Mechanical Approaches to Stroke Prevention in Atrial Arrhythmias

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ABSTRACT. Stroke is a common and perhaps the most feared complication of atrial fibrillation (AF) and other atrial tachyarrhythmias. The prevention of cerebrovascular and other thromboembolic events is one of the most important goals of AF therapy. Anticoagulation is the current gold standard for AF thromboprophylaxis. However, a large proportion of high-risk AF patients are not receiving pharmacologic antithrombotic therapy because of bleeding risk. Occlusion of the left atrial appendage (LAA) has emerged as an alternative non-pharmacologic strategy for stroke prevention in these patients, given the observation that most AF-related cardioembolic thrombi arise from the LAA. Innovative percutaneous transcatheter devices have been recently developed to emulate surgical exclusion of the LAA in AF patients who are not candidates for anticoagulation. Among those clinically tested are the PLAATO, Watchman, and Amplatz cardiac plug LAA closure systems. Initial results are encouraging; however, these devices remain largely experimental at the present time. Ongoing trials regarding their safety and efficacy would hopefully define their roles in AF stroke prophylaxis in the near future.

KEYWORDS. Amplatzer cardiac plug, atrial arrhythmia, atrial fibrillation, closure device, left atrial appendage, stroke, PLAATO, Watchman.

Introduction

Stroke is the third leading cause of mortality and is the most common reason for long-term disability in the United States. The close association between stroke and atrial tachyarrhythmias, specifically atrial fibrillation (AF) and atrial flutter, is well-established. AF increases the risk of embolic stroke fivefold, and accounts for almost half of all fatal cerebrovascular events. Over 20% of strokes in the elderly population are attributable to AF, and these are associated with higher morbidity and mortality than non-AF cerebrovascular events.

Even asymptomatic atrial arrhythmias significantly increase the risk of stroke. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) enrolled over 2500 high-risk patients with permanent pacemakers and without overt AF at baseline. Subclinical atrial tachyarrhythmias were detected in 10% of patients after 3 months of pacemaker monitoring, and these were independently predictive of a 2.5-fold higher incidence of ischemic stroke or systemic embolism, with a 13% population attributable risk, after 2.5 years of follow-up.

Because stroke is such a devastating consequence of atrial arrhythmias, the prevention of cerebrovascular events and other thromboembolic complications has become the most important goal of AF therapy. Pharmacologic antithrombotic strategies remain the mainstay of stroke thromboprophylaxis in AF. Oral anticoagulation, warfarin in particular, has been effective, reducing stroke rates by over 60%. Novel antithrombotic agents, including dabigatran and rivaroxaban, have recently emerged as efficacious alternatives to warfarin. However, less than half of high-risk patients with AF are actually on appropriate anticoagulant therapy in spite of its well-established benefits. Bleeding events are the most common adverse effect and the most
likely reason for discontinuation of anticoagulation in AF, with fatal and clinically relevant hemorrhagic events occurring at rates of around 1% and 20% per year, respectively.\textsuperscript{9,10}

AF patients who are at highest risk for thromboembolic events are often the same individuals who are at highest risk of bleeding from anticoagulant therapy, particularly in elderly individuals with multiple comorbid conditions.\textsuperscript{11} AF-related stroke risk dramatically increases just days after discontinuation of anticoagulation,\textsuperscript{12} leaving the most vulnerable patients unprotected from the most devastating complication of the disease. Clearly, alternative approaches to pharmacologic antithrombotic therapy are required for these high-risk individuals.

**Left atrial appendage exclusion**

The left atrial appendage (LAA) is the remnant of the primordial embryonic left atrium. Its walls are trabeculated, compared with the smooth-walled main cavity of the left atrium that develops later.\textsuperscript{13} In sinus rhythm, the LAA apex is highly contractile and usually obliterates during its systole. This characteristic emptying pattern that effectively ejects blood from the LAA is diminished or lost in atrial dysrhythmias.\textsuperscript{14} As a result, blood flow velocity in the LAA decreases, leading to stasis and predisposition to clot formation.\textsuperscript{15} LAA thrombus, as detected by transesophageal echocardiography (TEE), is present in about 13% of patients with AF, and accounts for most strokes in these patients, particularly the larger and more disabling ones.\textsuperscript{16,17} Since up to 90% of non-rheumatic AF-related left atrial thrombi arise from the LAA, obliteration or exclusion of this structure, at least in theory, should lead to a reduction in stroke risk.\textsuperscript{18} Surgical closure or excision of the LAA for this purpose has been practiced since the 1930s using different techniques with varying success. A reduction in the incidence of cerebrovascular events was seen in some of these surgical series.\textsuperscript{19,20} Routine prophylactic removal of the LAA during open-heart surgery in non-AF patients has been suggested to reduce subsequent stroke risk, and the technical feasibility of therapeutic LAA excision using minimally invasive thoracoscopic approaches has previously been demonstrated in those with AF.\textsuperscript{21} The insight gained from surgical experience has sparked the development of percutaneous transcatheter techniques and devices for LAA closure, with the prospect of less periprocedural morbidity and greater applicability across a broader range of patient populations. Recent innovations in the field have made device-based therapy a feasible alternative to pharmacotherapy for stroke prophylaxis in AF.

**The PLAATO device**

The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device (ev3 Inc., Plymouth, MN) was the first transcatheter LAA closure system to actually undergo clinical testing.\textsuperscript{22,23} The implant consists of an occlusive polytetrafluoroethylene ePTFE membrane which is laminated directly to a nitinol self-expanding cage frame. The implant is mounted on a delivery catheter and, utilizing femoral venous access, is introduced into the right atrium and across into the left atrium through a transseptal approach. The device is deployed inside the LAA such that the perimeter of the frame presses against the LAA wall while the occlusive membrane covers the orifice, closing off blood flow into the LAA cavity (Figure 1a). The ePTFE layer promotes eventual endothelialization of the surface facing the left atrial chamber.

The PLAATO device was first implanted successfully in humans in 2001. Subsequently, the safety and efficacy of this system was evaluated in the prospective, non-randomized, multicenter PLAATO Feasibility Trials,\textsuperscript{24} which enrolled 111 high-risk AF patients in whom anticoagulation was contraindicated to undergo transcatheter LAA closure. Implantation and procedural success was achieved in 97% of patients, with an 8% incidence of procedural serious adverse events. After median follow-up of ~10 months, the all-cause mortality rate was 5.4% (none were device related), and 1.8% of the patients had a stroke. The annual stroke rate was estimated at 2.2%, with an assumed 65% relative reduction in the risk of cerebrovascular events. Five-year follow-up data were available in 64 patients in the United States and Canada, of these 27% died (none were device related) and 12.5% had strokes. After long-term follow-up, the annualized stroke rate was 3.8%, or a 42% risk reduction compared with the anticipated 6.6% annual stroke rate as predicted by the CHADS2 scoring system.\textsuperscript{25}

![Figure 1: Transcatheter left atrial appendage closure systems: (a) PLAATO device, (b) WATCHMAN device, (c) Amplatzer cardiac plug device.](image-url)
The European PLAATO study\textsuperscript{26} enrolled 180 high-risk AF patients who were not eligible for anticoagulation to undergo percutaneous LAA occlusion. The device was successfully implanted in 90% of cases, with 1.1% procedural mortality, and 3.3% incidence of procedural cardiac tamponade. After nearly 10 months of follow-up, 1.7% of the patient had documented strokes. The estimated annual stroke rate of 2.3% with the PLAATO device, like that of the North American data, was lower than that expected for this patient population. Although results were encouraging, the PLAATO studies were prematurely terminated because of financial reasons, and the manufacturer subsequently halted further development of the device.

The PLAATO implant was relatively rigid. Its circular shape required 20–50% oversizing relative to the typically oval LAA orifice to achieve an adequate seal, and deep implantation was necessary to achieve stability within the LAA cavity. As such, certain anatomic variations of the LAA (e.g. short proximal portion, early separation into lobes) could not be completely closed by the PLAATO device. These limitations were addressed by the next generation of devices, which have greater flexibility and have flatter profiles.

The **WATCHMAN device**

The Watchman LAA occlusion device (Boston Scientific, Natick, MA) is comprised of a self-expanding nitinol frame structure with a series of fixation barbs. The atrial surface of the implant is covered with a permeable polyester fabric (Figure 1b). It is available in several diameter sizes to accommodate each unique LAA anatomy. The device size chosen is typically 10–20% larger than the orifice of the LAA. Like that of the PLAATO system, the Watchman delivery catheter is advanced from the right atrium across into the left atrium via a transseptal approach.\textsuperscript{27}

The Watchman LAA system was the first transcatheter LAA occlusion device tested in a large, randomized, multicenter fashion. The PROTECT-AF (Embolic Protection in Patients With Atrial Fibrillation)\textsuperscript{28} trial enrolled over 700 high-risk patients with AF who were randomized 2:1 to either percutaneous LAA closure with subsequent discontinuation of anticoagulation, or anticoagulation alone. Device implantation was successful in 91% of attempts, with a 7.7% incidence of procedural adverse events, including a 5% incidence of serious pericardial effusion and 0.9% procedural stroke rate. The procedural adverse event rate later went down to 3.7% with increased operator experience.\textsuperscript{29} After 6 months, 92% of the 385 patients in the closure group discontinued anticoagulation without an increased risk of subsequent stroke. After a median 18-month follow-up, the primary efficacy event rate (assessed as composite of stroke, systemic embolism and cardiovascular death) was 3 and 4.9 per 100 patient-years in the closure versus control groups respectively. The 62% risk reduction in primary efficacy events with LAA closure was driven by a 94% lower incidence of hemorrhagic stroke and a 74% reduction in cardiovascular mortality. There was, however, a 41% increase in primary safety events (major bleeding, pericardial effusion, device embolization) in the Watchman group compared with control. Overall, the study found that percutaneous LAA closure was non-inferior to standard anticoagulant therapy for stroke prophylaxis in high-risk AF patients.

The PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Version Long Term Warfarin Therapy) trial is a prospective, multicenter study designed to provide additional efficacy and safety information as a requirement prior to full approval by the US Food and Drug Administration. The trial is currently recruiting subjects, and primary outcome data collection is expected to be completed by late 2013.\textsuperscript{30}

The **Amplatzer device**

A variety of Amplatzer septal occluder devices (AGA/St. Jude Medical, St. Paul, MN) has been available for many years and used extensively for closure of atrial and ventricular septal defects and other cardiac shunts. Off-label use of these devices to close the LAA of AF patients for stroke prophylaxis has been reported since 2002.\textsuperscript{31} Eventually, a novel device, the Amplatzer Cardiac Plug (ACP), was developed for this specific purpose.

Like the other double-disk septal occluders, the ACP device consists of a self-expanding nitinol mesh containing polyester occlusion patches. The implant has an outer disc that seals the LAA orifice, connected by a central waist to a lobe with stabilizing hooks that get deployed inside the LAA cavity (Figure 1c). Like the Watchman device, the ACP system comes in different sizes, and the appropriate lobe size chosen is 10–20% larger than the narrowest diameter of the LAA body to allow sufficient fixation within the cavity. Similar to the other transcatheter LAA closure devices, the ACP system is delivered into the left atrium via a transseptal approach. The relatively short length of the ACP device allows for implantation in shallow LAA variants, which purportedly gives it an advantage over the PLAATO and Watchman devices that require a deeper LAA anatomy because of their longer profiles.

A retrospective analysis of the first 137 patients who underwent attempted ACP device deployment in Europe showed a 96% implantation success rate. Serious procedural complications occurred in 7% of patients, including a 3.5% incidence of significant pericardial effusion.\textsuperscript{32} A prospective series of 20 patients with high-risk AF who were not eligible for anticoagulation was subsequently reported. In this feasibility study, procedural success was achieved in 95% of patients without any device-related complications. No stroke or death was reported after 1 year clinical follow-up.\textsuperscript{33} A small, randomized, phase 1 trial is nearing completion in the United States.\textsuperscript{34} However, larger multicenter studies are required to definitively establish the clinical efficacy of the ACP system for stroke prophylaxis in AF.
Discussion

The PLAATO device is no longer available, leaving the Watchman and ACP percutaneous transcatheter LAA closure systems as the only non-pharmacologic, non-surgical alternatives for stroke prophylaxis in high-risk patients with atrial tachyarrhythmias at the present time. While these devices have been approved and used extensively in Europe and other countries, they are still considered experimental and are unavailable outside of the research setting in the United States.

The relatively high incidence (7–8%) of procedural serious adverse events associated with the implantation of these devices is a major concern. In the long term, however, the beneficial effects on stroke reduction appear to greatly outweigh these short-term risks. Continued technological innovations in device design, as well as advances in procedural techniques and operator training, are expected to increase the safety of these transcatheter systems and further reduce complication rates.

It is important to point out that while these LAA closure devices may significantly reduce the thromboembolic risk in appropriate AF patients, there remains a considerable residual stroke risk since over 30% of ischemic strokes in AF are non-thromboembolic in etiology. This is in addition to the fact that AF-related cardioembolic thrombi also form outside the LAA.

The definitive role of the LAA closure devices for AF thromboprophylaxis in real-world clinical practice currently remains unclear. The European guidelines for the management of AF do acknowledge that LAA occlusion might be considered for patients with contraindications to chronic anticoagulation. This limited recommendation will likely remain as such until more authoritative data are available as to their safety and efficacy. Individuals who will benefit from LAA closure are probably those who are at the highest risk for both stroke and hemorrhagic complications; therefore, patient selection is of paramount importance in order to realize the optimal protective potential of device-based antithrombotic therapy. The thrombotic risk in AF patients is easily estimated using the CHADS2 score or other risk-stratification schemes that assess the probability of stroke using comorbid factors such as advanced age, hypertension, heart failure, diabetes, previous cerebrovascular event, and vascular disease. The quantification of bleeding propensity is less well-defined, but recent prediction models identified advanced age, male sex, renal impairment, alcohol consumption, and previous bleeding episode as independent risk factors for hemorrhagic complications in anticoagulated AF patients.

Conclusion

Innovation paved the way for the emergence of device-based therapy as a viable alternative to standard pharmacologic strategies for stroke prevention in patients with atrial arrhythmias. Further technological advancements, refinements in procedural techniques, and increasing worldwide experience on this novel therapy should help overcome the many limitations of the current generation of LAA closure devices. Although preliminary data on mechanical strategies of stroke prophylaxis are favorable, their role in AF management remains undefined until more conclusive evidence establishes their safety and efficacy.

References