Stroke Prevention in Atrial Fibrillation: Is Left Atrial Appendage Closure Superior to Systemic Anticoagulation?

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Received: March 12, 2020
Published: April 01, 2020

Introduction
Atrial fibrillation (AF) is the most common arrhythmia worldwide [1], and has significant associated morbidity, including increased risk of stroke. Stroke prevention in non-valvular AF (NVAF) is a dynamic, rapidly evolving and challenging field. Oral anticoagulation (OAC) is well established as the gold standard in stroke prevention for patients meeting risk criteria defined by the CHA2DS2-VASc score [2]. However, these patients are often elderly, with multiple co-morbidities including ischaemic heart disease (IHD), chronic kidney disease and frailty [3] which increase risk of bleeding. Clinicians face daily conundrums on how to balance these risks with the benefits of stroke protection. Left Atrial Appendage closure (LAAC) is an emerging technology which some believe may help to resolve these issues.

Oral Anticoagulation in Stroke Prevention
The benefit of Vitamin K antagonists (VKA) such as warfarin for stroke prevention in NVAF was documented over 2 decades ago by the SPAF (Stroke Prevention in Atrial Fibrillation) trials [4]. A more recent Cochrane meta-analysis [5] demonstrated that VKA conferred a 64% benefit over no treatment, and a 37% benefit over aspirin monotherapy. The major advancement in the last decade has been the advent of Direct Oral Anticoagulants (DOACs). Dabigatran, Rivaroxaban, Apixaban and Edoxaban. The DOACs subverted the risks of sub-/supra-therapeutic treatment and multiple pharmacological interactions that were inherent to VKA, thus reducing the need for regular monitoring. The DOACs outperformed VKA in large randomised control trials, all 4 demonstrating non-inferiority in stroke prevention, with reduced risks of major bleeding [6-9]. As such, the consensus guidelines have expressed a preference for DOACs over VKA in stroke prevention for NVAF patients, with a 1A level of recommendation [2].

Challenges of Oral Anticoagulation
Despite its’ advantages over VKA, there are several drawbacks associated with DOAC therapy. Risk of haemorrhage remains a significant limitation. All agents displaying major bleeding exceeding 3% per year, with particularly increased risks of gastrointestinal bleeding for rivaroxaban and dabigatran [9]. Treatment of patients with IHD also remains problematic due to the need for concomitant antiplatelet therapy. PIONEER-AF PCI [10] compared rivaroxaban plus a P2Y [11] inhibitor versus warfarin plus dual antiplatelet therapy (DAPT) for patients with NVAF undergoing PCI (percutaneous coronary intervention) with stenting. Both arms displayed similar efficacy, and rivaroxaban was associated with a significantly lower risk of clinically significant bleeding (16.8% vs 26.7%, p<0.001). Similar results have been demonstrated for both dabigatran [11] and apixaban [12]. This improved safety profile is reflected in the the most recent consensus guidelines, where DOAC are advocated in preference to VKA in patients undergoing PCI [13]. However, it is clear that clinically significant bleeding rates are still prohibitively high (10-15%) for all DOAC agents when added to an antiplatelet, compared to the bleeding rates for DAPT, which is roughly 2% [14]. OAC compliance is also a major issue. 25-55% of patients are reported to be non-compliant with chronic cardiovascular medications [15]. The reasons for this include patient-related factors (e.g. socio-economic barriers), medication-related factors (e.g., cost, side effects) and provider-related factors (e.g., a lack of follow-up). Paradoxically, compared to VKA, lack of regular monitoring for DOACs limits the physicians’ ability to ensure compliance. This can be highly detrimental given their short half-lives, where discontinuation opens a larger window of risk to the patient. This window of risk is also disadvantage of any OAC strategy with regards to situations such as mandatory discontinuation for surgical procedures [16]. Given these inherent challenges, it may be that an alternative strategy may be superior to systemic anticoagulation, especially in certain circumstances.

Left Atrial Appendage Closure as a Stroke Prevention Strategy
The Left Atrial Appendage (LAA) has long been implicated in AF-related stroke. It’s anatomy and blood flow characteristics

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predispose to blood stasis and thrombus formation in AF [17], and echocardiographic studies have demonstrated that LA thrombus is responsible for over 90% of AF-related strokes [18]. Historically, open surgery was the only option for closure of the LAA; however, in more recent years, newer technologies have emerged, including endocardial closure devices (Watchman, Amplatzer), percutaneous-approach epicardial ligation (LARIAT), and open/thoracoscopic epicardial clipping (Atriclip). Surgical LAAC has been performed concomitantly with surgical AF ablation, valve surgery and coronary artery bypass grafting (CABG) for decades. However, data is limited to observational cohorts and small randomized studies. A retrospective review of patients undergoing mitral valve surgery suggested a reduction in stroke risk for those who had LAAC [19] (3.4% vs 17%, p=0.01). The LAACOS I [20] and II [21] pilot studies demonstrated the safety of concomitant LAAC plus CABG, and suggested a reduction in stroke rate in the LAAC arm. However, neither was adequately powered for stroke outcomes. The LAACOS III randomized trial is currently underway, investigating the additional benefit of LAAC to OAC therapy in patients with AF undergoing CABG [22].

Thus far, 2 randomized control trials have compared VKA to LAAC with the Watchman Device. PROTECT-AF [23] demonstrated non-inferiority of LAAC compared with VKA therapy, but with a higher rate of peri-procedural complications. The subsequent PREVAIL [24] trial had vastly improved safety outcomes, likely driven by increased operator experience, but failed to meet non-inferiority with regards to 12-month efficacy. However, the 5-year outcomes from these 2 trials demonstrated that LAAC provided stroke protection comparable to VKA, with reductions in major bleeding and mortality [25]. A separate analysis revealed that LAAC had a statistically significant net clinical benefit over VKA of 1.42% events per year [26]. In the first year after device implantation, there was a non-significant benefit for VKA because of peri-procedural complications of LAAC. However, the balance shifted between 1 to 2 years follow-up in favour of LAAC. No studies have compared LAAC with DOAC therapy: this is the aim of the ongoing PRAGUE-17 study [27]. As yet, there is no randomized data examining epicardial devices such as LARIAT or Atriclip, although both have US FDA approval for LAAC based on observational data. A large US registry demonstrated good safety outcomes for LARIAT, with a 2.2% acute complication rate, and 95% acute procedural success rate [28]. Pillarsetti et al compared retrospective outcomes of patients treated either with LARIAT or Watchman, showing no difference in thromboembolism outcomes [29]. Registry data from patients receiving the Atriclip and discontinuing NOAC revealed a relative risk reduction of 87.5% in ischaemic stroke rate, compared to what would have been expected in a group of patients with similar CHA2DS2-VASc scores [30].

**Perspective: Current and Future Directions for LAA Closure**

Whilst LAAC shows promise as a strategy for stroke prevention in NVAF, no data thus far suggests superiority efficacy over OAC. Concerns about peri-procedural complications and cost mean current indications are limited to patients with contraindications to systemic anticoagulation [31], generally due to high bleeding risk. LAAC also may be used concomitantly with cardiac surgery, where the additional risk is minimal. Serious thought should be given to performing LAAC in every AF patient undergoing CABG, especially considering the high bleeding risks of combination OAC and antiplatelet therapy. Potential use may expand if LAAC is used adjunctively with other procedures as part of a rhythm control strategy. The LAA is implicated in recurrence of persistent AF following catheter ablation [32], and both the LARIAT and Atriclip devices have been shown to provide electrical as well as mechanical isolation [33], which could be effective in reducing AF recurrence. The aMAZE trial will examine the anti-arrhythmic effects of LARIAT when combined with catheter ablation [34], and if successful, LAAC may deliver a crucial “2 birds with 1 stone” quality of life impact on a complex and difficult to treat group of patients.

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Citation: Nadeev Wijesuriya. Stroke Prevention in Atrial Fibrillation: Is Left Atrial Appendage Closure Superior to Systemic Anticoagulation?. LOJ Phar & Cli Res 2(1)- 2020. LOJPCRMS.ID.000127. DOI: 10.32474/LOJPCR.2020.02.000127