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REVIEW

Dealing With the Left Atrial Appendage for Stroke Prevention: Devices and Decision-Making

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Left atrial appendage (LAA) device occlusion represents a major evolution in stroke prevention for atrial fibrillation (AF). Left atrial appendage device occlusion is now a proven strategy which provides long-term thromboembolic stroke prevention for patients with non-rheumatic AF. Evidence supports its benefit as an alternative to long-term anticoagulation while mitigating long-term bleeding risks and improving cardiovascular mortality. The therapy offers expanded options to physicians and patients negotiating stroke prevention (both primary and secondary prevention), but a good understanding of the risks and benefits is required for decision-making. This review aims to summarise the evolution of LAA device occlusion therapy, current knowledge in the field and a snapshot of current status of the therapy in clinical practice in Australia and around the world.

Keywords Stroke prevention • Left atrial appendage • Device occlusion • Atrial fibrillation • WATCHMAN • Amplatzer Cardiac plug

Introduction

Embolic stroke is potentially the most serious complication from atrial fibrillation (AF) with an approximate five-fold increase in lifetime risk [1]. Atrial fibrillation-related stroke is generally associated with increased stroke severity, poorer survival and greater disability among survivors along with higher recurrence rates of stroke than other stroke aetiologies [2].

The recognition of the mechanism of stroke as thromboembolism led to the use of oral anticoagulation with Vitamin K antagonists for thromboprophylaxis. A meta-analysis of randomised controlled trials (RCTs) comparing Vitamin K antagonists with control or placebo suggested a risk reduction in stroke incidence of 64% in favour of warfarin [3]. Indeed, the widespread practice and use of warfarin anticoagulation has led to a decrease in the incidence of AF-related stroke over the past two decades according to observational studies [4,5].

However, warfarin has many well-known limitations including variable pharmacokinetics, narrow therapeutic window, risk of bleeding complications, requirement for monitoring and long-term patient compliance issues. A range of new oral anticoagulants with more predictable pharmacokinetics has recently penetrated global clinical practice with similar demonstrated stroke prophylaxis efficacy [6–8]. These agents have overcome many of the limitations of warfarin therapy and, importantly, have been shown to significantly decrease the risk of haemorrhagic stroke when compared with warfarin. However, they are still associated with a significant risk of bleeding complications and show surprisingly high non-compliance rates over time.

Left Atrial Appendage and Thromboembolism

There are now multiple lines of evidence to support the left atrial appendage (LAA) as being the predominant source of

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thrombi leading to thromboembolism in atrial fibrillation in patients with non-rheumatic aetiologies with over 90% of thrombi located in the LAA [9–11]. The incidence of cerebral emboli also appears to correlate with the structural complexity of the appendage [12]. These findings contributed to a hypothesis that a local solution of excluding the LAA from the systemic circulation might prove to be an effective strategy for stroke prophylaxis.

Interestingly, LAA exclusion or obliteration has existed as an open surgical procedure for almost seven decades with the first recorded resection of the LAA in a human in 1949 [13]. However, data from surgical LAA exclusion have shown mixed results with regards to efficacy of stroke prevention likely impacted by marked variation in exclusion techniques which have included attempts at suture ligation, clip fasteners and surgical amputation with oversew or stapling. The different techniques appear to have significant variation in achieved occlusion rates [14] as well as the documented potential for incomplete closure to actually increase the subsequent risk of thromboembolic stroke [15].

Device Occlusion of the LAA

Catheter-based delivery of a device to occlude the LAA was first conceived in 1998 with the development of the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device. It consisted of a self-expanding nitinol cage with external facing anchor struts and covered with an occlusive membrane of thromboresistant polytetrafluoroethylene (PTFE). Animal studies initially confirmed the feasibility of successful percutaneous implant, successful occlusion of the LAA and subsequent endothelialisation of the device surface [16]. The first LAA device occlusion procedure in a human was performed in 2001 with the PLAATO device [17]. Although the technology was subsequently withdrawn for commercial reasons, observational data from several hundred patients with (non-rheumatic) AF and contraindications to oral anticoagulation implanted with the PLAATO device pointed to a significant reduction in observed stroke rates when compared to the expected stroke rate as predicted by the $CHADS_2$ score [18].

The WATCHMAN device (Boston Scientific Corp, Marlborough, MA, USA) developed by Atritech Inc will remain the pivotal advance which demonstrated with RCT data that LAA device occlusion could provide effective stroke protection when compared with warfarin [19]. Also a self-expanding nitinol structure with external fixation barbs, the WATCHMAN device was initially patented as a filter with a permeable polyethyleneterephthalate (PET) membrane cover designed to sit in the ostium of the LAA (Figure 2, Panel A). Subsequent studies have pointed to the device atrial surface generally undergoing full endothelialisation over several months [20].

Two RCTs have compared WATCHMAN LAA implant with warfarin in patients with non-valvular (non-rheumatic) AF. Protection in Patients With AF (PROTECT-AF) enrolled 707 patients with a mean $CHADS_2$ score of 2.2 and a total follow-up time of five years [19]. Warfarin was continued up to 45 days in the WATCHMAN arm until satisfactory LAA occlusion was demonstrated on follow-up transoesophageal echo study, with 92% of WATCHMAN patients subsequently discontinuing warfarin. The primary efficacy endpoint of all cause stroke, systemic embolism and cardiovascular death met criteria for non-inferiority of WATCHMAN vs. warfarin at 18 months follow-up with event rates of 3.0% and 4.9% respectively. With longer follow-up at 3.8 years WATCHMAN demonstrated statistical superiority with event rates (per 100 patient years) of 2.3% and 3.8% respectively [21]. However, adverse event rates (procedure–related events and major bleeding) for the WATCHMAN arm were significant at 7.4% vs 4.4% in the warfarin group [19]. A learning curve for the pioneering procedure was acknowledged with already a significant reduction in peri-procedural complications (mainly peri-procedural stroke and pericardial effusion) noted for patients enrolled and implanted in the latter half of the trial as compared with initial subjects [22].

The WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study was a further RCT mandated by the FDA in the USA to re-examine the safety issues [23]. This study enrolled 407 patients with a higher mean $CHADS_2$ score of 2.6. The required safety endpoint was met with a seven-day safety event rate of 2.2% in the WATCHMAN arm. The primary efficacy composite endpoint (all cause stroke, systemic embolism and cardiovascular death) did not meet non-inferiority at 18 months in PREVAIL with annual event rates of 1.07% for WATCHMAN and 0.7% for warfarin. Discussion has centred around the unusually low event rate in the warfarin controls as compared with annual event rates for warfarin subjects in PROTECT AF or anticoagulation trials; PROTECT AF 1.6% [19], Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) 1.7% [6], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) 2.2% [7], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) 1.6% [8]. Subsequently a meta-analysis of the two RCTs has been published which showed comparable efficacy for WATCHMAN and warfarin with no statistically significant difference in the rates of all cause stroke or systemic embolism [24] (Figure 1). A significant reduction in haemorrhagic stroke was seen in favour of WATCHMAN (HR 0.22) as well as a reduction in major bleeding beyond seven days (HR 0.51) and a reduction in cardiovascular mortality (HR 0.48).

A number of other registries and case-control studies using the WATCHMAN device have further contributed to knowledge in the field. The ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology (ASAP) study enrolled 150 subjects with a mean $CHADS_2$ score of 2.8 who were contraindicated for anticoagulation and employed dual antiplatelet therapy for six months following implant [25]. At 14 months follow-up the observed ischaemic stroke rate was 1.7% per year which represented a