

COMMENTARY

Left atrial appendage occlusion: What is its role today?

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INTRODUCTION

The left atrial appendage (LAA), an embryonic remnant, is the source of approximately 90% of emboli originating from the heart in patients with atrial fibrillation (AF).⁽¹⁾ Use of oral anti-coagulant therapy (OACT), such as warfarin, has been shown to reduce the incidence of stroke and other embolic events by approximately 66% in patients where the INR is well controlled (target INR 2-3).⁽²⁾ However, achieving this INR target is difficult and many patients are either under or over anti-coagulated, putting them at risk of embolic events and/or major bleeding complications. The newer OACs such as Rivaroxaban and Dabigatran, depending on dosage used, have been shown to be equivalent or mildly superior to warfarin in terms of efficacy and safety.^(3,4)

However, all OACTs are contra-indicated in a large number of patients due to a history of previous intra-cerebral bleeding, gastrointestinal bleeding of unknown cause, recurrent falls and frailty, a high risk of bleeding (HASBLED score >3), and drug interactions. Even in patients without contra-indications to OACT, use is often less than 50%.⁽⁵⁾

Surgical amputation of the LAA at the time of cardiac surgery has been shown to reduce the incidence of stroke in patients with AF.⁽⁶⁾ On this basis percutaneous exclusion of the LAA has been developed – initially using the Plato device⁽⁷⁾ (no longer in production), and followed by the Watchman (Boston Scientific) and Amplatzer Cardiac Plug (ACP) (St Jude).

ABSTRACT

In many patients with paroxysmal or permanent non-valvular atrial Fibrillation and a CHA₂DS₂-VASc score of 2 or more, warfarin or other newer oral anti-coagulant therapies are contra-indicated, or are not prescribed, for a variety of reasons. These patients are therefore at risk of serious life threatening thrombo-embolic events particularly large stroke. Percutaneous occlusion of the left atrial appendage, the source of the majority of these emboli, is a therapy which should be considered in these patients. There is growing evidence that this procedure is as good as, if not superior in the long term, to chronic warfarin therapy.

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Occlusion of the LAA is an option in patients with non-valvular AF in whom OACT is recommended (CHA₂DS₂-VASc score >1) but either absolutely contra-indicated, perceived to be too risky by the treating physician due to relative contra-indications or refused. Below is a brief review of the current literature regarding the LAA occluders currently available in South Africa – the Watchman (Boston Scientific) and the Amplatzer Cardiac Plug (St Jude).

LEFT ATRIAL APPENDAGE OCCLUDERS

The Watchman device

This is the only device for which there is currently a randomised controlled trial of the device versus warfarin – the Protect-AF trial.^(8,10) Following on from this trial eligible patients were enrolled into a non-randomised registry, the Continued Access Protocol,⁽⁹⁾ mainly to allow for further study of periprocedural complications, those being pericardial effusion, device embolisation, stroke and air embolism. A second randomised study, the Prevail Study,⁽¹¹⁾ although not yet published (publication imminent) is presented below. Therefore to participate in these trials (as described below) eligible patients had to be able to take warfarin.

PROTECT-AF trial

The Protect-AF trial⁽⁸⁾ was a non-inferiority trial that randomised 707 patients with non-valvular AF and a CHADS₂ score of at least 1 to either the Watchman device (n=463) or continued warfarin (n=244) in a 2:1 ratio. After device implantation warfarin was continued for 45 days, followed by clopidogrel for 4.5 months and

lifelong aspirin. This study showed the device was non-inferior to Warfarin in terms of stroke prophylaxis, with a trend towards superiority.

In the successfully treated population the primary efficacy event rate in the intervention group who discontinued warfarin was 1.9 per 100 patient years compared to 4.6 per 100 patient years in the control group who received warfarin (RR 0.40). Warfarin was discontinued in 88% of the patients in the intervention group at 45 days after trans-oesophageal echocardiogram (TOE) showed complete closure or minimal peri-device flow into the left atrial appendage. At 6 months 92% of patients had discontinued warfarin after repeat TOE. Primary safety events occurred at a higher rate in the intervention group than in the control group (7.4 per 100 patient years vs 4.4 per 100 patient years. RR 1.69). The most frequent primary safety event in the intervention group was serious pericardial effusion which occurred in 4.8% of patients. No patients with pericardial effusion died. Most safety events occurred during the first 3 implant procedures (12.3% versus 5.9% subsequently).

In summary, the early results of this study showed occlusion of the LAA with the Watchman device was as effective as warfarin in preventing embolic events but at a cost of possible serious adverse events at the time of implantation.

The Continued Access Protocol (CAP) registry⁽⁹⁾

This is a non-randomised registry of patients undergoing Watchman implantation (Continued Access Protocol [CAP] Registry; n=460 patients). The safety end point included bleeding- and procedure-related events (pericardial effusion, stroke, device embolisation). The results showed a significant decline in the rate of procedure- or device-related safety events within 7 days of the procedure, which

occurred in 7.7% of patients in Protect-AF and in 3.7% of patients in CAP Registry (p=0.007). Serious pericardial effusion within 7 days of implantation, which had made up >50% of the safety events in PROTECT AF, was lower in the CAP Registry (5.0% versus 2.2%, respectively; P=0.019). Similarly the rate of procedure related stroke improved with experience (0.9% versus 0%, respectively; P=0.039). Overall the functional impact of these safety events, as defined by significant disability or death, was superior in the Watchman group compared to the warfarin group in PROTECT-AF study.

In summary, the CAP registry confirmed the findings seen in the Protect-AF study that serious adverse events at the time of implantation of the device decreased significantly with increasing operator experience.

The PROTECT-AF -4 year follow up⁽¹⁰⁾

Longer term (4 year) follow up of the PROTECT-AF trial showed the device group achieved superiority for the composite endpoint of all stroke, cardiovascular or unexplained death and systemic embolism. The observed adverse event rate was 2.3% and 3.8% in the Watchman and Control groups, respectively (RR= 0.60, posterior probability of superiority = 96%), demonstrating a 40% relative risk reduction in the Watchman group. In addition all cause mortality in the Watchman group was superior to Control: 3.2% for Watchman and 4.8% for Control, representing a 34% relative risk reduction in all-cause mortality in the Watchman group (HR = 0.66, p=0.0379). Cardiovascular mortality in the Watchman group was superior to Control: 1.0% for Watchman and 2.4% for Control, demonstrating a 60% relative risk reduction in cardiovascular death in the Watchman group (HR= 0.40, p=0.0045).

In conclusion, the PROTECT-AF 4 year follow-up data showed that the Watchman device was statistically superior to warfarin for reducing the relative risk of the composite primary endpoint of cardiovascular death, all stroke and systemic embolisation, as well as both all-cause mortality and cardiovascular mortality. The long-term efficacy from PROTECT-AF, coupled with the safety results of PREVAIL⁽¹¹⁾ and CAP⁽⁹⁾ studies, provide strong evidence that Watchman is a viable alternative to chronic warfarin therapy for stroke reduction in non-valvular AF patients.

The PREVAIL study⁽¹¹⁾

This trial has not been published yet. The PREVAIL trial was designed to confirm the results of the PROTECT-AF trial and validate the safety of the implant procedure, as requested by the FDA due to concern of safety events during implantation seen in the Protect-AF study. A total of 407 patients were randomised 2:1 device vs. warfarin control. Patients enrolled must have been warfarin eligible and have a CHADS₂ score of ≥2. Procedural safety events occurred in only 2.2% of patients receiving the device. Pericardial effusion occurred in 1.9% of patients. Longer term efficacy outcome data is still awaited.



FIGURE 1: Thrombus seen in left atrial appendage on trans-oesophageal echocardiogram.

The ASAP study⁽¹²⁾

This non-randomised study prospectively enrolled 150 patients with non-valvular AF and a CHADS₂ score of at least 1 who were INELIGIBLE for OACT. Patients underwent LAA closure with the Watchman device and were treated with clopidogrel for 6 months in addition to lifelong low dose aspirin. A history of bleeding (93%) was the most common reason for warfarin ineligibility.

After follow-up of 14.4 ± 8.6 months, the combined primary efficacy endpoint (ischaemic stroke, haemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death) occurred in 8 patients, a rate of 4.6 events per 100 patient-years. All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischaemic stroke in 3 patients (1.7% per year) and haemorrhagic stroke in 1 patient (0.6% per year). This ischaemic stroke rate was 77% less than that expected (7.3% per year) based on the CHADS₂ scores of 2.8 ± 1.2 in this patient cohort.

Serious procedure- or device-related safety events occurred in 8.7% of patients and included device embolisation without sequelae (n=2), pericardial effusion with (n=2) or without (n=3) tamponade, and device thrombus with ischaemic stroke (n=1). Six cases of device-related thrombus were seen during follow-up, but only 1 was associated with stroke.

In summary, this non-randomised study showed it was safe to implant the Watchman device in patients who are unable to take OAC therapy, provided they are able to take dual anti-platelet therapy for 6 months post implantation.

THE AMPLATZER CARDIAC PLUG (ACP)

The ACP design is a modification of the Amplatzer septal occluder which has been used very effectively to percutaneously seal atrial septal defects and patent foramen ovale for a number of years. The use of dual anti-platelet therapy for 1-3 months post implantation has been shown to be adequate to prevent thrombo-embolism following device implantation in these patients.

There are no randomised trials comparing the ACP versus OACT in patients with non-valvular AF, merely a series of registries⁽¹³⁻¹⁶⁾ of how the ACP performed in patients who are unable to take warfarin. Compared to the predicted stroke rate according to the CHADS₂ score, the actual stroke rate seen in these registries is approximately half of that predicted.

The randomised prospective Amplatzer Cardiac Plug Clinical Trial is currently enrolling up to 3 000 patients with non-valvular AF and a CHADS₂ score >2 to ACP vs warfarin or dabigatran in 90 centres across North America.⁽¹⁷⁾

The ACP is used extensively in Europe and Asia as an alternative to the Watchman device due to its perceived superiority in sealing the LAA orifice (Figure 2).

Left atrial appendage closure with Amplatzer Cardiac Plug in atrial fibrillation: Initial European experience⁽¹³⁾

This early study is a retrospective data collection to evaluate procedural feasibility and safety up to 24 hours after implantation of the ACP in patients with non-valvular AF. Device implantation was successful in 132 of 137 attempted cases (96%). There were serious complications in 10 (7.0%) patients (3 patients with ischaemic stroke; 2 patients experienced device embolisation, both percutaneously recaptured; and 5 patients with clinically significant pericardial effusions). Minor complications were insignificant pericardial effusions in 4, transient myocardial ischaemia in 2, and loss of the implant in the venous system in one patient. It concluded that implantation of the ACP device is a feasible method for percutaneous occlusion of the LAA, with a safety event rate similar to that seen in the Watchman studies.

The European Prospective Observational Study⁽¹⁴⁾

This non-randomised observational study used the ACP in patients (N=204) with non-valvular AF who have contra-indications for OAC therapy. Following device implantation the patients took DAP for 1-3 months followed by low dose aspirin alone for at least 6 months. There was a 96.6% implantation success rate with a total safety event rate of 2.9% (serious pericardial effusion 1.5%). There were no procedure related strokes or TIA. After 101 patient years follow up the actual stroke rate was 1.98%. The estimated annual stroke risk was 5.6% according to the average CHADS₂ score of 2.6. Similar to the Watchman studies, procedural safety events were significantly reduced with increasing operator experience.

CONCLUSION

Percutaneous occlusion of the LAA in patients with non-valvular AF appears to be a safe and effective alternative to OAC therapy in patients who have contra-indications to this therapy. One may even speculate that the benefit of a device-based approach could be more pronounced in clinical practice than that observed in clinical trials, given the observation that even in patients after an ischaemic stroke, the persistent use of warfarin in clinical practice after 2 years was lower than 50%.⁽¹⁸⁾ However, the compliance with anticoagulation may also improve with the novel anticoagulants. Although currently there are only randomised trials using the Watchman device compared to warfarin, these trials prove the concept that percutaneous closure of the LAA is equivalent, if not superior in the long term, to warfarin. The use of the ACP is, I believe, a reasonable alternative to the Watchman device, as it safely and effectively seals off the LAA orifice. Both devices have their merits and due to the wide variety of LAA anatomy, one

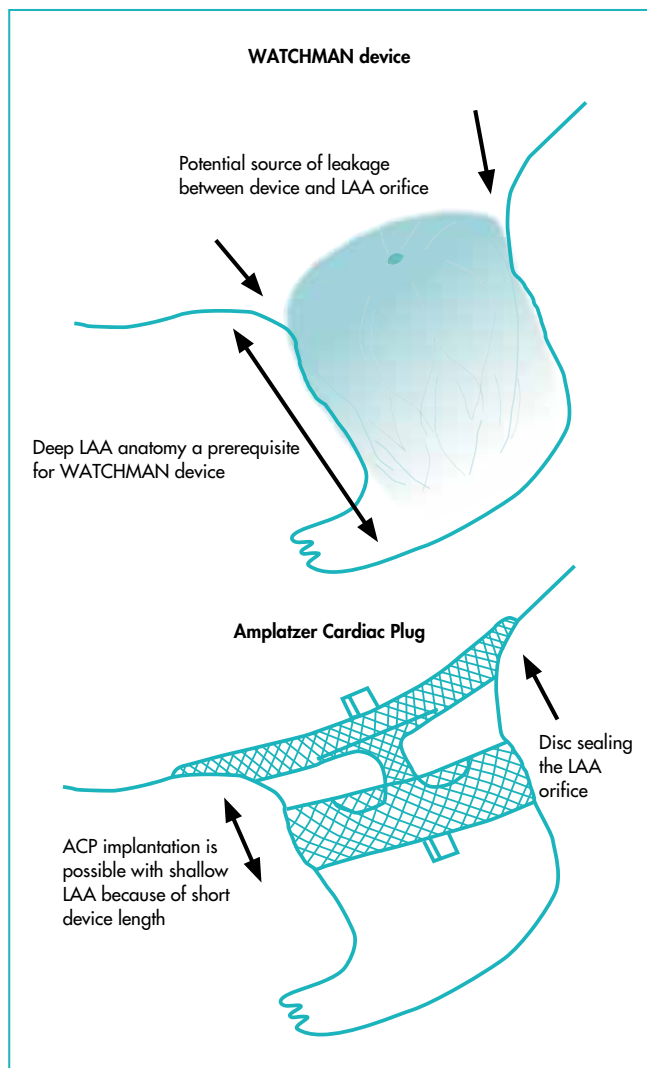


FIGURE 2: Schematic diagrams illustrating the essential difference between ACP and Watchman devices.

or the other may be better suited to that particular patient. Increasing operator experience with implantation has been shown in all studies to significantly reduce safety events. Therefore, I believe that it may be better for an operator to concentrate on using only one device initially, and become skilled at implanting that device, before implanting alternative devices as implantation techniques differ. Device implantation is difficult and requires a dedicated training programme and proctoring for at least the first 3 - 10 cases. Implantation also requires the assistance of a skilled trans-oesophageal echocardiographer. In the future, if increasing long term data continue to show superiority of these devices versus OACT, these devices may even be considered as an alternative to OACT de novo in patients who do not want to take long term OACT

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