Real World Outcomes of Left Atrial Appendage Occlusion

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Abstract
Percutaneous left atrial appendage occlusion (LAAO) is a device-based therapy for the prevention of stroke in patients with non-valvular atrial fibrillation (AF). Recently, the Watchman device (Boston Scientific, St Paul, MN, US) was approved in the US by the Food and Drug Administration (FDA) based on the results of two randomised clinical trials that evaluated LAAO in patients eligible for oral anti-coagulation (OAC) therapy. However, in real-world clinical practice LAAO is typically offered to patients ineligible for OAC therapy, as they appear to have limited treatment options and consequently worse prognosis. Although LAAO has shown favourable clinical outcomes in OAC-eligible patients, these results need to be confirmed in randomised clinical trials.

Keywords
Atrial fibrillation, stroke, prevention, device, closure

Atrial fibrillation (AF), the most common arrhythmia, is associated with a significantly increased risk of morbidity and mortality due to a fivefold increase in the frequency of thromboembolic stroke. The gold standard treatment for the prevention of AF-related thromboembolism is oral anti-coagulation (OAC), based on an individualised patient risk assessment with either the CHADS2 or the CHA2DS2-VASc score. However, up to 20% of patients with AF cannot take OAC therapy, and there exists a considerable bleeding risk among those that can tolerate OAC: intracranial bleeding occurs in 1% of patients taking warfarin per annum, whereas survivors of a haemorrhagic stroke are generally considered inappropriate for anti-coagulation for life. In addition, OAC is associated with significant morbidity and its associated cost implications: for example, OAC-related gastrointestinal (GI) bleeding causes repeated hospitalisations and blood transfusions, and carries a mortality rate of up to 10%. The HASBLED score is the most widely used tool to estimate the risk of major bleeding for patients on OAC therapy. Novel OACs have been shown to be either non-inferior or superior to warfarin therapy with equivalent or decreased bleeding events. Nevertheless, there remains an annual 2–3% incidence of major bleeding.

The left atrial appendage (LAA) is a well-documented source of cardiac emboli in patients with non-valvular AF. Percutaneous LAA occlusion (LAAO) is a device-based therapy that has emerged as an alternative to OAC in patients with non-valvular AF. Evidence confirming the efficacy of LAAO is largely derived from the PROTECT AF randomised clinical trial, in which the Watchman device (Boston Scientific, Marlborough, MA, US) was found to be non-inferior to warfarin for the primary efficacy endpoint of stroke, cardiovascular death and systemic embolism. Importantly, four-year follow-up data from the PROTECT AF trial demonstrated significantly reduced all-cause mortality with the Watchman device compared with warfarin therapy. Conversely, the PREVAIL study, a similar randomised trial that was performed to evaluate the high incidence of safety concerns in the PROTECT AF trial, failed to confirm non-inferiority of the Watchman device compared with warfarin due to an unexpectedly low number of events in the control group. Nevertheless, the study proved safety of the implantation process even in new centres. In Europe, the Watchman device acquired Conformité Européenne (CE) approval in 2005. The relatively small number of patients in randomised trials, however, has hindered the approval of the device in the US by the Food and Drug Administration (FDA) for several years. After three consecutive expert panels, the FDA eventually approved the Watchman device on 13 March 2015, based on all available data including new, unpublished data from the PREVAIL trial. The FDA stated that the device is indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular AF who:

1. Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
2. Are deemed by their physicians to be suitable for warfarin; and
3. Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared with warfarin.

Another device widely used for LAAO is the Amplatzer Cardiac Plug (ACP, St Jude Medical, Plymouth, MN, US). This device was also commercially available in Europe in 2008 following CE mark approval. The ACP has not been evaluated in a randomised setting; however, a large multicentre clinical study and several single-centre reports showed favourable results in terms of safety and efficacy.

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In December 2013, a second-generation Amplatzer device, the Amplatzer Amulet (St Jude Medical, Plymouth, MN, US), also received CE mark approval and initial small series have suggested promising clinical results. Additional devices that have acquired CE mark approval include the Lariat (Stereotaxis, Inc., Redwood City, CA, US), which is FDA-approved for specific ‘soft tissue occlusion’, and the Watchman device (Cook Medical, Salt Lake City, UT, US). Several other novel devices continue development in clinical or preclinical studies.

Today, the main controversy about LAAO relates to the absence of randomised clinical trial evidence evaluating its safety and efficacy in patients with contraindications to OAC therapy: the Watchman device was assessed in warfarin-eligible patients. In OAC-contraindicated patients, there remain however limited or no options that provide adequate stroke prevention. These patients present significant healthcare and social problems, especially the more elderly cohorts that suffer cardioembolic stroke. The most recent European Society of Cardiology (ESC) guidelines on the management of AF suggest that “Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation” (IIb indication, Level of evidence B). Furthermore, the 2014 ESC/European Association of Cardio-Thoracic Surgeons Guidelines on myocardial revascularisation state that "Percutaneous LAA closure and antiplatelet therapy may be considered in patients with atrial fibrillation undergoing PCI if a high stroke risk and contraindication for long-term combined antiplatelet + oral anticoagulation therapy is present" (IIb indication, Level of evidence B). In fact, these guidelines reflect the use of LAAO in the real world. In a 22-centre, non-randomised study that included 1,047 patients who underwent LAAO with the ACP device, the most common indication for LAAO were (1) previous major bleeding (4.7%), followed by (2) high risk for bleeding (35%), and (3) avoidance of triple (dual antiplatelet + OAC) therapy for coronary artery disease and coronary stenting (22%). In the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP) study, a non-randomised evaluation of the Watchman device in patients with a contraindication to OAC therapy, a history of haemorrhagic/bleeding tendencies was the most common reason for warfarin ineligibility (93%). Nevertheless, it should be noted that currently there is no universally accepted definition of contraindication to OAC therapy, so in the real world the criteria for offering LAAO vary significantly between centres.

Although contraindication to OAC is the most common indication for LAAO there is no standardised strategy for antithrombotic medication post-LAAO. For example, LAAO with Watchman should be followed by 45 days of warfarin plus aspirin therapy, and then aspirin monotherapy for life. This strategy arises from PROTECT AF trial protocol and does not take into consideration patients with contraindications to OACs. The ASAP study protocol warfarin was replaced by clopidogrel or ticlopidine. Dual anti-platelet therapy for a period of 1 to 3 months and aspirin for up to 6 months is recommended after LAAO with an Amplatzer device (either ACP or Amulet), however, this strategy is empirical and comes from experience with other Amplatzer closure devices; yet there are no data to support it. Therefore, in real world clinical practice, antithrombotic therapy after LAAO is individualised based on anecdote rather than clinic trial evidence. Physicians should take into account the patient’s history of bleeding, comorbid medical conditions, the completeness of LAAO, and potential for device thrombosis, etc.

Incomplete LAAO is defined as the presence of a leak on color flow Doppler on transesophageal echocardiography (TEE). A small leak (1–5 mm colour flow jet) is not infrequent after LAAO with the Watchman or the ACP device, but it was not reported to be associated with adverse clinical outcome. Post LAAO device thrombosis on follow-up TEE occurs in approximately 4% of patients and is usually successfully treated with a brief period (e.g. 4 weeks) of OAC or low molecular weight heparin. Similar to incomplete LAAO, device thrombosis has not been associated with increased adverse event rates. Management of device thrombosis, however, can be a challenge especially for patients with a very high risk of bleeding, and there remain few available data to guide treatment and follow-up strategies.

The LAA has a relatively fragile, thin-walled structure and considerable variability exists among patients. Moreover, a transseptal approach is almost always needed for endocardial LAAO, whereas a dry pericardial puncture is used for epicardial LAAO. Therefore, it is clear that the procedure requires special operator skills and has a significant learning curve. The most common safety event after LAAO is serious pericardial effusion. Periprocedural stroke, device embolisation and access-related major bleeding have also been reported. Nevertheless, procedural safety is anticipated to improve as operators increasingly perform LAAO and several other structural heart disease interventions and newer devices with improved design features become readily available.

Another significant challenge for LAAO therapy will be to prove its non-inferiority (or superiority) to the novel OAC drugs. Currently, there have been no randomised comparisons between these therapies. One argument against the widespread adoption of LAAO therapy is that the use of aspirin post-LAAO carries a bleeding risk equivalent to apixaban. However, the study on apixaban showing such low bleeding events excluded all patients with prior bleeding and recruited in general a low-risk population (average CHADS 2.1). Indeed, there exist a considerable number of patients who are contraindicated to all antithrombotic drugs, and in these patients the safety and efficacy of LAAO without any post-procedure antithrombotic medication should be tested. Several special patient populations could potentially benefit from LAAO: patients with severe renal impairment who are extremely difficult to manage with warfarin and cannot take the novel OACs, patients on dialysis or patients who suffer a 'stroke on OAC', one of the few occasions when OAC is not stopped after the procedure. Finally, the severity of stroke in the presence of a LAAO device needs to be assessed.

In conclusion, the management of patients with non-valvular AF is a major health problem. Warfarin or the novel OAC drugs are considered a first-line therapy for AF-related stroke prevention but many patients cannot take it due to a prohibiting high risk of bleeding. For those patients LAAO is a reasonable, device-based preventive therapy. Favourable clinical outcomes in observational studies need to be confirmed in randomised clinical trials.
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