Non-Pharmacologic Stroke Prevention For Atrial fibrillation: A Practical Review for the Practicing Cardiologist

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Synopsis

Atrial fibrillation related stroke is increasing in prevalence globally due to the elderly population. Oral anticoagulation has traditionally been used for stroke prevention. However these therapies are associated with increased risk of bleeding. Recently, non-pharmacologic percutaneous devices to prevent thrombus formation in the left atrial appendage, and thereby reduce the risk of stroke, have been developed and now being used in clinical practice. This review will summarize considerations regarding the use of percutaneous left atrial appendage devices for the practicing cardiologist.

Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia worldwide affecting 1%-2% of general population. It is anticipated that the number of individuals with AF will increase with time due to the elderly population. AF is an independent risk factor for stroke and thromboembolism with approximately 85% of all stroke in AF patients being thromboembolic in origin. A summary of echocardiographic, surgical and autopsy data suggest that the usual origin of the clot in AF is from the left atrial appendage (LAA). Non-pharmacologic methods for stroke prevention (NPSM)

The current methods for stroke reduction in AF include the use of oral anticoagulation (OAC). Until recently warfarin was the primary OAC used for stroke prevention. Warfarin is an effective anticoagulant shown to have 60-70% relative risk reduction versus no treatment. Warfarin has its own limitations including a narrow therapeutic window, frequent dose adjustments and monitoring tests. As a result of this, a significant proportion of the population achieves a suboptimal time in therapeutic range. Novel oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban are currently available and have been shown to be equivalent or superior to warfarin with regards to stroke prevention and bleeding. Despite these improvements, these agents too are not without their own limitations including inability to use in patients with severe renal dysfunction, patient side effects leading to discontinuation, bleeding especially when used in combination with dual antiplatelet agents, and the lack of clinically available antidotes. These limitations, in addition to the fact that many patients with AF have relative or absolute contraindications to OAC, have resulted in increased enthusiasm in non-pharmacologic methods for stroke prevention.

Non-pharmacologic methods for stroke prevention

Non-pharmacologic options to avert stroke among atrial fibrillation include restoration of sinus rhythm with catheter ablation and LAA occlusion. Recent work has suggested that patients post AF ablation have a low rate of stroke, approaching that of the general population. However, as most patients undergoing AF ablation are at low risk for stroke, and OAC use post ablation was heterogenous in these cases, LAA occlusion devices were developed to prevent clot formation in the LAA. The LAA occlusion devices have been shown to reduce the risk of stroke compared to OAC alone in patients with contraindications or intolerance to oral anticoagulation. However, the long-term efficacy of these devices is not yet established. It is important to note that the LAA is a thrombus prone area and can act as a source of emboli which can be shed and cause stroke. Therefore, LAA occlusion devices are used to prevent clot formation in the LAA and prevent stroke.

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studies of patients, it is not clear if catheter ablation should be considered a reliable method of stroke reduction. Indeed, a recent study with continuous monitoring of post catheter ablation for atrial fibrillation demonstrated a high proportion of asymptomatic AF, with at least 12% of all patients having only asymptomatic AF. As such, we may not be able to detect AF post ablation and potentially withhold appropriate therapy for stroke prevention. Given this, guidelines recommend OAC as a predominant strategy for prevention of CVA post ablation.

Rationale for LAA closure

As the LAA is the principle nidus for thromboembolic stroke among patients with AF, closing this structure (Figure 1) may result in a significant reduction in stroke risk without the need for OAC. This approach may represent an alternative for drug intolerant or drug ineligible patients.

Surgical LAA closure

Data on surgical LAA closure showed that such procedure is feasible and safe. This approach however is reserved for patients undergoing other open heart surgeries such as mitral valve repair. Despite its advantage of direct visualisation, this procedure still has high rates of incomplete closure rates (20-70% with various techniques of suturing, ligation and excision) related to the friability of the LAA which is prone to tearing during surgical manipulation, as well as the fact that this structure resides adjacent to critical structures such as the circumflex artery and mitral valve. These factors and others contribute to a high rate of stroke secondary to an incompletely ligated LAA.

Recently evolved minimally invasive techniques like atrial exclusion devices (Atriclip (Atricure) and Tigerpaw (Maquet)) have become available and have been suggested to be a better technique for achieving complete closure compared to suture ligation or stapling of the LAA. Preliminary data suggest a high rate of acute LAA closure, however longer term follow-up with these devices is lacking.

Percutaneous LAA closure

Percutaneous approaches to LAA closure have been developed and have the advantage of their minimally invasive nature with less morbidity when compared to standalone cardiac procedures for LAA closure. These procedures can be performed with an exclusive endocardial approach and/or with the addition of pericardial access.

Endocardial devices currently with CE mark include the Watchman device (Boston Scientific), Cardiac Plug (St. Jude Medical), and the WaveCrest occluder (Coherex Medical). Of these devices, only the Watchman has achieved FDA approval. The Lariat is a percutaneous epicardial method of LAA occlusion which has both FDA approval and CE mark.

Percutaneous endocardial LAA occlusion - the procedure

With these devices a transseptal puncture is performed and using transesophageal echocardiogram guidance, and a device, typically constructed of a nitinol frame with fabric mesh, placed at the ostium of the LAA (Figure 1). Minor variations in these devices are present and may impact their implantation in various LAA morphologies. For example, the double disc design of the Cardiac Plug makes it suitable for closure of short LAA (see Figure 2).

Post procedure some degree of OAC or antiplatelet therapy is required while these devices endothelialize to avoid acute thrombus formation on the device. The regimen from the PROTECT AF and PREVAIL studies require short term warfarin use for 6 weeks followed by dual antiplatelet use for an additional 6 months followed by lifelong aspirin use. The requirement for warfarin stems from animal work where autopsy work has demonstrated near complete endothelialization within 45 days post implantation. As patients may be at risk for acute device related thrombus formation and subsequent stroke during this period of endothelialiation, it seems rational to consider a short term course of anti-coagulant or anti-thrombotic therapy.

Even periods of short term OAC may not be suitable for patients with absolute contraindications to OAC. The ASAP trial evaluated patients with contraindications to OAC. In this study, patients post implantation of the Watchman device received aspirin and clopidogrel for 6 weeks. The stroke rate was low suggesting that this strategy may be a reasonable alternative to short term warfarin use.

Of note, the long term OAC strategy is not clear in the case of patients when perfect device and LAA match is not present. This scenario is not uncommon given the unique, often ovoid shape of the LAA ostium, and the fact that LAA occlusion devices are circular by design. Theoretically device leaks, or areas with residual flow post implantation, may place patients at risk for stroke. However, how much of a device leak is acceptable is not clear. Sub-group analysis of the PROTECT AF trial suggests that leaks <5mm are common, but may not be associated with increased stroke.

As with any invasive procedure, complications can occur and include cardiac perforation, pericardial effusion and tamponade, device embolization, and acute thrombus formation with resulting stroke, and air embolism due to the use or large bore transseptal sheets. Complications rates do decrease with user exposure and increasing procedural volume. For example, overall complications occurred in 10% of patients enrolled in the first half of the PROTECT AF
study, 7.7% of patients in the second half of this study, and 3.7% of patients in the subsequent Continued Access Registry. Specific complications such as pericardial effusions occurred in 5.5% of patients in the PROTECT AF study but only 2.2% of patients in the Continued Access Registry and procedure related stroke in 0.9% in the PROTECT AF study and 0% in the Continued Access Registry.

Percutaneous endocardial LAA occlusion - the evidence

To date, high quality long term efficacy data on non-pharmacologic methods of stroke prevention has been obtained from study of the Watchman device. Specifically, two pivotal randomized controlled data comparing this technology to OAC are available with this device11, 12 which will be discussed below. Case controlled series comparing to historical controls are available with alternative devices13, 14, 15. We will not discuss these studies further given the limitations of case-controlled research.

The PROTECT AF was the first randomized controlled trial evaluating non-pharmacologic stroke prevention with the Watchman device in relation to warfarin with a therapeutic INR. 707 patients with a CHADS2 score ≥1 (mean score of 2.2) were randomized 2:1 (Watchman:Coumadin). Patients in the warfarin arm were well managed with a time in therapeutic range of 70%. The primary endpoint was a composite of stroke, systemic embolism, and cardiovascular or unexplained death. At a mean follow-up of 3.8 years this endpoint was achieved in 8.4% of patients in the Watchman arm compared to 13.9% of patients in the warfarin arm16. Based on the pre-planned analyses the Watchman device was found to be superior to warfarin. An important finding of the study was a reduction in cardiovascular mortality and all-cause mortality with this non-pharmacologic approach compared to warfarin – indeed a 34% reduction in the hazard of death was observed with this device compared to warfarin, a magnitude of mortality reduction similar to that observed with novel oral anticoagulants17. The observed mortality benefit was driven by a reduction in death due to hemorrhagic stroke.

One criticism of this study was the fact that the annual rate of intracranial bleeds, an important event driving the observed improvement in survival, was 1.1% in the warfarin arm, a value higher than that reported in other anticoagulant trials (~0.4-0.5% annually). It is quite possible that the observed mortality benefit would no longer persist should the hemorrhagic stroke rate be similar to that observed in prior studies.

Additionally, ischemic strokes were numerically not reduced in patients receiving the Watchman, a device whose primary purpose was to reduce stroke due to preventing LAA thrombus formation. Indeed the observed ischemic stroke rate was 1.4 events per 100 patients years in the Watchman group compared to 1.3 events per 100 patient years in the warfarin group. Furthermore, this rate was present despite the use of agents which may also reduce stroke – that is warfarin for approximately 45 days and then aspirin and clopidogrel for 6 months post implantation. Understanding whether strokes are reduced with LAA occlusion is critical as this is central to the benefit of LAA occlusion. The authors of the PROTECT AF study suggested that it is quite possible that this increased stroke rate may be related to peri-procedural stroke and air embolism as a pre-specified analysis of patients completing warfarin and clopidogrel therapy (which thereby excluded procedure related strokes) demonstrated a reduction in stroke with the Watchman compared to warfarin.

The PREVAIL study randomized patients with a CHADS2 of ≥2 (mean CHADS2 score = 2.6) in a 2:1 fashion to the Watchman or warfarin with the same primary endpoint as that of the PROTECT AF study. To date, only 18 months of follow-up has been reported with no difference was observed between the two groups. After performing the appropriate statistical testing, the criterion for non-inferiority of the Watchman versus warfarin was not met. This result was counter to what was observed in the PROTECT AF study where the Watchman was superior to warfarin. The authors hypothesize that the findings observed in the PREVAIL study were mainly related to the fact that a lower than expected number of clinical events were observed in the warfarin arm (that is, in the PREVAIL study the stroke and systemic embolism rate was nearly half of that observed in pivotal trials evaluating novel oral anticoagulants). This low event rate likely prevented non-inferiority from being achieved. Consistent with the secondary analyses of the PROTECT AF study, the Watchman was also found to be non-inferior to warfarin with regards to strokes occurring >7 days post procedure in the PREVAIL trial (i.e. non-procedure related strokes). This consistency supports the LAA as a source of thrombus and embolism in patients with non-valvular AF.

FDA approval

After years of deliberation, in March 2015 the United States Food and Drug administration gave approval to the Watchman for stroke prevention in AF. This decision was achieved almost 2.5 years after this device achieved CE mark in Europe. Three independent FDA advisory panels reviewed the available data supporting the use of the Watchman for stroke prevention. Various issues arose including the study design and complex statistical analysis and the impact of stroke reduction with concomitant use of warfarin and dual anti-platelet agents. In the end, the panel agreed that this device is safe for use...
however the efficacy of the device for stroke prevention was not clear. Furthermore, its place in relation to novel oral anticoagulants which have a lower bleeding rate was also not clear. Nonetheless, FDA approval was achieved.

The role of the Watchman and other LAA occlusion devices in relation to novel OAC is not clear. It is unlikely that direct head-to-head comparisons of these agents to the Watchman will be performed as such trials will require thousands of patients and a long duration of follow-up to assess their efficacy given the low rates of stroke and bleeding with these novel LAA occlusion devices and novel oral anticoagulants. Decision models may help in the absence of these direct comparisons. A prior model evaluated dabigatran and LAA occlusion to warfarin in the setting of public health care in Ontario, Canada. This study demonstrated that while these novel therapies are more expensive compared to warfarin, they are associated with greater quality of life years when compared to warfarin. Both LAA occlusion and dabigatran were shown to be within accepted thresholds for cost-effectiveness when compared to warfarin, with LAA occlusion being favored. Future work comparing these therapies to all available novel oral anticoagulants and utilizing real world data rather than that derived from randomized clinical trials, will be important to truly assess the place of these non-pharmacologic therapies in relation to pharmacologic therapies for stroke prevention in AF.

Additional research and guidance from healthtechnology agencies and guidelines committees will help clinicians understand the appropriate role of these therapies in clinical medicine.

**Percutaneous epicardial LAA ligation**

Percutaneous epicardial LAA suture ligation may provide stroke reduction similar to percutaneous endocardial device placement (Figures 3 and 4). However, an epicardial approach may have further advantages including lack of need for periprocedural OAC due to the absence of any endocardial manipulation or device placement, lack of device embolization within the systemic circulation, and lack of endovascular infection as no endocardial foreign object is left behind. Furthermore, recent work has suggested that epicardial ligation may have an antiarrhythmic effect. Specifically, ligating the LAA has been shown to be associated with a reduction in the LAA electrical activity, (Figure 4) which may have a long term antiarrhythmic effect with a reduction in AF burden.

**Current systems include the Lariat (Sentreheart Medical) and the Aegis Suture Ligation System (Aegis Medical).** The Lariat system requires the use of a combined endocardial and epicardial approach (Figure 3), with the endocardial approach providing a stabilizing method to deliver the LAA suture loop. The Aegis suture ligation system utilizes an electrogram guided approach to identify the LAA and determine when appropriate ligation has occurred due to the subsequent loss of LAA electrical signals (Figure 4). This system is a pure epicardial approach.

Published human data is currently only available with the Lariat system which is currently used clinically in the United States as it has FDA approval via the 510K clearance. Indeed this approval is not specifically for stroke reduction in AF, or LAA occlusion, but rather for soft tissue approximation. A multicenter study in the acute and long-term safety and efficacy of the LARIAT demonstrated an acute LAA closure rate of 93%. However, this value was reduced to 76% (with residual LAA leak between 1-5mm) during long-term follow up. Furthermore, pericardial effusions were present in 20% of patients, and LAA tears present in 9% of patients (half of whom required surgical repair). Further long term safety and efficacy data to confirm stroke reduction efficacy is necessary to understand the place of this therapy in our armamentarium for stroke prevention in AF.

**Conclusion**

In summary, non-pharmacologic methods of stroke prevention in patients with AF are now present, with evolving data suggesting these therapies may be safe and efficacious. The role of these devices in relation to recently available novel oral anticoagulants remains unclear, but it is likely that their role will expand in clinical care. Given the paucity of data supporting these devices, we encourage ongoing real world data collection to fully understand the safety and efficacy of these therapies.

**References**

**Figures:**

Figure 1.
Left Atrial Appendage with WATCHMAN device implanted.


