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Safety of Percutaneous Left Atrial Appendage Closure

Results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) Clinical Trial and the Continued Access Registry

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Background—The Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) randomized trial compared left atrial appendage closure against warfarin in atrial fibrillation (AF) patients with CHADS₂ ≥1. Although the study met the primary efficacy end point of being noninferior to warfarin therapy for the prevention of stroke/systemic embolism/cardiovascular death, there was a significantly higher risk of complications, predominantly pericardial effusion and procedural stroke related to air embolism. Here, we report the influence of experience on the safety of percutaneous left atrial appendage closure.

Methods and Results—The study cohort for this analysis included patients in the PROTECT AF trial who underwent attempted device left atrial appendage closure (n=542 patients) and those from a subsequent nonrandomized registry of patients undergoing Watchman implantation (Continued Access Protocol [CAP] Registry; n=460 patients). The safety end point included bleeding- and procedure-related events (pericardial effusion, stroke, device embolization). There was a significant decline in the rate of procedure- or device-related safety events within 7 days of the procedure across the 2 studies, with 7.7% and 3.7% of patients, respectively, experiencing events ($P=0.007$), and between the first and second halves of PROTECT AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events ($P=0.006$). The rate of serious pericardial effusion within 7 days of implantation, which had made up >50% of the safety events in PROTECT AF, was lower in the CAP Registry (5.0% versus 2.2%, respectively; $P=0.019$). There was a similar experience-related improvement in procedure-related stroke (0.9% versus 0%, respectively; $P=0.039$). Finally, the functional impact of these safety events, as defined by significant disability or death, was statistically superior in the Watchman group compared with the warfarin group in PROTECT AF. This remained true whether significance was defined as a change in the modified Rankin score of ≥1, ≥2, or ≥3 (1.8 versus 4.3 events per 100 patient-years; relative risk, 0.43; 95% confidence interval, 0.24 to 0.82; 1.5 versus 3.7 events per 100 patient-years; relative risk, 0.41; 95% confidence interval, 0.22 to 0.82; and 1.4 versus 3.3 events per 100 patient-years; relative risk, 0.43; 95% confidence interval, 0.22 to 0.88, respectively).

Conclusion—As with all interventional procedures, there is a significant improvement in the safety of Watchman left atrial appendage closure with increased operator experience.

Clinical Trial Registration—URL: <http://clinicaltrials.gov>. Unique identifier: NCT00129545. (*Circulation*. 2011;123:417-424.)

Key Words: atrial fibrillation ■ interventions ■ left atrial appendage ■ stroke prevention ■ warfarin

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, estimated to afflict >5.5 million people in the United States alone today and to increase to >15 million by the year 2050.¹ Of its various clinical consequences, the most devastating is thromboembolic stroke. In patients with significant risk factors for stroke,

warfarin is the treatment of choice for stroke prevention.² However, because of the problems associated with long-term warfarin therapy, it is often not administered or tolerated.^{3,4} Accordingly, there has been intense interest in developing alternative treatment strategies. In addition to novel anticoagulant drugs that are at various stages of clinical testing,

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nonpharmacological approaches to left atrial appendage (LAA) closure⁵⁻⁸ have been developed on the basis of autopsy and echocardiographic data implicating the LAA as the most important cardiac source of thromboemboli in nonvalvular AF.^{9,10}

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The hypothesis that the LAA is the primary source of the thromboemboli causing stroke in nonvalvular AF patients was confirmed by the randomized Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) clinical trial.¹¹ This trial demonstrated the therapeutic noninferiority of LAA closure as an alternative to long-term warfarin in preventing stroke in nonvalvular AF patients with a CHADS₂ score ≥ 1 . In this randomized study, LAA closure was accomplished by percutaneous transseptal placement of a filter device at the ostium of the LAA. For the primary composite efficacy end point of stroke, systemic embolism, and cardiovascular death, patients randomized to the LAA closure strategy manifested a numerically lower event rate (3.0 per 100 patient-years) than patients randomized to standard warfarin treatment (4.3 per 100 patient-years). This relative rate ratio of 0.71 (credible interval, 0.44 to 1.30) translated to noninferiority of the LAA closure strategy to Warfarin treatment.

This trial also had a prespecified primary safety end point consisting of life-threatening and significant bleeding events such as intracranial bleeding and gastrointestinal bleeding requiring transfusion and device implantation-related complications such as procedure-related stroke, pericardial effusion requiring intervention, and device embolization requiring retrieval. The overall incidence of the safety end point was greater in those patients randomized to device implantation, in whom most of the events occurred periprocedurally and pericardial effusions constituted the majority of events. However, data have continued to accrue, with additional long-term follow-up in the PROTECT AF study and additional implant experience in the Continued Access Protocol (CAP), a nonrandomized registry that began at the conclusion of the PROTECT AF trial. This article examines the safety of LAA closure both as a function of occurrence over the course of the PROTECT AF study and in comparison to CAP, including both procedure/device safety events and serious pericardial effusions. In addition, because the composite safety and efficacy end point included a variety of events with different severities of clinical impact, this article also explores the functional effect of the safety and efficacy events occurring in each of the randomized groups of the PROTECT AF study.

Methods

Watchman LAA Closure Procedure

The Watchman device (Atritech, Inc, Minneapolis, MN), procedure, and results of the PROTECT AF trial have previously been described.^{8,11} Briefly, this filter device is made of a self-expanding nitinol frame with fixation barbs and a permeable polyester fabric cover. The procedure is performed under transesophageal echocardiographic (TEE) guidance. In some centers, intracardiac echocardiography was also used. After a transseptal puncture is performed, a pigtail catheter is maneuvered into the LAA to perform an LAA angiogram. Through the use of a combination of this angiographic

and TEE information, a Watchman device, ranging in size between 21 and 33 mm in diameter, is selected. The device comes prepackaged in a catheter-based delivery system that is advanced into the LAA through a 12F transseptal sheath (outer diameter, 14F). Proper positioning and stability of the device are verified by TEE and angiography before device release.

To minimize the chance of sheath-related air embolism, physicians were instructed to carefully flush the sheath with saline immediately before its introduction. Periodic flushing of the sheath was used because there is no clearance between the sheath and the delivery catheter to allow a continuous flush. Intravenous heparin was given as a bolus to achieve an activated clotting time >250 seconds before introducing the device into the body. Because of the short duration of the procedure, a continuous intravenous heparin infusion was not used; instead, additional boluses of intravenous heparin were administered whenever procedure time exceeded 60 minutes.

PROTECT AF Trial

After device implantation, Warfarin was administered for at least 45 days to avoid excessive thrombus formation on the device until device endothelialization supervened. Follow-up TEE imaging was performed at 45 days, 6 months, and 12 months to assess for device stability, peri-device leaks, and device-related thrombus. Assuming that the 45-day TEE revealed <5 mm of peri-device flow, warfarin was discontinued and the patients were prescribed clopidogrel (75 mg daily) until the 6-month visit and aspirin (81 to 325 mg daily) for life. Patients in the control group received standard warfarin treatment, with international normalized ratio monitoring to achieve a goal international normalized ratio between 2 and 3. This article includes data on patients followed up for a total of 1500 patient-years.

CAP Registry

This US Food and Drug Administration investigational devices exemption registry was designed to allow continued access to the Watchman device for a subset of the PROTECT AF study investigators and to gain further safety and efficacy data on the device. Although nonrandomized, this ongoing registry has the same inclusion and exclusion criteria and procedure/treatment protocol as PROTECT AF. This article includes data on the patients enrolled between August 2008 and April 2010 in whom all events were adjudicated by the Clinical Events Committee; this includes a total of 460 patients at 26 centers.

Operator Selection

The major prerequisite for selection of investigators was experience with the transseptal puncture procedure; all interventional cardiologists and electrophysiologists who participated in PROTECT AF were routinely performing procedures requiring transseptal punctures. In addition, before the first implantation, each operator underwent training using a simulation model that allowed the operator to understand and practice the various steps of the procedure. All the investigators in the CAP Registry had previously participated in PROTECT AF.

General Methods

The focus of this analysis is on primary safety end points that were determined to be procedure- or device-related and serious pericardial effusions, rather than the known complications of anticoagulant/antiplatelet therapies. The primary composite safety end point consisted of both procedure-related events (such as pericardial effusion/tamponade, procedure-related stroke, or device embolization) and excessive bleeding events (such as intracranial or gastrointestinal bleeding requiring transfusion). Pericardial effusions were considered to be serious either if they were of hemodynamic significance prompting intervention or if they extended hospitalization. For these analyses, patients included are those in whom an implant was attempted in either the PROTECT AF Trial (including both roll-in or randomized device patients) or the CAP Registry.

Table 1. Baseline Patient Demographics

	PROTECT AF (n=542)	CAP (n=460)	P
Age, mean±SD, y	72±9	74±8	<0.001
Male, %	70	65	0.088
Race, %			
Asian	<1	2	
Black/African American	2	2	
White	92	91	0.242
Hispanic/Latin American	5	4	
Hawaiian/Pacific Islander	<1	<1	
Other	<1	1	
CHADS ₂ score, mean±SD	2.2±1.2	2.4±1.2	<0.001
CHADS ₂ score, %			
1	33	25	
2	34	34	
3	19	21	0.012
4	8	14	
5	4	6	
6	<1	<1	

Statistical Methods

Numbers and percentages of patients experiencing events are given, with χ^2 tests used to assess differences between studies and trends over time. Patients from PROTECT AF were compared with the CAP study. In additional analysis, the patients in PROTECT AF were split into 2 equal-size groups, early and late implantations, based on their date of enrollment, ie, those patients enrolled in the first half versus second half of the entire cohort of patients enrolled in PROTECT AF. This analysis assessed the trends in the occurrence of safety events across time. Demographic comparisons between the studies were made with χ^2 or *t* tests as appropriate. Logistic regression was used to assess differences in the odds of events between studies adjusting for baseline differences. *P* values are 2 sided, and values <0.05 are considered statistically significant. For the analysis of events that resulted in significant disability or death, the event rates for the composite of the primary safety and primary efficacy end point of PROTECT AF (stroke, systemic embolism, or cardiovascular/unexplained death) were analyzed with a bayesian

Table 3. Safety Event Rates at Sites Participating in Both PROTECT AF and CAP

	PROTECT AF	CAP	P
Procedure time, mean±SD, min	56±27	50±21	<0.001
Implant success, n/total (%)	335/367 (91.3)	437/460 (95.0)	0.033
Procedure/device-related safety adverse event within 7 d, n/total (%)	24/367 (6.5)	17/460 (3.7)	0.061
Serious pericardial effusion within 7 d, n/total (%)	15/367 (4.1)	10/460 (2.2)	0.110
Procedure-related stroke, n/total (%)	2/367 (0.5)	0/460 (0.0)	0.113

Poisson model with a noninformative prior, the same methods used in the primary analysis of PROTECT AF.¹⁰

Results

Safety Events Overview

In PROTECT AF and CAP, there were 542 and 460 attempted implantations; these patients were followed up for a median of 2.5 years (range, 0 to 4.7 years) and 0.4 years (range, 0 to 1.6 years), respectively. The patient characteristics of the device patients in the 2 studies are shown in Table 1. As noted, patients in the 2 studies differed significantly by age and CHADS₂ score. The occurrence of safety events also varied significantly between the 3 study cohorts (early PROTECT AF, late PROTECT AF, and CAP). As shown in Table 2, on a per-patient basis, the procedure- or device-related safety end point occurred in 7.7% of patients (42 of 542) in PROTECT AF and 3.7% of patients (17 of 460) in CAP, a relative reduction of 56% (*P*=0.007). Results were consistent when adjusted for patient age and/or CHADS₂ score. As shown in Table 3, this remained true even when one analyzes only those patients enrolled in the 26 centers that participated in both PROTECT AF and CAP; however, it should be noted that because of the smaller number of patients, although the trends were all favorable, not all the numbers reached statistical significance. As shown in the Figure, the Kaplan–Meier curve of the primary safety procedure- or device-

Table 2. Safety Event Rates in PROTECT AF and CAP

	PROTECT AF			PROTECT AF		CAP	<i>P</i> *	<i>P</i> †	<i>P</i> ‡
	PROTECT AF	Early	Late	First 3 Patients	Other Patients				
Procedure time, mean±SD, min	62±34	67±36	58±33	82±40	55±29	50±21	<0.001	<0.001	<0.001
Implant success, n/total (%)	485/542 (89.5)	239/271 (88.2)	246/271 (90.8)	133/154 (86.4)	352/388 (90.7)	437/460 (95.0)	0.001	0.001	0.136
Procedure/device-related safety adverse event within 7 d, n/total (%)	42/542 (7.7)	27/271 (10.0)	15/271 (5.5)	19/154 (12.3)	23/388 (5.9)	17/460 (3.7)	0.007	0.006	0.012
Serious pericardial effusion within 7 d, n/total (%)	27/542 (5.0)	17/271 (6.3)	10/271 (3.7)	10/154 (6.5)	17/388 (4.4)	10/460 (2.2)	0.019	0.018	0.308
Procedure-related stroke, n/total (%)	5/542 (0.9)	3/271 (1.1)	2/271 (0.7)	1/154 (0.7)	4/388 (1.0)	0/460 (0)	0.039	0.039	0.675

P values are from χ^2 tests or ANOVA tests as appropriate.

*From tests comparing the PROTECT AF cohort with the CAP cohort.

†From tests for differences across 3 groups (early PROTECT AF, late PROTECT AF, and CAP). By definition, early and late refer to the first half and second half of the entire cohort of patients enrolled in PROTECT AF.

‡From tests for differences between the first 3 patients implanted at any given institution in PROTECT AF compared with all subsequent patients implanted at that institution.

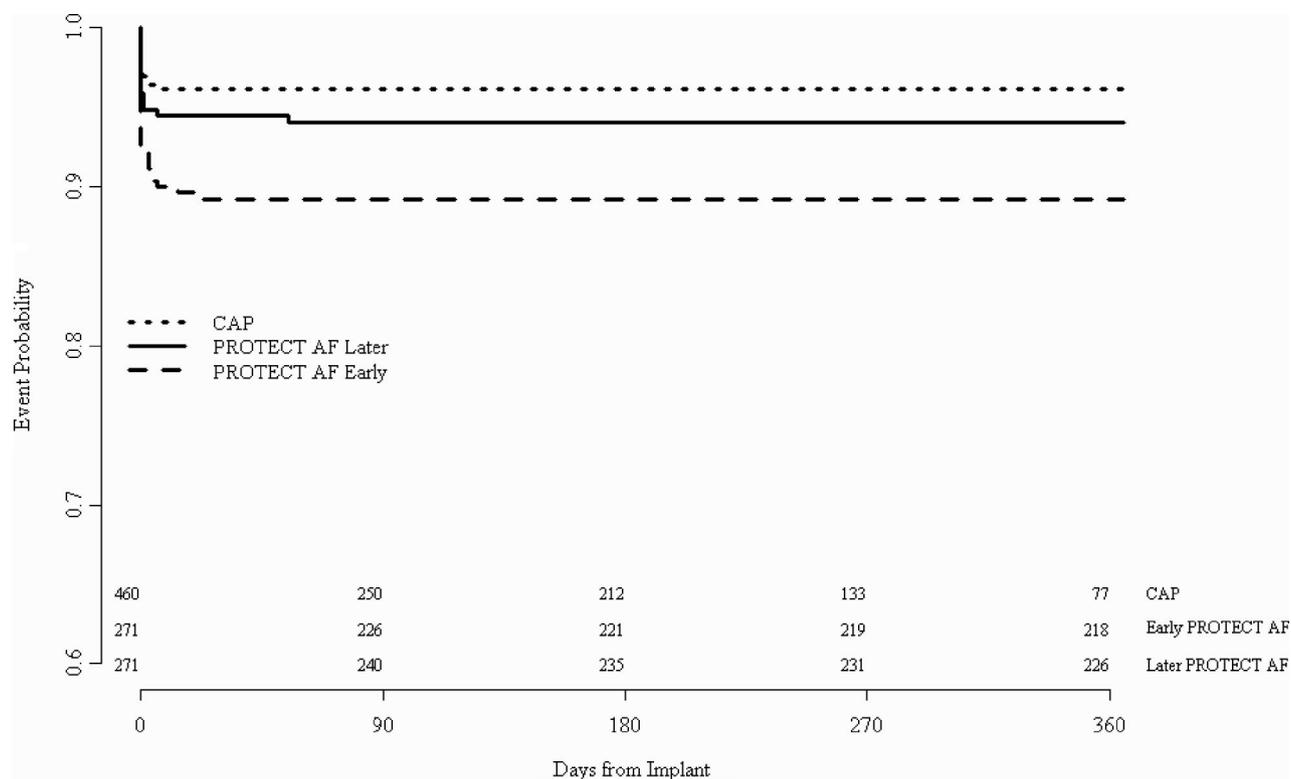


Figure. Kaplan–Meier curve of the incidence of procedure- or device-related safety events for PROTECT AF and CAP Registry device patients. The early and late PROTECT AF patient cohorts represent those patients enrolled in the first and second halves of the study, respectively.

related events reveals that the majority of events occurred perioperatively, with a low rate of later events. In PROTECT AF, there was also an uneven risk of these safety events over the course of enrollment in the study, with a lower incidence of events among patients enrolled later in the trial, ie, the second half of patients enrolled in the study (the Figure and Table 2). The safety event rate for the later PROTECT AF patients is similar to that for the CAP patients. As shown in Tables 2 and 3, there were significant experience-related improvements in both procedure duration ($P<0.001$) and successful implantation of the device ($P=0.001$). One of the other prespecified secondary analyses in PROTECT AF was to compare the outcomes in the first 3 device implants at any given site with all subsequent device implantations at that site. As shown in Tables 2 and 3, these data suggest that even per any given site, there were experience-related improvements: The procedure time improved by 33% and, importantly, the device-related safety event rate improved by 52%, both statistically significant improvements.

To examine the time dependence relative to the implant procedure, the various safety events that occurred early in follow-up (within 7 days of the procedure) are shown in Tables 2 and 3. Of the 46 and 17 procedure/device-related primary safety events observed in PROTECT AF and CAP, respectively, $\approx 94\%$ (59 of 63 events) occurred within 7 days of implantation. The respective event rates in PROTECT AF and CAP were 91% (42 of 46) and 100% (17 of 17). The 4 events that occurred after 7 days in PROTECT-AF include 1 late pericardial effusion (presented 14 days after implantation), an arteriovenous fistula, and 1 device embolization.

Pericardial Effusions

There were a total of 38 patients (3.8%) in whom a serious pericardial effusion was noted, with an incidence of 5.2% (28 of 542) in PROTECT AF and 2.2% (10 of 460) in CAP, a relative reduction of 58% ($P=0.014$). The serious effusion cases were discovered within 24 hours of the procedure in 34 of 38 of the cases (89%). In 4 PROTECT AF patients, the effusion was of no hemodynamic significance and did not require treatment, but the events were considered serious because the patients' hospital stays were extended by at least 1 day (range, 1 to 2 days). The pericardial effusions in the remaining 34 patients were serious because they were of hemodynamic significance requiring intervention. All but one of these effusions was recognized and received intervention within 7 days of the implant procedure; the last patient presented with symptoms of chest pain 14 days after the procedure and underwent pericardiocentesis 4 days later. Of the 34 patients with pericardial effusions requiring intervention, 26 were successfully drained percutaneously with a standard subxyphoid or transthoracic puncture approach, whereas the 8 remaining patients underwent surgical intervention. Six of these patients had a percutaneous pericardiocentesis attempted before surgery.

Of these 8 patients requiring surgical intervention for pericardial effusion, 7 were enrolled in PROTECT AF and 1 patient was in the CAP Registry. There was no systematic data collection as to whether the bleeding point was identified; however, all effusions did resolve. The device was left in place in 2 patients (1 patient each from PROTECT AF and the CAP Registry). In the remaining 6 patients, the implantation attempt

Table 4. Root Cause Analysis of the Pericardial Effusions in PROTECT AF

	Events, n (%)
Initial transseptal puncture	2/22 (9)
From adjunctive device to enter the LAA (such as a guidewire or catheter)	4/22 (18)
Manipulating delivery system within the LAA	3/22 (14)
Protruding delivery sheath from the transseptal access sheath	2/22 (9)
Watchman deployment process	4/22 (18)
No definitive cause identified	7/22 (32)

had been abandoned with development of the pericardial effusion; ultimately, 1 of these 6 patients underwent a maze procedure and 2 underwent surgical LAA ligation.

After catheter or surgical drainage of the pericardial effusion, all patients had good functional recovery; there was no long-term disability or death related to these effusions. For patients requiring either percutaneous or surgical intervention, the mean duration of hospitalization was extended by an average of 6 days (range, 0 to 26 days). Based on a review of the procedural details, fluoroscopy, and TEE imaging, a root cause analysis of the serious pericardial effusions was performed for a subset of patients (n=22) who developed pericardial effusions in the PROTECT AF trial. As shown in Table 4, there were a variety of causes, ranging from being a result of the transseptal puncture, the delivery sheath, or the actual manipulation of the Watchman device itself.

Procedure-Related Stroke

A total of 5 patients in PROTECT AF (0.9%) sustained a stroke during the procedure (Tables 2 and 3); no procedure-related strokes have been observed in the CAP Registry ($P=0.039$). Four of the 5 events manifested clinically on the day of the procedure; the fifth patient manifested clinical symptoms the day after the procedure. The cause of these strokes was clearly air embolism from the transseptal access sheath in 3 cases; ie, air was seen to escape into the left-sided circulation by fluoroscopy and/or echocardiography. Although not definitively known, air embolization was also the likely cause in the remaining patient who sustained a stroke on the day of the procedure. As a result of these strokes, the mean time of hospitalization was extended by 9 days (range, 5 to 19 days). Three of these patients recovered completely and sustained no long-term deficit. However, the remaining 2 patients had significant neurological deficits and were ultimately discharged to long-term nursing facilities. Both of these patients ultimately died as a result of renal failure and urosepsis at 4 and 8 months after the procedure, respectively.

Device Embolization

Of the 542 PROTECT AF patients, the device embolized in 3 patients (0.6%); there have been no device embolizations in the CAP Registry ($P=0.11$). In one of the device embolizations, device dislodgement was detected during the procedure. In this case, the Watchman device was entrapped in the left ventricle outflow tract, and the patient eventually underwent cardiac surgery. During the process of device removal, the barbs of the

device apparently caught onto and caused small tears in the left and right coronary leaflets of the aortic valve. Combined with the fact that the valve was mildly stenosed and regurgitant at baseline, the decision was made to replace the valve. The LAA was also surgically ligated during the procedure.

The timing of the other 2 embolizations is not known because the patients were asymptomatic; the dislodgements were recognized only during the scheduled 45-day follow-up visit. In both of these cases, the device was found lodged in the descending aorta, one in the thoracic aorta and the other in the abdominal aorta at bifurcation to the iliac vessels. The first of these was removed percutaneously with a snare using a femoral arterial puncture and retrograde aortic approach. Because of the absence of symptomatology, the other patient initially refused intervention to remove the device. By the time this patient agreed to have it removed at 23 months after the procedure, 22 months after it was first noted, it ultimately required surgical explantation. Ultimately, there was no long-term disability or mortality as a result of these embolizations.

Device Thrombus

Device-associated thrombus was observed in 20 of 478 successfully implanted patients (4.2%) in PROTECT AF. Of these patients, only 3 had experienced an ischemic stroke; the other patients were either asymptomatic or endothelialized with anticoagulation. This translates to a device thrombus-associated annualized stroke rate of 0.3% per 100 patient-years. The device thrombus was mobile in 4 patients (3 pedunculated and 1 laminar) and nonmobile in 10; in the remaining patients, the character of the thrombus was unknown. Of the 3 patients with a device thrombus who sustained a stroke, 1 occurred in a patient with a mobile/pedunculated thrombus.

Other Safety Events

Other procedure- or device-related safety events in PROTECT AF were bleeding (n=4), bruising/hematoma (n=2), arteriovenous fistula (n=1), arrhythmia (n=1), and other events (n=3: esophageal tear from the TEE probe, elective removal of the device, and hemopericardium requiring transfusion). The other procedure- or device-related safety events in CAP were bleeding (n=3), arrhythmia (n=2), pseudoaneurysm (n=1), and other events (n=5: tongue laceration, airway trauma, and postprocedure respiratory failure [in 2 patients]).

Impact of Events: Disability and Death

Because not all safety events have the same clinical impact on the patient, an analysis was conducted to determine the functional impact of being in either the Watchman or warfarin group in PROTECT AF. That is, the functional impact of the primary safety (including non-procedure- and device-related event) and efficacy events was assessed by determining whether they resulted in either significant disability (defined as an increase in the modified Rankin score [MRS]) or death. As shown in Table 5, this analysis revealed that regardless of how "significant" is defined, there was a statistically improved outcome in the Watchman group. That is, whether significant disability was defined as a change in MRS ≥ 1 , ≥ 2 , or ≥ 3 , the Watchman group fares significantly better than the warfarin group (each with relative risks of ≈ 0.40).

Table 5. Functional Impact of Safety Events

	Watchman Group Event Rate, % (n per 100 Patient-y)	Warfarin Group Event Rate, % (n per 100 Patient-y)	Relative Risk (95% CI)
MRS increase ≥ 1 or death	1.8 (19/1042.2)	4.3 (24/559.5)	0.43 (0.24–0.82)
MRS increase ≥ 2 or death	1.5 (16/1047.1)	3.7 (21/563.9)	0.41 (0.22–0.82)
MRS increase ≥ 3 or death	1.4 (15/1048.5)	3.3 (19/567.5)	0.43 (0.22–0.88)

CI indicates confidence interval.

Discussion

The PROTECT AF study was the first randomized study to show both the critical role of the LAA in the pathogenesis of AF-related stroke and the ability of a filter device strategy to emulate the clinical benefit of warfarin. However, the higher rate of safety events with LAA closure has been a source of concern. An accurate interpretation of the risk profile of Watchman implantation requires a nuanced understanding of the data, including a detailed assessment of the temporal distribution of events, the rate of adverse events with increased experience, and the functional significance of both efficacy and safety events. Here, we show that the safety events in the Watchman group are largely procedure-related events, that these safety events decrease in frequency with greater operator experience, and that regardless of the definition used for significant disability, the rates of events resulting in significant disability or death were statistically lower for the Watchman device compared with warfarin therapy in PROTECT AF.

Temporal Distribution of Safety Events

As expected, safety events in the control warfarin group occurred at approximately constant rates over time. However, the safety event rates in the Watchman group showed a skewed distribution, with a large initial event rate followed by a subsequent rate over the remainder of the follow-up. The single largest component of the periprocedural concentration of safety events in the Watchman group was pericardial effusion with tamponade physiology. This event constituted $\approx 50\%$ of all events. The cause of these effusions was multifactorial and incorporated all components of the procedure, from the initial transseptal puncture to accessing the LAA to manipulation of the device within the appendage.

Importantly, however, after the successful treatment of device patients (including cessation of warfarin therapy), the risk for complications for patients implanted with the device was reduced substantially compared with those receiving warfarin therapy.¹⁰ This is certainly of relevance during discussions with patients in terms of informing them of the residual risk once the procedure is successfully completed. It is also important to recognize that the safety events in the warfarin group would be expected to continue to accumulate linearly over time, potentially beyond the end of the study period.

Impact of Experience on Procedure-Related Safety Events

The Watchman device and, more generally, the strategy of LAA closure are novel, and a learning curve is expected.

Indeed, the effect of experience on the incidence of procedure-related complications in the PROTECT AF study was observed to be an important factor. This was evident by 3 separate analyses: comparing the first half of the PROTECT AF patient cohort enrolled in the study with the second half of the cohort, comparing the first 3 patients enrolled at any given site in PROTECT AF with all subsequent patients enrolled at the site, and comparing the nonrandomized CAP Registry patient cohort with the PROTECT AF cohort. Along with significant improvements in both procedure duration and the successful implantation of the device, there were significantly fewer safety events within 7 days of the procedure. Because the major component of these early safety events was serious pericardial effusion, this improved safety event rate was driven largely by an experience-related improvement in the rate of serious pericardial effusions. Indeed, the rate of serious pericardial effusion in the CAP Registry is less than half that seen in PROTECT AF.

Although this residual pericardial tamponade rate of $\approx 2\%$ is not trivial, it is worthwhile to put this number in context by examining the tamponade rate during other similarly invasive cardiac procedures such as catheter ablation of AF; in various studies, this has been reported to range between 1% and 6%.¹² Indeed, the largest multicenter registry of AF ablation outcomes including $>20\,000$ patients reported a pericardial tamponade rate of 1.31%, which in itself is likely an underestimate of the actual rate given that this was a self-reporting survey.¹³ However, this tamponade rate with AF ablation is considered clinically acceptable enough that AF ablation is now the most common ablation procedure performed in many electrophysiology laboratories in the world. Accordingly, the similar tamponade rate of $\approx 2\%$ associated with LAA closure does not seem unmanageable. Of course, our experience with this procedure is still relatively early, and there is likely to be continued evolution of both the implant procedure and the device to further improve the safety of LAA closure.

Also of particular significance, there was an experience-related improvement in the other major safety event, procedure-related stroke. This complication is related largely to the inadvertent introduction of air entrapped within the sheath (and possibly sheath-related thrombus) into the systemic circulation during the procedure. Although we cannot definitively rule out the possibility of dislodgment of a thrombus either within the LAA (and not seen on the preprocedural TEE) or acutely associated with the device itself, this is less likely because air was actually seen to escape into the circulation on fluoroscopy during the procedures of most patients who developed stroke (and fluoroscopic visualization of air suggests the introduction of a large amount of air) and the incidence of procedure-related stroke would not be expected to decrease with experience if the cause was either preexisting LAA thrombus or device-associated thrombus.

Because a relatively large 12F sheath is used during the procedure, the operator must be extremely diligent in properly flushing the sheath to prevent air from becoming entrapped within the sheath and then embolizing. In fact, if these procedure-related strokes had been avoided in the PROTECT AF study, the Watchman group would have actually proven to be statistically superior to the warfarin

group in the primary composite efficacy end point. With careful sheath management, there have been no procedure-related strokes in the CAP Registry. Thus, these data indicate that with experience, it is possible to implant the device with minimal risk of procedure-related stroke.

Similarly, there was an improvement in the Watchman device embolization rate from 0.6% in PROTECT AF to 0% in the CAP Registry. It is likely that this was due at least in part to the institution of a number of procedural protocol changes implemented over the course of PROTECT AF to minimize the chance of device embolization. These included measuring the left atrial pressure to verify that the chamber is not underfilled, positioning within the LAA to verify that the device is not protruding excessively out of the LAA, and applying traction on the device to verify that the barbs on the device have properly engaged the LAA wall for good stability.

Functional Significance of Safety Events

The safety end point is a composite of a number of adverse events that range in seriousness; eg, an air embolization or a bleed into the brain is likely to be of greater clinical importance than a pericardial effusion that is rapidly treated. Thus, because not all safety components have equivalent functional clinical importance, we assessed the overall functional significance of the individual components of this composite end point. The most important measure of clinical significance is overall mortality, an analysis that was shown in the PROTECT AF trial to be numerically superior and statistically equivalent in the Watchman group relative to the warfarin group.¹⁰ A more subtle analysis was the assessment of the rate of significant disability or death resulting from the safety events. Regardless of the definition of significant (using MRS increases of ≥ 1 , ≥ 2 or ≥ 3), this analysis demonstrated both numeric and statistical superiority of the Watchman group. The discordance between this statistic and the primary composite safety end point is driven largely by the fact that in PROTECT AF, pericardial effusions, while significantly prolonging hospitalization, had minimal overall long-term clinical impact. Although pericardial effusions are certainly concerning, the minimal long-term morbidity and mortality associated with them in this study are likely related to the fact that the procedure is performed under TEE guidance. That is, poor outcome related to pericardial effusion is typically the result of a delay in recognizing the development of pericardial tamponade and a consequent delay in performing the pericardiocentesis. Thus, because Watchman implantation is performed under TEE guidance, recognizing and addressing a developing pericardial effusion is straightforward.

Limitations

The comparisons of the safety event rates between PROTECT AF and the CAP Registry and the functional significance of the safety and efficacy events (significant disability or death) were posthoc analyses. Thus, we cannot rule out potential inherent biases of these analyses. The CAP Registry does not include all the centers that participated in the initial PROTECT AF trial but rather 26 of the higher-enrolling centers. This does impose some bias in the comparison in safety event rates between the 2 studies. However, the fundamental point that experience decreases the safety event rate remains true.

The necessity for TEE and, in most cases, endotracheal intubation to tolerate the TEE was also the cause of a few procedural complications observed in the trials. In the PROTECT AF cohort, there was 1 esophageal tear and 1 airway trauma; in the CAP Registry cohort, 2 patients had postprocedural respiratory failure and 1 had tongue laceration resulting in prolonged hospitalization that might have been avoided by not using TEE and endotracheal intubation. To avoid the clinical, logistical, and financial complexity that TEE adds to the procedure, one potential option is to place the device with angiographic guidance exclusively. However, fluoroscopy alone is not ideal because it may not be possible to rule out LAA thrombus, to accurately measure the LAA ostium in multiple dimensions, or to confirm satisfactory seal of the LAA ostium. Certainly, intracardiac echocardiography is an alternative using unusual visualization planes, eg, from the coronary sinus or directly from within the left atrium, sometimes after a second transeptal puncture.¹⁴ However, the present generation of single-plane intracardiac echocardiography probe does not allow facile multiplane accurate measurement of the LAA ostium, which is oval rather than round. Nonetheless, there have been selected cases outside these clinical trials in which the device has been placed with the use of fluoroscopy plus intracardiac echocardiography guidance (V.Y.R., P.N., and S.K.D., unpublished observation). In the future, with the development of multiplanar or 3-dimensional intracardiac echocardiography probes, it might be possible to routinely implant the device under local anesthesia without TEE. But for now, it should be emphasized that there is no well-studied large clinical experience with device implantation without TEE guidance, and little can be confidently stated about the safety and efficacy of this approach.

Because the Watchman device is placed in the neck of the LAA, there is often a small vestibule in the LAA neck. One cannot rule out the possibility that this vestibule might serve as a location for thrombus formation and, in theory, may compromise the efficacy of embolic protection.

Finally, because device-associated thrombus is not a clinical end point but rather an "imaging end point," it was not one of the end points of either PROTECT AF or the CAP Registry. However, the occurrence of device thrombus is certainly an important piece of information because it may portend future clinical events. Although the incidence of this phenomenon was 4.2%, not all patients with device thrombus experienced a clinical event; indeed, the attributable device thrombus-associated annualized stroke rate was only 0.2% per 100 patient-years.

Conclusions

The LAA closure trials have demonstrated that, as seen for other interventional procedures, complications associated with Watchman implantation are typically clustered early in the periprocedural period and significantly decrease in frequency with operator experience. In addition, despite a higher overall complication rate associated with LAA closure than warfarin treatment, the functional impact of these events favors LAA closure. Together, these data suggest a favorable safety profile for Watchman implantation.

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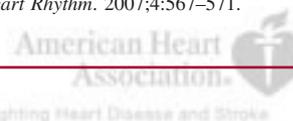
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Disclosures

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CLINICAL PERSPECTIVE

The Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) study randomized atrial fibrillation (AF) patients at risk for stroke to either usual therapy (warfarin) or percutaneous left atrial appendage closure with the Watchman filter device. It was the first randomized study to demonstrate both the critical role of the left atrial appendage in the pathogenesis of AF-related stroke and the ability of a filter device to recapitulate the clinical benefit of warfarin. However, the procedural safety of this new invasive procedure was a source of concern. Based on PROTECT AF and the Continued Access Protocol Registry, a registry that has followed the trial, we assessed the safety of left atrial appendage closure, including the temporal distribution of safety events, the rate of events with increased experience, and the functional significance of these events. This analysis revealed that the safety events in the Watchman group are largely clustered early in the periprocedural period and, after this point, the risk is minimal; that these safety events decrease in frequency with greater operator experience, particularly the rate of periprocedural stroke and pericardial effusion/tamponade; and that the rates of events resulting in significant disability or death were statistically significantly lower for the Watchman device compared with warfarin therapy in PROTECT AF. This article suggests that despite a higher numeric rate of complications with Watchman implantation compared with warfarin, a more nuanced understanding of these data indicates that the safety of left atrial appendage closure is more favorable when one considers the differential functional impact of these events and the significant decrease in the frequency of events with operator experience.

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