Left Atrial Appendage Occlusion Debate Revisited

Richard P. Whitlock, MD, PhD, FRCSC; Jeff S. Healey, MD, MSc, FRCPC, FHRS; David R. Holmes, MD

The left atrial appendage (LAA) has been deemed by some to be our “most lethal attachment,” and the concept of excluding it from systemic circulation has been thought to hold great promise. This concept has been around since 1948, when John Madden1 proclaimed it a plausible therapy for recurrent emboli in atrial fibrillation. Despite this, high-quality evidence in the field is only just emerging.

In 2009, we were asked to debate on the topic “Does left atrial appendage occlusion eliminate the need for warfarin?” Dr Holmes represented the protagonist viewpoint,2 while Dr Whitlock represented the antagonist viewpoint.3 The protagonist viewpoint was based on 3 key points to support the position that LAA occlusion can replace warfarin. First, the dominant source of stroke in patients with nonvalvular atrial fibrillation (AF) is cardioemboli, of which >90% are from the LAA.4 Second, oral anticoagulation (OAC) therapy requires long-term use, good control, and ongoing compliance to be effective. Warfarin is underused, is difficult to maintain in therapeutic range, and increases bleeding risk. On the contrary, LAA occlusion is a 1-time procedure that requires no long-term compliance. Third, the imbalance of safety that favored warfarin over the Watchman device in the Watchman LAA Closure Technology for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) clinical trial was driven by periprocedural events, which were thought to be decreasing with experience.5 The antagonist viewpoint raised 3 key points to support the position that LAA occlusion could not yet replace warfarin therapy. First, the success and safety of LAA occlusion were as yet incompletely understood. Second, the longer-term protection from stroke related to leaks around occlusion devices had not been shown, and the surgical literature suggests that these leaks may contribute to recurrent events.6 This has important implications for LAA occlusion with devices because some degree of peridevice flow has been observed in up to one third of patients.7 Third, local control of stroke may be insufficient given the coagulation and platelet disorders and atherosclerotic burden observed in AF patients, all of which could contribute to stroke from sources other than the LAA.8–10

Since 2009, the field of stroke prevention in AF has continued to advance. In fact, now the question is better posed as, “Does left atrial appendage occlusion in nonvalvular AF eliminate the need for oral anticoagulation?” Nonvalvular is highlighted because the extrapolation of any of the occlusion data to valvular AF patients is dangerous, given the existing data that left atrial thrombi occur more frequently outside the LAA in such patients.11 Thus, this article focuses on the nonvalvular AF patients in whom the dominant occlusion therapy is currently catheter based. Oral anticoagulation is highlighted because, since the publication of our original debate articles, 4 trials of novel oral anticoagulants (NOACs) in AF versus warfarin have been published, reporting on >70,000 patients.12–15 These trials have confirmed that NOACs overcome many of the traditional limitations of warfarin. They are easy to use, have fewer drug-drug interactions, and have a substantially lower rate of intracranial hemorrhage, and 2 NOACs have a lower rate of major bleeding compared with warfarin.16 Although there are relatively few stroke events in trials of LAA occlusion, evidence has also continued to emerge. The impact of this new evidence on the field is described in the following sections, which address the major points raised in our debate positions.

Safety of LAA Occlusion for Stroke Prevention

The PROTECT AF trial demonstrated that the Watchman device was noninferior to warfarin for the primary efficacy endpoint of stroke (either ischemic or hemorrhagic), cardiovascular death, or systemic thromboembolism using a noninferiority margin of a 2-fold increase.3 However, there was an increase in early adverse events in the device arm that included periprocedural stroke and periocular effusion. Holmes et al3 hypothesized that the periprocedural risk would decrease as experience with the device was gained, and this has been the case.

Two studies have been published that report on the longer-term experience with and safety of the Watchman device. The Continued Access Protocol (CAP) was a US Food and Drug Administration investigational devices exemption registry 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.17 The registry was nonrandomized but had the same inclusion and exclusion criteria and procedure/treatment protocol as PROTECT AF. It included 460 patients from 26 centers. The data from this registry were combined with those from PROTECT AF and demonstrated that there was a significant decrease in the periprocedural complications.17 The rate of serious pericardial effusion decreased from 27 of 542 (5.0%) in PROTECT AF to 10 of 460 (2.2%; P=0.019) in the CAP registry, and periprocedural stroke decreased from 5 of 542 (0.9%) to 0 of 460 (0%; P=0.039).
The second study was the Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial. This randomized trial was designed to document improved safety and to confirm the efficacy of the Watchman device demonstrated in the PROTECT AF trial. A total of 407 patients were randomized 2:1 to device versus warfarin control. The PREVAIL trial met the prespecified criteria for the coprimary safety end point (procedure-related safety <7 days): The observed adverse event rate was 6 of 269 (2.2%), resulting in an observed upper bound of 2.65%, which was less than the prespecified criterion of 2.67% (95% confidence interval [CI]). However, the PREVAIL trial did not meet the prespecified criteria for the first coprimary end point (efficacy of all stroke, cardiovascular death, and systemic embolism at 18 months). The observed adverse event rate at 18 months for both Watchman group and the control group was 0.064, resulting in a rate ratio of 1.07 for device versus control. The observed upper bound of the rate ratio was 1.89, slightly greater than the prespecified criterion of 1.75 (95% CI). The rate for the second coprimary efficacy end point (stroke or systemic embolism >7 days after randomization) was 0.0253 versus 0.0200 (risk difference, 0.0053; 95% credible interval, –0.0190 to 0.0273), achieving noninferiority. All patients will undergo 5 years of follow-up.

It is evident from CAP and PREVAIL that the safety of device implantation has improved; however, the safety will never be same as the short-term safety of no procedure. The comparison must be with the longer-term risks imposed by ongoing OAC (Table 1).

### Efficacy of LAA Occlusion for Stroke Prevention

The crux of the hypothesis that LAA occlusion is as effective as OAC in stroke prevention is that the dominant source of strokes in patients with nonvalvular AF is the LAA. This is supported by echocardiography and postmortem studies; however, the only way to prove this hypothesis with confidence is with continued follow-up of patients randomized to either therapy. In 2013, the 2.3-year follow-up of the PROTECT AF patients was published, and the final 4-year follow-up was presented as a late-breaking clinical trial at the Heart Rhythm Society meeting. At the 2.3-year follow-up, the primary efficacy event rates with the device remained noninferior to warfarin control: 3.0% per year (31 events per 1025.7 patient-years) with device versus 4.3% (24 events per 562.7 patient-years) in the control group (rate ratio, 0.71; 95% CI, 0.44–1.30)\(^\text{19}\) (Table 2). Importantly, the final 4-year follow-up of PROTECT AF changed the findings and conclusions.

### Table 1. Bleeding and Discontinuation of OACs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Discontinuation Rate in the Study, %</th>
<th>Major Bleeding Rate per Year, %</th>
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<tr>
<td>Dabigatran (150 mg)</td>
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<td>2.1</td>
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<tr>
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<td>34</td>
<td>2.8</td>
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OAC indicates oral anticoagulant.

After an aggregate of 2621 patient-years, superiority criteria of device over warfarin were met for the composite efficacy outcome. There were 2.3 events per 100 patient-years in the Watchman group compared with 3.8 in the warfarin group (hazard ratio, 0.61; 95% CI, 0.38–0.97; \(P=0.0348\); Figure).

There were fewer fatal or disabling strokes in the device group (relative risk, 0.37). Finally, the composite primary safety events between the 2 groups were noninferior (relative risk, 1.17; 95% credible interval, 0.78–1.95).

The longer-term follow-up of the PROTECT AF patients has contributed significantly to demonstrating that the LAA is a dominant source of stroke in patients with nonvalvular AF. With this proof of concept for this population, further data are required in other patient populations such as patients with valvular AF and patients in whom OACs are contraindicated.

### Impact of NOACs on the Field of Stroke Prevention

Warfarin remains the most commonly prescribed OAC; however, this distribution is dynamic as more NOACs emerge and evidence around efficacy and safety mounts. Since 2009, >70,000 patients have been randomized in trials examining the NOACs. Table 3 summarizes these trials examining dabigatran, rivaroxaban, apixaban, and edoxaban. All 4 medications have been shown to be at least as effective as warfarin, with fewer major bleeding events.\(^\text{20}\) In fact, on the basis of the available evidence, some guideline panels now recommend using the NOACs in preference to warfarin when OAC therapy is initiated in patients with AF.\(^\text{21}\)

There remains little doubt that the NOACs have improved care for patients with AF. Does this eliminate the need for alternative therapies such as mechanical occlusion of the LAA? No. Limitations of NOACs still exist, and this will likely be the case for any antithrombotic. These limitations are increased risk of bleeding; patient noncompliance with OACs, a problem with all long-term medications; nonprescription or permanent discontinuation of therapy, especially in elderly patients; and frequent need for therapy discontinuations for surgery, procedures, and diagnostic tests.

Increased bleeding is inherent in all antithrombotic therapy. For example, in the recent Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial, the annual rates of major bleeding were 3.4%, 2.7%, and 3.1% for dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, and warfarin, respectively, and minor bleeding rates were 13%, 15%, and 16% per year. Major bleeding is serious. One of the biggest problems with bleeding, major or minor, is that it often leads to permanent discontinuation of antithrombotic therapy, even when the immediate cause of bleeding appears to be controlled; fear of rebleeding is a very strong emotion for many patients and physicians. Table 1 presents the discontinuation rates of NOACs in the major trials. Discontinuation rates include permanent discontinuation because of adverse events and temporary stoppage for surgical procedures and the like. Permanent discontinuation would have greater implication than temporary discontinuation; however, any stoppage exposed the patients to a window of risk.

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**Table 1.** Bleeding and Discontinuation of OACs

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OAC indicates oral anticoagulant.
Table 2. Results of the 2.3-Year Follow-Up of PROTECT AF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Device, events/100 patient-y (95% CrI)</th>
<th>Control, events/100 patient-y (95% CrI)</th>
<th>Rate Ratio, Device/Control (95% CrI)</th>
<th>Noninferiority Probability*</th>
<th>Superiority Probability†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>3.0 (2.1–4.3)</td>
<td>4.3 (2.6–5.9)</td>
<td>0.71 (0.44–1.30)</td>
<td>&gt;0.99</td>
<td>0.88</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.9 (1.1–2.9)</td>
<td>1.4 (0.6–2.4)</td>
<td>1.30 (0.66–2.60)</td>
<td>0.76</td>
<td>0.18</td>
</tr>
<tr>
<td>Cardiovascular/ unexplained death</td>
<td>1.0 (0.5–1.8)</td>
<td>2.8 (1.5–4.2)</td>
<td>0.38 (0.18–0.85)</td>
<td>&gt;0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.3 (0.1–0.7)</td>
<td>1.2 (0.5–2.3)</td>
<td>0.23 (0.04–0.79)</td>
<td>&gt;0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.3 (0.1–0.7)</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>All stroke</td>
<td>2.0 (1.3–3.1)</td>
<td>2.7 (1.5–4.1)</td>
<td>0.77 (0.42–1.62)</td>
<td>&gt;0.99</td>
<td>0.73</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.2 (2.3–4.5)</td>
<td>4.5 (2.8–6.2)</td>
<td>0.71 (0.46–1.28)</td>
<td>&gt;0.99</td>
<td>0.85</td>
</tr>
</tbody>
</table>

CrI indicates Credible Interval; and PROTECT AF, Watchman LAA Closure Technology for Embolic Protection in Patients With Atrial Fibrillation.

*Using a 2-fold noninferiority margin based on the ratio of primary efficacy event rates.
†Significance based on posterior probabilities for superiority exceeding 95%.

Patient noncompliance is a major limitation inherent to all long-term prophylactic medical therapy, including warfarin and the NOACs. In a major review of medication compliance for cardiovascular disease, it was estimated that 25% to 55% of patients do not take their long-term cardiac medications as prescribed. Medication adherence for asymptomatic or long-term conditions is typically lower than that for acute or symptomatic conditions and drops substantially after the initial months of therapy. Nonadherence is strongly skewed toward underdosing rather than overdosing and is associated with an increased risk of death, disability, hospitalization, and avoidable healthcare costs. A recent study of point-of-care testing in 53 Australian general practices is instructive. The study included patients who required OAC, and only 43% of patients on anticoagulants reported consistent adherence to therapy during the study. There is also substantial evidence that physicians underestimate the degree of medication noncompliance even in patients whom they “know well.” Compliance issues continue to be a problem with all medications and may have a bigger problem with new anticoagulants than with warfarin because of the short half-lives and lack of need for regular monitoring.

Many patients do not receive OACs. In the Canadian Cardiovascular Outcomes Research Team (CCORT) AF study, using prescription claims databases in Alberta, British Columbia, and Ontario from 1997 to 2000, researchers discovered that fewer than one half of AF patients filled a prescription for warfarin within 90 days of discharge after an AF hospitalization. After initiation of warfarin, discontinuation is very common. Using a large administrative database registry from the United Kingdom, Gallagher et al reported warfarin discontinuation rates of 50% within a 4-year follow-up period. A very recent analysis of Ontario Drug Benefit claims data in 125,195 patients >65 years of age with AF who initiated warfarin therapy found that almost one third (31.8%) discontinued warfarin within 1 year of initiation and that the median time to discontinuation was 2.9 years. The main limitation of warfarin is concern about bleeding, and this often prevents its use in otherwise suitable patients. This suggests that even with the new anticoagulants, nonuse and discontinuation of anticoagulants will remain a problem for the foreseeable future. There is no evidence that the introduction of these agents has improved community uptake of OACs.

Implications of Leaks Around LAA Occlusion Devices

The size and shape of the LAA are variable among patients. With this anatomic consideration, complete occlusion as an issue has been described for a variety of approaches to LAA occlusion. The original debate articles raised concern about the clinical implications of residual leak after LAA occlusion. This issue was addressed directly by a Viles-Gonzalez et al.
Evidence for Patients Unable to Take OACs Is Lacking

The current evidence for LAA occlusion has focused on patients who are candidates for short-term OACs. Contemporary surveys of practice patterns demonstrate that at least 40% of patients with AF at moderate or high risk for stroke do not receive OACs.37–32 Reasons for this nonuse are broadly categorized as unwillingness versus inability to take the anticoagulant. Those patients who are unable to take OACs have been excluded from the current trials of LAA occlusion and are clearly at increased risk of complications from AF. Thus, this is an important group of patients for whom data are lacking.

The ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP) registry provides some insight into the use of the Watchman device in such patients.33 In ASAP, 150 patients in whom the device was implanted were treated with acetylsalicylic acid and clopidogrel alone. The mean CHADS2 score of the patients was 2.8, which predicts an event rate for ischemic stroke of 7% per year off OAC. The observed event rate was 1.7% per year (3 events per 176.9 patient-years), suggesting benefit for patients not able to take OACs. Two caveats are that ASAP is underpowered for clinical events and is not a randomized comparison and that the combination of acetylsalicylic acid and clopidogrel has been shown to have bleeding risks similar to those of warfarin.34

Clinical trials are underway that will directly address this population. The Left Atrial Appendage Occlusion Study (LAAOS) III, a trial of surgical occlusion of the LAA during concomitant cardiac surgery, permits entry of such patients (http://www.clinicaltrials.gov; NCT01561651). LAAOS III will recruit 4700 patients in a multicenter, multinational effort and will analyze patients not taking OAC as a prespecified subgroup. AtriCure, Inc has also started the Feasibility Clinical Investigation of a Minimally Invasive Surgically Deployed AtriCure Left Atrial Appendage Exclusion System for Stroke Prophylaxis in Patients With Non-Valvular Atrial Fibrillation and in Whom Long Term Oral Anticoagulation Therapy Is Medically Contraindicated (http://www.clinicaltrials.gov; NCT01997905). This trial seeks to demonstrate the feasibility of a larger pivotal trial that will demonstrate whether the use of the Atriclip reduces stroke risk in at-risk AF patients unable to take OACs.

Summary/Consensus Statement
With Future Directions

We are proud to report that the evidence in the field of LAA occlusion has advanced since the original debate articles in 2012. They sought to establish the frequency and clinical impact of peridevice leaks in PROTECT AF patients randomized to device. Transeosophageal echocardiography at 12 months demonstrated that 32.0% of implanted patient had at least some degree of peridevice flow. Compared with patients with no peridevice flow, the hazard ratios were 0.85 (95% CI, 0.11–6.40), 0.83 (95% CI, 0.33–2.09), and 0.48 (95% CI, 0.11–2.09) for minor, moderate, and major peridevice flow, respectively (P=0.798). Compared with patients with no peridevice flow who discontinued warfarin, the hazard ratio for patients with any peridevice flow who continued warfarin was 0.63 (95% CI, 0.14–2.71; P=0.530). The data suggest that peridevice flow after LAA closure with the Watchman device is not associated with increased risk of stroke. However, the low event rate in the analysis limits the confidence around this conclusion.

Data from Garcia-Fernández et al34 suggest that leak has clinical relevance, although this study (n=58) was of lower quality and involved a very different population and approach. They reported that LAA exclusion was effective in reducing thromboembolic events in patients with valvular AF. In that study, the absence of LAA ligation was an independent predictor of an embolic event (odds ratio, 6.7; 95% CI, 1.5–31.0; P=0.02) via multivariate analysis. When incomplete ligation was included in the model, the odds ratio increased to 11.9 (95% CI, 1.5–93.6; P=0.02).

The clinical implications of residual communication of the left atrium proper with the LAA after attempted occlusion are still unclear. Early data from the PROTECT AF patients are encouraging, but the results must be confirmed by ongoing surveillance of patients who have been occluded.

Table 3. Trials of NOACs and Outcomes*

<table>
<thead>
<tr>
<th>Trial (n)</th>
<th>NOAC</th>
<th>Stroke or Systemic Emboli, RR Versus Warfarin (95% CI)</th>
<th>Major Bleeding, RR Versus Warfarin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (18 113)</td>
<td>Dabigatran 150, 110 mg</td>
<td>0.66 (0.53–0.82)</td>
<td>0.94 (0.82–1.07)</td>
</tr>
<tr>
<td>ROCKET AF (14 262)</td>
<td>Rivaroxaban</td>
<td>0.88 (0.75–1.03)</td>
<td>1.03 (0.90–1.18)</td>
</tr>
<tr>
<td>ARISTOTLE (18 201)</td>
<td>Apixaban</td>
<td>0.80 (0.67–0.95)</td>
<td>0.71 (0.61–0.81)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (21 105)</td>
<td>Edoxaban 60, 30 mg</td>
<td>0.88 (0.73–0.91)</td>
<td>0.80 (0.71–0.90)</td>
</tr>
</tbody>
</table>

ARISTOTLE indicates Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; CI, confidence interval; ENGAGE AF-TIMI 38, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176a) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; NOAC, novel oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non–Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; and RR, risk ratio.

*For dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily.
However, several unresolved issues remain in the field. First, an important application of occlusion devices is in patients who are ineligible for OACs. However, LAA occlusion in such patients has not been tested reliably, and further evidence is needed. Second, the extrapolation of the results in nonvalvular AF to patients with valvular AF is problematic, with studies suggesting a less dominant role of LAA thrombus in such patients. Studies focused on such patients are needed. Third, there is little experience in regard to what happens to occlusion devices over a period of many years. Delayed cardiac erosion and perforation are possibilities over time and have been described. Finally, the clinical significance of leaks after LAA occlusion, no matter the approach, must be established. The most efficient way of doing so is likely via a registry, given the rate of LAA occlusion therapy, the rate of leaks, and the incidence of thromboembolic events after such therapy.

For regulatory-approved devices, postmarketing registries that include standardized data forms, detailed inclusion criteria, procedural outcomes, and clinical follow-up focusing on stroke events and bleeding are essential. The Transcatheter Valve Registry for surveillance of transcatheter aortic valve replacement is an example of such a registry. These registries can yield rigorous surveillance up to 5 years to establish knowledge of the risks and benefits of such devices for a broader population.

Disclosures
Both the Mayo Clinic and Dr Holmes have financial interest in technology related to this article. That technology has been licensed to Boston Scientific. Drs Whitlock and Healey report no conflicts.

References


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