Left Atrial Appendage and Closure
Who, When, and How

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Abstract—Patients with nonvalvular atrial fibrillation have a 4- to 5-fold increase in strokes and that rhythm may be responsible for 15% to 20% of all strokes, particularly in the elderly. In this setting, thrombus in the left atrial appendage has been found to be the source of stroke in 90% of cases. Although oral anticoagulants have been found effective in reducing stroke rates, for a variety of issues, they may only be used in 40% to 50% of patients at increased risk for stroke. Given pathophysiology of stroke, site-specific therapy directed at left atrial appendage occlusion has been now studied for stroke prevention, and one device is FDA approved (Watchman). A meta-analysis of 2 randomized clinical trials and 2 registries with this device documented the following: (1) patients receiving the device had significantly fewer hemorrhagic strokes (hazard ratio 0.22, \( P=0.004 \)); (2) a significant reduction in cardiovascular or unexplained death (hazard ratio 0.48, \( P=0.004 \)); (3) more ischemic strokes in the device group; however, when periprocedural events were excluded, the difference was not significant; and (4) a significant reduction in nonprocedural bleeding with the device (hazard ratio 0.51, \( P=0.006 \)) versus control. At present, the only device approved in the United States is indicated in patients with nonvalvular atrial fibrillation with acceptable anatomy who are at increased risk for stroke and would be candidates for anticoagulation in whom there is concern about the risk/benefit ratio for chronic anticoagulation. Unresolved issues include optimal patient selection criteria, the role of devices in patients in whom anticoagulation is contraindicated, and the relative role of novel oral anticoagulants versus the device which has not been tested in randomized trials. (Circ Cardiovasc Interv. 2016;9:e002942. DOI: 10.1161/CIRCINTERVENTIONS.115.002942.)

Key Words: atrial fibrillation ■ left atrial appendage ■ randomized controlled trial ■ stroke ■ stroke prevention ■ thrombosis

The left atrial appendage (LAA) has attracted considerable attention given its relationship with atrial fibrillation (AF) and stroke. Early surgical work in the 1940s led to an initial description of “Resection of the Left Auricular Appendix: A Prophylaxis for Recurrent Arterial Emboli.”1 Much later, now with changed terminology, the LAA has been termed our most lethal human attachment.2 This attention has been the result of increased information from several sources, including among others echocardiography, electrophysiology, interventional cardiology, pathology, cardiovascular surgery, and stroke neurology.3-10 It has also come about as a result of increased attention being paid to stroke prevention, risk assessment, and treatment because of its associated major morbidity and mortality. Recent data estimates that the total yearly US costs of stroke which includes healthcare services, medications to treat stroke, and missed days of work are $34 billion.11

One of the earliest more comprehensive pieces of information studied the results of multiple investigations from various which identified the role of the LAA in the pathophysiology of stroke.12-14 Based on echocardiography and autopsy studies in patients with nonvalvular AF, 90% of strokes appeared to be the result of thrombus in the LAA12 (Figure 1). This may be related to inflammation and fibrosis of the wall of the LAA, as well as the specific anatomy of the pectinate muscles. These data and other studies have resulted in the expanded interest in site-specific therapy for stroke prevention in this patient group that could obviate the need for chronic systemic oral anticoagulation. However, it must be remembered that in patients with AF associated with rheumatic mitral valve disease, stroke may result from thrombus in the body of the left atrium itself.12 Obviously, in these latter patients, local LAA therapy would not substantially decrease stroke rates. In addition, it must also be remembered that in some patients with nonvalvular AF, stroke may result from other causes, such as mobile ascending aortic atheroma or carotid arterial disease.

The relationship between AF-related stroke and increasing age has been well delineated.15-16 AF increases the risk of stroke by 4-fold and is responsible for 15% to 20% of all strokes, particularly in the elderly >70 years old. It is confounded by the fact that these geriatric patients are often taking multiple medications, thereby increasing the potential for drug–drug interactions and making long-term anticoagulation problematic. In addition, because these strokes are cardioembolic, they tend to be larger and also have more frequent and severe hemorrhagic transformation with higher rates of recurrence and mortality.17-24
Anticoagulants have been the standard of care for stroke prevention in patients with nonvalvular AF. Warfarin has a long-established record of reducing strokes by ≈60%.31–33 Despite this, it has significant disadvantages. In a National Estimate Survey of Medications implicated in emergency hospitalizations for adverse drug events in older US adults, warfarin was the most commonly implicated medication.34 In actual practice, warfarin is severely underutilized; Lewalter, et al19 identified that even after an AF-related stroke, only 30% to 70% of patients are anticoagulated. Furthermore, at 3 years after initiation of warfarin, only ≈50% of patients remain on the drug. Other problems include the need for frequent blood tests for assessment of international normalized ratio, as well as the requisite frequent adjustments in dose. Finally, the issues of drug–drug and drug–diet interactions are a major disincentive. For these reasons, 5 new oral anticoagulants (NOACs)—either factor Xa inhibitors or thrombin inhibitors—have been developed and tested for the indication of stroke prevention in nonvalvular AF. An increasing number of meta-analyses have been performed with the large data set of randomized clinical trials (RCTs) of these new agents versus standard of care warfarin.36 None of these trials have directly compared any of the new agents head to head. In a meta-analysis of 71 683 patients, Ruff et al36 found that NOACs significantly decreased all-cause mortality (relative risk [RR] 0.90, 95% confidence interval 0.86–0.95) and intracranial hemorrhage (RR 0.48, 95% confidence interval 0.349–0.59), but also significantly increased gastrointestinal bleeding (RR 1.25, 95% confidence interval 1.01–1.55). Despite these favorable results, these agents have still not become dominant in many practices for several reasons, including cost, lack of reversibility strategies if bleeding occurs, and the need for twice daily dosing with some of these agents. In addition, at 2 years, 20% to 25% of patients have discontinued the drugs in the clinical trials.

Despite the favorable outcome of anticoagulant strategies in patients with nonvalvular AF, a large percentage of patients (30%–50%), particularly the elderly, are not treated and therefore remain unprotected and at increased risk of stroke. There are multiple reasons for this—some relate to patient reluctance, some relate to physician concerns about an adverse risk benefit ratio based on assessment of fall risk or frailty, and some based on absolute contraindications to anticoagulation—such as a history of prior central nervous system bleed. The issue of relative or absolute contraindication to either warfarin or one of the NOACs is complex. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT AF)37 evaluated 10 130 patients with AF who were enrolled at 176 sites from 2010 to 2011. In this registry, 13.1% were felt to have a contraindication to either warfarin or dabigatran. Patients with contraindications were older and had a significantly higher incidence of prior stroke, prior MI, chronic kidney disease, peripheral vascular disease, and frailty. These resulted in a higher CHADS2-VASc score (4.3 versus 3.8; P<0.001), as well as a higher risk of bleeding (3.5 versus 2.7; P<0.001). Thus, patients felt to be contraindicated for oral anticoagulants (OAC) were those who also potentially stood the most to gain in stroke prevention. The most common reasons for the impression that anticoagulation was contraindicated were prior bleeding or high bleeding risk, patient refusal, and frequent falls/frailty (Table 1).37 Despite a contraindication to being treated with OAC, 30% were actually taking one. In conclusion, the authors suggested that the perceived benefit outweighed the potential harm posed by the relative contraindication. In actual clinical practice, an unmet clinical need remains for stroke prevention in a large number of patients with nonvalvular AF.

Given the information available on the pathophysiology, there has been great interest in site-specific therapy with occlusion of the LAA; several catheter-based options have been approved and used clinically. Analysis of the worldwide experiences in registries of patients treated with a variety of devices is limited by the constraints of registries themselves. There are only 2 RCTs in the field, and only one device (Watchman) has been the focus of these 2 trials, although others are planned.38–42 The RCTs and accompanying registries led to US FDA approval for this single device.

Figure 1. Surgically excised left atrial appendage (windsock morphology) containing thrombus. Image courtesy of Joseph J. Maleszewski, MD, Mayo Foundation.
Indications for use can be seen in Table 2. A meta-analysis of the 2 RCTs (Watchman Left Atrial Appendage System for Embolus Protection in Patients With Atrial Fibrillation [PROTECT AF] and Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin [PREVAIL]) and the 2 paired registries (continued access protocol [CAP] 1 and CAP 2) included 2406 patients with 5931 patient-years of follow-up (mean follow up of 2.69 years). These cohorts had CHA2DS2-VASc scores ranging from 3.5 to 4.5, while a moderate risk HAS-BLED score (a scoring system that includes hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs or alcohol) was seen in 61.0% to 73.7% of patients. A high-risk HAS-BLED score (≥3) was seen in 19.9% in PROTECT AF and 36.2% in CAP. During follow-up, patients receiving the Watchman device had significantly fewer hemorrhagic strokes (hazard ratio 0.22, 0.15 versus 0.96 events/100 patient-years; P=0.004) and cardiovascular/unexplained death (hazard ratio 0.48, 1.1 versus 2.3 events/100 patient-years; P=0.006). This latter finding of a reduction in cardiovascular/unexplained death with the Watchman device should be noted in comparison with the meta-analyses of the NOACs, which as previously mentioned identified a RR of 0.90 compared with warfarin, which although significant is not of the same magnitude. In the meta-analysis of both PROTECT and PREVAIL, there was also a reduction with the device in the incidence of nonprocedural bleeding (hazard ratio 0.51, 6.0% versus 11.3%; P=0.006) compared with the control warfarin group. As can be seen (Figure 2) in the 2 RCTs, overall efficacy was not different, and all-cause stroke or systemic embolization (SE) was identical. The major difference between device and control was in hemorrhagic stroke. There was an imbalance between ischemic stroke or SE which occurred somewhat more frequently in the device group (P=0.05); however, when periprocedural events were excluded, there was no statistically significant difference in ischemic stroke or SE between the 2 groups. The specific pathogenesis of stroke has important implications because hemorrhagic strokes have the highest morbidity and mortality. In an analysis from the Watchman trials, persistent disability assessed using the modified Rankin score was less in the patients receiving the device. In addition, in an analysis of quality of life, patients treated with the device had improved outcome.

The issue of bleeding continues to be of concern. Price et al assessed a pooled patient-level analysis of the 2 Watchman RCTs of 1114 patients with a median follow-up of 3.1 years to assess the relative risk of major bleeding with device versus warfarin. It must be remembered that as per the protocol,
patients treated with the device are given acetylsalicylic acid-aspirin (ASA) and warfarin for 6 weeks post implantation; at that time, a follow-up transesophageal echocardiography (TEE) is performed, and if device implantation is stable without significant residual leak, the warfarin is discontinued and the patient is treated with ASA and Plavix for a total of 6 months and then ASA alone. In the landmark analysis, Price et al found that LAA closure significantly reduced bleeding beyond the procedural period, particularly when adjunctive dual antiplatelet therapy was discontinued (Table 3).44 Beyond 6 months, the RR of bleeding was 0.28 (1.0 versus 3.5 events/100 patient-years), \( P<0.001 \). This decrease in bleeding was driven by reductions in both gastrointestinal bleeding and hemorrhagic stroke.

The Watchman device is the only approved device in the United States specifically for stroke prevention in this clinical setting. Given this approval, there are several important considerations:

1. Which patients?
2. Procedural setting and operator/site qualifications
3. Specific protocols of care
4. Funding

### Which Patients?

As previously mentioned, the instructions for use45 is reasonably broad in terms of patient selection criteria. However, the device is not intended to be a broad replacement for OAC. Balancing the risk benefit ratio is an inexact science. In clinical practice, information from the Watchman registries may aid in what the clinical practice may look like.41,43 These registries which occurred after closure to enrollment in the RCTs reflected more real-world practice patterns and included 1145 patients. In these patients, the CHA2DS2-V ASc score ranged from 3.9 to 4.5, and 61.0% to 69.9% of patients had HAS-BLED scores of 1 to 2, indicating moderate risk for bleeding, whereas 28.3% to 36.2% had HAS-BLED scores of \( \geq 3 \), indicating high risk. Given that these 2 registries reflected actual experience with established experts and centers in the field, these patient characteristics in terms of risk/benefit ratio may be a guide to practice and patient selection. It must be remembered that patient preference and physician experience both play important roles here. In most patients, protection from stroke is dominant, but for many patients, the chance to avoid chronic anticoagulation with the potential for bleeding is also a major factor.

An important group of patients to be considered are those in whom anticoagulation is felt to be contraindicated. As previously mentioned, that occurred in 13.1% in the ORBIT Registry. These patients would be a group in whom a Watchman would be a potential excellent device. Unfortunately, there is no randomized trial data to guide

### Table 3. Major Bleeds After 6 Months After the Index Procedure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N, % (LAA Closure)</th>
<th>N, % (Warfarin)</th>
<th>HR (95% CI)</th>
<th>( P ) Value</th>
<th>( P ) Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤75 y</td>
<td>1.4 (6/436)</td>
<td>7.8 (17/217)</td>
<td>0.17 (0.147–0.196)</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>4.4 (13/296)</td>
<td>10.9 (18/165)</td>
<td>0.43 (0.264–0.701)</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Female</td>
<td>1.8 (4/224)</td>
<td>12.0 (13/108)</td>
<td>0.17 (0.074–0.369)</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>3.0 (15/508)</td>
<td>8.0 (22/274)</td>
<td>0.35 (0.320–0.393)</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Modified HAS-BLED &lt;3</td>
<td>1.4 (8/561)</td>
<td>7.9 (23/291)</td>
<td>0.17 (0.173–0.174)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Modified HAS-BLED ≥3</td>
<td>6.4 (11/171)</td>
<td>13.2 (12/91)</td>
<td>0.55 (0.282–1.070)</td>
<td>0.078</td>
<td>0.001</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≤4</td>
<td>1.8 (10/551)</td>
<td>8.5 (22/258)</td>
<td>0.21 (0.138–0.321)</td>
<td>&lt;0.001</td>
<td>0.289</td>
</tr>
<tr>
<td>CHA2DS2-VASc &gt;4</td>
<td>5.1 (9/178)</td>
<td>10.7 (13/121)</td>
<td>0.47 (0.161–1.378)</td>
<td>0.17</td>
<td>0.289</td>
</tr>
<tr>
<td>No Hx TIA/Stroke</td>
<td>2.3 (13/570)</td>
<td>8.9 (26/292)</td>
<td>0.26 (0.216–0.305)</td>
<td>&lt;0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>Hx TIA/Stroke</td>
<td>3.7 (6/162)</td>
<td>10.0 (9/90)</td>
<td>0.35 (0.102–1.225)</td>
<td>0.10</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CHA2DS2-VASc indicates a score that includes clinical baseline factors of age, sex, history of congestive heart failure, hypertension, stroke/TIA/thromboembolism, vascular disease and diabetes; CI, confidence interval; HAS-BLED, a scoring system that includes hypertension, abnormal renal and liver function, stroke, bleeding, table INRs, elderly, drugs or alcohol; HR, hazard ratio; Hx, history; INR, international normalized ratio; LAA, left atrial appendage; and TIA, transient ischemic attack.
practice in this patient group. The largest published experience in this group with the Watchman device is the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP) trial, which prospectively evaluated Watchman implantation in 150 patients in whom OAC was contraindicated.46 These patients were instead maintained on 6 months of thienopyridine, as well as lifelong ASA. At a mean follow-up of 14.4 months, there was approximately a 75% reduction in the observed versus expected (based on baseline CHADS2 score) event rate; in this group with a follow-up of 176.9 patient-years, there were 1.7 events/100 patient-years (Figure 3). This group of patients is the focus of a planned worldwide randomized trial of Watchman.

**Procedural Setting and Operator Experience**

Safety considerations with increased adverse events were documented in the PROTECT AF trial. These primarily consisted of pericardial effusions which, although not resulting in mortality, did increase the hospital duration of stay. These safety concerns were addressed in an analysis of a combined group of 542 patients from PROTECT AF and the accompanying nonrandomized continued access protocol of 460 patients.41 Across these 2 patient groups, there was a significant decline in the rate of procedural or device-related safety events within 7 days of the index procedure. Between PROTECT AF and CAP, the rate of serious pericardial effusions decreased from 5.0% to 2.2% (P=0.019), whereas the procedure-related stroke rate decreased from 0.9% to no events (P=0.039; Figure 4). A part of this analysis evaluated the functional impact of safety events as defined by significant disability or death. Using a change in modified Rankin score as the metric, patients in the Watchman group had superior outcome compared with the control group.

Further information on the safety profile of the Watchman device was obtained in the second RCT—PREVAIL.42 Periprocedural safety events occurred in 2.2% of patients in the device limb—significantly better than had been documented in PROTECT AF. Specifically, pericardial effusions treated with urgent cardiovascular surgery decreased from 1.6% to 0.4% (P=0.027), and the frequency of pericardiotomy decreased from 2.9% to 1.5% (P=0.36). The composite data from the RCTs and Registries indicate both significantly

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**Table 4. Minimum New Operator Procedural Experience Required: Physician Training Program**

<table>
<thead>
<tr>
<th>Training as a primary operator</th>
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<tr>
<td>Must have completed a minimum of 25 transeptal (TS) procedures, with at least 10 of those occurring over the most recent 12 mo period</td>
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<table>
<thead>
<tr>
<th>Training as a secondary operator</th>
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<tbody>
<tr>
<td>If a physician has completed a minimum of 10 TS procedures and has a physician who meets the minimum TS requirements willing to scrub-in as a partner and mentor, that physician may enroll in the Watchman training program</td>
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</tbody>
</table>

| The trainee physician will only be certified as a Secondary Operator until such time as he/she has partnered with a qualified physician to achieve the minimum requirements as a Primary Operator |

**Table 5. Hospital Infrastructure**

<table>
<thead>
<tr>
<th>Dedicated interventional/heart team to support Watchman procedures including:</th>
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<tbody>
<tr>
<td>Interventional/heart team coordinator</td>
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<tr>
<td>Dedicated echocardiologist</td>
</tr>
<tr>
<td>Anesthesiology procedure support (general anesthesia)</td>
</tr>
<tr>
<td>Cardiac surgery back-up</td>
</tr>
<tr>
<td>Experience and teamwork approach in performing other complex interventional cardiac procedures</td>
</tr>
<tr>
<td>Transcatheter aortic valve replacement</td>
</tr>
<tr>
<td>Atrial septal defect/Patent foramen ovale</td>
</tr>
<tr>
<td>Mitral valve interventions</td>
</tr>
<tr>
<td>Ablation procedures</td>
</tr>
<tr>
<td>Other left atrial appendage closure procedures</td>
</tr>
</tbody>
</table>

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**Figure 3.** The ASAP trial registry included 150 patients in whom anticoagulation was felt to be contraindicated. The observed rate of events was compared with the expected rate based on the baseline CHADS2 score. There was a 77% reduction from the expected event rate. ASA indicates acetylsalicylic acid-aspirin; ASAP, ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology; and CHADS2, a score that includes clinical baseline factors of age, history of congestive heart failure, hypertension, stroke/TIA/thromboembolism, vascular disease and diabetes; and TIA, transient ischemic attack.

**Figure 4.** The event rate in patients treated with the Watchman device has progressively declined from the initial PROTECT AF trial to the PREVAIL trial. CAP indicates continued access protocol; LAA, left atrial appendage; PREVAIL, Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin; and PROTECT AF, Watchman Left Atrial Appendage System for Emboli Protection in Patients With Atrial Fibrillation.
improved safety along with documented efficacy in hard clinical end points.

The operator experience and procedural setting are other crucial elements. After FDA approval, working in concert with the regulatory agencies, training requirements have been developed for new operators as well as the components of the hospital infrastructure. Similar to other structural heart disease interventions, the recommendations include details of the heart concept embracing both interventional cardiology and electrophysiology disciplines along with expert echocardiography (Tables 4–6). These include criteria for the number of cases required or recommended as either primary or secondary operator. In addition, details about optimal hospital infrastructure were outlined, including members of the Heart Team focused on LAA occlusion including the implanting physician, either or both interventional cardiology and electrophysiology, as well as imaging specialists. Finally, the recommendation has been to develop shared decision-making tools so that the patients can be more fully informed about alternatives to their specific case and facilitate their role in patient-centric care.

The key role of echocardiography has been repeatedly emphasized to optimize patient selection criteria and then enhance procedural performance. TEE is the routine imaging approach. It is essential for screening to identify the potential presence of LAA thrombus as well as in identifying details of the other cardiac chambers and specifically identifying the intraatrial septum. In addition, details of the LAA in terms of number of lobes, the size of the ostium, its angulation, and depth can be studied. The specific shape of the LAA has been evaluated, and 4 specific shapes have been identified. Identification of the specific shape may help the operator plan the procedure in terms of size and access and thereby optimize the success rate of implantation. Computed tomography is also used in some patients before the procedure to assess the detailed features of the LAA and its relationship to other cardiac structures.

Intraprocedural guidance is typically performed with TEE (Figure 5). Both TEE and conventional angiography provide complementary data and are essential parts of the procedure. Guidance of the site for transseptal puncture is important because a position low and posterior in the intraatrial septum at least for Watchman implantation is needed to optimize intubation of the LAA and placement of the device. TEE is also used to measure the dimensions of the ostium and the length of the LAA and identify the lobe into which the device is optimally placed as well as to identify the angles most useful for device placement. It is also essential in confirming an adequate placement, including the presence and extent of device leak and stability of the device placement (Figure 6). In some institutions, intracardiac ultrasound is also used to obtain similar information about the LAA diameter, size, and shape, including identification of multiple lobes and adequacy and stability of device placement.

Although the most scientifically controlled data with RCTs and carefully managed registries have been obtained with the Watchman device, there is a significant amount of registry information with a second LAA occlusion device. The Amplatzer Cardiac Plug (ACP) is a self-expandable device which has demonstrated favorable results. The largest series is the European multicenter experience obtained from 22 centers and included 1047 consecutive patients being treated with the ACP device between December 2008 and November 2013. All patients were included in this dedicated database without roll-in subjects, though it should be acknowledged that the majority of operators did have prior experience with device implantation.

In this series, follow-up was complete in 98.2% of successfully implanted patients at an average of 13 months. Importantly, the recommendation for postprocedural care was ASA 80 to 100 mgm and clopidogrel 75 for 1 to 3 months and then ASA 80 to 100 mgm for ≥3 months. However, as the article points out, this was individualized and varied between patients, physicians, and centers.

There were common definitions used in this multicenter experience. Procedural success was successful implantation of the ACP device in the LAA. Periprocedural adverse events included death, myocardial infarction, stroke, TIA, SE, air or device embolization, significant pericardial effusions or tamponade, and major bleeding. Adverse events during follow-up included all-cause mortality, stroke/TIA, systemic embolism, and major bleeding. The primary end point was device efficacy to prevent stroke, TIA, and systemic embolism.

The baseline characteristics including CHA2DS2-VASc and HAS-BLED scores of this large registry can be seen in
Table 7. Procedural success was achieved in 97.3%. Major adverse events were documented in 4.97%, whereas other adverse events were seen in 1.53%; cardiac tamponade was seen in 1.24%, stroke in 0.86%, and device embolization in 0.77%. The effectiveness and safety were estimated based on the baseline CHA2DS2-VASc score and HAS-BLED score (Figure 7). As can be seen, the estimated stroke rate was 5.62%/y and was reduced with the device by 59%/y to 2.30%/y. In terms of bleeding, there was a reduction in the observed to expected rate by 61%, with the actual annual major bleeding rate being 2.08%. Based upon these favorable results, a large RCT is to be implemented.

Residual Issues

Multiple residual issues remain in the field despite these 2 large data sets.

1. What is the impact of residual leak around the device? It must be remembered that the current devices are circular but the origin of the LAA is typically oval. The data concerning the impact of peri-device leak is limited. In the field of surgical ligation, residual leaks are associated with a higher risk of recurrent stroke or systemic embolism. In a subset of PROTECT AF, residual leaks were identified overall in 32% but were typically minor and <1 to 3 mm. There was a lack of interaction between residual flow and clinical outcome; that is, residual peri-device flow was not associated with an increased risk of thromboembolism. With ACP, residual leak was identified in 11.6% but also did not correlate with adverse follow-up events. However, additional studies are required to substantiate these findings, and better devices need to be developed to more reproducibly completely occlude the orifice.

2. The specific patient population to be selected. The RCT trial data included only patients who could safely receive warfarin for 45 days. However, registry data with both devices document excellent efficacy.

Table 7. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=1047</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75±8</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>939 (90)</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>577 (55)</td>
</tr>
<tr>
<td>Male</td>
<td>648 (62)</td>
</tr>
<tr>
<td>AF: permanent</td>
<td>594 (57)</td>
</tr>
<tr>
<td>AF: paroxysmal/persistent</td>
<td>453 (43)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>274 (26)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>909 (87)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>306 (29)</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>404 (39)</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>87 (8)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>367 (36)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>4.5±1.6</td>
</tr>
</tbody>
</table>

0 | 2 (0.2) |
1 | 17 (1.6) |
2 | 99 (9.5) |
3 | 181 (17.3) |
4 | 243 (23.2) |
5 | 246 (23.5) |
6 | 153 (14.6) |
7 | 75 (7.2) |
8 | 24 (2.3) |
9 | 7 (0.7) |

Annual risk of thromboembolism, % | 5.7±2.8 |
HAS-BLED score | 3.1±1.2 |
0 | 7 (0.7) |
1 | 78 (7.5) |
2 | 218 (20.8) |
3 | 387 (37.0) |
4 | 225 (21.5) |
5 | 94 (9.0) |
6 | 36 (3.4) |
7 | 1 (0.1) |
8 | 1 (0.1) |

Annual risk of major bleeding, % | 5.4±3.8 |

AF indicates atrial fibrillation; CHA2DS2-VASc, a score that includes clinical baseline factors of age, sex, history of congestive heart failure, hypertension, stroke/TIA/thromboembolism, vascular disease and diabetes; HAS-BLED, a scoring system that includes hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol; INR, international normalized ratio; and TIA, transient ischemic attack.
and safety compared with expected rates based on baseline CHA2DS2-VASc scores in patients in whom anticoagulation is contraindicated. Accordingly, the OAC-contraindicated patient population is currently the focus of the next Watchman device RCT.

3. The basic patient selection criteria should include patients at increased risk for stroke or SE in whom there is concern about the safety of chronic anticoagulation because of anticipated bleeding risk. At the present time, there will be a fundamental difference between the 2 devices. On-label use of the Watchman device (mandated in the United States) will include the recommendation for warfarin for 45 days to facilitate device endothelialization but subject to individualization globally. For the Amplatzer ACP device, not available in the United States, the practice pattern will recommend dual antiplatelet therapy initially followed by ASA. Whether this practice will be confirmed in a randomized trial remains to be seen.

4. The impact of NOACs. It is important to recognize that although there is substantial data to suggest either the superiority, or at least noninferiority, of Watchman over warfarin, there is no randomized data comparing Watchman or any other LAA closure device to the NOACs. The ease of use and improved hemorrhagic stroke rates associated with NOACs, combined with clinical data involving tens of thousands of patients, all lead to the undeniable conclusion that NOACs should be strongly considered as a first-line approach to stroke prevention in AF. Moreover, there are still substantial number of patients who will prove to be poor candidates for long-term treatment even with the NOACs; these patients may benefit from device-based LAA closure. But ultimately, it will be necessary to conduct RCTs of NOACs versus mechanical LAA closure in selected patient populations.

5. An additional residual issue or new frontier relates to the relationship between LAA occlusion and pulmonary vein isolation. The later has become a treatment of choice for an increasing number of patients with AF, although its role for stroke prevention remains unproven. Indeed, in practice and reflected in the guidelines, anticoagulation is used after AF for at least a relatively short period of time, and in patients at high risk for stroke, anticoagulation may be considered indefinitely. With those issues in mind, combining pulmonary vein isolation with LAA occlusion might potentially be an approach to prevention of stroke as well as ablation of AF. Small series have now been reported using this combination. Calvo et al evaluated the approach in 35 patients who had a median CHA2DS2-VASc and HAS-BLED score of 3.

6. Finally, there are several other devices which have received CE Mark (Conformité Européenne) approval and have been evaluated in small series. The eventual role of these devices in the United States is difficult to determine. RCTs will undoubtedly be required for FDA approval. The specifics of these trials remain to be seen. Some of them may be head to head trials against an approved device such as Watchman, whereas some may be studied against NOACS or in different patient groups, such as those who have contraindications to OAC. The end points of these trials will be important, for example, will 5 years end points be required or will the end point be all-cause stroke or just hemorrhagic stroke. Resolution of these issues will have a major impact on the field. In addition, a hybrid approach using both pericardial and endocardial access has been studied in registry experiences. The largest US study to date evaluated outcome in 154 patients at 8 sites. The primary end point was procedural success and no major complication at discharge. Device success was documented in 94% and procedural success in 86%. A significant pericardial effusion was seen in 16 patients (10.4%), whereas major bleeding requiring transfusion was documented in 9.1%. The role of this composite transseptal/transpericardial approach continues to evolve.

7. A final issue relates to reimbursement for LAA occlusion. In the United States, coverage has been variable depending on local and regional carriers. In some regions, coverage is granted according to the FDA instructions for use. In other regions, there has been a policy of either limited or no coverage. A proposed National Coverage Determination has been published by Centers for Medicare and Medicaid Service. Exact final details
of this National Coverage Determination will have major implications for all devices targeting LAA occlusion.

Summary

In summary, stroke prevention is one of the major goals in the management of patients with nonvalvular AF. Systemic anticoagulation with warfarin while very effective has multiple limitations; the advent of the NOACs has considerably expanded the options for pharmacological stroke prophylaxis in AF. However, there are still many patients who are poor candidates for long-term or in some cases even short-term oral anticoagulation, and it is these patients who may benefit from mechanical LAA closure. The majority of the clinical evidence is derived from the Watchman randomized trials, which demonstrated that as compared with warfarin, LAA closure results in equivalent reduction in all strokes, ≈80% reduction in hemorrhagic strokes, ≈50% reduction in cardiovascular deaths, and ≈50% reduction in late major bleeding. However, it should also be remembered that procedure-related complications do occur, though these have become less frequent with improved operator experience. Future clinical trials will provide more information regarding the safety and efficacy of other LAA closure devices, the role of LAA closure in OAC–contraincipated patients, and the comparative benefits of LAA closure with novel OAC.

Disclosures

Both Mayo Clinic and Dr Holmes have a financial interest in technology related to this research. That technology has been licensed to Boston Scientific. Dr Reddy has received grant support and has served as a consultant to Boston Scientific, Coherex, and St Jude Medical.

References


