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, 0.43; 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.


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,
nonpharmacological approaches to left atrial appendage (LAA) closure\textsuperscript{5–8} 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.\textsuperscript{9,10}

**Clinical Perspective on p 424**

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.\textsuperscript{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 CHADS\textsubscript{2} score $\geq 1$. 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 includes data on the patients enrolled 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 severity levels 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.\textsuperscript{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 $\geq 250$ 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

<table>
<thead>
<tr>
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<th>PROTECT AF (n=542)</th>
<th>CAP (n=460)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>72±9</td>
<td>74±8</td>
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<td>Male, %</td>
<td>70</td>
<td>65</td>
<td>0.088</td>
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<td>91</td>
<td>0.242</td>
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<tr>
<td>Hispanic/Latin American</td>
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<td>4</td>
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<tr>
<td>Other</td>
<td>&lt;1</td>
<td>1</td>
<td></td>
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<tr>
<td>CHADS2 score, mean±SD</td>
<td>2.2±1.2</td>
<td>2.4±1.2</td>
<td>&lt;0.001</td>
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<tr>
<td>CHADS2 score, %</td>
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<tr>
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<td>33</td>
<td>25</td>
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<td>6</td>
<td>&lt;1</td>
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Statistical Methods

Numbers and percentages of patients experiencing events are given, with $\chi^2$ tests used to assess differences between studies and trends over time. Patients from PROTECT AF were compared with the CAP study. In addition, the analyses in 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 $\chi^2$ 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 Poisson model with a noninformative prior, the same methods used in the primary analysis of PROTECT AF.

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-related stroke event rate for patients enrolled in early PROTECT AF reached statistical significance. As shown in the Figure, the Kaplan–Meier curve of the primary safety procedure- or device-related stroke event rate for patients enrolled in early PROTECT AF reached statistical significance. As shown in the Figure, the Kaplan–Meier curve of the primary safety procedure- or device-related stroke event rate for patients enrolled in early PROTECT AF reached statistical significance.
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, 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%). 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.

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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.
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 anti-coagulation. 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 postprocedural 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).
recognize that the safety events in the warfarin group would be
procedure is successfully completed. It is also important to
patients in terms of informing them of the residual risk once the
LAA closure are novel, and a learning curve is expected.
The Watchman device and, more generally, the strategy of
therapy. This is certainly of relevance during discussions with
reduced substantially compared with those receiving warfarin
a subsequent rate over the remainder of the follow-up. The
skewed distribution, with a large initial event rate followed by
increased frequency with greater operator experience, and that
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 de-
crease 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
≈50% of all events. The cause of these effusions was
multifactorial and incorporated all components of the proce-
dure, 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 re-
duced substantially compared with those receiving warfarin
therapy. 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, poten-
tially 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 signifi-
cantly 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 ≈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 out-
comes including >20,000 patients reported a pericardial
tamponade rate of 1.31%, which in itself is likely an under-
estimate 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 ≈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 inad-
vertent 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
(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 proper-
ly flushing the sheath to prevent air from becoming en-
trapped 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 bars 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 equal 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. 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 transseptal puncture. 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.
Sources of Funding
Both the PROTECT AF trial and the CAP Registry were supported by Atritech, Inc.

Disclosures
Drs Reddy, Neuville, and Holmes have received research grant support from Atritech, Inc. In addition, the Watchman LAA closure technology has been licensed to Atritech, and both Mayo Clinic and Dr Holmes have contractual rights to receive future royalties from this license. To date, no royalties have been received. Drs Doshi, Kar, and Saital have received research grant support from and are consultants to Atritech, Inc.

References

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 peri-procedural period and, after this point, the risk is minimal; that these safety events decrease in frequency with greater operator experience, particularly the rate of peri-procedural 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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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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중재시술을 통한 약물 없는 심방세동의 혈전예방: 가능할까?

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Summary

배경

‘Watchman Left Atrial Appendage(좌심방귀) System for Embolic Protection in Patients With AF(PROTECT AF)’ 무작위배정 연구는 CHADS2, 점수가 1 이상인 심방세동 환자에서 좌심방귀 폐쇄시술과 와파린 투약을 비교하였다. 이 연구에서는 1차 연구목표인 뇌졸중, 전신성 혈栓, 심혈관계 사망의 예방에서 와파린에 대한 비효율성을 입증하였으나, 유의하게 발생률(주로 심장내심장과 공기장해증과 연관된 뇌졸중)의 발생이 증가하였다. 본 연구는 심장경이 좌심방귀의 경피적 폐쇄시술의 안정성에 미치는 영향을 평가하고자 한다.

방법 및 결과

본 연구는 PROTECT AF 연구에서 좌심방귀 폐쇄시술이 시도되었던 542명의 환자와 그 이후에 진행된 Watchman 기구의 등록연구인 Contemporary Access Protocol(CAP)에 등록된 460명을 대상으로 진행되었다. 출혈과 심장관련 사망(심장내실, 뇌졸중, 기구 작전 중)과출혈을 포함하여 안전성 지표로 삼았다. 분석결과, 심장 후 7일 이내의 심장 관련 안전사고의 발생률은 PROTECT AF, 그리고 CAP 등록연구의 두 연구에 걸쳐 비교하면 7.7%와 3.7%(P=0.007)였고, PROTECT AF의 저해 결과가 나중 결과 그에 따라 CAP 등록연구로 나누어 비교하면 안전사고의 발생률은 10.0%, 5.5% 그리고 3.7%(P=0.006)였다. 심장 후 7일 이내의 중대한 심장 채혈 발생률(PROTECT AF 전체 안전사고의 50% 이상을 차지할)이 CAP 등록연구에서는 유의하게 높았다(5.0% vs. 2.2%, respectively; P=0.039). 심장관련 뇌졸중의 발생률 또한 심장의 경피적 치료에 따라 감소가 관찰되었다(0.9% vs. 0%, respectively; P=0.039). 따라서 이로 이음 안전사고의 기능적인 손상발생(유의한 장애 혹은 사망)을 비교하면 PROTECT AF 연구에서 심장관계 와파린에 비해 우수하였다. 이와 같은 현상은 modified Rankin score를 ≥1, ≥2, or ≥3으로 나누어 비교하여도 마찬가지였다(1.8 vs. 4.3 events per 100 patient-years; relative risk, 0.43; 95% CI, 0.24-0.82; 15 vs. 3.7 events per 100 patient-years; relative risk, 0.41; 95% CI, 0.22-0.82; and 1.4 vs. 3.3 events per 100 patient-years; relative risk, 0.43; 95% CI, 0.22-0.88).

결론

본 연구를 통해 좌심방귀 폐쇄시술의 경우 심장의 경피적 치료에 따른 유의한 심장의 안전성에서 개선이 있음을 보고하였다.
Commentary

역세와 달리 새로운 시술이나 장비는 시술자의 경향에 따라 이 치료 성과에 큰 영향을 미치는 경우가 많다. 만일 시술의 숭련도가 시술의 성공에 상당한 영향을 미치고, 그 시술의 숙련도가 비교적 단기간 내에, 대수의 시술자에게서 항상될 수 있다면 이는 시술의 실제적 적용 및 총론에 영향을 미칠 수 있는 중요한 변수가 될 수 있다. 그러나 이 같은 시술 숙련도의 객관적인 관례화가 쉽지 않다는 현실적인 문제가 있으며 본 연구가 되기 위해 배정 연구와 등록연구의 직접적인 비교는 많은 제약이 따르는 것이 사실이다. 하지만 저자들은 비교적 합리적인 비교 분석을 통해 새로운 심방세동의 사지주 예방법인 침습방범의 폐쇄도구가 외파원과 비교하였을 때 실제적인 대안이 될 수 있다는 가능성이 있다. 만일 이들 일련의 시술관련 합병증의 발생을 제거하면 다. 심혈관계 질환의 발생 및 유해성을 개선하기 위한 노력은 통해 많은 심혈관계 질환의 예후가 개선되었으나, 심방세동에 의한 사지주의 위험도는 최근까지도 고지의 치료범위 외파원을 통한 항응고제가 표준으로 자리 잡아 왔다. 그러나 최근에 전극으로 치유술이나 darbipirosan 등의 새로운 경구용 항응고제가 새로운 치료 혹은 예방의 대안으로 주목받고 있다. 그러나 실제 안전성이 개선된 항응고제가 실제 환자 진료에서는 사용이 적어 경과를 도출할 수 없을 수 있다. 이와 같은 환자들에게 점차적으로 지만 새로운 대안이 될 수 있는 치료법이 제시되고 있다는 점은 매우 의미 있는 발전이라 생각된다. 화성형력의 폐쇄 시술이 단기간에 외파원을 대체하는 치료법이 될 가능성이 아직은 작으나, 외파원은 다른 항응고제에 비해 목표성을 보일 수 있는 점의 선별 기준이나, 높은 성공률 혹은 혈병 증을 예방할 수 있는 적절한 적응증 선별, 그리고 무엇보다 중요한 정기 성장을 통한 효능과 안전성 평가를 위한 연구를 거쳐야 하는데 본 연구 결과를 통해 좀 더 평판적으로 고려할 수 있는 대안의 하나로 발전할 가능성을 확인할 수 있다는 점에서 큰 의미가 있다고 하겠다.

Reference