Left Atrial Appendage Occlusion, A Misnomer?: Where Do We Go From Here?

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Abstract

The importance of the left atrial appendage (LAA) as the source of thromboembolism including stroke in patients with nonvalvular atrial fibrillation is well documented, with more than 90% of ischemic strokes related to a LAA thrombus. Although oral anticoagulation has been the standard of care, approximately 50% to 60% of patients either have contraindications to oral anticoagulation or do not continue the medication beyond the first year. This led to the development of local site-specific therapy to occlude the LAA by either surgical or transcatheter means. Despite marked advancements, incomplete LAA closure with surgical and transcatheter approaches remains frequent. The etiology of incomplete LAA closure and its clinical implications remain unclear. Multiple strategies are in development including changes in deployment techniques, a new device design, and alternative approaches to leak closure.

Atrial fibrillation (AF) occupies an important position in cardiovascular disease related to its prevalence (predicted to affect approximately 15 million individuals by 2030) and the complications associated with it include rapid ventricular response, the potential for tachycardia-induced cardiomyopathy, bradycardia, and very prominently the risk of stroke/systemic embolism (SE). In patients with nonvalvular atrial fibrillation (NVAF), there is a five-fold increase in SE; the triad of increasing patient age, increasing risk of AF, and increased rates of SE is well appreciated by general medicine physicians, family care specialists, cardiologists, electrophysiologists, and geriatricians. Efforts to mitigate the risk of stroke have included oral anticoagulation, surgical and invasive catheter-based approaches, as well as AF ablation. Stroke prevention has been driven by the putative hypothesis that the source of systemic embolism of thrombus in this setting is the left atrial appendage (LAA). Blackshear et al reviewed 23 studies that included imaging, operative, or post-mortem information in 3726 patients. They found that in patients with NVAF, thrombi were isolated to or originated in the LAA in 90% of cases. These findings were replicated by Cresti et al in a contemporary cohort of 1420 consecutive AF patients undergoing transesophageal echocardiography (TEE). Because of these findings, complete occlusion of the LAA would, in theory, markedly decrease ischemic stroke rates in patients at increased risk. These observations led to the development of a class of new percutaneous devices categorized as LAA occlusion. The therapeutic goal would follow that the device should completely occlude the LAA. However, as the field evolved, the goal of complete occlusion has remained remote, with residual flow commonly observed at 1 year in greater than 30% of patients treated with these devices. The etiology of this residual flow may stem from several mechanisms including an undersized device, changing compliance of the LAA ostium during follow-up, or geometric placement of a typically round device in an oval LAA ostium such that obligate flow may remain. Although ongoing efforts have focused on improving the success of achieving complete occlusion, considering the consequences of lesser degrees of occlusion spurs several
questions: 1) What are the clinical consequences of incomplete LAA occlusion? 2) How much residual leak is too much? 3) Is there a leak size response relationship? 4) What are the approaches to treat the leaks and what are the results? and 5) Might new device designs obviate the issue?

EVALUATION AND CONSEQUENCES OF RESIDUAL LEAKS

Surgical Experience
In the surgical field, exclusion of the LAA can be achieved with stapling, clipping, or suture ligation.6-8,12 In some patients, these procedures are part of a surgical maze strategy whereas others are stand-alone interventions. This strategy has yielded variable results for both success rates of surgical closure and the effect on stroke and systemic embolism. In a series of 137 patients who had undergone surgical LAA closure from 1993 to 2004 and then had a TEE after surgery, only 55 (40%) had complete closure at a mean follow-up time of 81±12 months. In the patients with incomplete closure, LAA thrombus was present in 41%, compared to 0% among patients with complete closure. However, clinical outcomes were similar between the two groups. At the time of follow-up echocardiography, patients were assessed for a history of intervening neurologic event since surgery. Of the patients with successful LAA closure, six (11%) had experienced a stroke/transient ischemic attack (TIA), compared with 12 (15%) patients with unsuccessful LAA closure (P=0.61).6 An important caveat relates to the low amplitude number of events which reduces the potential to identify significant differences. In another series of 50 patients who had undergone ligation of the LAA during mitral valve surgery, the LAA remained patent in 18 (36%). Among patients with incomplete occlusion, spontaneous echo contrast or thrombus was seen in nine of the patients (50%), and four of those had experienced thromboembolic events.8 The impact of incomplete surgical closure on longer-term outcome was studied in 72 patients undergoing surgical LAA ligation using an oversewing technique in combination with mitral valve/AF surgery between 2008 and 2012.6 At greater than or equal to 3 months postoperatively, computed tomography (CT) analysis for residual leak showed complete closure in 46 of 72 patients (64%), with incomplete ligation in 17 (24%) or a residual stump in 9 (12%). The overall incidence of SE at a mean follow-up of 44 months was 24% in those patients with incomplete ligation vs only 2% with complete ligation; incomplete closure was the sole predictor of SE in the multivariable analysis. The annualized risk of SE was 6.5% for all the patients with incomplete ligation, 14.4% for those patients not receiving long-term oral anticoagulants (OAC), and 19% for patients with a neck diameter less than or equal to 5.0 mm. The investigators postulated several possibilities. A small neck size of the leak (<5 mm) had the highest rate of SE, perhaps related to greater stasis within the LAA itself if there are prominent trabeculae distal to the site of attempted closure and/or reduced peak LAA emptying velocities. This size relationship has been identified as a predictor of thromboembolic stroke in patients with non-ligated LAAs.13 Taken together, the surgical experience has highlighted the technical challenges of achieving complete closure, with a signal that the clinical implications of incomplete closure are considerable. Newer surgical devices have become more widely used. A meta-analysis of 11 studies...
and 922 patients using AtriClip has been performed. Success rates ranged from 93.9% to 100%. The definition of complete closure varied widely including such descriptors as “absence of a residual stump [greater than or equal to] 10 mms, and placement of the AtriClip to the satisfaction of the cardiology service,” among others.14 With this definition, the ability to document the degree of residual flow is now possible.14 Well-controlled protocol-driven randomized clinical trial (RCT) data are needed.

**Percutaneous Experience, LAA Occlusion Device Experience, and Watchman**

Evaluation of residual leaks with percutaneous LAA occlusion devices remains complex because of a lack of standardization in postdevice assessment. Challenges include 1) differing modalities for leak assessment including both TEE and CT; 2) defining the criteria of what constitutes a significant leak in each modality (>1, 3, or 5 mm); 3) the optimal timing of postimplantation assessment; and 4) device-specific differences. The need for standardization of postimplantation assessment of complete closure cannot be overstated.

The relationship between leak and clinical events with Watchman has been a focus of interest since the initial RCT, Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF). Viles-Gonzalez et al9 evaluated 485 patients following successful implantation of the Watchman device.9 Of these patients, 445 who had not had any efficacy event (no SE) had a 45-day and 1-year TEE with data adjudicated by the echocardiography core lab (Table). In these patients, there was a high prevalence (40.9%) of residual flow into the LAA at 45 days, but this decreased to 32.1% at 1 year (P=0.0001). Potential mechanisms for this decrease in leak size, which has been identified in multiple studies, may be remodeling of the ostium given marked reduction in flow after LAA occlusion or development of fibrosis with some contraction of the ostium itself. There was no relationship between leak size and the composite of stroke, SE, or cardiovascular death. Despite being underpowered, this initial data generated the current rather arbitrary approach that leaks less than 5 mm are believed to be without major clinical consequence and, therefore, did not require any corrective intervention or prolongation of adjunctive anticoagulation. Conversely, leaks larger than 5 mm have been empirically treated with continued anticoagulation. More recently, Afzal et al15 reviewed data on 1039 successful Watchman device procedures. Follow-up data were available in 108 patients who had peridevice leaks (PDLs) at 45 to 90 days following successful implantation with an average leak size of 3.2±1.6 mm (median, 3 mm). The cohort was dichotomized based on whether the leak was less than or equal to 3 mm (n=73) or greater than 3 mm (n=35). This yielded similar TIA or stroke event rates between the two groups — 7 (10%) with leak less than or equal to 3 mm and 2 (6%) with leak greater than 3 mm. However, these data are inherently limited by differences in the management of each group, including continued use of OACs, the presence of device-related thrombus, and use of coil or plug closure of the defect. These limitations in the context of the small sample

| TABLE. Prevalence of Peridevice Flow and Flow Severity on Follow-up TEE\(^ab\) |
|-----------------|---------|--------|--------|--------|
| Residual leaks in PROTECT AF | 45 days | 6 mo | 12 mo | P |
| Patients with TEE evaluations | 445 (100) | 414 (100) | 389 (100) | |
| Flow around device filter | | | | |
| Yes | 182 (40.9) | 140 (33.8) | 125 (32.1) | .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 (0.5) | 0 (0.0) | |

\(^a\)PROTECT AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation study; TEE = transesophageal echocardiogram.
\(^b\)Values are n (%) unless otherwise stated. Evaluation of peridevice flow and flow severity on follow-up TEE in the PROTECT AF trial is from Viles-Gonzalez et al.9
size preclude more definitive conclusions in this patient cohort.\textsuperscript{15}

The most recent data from the Watchman 2.5 investigators evaluated the impact of PDL on 5-year outcomes in 1054 patients enrolled in PROTECT AF, PREVAIL, and Continued Access to PREVAIL (CAP2). All patients had protocol-mandated TEE examinations at 45 days and 1 year. Five-year outcomes were stratified according to the absence or presence of PDL of less than or equal to 5 mm.\textsuperscript{10} At 45 days, 634 patients (60.2\%) had no leak, whereas 404 (38.3\%) had a leak of less than or equal to 5 mm. At 1 year, there had been an increase in patients with no residual leak to 704 (71.6\%) patients during follow-up. The presence of a PDL less than or equal to 5 mm was not associated with an increased risk of the hard endpoints of either all-cause death (HR, 1.90; \(P = .093\)) or cardiovascular/unexplained death (HR, 1.3; \(P = .34\)). In contrast, PDL greater than 5 mm was associated with an increased 5-year risk of ischemic stroke or SE (adjusted HR, 2.0; 95\% CI, 1.2 to 3.3; \(P = .011\)). Disabling/fatal stroke rates were similar; the increased risk was related mainly to an increase in nondisabling strokes (\(P = .033\)). A dose response curve of leak severity was assessed comparing leaks less than or equal to 3 mm, greater than 3 mm to less than or equal to 5 mm, or greater than 5 mm. At 1 year, only small leaks less than or equal to 3 mm and those greater than mm were associated with ischemic stroke or SE.

Since that pivotal study, the Watchman device has undergone multiple iterations with improved structural features that includes increasing the number struts to 18 to provide better anchoring, reducing the area of the metal connector pin aimed at facilitating endothelialization, and manufacturing larger device sizes to accommodate wide LAA ostia (ie, Watchman FLX). An important modification of this later technology included the potential to withdraw and reposition the device on multiple occasions with the goal of optimizing device placement and mitigating the risk of residual leak. In addition, the Watchman FLX has a closed-end configuration which may result in a more complete occlusion. In a subsequent nonrandomized clinical registry of the Watchman FLX, no patient had a leak greater than 5 mm, and 17.2\% had a leak that was 0 to 5 mm in size. At 1 year, with core laboratory assessment, 90\% had no detectable PDL. The incidence of stroke in the entire cohort at 1 year was 2.6\%.\textsuperscript{16}

### Amplatzer
Leak has also been the focus of investigations with another LAA occlusion device, namely, the Amplatzer occluder. In a prospective registry of 339 patients who had LAA occlusion with the initial Amplatzer cardiac plug, Saw et al\textsuperscript{17} documented PDL in 11 patients (19.8\%) (<1 mm in 17 [5\%], 1 to 3 mm in 18 [5.3\%], 3 to 5 mm in 2 [0.6\%], and >5 in 2 0.6\%]). During a median clinical follow-up of ~1 year, PDLs were not associated with increased risk of cardiovascular events.

Similar to Watchman, the Amplatzer device has evolved with a second-generation device (ie, the Amulet device), which is now approved commercially in the United States and Europe. This device was studied in a pivotal trial which randomized 1878 patients to either the Amulet or the initial Watchman 2.5 device.\textsuperscript{11} The primary mechanism of action endpoint was successful LAA occlusion defined as a PDL less than or equal to 5 mm at 45 days using TEE. There was a significant difference in the rate of complete closure between the two devices. There was no residual leak in 63\% of patients randomized to Amulet vs 46\% of those treated with Watchman 2.5, with a residual leak of 0 to 3 mm in 27\% and 29\% of Amulet and Watchman 2.5 respectively; differences which persisted at 1 year.\textsuperscript{18} At 12 months, there was no difference in ischemic stroke (2.5\% and 2.7 \%, respectively for Amulet and Watchman patients). At a later follow-up of 18 months, there were no significant differences observed between the two groups in TIA (15 [1.5\%] with Amulet, and 13 [1.4\%] with Watchman 2.5) or hemorrhagic stroke (3 patients [0.3\%] with Amulet, and 6
patients [0.7%] with Watchman 2.5). The secondary endpoints of stroke, systemic embolism, and cardiovascular death were not different out to 548 days (composite, 5.6% vs 7.7%) and met the noninferiority boundary despite the marked difference in device leak closure rates. More recent registry data has been presented in 300 patients, 150 of whom had been treated with Amulet and 150 with Watchman FLX. Leak was assessed using CT imaging at 8 weeks. Complete occlusion was achieved in 30.5% of patients who had the Amulet device compared with 72.6% with the Watchman FLX with notable differences in the size of the leak between the two devices (Figure 1). The PDL area was greater in those patients treated with Amulet (90 mm²) compared with the Watchman FLX (32 mm²) the clinical impact of which remains to be seen.

Lariat
A third device for LAA occlusion has been studied in this regard. The LARIAT device uses a strategy of endocardial access to identify the specific location of the LAA and use it to guide a pericardial ligature (lasso) to be placed over the LAA. After proper positioning is obtained, the lasso is tightened to occlude the LAA. A multicenter trial of 306 patients evaluated the risk of thromboembolic events after this device with a 4-week TEE revealing leaks in 81 patients (26.5%) all of which were less than 5 mm and were usually central. In this group, 26 patients (32%) underwent leak closure, 34 (42%) were placed on OACs, and 21 (25.9%) had spontaneous closure. At a median follow-up of 15.9±9.2 months, there were nine thromboembolic events (2.9%), seven of which occurred in patients with persistent leaks, whereas two occurred in patients without leaks (P<.001).

MANAGEMENT OF INCOMPLETE LAA CLOSURE
The treatment of patients with residual leaks presents several challenges depending on baseline patient characteristics, the initial occlusion strategy (surgical or transcatheter), the size and location of the leak, the experience of the center, and the specific device (Figure 2). In the early RCTs, continuing anticoagulation was recommended with large leaks (≥5 mm). This option is complicated by the fact that patients have often been selected for LAA occlusion because of relative or absolute contraindications to longer-term anticoagulation. The feasibility of placing another transcatheter device following failed surgical occlusion has been documented. For smaller leaks, detachable coils have been used to close residual leaks after transcatheter and surgical LAA occlusion. A recent multicenter experience of 72 patients with either Watchman devices (53 patients) or surgical LAA (19 patients) has been reported. The baseline leak size was 5.9±1.3 mm, with leaks closed using a variety of strategies including Amplatzer Vascular Plug (AVP-II), Amplatzer Duct Occluder (ADO-II) or, most frequently, with coils (Figure 2). The overall reduction in leak size was 94%, which was maintained. Two patients had subsequent cerebrovascular events — one with a TIA 2-days postprocedure, and the other 10 months later. Further information on optimal closure strategies and the effect of longer-term outcome is needed. The location and etiology of the leak varies depending on the specific device (Figure 3).
CURRENT UNDERSTANDING AND FUTURE DIRECTIONS

Left atrial appendage occlusion was developed to occlude the source of SE in 90% of the patients with NVAF who are at increased risk of stroke. However, rates of incomplete closure with either surgical or interventional techniques approach 30% to 45%, with a signal of increased ischemic stroke risk in that setting. In the three US Food and Drug Administration clinical trials of the Watchman device and the accompanying registry, leaks less than or equal to 5 mm were associated with a two-fold increase in the 5-year risk of ischemic stroke or SE (adjusted HR, 2.0; 95% CI, 1.2-3.3; \( P = .011 \)).\(^{10}\)

Although the relationship between the presence of a leak and increased events in the surgical literature has been accepted, there are less data with percutaneous LAA occlusion. This is complicated by the issues of the definition that has been used, the specifics of the leak in terms of its measurement as an area or the presence of multiple leaks, and lack of any information on characteristics of leak flow. The physiology of flow through the leaks may depend upon multiple issues and may impact subsequent ischemic events. Detailed assessment is further challenged by the low incidence and clinical event rates. The largest study on this issue involves data from the LAA occlusion registry (LAAO) of 51,333 patients undergoing LAA occlusion between January 2016 and December 2019. Even small leaks in this registry were associated with a modest but a statistically significant increase in the rate of ischemic stroke or SE.\(^{28}\)

A central issue in developing a scientifically based strategy relates to the clinical response to identification and documentation...
of a leak. Clinical decisions vary, including addition of anticoagulants if the patient was not on one, prolonged administration of an OAC, antiplatelets, or percutaneous closure with plugs, coils, or occasionally placement of another occlusion device. Each of these may have an impact on subsequent events of stroke and systemic embolization, as well as bleeding in this high-risk cohort.

Mitigating PDL requires the investigation and resolution of several issues. Procedural performance minimizing initial leak by optimizing placement of the current devices will be fundamental. Device improvements will enable more optimal placement, whereas imaging advancements with three-dimensional echocardiography will enable a more thorough device interrogation to ensure mitigation of PDL as much as possible at the time of implantation. Further insights into important technical factors, such as device depth, may also be important, with prior studies showing an association of implant position with device-related thrombus.\(^{29}\) These same concepts may hold for device leak and warrant further investigation.

Identification of the pathophysiology will also be essential to drive strategies for prevention. Anatomic factors including the impact of geometry is important as the devices are circular in contrast to the shape and anatomy of the ostium of the LAA which is more often oval. The development of more geometric and conformable devices may help in that regard. Potentially a self-expanding, more compliant device may be an important design development, although the potential of migration might become an issue. A second issue has been that ostial compliance may change over time as increased compliance could potentially result in increasing leak. Other forward-looking strategies include the increasing interest in using targeted ablation strategies which could be modified to yield the development of fibrosis in the leak area, upon which contracture would seal.\(^{30}\) As the understanding of the pathophysiology and technical advancements continues to improve, so will our understanding of the optimal patient populations that may benefit from targeted interventions.

**FIGURE 3.** Location of the residual jet after left atrial appendage according to the device type. A. With Amplatzer devices, leaks may occur around the edges. B. With LARIAT devices, leaks are typically central. C. With Watchman devices, leaks may occur around the device or through the fabric.
CONCLUSION
Left atrial appendage occlusion by one of several methods including surgical, transcatheter, or combined approaches is being applied in an increasing number of patients and clinical conditions. All of these are based on the premise that embolic episodes, both cerebral and systemic, are the result of thrombus in the LAA in the majority of patients with NVAF. Accordingly, closure of that structure is a cornerstone goal of therapy. To date, success rates of the many approaches in achieving persistent complete closure without any residual flow have been variable. Identification of these small, but significant risks of embolic events in patients with residual flow (leak) has spurred the interest achieving what has always been the initial goal — persistent complete occlusion. This is the focus of multiple new, evolving strategies.

POTENTIAL COMPETING INTERESTS
The authors report no potential competing interests.

Abbreviations and Acronyms: LAA, left atrial appendage; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulants; PDL, peridevice leak; RCT, randomized clinical trial; SE, stroke/systemic embolism; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

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