JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 1, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.029

ORIGINAL INVESTIGATIONS

Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy

The PREVAIL Trial

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ABSTRACT

BACKGROUND In the PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trial that evaluated patients with nonvalvular atrial fibrillation (NVAF), left atrial appendage (LAA) occlusion was noninferior to warfarin for stroke prevention, but a periprocedural safety hazard was identified.

OBJECTIVES The goal of this study was to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy.

METHODS This randomized trial further assessed the efficacy and safety of the Watchman device. Patients with NVAF who had a $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). Two efficacy and 1 safety coprimary endpoints were assessed.

RESULTS At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (CrI): 0.57 to 1.89]) and did not achieve the prespecified criteria noninferiority (upper boundary of 95% CrI ≥1.75). The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' postrandomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% CrI: −0.0190 to 0.0273]), achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the pre-specified safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p = 0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small.

CONCLUSIONS In this trial, LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved. This trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy. (J Am Coll Cardiol 2014;64:1–12) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

LAA = left atrial appendage

NOACs = new oral anticoagulants

NVAF = nonvalvular atrial fibrillation

SE = systemic embolism

TEE = transesophageal echocardiography

Stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) has been the focus of substantial clinical investigation related to the increasing frequency of this arrhythmia with the aging population, the well-documented relationship between increasing age and increased stroke, and the particularly major morbidity/mortality from cardioembolic stroke (1–5). Traditional treatment strategies have relied on chronic anticoagulation, either with warfarin or the newer anticoagulant agents (6–9). Growing information regarding the central role of left atrial appendage (LAA) thrombus has led to mechanical approaches for stroke prevention in this setting.

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A number of catheter- and surgical-based strategies have been studied (10–16); with the exception of one randomized clinical trial (17), the majority of the information regarding these approaches has been gathered from smaller registries (12–16). In the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study, LAA occlusion was documented to be noninferior to warfarin for the primary efficacy endpoint of stroke, cardiovascular death, and systemic embolism (SE) (17,18). However, several concerns were raised by the U.S. Food and Drug Administration regarding patient selection criteria (e.g., inclusion of patients with $CHADS_2$ [congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack] scores of 1) and acute safety events, particularly in the early portion of the trial, and a second trial was recommended (19). To further evaluate the safety and efficacy of this approach for stroke prevention and to address these concerns, we performed the PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial. (A listing of the PREVAIL investigator sites is given in the Online Appendix.)

MATERIALS AND METHODS

The multicenter, randomized clinical trial PREVAIL (NCT01182441) assessed the safety and efficacy of LAA closure with the Watchman device (Boston Scientific, St. Paul, Minnesota) compared with warfarin in patients with NVAF (paroxysmal, persistent, or permanent) and a $CHADS_2$ score ≥2. In accordance with contemporary guidelines for stroke prevention in AF, patients could be enrolled with a $CHADS_2$ score of 1 if they also had any of the following higher-risk characteristics: female age ≥75 years, baseline ejection fraction ≥30% but <35%, age 65 to 74 years and either diabetes or coronary disease, and age ≥65 years with congestive heart failure. These inclusion criteria were meant to include a higher risk group than had been evaluated in PROTECT AF. Exclusion criteria included requirement for long-term anticoagulation therapy for reasons other than AF, contraindication to warfarin or aspirin, previous stroke/transient ischemic attack within 90 days of enrollment, symptomatic carotid disease, or a patent foramen ovale or atrial septal defect requiring treatment. Patients in whom clopidogrel therapy was indicated were also excluded to minimize the confounding variable of chronic thienopyridines, which potentially could influence the incidence of stroke, thromboembolism, or bleeding (20).

There were 3 coprimary endpoints. The first was primary efficacy, a composite of hemorrhagic or ischemic stroke, SE, and cardiovascular/unexplained death. The second was late-ischemic efficacy, a composite of ischemic stroke or SE, excluding the first 7 days after randomization. This endpoint had the goal

School of Medicine, New York, New York. This study was sponsored by Atritech/Boston Scientific. Dr. Holmes (along with the Mayo Clinic) have a financial interest in technology related to this research; that technology has been licensed to Atritech. Dr. Kar receives research grants from Boston Scientific; is a member of the advisory board for left atrial appendage closure; is the national principal investigator of the Continuous Access Registry (CAP2); receives research grants from St. Jude Medical and Abbott Vascular; and is a consultant for Abbott Vascular. Dr. Price has received consulting honoraria from Boston Scientific, St. Jude, Janssen Pharmaceuticals, Daiichi-Sankyo, and Terumo; and his institution receives research support from Boston Scientific, St. Jude, and SentreHEART. Dr. Whisenant is a stockholder in Coherex Medical. Dr. Sievert receives study honoraria, travel expenses, consulting fees <$25,000 from Abbott, Access Closure, AGA, Angiomed, Aptus, Atrium, Avinger, Bard, Boston Scientific, Bridgepoint, Cardiac Dimensions, CardioKinetix, CardioMEMS, Coherex, Contego, Covidien, CSI, CVRx, EndoCross, ev3, FlowCardia, Gardia, Gore, Guided Delivery Systems, InSeal Medical, Lumen Biomedical, HLT, Lifetech, Lutonix, Maya Medical, Medtronic, NDC, Occlutech, Osprey, Ostial, PendraCare, pfm Medical, Recor, ResMed, Rox Medical, SentreHEART, Spectranetics, SquareOne, Svelte Medical Systems, Trireme, Trivascular, Venus Medical, Veryan, and Vessix; he has received grant research support <$25,000 from Cook and St. Jude Medical; and he has stock options <$25,000 from Cardiokinetix, Access Closure, Velocimed, Lumen Biomedical, Coherex, and SMT. Dr. Doshi is a consultant for Atritech/Boston Scientific. Dr. Huber is on the Watchman Advisory Board for Boston Scientific. Dr. Reddy has received research grant support and consultant fees from Boston Scientific, Coherex, and St. Jude Medical.

Manuscript received December 20, 2013; revised manuscript received February 25, 2014, accepted April 3, 2014.

of evaluating the mechanism by which placement of the LAA occlusion device might improve outcome. This specific efficacy endpoint could then provide additional information to evaluate the hypothesis that the LAA is the source of thromboembolism in patients with NVAF; that hypothesis would be substantiated if local treatment with occlusion of the LAA was noninferior to systemic anticoagulation. The third coprimary endpoint was early safety, a composite of all-cause death, ischemic stroke, SE, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention such as surgical treatment of a pseudoaneurysm between randomization and within 7 days of the procedure or during the index hospitalization. Percutaneous catheter drainage of pericardial effusions, snaring of the embolized device, and nonsurgical treatments of access complications were excluded from this safety endpoint. Each endpoint was powered separately or had a pre-specified performance goal necessary to achieve success.

Other endpoints included stroke (both ischemic and hemorrhagic) or SE that resulted in significant disability, death, or all-cause mortality.

RANDOMIZATION AND MASKING. The study, which included up to 50 investigational sites in the United States, enrolled up to 475 patients; 407 were enrolled through randomization, and the remaining patients were enrolled through the roll-in process. A minimum of 20% of randomized patients were enrolled in institutions that had not participated in previous Watchman studies, and a minimum of 25% of the randomized patients were to be treated by new operators.

After screening, patients meeting the inclusion/exclusion criteria were randomly assigned (by computer-generated randomization) to the device intervention or the control group (2:1 ratio). Randomization was stratified according to clinical center and was performed by using a centralized system using block sizes of 6 (4 interventions and 2 controls). The centralized computer system was password protected and accessed by the principal investigator and study coordinator after the patient gave consent and met inclusion criteria. Participants and clinicians were not masked to treatment assignment.

PROCEDURES. The Watchman device was implanted as previously described (17). It is a self-expanding, nickel titanium (nitinol)-framed structure ranging in

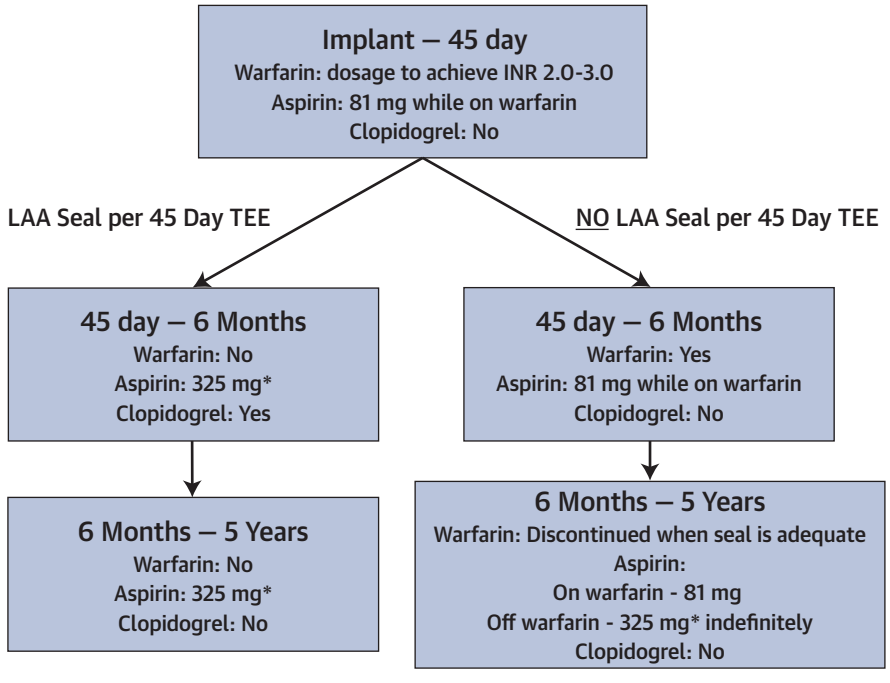


FIGURE 1 Medication Guidelines for Subjects in the Device Group

Post-implant protocol-specified medication requirements and warfarin cessation requirements. Aspirin dosage was recommended and seal was defined as transesophageal echocardiography (TEE)-documented residual peridevice flow <5 mm in width and no definite visible large thrombus on the device. *Recommended dosage. INR = international normalized ratio; LAA = left atrial appendage.

TABLE 1 Baseline Demographic Characteristics and Risk Factors (Randomized Subjects)

	Device Group (n = 269)	Control Group (n = 138)	p Value
Characteristics			
Age, yrs	74.0 ± 7.4 (269) (50.0, 94.0)	74.9 ± 7.2 (138) (53.0, 90.0)	0.260
Height, in	68.4 ± 4.3 (269) (57.0, 80.0)	68.5 ± 4.0 (138) (57.0, 78.0)	0.944
Weight, lbs	196.3 ± 44.9 (269) (106.0, 333.0)	197.1 ± 43.3 (138) (112.0, 317.0)	0.851
Sex			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
White	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	
Risk			
$CHADS_2$ score (categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
$CHADS_2$ score (continuous)	2.6 ± 1.0 (269) (1.0, 6.0)	2.6 ± 1.0 (138) (1.0, 5.0)	0.838
CHF	63/269 (23.4%)	32/138 (23.2%)	0.958
History of hypertension	238/269 (88.5%)	134/138 (97.1%)	0.003
Age ≥75 yrs	140/269 (52.0%)	78/138 (56.5%)	0.391
Diabetes	91/269 (33.8%)	41/138 (29.7%)	0.401
Previous TIA/ischemic stroke	74/269 (27.5%)	39/138 (28.3%)	0.873
AF pattern			0.873
Paced	7/269 (2.6%)	5/138 (3.6%)	
Paroxysmal	131/269 (48.7%)	71/138 (51.4%)	
Permanent	42/269 (15.6%)	22/138 (15.9%)	
Persistent	85/269 (31.6%)	39/138 (28.3%)	
Unknown	4/269 (1.5%)	1/138 (0.7%)	
LVEF, %	55.4 ± 10.0 (268) (30.0, 80.0)	56.0 ± 9.8 (137) (30.0, 77.0)	0.571
CHA_2DS_2-VASc score (categorical)			0.300
1	0/269 (0.0%)	1/138 (0.7%)	
2	19/269 (7.1%)	7/138 (5.1%)	
3	78/269 (29.0%)	44/138 (31.9%)	
4	95/269 (35.3%)	35/138 (25.4%)	
5	50/269 (18.6%)	37/138 (26.8%)	
6	20/269 (7.4%)	12/138 (8.7%)	
7	6/269 (2.2%)	3/138 (2.2%)	
8	1/269 (0.4%)	0/138 (0.0%)	
CHA_2DS_2-VASc score (continuous)	3.8 ± 1.2 (268) (1.0, 8.0)	3.9 ± 1.2 (137) (1.0, 7.0)	0.467

Values are mean ± SD (n, minimum, maximum) or n/N (%). The p values are based on *t* tests for continuous variables and chi-square tests for other variables.

AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack; CHA_2DS_2-VASc = $CHADS_2$ variables but also incorporating age 65 to 74 years, female sex, and vascular disease; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

diameter from 20 to 33 mm to accommodate varying LAA anatomy and size. The device has fixation barbs to minimize embolization and a permeable polyester fabric cover. Implantation was performed via a transseptal approach and was guided by fluoroscopy and transesophageal echocardiography (TEE) to verify proper positioning and stability. On rare occasions, intracardiac echocardiography was used during implantation (although it was not required).

After implantation, patients were treated with warfarin (Coumadin, Bristol-Myers Squibb, New York, New York) and aspirin (81 mg) for 45 days, the same regimen used in the PROTECT AF trial (17) to prevent large thrombus formation on the device during its endothelialization. TEE was performed at 45 days', 6 months', and 12 months' follow-up to assess device stability, document optimal ostial position, and evaluate the presence and degree of residual peridevice flow. If the 45-day TEE documented either complete closure of the LAA, or if residual peridevice flow was <5 mm in width and there was no definite visible large thrombus on the device, warfarin was discontinued. After discontinuation of warfarin, only daily clopidogrel 75 mg and aspirin 81 to 325 mg were prescribed until the 6-month follow-up visit, at which time clopidogrel was discontinued and aspirin alone was continued indefinitely (Fig. 1).

Control patients received warfarin during the duration of the study with a target international normalized ratio between 2.0 and 3.0. This ratio was monitored at least every 2 weeks for 6 months and at least 1 month thereafter to assess the need for dose adjustment.

Follow-up visits occurred at 45 days, 6 months, 9 months, and biannually thereafter. Neurologic assessment was performed at baseline, 12 months, and 24 months, as well as whenever a neurologic event was suspected or had occurred.

STATISTICAL ANALYSIS. Statistical analysis was performed by using data from the previously reported randomized PROTECT AF trial of LAA closure compared with warfarin with a Bayesian model and adaptive sample size methods (21). Data on endpoints from PROTECT AF subjects meeting the inclusion/exclusion criteria for PREVAIL were used in a historical previous distribution, with 50% discounting to reduce the influence of the earlier data. The primary study model was a piecewise exponential model with 4 time periods (0 to 7, 8 to 60, 61 to 182, and ≥183 days) and conjugate gamma priors with parameters based on the follow-up time and events from PROTECT AF. The primary treatment comparison was made by calculating, via Monte Carlo simulation, the

posterior distributions for the 18-month event rates and calculating the probability of noninferiority. All follow-up information from the post-182-day period was used in the final hazards analysis in the model, contributing to the calculation of the probability of 18-month events.

For the primary efficacy endpoint, the rate ratio of 18-month event rates of the device and control groups were compared, and a risk ratio criterion (treatment over control) of 1.75 was used to establish noninferiority. The late-ischemic primary endpoint was defined to isolate periprocedural events of ischemic stroke and SE >7 days' post-randomization. The second endpoint was based on a 1-tailed test, in which the null hypothesis would be rejected if either the ratio or the difference between rates in the randomized groups satisfied the noninferiority criteria. No adjustment was made for multiple comparisons. A composite criterion for either the risk ratio or risk difference was used, with criterion of the 95% upper credible interval (CrI) <2.0 and <0.0275, respectively. The risk ratio criterion was used to mirror and expand on the criterion for the first endpoint. However, as the second endpoint of late stroke/SE is rarer than the first composite endpoint, the risk difference was established as part of the criteria for the second endpoint to provide adequate power. Achievement of either of these 2 criteria would satisfy noninferiority. The sample size was determined based on an adaptive interim analysis in which the predictive probabilities of success for the 2 endpoints were calculated; enrollment was to be stopped early if the predictive probability of success at an interim analysis exceeded 0.95. Enrollment continued to the full maximum planned sample size because this threshold was not achieved during enrollment. Per the adaptive design, follow-up continued for 6 months after completion of enrollment, at which time the final analysis occurred. The early safety primary endpoint was specific to the device arm and was analyzed simultaneous to the final analysis of the first 2 endpoints described earlier. This model was a beta-binomial model with an historical prior, based on data from the device subjects in PROTECT AF and CAP (Continued Access PROTECT AF Registry) studies. This method became the performance goal for comparison (19). The CAP study was conducted similarly to PROTECT AF in that patients were treated with warfarin up until the 45-day TEE. This early safety primary endpoint was not incorporated into the Bayesian adaptive design. However, because of those safety endpoints, a safety guideline was used. The statistical criterion for success was a 1-sided 95% upper credible bound of <2.67% to ensure that the rate of procedural safety events was sufficiently low. All endpoints for the study are based on 1-sided tests.

TABLE 2 Coprimary Efficacy Endpoint Results (Stroke, Systemic Embolism, or Cardiovascular/Unexplained Death)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Noninferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI upper bound <1.75

CrI = credible interval.

RESULTS

PREVAIL enrolled 407 patients; 269 were randomized to the device group and 138 to the control group. Baseline characteristics were similar between the 2 arms: mean age 74.0 ± 7.4 years versus 74.9 ± 7.2 years (device vs. control) (p = 0.260); $CHADS_2$ score 2.6 ± 1.0 versus 2.6 ± 1.0 (p = 0.838); and CHA_2DS_2-VASc score (using the $CHADS_2$ variables but also incorporating age 65 to 74 years, female sex, and vascular disease) 3.8 ± 1.2 versus 3.9 ± 1.2 (p = 0.467) (Table 1). As pre-specified, 38.8% of patients were enrolled at new sites, and 39.1% of procedures were performed by new operators. The device was successfully implanted in 95.1% of the patients in whom it was attempted (252 of 265). There were 4 patients in whom an implant was not attempted, even though they had been randomized to the device arm group. Reasons for the aborted attempts were that the patient did not stop anticoagulation before the procedure (n = 1), pre-implant TEE revealed a new LAA thrombus (n = 1), and LAA size and shape were not optimal for the device (n = 2). All patients had a minimum follow-up of 6 months. For randomized subjects, the mean follow-up was 11.8 ± 5.8 months, and the median follow-up was 12.0 months (range: 0.03 to 25.9 months). After successful implantation, 92.2% (227 of 246), 98.3% (235 of 239), and 99.3% (141 of 142) of patients were able to discontinue warfarin after 45 days, 6 months, and 12 months, respectively.

TABLE 3 Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL Subjects Only (Intention-to-Treat)*

	Device Group			Control Group		
	No. of Events	% of Subjects	% of Endpoints	No. of Events	% of Subjects	% of Endpoints
Ischemic stroke	5	1.9	35.7	1	0.7	25.0
Hemorrhagic stroke	1	0.4	7.1	0	0.0	0.0
Death (cardiovascular/unexplained)	7	2.6	50.0	3	2.2	75.0
Systemic embolism	1	0.4	7.1	0	0.0	0.0

*Endpoint analysis was based on the initial event per-patient even if a patient experienced multiple events.
PREVAIL = Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy.

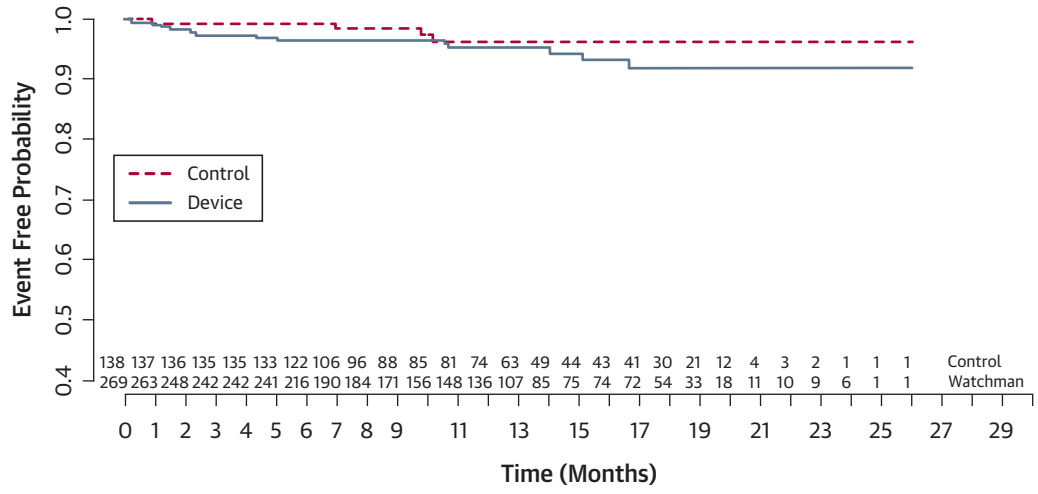


FIGURE 2 Kaplan-Meier Curve: Freedom From First Primary Endpoint (Intention-to-Treat)

Primary efficacy rates for Watchman **(solid line)** versus warfarin **(dotted line)** in the intention-to-treat population show similarly high 18-month event-free rates.

PRIMARY EFFICACY ENDPOINT. The 18-month event rates of the first primary efficacy endpoint were similar and expectedly low in both the device group (0.064) and the control group (0.063), yielding a mean 18-month rate ratio of 1.07 (95% CrI: 0.57 to 1.89). The upper bound of 1.89 was not lower than the pre-specified noninferiority margin of 1.75 predefined in the statistical analysis plan. Therefore, statistical noninferiority was not achieved (Tables 2 and 3). Kaplan-Meier estimates for freedom from the primary efficacy endpoint are presented in Figure 2. One stroke or SE occurred with warfarin (0.71%/patient-year), despite a mean $CHADS_2$ score of 2.6.

LATE-ISCHEMIC PRIMARY EFFICACY ENDPOINT. The rate of stroke or SE >7 days after randomization (Table 4) was 0.0253 for the device group and 0.0200 for the control group (18-month risk difference 0.0053 [95% CrI: -0.0190 to 0.0273]). Because the 95% upper CrI of the risk difference was <0.0275, noninferiority of the device group to the control group was achieved. Kaplan-Meier estimates for this endpoint are presented in Figure 3.

TABLE 4 Late-Ischemic Coprimary Endpoint: PREVAIL Subjects Only (Intention-to-Treat)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Noninferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Noninferiority Criterion
0.0253	0.0200	1.6 (0.5 to 4.2)	95% CrI upper bound <2.0	0.0053 (-0.0190 to 0.0273)	95% CrI upper bound <0.0275

Abbreviations as in Tables 2 and 3.

EARLY SAFETY PRIMARY ENDPOINT. The primary safety endpoint was evaluated only in the device group. CrIs were calculated from a Bayesian model that used PROTECT AF and the CAP Registry as prior sources and calculation of first event per subject. Success for this endpoint was defined as being achieved if the percentage of patients experiencing one of the events was statistically less than the performance goal, defined as 2.67% with an upper bound of the 1-sided 95% CrI less than the performance goal (Table 5). There were only 6 events meeting this safety primary endpoint in the 269 patients with device implantation. Accordingly, 2.2% of subjects experienced an event, and the 1-sided 95% CrI upper bound was 2.652%; therefore, success for this endpoint was achieved.

COMPARISON WITH EARLIER STUDIES. An early procedural hazard was of particular concern in the initial experience with LAA occlusion (19); therefore, several pre-specified comparisons were performed to assess the evolution of safety events over the course of the studies of the Watchman device. A total of 1,298 patients were treated with the Watchman device in 3 studies (PROTECT AF, CAP, and PREVAIL). As per the protocol design, PREVAIL and CAP patients were at higher risk (Table 6) than PROTECT AF patients, with older age (74.0 ± 7.4 years and 74.0 ± 8.3 years vs. 71.7 ± 8.8 years [$p < 0.001$]) and a higher $CHADS_2$ score (2.6 ± 1.0 and 2.5 ± 1.2 vs. 2.2 ± 1.2 [$p < 0.001$]). Compared with other trials, PREVAIL had more patients >75 years of age. PREVAIL patients

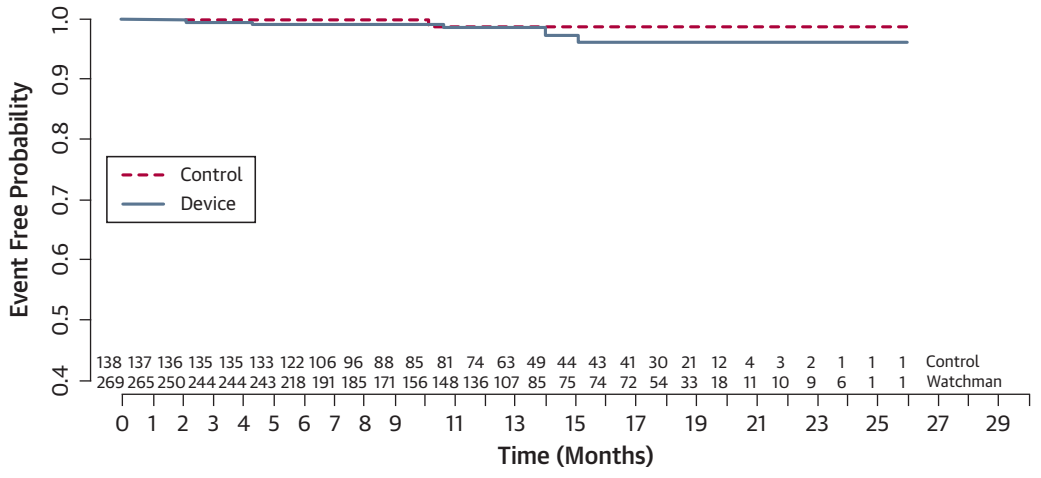


FIGURE 3 Kaplan-Meier Curve: Freedom From Second Primary Endpoint Event (Intention-to-Treat)

Late-ischemic events (stroke or systemic embolism >7 days' post-randomization) for Watchman **(solid line)** versus warfarin **(dotted line)** in the intent-to-treat population demonstrated noninferiority for the rate difference endpoint.

also had a higher incidence of diabetes mellitus and a higher incidence of previous stroke/transient ischemic attack.

Procedural success, defined as device deployment and release, increased from 90.9% in PROTECT AF to 95.1% in PREVAIL ($p = 0.04$). To evaluate the complications in PREVAIL by using the identical definitions used in PROTECT AF, we assessed all 7-day procedure-related complications, defined as a composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications occurring in the first 7 days after implant. These decreased from 8.7% in PROTECT AF to 4.2% in PREVAIL ($p = 0.004$). Pericardial effusions requiring surgical repair also decreased from 1.6% to 0.4% ($p = 0.027$); effusions requiring pericardiocentesis or a pericardial window were numerically lower in PREVAIL (1.5% [4 of 265] vs. PROTECT AF 2.9% [13 of 449]; $p = 0.36$), although the absolute number of events was small. Procedural and device-related strokes decreased, from 1.1% in PROTECT AF to 0.4% in PREVAIL ($p = 0.007$). Device embolization was infrequent, occurring in only 4 patients (2 in PROTECT AF, 2 in PREVAIL) and was not statistically significantly different across the studies (Table 7).

An important component of this analysis was evaluation of the learning curve with new versus experienced operator sites. Implantation success was achieved in 95.1% overall and in 96.3% with experienced operators versus 93.2% with new operators ($p = 0.256$); there were no significant differences in complication rates between the 2 groups.

DISCUSSION

The PREVAIL trial adds information to the initial pivotal PROTECT AF trial by using a Bayesian noninferiority design approach (21). The major findings of the trial were: 1) LAA occlusion with the Watchman device was not noninferior to warfarin for the primary efficacy composite endpoint of all-cause stroke, cardiovascular or unexplained death, and SE, although the event rates with warfarin were significantly lower than expected, affecting the ability of the study to establish noninferiority; 2) the Watchman device was noninferior to warfarin for the occurrence of late ischemic events, such as ischemic stroke or SE

TABLE 5 Safety Coprimary Endpoint Results and Events by Type (Intention-to-Treat): Device Group Only

	% (n/N)	95% CrI
Safety primary endpoint results	2.2% (6/269)	2.652%
	No. of Events	**% of Subjects**
Safety events by type		
Device embolization	2	0.7
Arteriovenous fistula	1	0.4
Cardiac perforation	1	0.4
Pericardial effusion with cardiac tamponade	1	0.4
Major bleed requiring transfusion	1	0.4

Abbreviation as in Table 2.

TABLE 6 Demographic Characteristics of Patients Receiving the Watchman Device in PROTECT AF, CAP, and PREVAIL

	PROTECT AF (n = 463)	CAP (n = 566)	PREVAIL (n = 269)	p Value
Age, yrs	71.7 ± 8.8 (46.0, 95.0)	74.0 ± 8.3 (44.0, 94.0)	74.0 ± 7.4 (50.0, 94.0)	<0.001
Male	326/463 (70.4%)	371/566 (65.5%)	182/269 (67.7%)	0.252
$CHADS_2$ score (continuous)	2.2 ± 1.2 (1.0, 6.0)	2.5 ± 1.2 (1.0, 6.0)	2.6 ± 1.0 (1.0, 6.0)	<0.001
$CHADS_2$ risk factors				
CHF	124/463 (26.8%)	108/566 (19.1%)	63/269 (23.4%)	
Hypertension	415/463 (89.6%)	503/566 (88.9%)	238/269 (88.5%)	
Age ≥75 yrs	190/463 (41.0%)	293/566 (51.8%)	140/269 (52.0%)	
Diabetes	113/463 (24.4%)	141/566 (24.9%)	91/269 (33.8%)	
Stroke/TIA	82/463 (17.7%)	172/566 (30.4%)	74/269 (27.5%)	

Values are mean ± SD (minimum, maximum) or n/N (%).

CAP = Continued Access PROTECT AF; PROTECT AF = Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation; other abbreviation as in Tables 1 and 3.

occurring after the first 7 days following randomization to isolate the effect of early periprocedural events from a longer term mechanism of action; and 3) the Watchman procedure met the pre-specified success criterion for safety events, even with a large proportion of operators without previous experience implanting the device within a higher risk patient population (**Central Illustration**).

The relationship between AF and stroke has been the subject of exhaustive study. Stroke in this setting has been predominantly thromboembolic in nature, secondary to LAA thrombus. This pathophysiology led to the widespread application of anticoagulant therapy, initially with warfarin, which has been proven superior to aspirin for stroke prevention (22). Multiple problems with warfarin, however, have been identified, including bleeding, contraindications to its application, patient compliance, and the need for routine monitoring (23–26). Thus, it is estimated that anticoagulation is not currently used in up to 50% of eligible AF patients, which led to the development of new oral anticoagulants (NOACs), whose efficacy have been established in randomized clinical trials (7–9). The rates of bleeding with approved doses of NOACs are either similar to warfarin, or, in the case of apixaban, lower, but rivaroxaban and dabigatran had an increased risk of gastrointestinal bleeding. In older patients or those with renal dysfunction, the bleeding risks associated with dabigatran were equal or greater than warfarin (27). This bleeding risk, combined with the perceived absolute or relative contraindications by the patient or physician, as well as issues with long-term compliance, cost, and the lack of widely available antidotes, represent substantial challenges for the management of stroke prevention in patients with AF (28).

In patients with NVAF, the LAA is the location of the thrombus felt to be the putative cause of stroke in approximately 90% of cases (10). In the pivotal PROTECT AF trial, comparing LAA occlusion with warfarin, placement of the Watchman device was noninferior for prevention of the primary composite endpoint of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and SE (17). An early safety hazard was identified: an increase in periprocedural events of pericardial effusions, which did not result in mortality but did prolong hospital stay. A risk for periprocedural stroke was also identified, usually the result of air embolization during catheter placement.

Longer term follow-up of PROTECT AF has confirmed the efficacy of LAA occlusion. At a mean follow-up of 2.3 ± 1.1 years, the primary efficacy endpoint remained noninferior for device (3.0 vs. 4.3 [per 100 patient-years]; rate ratio 95% CrI: 0.44 to 1.30; probability of noninferiority >0.999) (18). At 45 months of follow-up, LAA occlusion was superior to warfarin for the primary composite efficacy endpoint. At 45 months, the primary safety endpoint was noninferior for the device group because of the continued increase in adverse safety events with warfarin,

TABLE 7 Comparison of Outcomes in Device Patients in PROTECT AF, CAP, and PREVAIL

	PROTECT AF	CAP	PREVAIL	p Value
Implant success	90.9	94.3	95.1	0.04
All 7-day procedural complications	8.7	4.2	4.5	0.004
Pericardial effusion requiring surgery	1.6	0.2	0.4	0.03
Pericardial effusion with pericardiocentesis	2.4	1.2	1.5	0.318
Procedure-related strokes	1.1	0.0	0.7	0.02
Device embolization	0.4	0.2	0.7	0.368

Abbreviations as in Tables 3 and 6.

emphasizing the long-term hazard of anticoagulants that could be avoided with mechanical intervention (29). Within the early and late PROTECT AF experience, as well as the CAP Registry, procedural/device-related safety events (including pericardial effusions) declined significantly, suggesting that the procedural safety of Watchman implantation improved with increasing experience. The fact that the acute procedural success and complication rates continued to be low even among new centers and new operators suggest that the knowledge gained during the initial experience could be successfully transferred to new sites and operators.

Against this background of improving results of LAA occlusion compared with control warfarin, and because of initial concerns about trial design and endpoint definition, the U.S. Food and Drug Administration requested this second trial (PREVAIL). A Bayesian analysis design was agreed upon using priors from PROTECT AF and CAP. Trial design included a higher risk group, which was achieved in that PREVAIL patients were older and had higher $CHADS_2$ and CHA_2DS_2VASc scores. Within PREVAIL, there were 3 primary endpoints, each aimed at addressing particular concerns. With the first primary efficacy endpoint (a composite of all-cause stroke, cardiovascular or unexplained death, and SE), the absolute event rates were similar with LAA occlusion and warfarin, but noninferiority was not met, given the wide 95% CrIs. One potential reason for this finding was the substantially lower-than-expected number of events, particularly in the control group: the rate of stroke or SE with warfarin was significantly less than in other contemporary trials of stroke prevention in AF that had included a warfarin control (RE-LY [Randomized Evaluation of Long Term Anticoagulant Therapy], ARISTOTLE [Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation], 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]) (7–9). In these trials, stroke and SE rates in the warfarin control arms were 1.7, 1.6, and 2.2 per 100 patient-years, respectively. In contrast, in PREVAIL, ischemic stroke in the warfarin control group was 0.71 per 100 patient-years (**Fig. 4**). This unexpected, overperforming control group reduced the ability to establish noninferiority given the statistical trial design. One partial explanation for this finding may be related to the time-in-therapeutic range, which was 68% for PREVAIL versus 64%, 62%, and 55%, respectively, for RE-LY (7), ARISTOTLE (8), and ROCKET AF (9). The lower rate of stroke also may have occurred in the present trial given the relatively smaller sample size.

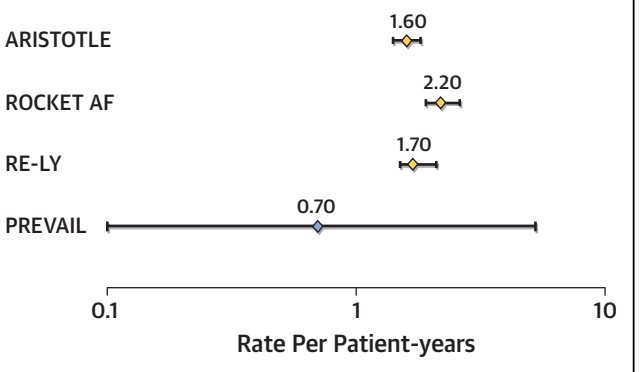


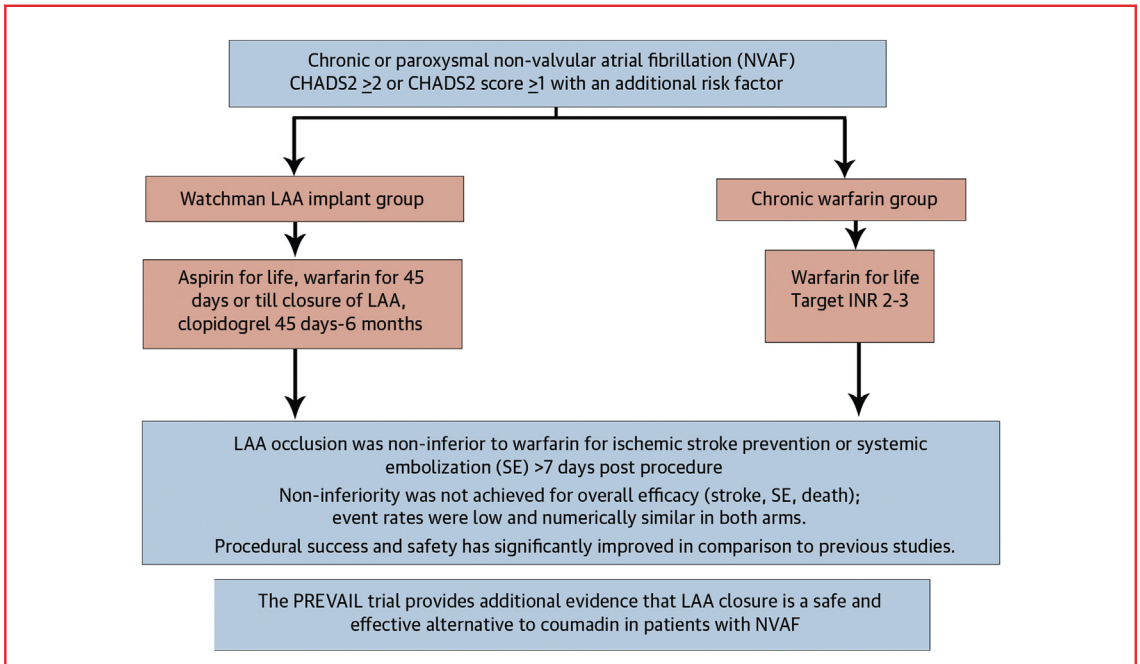
FIGURE 4 Ischemic Stroke Rates in Warfarin Control Groups

Control (warfarin) ischemic stroke rates per 100 patient-years in new oral anticoagulant NOAC trials and the PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial. The relatively small sample size and an unexpected overperforming control group could have contributed to the results seen in the first primary endpoint.

The late-ischemic primary efficacy endpoint excluded events occurring within 7 days of randomization and was designed to look at specific device performance once implanted in subsequently reducing ischemic stroke or SE. This achieved the pre-specified noninferiority criteria, supporting the contention that LAA occlusion can prevent longer term ischemic events in the absence of chronic anticoagulation.

The third primary endpoint assessed the effect of adding early safety signals with events within the first 7 days or during the index hospitalization, based on the PROTECT AF finding that device-related safety events occurred within the first 7 days and were procedurally related for the most part. This third endpoint used priors from both PROTECT AF and the CAP Registry and met its pre-specified criterion for success. In the safety endpoint analysis, a frequentist approach identified that the composite of all 7-day periprocedural complications had decreased significantly from PROTECT AF to PREVAIL; both pericardial effusions requiring surgical treatment and stroke were significantly less frequent.

STUDY LIMITATIONS. In the PROTECT AF and PREVAIL trials, patients were required to be candidates for long-term anticoagulation to facilitate randomization against a control group treated with warfarin. The present trial does not address the safety and efficacy of LAA occlusion in patients in whom anticoagulation is believed to be either relatively or



CENTRAL ILLUSTRATION Design and Outcomes of the PREVAIL Trial

The multicenter, randomized controlled PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial assessed the safety and efficacy of left atrial appendage (LAA) closure with the Watchman device compared with warfarin in patients with nonvalvular atrial fibrillation (paroxysmal, persistent, or permanent) with a $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2. PREVAIL enrolled 407 patients; 269 were randomized to the device group and 138 to the control group. After successful implantation, 92.2%, 98.3%, and 99.3% of patients were able to discontinue warfarin after 45 days, 6 months, and 12 months, respectively. The 18-month event rates of the first primary efficacy endpoint were similar and expectedly low in both the device (0.064) and control (0.063) groups, yielding a mean 18-month rate ratio of 1.07. INR = international normalized ratio.

absolutely contraindicated. This population was evaluated in the observational ASAP (ASA Plavix) study, but there are no randomized data available (30). Also, neither PREVAIL nor PROTECT AF compared the safety and efficacy of Watchman with NOACs. It is also unknown whether the loss of the mechanical function of the LAA after occlusion may have any clinical significance. Finally, due to the low overall trial event rates, there was limited power with the planned sample size in PREVAIL to establish noninferiority for the primary efficacy endpoint, which was based on a rate ratio.

CONCLUSIONS

The PREVAIL trial documented the following findings in patients with NVAF at risk for stroke: 1) procedural complications occurring after Watchman LAA occlusion were infrequent and significantly improved compared with the PROTECT AF trial; 2) Watchman LAA occlusion was noninferior to chronic warfarin for the prevention of stroke and SE beginning 1 week after randomization, consistent with the hypothesis that the LAA is the nidus for embolism in AF; and 3) the primary efficacy endpoint of early and late events was similar and did not achieve noninferiority with the Watchman device. Overall event rates were lower than expected, which may have contributed to this last finding. The totality of the data now available on the procedural safety and long-term efficacy for the Watchman device support that closure of the LAA remains a reasonable alternative to chronic long-term warfarin therapy for prevention of stroke/systemic embolization in patients with NVAF.

ACKNOWLEDGMENT The authors thank Nicole Gordon (Boston Scientific) for her assistance in the preparation of the manuscript.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: In patients with NVAF, the LAA is the main source of thromboembolism. In this setting, stroke is usually highly morbid, often fatal, and associated with increased risk of recurrent events.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Oral anticoagulation with warfarin has been the traditional approach for stroke prevention in these patients who are deemed to be at increased risk. For various reasons, including bleeding and the need for routine coagulation monitoring, warfarin is used in only approximately 50% of patients. Newer oral anticoagulants have been developed that have advantages relative to warfarin, but they carry certain disadvantages, such as an increased risk of gastrointestinal bleeding and a lack of proven reversal strategies.

COMPETENCY IN MEDICAL KNOWLEDGE 3: Randomized trials of patients with NVAF have documented that LAA occlusion performed with an implantable device is noninferior to warfarin for stroke prevention.

COMPETENCY IN PATIENT KNOWLEDGE: In patients with an elevated risk of stroke in the setting of NVAF, in whom there is concern about the long-term risk of bleeding with warfarin therapy, the use of an LAA occlusion device (Watchman) may be considered.

TRANSLATIONAL OUTLOOK: Previous studies using pathologic, surgical, and echocardiographic data have suggested that the LAA was the source of thromboembolism in patients with NVAF. The randomized PROTECT AF and PREVAIL trials have confirmed that occlusion of the LAA by the Watchman device was noninferior to the conventional approach of using systemic warfarin anticoagulation.

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KEY WORDS atrial fibrillation, left atrial appendage, stroke prevention

APPENDIX For a listing of the PREVAIL investigators, please see the online version of this article.