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The Clinical Impact of Incomplete Left Atrial Appendage Closure With the Watchman Device in Patients With Atrial Fibrillation

A PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Substudy

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Objectives The purpose of this study was to investigate the frequency and clinical impact of incomplete left atrial appendage (LAA) sealing and consequent peri-device residual blood flow in patients undergoing percutaneous LAA closure with the Watchman device (Atritech, Inc., Plymouth, Minnesota).

Background During percutaneous LAA closure for stroke prophylaxis, the geometric variability of the LAA ostium may result in an incomplete seal of the LAA. On the one hand, this could enhance thrombus formation and embolization of thrombi around the device into the circulation; on the other hand, the relatively small size of these leaks may preclude clinically relevant embolizations.

Methods Patients randomly assigned to device implantation in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial were analyzed. Transesophageal echocardiography was performed at 45 days, 6 months, and 12 months. Per the study protocol, patients discontinued warfarin therapy if the 45-day Transesophageal echocardiogram revealed either minimal or no peri-device flow (jet ≤5 mm width). The impact of peri-device flow severity, defined as minor, moderate, or major (<1 mm, 1 mm to 3 mm, >3 mm, respectively) on the composite primary efficacy endpoint (stroke, systemic embolism, and cardiovascular death) is expressed as hazard ratio (HR) with 95% confidence interval (CI).

Results Transesophageal echocardiography follow-up revealed that 32.0% of implanted patients had at least some degree of peri-device flow at 12 months. The HR of the primary efficacy endpoint per 1 mm larger per-device flow was 0.84 (95% CI: 0.62 to 1.14; p = 0.256). Compared to patients with no peri-device flow, the HRs were 0.85 (95% CI: 0.11 to 6.40), 0.83 (95% CI: 0.33 to 2.09), and 0.48 (95% CI: 0.11 to 2.09) for minor, moderate, and major peri-device flow, respectively (p = 0.798). Compared to patients with no peri-device flow who discontinued warfarin, the HR for patients with any peri-device flow and continuing warfarin was 0.63 (95% CI: 0.14 to 2.71; p = 0.530).

Conclusions These data indicate that residual peri-device flow into the LAA after percutaneous closure with the Watchman device was common, and is not associated with an increased risk of thromboembolism. This finding should be interpreted with caution as the low event rate decreases the confidence of this conclusion. (J Am Coll Cardiol 2012;59:923–9) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
LAA = left atrial appendage
TEE = transesophageal echocardiogram

Atrial fibrillation (AF) causes 15% to 20% of ischemic strokes, and the overall risk of stroke in patients with nonvalvular AF is as high as 5% per year (1). Warfarin has long been the cornerstone for decreasing risk of stroke in patients with AF, and its efficacy has been well established (2,3). However, the risk of bleeding, inconvenience of frequent monitoring and dose adjustments, drug interactions, and restrictions on diet and alcohol intake perhaps explain why warfarin discontinuation rates are estimated to be as high as 38% per year (3). Other novel anticoagulants are also in various stages of development and clinical use, but all oral medication therapy is limited by the drug-specific incidence of side effects, and the patient-specific propensity for bleeding from these systemically administered agents (4–8).

Autopsy and surgical data have suggested that 90% of atrial thrombi in nonvalvular AF patients originate from the left atrial appendage (LAA) (9). Accordingly, devices that can isolate this structure from the systemic circulation to obviate the need for long-term systemic anticoagulation therapy have been developed. The critical role of the LAA in stroke pathogenesis was recently demonstrated by the use of the Watchman LAA closure device (Atritech, Plymouth, Minnesota) in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) study (10). In this multicenter trial, nonvalvular AF patients with a $CHADS_2$ (acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack) risk score ≥1 were randomly allocated to either standard warfarin therapy or percutaneous implantation of the LAA closure device. As per the protocol design, patients undergoing LAA closure continued warfarin for at least 45 days; transesophageal echocardiogram (TEE) confirmation of LAA closure triggered cessation of warfarin therapy and institution of clopidogrel therapy to the 6-month timepoint, with life-long aspirin therapy. Using the pre-determined primary composite efficacy endpoint of stroke, systemic embolization or cardiovascular death, this study demonstrated non-inferiority of the LAA closure strategy as compared to usual warfarin therapy.

To understand some of the technical limitations of LAA closure, it is important to consider the anatomical variations of the LAA. There is a wide range of LAA ostial diameters and lengths, and most importantly, the morphology of the LAA ostium is elliptical rather than round (11). The Watchman device comes in a finite number of sizes and has a round shape. While the device has 10 individually articulating splines to permit a more oval shape to accommodate LAA orifices that are not perfectly circular, there is a limit to its deformability. This is potentially of concern as a round implant into an oval-shaped orifice may lead to incomplete sealing of the orifice (12). That could create a pouch with stagnant blood flow, which could enhance thrombus formation and embolization of thrombi past the device into the circulation—potentially leading to further stokes (13). Indeed, incomplete occlusion of the LAA has been a concern during surgical ligation (14,15). Conversely, it is possible that with LAA device implantation, the presence of a small area of incomplete sealing may not potentiate any clinically relevant embolization. That is, any large embolic thrombi that might develop may not be able to pass around the device and out of the LAA, provided that the size of the leak is small.

As a practical acknowledgement of the size and shape mismatch between the LAA ostium and the Watchman device, the PROTECT AF trial design defined "LAA closure" as any seal with ≤3 mm width (±2 mm) of peri-device flow. That is, LAA closure with the Watchman device was deemed successful even in cases with a residual gap of up to 5 mm around the device. This degree of "acceptable" peri-device flow was chosen as a reasonable cut-off value but the long-term clinical consequences of such flow were unknown. The frequency of peri-device LAA flow because of an incomplete LAA seal, and its consequent clinical effect remains unclear. Understanding the clinical impact of incomplete closure of the LAA would be critical when assessing thromboembolic risk post-implantation. Consequently, this manuscript details a post-hoc analysis of the Watchman implantation cohort in the PROTECT AF study to study the incidence and natural history of peri-device flow, and to determine its functional impact on clinical outcomes.

Methods

Data collected prospectively from the patients who were randomly assigned to the Watchman device in the PROTECT AF trial and followed up for the full duration of the trial were used for this retrospective analysis. After the device had been implanted, patients were treated with warfarin for 45 days. The TEE imaging was performed at 45 days, 6 months, and 12 months to assess for residual peri-device flow and device stability and positioning. Patients discontinued warfarin therapy if the 45-day TEE showed either complete sealing of the LAA or if there was residual peri-device flow ≤3 ± 2 mm width, that is, ≤5 mm. All patients received clopidogrel from 45 days to 6 months after implantation and life-long aspirin.

Device. The Watchman LAA closure device is composed of a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric (Fig. 1) that covers

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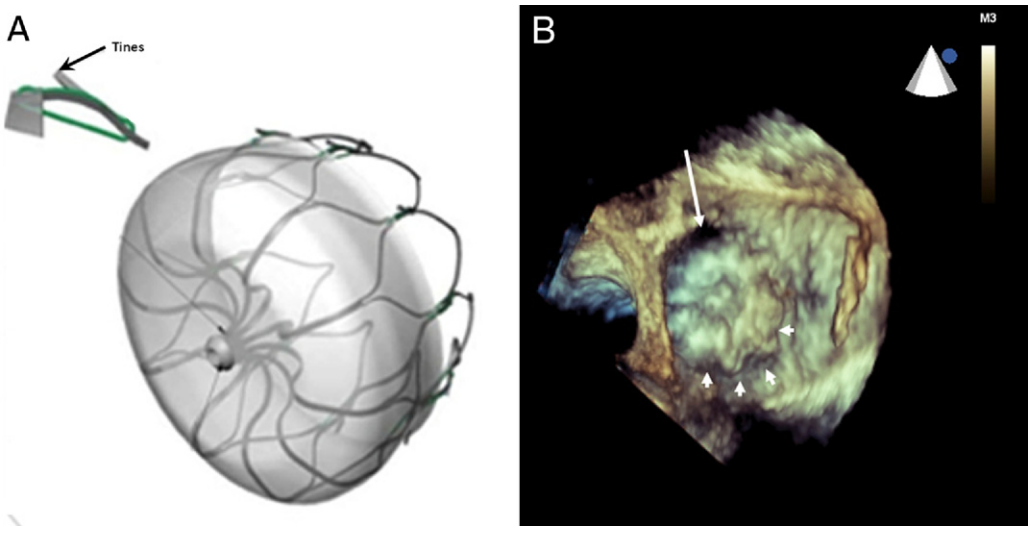

Figure 1 **LAA Ostium by 3-Dimensional TEE and Watchman Device**

(A) Shown is the Watchman filter device; notice the 10 equally-spaced struts, each with a small anchoring time. **(B)** Third-generation Watchman device with spherical shape **(small arrows)**. These 2 illustrations highlight the discrepancy between the shape of the left atrial appendage (LAA) ostium and the Watchman device, which in turn explains the reason for incomplete sealing **(large arrow)** and residual blood flow in some of the patients. TEE = transesophageal echocardiography.

the surface of the device facing the left atrium. Currently, the device is available in 5 sizes ranging in maximal diameter from 21 mm to 33 mm. For any given patient, the device size is chosen to be 10% to 20% larger than the diameter of the LAA ostium to ensure sufficient and stable positioning of the device.

Endpoints. The composite primary endpoint for efficacy consisted of the occurrence of stroke (including ischemic or hemorrhagic stroke), systemic embolism, or cardiovascular or unexplained death. Follow-up visits occurred at 45 days, at 6 and 12 months, and twice a year thereafter. Neurological assessments were performed at baseline, 12 months, and 24 months, and whenever a neurological event occurred.

Leak severity and events. Color Doppler by multiplane TEE was used to check for any communication between the atrium and the LAA and to determine peri-device flow width (Fig. 2). For the purposes of the present analysis, peri-device flow severity was defined as minor (<1 mm), moderate (1 mm to 3 mm) or major (>3 mm). When the PROTECT AF study began enrollment in 2005, the core laboratory responsible for reviewing images was St. Louis University Core Lab Echocardiography Laboratory. In July 2006, Duke Clinical Research Institute assumed responsibility as the core laboratory. Data are based on the 1,500 patient-year dataset and the final core laboratory data. Study centers followed a standard imaging protocol to record TEE views in a consistent manner across all centers. The echocardiography core laboratory over-read all baseline and follow-up imaging to provide LAA measurements, peri-device flow, and device position.

Statistical analysis. The original sample size for the PROTECT AF trial was based on a planned aggregate of between 600 and 1,500 patient-years of follow-up, a 2-fold noninferiority margin, and a desire for 80% power under a rate of 6.15 events per 100 patient-years. As a logical consequence of the original study design, this subanalysis has relatively limited power. Means, standard deviations, minimums, maximums, or counts and percentages are used for descriptive statistics. Trends in echocardiography measurements over time were modeled with generalized linear mixed models, accounting for the repeated measurements on subjects over time, with a binomial or multinomial link function as appropriate. Time in these models was treated as a factor with 3 levels, which allows for departures from linear changes. In analyses relating echocardiography measurements to clinical events, the time-to-event was calculated from the date of the 45 day visit. Event rates were compared by proportional hazards regression and Poisson regression models, with the logarithm of follow-up time as an offset term for the latter. Hazard ratios (HR) >1 indicate an increased risk of a primary efficacy event. To include a sufficient number of events for the time-to-event analyses, patients without peri-device flow were attributed to have flow of size zero. All p values are 2-sided, and values < 0.05 are considered statistically significant.

Results

Patient population. Of the 485 patients with a successfully implanted Watchman device, 445 had a 45-day visit with TEE data adjudicated by the echocardiography core laboratory data and without an efficacy event before the 45-day visit. During follow-up of the 445 patients included in this analysis, 414 and 389 patients had 6-month and 12-month

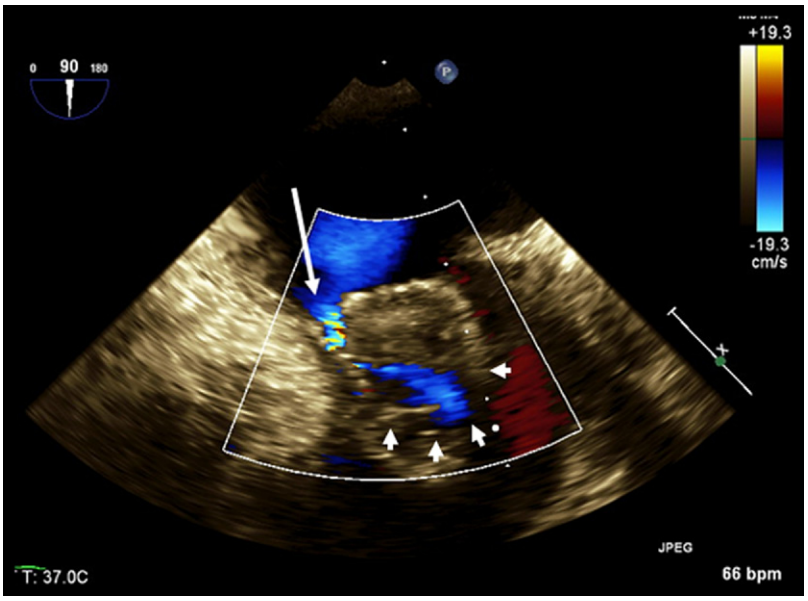

Figure 2 Peri-Device Leak by TEE Imaging

The transesophageal echocardiogram (TEE) illustrates the existence of incomplete sealing of the left atrial appendage (LAA) with peri-device residual flow noted by color Doppler **(large arrows)**.

follow-up TEEs, respectively, analyzed by the core laboratory. A total of 5 patients in the PROTECT AF study (0.9%) sustained a stroke during the procedure. The incidence of pericardial effusion was 5.2%. The device embolized in 3 patients (0.6%). Device-associated thrombus was observed in 15 of 445 successfully implanted patients (3.4%). Of these patients, only 2 had experienced an ischemic stroke (0.45% of patients, 0.17 events per 100 patient-years); the other patients were either asymptomatic or endothelialized with continued anticoagulation therapy for 3 to 6 months. Other procedure- or device-related safety events in the PROTECT AF study 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).

Anatomic characteristics of the LAA at implantation and follow-up. There was a wide variation on the size of the LAA ostium width and length at baseline, underscoring the challenges of occluding the LAA with a device that comes in a finite number of sizes. The mean LAA ostium width at baseline was 21.9 ± 4.1 mm, with a maximum and minimum size of 12.1 mm and 38.8 mm, respectively. The mean LAA ostium length at baseline was 49.4 ± 9.1 mm, with a maximum and minimum size of 24.9 mm and 85.7 mm, respectively. Tables 1 and 2 summarize patients' demographics and the anatomic parameters of the LAA at baseline.

Prevalence of peri-device flow. As shown in Table 3, the vast majority of the 45-day TEEs (419 of 445 patients, 94.2%) were of sufficient quality to be included in the core laboratory analysis. The prevalence of any flow around the device decreased with time from 40.9% at the 45-day TEE, to 33.8% at 6 months, and to 32.1% at 12 months (p = 0.001). Among patients who had documented residual flow, the severity of the flow was minor in only a small percent of patients (7.7%). Moderate and major peri-device flow were most frequent (59.9% and 32.4%, respectively). The mean and maximum width of the leak measured were 2.8 and 6.2

Table 1 Patient Demographics

Age, yrs	72 ± 9
Male	70
Race	
Asian	1
Black	2
White	92
Hispanic	5
Pacific Islander	<1
Other	<1
$CHADS_2$ score	2.2 ± 1.2
$CHADS_2$ score distribution	
1	33
2	34
3	19
4	8
5	4
6	<1

Values are mean ± SD or %.

$CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

Table 2 Baseline Descriptive Anatomy of Left Atrial Appendage

Anatomy of LAA	Baseline TEE
Maximum LAA ostium width, mm	
Mean ± SD	21.9 ± 4.1
Minimum, maximum	12.1, 38.8
Maximum LAA ostium length, mm	
Mean ± SD	49.4 ± 9.1
Minimum, maximum	24.9, 85.7
LAA area measured at 0°, mm^2	
Mean ± SD	580.0 ± 204.8
Minimum, maximum	173.0, 1261.0
LAA pulsed wave peak velocity, cm/s	
Mean ± SD	35.5 ± 18.4
Minimum, maximum	1.4, 117.2

LAA = left atrial appendage; TEE = transesophageal echocardiography.

mm, 2.9 and 6.8 mm, and 2.9 and 6.0 mm, at 45 days, 6 months, and 12 months of follow-up, respectively. This distribution of peri-device flow severity did not appreciably change over the 6- and 12-month timepoints (p = 0.731).

Peri-device flow and clinical outcomes. The primary outcome was determined as a function of both the presence of any peri-device flow as well as the severity of the flow. To the former, the primary efficacy event rate was not significantly different between patients with no peri-device flow (2.8%, or 18 events per 642 patient-years) versus patients with any peri-device flow (2.0%, or 9 events per 450 patient-years; p = 0.635). As shown in Figure 3, there was also no statistical interaction between the severity of the peri-device flow and the primary endpoint. In addition to the primary composite endpoint of the PROTECT AF study, we also assessed a composite embolic endpoint of stroke and systemic embolization. Again, there was no significant statistical relationship between the presence or severity of peri-device flow and this clinical endpoint (Fig. 3).

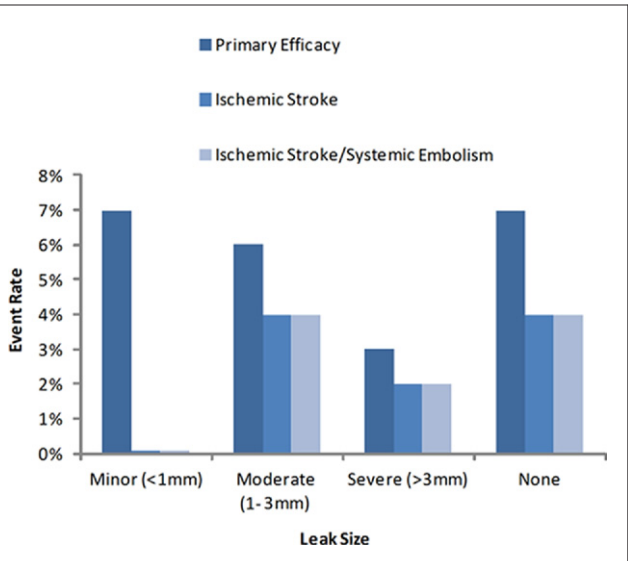

Figure 3 Primary Efficacy Endpoint Rates by Leak Severity

Comparison of primary efficacy **(dark blue bars)**, ischemic stroke **(medium blue bars)**, and a composite endpoint of stroke and systemic embolization **(light blue bars)**, showing no significant statistical relationship between the presence or severity of peri-device flow.

Of the 445 patients who underwent TEEs at 45 days, 59 patients (13%) continued warfarin treatment for some additional period. The reason for continuing warfarin was peri-device flow in 38 patients (64%), physician order in 13 patients (22%), and "other" in 8 patients (14%). For patients who did not continue warfarin, the primary efficacy event rates (expressed as events per 100 patient-years) were 2.1 (7 of 338) for patients with any peri-device flow compared to 2.8 (17 of 601) for patients with no peri-device flow (p = 0.486) (Table 4). When analyzing the events of patients who continued anticoagulation therapy beyond 45 days, the event

Table 3 Prevalence of Peri-Device Flow and Flow Severity On Follow-Up TEE

	45 Days	6 Months	12 Months	p Value
TEE evaluations	445	414	389	
Flow around device filter (%)				
Yes	182 (40.9)	140 (33.8)	125 (32.1)	0.001
No	237 (53.3)	253 (61.1)	249 (64.0)	
Unable to evaluate	18 (4.0)	19 (4.6)	15 (3.9)	
Field not completed	8 (1.8)	2 (0.x5)	0 (0.0)	
If leak present				
Flow severity (%)				
Minor <1 mm	14 (7.7)	4 (2.9)	1(0.8)	0.275
Moderate 1–3 mm	109 (59.9)	84 (60.0)	78 (62.4)	
Major >3 mm	59 (32.4)	52 (37.1)	46 (36.8)	
Flow measurement, mm				
Mean ± SD	2.8 ± 1.0	2.9 ± 1.1	2.9 ± 1.0	0.902
Minimum, maximum	0.9, 6.2	0.8, 6.8	1.1, 6.0	

Values are n, n (%), mean ± SD. *The p values are for tests of differences over time from generalized linear mixed models, accounting for repeated measures on subjects. The models examined prevalence of yes versus no for peri-device flow, prevalence of minor/moderate/major flow, and mean flow measurement.

TEE = transesophageal echocardiography.

Table 4 Primary Efficacy Event Rates According to Peri-Device Flow and Warfarin Use

Group	n	Rate (Events/Patient-Yrs)	Hazard Ratio (95% CI)	Overall p Value
No flow, discontinued warfarin	245	2.8 (17/601)	1.00	0.857
No flow, continued warfarin	18	2.4 (1/41)	0.89 (0.12–6.73)	
Any flow, discontinued warfarin	141	2.1 (7/338)	0.74 (0.31–1.79)	
Any flow, continued warfarin	41	1.8 (2/112)	0.63 (0.14–2.71)	

CI = confidence interval.

rate was 2.4 events per 100 patient-years (1 of 41) for patients without peri-device flow and 1.8 events per 100 patient-years (2 of 112) for patients with peri-device flow (p = 0.802).

Association of peri-device flow size and clinical events. The HR for the primary efficacy events per 1 mm increase in the leak size was 0.84 (95% confidence interval [CI]: 0.62 to 1.14; p = 0.256). For patients who did not continue warfarin, the HR was 0.74 (95% CI: 0.31 to 1.79) for patients with any peri-device flow as compared to patients with no flow (p = 0.509). When compared to patients with no flow, the HRs were 0.85 (95% CI: 0.11 to 6.40), 0.83 (95% CI: 0.33 to 2.09), and 0.48 (95% CI: 0.11 to 2.09) for patients with minor, moderate, and major peri-device flow, respectively (p = 0.798). In sum, there is no clear interaction among either peri-device flow severity or warfarin use and the subsequent risk of clinical events.

Discussion

The main finding of this study is the lack of interaction between residual flow around the LAA closure device and clinical outcome, including thromboembolic events, in a large sample of patients. Patients with peri-device flow did not experience a higher rate of events, and continued anticoagulation therapy did not significantly decrease the primary event rate compared to that of patients who discontinued anticoagulation. Although the results suggest that it might be safe to stop anticoagulation therapy at 45 days regardless of the presence of peri-device flow, these findings should be construed with caution. This retrospective analysis may also be confounded by continued anticoagulation therapy in some patients with residual flow. These data suggest the safety of warfarin discontinuation after Watchman implantation regardless of the presence of the residual peri-device flow, provided that the size of the leak is ≤5 mm. Furthermore, the increased experience of our operators, which has been shown to improve the safety of the procedure (16), should be taken into account when interpreting the results of our study.

The multiple problems associated with anticoagulant therapy have led to a search for alternative approaches for stroke prevention in AF. These approaches are predicated on the fact that in nonvalvular AF, the embolus is thought to originate from the LAA in the majority of cases (4). That has led to a strategy of mechanically excluding the LAA from the systemic circulation (17). Until recently, the benefit of LAA exclusion on reducing stroke risk had not been rigorously compared with anticoagulation therapy in patients with nonvalvular AF. However, the PROTECT AF trial, which demonstrated the noninferiority of LAA closure with the Watchman device to anticoagulation therapy, has sparked intense interest in LAA exclusion strategies. Although a number of complications have been reported associated with endovascular device placement, these are largely experience-related events that have diminished in number and importance with increased operator experience (16). Nevertheless, an issue that remains a concern is the mismatch between the circular device and the typically oval LAA orifice, the subsequent inadequacy of circumferential LAA sealing, and the implications this has for the necessity for ongoing anticoagulation therapy (7).

The problem of incomplete occlusion of the LAA has been reported even when this procedure is performed surgically (7). With any of the surgical techniques, there is a significant risk of incomplete exclusion, ranging from 10% to 72% depending upon the surgical technique utilized and the definition of surgical failure (14,15). There are fewer data on the true closure rates of percutaneously placed devices. In the recently published PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) follow-up study, the investigators report a prevalence of incomplete "closure" of only 10% at 2 months; however, "closure" was defined as successful if the leak was ≤3 mm. Furthermore, these data were largely derived from a few large-volume experiences, and were not independently adjudicated by a core echocardiography laboratory. Indeed, the true closure rate for the PLAATO device—that is, closure as defined as zero flow—may be considerably less than this. In our own experience of 25 patients followed up for 5 years after PLAATO implantation, the true closure rate was only ~25% (submitted for publication) (10,18,19).

The interaction of incomplete occlusion of the LAA and risk of thromboembolism remains poorly understood. All the available evidence comes from small studies using different surgical closure techniques that are usually associated with modified Maze, coronary bypass, or valvular surgery (14,15). Kanderian et al. (20) reported that there

Table 5 Primary Efficacy Event Rates in Patients With and Without Peri-Device Flow

	Any Residual Flow	No Flow	p Value
Efficacy	9/182 (5%)	18/263 (7%)	0.572
Ischemic stroke/systemic embolism	5/182 (3%)	11/263 (4%)	0.669

was no difference of stroke rate among patients with successful closure versus incomplete closure. Perhaps the association of incomplete surgical closure and presence of LAA thrombus may be due to the inherent thromboembolic risk of these surgical patients (valvular disease, Maze procedure, post-operative state). In our analysis, the presence of peri-device flow using the Watchman device was not associated with the development of LAA-related thromboembolic events. Hence, this intracardiac device approach in patients with nonvalvular AF appears to carry a different risk of stroke than after surgery when there is incomplete LAA closure.

Study limitations. It should be underscored that the main limitation of this analysis arises from its retrospective nature and relatively limited number of events, which in turn limits the power of the analysis; that is reflected by the wide confidence interval around the hazard ratio. A study with a larger sample size or a study with higher event rates would likely narrow the confidence interval and make the results more definitive. Therefore, our conclusions should be considered strictly hypothesis generating. Nevertheless, the strength of the data is that this cohort from the PROTECT AF study is the largest sample available, and it is the first report studying stroke risk in patients with incomplete LAA closure. It is also important to recognize that it is not known whether the principles of this study can be applied to other percutaneous device- or suture-based approaches. That is, while it would be reasonable to conclude from these data that minimal leak around the Watchman device does not portend worse prognosis, the same may or may not be true with other devices. Any substantial differences in the anatomical crevices associated with another device (different from the Watchman device) might have a different outcome. Thus, data on leak past the closure strategy should be collected for each new device and approach. Table 5.

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