Does left atrial appendage occlusion eliminate the need for warfarin?

**Left Atrial Appendage Occlusion Does Not Eliminate the Need for Warfarin**

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Atrial fibrillation (AF) is the most common sustained heart rhythm disorder. It is increasing in incidence, which has major societal implications for our aging population.1–3 It is estimated to affect 1% to 1.5% of the developed world, and the incidence increases with age to a rate of 19.2 per 1000 patient-years in those 65 years of age and older. The most important aspect of the treatment of patients with AF is the prevention of stroke. The average annual stroke rate across risk groups is 5%, and AF-associated strokes confer worse outcomes than those occurring in the absence of AF.1,4 Furthermore, Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) data suggest that 15% of patients with AF suffer silent cerebral infarctions on computed tomography, the implications of which are unknown.5

**Response by Holmes and Schwartz on p 1932**

Oral anticoagulant (OAC) therapy with warfarin has been established as the standard for stroke prevention in patients with AF and more than 1 risk factor for stroke.6 Hart et al have summarized this literature in meta-analyses that include 29 trials and 28 044 patients.7,8 Compared with placebo, warfarin reduced the rate of stroke by 64% (95% confidence interval [CI], 49% to 74%), and in trials of warfarin versus antiplatelet, warfarin reduced the rate of stroke by 37% (95% CI, 23% to 48%). This is a large treatment effect when compared with other drug therapies in cardiovascular medicine. Further, even with an absolute risk increase in intracerebral hemorrhage and major hemorrhage of 0.2% per year over antiplatelet therapy, warfarin still produces a statistically significant 26% reduction in overall mortality compared with placebo.7 Despite its demonstrated benefit, warfarin therapy is administered to as few as 25% of patients with AF and only to 70% of patients who are considered to be “ideal” candidates for warfarin.9–15 In the Canadian Cardiovascular Outcomes Research Team AF study, using prescription claims databases in Alberta, British Columbia, and Ontario from 1997 to 2000 (pre-AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management] trial), less than one half of patients with AF filled a prescription for warfarin within 90 days of discharge for an AF hospitalization.13 Also concerning is the rate of warfarin discontinuation, which has been documented in the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) as 20% over a 2.5-year period.14 Many patient, prescriber, and system barriers have been identified. However, the main limitation of warfarin is concern about bleeding, and this often prevents its use in potentially suitable patients.16,17 In study patients assigned to warfarin therapy, it has been noted that patients are in the therapeutic range on only 50% to 68% of monitored days.18 The relationship between international normalized ratio (INR) and outcomes has been well documented: that low INR results in an increased risk of stroke and high INR is associated with increased risk of bleeding.19 This is an even greater issue in routine medical care, where...
time in range has been documented to be even lower.\textsuperscript{20,21} An effective low-risk therapy that could eliminate the need for OACs and their associated risks to the patient is therefore very attractive.

The left atrial appendage (LAA) is a 2- to 4-cm tubular structure attached to the left atrium and has been deemed by some to be “our most lethal attachment.”\textsuperscript{22} The failure of the fibrillating atrium to contract results in atrial stretch and dilation, promoting stasis and thrombus formation in the LAA (Figure 1). Transesophageal echocardiogram allows for clear imaging of the LAA, and several studies have examined the formation of thrombus in the hearts of patients with AF. In 1 study of 233 patients with AF who were not taking warfarin, 34 patients (15\%) had left atrial thrombus. All but one of these were located in the LAA.\textsuperscript{23} In a similar study, 272 nonrheumatic AF patients had an 8\% incidence of left atrial clot, all of which were in the LAA. A review of these and other studies concluded that at least 90\% of left atrial thrombi are found in the LAA.\textsuperscript{24} These observations have lead to the concept of LAA exclusion as a means of reducing stroke and other embolic events in AF.

To determine the current role of LAA exclusion in the management of patients with atrial fibrillation, we must consider the following questions: Does the pathophysiology of stroke in AF implicate LAA thrombus as the sole or predominant cause? Can the LAA be reliably and safely excluded or eliminated? And lastly, what is the evidence that LAA occlusion reduces stroke compared with either no treatment or warfarin?

**Pathophysiology of Stroke in Atrial Fibrillation**

The echocardiographic evidence suggests that many strokes do originate from the left atrium in AF patients. However, investigators have come to recognize that important factors other than stasis leading to thrombus formation in the LAA are involved, including systemic atherosclerosis, disorders of coagulation, and increased platelet activation. In a study of 72 nonvalvular AF patients with completed ischemic stroke undergoing echocardiography, Okura et al\textsuperscript{25} demonstrated that other sources of embolism, including patent foramen ovale, atrial septal aneurysm, and particularly proximal aortic atherosclerotic plaque, can be found in >50\%. The clinical relevance of these findings is supported by a posthoc exploratory analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I–III trials.\textsuperscript{26} The 217 strokes that occurred within these trials were classified as cardioembolic versus noncardioembolic according to clearly stated criteria. Of the classifiable strokes, 32\% were presumed to be noncardioembolic. Further, Blackshear’s echocardiographic substudy of 770 patients in the SPAF III trial highlighted the burden of atherosclerosis in AF. Fifty-seven percent of the patients were noted to have plaque within the thoracic aorta.\textsuperscript{27} The absence of such plaque in AF patients who are considered high-risk for thromboembolism is associated with a lower than expected rate of stroke, even without adequate anticoagulation (1.2\%/year, 95\% CI 0.2\% to 8.7\%).\textsuperscript{28}

AF patients who are at elevated risk of thromboembolism have been demonstrated to have systemic factors that increase the risk of thrombotic disorder. Endothelial dysfunction has been associated with AF, as documented by reduced plasma nitrite/nitrate levels and impaired acetylcholine-mediated blood flow increase.\textsuperscript{29} Endothelial dysfunction is known to increase oxidative stress and proinflammatory agents. AF is also associated with a systemic hypercoagulable state. Platelet function is enhanced with increased plasma levels of β-thromboglobulin and platelet factor 4.\textsuperscript{30} Systemic markers of activation of the coagulation cascade, such as thrombin-antithrombin II complex, D-dimers, fibrinogen, and prothrombin fragments 1 and 2, are also increased.\textsuperscript{31} In summary, AF patients have heavy atherosclerotic burden and a systemic prothrombotic state that increases the chance of thrombosis and embolism from multiple sources in addition to the LAA, such as the aorta, left ventricle, and cerebral vasculature. From these data, one can speculate that in patients with AF, the LAA likely accounts for much less than 90\% of strokes, suggested by echo studies. As the efficacy of LAA occlusion therapy for stroke prevention in AF will depend on the proportion of strokes that are actually caused by LAA thrombus, the uncertainty surrounding the pathogenesis of stroke in AF requires that the concept of LAA occlusion for prevention of stroke must be proven in well-designed trials before it can be accepted as clinically indicated.

**Technical Issues and Safety**

Two different general approaches are being developed for excluding the LAA from circulation: a surgical approach that amputates or externally occludes the LAA and a percutaneous approach that uses devices to occlude the appendage (Figure 2). The success and safety of both approaches are incompletely understood. In our own pilot study, the Left Atrial Appendage
Occlusion Study (LAAOS), oversewing the appendage without amputation produced successful exclusion in only 45% of patients. This rate increased to 72% if a stapler device was used; however, failure was secondary to the presence of a residual stump and not due to leaks. Schneider et al reported on a small number of patients in whom the LAA was suture-closed from within the atrium. Transesophageal echocardiogram demonstrated complete closure in only 1 of 6 patients at a mean of 51 days postoperative. The incomplete closure was observed to result in increased blood stagnation and higher velocity at the appendage ostium, which might actually increase the risk of stroke. This is supported by a case report of a patient with stroke in whom the only source identified was an incompletely occluded LAA containing clot. Kanderian et al reported no leaks with excision and suture closure of the appendage in a series of 137 patients, but 27% were left with residual stump >1 cm. The clinical implications of leaving a residual stump are unknown.

Blackshear et al have published on the thoracoscopic obliteration of the LAA using loop snare as an isolated procedure in 15 patients. This series raised safety concerns in that 3 of the 15 patients suffered serious adverse events related to the procedure. One patient required an urgent thoracotomy to control bleeding, 1 suffered a prolonged air leak, and 1 developed refractory cardiac failure. Within the LAAOS pilot, 15% (8/52) of patients having the LAA occluded experienced a tear necessitating additional sutures, not causing any major morbidity in an on-pump setting, but raising concerns about the safety of off-pump procedures. These procedural risks, combined with evidence suggesting the LAA elimination may decrease cardiac function, impair hemodynamic response to volume and pressure changes, impede thirst, and promote heart failure, suggests that the effects of removing the LAA may not be benign. From the surgical standpoint, the most reliable and safe way to exclude the LAA has not yet been established.

The percutaneous approach to LAA exclusion is a newer technique, and to date, little evidence exists on its efficacy. The PLAATO device was a self-expanding nitinol frame with fixation barbs and a polytetrafluoroethylene covering that faces the left atrium. It was placed through a transseptal approach via a catheter-based delivery system using ultrasound, fluoroscopic, and angiographic guidance. This device has been assessed within 2 prospective, nonrandomized, multicenter pilot trials including 111 patients. Three patients did not receive the device due to presence of LAA thrombus, access issues, and tamponade. There were 7 major adverse events in 5 patients and 9 procedure-related serious adverse events, including 4 pericardial effusions, 3 of which required pericardiocentesis. The study defined implant success as mild to no leak. Eighty-seven percent showed trace or no leak and 13% showed mild leak at implantation. By 6 months, of 50 patients, 64% showed trace or mild leak. That such leaks are benign has not been demonstrated. Further, placement of these intravascular devices necessitates postintervention acetylsalicylic acid, clopidogrel, or OAC for a short time, which may limit its use. Concerns have also been raised around appropriate device deployment. Schwartzman et al have raised concerns about the geometric complexity and interindividual variation in the LAA. They suggest, on the basis of...
computed tomography imaging, that current assessment of echocardiographic information for detection of peri-device leak may be inadequate.

**Clinical Results From Nonrandomized Trials**

No conclusive evidence exists to demonstrate that LAA exclusion reduces stroke in AF patients. Results from case series of maze procedure patients have been cited to support the amputation of the LAA. The maze procedure attempts to eliminate AF through a series of cuts in the right and left atria, suturing them closed, and excising both atrial appendages in a similar fashion. Cox et al published a case series of 306 patients who underwent a “cut and sew” maze procedure. The perioperative stroke rate was 0.7% and 0.4% in the follow-up of 11.5 years, which was low. However, the majority of patients in this series had lone AF and no risk factors for stroke (n=162) and thus had a very low anticipated rate of stroke. In the absence of randomization, it is difficult to conclude that the Cox-maze surgery actually reduced their risk of stroke. Furthermore, the low rate of stroke could in part be the result of the restoration of sinus rhythm, rather than from the removal of the LAA.

LAA occlusion is often performed in association with mitral valve surgery. In another retrospective study examining 205 patients after mitral valve surgery, the success rate of closure when attempted approached 90%. Multivariate analysis demonstrated the absence of LAA ligation as an independent predictor of occurrence of an embolic event (odds ratio 6.7; 95% CI 1.5 to 31.0). When incomplete ligation was grouped with no ligation, the odds ratio increased to 11.9. However, in another observational cohort of 137 similar patients published by Almahameed et al, it was reported that 12% of patients suffered a thromboembolic event over 3.6 years. Ultimately, these and several other small observational studies have failed to show consistent benefit. Thus, there may be promise in surgical closure; however, the best approach to accomplish this is not yet established, and the definitive demonstration of efficacy for stroke protection does not exist.

**Randomized Controlled Trials**

There are no major surgical randomized trials of LAA closure published that examine stroke as the primary outcome in the surgical literature. The LAAOS randomized 77 patients to demonstrate the efficacy and safety of LAA closure at the time of open-heart surgery. The study did suggest that surgical occlusion could be safely performed; however, with so few patients randomized, no conclusions could be made about clinical benefit of LAA occlusion. The first randomized controlled trial within the interventional literature was recently presented at the 2009 American College of Cardiology and commented on after a US Food and Drug Administration advisory committee review. The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF) trial was a randomized, prospective, multicenter study that sought to evaluate WATCHMAN device closure of the LAA compared with warfarin in patients with nonvalvular AF. The WATCHMAN device is a self-expanding, covered nitinol cage that is placed into the LAA via a transeptal approach using femoral access (Figure 2). There were 707 patients randomized 2:1 between the device and warfarin. Two thirds of the patients had a CHADS score of 1 or 2. In the device arm, 87% of patients stopped warfarin at 45 days, with 10% subsequently restarting for clinical reasons.

With mean follow-up of just more than a year, the rates of the primary efficacy outcome of cardiovascular death, stroke, or systemic embolism were 3.4 events per 100 patient-years in the device group versus 5.0 in the warfarin group (relative risk 0.68; 95% CI 0.37 to 1.41). Stroke event rates were 2.6 events per 100 patient-years versus 3.5, respectively (relative risk 0.74; 95% CI 0.36 to 1.76). Implantation of the WATCHMAN device was challenging. Of 449 attempted procedures, 408 were successful, with 12.3% of patients experiencing serious procedural complications, including pericardial effusions requiring drainage or surgery (5%) and acute stroke due to air or thrombus (1.1%). Four patients subsequently had to have the device removed because of device embolization or sepsis. The rate of ischemic stroke was 50% higher in the device group (3.0% versus 2.0%), in part due to events occurring early after implantation in the device group.

The PROTECT AF investigators are to be congratulated on generating these very promising results. However, as pointed out by Maisel, the trial is too small to conclusively claim noninferiority to warfarin, reflected by the wide 95% CI (0.36 to 1.76) for the outcome of greatest interest, stroke. Based on these promising results, a definitive randomized trial is indicated.

Another way of evaluating the concept that LAA occlusion reduces stroke in AF is to perform LAA occlusion at the time of routine cardiac surgery (either coronary artery bypass graft or valve surgery). Antithrombotic therapy would not be required or prohibited. A pilot study is underway to assess the feasibility of randomizing adult patients undergoing any cardiac surgical procedure who have ECG-documented paroxysmal or permanent AF with a CHADS score of 2 or greater. Excluded patients are those undergoing the maze procedure, heart transplant, complex congenital surgery, planned ventricular assist device insertion, and re-operation. The primary outcome is stroke, non–central nervous system systemic embolism, or major bleed. Secondary outcomes include mortality, hospitalization for heart failure, bleeding, and need for surgical re-exploration. This study will need to randomize at least 2000 to 4000 patients and follow them for a mean of 2 to 4 years to have sufficient statistical power to determine whether LAA occlusion is superior to no occlusion. The advantage of this approach is that it uses a superior design, which will yield clear results. The disad-
vantage is that it requires enrollment of large numbers of high-risk AF patients and therefore many cooperating centers.

Conclusions

LAA occlusion has been an exciting idea for stroke prevention in AF for decades, but it still lacks conclusive proof that it is effective and safe. Given the extent of atherosclerotic disease in some AF patients and the presence of a systemic disorder of coagulation and platelet function in most high-risk AF patients, a local approach that controls only the LAA may not be sufficient. Although recent results with the percutaneous closure device are promising, the evidence of efficacy and safety is insufficient to recommend this approach for any patients other than those in whom long-term warfarin is absolutely contraindicated. More large randomized trials of the device and surgical approaches should be done. At present, antithrombotic medications will remain the standard treatments to prevent stroke in patients with AF.

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Response to Whitlock et al

David R. Holmes Jr, MD; Robert S. Schwartz, MD

Whitlock et al write an outstanding review of left atrial appendage (LAA) thrombus and stroke in atrial fibrillation. There is no debate that LAA thrombus causes stroke and that warfarin reduces its incidence, but a central question was not addressed. This question is whether device-based LAA occlusion reduces stroke in nonvalvular atrial fibrillation compared with warfarin. The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial is the only randomized trial testing this hypothesis. Though small compared with atrial fibrillation drug trials, it met a key predefined effectiveness end point: cardiovascular mortality, stroke, and systemic embolization were noninferior to long-term warfarin. Moreover, for the prespecified end point of hemorrhagic stroke prevention, the device was superior to long-term warfarin. Safety issues occurred in PROTECT AF, as with most new invasive approaches. These were mostly procedural pericardial effusions that occurred early and caused neither mortality nor long-term morbidity. These effusions stand in contrast to warfarin complications that accrue progressively over time and may be quite serious. Subsequent device iteration and increased operator experience has decreased the pericardial effusion rate to 1.5%. The time has clearly come to question warfarin as primary therapy in atrial fibrillation. Patient compliance is poor, therapeutic international normalized ratio range is achieved in only 40% of patients, and even when therapeutic, catastrophic complications can occur. These are perhaps most frequent in the elderly, the very population that needs it most. PROTECT-AF answers the debate about local device versus systemic drug treatment and suggests that most cardioembolic events originate in the LAA. Device-based occlusion is an emerging viable clinical strategy that should be tested further.
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