Left atrial appendage exclusion: An alternative to anticoagulation in nonvalvular atrial fibrillation

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The Watchman endocardial left atrial occlusion device (*left*) and the AtriClip epicardial left atrial occlusion device (*right*).

Central Message

This article reviews the evidence behind the options for stroke risk reduction in patients who cannot have or do not want AC.

Perspective

Despite the advent of new anticoagulants, bleeding continues to be an inherent risk of anticoagulation (AC). There is a need for an alternative to AC in patients with atrial fibrillation who cannot have or do not want AC.

Patients with atrial fibrillation (AF) are 5 times more likely to have a stroke than individuals in sinus rhythm, and 1 in every 5 strokes is secondary to AF.[1-3] Unfortunately, AF-related thrombo-emboli are larger and result in ischemic strokes that are more devastating than those secondary to carotid artery disease or other etiologies.[4,5] Lifelong oral anticoagulation with warfarin has been the guideline-based therapy to reduce the risk of AF-related ischemic strokes in patients with a CHA_2DS_2-VASc (congestive heart failure, hypertension, age >75 and diabetes mellitus, previous history of stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex category) score $\geq$2. Anticoagulation (AC), however, inherently predisposes to bleeding, including hemorrhagic stokes. Moreover, a significant percentage of patients with AF have relative or absolute contraindications to AC. Even those who can take it do not necessarily experience maximum anticoagulant protection. Despite demonstrating warfarin's benefit in preventing approximately one-half of AF-related strokes, the target international normalized ratio (INR) is achieved in only approximately 60% of patients despite best practices in dosing and monitoring.[6,7] A recent registry reported that among patients on warfarin for AF, only 26% were found to have a stable INR within therapeutic range.[8] The 4 major randomized controlled trials (RCTs) for non–vitamin K oral anticoagulants (NOACs) have shown the time in therapeutic range (TTR) in the warfarin-treated arms to range from 55% to 68% despite optimal dosing and INR monitoring.[9] In their meta-analysis of the 4 RCTs comparing NOACs with warfarin, Ruff et al[10] found NOACs to be superior to warfarin in reducing intracranial bleeding, but not bleeding elsewhere. Like warfarin, NOACs still subject the patient to an above-baseline predisposition to bleeding. They also both subject the patient to lifelong therapy, and despite NOACs eliminating the need for frequent blood tests, dabigatran and apixaban replace the daily warfarin dosing with a twice-daily dosing regimen. Finally, approximately 20% to 25% of patients on NOACs have discontinued the agent at 2 years of follow-up.

These shortcomings of anticoagulation triggered a search for alternatives. If thrombi are identified in the left heart of patients with nonvalvular AF-related strokes, they are in the left atrial appendage (LAA) 90% of the time.[11] This observation led to an increased interest in closing the LAA mechanically as a potential means of reducing the stroke rate in patients with nonvalvular AF. Successful LAA occlusion can potentially provide patients who cannot tolerate OAC therapy a means of stroke risk reduction, and to spare those who can receive OAC the potential hazards, inconveniences and costs of lifelong anticoagulation. In this review, we discuss techniques and devices aimed at LAA exclusion.

LAA OCCLUSION OR EXCISION

The first known attempt at occluding or excising the LAA to prevent stroke was reported in 1949 and the outcomes were dismal.[12] More than 40 years later, Johnson et al[13] revived interest in excluding what they called "…our most lethal human attachment" (the LAA) from the systemic circulation. Johnson et al[13] excised the LAA in 437 patients undergoing cardiac surgery with no increased morbidity or mortality. Despite demonstrating the safety of LAA excision, the efficacy of eliminating the LAA in reducing stroke was not well documented. In the early

2000s, Garcia-Fernandez et al[14] demonstrated a therapeutic benefit of LAA occlusion but also noted that an incomplete occlusion was detrimental because the residual was thrombogenic. In their retrospective report on patients undergoing mitral valve replacement, they found that leaving the LAA intact was an independent predictor of stroke with a 6.7-fold increased risk, whereas incomplete closure of the LAA increased the risk of stroke by 11.9-fold. Although the benefits of successfully closing the LAA could not always be reproduced by other investigators, the detrimental consequences of incomplete LAA closure were consistent.[15,16] Because at that time only approximately 60% of the LAAs could be closed completely, 40% of the patients were left with a higher stroke risk than those with an intact LAA.[17,18] The inability to attain complete LAA closure not only increased the stroke risk but it also precluded an accurate determination of the relationship between LAA occlusion and stroke reduction. However, in 2006, the American College of Cardiology and the American Heart Association (ACC/AHA) recommended exclusion of the LAA surgically during surgical ablation of AF or mitral valve surgery.[19] Nevertheless, controversy persisted regarding the potential value versus the potential harm of occluding the LAA for stroke in patients with nonvalvular AF.[20]

Approximately 110 publications discussed the LAA over the 30 years from 1960 to 1990. Interestingly, more than 1000 publications exist discussing the LAA from 2000 to date.[21] Unfortunately, this exponential increased interest in the LAA was not translated into well-powered RCTs except recently. The literature is abundant in single-institution pilot studies and case series, but only 1 adequately powered RCT was completed. In 2014, results from the intermediate to late follow-up of this RCT have, for the first time, provided objective evidence for LAA exclusion as an alternative to AC in patients with AF.[22]

ENDOCARDIAL LAA OCCLUSION DEVICES

The first device designed specifically to close the LAA mechanically was the PLAATO device (Ev3; Plymouth, Minn) that consisted of a self-expanding nitinol frame covered by an impermeable polytetrafluoroethylene membrane (Figure 1). High-risk patients with AF who were not candidates for warfarin therapy showed an acceptable safety profile and a complete LAA occlusion rate approaching 98% with a reduction of stroke risk ranging from 42% to 65% compared with their estimated risk based on the $CHADS_2$ (congestive heart failure, hypertension, age = 75 years, diabetes mellitus, stroke [doubled]) scoring system.[23-25] In 2007, Atritech (Plymouth, Minn) acquired the PLAATO intellectual property from Ev3, stopped production of the PLAATO, and developed the Watchman device.

The Watchman

The Watchman device (Boston Scientific, Maple Grove, Minn) is a self-expanding nitinol-based device with distal fixation barbs and a permeable polyester fabric (Figure 1). The Watchman was evaluated in the PROTECT-AF clinical trial that prospectively randomized (2:1) 707 patients with nonvalvular AF ($CHADS_2$ score ≥ 1) to receive either the Watchman device or warfarin therapy. Rates of successful Watchman implantation and complete LAA occlusion were 91% and 88%, respectively. Warfarin was also administered to the Watchman group but it was stopped when transesophageal echocardiography (TEE) documented sealing of the LAA with either no residual leak or a leak ≤ 5 mm. At 6 weeks, 86% of the Watchman group was able to stop warfarin, and 92% had stopped warfarin at 6 months. After 5 years of follow-up, the primary efficacy endpoint (decrease in stroke, systemic thromboembolism, and cardiovascular death) was 3% annually with the Watchman device and 4.3% in the warfarin group, a 99.9% probability of noninferiority of the Watchman compared with warfarin therapy.[26,27]

Despite demonstrating efficacy, the Watchman group demonstrated a significantly higher incidence of safety events. The primary safety event rate (procedural stroke, major bleeding, device embolization, and pericardial effusion) was 7.4 events per 100 patient-years in the Watchman

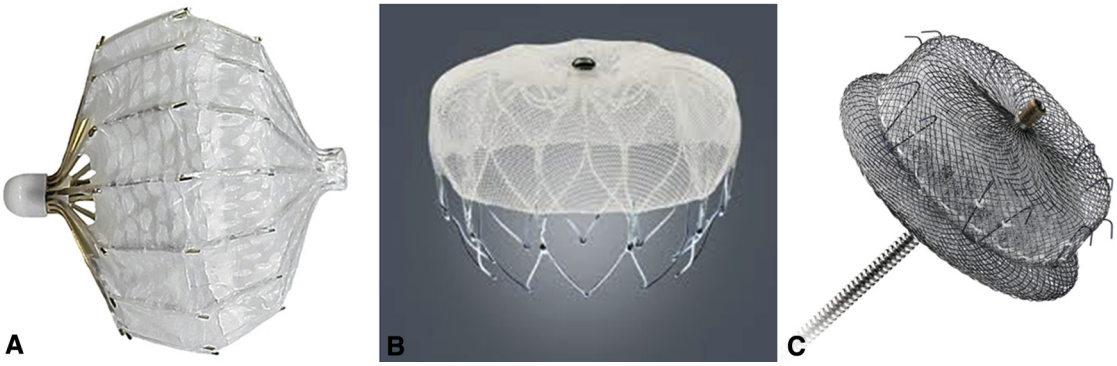

FIGURE 1. Endocardial left atrial appendage occluding devices. A, The PLAATO device. B, The Watchman. C, The Amplatzer cardiac plug.