anticoagulation with Warfarin, the most commonly employed anticoagulant, could be replaced by closure of the LAA with a percutaneously-deployed filter device.\textsuperscript{11} This trial hypothesized that LAA closure with the Watchman device would be non-inferior to Warfarin therapy. The principal analysis was based on assessment of noninferiority using a Bayesian design permitting assessments at multiple durations of follow-up. The interim results for the composite primary efficacy endpoint of stroke, systemic embolism and cardiovascular death were published based on 1,050 patient-years observation, when the event rate of 3.0%/y in patients undergoing LAA closure was noninferior to continued warfarin therapy (4.9%/y; relative risk = 0.62; 95% confidence interval [CI] 0.35-1.25).\textsuperscript{11}

While the initial results validated the hypothesis that the LAA is the principal source of thromboembolism in patients with nonvalvular AF, several factors limited interpretation and generalizability. Relatively few patients (214/707, 30%) had been followed for ≥2 years, raising questions about efficacy over time. The protocol called for continuation of warfarin for 45 days following LAA closure and for antiplatelet therapy with clopidogrel for 4.5 months thereafter,
either of which could reduce stroke risk in patients assigned to the device arm.\textsuperscript{4,12} Beyond this initial period, aspirin alone was employed while the trial continued to accrue a specified exposure of 1,500 patient-years after randomization. In this report we describe the long-term efficacy of LAA closure, secondary analyses intended to isolate the outcome of successful device deployment from the confounding effects of concomitant antithrombotic therapy and implant-related complications, and an analysis of treatment efficacy in patients with prior thromboembolism, the group at highest risk for recurrent stroke.

**Methods**

**LAA Closure Procedure**

The design, structure and method of deploying the Watchman device (Atritech, Inc., Minneapolis, MN) has been described.\textsuperscript{10} Briefly, the device consists of a self-expanding nitinol frame with fixation barbs and a permeable, polyester fabric covering. The device is delivered under fluoroscopic and transesophageal echocardiographic (TEE) guidance. After transseptal puncture, contrast is injected to define the LAA anatomy. Then, an appropriately-sized Watchman device (21-33 mm diameter) is advanced to the ostium of the LAA through a 12-French sheath. Proper positioning and stability is verified by TEE and angiography prior to device release.

**PROTECT AF Trial**

The PROTECT AF trial has been described.\textsuperscript{13} Briefly, this was a prospective, unblinded, randomized trial conducted at 59 centers in the U.S. and Europe. Patients were enrolled from February 2005 until June 2008, and final clinical follow-up for the 1,500 patient year analysis occurred in April 2010. The protocol was approved by the institutional review board governing
research involving human subjects at each participating site and enrolled subjects were required
to provide signed informed consent. Efficacy and safety endpoint events were adjudicated by an
independent Clinical Events Committee, and a Data Safety and Monitoring Board oversaw trial
conduct.

The main inclusion criteria were age >18 years, a history of paroxysmal, persistent or
permanent nonvalvular AF plus at least one additional stroke risk factor (age ≥75 years,
hypertension, diabetes mellitus, heart failure, or prior stroke, transient cerebral ischemic attack
or systemic thromboembolism), and eligibility for warfarin therapy. Exclusion criteria were
centered around minimizing the possibility of thromboembolism unrelated to AF, specifically
atrial septal defect, mechanical prosthetic heart valve, patent foramen ovale accompanied by
atrial septal aneurysm (because of the potential for paradoxical embolization), left ventricular
ejection fraction <30%, intracardiac thrombus, morphologically complex (mobile or ulcerated)
aortic atheroma, or symptomatic carotid artery disease. Eligible patients underwent formal
neurological examination and those with a history of thromboembolism underwent baseline brain
imaging by MRI or CT.

All patients (including those who had previously sustained a stroke/TIA prior to
enrollment) were randomized in a 2:1 ratio to undergo either Watchman implantation or to a
control arm involving continued warfarin treatment. Patients in the intervention arm initially
received concomitant antithrombotic medication to allow endothelialization of the device
surface; warfarin was continued for at least 45 days and TEE imaging was repeated at 45 days,
six months and one year after implantation to assess for device stability, flow leaks around the
margins of the filter and thrombus formation. If satisfactory at 45 days after deployment,
warfarin was stopped and clopidogrel, 75 mg daily, plus aspirin, 81-325 mg daily was

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substituted until six months after device implantation, following which clopidogrel was stopped and aspirin alone was continued. Patients in the control group received warfarin treatment with INR monitoring performed no less often than every two weeks for six months and monthly thereafter to maintain the international normalized ratio (INR) between 2.0 and 3.0. Follow-up visits were scheduled at 45 days, 6, 9 and 12 months, and twice annually thereafter. Neurological assessments were performed whenever a neurological event was suspected and at 12 and 24 months for all subjects.

**Statistical Analysis**

The trial was designed to determine whether the LAA closure strategy would be noninferior to continued anticoagulation with respect to the composite primary efficacy endpoint of all stroke (ischemic or hemorrhagic), systemic embolism or cardiovascular death (including unexplained death). The primary safety endpoint included both procedure-related events (e.g., pericardial effusion requiring intervention or hospitalization, procedure-related stroke or device embolization) and major bleeding (intracranial bleeding or gastrointestinal bleeding requiring transfusion). Both the primary efficacy and safety analyses were based on intention-to-treat (ITT). In addition, several prespecified secondary analyses and two *post hoc* tertiary analysis were performed to isolate the stroke prophylactic effect of LAA closure. These included a “post-procedure” analysis of events occurring following device implantation, a “per-protocol” analysis confined to patients in the device group who stopped warfarin after the specified period and patients in the control group who sustained warfarin therapy, and the two *post hoc* analyses; a “terminal therapy” analysis that compared outcomes in patients with the device who discontinued warfarin treatment and completed treatment with clopidogrel and a “landmark” analysis that evaluated results from 6 months post-randomization onward. No α-level adjustment
was made for these sensitivity analyses to account for multiple comparisons.

The composite primary efficacy and safety event rates were analyzed using a Bayesian Poisson model, stratified by CHADS$_2$ risk score, with a non-informative gamma-conjugate prior distribution.\textsuperscript{14} Posterior sampling was used to calculate probabilities and 95% confidence intervals (CI) with criteria for success based on posterior probabilities for noninferiority and superiority exceeding 97.5 and 95%, respectively. The model encompassed data from this study only, assuming a constant hazard over time and a Poisson distribution of events. Differences in event rates over time were assessed using the Kaplan-Meier method. The number and proportion of patients experiencing events are reported with chi-square testing to assess trends. Statistical analyses were performed using SAS version 9.2 software.

The sample size was estimated based on data from the Stroke Prevention in Atrial Fibrillation (SPAF) studies, with an expected primary efficacy event rate 6.15%/y in the control group. Simulations were performed to ensure 80% power and 5% type I error rate under a group sequential analysis plan that included a first interim analysis after 600 patient-years of follow-up, and additional analyses after 150 patient-years of further follow-up to a maximum of 1,500 patient-years. A one-sided noninferiority probability criterion of at least 97.5% was selected with the use of a two-fold non-inferiority margin based on the ratio of primary efficacy event rates (Watchman / control). The study was registered with Clinicaltrials.gov, number NCT00129545.

Results

Cohort Characteristics

The enrolled cohort consisted of 707 randomized patients, 463 and 244 patients randomized to the LAA closure and control arms, respectively; a consort diagram is shown in Figure 1.
Patients were followed for an aggregate of 1,588.4 patient-years (1025.7 in the device group and 562.7 in the control group). The mean follow-up interval was 2.3±1.1 (range 0-5.9 years) and median follow-up was 2.4 years, with 469 patients completing 2 years of follow-up (319 in the device group and 150 in the control group).

All patients except for 3 in the control group received warfarin therapy and the time in therapeutic INR range was 66% based on the Rosendaal method. During the follow-up period, 34% of patients interrupted anticoagulation at some point, most often for invasive procedures (58%), but also because of hemorrhage (17%), elevated INR values (9%) or other reasons (18%). Patients in the control group were on warfarin for 88% of the follow-up period, and by two years, 16% were off warfarin. The primary efficacy event rate among patients in the control group who took warfarin consistently (4.4%/y) did not differ significantly from that in patients who interrupted warfarin at least once during the study (4.1%/y).

Among the 463 patients assigned to undergo LAA closure, the device was implanted in 408 (88%). During follow-up of this group, 86.8, 92.2 and 93.2%, respectively, stopped warfarin after evaluations at 45 days, 6 months and 1 year. Patients continued warfarin either because blood flow around the device into or out of the LAA was detected by TEE across an area >5 mm in 7.5, 3.6 and 2.7% or on the advice of the treating physician in 5.7, 4.2 and 4.1% of patients at 45 days, 6 months and 1 year after deployment, respectively (Table 1).

**Intention-to-Treat Efficacy and Safety Results**

Key clinical outcomes are shown in Table 2. The composite primary efficacy event rate was 3.0%/y (95% CI 2.1–4.3%/y) in the group assigned to LAA closure and 4.3%/y (2.6–5.9%/y) in the control group (rate ratio [RR] 0.71, 95% CI 0.44–1.30; probability of noninferiority >0.999). The components of the primary efficacy endpoint are delineated separately in Table 2 and
Figures 2 and 3.

Efficacy was consistent across a number of subgroups distinguished by gender, age, pattern of AF and LAA morphology (Figure 4). When patients with no more than one moderate risk factor (CHADS$_2$ score = 1) were excluded from the analysis, primary efficacy event rates were 3.9%/y in the device group and 5.0%/y in the control group (RR 0.79; 95% CI 0.44–1.43; probability of non-inferiority = 0.999).

With regard to safety, the primary adverse outcome rate was higher in the LAA closure group (5.5%/y, 95% CI 4.2–7.1%/y) than in the control group (3.6%/y; 95% CI 2.2–5.3%/y; RR 1.53, 95% CI 0.95–2.70) with most such events occurring early (Table 2 and Figure 5). Over extended follow-up, few additional adverse safety events accrued in the LAA closure group (10.1% at 1 year, 10.4% at 2 years and 13.6% at 3 years). While such events continued to occur in the control group 4.3% at 1 year, 6.7% at 2 years and 8.9% at 3 years, the incidence remained lower than in the device deployment group throughout the course of follow-up.

Secondary and Tertiary Analyses

The composite efficacy event rates in the post-procedure, per-protocol, and terminal therapy subgroups are shown in Table 3. Excluding events occurring on the day of device deployment, fewer patients in the group randomized to receive the Watchman device experienced primary efficacy events than in the control group (post-procedure: 2.5%/y vs. 4.3%/y, probability of superiority = 0.953). The same was true when analysis was confined to patients stopping warfarin after successful device deployment (per-protocol: 2.3%/y vs. 4.1%/y, probability of superiority = 0.955). When extended to patients who completed therapy with warfarin and clopidogrel and were taking only aspirin after device insertion, primary efficacy events occurred in 2.3%/y, compared with 4.1%/y in the control group (terminal therapy: probability of
superiority=0.945). Taken together, these results suggest that after successfully deployment, the LAA closure device was more effective than continued warfarin anticoagulation.

As shown in Table 4, when these subsidiary cohorts were analyzed with respect to safety, adverse events (mainly bleeding) occurred no more frequently in the LAA closure group than with continued anticoagulation (RR 0.77, 95% CI 0.45-1.45), and after interim antithrombotic therapy with warfarin followed by clopidogrel was completed and patients in the device-based treatment arm were taking aspirin alone the rate of major bleeding was significantly lower than in the group assigned to warfarin (RR 0.35, 95% CI 0.16-0.79).

When the functional impact of the primary efficacy and safety events (including both device-related and non–procedural events) are considered in terms of disability (increase in modified Rankin score [MRS] by ≥2 points) or death,16 device-based therapy was associated with improved outcomes (RR=0.41, 95% CI 0.22-0.82). As shown in Table 5, all analyses (including the intention-to-treat and the secondary analyses) demonstrated a statistically improved clinical outcome in the LAA closure group over the Control group with upper credible intervals well below unity.

**LAA Closure for Secondary Prevention of Stroke:** A shown in Figure 6, patients with previous stroke or TIA face a high risk of recurrent stroke even when treated with warfarin, and in the 131 patients (19%) meeting this criterion at entry the rate of primary efficacy events was 5.3%/y in the group assigned to LAA closure vs. 8.2%/y in those randomized to ongoing anticoagulation (RR 0.64, 95% CI 0.24–1.74, probability of non-inferiority = 0.987).

**Discussion**

This final analysis of outcomes in the PROTECT AF trial after more than 1,500 patient-years of
observation found that: i) by intention-to-treat, long-term efficacy of “local” therapy with the Watchman LAA closure device is non-inferior to systemic treatment with Warfarin, ii) the failure LAA closure to achieve superiority over Warfarin was related to the acute, procedure-related stroke events, iii) secondary analyses to isolate the effect of LAA closure from transient concomitant antithrombotic therapy (Warfarin and Clopidogrel) not only continued to reveal non-inferiority of LAA closure to Warfarin, but actually revealed superiority of the LAA closure strategy, and iv) the AF patients at greatest risk for cardioembolic events, the “secondary prevention” patients who previously sustained an embolic event, also received sustained benefit from the LAA closure strategy – both in the intention-to-treat analysis, and the secondary analyses that isolated the effect of LAA closure.

**Analysis of Study Population and Conduct**

Follow-up of patients enrolled in this study averaged 2.3 years; this compared favorably with 2.0, 1.0 and 1.9 years in RELY (study of Dabigatran), AVERROES (study of Apixaban) and ROCKET-AF (study of Rivaroxaban), respectively – other contemporary stroke prevention studies involving patients with nonvalvular AF. Participants were representative of patients with AF encountered in clinical practice: the mean age was 72 years, mean CHADS2 score 2.2, and approximately one in five had experienced prior stroke or TIA. Again for comparison, these baseline characteristics in RELY, AVERROES and ROCKET-AF were 71.5 years, 2.1 and 20.0%; 70.0 years, 2.1 and 13.5%; and 73 years, 3.5 and 55%, respectively.

In the control arm of the study, warfarin was generally well managed, with INR levels in the therapeutic range 66% of the time. This value was 64% in the RE-LY trial and less in the ROCKET-AF study (which involved patients with a mean CHADS2 score of 3.5). While the Rosendaal method for calculation of the time in therapeutic range does not account for the
frequency of INR monitoring, only 4% of INR measurements were separated by more than 8 weeks. In the ATRIA cohort of over 7,000 patients with nonvalvular AF receiving warfarin in routine clinical practice, this metric was 14%. Over two years, the warfarin discontinuation rate in the control group (16%) was similar to that in the RE-LY trial (16.6%). And while 34% of patients in the control group interrupted warfarin at some point during follow-up, these interruptions were generally temporary and did not measurably affect the overall event rates when compared to patients who did not interrupt treatment.

**Efficacy of LAA Closure**

The Watchman LAA closure strategy involved not only placement of the device in the LAA but a post-procedural period of anticoagulation with warfarin followed by temporary dual antiplatelet therapy with clopidogrel plus aspirin. In the ACTIVE trials, the combination of clopidogrel plus aspirin was less effective than anticoagulation with Warfarin but reduced the risk of stroke by 28% compared to aspirin alone, at the expense of increased bleeding. Hence, treatment efficacy in patients undergoing LAA closure could have been related to the requisite adjunctive antithrombotic therapy.

To assess for this possibility, a secondary analysis was conducted excluding events that occurred during or immediately following device deployment, and confined to the period after warfarin was discontinued in the device-based arm of the study. By this assessment, the device group experienced statistically fewer primary efficacy events than patients receiving warfarin. The same held true during the “terminal” therapy analysis (aspirin only in the device group and warfarin in the warfarin group), whereas previous trials involving the direct comparison of warfarin versus aspirin leave no doubt about the superior efficacy of warfarin. These sensitivity analyses support the view that LAA closure is an effective alternative to systemic
anticoagulation, and that this assessment is not appreciably confounded by the requisite antithrombotic treatment.

**Safety of LAA Closure**

In this trial, as in all drug versus device evaluations, there was a higher initial rate of adverse events in patients undergoing device implantation. Over time, adverse events continued to accrue in the control group, while the majority of events in the device group occurred proximate to the implantation procedure, particularly pericardial tamponade and procedure-related stroke – presumably air or thrombus embolism related to catheter manipulation. Indeed, one of the limitations of LAA closure remains these procedure-related events. While operator experience can certainly minimize the rate of these events, it will likely be further improvements in device design that will ultimately serve to minimize these complications to a minimal level.

Not surprisingly, excluding periprocedural adverse events favored the device strategy. The additional analyses of event rates after completion of successive treatment with warfarin and clopidogrel in the device group, however, yielded less intuitive results suggesting that safety in the device arm was adversely affected during six weeks of warfarin followed by clopidogrel plus aspirin until half a year had elapsed following the initial procedure. Among the implications of these observations is that the safety of LAA closure might be improved by reducing exposure to concurrent therapy with potent antithrombotic drugs. This hypothesis must be verified, however, in future studies. Implantation of LAA closure devices without concomitant transient Warfarin therapy has been reported, but whether this improves or worsens the safety of the procedure must be tested in prospective clinical trials.

**Functional Impact of Events**

The events adjudicated to assess the safety and efficacy of these treatments can have a highly
variable functional impact on patients related to their intensity and duration. To address this, we considered whether these events resulted in either important clinical disability (increase in modified Rankin score ≥2 points) or death. By this analysis, the LAA closure strategy was superior to anticoagulation. This suggests that the complications associated with LAA closure had less long-term impact compared with adverse events occurring in patients assigned to Warfarin – which include not only hemorrhagic events but perhaps more pertinent, the consequences of cardioembolic stroke.

**Secondary Stroke Prevention**

The importance of the LAA in the pathogenesis of stroke was corroborated by analysis of patients in whom the device was employed for prevention of recurrent stroke associated with AF. Warfarin is known to be less effective for prevention of recurrent thromboembolism in this high-risk subgroup, with event rates approximately double those reported in primary prevention cohorts. Observations in this subgroup, which constituted 18.5% of the patients enrolled in PROTECT AF, favored the Watchman device over warfarin, albeit with wide confidence intervals. Interestingly, while these wide confidence intervals preclude any firm conclusions, the relative risk in these patients with prior stroke/TIA (RR 0.64, 95% CI 0.24–1.74) was not dissimilar to the relative risk in the full PROTECT AF cohort (RR = 0.71, 95% CI 0.44–1.30); for comparison, in ROCKET AF, wherein 55% of the patients had a previous stroke or TIA and the mean CHADS2 score was 3.5, the relative risk reduction in these “secondary prevention” patients was 0.98 (95% CI 0.8–1.2).

**Limitations**

One limitation of this study is the relatively small number of patients enrolled; while large for an
interventional study, the sample size is considerably smaller than many anticoagulation drug trials for stroke prevention.\textsuperscript{17-19} On the other hand, the statistical methodology is rigorous and the primary efficacy and safety endpoints were well-validated, substantiating the main conclusions.

The composite primary endpoint was not ischemic stroke / systemic embolism alone, but rather all stroke (ischemic or hemorrhagic), systemic embolism or cardiovascular death (including unexplained death). If one looks at the rates of ischemic stroke alone were statistically not different: the event rates were 1.9 \textit{versus} 1.4 per 100 pt-yrs in the device and warfarin arms, respectively (RR=1.3; 95\% CI of 0.66 – 3.60). But importantly, without the procedure-related strokes seen in the device arm, the rate of ischemic stroke would be 1.4 events/100 pt-yrs. Thus, looking beyond the technical issues related to the Watchman device, these data suggest that the concept of “local” LAA closure is a scientifically valid approach to decrease stroke in AF patients.

Since a third of patients were randomized to continued Warfarin therapy, patients with absolute contraindications to Warfarin were not included in this trial. Thus, one cannot comment on the safety and efficacy of the Watchman device in patients with absolute contraindications to Warfarin.

In PROTECT-AF, patients with other potential sources of thromboemboli, such as patients with complex aortic plaque or left ventricular aneurysms, were excluded from the study. Thus, the efficacy of local therapy with the Watchman device in these patients is unknown. On the other hand, in a screening study to assess the potential utility of the Watchman device, it was determined that 4 of 5 AF patients fit the PROTECT AF inclusion/exclusion criteria; thus, this trial is applicable to the vast majority of AF patients.\textsuperscript{24}

Also, while the primary and secondary analyses were predefined, the assessment of
outcomes on terminal therapy and evaluation of the functional endpoint of events on disability or death were designed *post hoc* and should therefore be considered exploratory.

The number of patients in the secondary prevention subgroup was small and the confidence intervals surrounding estimates of treatment efficacy were necessarily wide. While the outcome results in this subgroup were concordant with the overall population, further studies are needed to define which subgroups of patients with AF stand to gain the most from LAA closure.

The Watchman device studied in PROTECT AF is one of several such devices that are currently at various stages of clinical testing. Whether or not the stroke prophylactic effect realized in PROTECT AF is generalizable to these other devices is unknown and requires dedicated randomized clinical trials.

Conclusions

This final analysis of the entire PROTECT AF trial cohort followed for an accumulated exposure of 1,588 patient-years revealed closure of the LAA with the Watchman device to be noninferior to ongoing warfarin therapy with regard to prevention of stroke, systemic embolism and cardiovascular death. However, the LAA closure arm did sustain an increased number of procedure-related safety events – mainly pericardial tamponade and procedure-related stroke. After successful deployment, the local therapy of LAA closure proved to be superior to well-controlled systemic anticoagulation, and this was particularly true when the functional impact of major adverse clinical events is considered. Based on the data available (mostly the PROTECT-AF trial), LAA closure has been given a Class IIb recommendation in the 2012 Focused Update of the European Society of Cardiology’s Atrial Fibrillation Guidelines.
Funding Sources: The PROTECT AF trial was supported by Atritech, Inc.

Conflict of Interest: Vivek Y. Reddy has received research grant support and consultant fees from Atritech, Inc. Shephal K. Doshi has received research grant support and consultant fees from Atritech, Inc. Horst Sievert has received study honorary, travel expenses, consulting fees from Atritech, Inc. Maurice Buchbinder has received research grant support from Atritech, Inc. Petr Neuzil has received research grant support from Atritech, Inc. Jonathan L. Halperin has served as a consultant with developers of novel antithrombotic agents for stroke prevention in AF. David Holmes has received research grant support from Atritech, Inc. Also, the Watchman LAA closure technology has been licensed to Atritech, and both Mayo Clinic and Dr Holmes have contractual rights to receive future royalties from this license. But to date, no royalties have been received.

References:


19. JMT.


Table 1. Warfarin Discontinuation for the LAA Closure Group.

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<thead>
<tr>
<th>Reason for Warfarin Continuation</th>
<th>45 Days</th>
<th>6 Months</th>
<th>1 Year</th>
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<td>348/401 (86.8%)</td>
<td>355/385 (92.2%)</td>
<td>345/370 (93.2%)</td>
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<td>Residual Shunt As Per Protocol</td>
<td>30 (7.5%)</td>
<td>14 (3.6%)</td>
<td>10 (2.7%)</td>
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<td>Other Physician Discretion</td>
<td>22 (5.5%)</td>
<td>16 (4.2%)</td>
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Table 2. Efficacy and Safety Results

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<td>patient-years</td>
<td>patient-years</td>
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<td></td>
<td>Observed rate</td>
<td>Observed rate</td>
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<td></td>
<td>(events per 100 patient-years)</td>
<td>(events per 100 patient-years)</td>
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<tr>
<td></td>
<td>(95% CrI)</td>
<td>(95% CrI)</td>
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<td>Primary Efficacy</td>
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<td>Systemic Embolism</td>
<td>3/1049.8</td>
<td>0/573.2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>All stroke</td>
<td>21/1026.3</td>
<td>15/562.7</td>
<td>0.77</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>34/1050.4</td>
<td>26/573.2</td>
<td>0.71</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Primary safety</td>
<td>54/979.9</td>
<td>20/554.6</td>
<td>1.53</td>
<td>--</td>
</tr>
</tbody>
</table>

Crl = credible intervals

* "Other" events include anemia, arrhythmia, device migration, esophageal tear, and hemopericardium
### Table 3. Primary Efficacy Results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Device Events/Total Pt-Yrs</th>
<th>Rate (95% CI)</th>
<th>Control Events/Total Pt-Yrs</th>
<th>Rate (95% CI)</th>
<th>Relative Risk (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>31/1025.7</td>
<td>3.0 (2.1, 4.3)</td>
<td>24/562.7</td>
<td>4.3 (2.6, 5.9)</td>
<td>0.71 (0.44, 1.30)</td>
<td>&gt;0.99</td>
<td>0.85</td>
</tr>
<tr>
<td>Post-procedure</td>
<td>25/1015.7</td>
<td>2.5 (1.6, 3.6)</td>
<td>24/562.7</td>
<td>4.3 (2.6, 5.9)</td>
<td>0.58 (0.35, 1.09)</td>
<td>&gt;0.99</td>
<td>0.95</td>
</tr>
<tr>
<td>Per-protocol</td>
<td>21/924.1</td>
<td>2.3 (1.5, 3.5)</td>
<td>23/562.1</td>
<td>4.1 (2.5, 5.7)</td>
<td>0.56 (0.33, 1.09)</td>
<td>&gt;0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>Terminal Therapy</td>
<td>16/705.3</td>
<td>2.3 (1.4, 3.7)</td>
<td>23/562.1</td>
<td>4.1 (2.5, 5.7)</td>
<td>0.55 (0.31, 1.12)</td>
<td>&gt;0.99</td>
<td>0.95</td>
</tr>
</tbody>
</table>

### Table 4. Primary Safety Results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Device Events/Total Pt-Yrs</th>
<th>Rate (95% CI)</th>
<th>Control Events/Total Pt-Yrs</th>
<th>Rate (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>54/979.9</td>
<td>5.5 (4.2, 7.1)</td>
<td>20/554.6</td>
<td>3.6 (2.2, 5.3)</td>
<td>1.53 (0.95, 2.70)</td>
</tr>
<tr>
<td>Post-procedure</td>
<td>27/969.8</td>
<td>2.8 (1.9, 4.0)</td>
<td>20/554.6</td>
<td>3.6 (2.2, 5.3)</td>
<td>0.77 (0.45, 1.45)</td>
</tr>
<tr>
<td>Per-protocol</td>
<td>14/921.8</td>
<td>1.5 (0.9, 2.5)</td>
<td>20/554.0</td>
<td>3.6 (2.2, 5.3)</td>
<td>0.42 (0.22, 0.87)</td>
</tr>
<tr>
<td>Terminal Therapy</td>
<td>9/708.8</td>
<td>1.3 (0.6, 2.4)</td>
<td>20/554.0</td>
<td>3.6 (2.2, 5.3)</td>
<td>0.35 (0.16, 0.79)</td>
</tr>
</tbody>
</table>
Table 5. Functional Impact of Clinical Events: Significant Disability or Death

<table>
<thead>
<tr>
<th></th>
<th>LAA Closure Group Events (per 100 pt-ys)</th>
<th>Warfarin Group Events (per 100 pt-ys)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>1.5</td>
<td>3.7</td>
<td>0.41 (0.22, 0.82)</td>
</tr>
<tr>
<td>(16 / 1047.1)</td>
<td>(21 / 563.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-procedure</td>
<td>1.3</td>
<td>3.7</td>
<td>0.34 (0.17, 0.70)</td>
</tr>
<tr>
<td>(13 / 1037.0)</td>
<td>(21 / 563.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-protocol</td>
<td>1.2</td>
<td>3.6</td>
<td>0.33 (0.16, 0.71)</td>
</tr>
<tr>
<td>(12 / 1011.6)</td>
<td>(20 / 563.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal Therapy</td>
<td>1.3</td>
<td>3.6</td>
<td>0.36 (0.16, 0.79)</td>
</tr>
<tr>
<td>(9 / 713.1)</td>
<td>(20 / 563.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Functional impact endpoint is either an MRS Increase ≥ 2 or Death.

Figure Legends:

Figure 1. Trial Patient Profile.

Figure 2. Kaplan-Meier Curves of the Primary Efficacy Endpoint. Incident probabilities for the intention-to-treat analysis are shown with time calculated as the days since randomization for the i) composite primary efficacy endpoint of stroke, systemic embolism and cardiovascular death, ii) stroke alone, and iii) all-cause mortality.

Figure 3. Kaplan-Meier Curves of Landmark Analyses of the Primary Efficacy Endpoint. Incident probabilities for the intention-to-treat analysis are again shown in Landmark Analyses for the i) composite primary efficacy endpoint of stroke, systemic embolism and cardiovascular death, ii) stroke alone, and iii) all-cause mortality.

Figure 4. Primary Efficacy Results by Patient Subgroup. The hazard ratios (HR) and 95% confidence intervals (CIs) are shown for the primary efficacy endpoint for all patients and for
prespecified patient subgroups. Results are from Cox proportional hazards models, with each subgroup examined in a separate model. The number of randomized patients with data available for the subgroup variable are shown. For LAA ostium width, LAA length, and LVEF, the values shown (21mm, 30mm and 60%, respectively) represent the median values. LVEF = left ventricular ejection fraction.

Figure 5. Kaplan-Meier Curves of the Primary Safety Endpoint. The incident probabilities for the intention-to-treat analysis are shown with time calculated as the days since randomization for the composite primary safety endpoint. This endpoint included serious adverse events related to excessive major bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (eg, serious pericardial effusion, device embolization, and procedure-related stroke).

Figure 6. Primary Efficacy Results of the Secondary Prevention Group. The hazard ratios (HR) and 95% confidence intervals (CIs) are shown for the primary efficacy endpoint for all four analyses: intention-to-treat (ITT), post-procedure (PostP), per-protocol (PerP) and terminal therapy (TermT). Results are from Cox proportional hazards models, with each subgroup examined in a separate model. The number of randomized patients with data available for each analysis are shown.
Figure 1

Randomized
n=707

Device
n=463

- Device Implanted, n=408
  - Not implanted, n=55
    - No attempt, n=14
    - Failed attempt, n=41

- Withdrew, lost-to-follow-up, n=77

Control
n=244

- Received Warfarin, n=241
  - Did not receive Warfarin, n=3

- Withdrew, lost-to-follow-up, n=51

463 included in analysis
244 included in analysis
Figure 2

Primary Efficacy

Stroke

All-Cause Mortality
Figure 3

Primary Efficacy

Stroke

All-Cause Mortality
Figure 4
Figure 5
Secondary Prevention Patients: Primary Efficacy Results

<table>
<thead>
<tr>
<th>Group</th>
<th>N Device/Control</th>
<th>RR (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>84/49</td>
<td>0.64 (0.24, 1.74)</td>
</tr>
<tr>
<td>PostP</td>
<td>79/49</td>
<td>0.51 (0.17, 1.43)</td>
</tr>
<tr>
<td>PerP</td>
<td>66/48</td>
<td>0.49 (0.15, 1.41)</td>
</tr>
<tr>
<td>TermT</td>
<td>57/48</td>
<td>0.54 (0.15, 1.60)</td>
</tr>
</tbody>
</table>

Non-Inferiority Margin Superiority

Figure 6
Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients with Atrial Fibrillation: 2.3 Year Follow-Up of the PROTECT AF Trial
Vivek Y. Reddy, Shephal K. Doshi, Horst Siever, Maurice Buchbinder, Petr Neuzil, Kenneth Huber, Jonathan L. Halperin and David Holmes

Circulation, published online January 16, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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