Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients With Atrial Fibrillation

2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) Trial

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Background—The multicenter PROTECT AF study (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was conducted to determine whether percutaneous left atrial appendage closure with a filter device (Watchman) was noninferior to warfarin for stroke prevention in atrial fibrillation.

Methods and Results—Patients (n=707) with nonvalvular atrial fibrillation and at least 1 risk factor (age >75 years, hypertension, heart failure, diabetes, or prior stroke/transient ischemic attack) 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 end point included stroke, systemic embolism, and cardiovascular death, and the primary analysis was by intention to treat. After 1588 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 (relative risk, 0.71; 95% confidence interval, 0.44%–1.30% per year), which met the criteria for noninferiority (probability of noninferiority >0.999). There were more primary safety events in the Watchman group (5.5% per year; 95% confidence interval, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% confidence interval, 2.2%–5.3% per year; relative risk, 1.53; 95% confidence interval, 0.95–2.70).

Conclusions—The "local" strategy of left atrial appendage closure is noninferior to "systemic" anticoagulation with warfarin. PROTECT AF has, for the first time, implicated the left atrial appendage in the pathogenesis of stroke in atrial fibrillation.

Clinical Trial Registration:—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00129545. **(*Circulation*. 2013;127:720-729.)**

Key Words: anticoagulation ■ atrial fibrillation ■ catheters ■ left atrial appendage ■ pericardial effusion ■ stroke prevention ■ warfarin

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.[1–3] Systemic anticoagulant drug therapy is highly effective but difficult for many patients to sustain over time, which has led to an intensive quest for alternative strategies, especially for patients at highest risk.[4,5] Nonpharmacological approaches are under development to isolate the left atrial appendage (LAA) from the systemic circulation, based on evidence that suggests this to be the main site of thrombus formation and subsequent cardioembolic stroke in AF patients.[6–10] The PROTECT AF trial (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was designed to evaluate

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whether systemic anticoagulation with warfarin, the most commonly used anticoagulant, could be replaced by closure of the LAA with a percutaneously deployed filter device.[11] This trial hypothesized that LAA closure with the Watchman device would be noninferior to warfarin therapy. The principal analysis was based on assessment of noninferiority with a bayesian design that permits assessments at multiple durations of follow-up. The interim results for the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death were published based on 1050 patient-years of observation, when the event rate of 3.0% per year in patients undergoing LAA closure was noninferior to continued warfarin therapy (4.9% per year; relative risk, 0.62; 95% confidence interval [CI], 0.35–1.25).[11]

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Although 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 up for >2 years, which raises questions about efficacy over time. The protocol called for continuation of warfarin for 45 days after 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.[4,12] Beyond this initial period, aspirin alone was used while the trial continued to accrue a specified exposure of 1500 patient-years after randomization. In the present 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) have been described previously.[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 guidance. After transseptal puncture, contrast is injected to define the LAA anatomy. Then, an appropriately sized Watchman device (21–33 mm in diameter) is advanced to the ostium of the LAA through a 12F sheath. Proper positioning and stability are verified by transesophageal echocardiography and angiography before device release.

PROTECT AF Trial

The PROTECT AF trial has been described previously.[13] Briefly, this was a prospective, unblinded, randomized trial conducted at 59 centers in the United States and Europe. Patients were enrolled from February 2005 until June 2008, and final clinical follow-up for the 1500 patient-year analysis occurred in April 2010. The protocol was approved by the institutional review board that governed research involving human subjects at each participating site, and enrolled subjects were required to provide signed informed consent. Efficacy and safety end-point 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 1 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 magnetic resonance imaging or computed tomography.

All patients (including those who had previously sustained a stroke/transient ischemic attack before enrollment) were randomized in a 2:1 ratio either to undergo Watchman implantation or to a control arm that involved 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 transesophageal echocardiographic imaging was repeated at 45 days, 6 months, and 1 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/d plus aspirin 81 to 325 mg/d was substituted until 6 months after device implantation, after which clopidogrel was stopped and aspirin alone was continued. Patients in the control group received warfarin treatment with international normalized ratio (INR) monitoring performed no less often than every 2 weeks for 6 months and monthly thereafter to maintain the 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 end point of all stroke (ischemic or hemorrhagic), systemic embolism, or cardiovascular death (including unexplained death). The primary safety end point included both procedure-related events (eg, pericardial effusion that required intervention or hospitalization, procedure-related stroke, or device embolization) and major bleeding (intracranial bleeding or gastrointestinal bleeding that required transfusion). Both the primary efficacy and safety analyses were based on intention to treat. In addition, several prespecified secondary analyses and 2 post hoc tertiary analyses were performed to isolate the stroke prophylactic effect of LAA closure. These included a postprocedure analysis which examined events that occurred after device implantation; a per-protocol analysis confined to patients in the device group who stopped taking warfarin after the specified period and patients in the control group who sustained warfarin therapy; and the 2 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 after 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 with a bayesian Poisson model, stratified by $CHADS_2$ risk score (a score based on presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack), with a noninformative γ-conjugate prior distribution.[14] Posterior sampling was used to calculate probabilities and 95% CIs with criteria for success based on posterior probabilities for noninferiority and superiority exceeding 97.5% and 95%, respectively. The model encompassed data from the present study only, assuming a constant hazard over time and a Poisson distribution of events. Differences in event rates over time were assessed by

the Kaplan-Meier method. The number and proportion of patients experiencing events are reported with χ^2 testing to assess trends. Statistical analyses were performed with SAS version 9.2 software.

The sample size was estimated on the basis of data from the Stroke Prevention in Atrial Fibrillation studies, with an expected primary efficacy event rate of 6.15% per year 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 1500 patient-years. A 1-sided noninferiority probability criterion of at least 97.5% was selected with the use of a 2-fold noninferiority 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 up for an aggregate of 1588.4 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.[15] 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 took warfarin for 88% of the follow-up period, and by 2 years, 16% were no longer taking warfarin. The primary efficacy event rate among patients in the control group who took warfarin consistently (4.4% per year) did not differ significantly from that in patients who interrupted warfarin at least once during the study (4.1% per year).

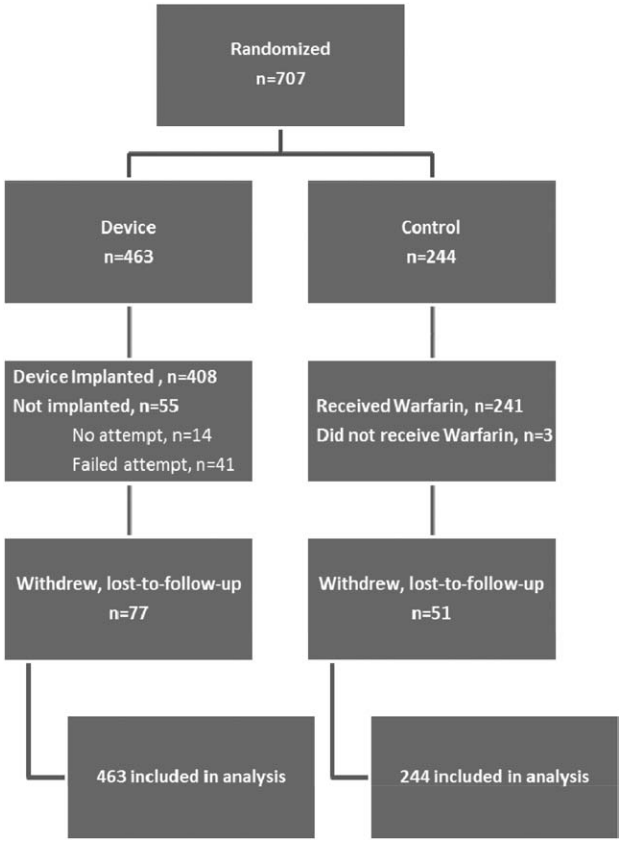

Figure 1. Trial patient profile.

Table 1. Warfarin Discontinuation for the LAA Closure Group

	45 Days	6 Months	1 Year
Warfarin discontinuation	348/401 (86.8)	355/385 (92.2)	345/370 (93.2)
Reason for warfarin continuation			
Residual shunt as per protocol	30 (7.5)	14 (3.6)	10 (2.7)
Other physician discretion	23/401	16 (4.2)	15 (4.1)

Values are n (%).
LAA indicates left atrial appendage.

Among the 463 patients assigned to undergo LAA closure, the device was implanted in 408 (88%).[11] During follow-up of this group, 86.8%, 92.2%, and 93.2%, respectively, stopped taking warfarin after evaluations at 45 days, 6 months, and 1 year. Patients continued taking warfarin either because blood flow around the device into or out of the LAA was detected by transesophageal echocardiography across an area >5 mm in 7.5%, 3.6%, and 2.7% of patients 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% per year (95% CI, 2.15%–4.3% per year) in the group assigned to LAA closure and 4.3% per year (2.6%–5.9% per year) 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 end point are delineated separately in Table 2 and Figures 2 and 3.

Efficacy was consistent across a number of subgroups distinguished by sex, age, pattern of AF, and LAA morphology (Figure 4). When patients with no more than 1 moderate risk factor ($CHADS_2$ score=1) were excluded from the analysis, primary efficacy event rates were 3.9% per year in the device group and 5.0% per year in the control group (RR, 0.79; 95% CI, 0.44–1.43; probability of noninferiority=0.999).

With regard to safety, the primary adverse outcome rate was higher in the LAA closure group (5.5% per year; 95% CI, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% CI, 2.2%–5.3% per year; RR, 1.53; 95% CI, 0.95–2.70), with most such events occurring early (Table 2; 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). Although 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

Table 2. Efficacy and Safety Results

	Device		Control				
	Events/ Patient-Years	Observed Rate: Events per 100 Patient-Years (95% CrI)	Events/Patient-Years	Observed Rate: Events per 100 Patient-Years (95% CrI)	Rate Ratio (Intervention/Control) (95% CrI)	Posterior Probabilities	
						Noninferiority	Superiority
Primary efficacy	31/1025.7	3.0 (2.1–4.3)	24/562.7	4.3 (2.6–5.9)	0.71 (0.44–1.30)	>0.99	0.88
Ischemic stroke	19/1026.3	1.9 (1.1–2.9)	8/564.9	1.4 (0.6–2.4)	1.30 (0.66–3.60)	0.76	0.18
Cardiovascular/unexplained death	11/1050.4	1.0 (0.5–1.8)	16/573.2	2.8 (1.5–4.2)	0.38 (0.18–0.85)	>0.99	0.99
Hemorrhagic stroke	3/1050.3	0.3 (0.1–0.7)	7/571.0	1.2 (0.5–2.3)	0.23 (0.04–0.79)	>0.99	0.99
Systemic embolism	3/1049.8	0.3 (0.1–0.7)	0/573.2	0	…	…	…
All stroke	21/1026.3	2.0 (1.3–3.1)	15/562.7	2.7 (1.5–4.1)	0.77 (0.42–1.62)	>0.99	0.73
All-cause mortality	34/1050.4	3.2 (2.3–4.5)	26/573.2	4.5 (2.8–6.2)	0.71 (0.46–1.28)	>0.99	0.85
Primary safety	54/979.9	5.5 (4.2–7.1)	20/554.6	3.6 (2.2–5.3)	1.53 (0.95–2.70)	…	…

CrI indicates credible interval.

"Other" events include anemia, arrhythmia, device migration, esophageal tear, and hemopericardium.

lower than in the device deployment group throughout the course of follow-up.

Secondary and Tertiary Analyses

The composite efficacy event rates in the postprocedure, per-protocol, and terminal therapy subgroups are shown in Table 3. After exclusion of events that occurred 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 (postprocedure, 2.5% per year versus 4.3% per year; probability of superiority=0.953). The same was true when analysis was confined to patients who stopped taking warfarin after successful device deployment (per-protocol, 2.3% per year versus 4.1% per year; probability

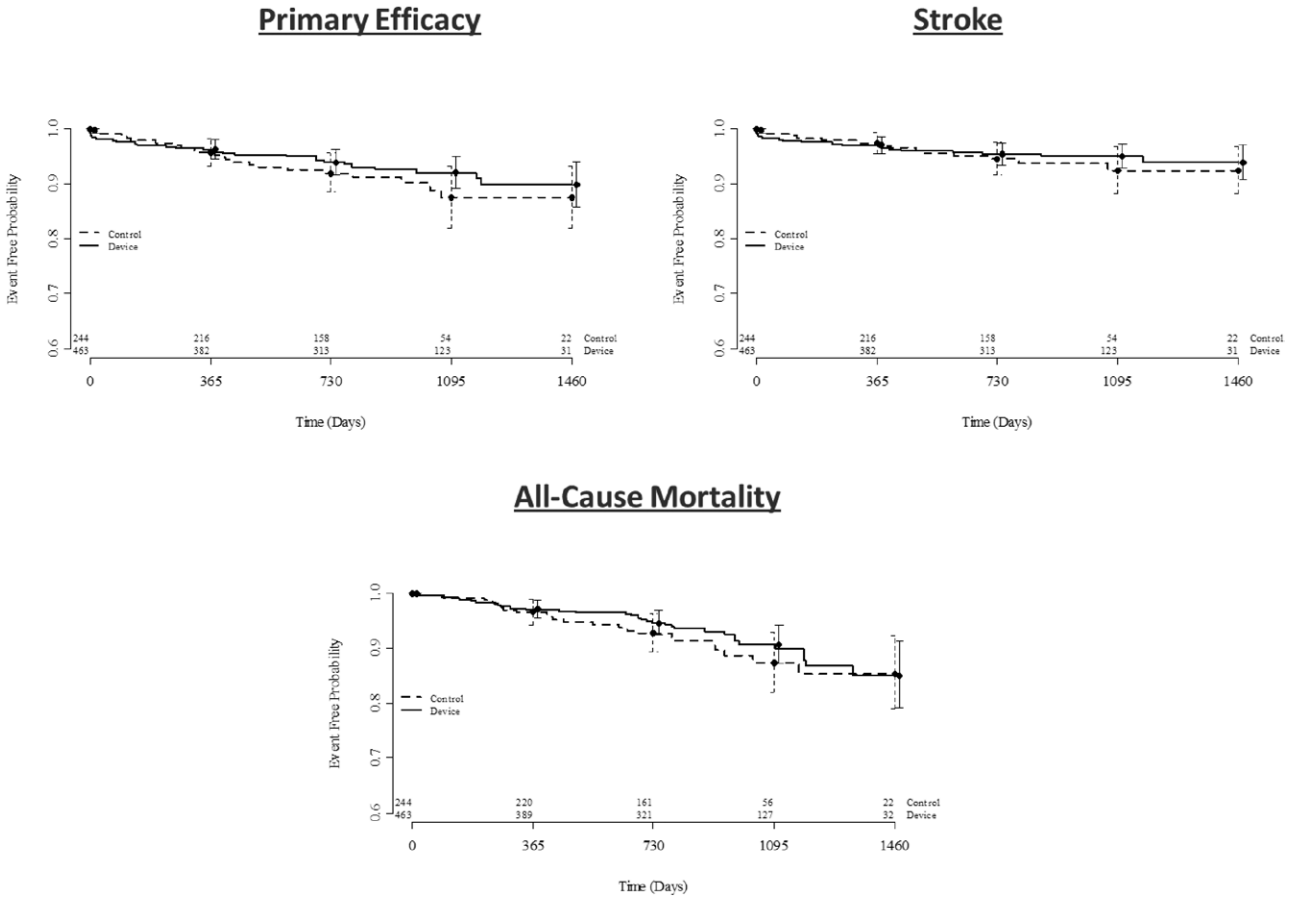

Figure 2. Kaplan-Meier curves of the primary efficacy end point. Incident probabilities for the intention-to-treat analysis are shown with time calculated as the days since randomization for the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death; stroke alone; and all-cause mortality.

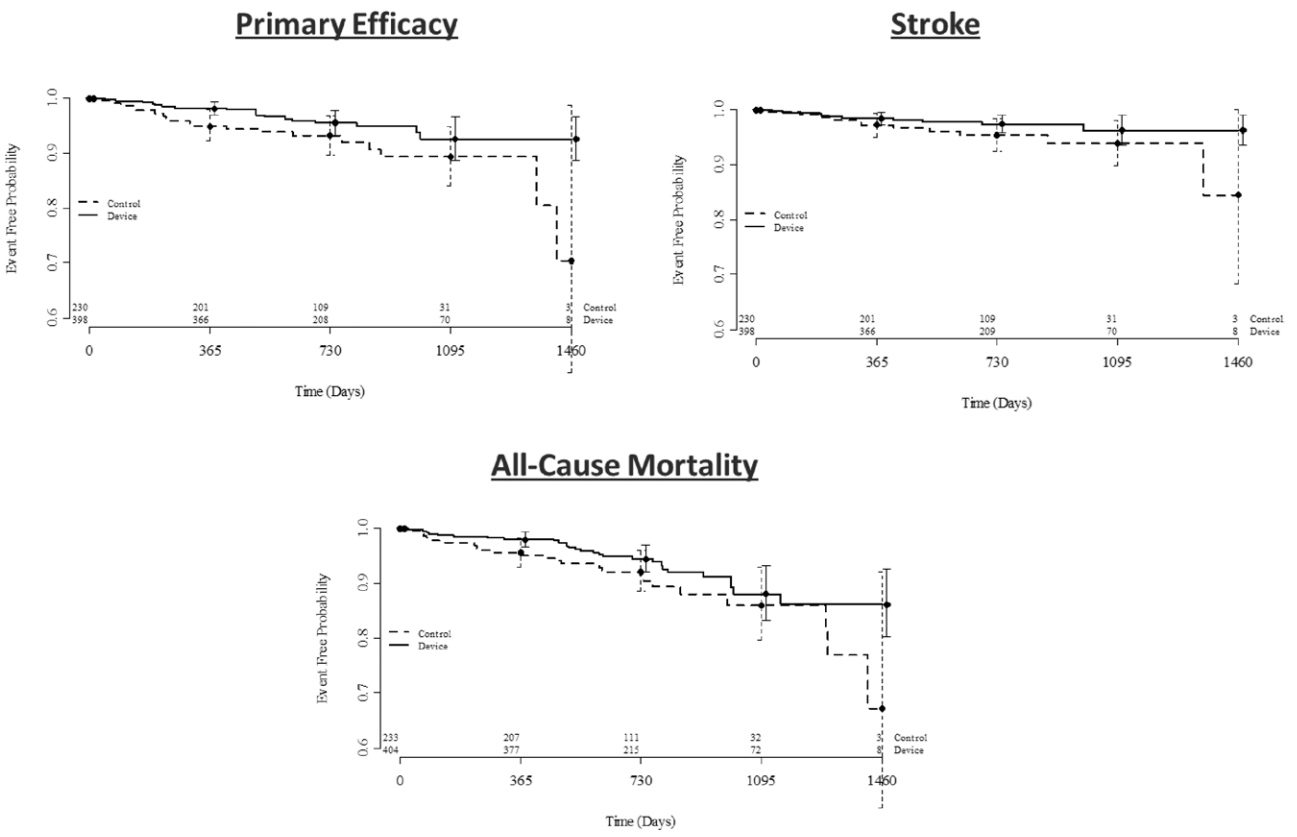

Figure 3. Kaplan-Meier curves of landmark analyses of the primary efficacy end point. Incident probabilities for the intention-to-treat analysis are again shown in landmark analyses for the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death; stroke alone; and all-cause mortality.

of superiority=0.955). When analysis was 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% per year compared with 4.1% per year in the control group (terminal therapy, probability of superiority=0.945). Taken together, these results suggest that after successful 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 nonprocedural events) was considered in terms of disability (increase in modified Rankin score 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

As shown in Figure 6, patients with previous stroke or transient ischemic attack face a high risk of recurrent stroke even when treated with warfarin, and for the 131 patients (19%) who met this criterion at entry, the rate of primary efficacy events was 5.3% per year in the group assigned to LAA closure versus 8.2% per year in those randomized to ongoing anticoagulation (RR, 0.64; 95% CI, 0.24–1.74; probability of noninferiority=0.987).

Discussion

This final analysis of outcomes in the PROTECT AF trial after >1500 patient-years of observation found that (1) by intention-to-treat analysis, long-term efficacy of "local" therapy with the Watchman LAA closure device was noninferior to systemic treatment with warfarin; (2) the failure of LAA closure to achieve superiority over warfarin was related to the acute, procedure-related stroke events; (3) secondary analyses to isolate the effect of LAA closure from transient concomitant antithrombotic therapy (warfarin and clopidogrel) not only continued to reveal noninferiority of LAA closure to warfarin but actually revealed superiority of the LAA closure strategy; and (4) 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 in the secondary analyses that isolated the effect of LAA closure.

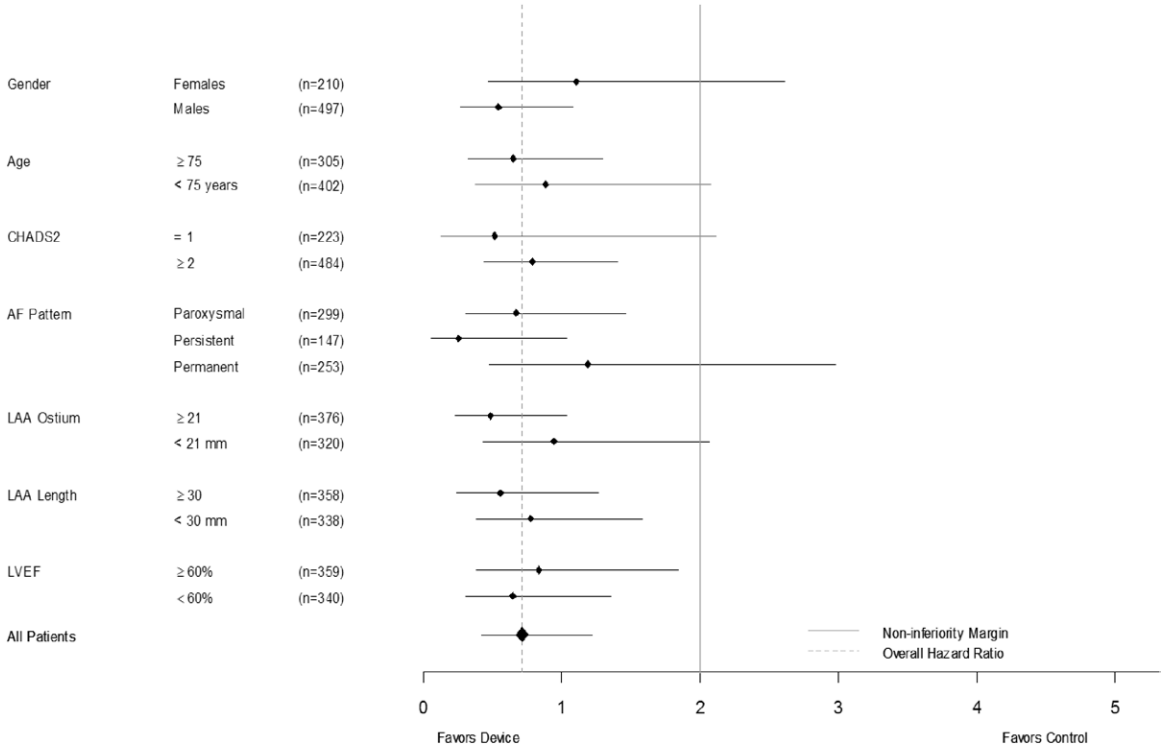

Figure 4. Primary efficacy results by patient subgroup. The hazard ratios and 95% confidence intervals are shown for the primary efficacy end point for all patients and for prespecified patient subgroups. Results are from Cox proportional hazards models, with each subgroup examined in a separate model. The number of randomized patients with data available for the subgroup variable is shown. For left atrial appendage (LAA) ostium width, LAA length, and left ventricular ejection fraction (LVEF), the values shown (21 mm, 30 mm, and 60%, respectively) represent the median values. AF indicates atrial fibrillation; and CHADS2, a score based on presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

Analysis of Study Population and Conduct

Follow-up of patients enrolled in the present study averaged 2.3 years; this compared favorably with 2.0, 1.0, and 1.9 years, respectively, in RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate), AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment), and ROCKET-AF (Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), other contemporary stroke prevention studies that involved patients with nonvalvular AF.[17–19] Participants were representative of patients with AF encountered in clinical practice: The mean age was 72 years, mean $CHADS_2$ score was 2.2, and ≈1 in 5 had experienced prior stroke or transient ischemic attack. 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

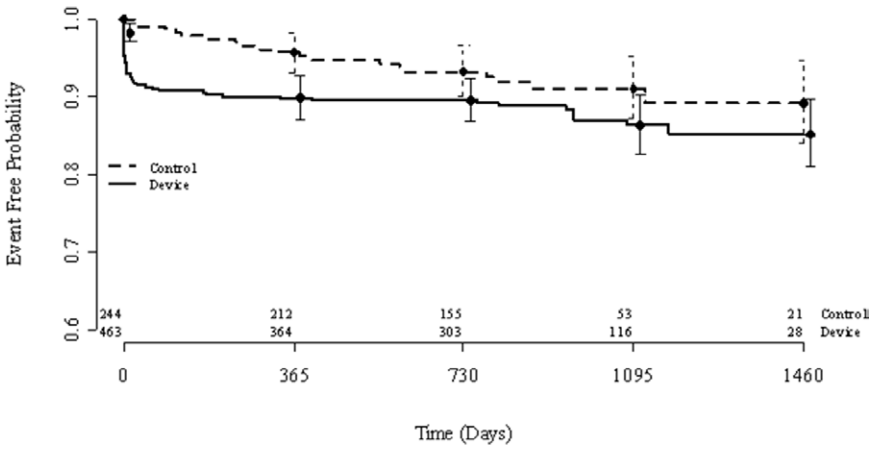

Figure 5. Kaplan-Meier curves of the primary safety end point. The incident probabilities for the intention-to-treat analysis are shown with time calculated as the days since randomization for the composite primary safety end point. This end point included serious adverse events related to excessive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

Table 3. Primary Efficacy Results

Analysis	Device		Control		Relative Risk (95% CI)	Posterior Probabilities	
	Events/Total Patient-Years	Rate (95% CI)	Events/Total Patient-Years	Rate (95% CI)		Noninferiority	Superiority
ITT	31/1025.7	3.0 (2.1–4.3)	24/562.7	4.3 (2.6–5.9)	0.71 (0.44–1.30)	>0.99	0.85
Postprocedure	25/1015.7	2.5 (1.6–3.6)	24/562.7	4.3 (2.6–5.9)	0.58 (0.35–1.09)	>0.99	0.95
Per-protocol	21/924.1	2.3 (1.5–3.5)	23/562.1	4.1 (2.5–5.7)	0.56 (0.33–1.09)	>0.99	0.96
Terminal therapy	16/705.3	2.3 (1.4–3.7)	23/562.1	4.1 (2.5–5.7)	0.55 (0.31–1.12)	>0.99	0.95

CI indicates confidence interval; and ITT, intention to treat.

$CHADS_2$ score of 3.5).[17,19] Although 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 >8 weeks. In the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) cohort of >7000 patients with nonvalvular AF receiving warfarin in routine clinical practice, this metric was 14%.[20] Over 2 years, the warfarin discontinuation rate in the control group (16%) was similar to that in the RE-LY trial (16.6%).[17] In addition, although 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 with 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 postprocedural period of anticoagulation with warfarin followed by temporary dual-antiplatelet therapy with clopidogrel plus aspirin. In the ACTIVE trials (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), the combination of clopidogrel plus aspirin was less effective than anticoagulation with warfarin but reduced the risk of stroke by 28% compared with aspirin alone, at the expense of increased bleeding.[4,12] 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 that excluded events that occurred during or immediately after device deployment and that was 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, whereas the majority of events in the device group, particularly pericardial tamponade and procedure-related stroke (presumably air or thrombus embolism related to catheter manipulation), occurred proximate to the implantation procedure.[16] Indeed, one of the limitations of LAA closure remains these procedure-related events. Although operator experience can certainly minimize the rate of these events,[16] it will likely be further improvements in device design that will ultimately serve to reduce these complications to a minimal level.

Not surprisingly, the exclusion of 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 6 weeks of warfarin followed by clopidogrel plus aspirin until half a year had elapsed after 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.[21,22]

Table 4. Primary Safety Results

Analysis	Device		Control		Rate Ratio (95% CI)
	Events/Total Patient-Years	Rate (95% CI)	Events/Total Patient-Years	Rate (95% CI)	
ITT	54/979.9	5.5 (4.2–7.1)	20/554.6	3.6 (2.2–5.3)	1.53 (0.95–2.70)
Postprocedure	27/969.8	2.8 (1.9–4.0)	20/554.6	3.6 (2.2–5.3)	0.77 (0.45–1.45)
Per-protocol	14/921.8	1.5 (0.9–2.5)	20/554.0	3.6 (2.2–5.3)	0.42 (0.22–0.87)
Terminal therapy	9/708.8	1.3 (0.6–2.4)	20/554.0	3.6 (2.2–5.3)	0.35 (0.16–0.79)

CI indicates confidence interval; and ITT, intention to treat.

Table 5. Functional Impact of Clinical Events: Significant Disability or Death

	LAA Closure Group: Events (per 100 Patient-Years)	Warfarin Group: Events (per 100 Patient-Years)	Relative Risk (95% CI)
ITT	1.5 (16/1047.1)	3.7 (21/563.9)	0.41 (0.22–0.82)
Postprocedure	1.3 (13/1037.0)	3.7 (21/563.9)	0.34 (0.17–0.70)
Per-protocol	1.2 (12/1011.6)	3.6 (20/563.3)	0.33 (0.16–0.71)
Terminal therapy	1.3 (9/713.1)	3.6 (20/563.3)	0.36 (0.16–0.79)

Functional impact end point is either an increase in the Modified Rankin Scale score of ≥2 or death.
CI indicates confidence interval; ITT, intention to treat; and LAA, left atrial appendage.

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.[16] 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 than adverse events that occurred in patients assigned to warfarin, which included not only hemorrhagic events but, perhaps more pertinently, 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 used 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.[23] Observations in this subgroup, which constituted 18.5% of the patients enrolled in PROTECT AF, favored the Watchman device over warfarin, albeit with wide CIs. Interestingly, although these wide CIs preclude any firm conclusions, the rate ratio in these patients with prior stroke/transient ischemic attack (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 transient ischemic attack and the mean $CHADS_2$ score was 3.5, the relative risk reduction in these "secondary prevention" patients was 0.98 (95% CI, 0.8–1.2).

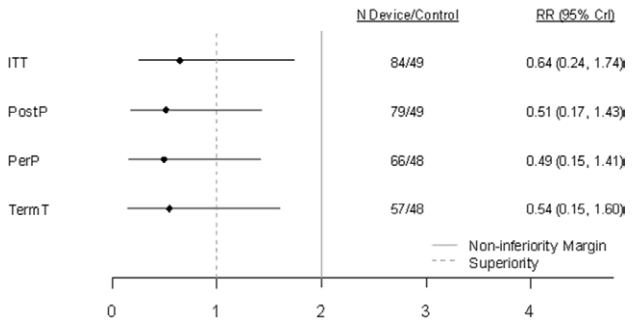

Figure 6. Primary efficacy results of the secondary prevention group. The rate ratios (RR) and 95% credible intervals (CrI) are shown for the primary efficacy end point for all 4 analyses: intention-to-treat (ITT), postprocedure (PostP), per-protocol (PerP), and terminal therapy (TermT). The number of randomized patients with data available for each analysis is shown.

Study Limitations

One limitation of the present study is the relatively small number of patients enrolled; although large for an interventional study, the sample size was considerably smaller than many anticoagulation drug trials for stroke prevention.[17–19] On the other hand, the statistical methodology was rigorous, and the primary efficacy and safety end points were well validated, which substantiates the main conclusions.

The composite primary end point 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, they were not statistically different: The event rates were 1.9 versus 1.4 per 100 patient-years in the device and warfarin arms, respectively (RR, 1.3; 95% CI, 0.66–3.60). Importantly, without the procedure-related strokes seen in the device arm, the rate of ischemic stroke would be 1.4 events per 100 patient-years. 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.

Because a third of the patients were randomized to continued warfarin therapy, patients with absolute contraindications to warfarin were not included in the present 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.[24] In addition, although the primary and secondary analyses were predefined, the assessment of outcomes on terminal therapy and evaluation of the functional end point 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 CIs surrounding estimates of treatment efficacy were necessarily wide. Although 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.[21,22,25] 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 up for an accumulated exposure of 1588 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 was considered. On the basis of 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.

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CLINICAL PERSPECTIVE

Although effective, oral anticoagulation with warfarin to prevent stroke in patients with atrial fibrillation has limitations. The multicenter PROTECT AF trial was conducted in 707 patients with nonvalvular atrial fibrillation and $CHADS_2$ score ≥1 to compare a strategy of percutaneous left atrial appendage closure with a filter device (Watchman) versus oral anticoagulation with warfarin. For patients randomized to Watchman implantation, warfarin was continued for ≈45 days, followed by clopidogrel for 4.5 months and lifelong aspirin. After 2.3±1.1 years of follow-up (1588 patient-years), the event rates of the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death were 3.0% and 4.3% (percent per 100 patient-years) in the Watchman and warfarin groups, respectively (rate ratio [RR], 0.71; 95% confidence interval [CI], 0.44%–1.30% per year), which met the criteria for noninferiority. There were more primary safety events in the Watchman group (5.5% per year; 95% CI, 4.2%–7.1% per year) than in the control group (3.6% per year, 95% CI, 2.2%–5.3% per year; RR, 1.53; 95% CI, 0.95%–2.70% per year). When the effect of left atrial appendage closure was isolated from complications of implantation and concomitant transient anticoagulation in a secondary analysis, the Watchman was superior to warfarin (probability of superiority=0.953). Among patients with stroke before they entered the study, the 2 strategies were equally effective, with rates of 5.3% per year and 8.2% per year, respectively, (RR, 0.64; 95% CI, 0.24%–1.74% per year). Thus, the "local" strategy of left atrial appendage closure with the Watchman device is noninferior to "systemic" anticoagulation with warfarin. PROTECT AF has, for the first time, implicated the left atrial appendage in the pathogenesis of stroke in atrial fibrillation.