

Review Article

Left Atrial Appendage Closure in Atrial Fibrillation: A World without Anticoagulation?

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Atrial Fibrillation (AF) is a common arrhythmia with an incidence that is as high as 10% in the elderly population. Given the large proportion of strokes caused by AF as well as the associated morbidity and mortality, reducing stroke burden is the most important part of AF management. While warfarin significantly reduces the risk of AF-related stroke, perceived bleeding risks and compliance limit its widespread use in the high-risk AF population. The left atrial appendage is believed to be the “culprit” for thrombogenesis in nonvalvular AF and is a new therapeutic target for stroke prevention. The purpose of this review is to explore the evolving field of percutaneous LAA occlusion. After briefly highlighting the risk of stroke with AF, problems with warfarin, and the role of the LAA in clot formation, this article discusses the feasibility and efficacy of various devices which have been developed for percutaneous LAA occlusion.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It has an estimated prevalence of 1% in the adult population translating into greater than two million cases in the United States [1]. The projected number of individuals with AF in the United States of America is expected to be approximately 10 million by 2050 [2]. With better methods of diagnosing AF, especially paroxysmal AF, as well as increasing physician awareness, the actual burden may be higher than expected. AF is fraught with the serious complication of thromboembolism. Although anticoagulation is effective, patients and physicians both seek alternative means to avert the risk of stroke from thromboembolism due to the need for monitoring and bleeding complications as well as the potential for drug interactions. Left atrial appendage (LAA) closure devices have become an attractive option for this purpose. In this review, we will summarize the available literature and evidence for use of percutaneous left atrial appendage closure as an alternative to chronic anticoagulation.

2. Stroke Risk in Atrial Fibrillation

AF increases the risk of stroke by 4 to 5 folds in nonrheumatic patients [3] and 17 folds in the setting of rheumatic mitral stenosis [4]. It is responsible for 10% of all ischemic strokes and half of all cardioembolic strokes [5]. The impact of AF as a risk factor for stroke increases with age. While the annual incidence of stroke due to atrial fibrillation is 1.5% in patients aged 50–59 years, almost a quarter of the strokes in patients aged 80 to 89 years are secondary to AF [3]. Perceived adverse effects related to anticoagulation also increase with age, which may result in a paradoxical underuse in a population at highest risk for stroke [6].

Paroxysmal AF (PAF), which accounts for 25% of AF, has the same risk of stroke as permanent/persistent AF [7]. In a recent study, up to 23% patients with stroke/TIA of unknown etiology (cryptogenic stroke) were found to have PAF on subsequent monitoring [8]. Given that cryptogenic stroke accounts for 36% of all strokes [9], the stroke burden attributed to PAF has been hitherto significantly underestimated. With better methods of diagnosing PAF in patients

with cryptogenic stroke, such as transtelephonic EKG monitoring [10] and mobile cardiac outpatient telemetry [8], the number of patients potentially requiring anticoagulation is expected to increase in the future.

Apart from a sheer increase in numbers, AF-related strokes also tend to be more severe when compared to other causes of thromboembolism, likely due to the larger size of thrombi [11, 12]. Consequently, there is a significant impact on the quality of life as well as longevity with an estimated 28-day mortality of 20% post-AF-related stroke [13]. Thus, reducing the stroke burden is a *sine qua non* of AF management.

3. Underuse of Anticoagulation in AF

Warfarin dramatically decreases the risk of stroke in patients with valvular as well as nonvalvular AF. In a meta-analysis of randomized controlled trials, warfarin resulted in a 64% relative risk reduction for stroke when compared to placebo [14]. Another meta-analysis revealed that warfarin is almost three times more effective than antiplatelet agents in preventing strokes (relative risk reduction 64% for warfarin versus 20% for antiplatelet agents) [15].

However, several studies have reported underuse of warfarin in eligible patients with AF. In a large cross-sectional study, 45% patients with moderate to high-risk AF did not receive warfarin [16]. Similarly, a recent cohort study of Medicare beneficiaries with atrial fibrillation revealed that only two thirds of ideal anticoagulation candidates were prescribed warfarin, with significant differences in use, monitoring, and effectiveness of warfarin among different ethnic groups [17]. Given the high incidence of atrial fibrillation and associated risk factors for stroke, a small percentage of underuse could translate into a huge hurdle to stroke prevention in the population.

Table 1 outlines important reasons for warfarin underutilization. Fear of major bleeding, especially hemorrhagic strokes and gastrointestinal bleeding, is a major reason for this underuse [18, 19]. This fear is not without reason; a meta-analysis revealed that the risk of intracranial hemorrhage is doubled with warfarin when compared with aspirin [15]. Anticoagulants ranked first in 2003 and 2004 in the number of deaths from drugs causing “adverse effects in therapeutic use” [20]. The perceived risk is greater in elderly patients with AF [21], and “fall risk” is estimated in rather ambiguous ways in this population. Inconvenience of INR monitoring for rural populations, drug, and dietary interactions as well as compliance are other limiting factors [22]. For unclear reasons, warfarin is also underused in females compared to males [23].

Novel anticoagulants, such as the thrombin inhibitors (dabigatran) and the factor Xa inhibitors (rivaroxaban) have a wider therapeutic window. There is minimal dietary and drug interference with these agents and INR monitoring is not required. While these may decrease many of the concerns associated with warfarin, they do not address issues related to bleeding and compliance [24]. A case in point is that of dabigatran, which is superior to warfarin in preventing

TABLE 1: Causes of warfarin underutilization.

(1) Risk of bleeding (perceived or real)
(a) Intracranial hemorrhage
(b) Gastrointestinal bleeding
(c) Other major bleeds (retroperitoneal, hematuria, etc.)
(2) Perceived Fall Risk (and associated bleeding risk)
(3) Difficulty with INR monitoring
(a) Geographical barriers
(b) Lack of insurance/primary care physician
(4) Non-compliance
(5) Patient preference
(6) Physician unawareness (such as need in paroxysmal AF*)
(7) Pharmacokinetic interference
(a) Drug interaction
(b) Dietary interference
(8) Ethnic and gender disparities

* AF: atrial fibrillation.

strokes but has a similar risk of major bleeding at the currently approved dose [25]. Similarly, there was no difference in major bleeding event rates between rivaroxaban and warfarin groups in the recent ROCKET-AF trial [26]. Also, cost-effectiveness and efficacy of these novel agents in real world setting remain to be seen.

4. Left Atrial Appendage: The Culprit?

The left atrial appendage is an embryological remnant that functions during conditions of volume overload as a reservoir and mediator of adaptive responses to decrease circulating blood volume [27]. Compared to the right atrial appendage, the LAA is anatomically prone to stasis by virtue of having a long, tubular structure as well as a narrow junction with the atrium [28]. Multiple studies have found a predilection for thrombus to form within the LAA in patients with mitral valve disease (irrespective of underlying rhythm) and nonvalvular AF.

The hematological and endocardial substrate for thrombogenesis in the LAA is yet to be elucidated, but the structural basis has been defined. All known variables associated with thrombus formation, including LAA size and flow pattern, are altered due to AF-associated LAA dysfunction [27]. Post-mortem LAA cast analysis from patients with AF revealed that its size was much larger in patients with AF [29]. A specific type of LAA flow pattern in patients with AF (Type III indicating no identifiable flow waves with AF) was associated with a higher incidence of LAA thrombus [30]. These represent the macroscopic basis of LAA thrombus formation in the setting of AF.

In contrast to patients with valvular AF, it is hypothesized that the LAA may be the major source for emboli in nonvalvular AF. This is based on an analysis of 23 studies utilizing echocardiographic, operative, and postmortem evaluations of the left atrium and LAA in patients with AF (Table 2). The percentage of thrombi found in the LAA was significantly higher in patients with nonvalvular AF than in valvular

TABLE 2: Left atrial appendage as a source of thrombi in nonatrial fibrillation.

(i) Hypothesis is based on a landmark study by Blackshear and Odell [31]
(ii) Findings from studies in settings of operation, autopsy, or transesophageal echocardiography were combined
(iii) 23 studies including close to 5,000 subjects with rheumatic or nonrheumatic AF* were reviewed
(iv) Thrombi presented in the appendage but extending into the atrium was classified as a LAA** thrombus
(v) While 57% of atrial thrombi in rheumatic AF occurred in the appendage, 91% of left atrial thrombi were located in the atrial appendage in nonrheumatic AF ($P < .0001$)
(vi) Many have pointed out that merely finding a thrombus in the LAA does not prove that it is the source of cardio-emboli in AF-related ischemic stroke [32]
(vii) This study set the stage to investigate the benefit of LAA occlusion in reducing nonrheumatic AF-related stroke burden

* AF: atrial fibrillation; ** LAA: left atrial appendage.

AF (91% versus 57%; $P < .001$) [31]. This data, however, does not confirm that the LAA is the “source” of emboli in AF-related ischemic stroke, and many have questioned this theory [32]. Nevertheless, many surgical as well as non-invasive methods to occlude the LAA have been assessed to reduce stroke burden and confirm this hypothesis.

5. Methods of LAA Occlusion

5.1. Surgical. Several studies have assessed the feasibility, safety, and efficacy of surgical LAA occlusion [33, 34]. Given its invasive nature, surgical LAA occlusion is only performed in patients requiring other cardiac surgery such as mitral valve surgery and maze procedures. The addition of this simple, quick procedure to the aforementioned surgeries can reduce stroke burden in many patients with established AF or at high risk for AF. However, its efficacy for occluding the LAA and preventing thromboembolic events has been questioned, with a study demonstrating that surgical LAA occlusion is frequently incomplete [35]. Continuous advancements in open surgical LAA occlusion technique are being made with better methods for intra-operative confirmation of success (TEE), and outcomes are expected to improve in the future.

5.2. Nonsurgical. There are several percutaneous devices, which have been used for LAA occlusion. Of these, only the WATCHMAN device is FDA approved. Table 3 summarizes studies, which have analyzed the feasibility and efficacy of different devices.

6. The Amplatzer Septal Occluder (AGA Medical Corp., Golden Valley, Minn)

The Amplatzer septal occluder, which was originally used for patent foramen ovale or atrial septal defect closure, was tested for LAA closure in a preliminary analysis of 16

patients across four centers [36]. There was a single event of asymptomatic device embolization due to inappropriate size; no other complications or thromboembolic episodes were reported in a short followup period of four months. However, no further trials were conducted with this system, which paved the way for the LAA-specific devices. The Amplatzer Cardiac Plug is another device by the same manufacturer which is currently being compared with warfarin in the Amplatzer Cardiac Plug trial.

7. The PLAATO System (eV3, Plymouth, Minn)

The PLAATO implant consists of a self-expanding nitinol cage coated with a special expanded polytetrafluoroethylene (ePTFE) membrane to occlude blood flow into the orifice while allowing tissue incorporation. The ePTFE membrane ensures benign healing [42], resulting in endothelialization of the implant in 2 to 3 months. A custom 14Fr transseptal sheath is used to deliver the implant into the LAA, and small anchors along the struts of the implant hold it in position.

After initial animal studies confirmed safe LAA occlusion with this system [43], a feasibility study was conducted in Europe in 15 patients with chronic, nonrheumatic AF and contraindications to warfarin therapy [37]. All patients were at high risk for thromboembolism based on CHADS2 criteria [44] or spontaneous echo contrast in the LAA on TEE. The device was successfully implanted in all patients with an average implant time of 90 minutes. Periprocedural hemopericardium delayed successful implantation in one patient by a month, and the device needed to be exchanged due to inappropriate size in 4 patients. A one month followup showed stable implant position, and there were no reported late complications or embolic events. An addendum to this study reported successful implantation in 16 additional patients (with another case of hemopericardium).

Subsequently, the larger PLAATO multicenter study reported results from multiple sites in North America and Europe with a followup period of up to 17 months [38]. Patients with nonrheumatic AF of at least three months duration with contraindications to warfarin and high risk for thromboembolic events were included. The latter was based on CHADS2 criteria, presence of coronary artery disease, or echographic criteria (moderate to dense spontaneous echocardiographic contrast or blood flow velocity <20 cm/s within the LAA), thus expanding inclusion criteria from the previous feasibility study. Percutaneous LAA occlusion was successful in 108 of 111 patients, with an average procedure time of 68 minutes. There were two reported major adverse events in a single patient within the first month. A total of 5 patients (4.5%) experienced hemopericardium during the entire followup; four of these five had no long-term sequelae. Based on a mean CHADS2 score of 2.5, the estimated stroke risk in the population was 6.5%. This was reduced to almost a third (2.2%/year) with the PLAATO system for strokes alone; TIA was not included.

The largest feasibility study for the PLAATO system was conducted in North-America and utilized a prospective, nonrandomized study design enrolling 64 patients across

TABLE 3: Studies evaluating percutaneous left atrial appendage closure devices.

No.	Study	Study design	Year	Device	Comparison	Subjects (n)	Population	Followup (mean)	Results	Adverse events
(1)	Meier et al. [36]	Prospective	2003	Amplatzer Septal Occluder	None	16	AF-continuous/paroxysmal; c/i to coumadin	4 months	0% stroke/TIA	Device embolization (1)
(2)	Sievert et al. [37]	Prospective	2002	PLAATO	None	15	Chronic, nonrheumatic AF; c/i to coumadin	1 month	0% stroke/TIA	Hemopericardium (1), device exchange (4)
(3)	Ostermayer et al. [38]	Prospective	2005	PLAATO	None	111	Chronic nonrheumatic AF patients at risk for stroke; c/i to coumadin	10 months	Stroke/TIA 2.2% (versus estimated 6.3%)	Implant failure (3), Hemopericardium (5)
(4)	Block et al. [39]	Prospective	2009	PLAATO	None	64	C/P AF; CHADS ₂ ≥ 2; c/i to coumadin	5 years	Stroke 3.8% (versus estimated 6.6%)	Cardiac tamponade (1), (%)
(5)	Sick et al. [40]	Prospective	2007	WATCHMAN	None	75	C/P AF; CHADS ₂ ≥ 1; eligible for coumadin	2 years	0% stroke/TIA	Implant failure (2), device failure, embolization, or pericardial effusion (6), TIAs (2)
(6)	PROTECT AF [45]	Randomized Controlled Trial	2009	WATCHMAN	Warfarin	707	C/P AF; CHADS ₂ ≥ 1; eligible for coumadin	18 months	>99% probability of noninferiority for stroke/TIA prevention	Adverse events higher among controls

AF: atrial fibrillation, c/i: contraindication, C/P: Chronic/Paroxysmal, PLAATO: percutaneous left atrial appendage transcatheter occlusion, and PROTECT AF: WATCHMAN left atrial appendage system for embolic protection in patients with atrial fibrillation.

10 centers [39]. The inclusion criteria for this study were broader than the previous, smaller feasibility studies. Due to the similar risk for thromboembolic events, patients with either permanent or paroxysmal AF were selected for inclusion. Risk for developing thromboembolic events was defined by a CHADS2 score ≥ 2 or the presence of any of the multiple high-risk echocardiographic findings. More than 98% of the patients met the primary end point of no major adverse events (i.e., stroke, cardiac, or neurological death, MI or requirement of surgery related to the PLAATO procedure). In the five-year followup, there was only one adverse event (cardiac tamponade) attributed to the procedure, indicating an improved safety profile with time and experience (the learning curve effect). There were no other procedure-related adverse events, device failures, or malfunctions throughout the study period. The estimated yearly combined rate of stroke/TIA was 6.6%, calculated from the mean CHADS2 score of 2.6 in the study population. This was reduced to a rate of a 3.8%/year with the PLAATO system. Despite the encouraging results, there were no subsequent studies comparing the device to warfarin therapy.

8. WATCHMAN Device (Atritech Inc., Plymouth, Minn)

Similar to the PLAATO implant, the WATCHMAN LAA closure device consists of a self-expanding nitinol frame [41]. It also has fixation barbs; however, the permeable polyester fabric only covers the surface exposed to the left atrium. It is available in five different sizes ranging from a diameter of 21 to 33 mm. The implant is preloaded within a catheter and requires an access sheath for delivery into the LAA.

A preliminary feasibility study tested this device in 75 patients across multiple centers in Europe and North America. Subjects with chronic or paroxysmal nonvalvular AF eligible for warfarin therapy and a CHADS2 score ≥ 1 were included [40], thus having broader inclusion criteria than feasibility studies for PLAATO. After implantation, patients were discharged on warfarin which was discontinued at 45 days if LAA remained successfully sealed by echocardiographic criteria. The initial 16 patients received the first generation device. The device was subsequently redesigned and implantation of a second-generation device was attempted in 59 patients. Adverse effects were much lesser with second- than first-generation device, including core wire failure (0/59 versus 2/16), device embolization (0/59 versus 2/16), and internal bleeding (0/59 versus 1/16). Though minor pericardial effusions were more common with the second-generation device (3/59 versus 0/16 with first generation), there was one case of pericardial effusion requiring treatment in each group. Based on the CHADS2 score, the expected annual stroke risk of 1.9% was reduced to 0% with this device over a followup period of two years.

The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) is the first study that directly compared a LAA occlusion device head-to-head with warfarin therapy [45]. It was primarily designed to assess noninferiority of

the WATCHMAN device against warfarin. This prospective randomized control trial used inclusion criteria similar to the initial feasibility study, choosing patients with paroxysmal, persistent or permanent nonvalvular atrial fibrillation, and a CHADS2 score of ≥ 1 . A computer-generated sequence randomized selected patients ($n = 707$) to the device ($n = 463$) and warfarin therapy ($n = 244$) in a 2:1 ratio. Those randomized to intervention subsequently discontinued warfarin after transesophageal echocardiographic (TEE) demonstration of complete LAA closure or a residual jet < 5 mm in width. Following this, dual antiplatelet therapy (aspirin and clopidogrel) was prescribed until the end of a 6-month followup period. This was in contrast to the PLAATO recipients, who only received dual antiplatelet therapy for four to six weeks without any warfarin therapy. The device was successfully implanted in 88% of those assigned to the intervention group, of which 92% could stop taking warfarin at 6 months. The primary efficacy event rate for occurrence of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism was 3/100 patient-years in the intervention group and 4.9/100 patient-years in the control group (rate ratio [RR] 0.62, 95% CI 0.35–1.25) with a greater than 99% probability of noninferiority. Though the primary safety event rate for occurrence of hemorrhage or procedure related complications was greater in the intervention group of the “intention to treat” population (7.5 versus 4.4 per 100 patient-years; RR 1.69 (95% CI 1.01–3.19)), the rate was higher in the control group amongst those successfully treated with device or warfarin (1.5 versus 4.4 per 100 patient-years; RR 0.35 (95% CI 0.15–0.80)).

There were several concerns about the trial design, such as using a noninferiority hypothesis to compare two different modalities of treatment, that is, a drug and a device. The risk of hemorrhagic stroke in the warfarin group (1.6 per 100 patient-years) was much higher than that reported in previous trials (0.5 per 100 patient-years in a meta-analysis of 6 randomized clinical trials [46]) and this may have influenced the noninferiority results for primary efficacy. Also, the rate of serious pericardial effusion requiring drainage was fairly high in the device group (4.8% versus 0%). The FDA has recommended longer followup studies with this device, and another trial is being planned by investigators.

9. Future Perspective

Percutaneous LAA occlusion devices may represent the “holy grail” in reducing nonvalvular AF-related stroke burden. Researchers have been constantly looking for easier methods for this, and a single procedure with short-term anticoagulation is more feasible than life-long anticoagulation and associated bleeding risks. Oral anticoagulants may become “alternative” agents in nonvalvular AF subjects who are not suitable for device implantation.

However, there are many questions that remain unanswered. Though only the WATCHMAN device is under consideration for FDA approval, results from feasibility studies of PLAATO are encouraging. A trial with the

Amplatzer Cardiac Plug device is also underway. Long-term studies with these devices and head-to-head comparisons may be necessary before deciding the “best” device. Different trials have used varied regimens for periprocedural antiplatelet/anticoagulant therapy and contrasting these protocols is imperative. If postprocedural warfarin therapy is needed, populations at high-risk or ineligible for warfarin therapy may also be unsuitable for device implantation. This will leave a huge proportion of the AF population at high-risk for stroke without any therapeutic modality. Despite the benefit of LAA occlusion, procedure-related adverse events such as pericardial effusion and device embolization remain concerning. Once this procedure gains popularity, longer followup studies in real-world settings will help assess the actual risk of adverse events. The role of this device in the face of newer, safer, and more efficacious oral anticoagulants, such as dabigatran and rivoroxaban, also remains to be seen. A recent indirect comparison of data from the PROTECT-AF and RE-LY trial revealed that the Watchman device would fail to meet noninferiority when compared to dabigatran [47]. Prospective, head-to-head trials are required to address this question.

10. Conclusion

While warfarin has significantly reduced stroke risk in patients with AF, it is still underused secondary to perceived risk for hemorrhagic complications and drug interactions. The LAA is considered to play a major role in thrombogenesis in patients with nonvalvular AF and is a new target for stroke prevention. The FDA has withheld the approval of WATCHMAN device, and better designed trials with a longer followup are necessary to evaluate this method in comparison to warfarin and novel oral anticoagulants.

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