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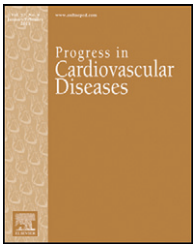

Left Atrial Appendage Closure

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ABSTRACT

Stroke or systemic embolism is a devastating consequence of atrial fibrillation (AF) due to thrombus formation in the left atrial appendage (LAA). AF causes thrombus formation in the LAA due to both the loss of atrial systole and the unique anatomic features of the LAA. Oral anticoagulation is a well established and effective therapy to reduce the risk of stroke in AF patients, albeit with a risk of bleeding. LAA closure is a possible alternative to oral anticoagulation in the prevention of stroke or systemic embolism in AF.

Atrial fibrillation (AF) affects 1–2% of the US population, and an estimated 2.3 million persons in the United States (US) in 2001, with the expected number of affected individuals in the US to double by 2050.[1]

AF independently increases the risk of stroke by 4 to 5 fold and is responsible for 15% of all strokes regardless of age and 30% of all strokes in affected individuals over the age of 80.[2,3] In addition, cardio-embolic strokes are particularly severe with the worst prognosis among the various causes of stroke.[4]

Stroke is ranked as the fourth most common cause of death in the US and, along with cardiovascular (CV) disease, is the second leading cause contributing to disability adjusted life years.[5]

Echocardiographic and anatomic studies in non-valvular AF (NVAF) suggest that 90% of the strokes caused by AF are thromboembolic events originating from the left atrial (LA) appendage (LAA).[6] In one study using trans-esophageal echocardiography (TEE) prior to electrical cardioversion of AF, 15% of patients not on anticoagulation demonstrated evidence for LA thrombus after greater than 48 hours of AF.[7] Of the 34 LA clots in this study, all but one of the thrombi were found in the LAA. The LAA is particularly prone to thrombus formation in AF due to increased blood stasis and extensive trabeculations.[8]

The recognition of thrombus formation in the LA in AF has led to the strategy of using systemic oral anticoagulation (OAC) to prevent cardioembolic strokes; OAC is clearly very effective in preventing thromboembolic events in AF.[9] There are now several options for OAC with substantial clinical evidence of their efficacy in reducing the risk of thromboembolic events in patients with NVAF ranging from warfarin to the novel oral anticoagulants (NOAC).[10] However, all forms of OAC suffer from disadvantages inherent in systemic anticoagulation, which is predicated upon compliance with an oral medication. The recognition that thrombus formation within the LA is almost exclusively seen in the LAA raises the possibility of an anatomically *local* approach to thromboembolism prevention in AF through LAA closure (LAAC). In addition, some techniques of LAAC may play an adjunctive role in maintaining normal sinus rhythm through eliminating non-pulmonary vein triggers, decreasing atrial mass and reverse atrial electrical remodeling.[11–13]

Statement of Conflict of Interest: see page 200.

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Abbreviations and Acronyms
AF = atrial fibrillation
CHF = congestive heart failure
CV = cardiovascular
DM = diabetes mellitus
FDA = Federal Drug Administration
HTN = hypertension
INR = International Normalized Ratio
LA = left atrial
LAA = left atrial appendage
LAAC = left atrial appendage closure
NVAF = non-valvular atrial fibrillation
OAC = oral anticoagulation
NOAC = novel oral anticoagulant
TEE = trans-esophageal echocardiography
US = United States

Oral anticoagulation — Advantages and pitfalls

A fundamental judgment clinicians face in recommending OAC to patients presenting with NVAF is the risk of stroke balanced by the risk of bleeding.

The most commonly used models for assessing the risk of thromboembolism based upon demographic and clinical risk factors are the $CHADS_2$ and the CHA_2DS_2-VASc tools. The $CHADS_2$ scoring system uses risk factors of congestive heart failure (CHF; 1 point), hypertension (HTN; 1 point), age >75 (1 point), diabetes mellitus (DM; 1 point), and previous stroke or TIA (2 points). The risk of stroke is considered low with a score of 0, intermediate with a score of 1, and high with a score ≥2. The CHA_2DS_2-VASc scoring system risk factors include CHF or left ventricular ejection fraction <40% (1 point), HTN (1 point), age >75 (2 points), DM (1 point), previous stroke, TIA, or cardio-embolic event (2 points), vascular disease (1 point), age >65, <75 (1 point), and female sex (1 point). Low risk is defined as 0 (or 1 point for a woman in the absence of other risk factors). A score of ≥2 is considered high risk. High risk corresponds to a yearly stroke risk of at least ~2%.

To better assess the risk of bleeding on OAC, several scoring systems have been evaluated, with the HAS-BLED score (HTN, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio (INR), age >65, drug or alcohol use) being the most common. A HAS-BLED score of >3 is considered high risk for significant bleeding. In a 2012 study of 2293 patients with NVAF randomized to idraparinux or dose adjusted warfarin, the HAS-BLED score was the best predictor of clinically relevant bleeding issues when compared to other scoring systems such as ATRIA and $HEMORR_2HAGES$.[14] However, what makes the everyday clinical utility of scoring systems for bleeding difficult is not only the modest performance of HAS-BLED, ATRIA, and $HEMORR_2HAGES$ in predicting clinically relevant bleeding, but also that the risk of stroke in AF and the risk of significant bleeding share several common risk factors. This muddies the ability of a clinician to delineate a clear choice.

While OAC is the dominant and effective therapy at preventing thromboembolism in AF there are several significant limitations inherent in OAC.

1. Fewer than 50% of patients with AF are considered candidates for OAC due to the risk of bleeding or other considerations such as wide swings in INR.[1,15,16] Even in AF patients considered candidates for OAC with warfarin, only 38% of patients had warfarin prescribed.[17]
2. Despite the superior convenience of the NOACs compared to warfarin, the discontinuation rate of study NOAC in the NOAC clinical trials ranged from 21–25% and up to 28% in the warfarin control arms.[18–20]
3. Compliance with poly-pharmacy in patients with the co-morbidities frequently associated with AF may limit the continuity of OAC, and, in the case of warfarin, time in therapeutic INR range is commonly ~60%.[18–20]
4. The risk of increased bleeding with OAC in combination with anti-platelet agents required with drug-eluting coronary stents presents a particular clinical challenge in patients with concomitant coronary heart disease and AF.[21]

Given the challenges of OAC and the evidence that the LAA is the source of atrial thrombi in 90% of patients with AF, LAAC is a strategy that has been vigorously pursued.

In contrast to pharmaceutical trials of OAC, LAAC trials highlight the difficulties inherent in device-based trials including much smaller numbers of enrolled patients, the upfront risk of the procedure, and the impossibility of blinding therapy arms. Despite these challenges, the Federal Drug Administration (FDA) has approved the use of the Watchman device as an alternative to warfarin OAC based upon data from the PREVAIL and PROTECT-AF trials. In addition, FDA approval of the LARIAT suture delivery system (SentreHeart, Redwood City, CA) for soft tissue closure has resulted in the off-label use of the system for LAAC in well over 2000 patients worldwide. Other devices such as the Amplatzer cardiac plug (St. Jude Medical, St. Paul, MN) or surgical closure with the AtriClip device system (AtriCure, West Chester, OH) have shown promise but lack clinical data.

Percutaneous occlusion

The Watchman device

The Watchman device (Boston Scientific, Natick, MA) is a self-expanding nitinol structure with fixation barbs and a membrane made of polyethylene terephthalate covering the nitinol structure (see Fig 1). The Watchman device is implanted via a trans-septal puncture and occludes the LAA at the level of LAA ostium (see Figs 2 and 3).

The Watchman device has been evaluated in 2 clinical trials. The PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial randomized NVAF patients ($CHADS_2 \geq 1$) in a 2:1 ratio of device to warfarin therapy[22]; 707 patients were randomized from 59 centers worldwide. Patients receiving the Watchman device were required to undergo warfarin OAC for 45 days after implant. If a TEE at 45 days demonstrated either complete LAA closure or a peri-device leak of less than 5 mm, patients were taken off of warfarin OAC and continued with clopidogrel and aspirin for 6 months, and then aspirin indefinitely. The study used a Bayesian sequential model with planned analysis at 600 patient-years follow-up and every 150 patient-years until 1500 patient-years follow-up occurred.