1347

Final protocol to guide the assessment of transcatheter occlusion of the left atrial appendage for patients with non-valvular atrial fibrillation

June 2014

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention;
Comparator – specification of the therapy most likely to be replaced by the proposed intervention; and
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of application

A proposal for an application requesting MBS listing for transcatheter occlusion of left atrial appendage (LAA) was received from Boston Scientific Pty Ltd (the applicant) by the Department of Health in January 2013.

Background

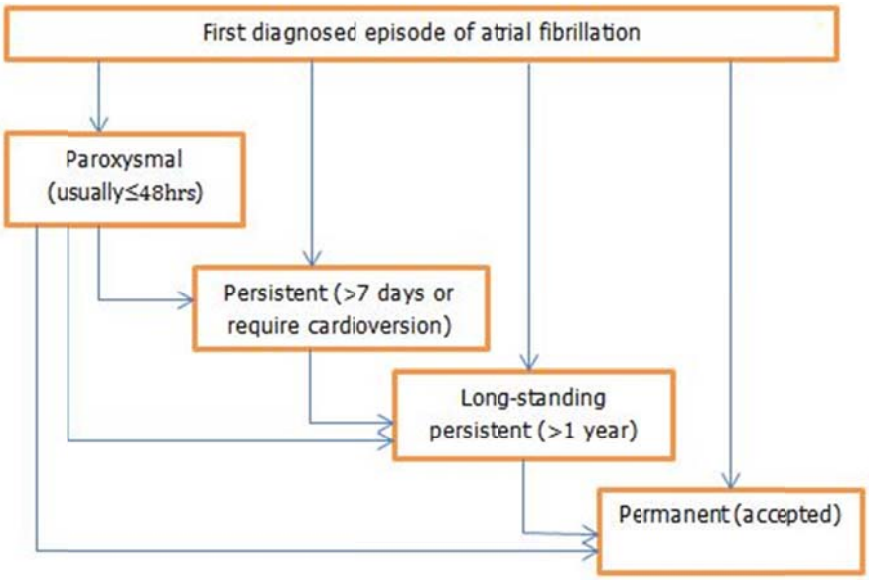
Atrial fibrillation (AF) is a condition characterised by disorganised atrial activity without discrete P waves on the 12 lead electrocardiogram[6]. It is caused by a malfunction in the sequence of electrical impulses controlling the rate and order of contraction of the chambers of the heart. AF is the most common form of irregular heart rhythm. A minority (10%) of AF cases occur in people with rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair; this is described as valvular AF. The other 90 per cent of AF is described as non-valvular AF (NVAF)[1]. AF is associated with substantial morbidity and mortality from heart failure, stroke, and other thromboembolic complications[2]. AF affects quality of life across areas of physical, mental, social, and functional measures. Patients with asymptomatic AF have lower global life satisfaction compared with healthy subjects[3]. Costs of AF to the Australian economy are at least $1.25 billion per annum through medical costs, costs of long-term care for those with a disability, and lost productivity[4]. People disabled by stroke are more likely to need ongoing assistance with activities of daily living compared with people disabled by other diseases. For example, those disabled by stroke were twice as likely to need ongoing assistance with these activities as those whose disability was caused by coronary heart disease (42.1% compared with 21.6%)[5].

AF tends to be progressive from short, rare episodes, to longer and more frequent attacks. Many patients will develop sustained forms of AF over time and only a small proportion of patients without AF-promoting conditions will remain in paroxysmal AF over several decades (2–3% of AF patients). The distribution of paroxysmal AF recurrences is not random, but clustered. 'AF burden' can vary markedly over months or even years in individual patients. Asymptomatic AF is common even in symptomatic patients, irrespective of whether the initial presentation was persistent or paroxysmal[6].

The current guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology provide a classification of AF based on arrhythmia progression (Figure 1)[6-8]:

1. Every patient who presents with AF for the first time is considered a patient with first diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
2. Paroxysmal AF is self-terminating, usually within 48hrs. Although AF paroxysms may continue for up to 7 days, the 48-hour time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered.
3. Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.
4. Long-standing persistent AF has lasted for ≥1 year when it is decided to adopt a rhythm control strategy.
5. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF[6].

Figure 1 Types of atrial fibrillation[6]



The symptoms of AF can include palpitations, dizziness, chest pain and shortness of breath, often noticed as an inability to tolerate exercise. However, approximately 10–30 per cent of people with AF have no symptoms; many of these people are not diagnosed and thus do not receive appropriate treatment for stroke risk[9].

The left atrial appendage and its role in stroke

The left atrial appendage (LAA) forms during the third week of gestation and serves as the left atrium of the foetus. It is approximately the size of an adult thumb and the opening ranges in size from 10mm to 40mm.

AF is a risk factor for ischaemic strokes[4,7]. A thrombus can form when blood becomes trapped in the LAA due to fibrillation. In non-rheumatic AF, more than 90 per cent of left atrial thrombi originate in the LAA[10]. When the thrombus becomes dislodged, it migrates through the arterial system towards the brain, resulting in vascular occlusion from the thromboembolism, which may cause an ischaemic stroke. AF associated ischaemic strokes may occlude a larger-sized intracranial artery depriving a larger territory of the brain of blood flow[11], and thirty-day mortality is greater in AF strokes than in non-AF strokes (25% versus 14%)[12]. Compared with non-AF stroke patients, patients with AF have poorer survival and more recurrences of stroke[12].

Ischaemic strokes can lead to a range of complications including hemi-paralysis, speech deficits, dysphasia, and death. About 20 per cent of all strokes occur in patients with AF[13]. Stroke is more severe for patients with AF, as they have a 70 per cent chance of death or permanent disability[14]. In people over age 75, AF is the most important single cause of ischaemic stroke and has been implicated in 15—25 per cent of all ischaemic strokes. AF increases a person's risk for ischaemic stroke by about five-fold, whether or not symptoms of AF are present[15]. Risks of stroke prevention and ability to sustain stroke preventive therapies are problems for the very elderly[13].

Incidence and prevalence

Atrial fibrillation

There were 51,381 hospital separations for AF and flutter (ICD-10-AM – I48) in 2009—10[16]. This is up 5 per cent from 2008—2009 where there were 48,869 hospital separations (Table 1). Over the period 2008—09 there

were 8,963 hospital separations for stroke, not specified as haemorrhage or infarction (ICD-10-AM – I64). The number of separations for stroke during 2009—10 was 8,021[16]. The annual growth rate in hospital separations for patients with AF and flutter has ranged between 3 to 10 per cent between 2004 and 2010.

Table 1 Annual growth rate in hospital separations for patients with atrial fibrillation[16]

ICD-10-AM I48: AF and Flutter	2004—05	2005—06	2006—07	2007—08	2008—09	2009—10
Number of separations	38,296	41,510	45,619	47,164	48,869	51,381
Change from previous year	6%	8%	10%	3%	4%	5%

AF: atrial fibrillation; ICD-10-AM: Australian modification of the WHO International classification of diseases – version 2010

AF increases the risk of mortality by 40 to 90 per cent[17, 18]. Risk factor-adjusted odds ratio estimates of mortality from the Framingham Heart Study for men and women with AF are between 1.5 and 1.9 respectively[18]. This is consistent with large-scale studies that have shown increased risk of all-cause mortality and death from cardiovascular causes, ranging from 1.3- to 1.8-fold for men and 1.9- to 2.8-fold for women[17, 19, 20].

PriceWaterhouse Coopers has estimated that approximately 240,000 people in Australia have AF as at 30 June 2009. This is claimed to be a conservative estimate based on the assumption of 1.1 per cent of the population where other population-based studies have estimates up to two per cent[4]. Based on these ranges and the Australian population in 2012 the total estimated number of patients with AF is between 252,100 and 454,300. It is estimated that 1 in 20 people over the age of 65 years have NVAF, and this proportion increases to 1 in 10 for people aged over 75[15].

Stroke

Stroke is Australia's second single greatest killer after coronary heart disease, claiming 12,533 lives in 2002[5]. It is unclear how many of these deaths were caused by AF. Age-standardised death rates from stroke have fallen dramatically since the late 1960s, by around 68 per cent. These declines appear to have been largely driven by improvements in some risk factor levels, great increases in the use of drugs to lower blood pressure and to treat and prevent blood clots, and other advances in treatment. Despite these declines in death rates, the number of people dying from stroke and those surviving with a permanent disability is proposed to increase in the future, given the ageing Australian population, and a slowing in the decline of stroke death rates in recent years[5]. There are no national data on the incidence of stroke. Estimates have been obtained from local registers in Melbourne and Perth. From these, it has been estimated that each year there are about 40,000–48,000 stroke events among Australians, which equates to a stroke occurring every 11–13 minutes. The majority (around 70%) of these are first-ever strokes. Each year about 12,000 people who have previously had a stroke suffer another stroke[28].

General management of atrial fibrillation

In general, the management goals for a patient with AF include management of symptoms, prevention of systemic thromboembolism including ischaemic stroke and treatment for concomitant cardiac disease[6]. AF symptom management includes cardiac rate control and rhythm control. Rate control strategies alone are suited for asymptomatic AF patients. They include antiarrhythmic drugs such as beta-blockers and may encompass AV node ablation with implant of permanent pacemaker. Treatments which aim to restore or maintain normal sinus

rhythm are referred to as rhythm control. It is generally preferred for patients who are highly symptomatic from AF or have significant underlying cardiac disease. Rhythm control strategies may include left atrial catheter ablation and antiarrhythmic drugs, which are sometimes used in conjunction with cardioversion.

Although patients with AF may receive a range of therapies such as rate control or rhythm control, they may still be at risk of stroke.

Stroke risk assessment

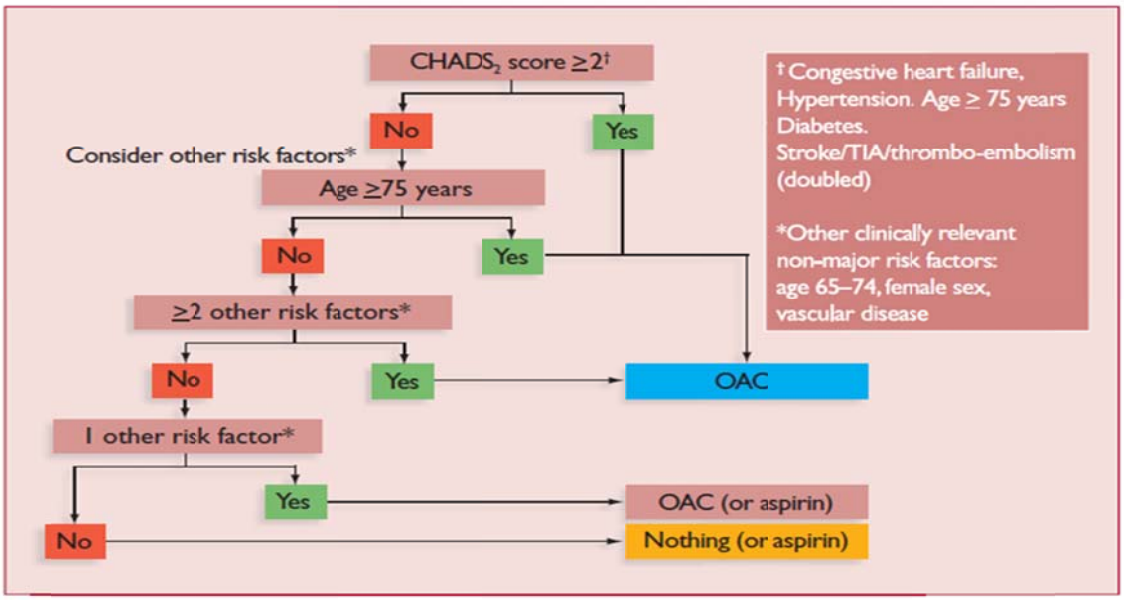
$CHADS_1$ and $CHADS_2$ are scoring systems developed to determine stroke risk in patients with NVAF (Table 9)[21]. Patients are awarded points based on comorbidities. CHA_2DS_2-VASc is a refinement of the $CHADS_2$ score, which includes additional stroke risk factors and puts greater emphasis on age as a risk factor (Table 10)[6, 22]. Generally, $CHADS_2$ and CHA_2DS_2-VASc result in similar treatment recommendations as both scoring systems assign one point each for presence of congestive heart failure (any), hypertension and diabetes, and two points for prior transient ischaemic attack (TIA) or stroke. There are small differences between the systems in that CHA_2DS_2-VASc assigns one point for age between 65-74 years, and two points for age ≥75 years while $CHADS_2$ assigns one point for age ≥75 years. CHA_2DS_2-VASc also adds one point each for presence of any vascular disease and female gender, which are not included in the $CHADS_2$ score.

Stroke risk scoring tools are summarised in Appendix A.

Pharmacological therapy to reduce the risk of stroke

Pharmacological therapy to reduce the risk of stroke is recommended in best practice clinical guidelines for patients with newly discovered AF. American Heart Association and European Society of Cardiology guidelines recommend both rhythm control and anticoagulation for AF patients guided by $CHADS_2$ scoring (Figure 2)[6].

Figure 2 Clinical flowchart for the use of oral anticoagulation for stroke prevention in atrial fibrillation[6]



AF: atrial fibrillation; OAC: oral anticoagulants; TIA: transient ischaemic attack

Oral anticoagulation therapy (OAT) is recommended for patients with a $CHADS_2$ score ≥2 and may also be recommended for patients with a $CHADS_2$ score <2 if other risk factors are present. The decision to use OAT is

complex and should be balanced with the increased risk of ischaemic stroke and minimising the risk of bleeding (particularly intracerebral haemorrhage). HAS-BLED, developed by Pisters et al (2010), allows clinicians to assess an individual's risk of bleeding based on comorbidities[23]. Appropriate balance of OAT (or antiplatelet therapy) is determined through the $CHADS_2$ or CHA_2DS_2VASc stroke risk score compared with HAS-BLED bleeding risk (Appendix A).

Warfarin

Warfarin is considered the standard of care for stroke prevention and has been used for the prevention of thromboembolisation in AF for more than 50 years. Warfarin is a vitamin K antagonist. It works by depleting functional vitamin K reserves, which are required for the synthesis of clotting factors in the liver. There is a narrow therapeutic range for warfarin effectiveness, which requires regular monitoring to determine and confirm optimal dosing for stabilised anticoagulation. Warfarin has a high rate of discontinuation and non-adherence to therapy[24]. Patients who do not adhere to their warfarin regime are at increased risk of ischaemic and haemorrhagic stroke[25]. A recent Australian Government report estimated that only 40–60 per cent of patients who are appropriate candidates for warfarin therapy receive it due to a range of reasons including patient reluctance, compliance or clinical reasons such as contraindications (Table 2)[26].

Table 2 Contraindications to warfarin[27]

Type	Absolute contraindications	Relative contraindications
Medical	Bleeding disorder Complicated liver disease Active gastrointestinal ulceration or bleeding in past 3 months Previous intracranial haemorrhage/surgery Previous intracerebral aneurysm/tumour Ophthalmic surgery in past 3 months Diabetic proliferative retinopathy	Uncomplicated liver disease Previous gastrointestinal bleeding or ulceration
Functional	Fall in past 6 months associated with major bleeding	High risk of falls No medication supervision and either visual or colour blindness, deafness, or language barrier
Cognitive	Uncontrolled psychosis Dementia	No medication supervision and mild cognitive impairment (Mini Mental State Examination score 15–24/30)
Social	Current alcoholism (male > 60 g alcohol/day; female >40 g alcohol/day)	Nursing home resident, socially isolated
Iatrogenic	No medication supervision and poor compliance likely Unable to self-medicate High-risk drug interactions Previous adverse drug reaction to warfarin	Frequent use of nonsteroidal anti-inflammatory drugs

Warfarin therapy is not suitable for all patients with NVAF and long-term warfarin therapy is contraindicated in 14—44 per cent of patients with AF[34]. Some patients are warfarin intolerant due to allergy, difficulty with international normalised ratio (INR) monitoring or adherence to therapy. Also, warfarin is contraindicated in some patients because of risk of bleeding or propensity to fall, dementia, alcoholism, kidney disease, cancer or the need for non-steroidal anti-inflammatory drugs or other drugs contraindicated with warfarin (Table 2). Warfarin is successful at reducing the rate of stroke by 60—70 per cent compared to no treatment. However,

patients taking warfarin are at increased risk of uncontrolled bleeding in other parts of the body. Warfarin interacts with many common medications and is not recommended for a list of comorbidities associated with cardiovascular arrhythmias. The elderly are especially susceptible to these complications. Factors considered to be contraindications to warfarin according to the New South Wales Therapeutic Advisory Group's Indicators for Quality Use of Medicines in Australian Hospitals[27, 28], are outlined in Table 2.

Currently, patients with NVAF who have one or more risk factors for stroke (i.e. prior stroke/TIA, age ≥75 years, hypertension, diabetes mellitus, heart failure/ LVEF ≤35%) are eligible for warfarin through the Pharmaceutical Benefits Scheme (PBS).

Novel oral anticoagulants

The novel oral anticoagulants (NOAC) include rivaroxaban, apixaban and dabigatran. Rivaroxaban and apixaban are direct factor Xa inhibitors. Dabigatran is a direct thrombin inhibitor. These drugs are currently listed on the PBS for prevention of venous thromboembolism in patients undergoing total hip/knee replacement, and patients with deep venous thrombosis, recurrent thromboembolism and NVAF with risk of stroke. Patients must have one or more risk factors for stroke: prior stroke or TIA; age ≥75; hypertension; diabetes mellitus; HF or left ventricular ejection fraction (LVEF) ≤35 per cent[28]. In 2011, the Australian Government commissioned a review of anticoagulation therapies in AF to inform the Government on options for improving the health outcomes of patients treated with anticoagulation therapies, including optimising the use of currently available treatments in Australia as well as the future role of newer therapies such as NOAC for the treatment of AF. The Review report was finalised in late 2012 and included a number of recommendations for consideration by the Government.

For the purposes of this protocol, the term 'oral anticoagulant therapy' (OAT) includes warfarin and NOAC.

Antiplatelet therapy

Antiplatelet therapy includes aspirin and clopidogrel. Evidence from the literature indicates that warfarin is approximately 40 per cent more effective at reducing stroke than antiplatelet agents[29-31]. However, for patients in whom OAT is contraindicated, standard treatment consists of aspirin—clopidogrel combination therapy, aspirin alone, or other antiplatelet drugs. Combination therapy is more effective than aspirin alone.

Clinical practice guidelines recommend that patients with AF with low risk of stroke should receive either no therapy, or aspirin (75–325 mg daily). The use of OAT or combination antiplatelet therapy is not recommended in this patient group. For patients with AF who have a moderate-to-high risk of stroke, OAT is recommended. In patients in whom OAT is contraindicated or not tolerated, combined clopidogrel and aspirin is recommended in the guidelines[8, 32, 33]. If the patient is contraindicated for aspirin or clopidogrel other antiplatelet drugs are considered.

Intervention

Left atrial appendage occluders

A left atrial appendage occluder is intended for patients with NVAF (paroxysmal, persistent or permanent) who require treatment for potential thrombus formation and for whom long-term OAT is contraindicated. The procedure aims at preventing ischaemic stroke and systemic thromboembolism by closing off the LAA permanently to avoid the formation and migration of emboli to the brain.

WATCHMAN™ (Boston Scientific), AMPLATZER Cardiac Plug™ (St Jude Medical) and WAVECREST™ (Coherex Medical) are currently available, and their details are provided below.

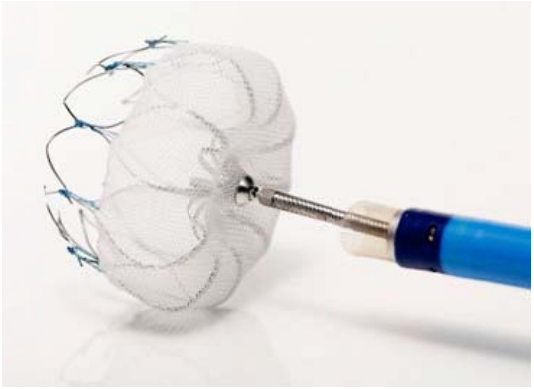


Figure 3 WATCHMAN™ left atrial appendage occluder
Resource: Cardiac Rhythm News <www.CardiacRhythmNews.com>

WATCHMAN™ is a self-expanding nitinol frame structure with fixation anchors and a permeable polyester fabric that covers the atrial facing surface of the device (Figure 3). It is available in five sizes to accommodate the unique anatomy of each patient's LAA. The occluder is preloaded into a delivery catheter. The WATCHMAN™ access sheath is used to gain access into the LAA and serves as a conduit for the delivery catheter. The access sheath and delivery catheter permit device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium.

Figure 4 AMPLATZER Cardiac Plug™ left atrial appendage occluder
Resource: Cardiac Rhythm News <www.CardiacRhythmNews.com>

The AMPLATZER Cardiac Plug™ (St Jude Medical Australia Pty Ltd) is a self-expanding device constructed with a nitinol mesh and polyester patch (Figure 4). It consists of a lobe and a disc connected by a central waist. It is designed to provide optimal occlusion with full cross-sectional orifice coverage of the LAA, regardless of the LAA anatomy.

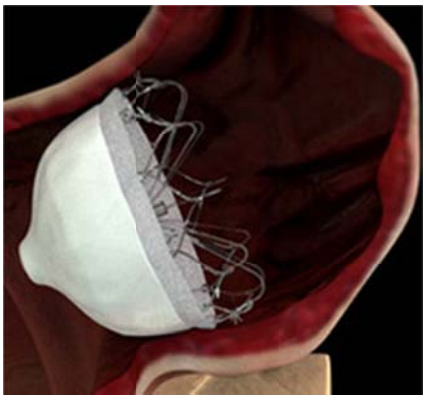


Figure 5 WAVECREST™ left atrial appendage occlude in situ
Resource: Cardiac Rhythm News <www.CardiacRhythmNews.com>

WAVECREST™ (Coherex Medical Inc.) LAA occluder is consisted with self-expanding nitinol coils and a polytetrafluoroethylene mesh. The device provides occlusion at the LAA ostium (Figure 5).

Devices such as AtriClip (ARTG 175070) are also used for LAA exclusion. However, these procedures are not comparable with the above transcatheter LAA occlusion devices, as AtriClip is implanted under direct visualisation in conjunction with other open cardiac surgical procedures. AtriClip and similar devices are excluded from this protocol.

The intervention for the purpose of this protocol is transcatheter occlusion of the LAA. PASC agreed that from a clinical perspective all LAA occlusion devices are similar, and for the assessment all LAA technologies should be grouped together in a generic approach.

Regulatory status

The WATCHMAN™ (Boston Scientific) and AMPLATZER Cardiac Plug™ (St Jude Medical) are currently listed in the Australian Register of Therapeutic Goods (ARTG) (

Table 3 and Table 4). WATCHMAN™ LAA occluder is registered by the FDA. It has received the CE Mark for expanded indications to include patients who have a contraindication to OAT based on results from the ASAP Study[34]. AMPLATZER Cardiac Plug™ and WAVECREST™ (Coherex Medical Inc.) devices are currently not registered by the FDA, although they have received CE Mark for marketing in Europe. The WAVECREST™ is currently seeking Therapeutic Goods Administration (TGA) approval. The PLAATO™ (Appriva Medical) LAA occluder was withdrawn for commercial reasons after having been implanted in observational trials in Europe and USA.

The WATCHMAN™ and AMPLATZER Cardiac Plug™ are currently in use at the Prince Charles Hospital (QLD), the Princess Alexandra Hospital (QLD), the Royal Perth Hospital (WA), St Vincent's Public Hospital (NSW), the Royal Prince Alfred Hospital (NSW), the Monash Medical Centre (VIC), the Royal Melbourne Hospital (VIC) and the Royal Adelaide Hospital (SA).

Table 3 TGA registered WATCHMAN™ left atrial appendage occluders

ARTG number	Approval date	Manufacturer	Product name	Intended purpose
198829	28/06/2012	Boston Scientific Pty Ltd	WATCHMAN LAA Closure Device with Delivery System - Cardiac occluder	The technology intended to prevent embolization of thrombi that may form in the appendage and to prevent the occurrence of ischaemic stroke and systemic thromboembolism, in patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation and are eligible for warfarin therapy.
198855	28/06/2012	Boston Scientific Pty Ltd	Watchman Access System - Cardiac occluder delivery kit	Intended to provide vascular and transseptal access for the WATCHMAN Delivery System and Left Atrial Appendage Closure Device. The Watchman Access System (WAS) consists of an access sheath (AS) and dilator. The AS is intended to assist in sizing and positioning of the Watchman Implant in the left atrial appendage via a septal crossing.
167176	30/11/2009	Boston Scientific Pty Ltd	WATCHMAN LAA Closure Device with Delivery System - Cardiac occluder	The technology intended to prevent embolization of thrombi that may form in the appendage of patients with non-valvular atrial fibrillation to prevent the occurrence of ischaemic stroke and systemic thromboembolism, in patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation and are eligible for warfarin therapy.
167374	8/12/2009	Boston Scientific Pty Ltd	Watchman Access System - Cardiac occluder delivery kit	The Watchman Access System (WAS) consists of an access sheath (AS) and dilator. The AS is intended to assist in sizing and positioning of the Watchman Implant in the left atrial appendage via a septal crossing.
198831	28/06/2012	Boston Scientific Pty Ltd	Watchman Obturator - Cardiac occluder delivery kit	The Watchman Obturator is intended to facilitate placement of the Watchman LAA Closure Device in the Left Atrial Appendage by providing a smooth transition from the Access Sheath to a 6Fr pigtail catheter
216434	23/10/2013	Boston Scientific Pty Ltd	Watchman Left Atrial Appendage Closure Device Delivery System - Cardiac occluder	The WATCHMAN LAA Closure Technology is intended to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy.
216435	23/10/2013	Boston Scientific Pty Ltd	Watchman Access System - Cardiac occluder delivery kit	The WATCHMAN Access System is intended to provide vascular and transseptal access for the WATCHMAN Left Atrial Appendage Closure Device with Delivery

ARTG number	Approval date	Manufacturer	Product name	Intended purpose
				System.

Taken from https://www.ebs.tga.gov.au, accessed 13 January, 2014

Table 4 TGA registered AMPLATZER Cardiac Plug™ left atrial appendage occluders

ARTG number	Approval date	Manufacturer	Product name	Approved indication
162137	1/06/2009	St Jude Medical Australia Pty Ltd	AMPLATZER Cardiac Plug - Cardiac occlude	The AMPLATZER Cardiac Plug is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have non-valvular atrial fibrillation.
216398	23/10/2013	St Jude Medical Australia Pty Ltd	AMPLATZER Amulet Left Atrial Appendage Occluder	The AMPLATZER Amulet Left Atrial Appendage Occluder is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have non-valvular atrial fibrillation.

Taken from https://www.ebs.tga.gov.au, accessed 13 January, 2014

Proposed clinical place of the transcatheter LAA occluder

OAT with warfarin or a NOAC is accepted as first line therapy for stroke prevention in patients with AF[6]. Patients with NVAF for whom OAT is contraindicated are typically referred to a cardiologist for further assessment and treatment. Usually these patients receive antiplatelet therapy, and their risk of stroke remains relatively high.

Patient population

Transcatheter LAA occlusion is proposed for patients with NVAF (paroxysmal, persistent or permanent) for whom OAT (i.e. warfarin or NOAC) is contraindicated for stroke prevention, as these patients have a high risk of stroke despite treatment with antiplatelet therapy. Patients should have one or more risk factors for stroke including, but not limited to;

- history of stroke or TIA,
- cardiac failure and/or LVEF ≤35 per cent,
- hypertension,
- age of ≥75 years, and
- diabetes mellitus.

The proposed service provides an additional option to the currently available stroke prevention options (i.e. antiplatelet therapy) in this population and would not replace them.

At this time, warfarin and NOAC such as rivaroxaban, dabigatran and apixaban are listed on the PBS for use in patients with NVAF. Patients must have one or more of the following, in addition to NVAF, to be eligible for these drugs from the PBS: history of prior stroke, age ≥75, hypertension, diabetes mellitus, heart failure and/or left ventricular ejection fraction ≤35 per cent.

In this context, a patient could have contraindications to OAT due to: adverse reactions; inability to tolerate or adhere to OAT; or having failed OAT. PASC recognised that a minority of patients would be considered to have

contraindications to OAT even if they have not received these drugs (eg patient refusal). Clinical judgement will play a major role in the final decision of identifying patients for the proposed intervention.

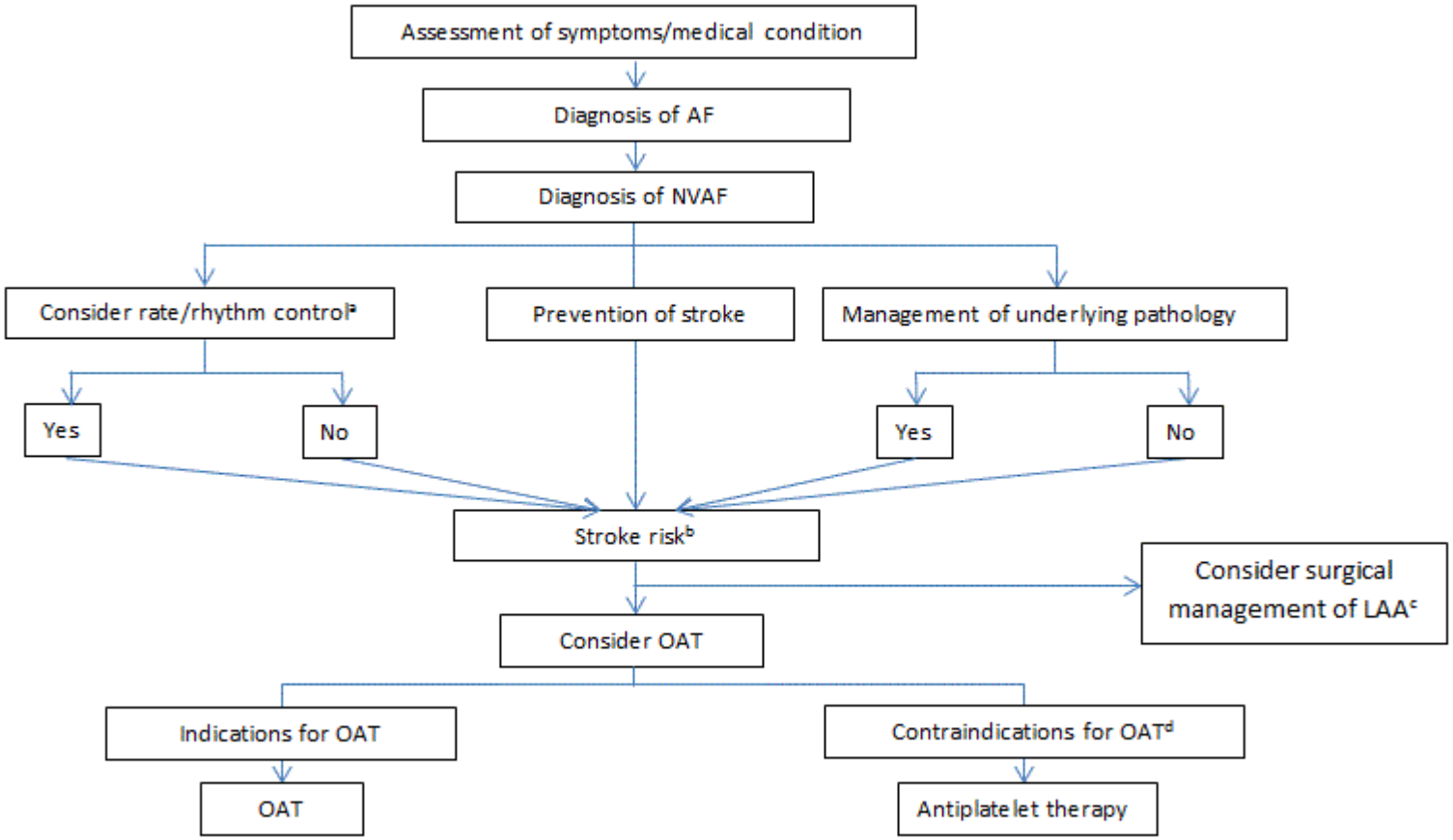
The current clinical management algorithm

The European Society of Cardiology guidelines recommend that patients with AF who have a low risk of stroke (e.g. ≤1 CHA_2DS_2-VASc score) should receive either no therapy, or aspirin (75–325 mg daily)[6]. The use of anticoagulation or antiplatelet therapy is not recommended in this patient group. Patients with NVAF (paroxysmal, persistent or permanent) who are identified as having a moderate to high risk for stroke will initially be considered for OAT. Patients for whom OAT is contraindicated are currently managed for prevention of embolic stroke with antiplatelet therapy[32,8,33].

Surgical LAA closure is generally conducted as a concomitant open chest procedure in association with another open cardiac procedure such as valve replacement or coronary artery bypass grafting. It is unlikely that open surgery for management of LAA would be performed as a stand-alone procedure.

The current clinical decision algorithm for prevention of stroke in patients with AF is provided in Figure 6.

Figure 6 The current clinical decision algorithm for prevention of stroke in patients with atrial fibrillation



AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; OAT: oral anticoagulant therapy (currently includes warfarin, rivaroxaban, apixaban and dabigatran); LAA: left atrial appendage.

a Rate control strategies may include antiarrhythmic drugs such as beta-blockers, and AV node ablation with implant of permanent pacemaker. Rhythm control strategies may include left atrial catheter ablation and antiarrhythmic drugs, which are used in conjunction with cardioversion.

b Stroke risk can be assessed by $CHADS_1$, $CHADS_2$ or CHA_2DS_2-VASc scoring system. Based on $CHADS_2$, risk factors for stroke are history of stroke or transient ischaemic attack, cardiac failure and/or LVEF $\leqslant$35%, hypertension, diabetes mellitus and age $\geqslant$75 years. Clinical judgement will play a major role in the final decision of identifying patients with high stroke risk, once they have any of these risk factors for stroke.

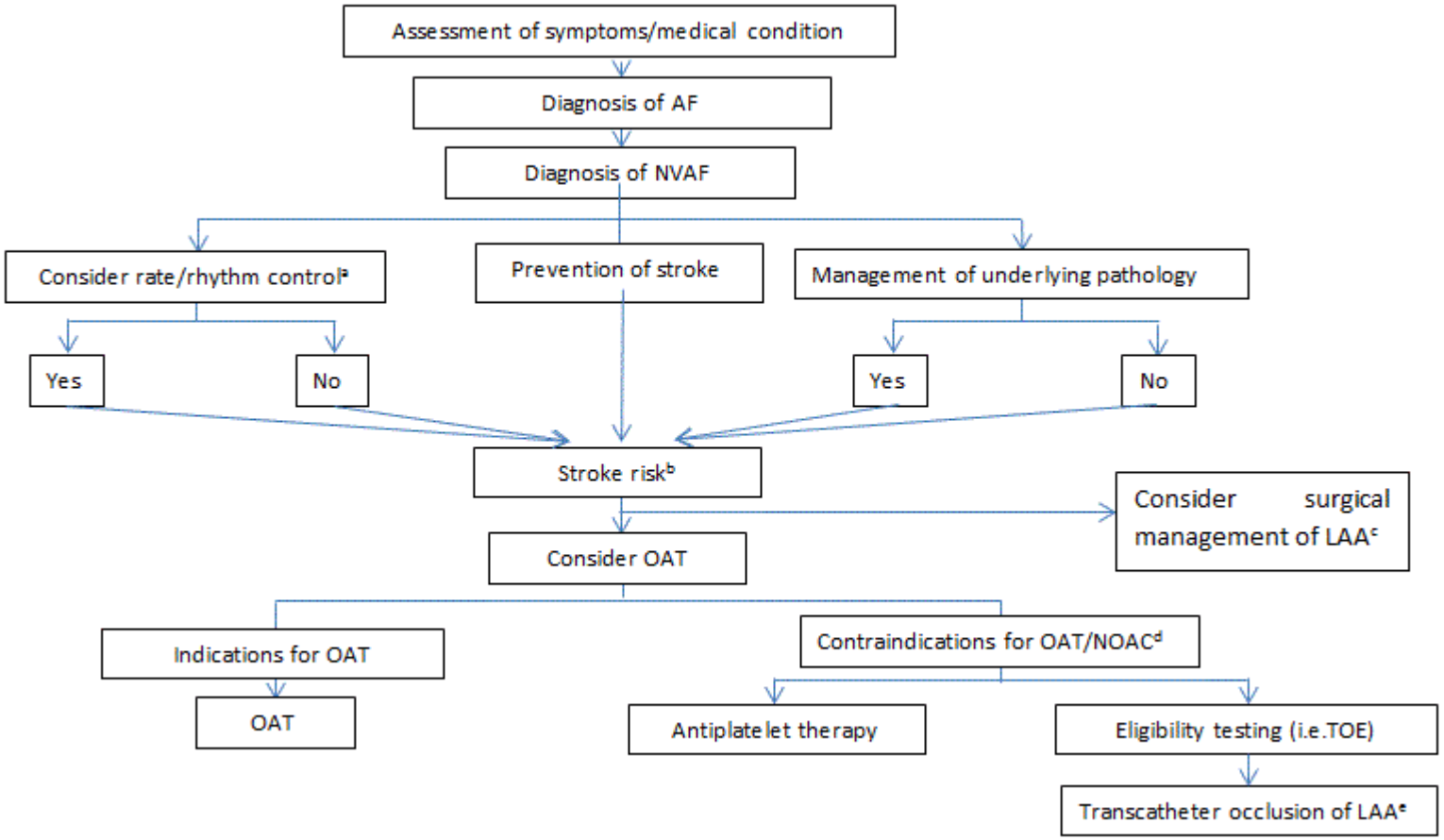
c Surgical closure of LAA may be performed concomitantly with other open or percutaneous surgical procedures (e.g. mitral valve replacement). Devices, such as AtriClip may be used for LAA exclusion; however, these procedures are performed under direct visualisation.
d Contraindications to warfarin include absolute and relative contraindications (see Table 2)

The proposed clinical management algorithm

Transcatheter occlusion of LAA is proposed for the patients for whom OAT is contraindicated. LAA occlusion should be available in addition to the current antiplatelet treatment in these patients. Patients receive clopidogrel 75mg daily and aspirin 300—325mg daily for 6 months post-implant and remain on aspirin indefinitely.

The proposed clinical decision algorithm for prevention of stroke in patients with AF is provided in Figure 7.

Figure 7 The proposed clinical decision algorithm for prevention of stroke in patients with atrial fibrillation



AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; OAT: oral anticoagulant therapy (currently includes warfarin, rivaroxaban, apixaban and dabigatran); LAA: left atrial appendage; TOE: trans-oesophageal echocardiography.

a Rate control strategies may include antiarrhythmic drugs such as beta-blockers, and AV node ablation with implant of permanent pacemaker. Rhythm control strategies may include left atrial catheter ablation and antiarrhythmic drugs, which are used in conjunction with cardioversion.

b Stroke risk can be assessed by $CHADS_1$, CHADS2 or CHA_2DS_2-VASc scoring system. Based on $CHADS_2$, risk factors for stroke are history of stroke or transient ischaemic attack, cardiac failure and/or LVEF ≤35%, hypertension, diabetes mellitus and age ≥75 years. Clinical judgement will play a major role in the final decision of identifying patients with high stroke risk, once they have any of these risk factors for stroke.

c Surgical closure of LAA may be performed concomitantly with other open or percutaneous surgical procedures (e.g. mitral valve replacement). Devices, such as AtriClip may be used for LAA exclusion; however, these procedures are performed under direct visualisation.

d Contraindications to warfarin include absolute and relative contraindications (see Table 2)

e Patients receive x-ray and/or TOE prior to discharge from hospital. At 6 weeks to 6 months post-implantation, another TOE is performed. Some patients may require repeated imaging, if post procedural adverse events are suspected.

Delivery of the intervention

The following section explains the delivery of a WATCHMAN™ device at the LAA. In general, steps involved in deliverying AMPLATZER™ and WAVECREST™ devices are similar to WATCHMAN™ device delivery.

The treating physician (e.g. cardiologist) refers patients to an interventional cardiologist or cardiac electrophysiologist for consideration of transcatheter occlusion of LAA. Patients are pre-screened with transoesophageal echocardiogram (TOE) to ensure eligibility for the procedure (absence of thrombus and appendage size/morphology suitable for occlusion). Appendage ostial diameter should be between 15mm and 31mm to be appropriate for device insertion. After the inter-atrial septum is crossed using a standard trans-septal access system, the occluder, access sheath and dilator are advanced over a guidewire into the left atrium. The access sheath is then advanced into the distal portion of the LAA over a catheter. The delivery system is advanced under fluoroscopic guidance. Once located, the device is deployed and released into the LAA. According to the applicant, the deployment of a WATCHMAN™ device can be reversed if required prior to the device being released[35]. This allows the size and stability of the occluder to be confirmed prior to deployment.

The proposed medical service is provided in a public or private hospital. The procedure is performed under general anaesthesia by an interventional cardiologist or cardiac electrophysiologist in a catheterisation laboratory under guidance of fluoroscopy and TOE. The procedure takes approximately 60 minutes, which includes pre-, intra- and post-service components (see below). In general, patients stay overnight in the hospital after the procedure and are discharged the following day. Patients may also require additional pre-discharge imaging services (e.g. pre-discharge chest x-ray or TOE).

- **Pre-service component**: 5—10 min. The physician will review patient notes and acquire patient consent for the procedure.
- **Intra-service component:** mean LAA occlusion procedure time is 51.5 ± 27.7 minutes (ASAP study).
- **Post-service component:** 5 minutes. This may include procedures notes.

Cardiologists who intend to perform transcatheter occlusion of LAA undergo a comprehensive training program, which is provided by the manufacturer. The requirements to participate in the WATCHMAN™ training program are as follows:

- Proficiency in trans-septal skills and left sided procedures
- Expertise in TOE
- Access to surgical back-up
- Willingness to complete the LAA Closure Training Program
- Committed to routine implantations to maintain skill set.

Initial proctoring is provided by an experienced and certified WATCHMAN™ implanting physician. To be considered an independent treating cardiologist the successful completion of at least 12 procedures under supervision would be required.

Postoperatively, patients continue to take antiplatelet medication to achieve optimal results. Commonly patients receive clopidogrel 75mg and aspirin 300—325mg daily for 6 months post-implant and remain on aspirin indefinitely. The appropriate dose of antiplatelet therapy post-procedure is guided by the clinical evidence and physician discretion. Patients require pre-discharge pathology and imaging services (e.g. TOE) to confirm device position and that there is no pericardial effusion. Another follow-up examination with TOE is performed at six weeks or six months. A physician may choose to perform an additional TOE after the six-month follow-up if any complications are suspected.

The LAA occluder is designed to be implanted permanently into the heart. It is therefore expected that a majority of patients will only receive a single procedure in their lifetime. However, in rare circumstances (e.g. embolisation or infection) device removal would be required. This is achieved as a peripheral transcatheter procedure or concomitantly with another open cardiac procedure. If removal is needed, an interventional cardiologist and/or cardiac surgeon can perform the removal.

Proposed MBS listing

The proposed MBS item descriptor is provided in Table 5. The proposed fee is based on MBS item 38272 (atrial septal defect closure, with septal occluder or other similar device, by transcatheter approach).

TOE is performed by a different specialist (e.g. echocardiologist) and is claimed using a separate item.

Table 5 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
MBS XXXXX Transcatheter occlusion of left atrial appendage, including any associated imaging and cardiac catheterisation performed by the same practitioner, for stroke prevention in a patient who: • has non-valvular atrial fibrillation; • has contraindications to oral anticoagulation therapy; and • has one or more risk factors for developing stroke. (Anaes.) (Assist.) Fee: $912.30 Benefit: 75%=$684.25 [Explanatory Notes] Risk factors for developing stroke include, but not limited to: (i) Prior stroke (ischaemic or unknown type), transient ischaemic attack or non-central nervous system (CNS) systemic embolism; (ii) age 75 years or older; (iii) hypertension; (iv) diabetes mellitus; (v) heart failure and/or left ventricular ejection fraction 35% or less.

Category 3 – THERAPEUTIC PROCEDURES
Contraindications for oral anticoagulation therapy include adverse reactions, inability to tolerate therapy, failed therapy or intolerance to therapy. These include both absolute and relative contraindications. The practitioner is required to undergo appropriate training and credentialling. The procedure is performed as a hospital service.

Comparator

For patients in whom OAT is contraindicated in the population of interest, antiplatelet therapy is used for stroke prevention. These patients have sub-optimal anticoagulation and remain at a high risk of ischaemic events, as such have increased mortality rates compared with patients who receive OAT[36]. Antiplatelet therapy is the comparator to transcatheter occlusion of LAA.

Surgical closure of the LAA is rarely performed in Australia; therefore, it is not considered as a comparator for the proposed intervention. Surgical devices, such as AtriClip are not considered as comparators since they are inserted under direct visualisation in an open procedure.

Clinical claim

Transcatheter occlusion of LAA reduces the risk of thromboembolism in patients with NVAF who have high stroke risk but in whom OAT is contraindicated.

There are no clinical data that directly compare outcomes for patients following transcatheter occlusion of LAA against antiplatelet therapy. Therefore, based on the available clinical evidence, the following approach is recomended to establish non-inferiority of the intervention compared to antiplatelet therapy:

- Conducting an indirect comparison of transcatheter occlusion of LAA against antiplatelet therapy using OAT as a common comparator.
- Validate these findings with the results of the available evidence, which compares outcomes of patients treated with LAA occluders against the outcomes expected in patients treated with antiplatelet therapy.

The intervention is proposed to be superior in regards to effectiveness and non-inferior in terms of safety (

Table 6).

Table 6: Classification of an intervention for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="5">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Effectiveness

Effectiveness outcomes to be measured include:

Primary effectiveness

- Stroke rate (ischaemic stroke and haemorrhagic stroke)
- All-cause mortality
- Health-related quality of life (HRQoL)

Secondary effectiveness

- Procedure success i.e. successful transcatheter occlusion of LAA

Safety

All adverse events should be recorded. These include any untoward medical condition that results in death, was life-threatening, required device removal, required inpatient hospitalisation, or prolongation of existing hospitalisation, or resulted in persistent or significant disability/incapacity. Any other adverse events or complications that occur following the use of the intervention also should be considered as a safety concern and compared against antiplatelet therapy (or other surgical management strategies of LAA closure or AF), where possible.

Health care resources

Healthcare resources relevant to delivery of LAA occlusion include;

- Fluoroscopy (intra-service, considered to be integral to the service and is included within the proposed MBS item when performed by the same practitioner)
- TOE (pre-service, intra-service, pre-discharge, follow-up six weeks to six months, considered to be provided by a separate specialist and claimed through separate existing MBS items)
- Specialists (intra-service: interventional cardiologist [or cardiac electrophysiologist], echocardiologist and anaesthetist)

The list price of LAA occluder devices ranges from $7,000 to $13,000.

The service will be limited to hospitals with the following facilities:

- Cardiologist (interventional and/or electrophysiologist) with skills in trans-septal / left heart and structural heart procedures, trained in transcatheter occlusion of LAA
- Cardiac catheterisation laboratory
- Anaesthetic support
- Transoesophageal equipment and echocardiologist/cardio-thoracic anaesthetist able to perform intra-operative TOE
- Access to surgical back-up

The applicant calculated the likely number of patients who would utilise the proposed medical service for the first fully funded provisional year and accordingly approximately 250 services are expected to be utilised if funded in 2015. This estimate is based on the number of facilities and doctors who could conduct the procedure. The applicant believes that 'an epidemiological approach would result in an over-estimation of the number of procedures that could be conducted due to the limited availability of resources and trained clinicians'.

The attendance of an anaesthetist and echocardiologist is required for the duration of the procedure. If accredited, a cardiothoracic anaesthetist may perform the TOE in conjunction with anaesthetic duties. However, this occurs rarely (<5%). The following MBS items are used during the procedure and need to be considered in the cost-effectiveness analysis:

- MBS Item 21941: Initiation of management of anaesthesia for cardiac catheterisation
- MBS Item 22025: Intra-arterial cannulation when performed in association with the administration of anaesthesia
- MBS Item 22012: Blood pressure monitoring
- MBS Item 21936: Anaesthesiology for TOE
- MBS Item 22051: Intra-operative TOE

A list of resources to be considered in the economic analysis is provided in Table 7.

Table 7: List of resources to be considered in the economic analysis

Resource	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units[a]
Resources provided to identify the eligible population that would vary from current clinical practice (from Step 2, e.g., diagnostic and other investigative medical services, prior therapeutic interventions). *Identify variations where these may vary across different decision options.*				
Transoesophageal echocardiography	Cardiologist	Screening	$275.50	MBS Item 55118
Anaesthesiology for Transoesophageal echocardiography	Anaesthesiologist	Screening	$118.80	MBS Item 21936
Cardiology consultation	Cardiologist	Screening	$263.90	MBS Item 132
Resources provided in association with the proposed medical service to deliver the proposed intervention (from Step 1, e.g., pre-treatments, co-administered interventions). *Identify variations where these may vary across different decision options.*				
Intra-operative Transoesophageal echocardiography	Echo-cardiographer	Intervention	$178.20	MBS Item 22051
Anaesthesiology for Transoesophageal echocardiography	Anaesthesiologist	Intervention	$118.80	MBS Item 21936
Initiation of management of anaesthesia for cardiac catheterisation	Anaesthesiologist	Intervention	$138.60	MBS Item 21941
Intra-arterial cannulation when performed in association with the administration of anaesthesia	Anaesthesiologist	Intervention	$79.20	MBS Item 22025
Blood pressure monitoring	Anaesthesiologist	Intervention	$59.40	MBS Item 22012
LAA occluder	Prostheses	Intervention	$7,000—$13,000	Manufacturers
Transcatheter occlusion of LAA	Cardiologist	Intervention	TBC	TBC
Hospital procedure and admission costs e.g. OR, accommodation, nursing, allied health etc.	Hospital	Hospital Episode	TBC: $3,311	AR-DRG for similar service as reported in NHCDC. See D4 for itemisation of costs
Resources provided to deliver the comparator to deliver the current intervention (from Step 4, e.g., pre-treatments, co-administered interventions). *Identify variations where there may be more than one*				

Resource	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units[a]
comparator or where these may vary across different decision options.				
Cardiology consultation	Cardiologist	Medical - Embolic Management	$263.90	MBS Item 132
Annual cost of aspirin	Cardiologist	Embolic Management	$31.44	PBS (2013) Aspirin 300mg DPMQ $8.27 / Qty 96 [300mg/day]
Annual cost of clopidogrel (Plavix)	Cardiologist	Embolic Management	$653.74	PBS (2013) Clopidogrel 75mg DPMQ $50.15 / Qty 28 [75mg/day]
Resources provided following the proposed intervention with the proposed medical service (from Step 8, e.g., resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions conditioned on the results of the proposed intervention). *Identify variations where these may vary across different decision options.*				
Annual cardiology consultation	Cardiologist	Screening	$263.90	MBS Item 132
Chest x-ray	Cardiologist	Pre-discharge	$47.15[b]	MBS Item 58503
Transoesophageal echocardiography	Cardiologist	Pre-discharge	$275.50	MBS Item 55118
Anaesthesiology for Transoesophageal echocardiography	Anaesthesiologist	Pre-discharge	$118.80	MBS Item 21936
Non intra-operative TOE	Cardiologist	Post-discharge within 6 months	$275.50[b]	MBS Item 55118
Incident Cost of Major Bleeding	Hospital episode	Adverse Event	$6,020	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG =G61A, Gi Haemorrhage A>64/+CSCC]
Incident Cost of Minor Bleeding	Hospital episode	Adverse Event	$2,436	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG =G61B, Gi Haemorrhage A<65 - CSCC]
Incident Cost of Haemorrhagic stroke	Hospital episode	Adverse Event	$9,920	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = B70B, Stroke +SCC]
Incident Cost of Ischaemic Stroke	Hospital episode	Adverse Event	$9,920	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = B70B, Stroke +SCC]
Incident Cost of Pericardial Effusion	Hospital episode	Adverse Event	$8,781	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = F21B, Oth Circ Sys OR Pr -CCC]
Incident Cost of	Hospital episode	Adverse Event	$12,067	NHCDC Rd 14 (2009—10) Public

Resource	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units[a]
Systemic Embolism with Catastrophic Complications or Comorbidities				Sector - Avg direct cost per DRG [DRG = E61A, Pulmonary Embolism + CSCC]
Incident Cost of Systemic Embolism with Catastrophic Complications or Comorbidities	Hospital episode	Adverse Event	$5,879	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = E61B, Pulmonary Embolism - CSCC]
Cost of femoral pseudoaneurysm	Hospital episode	Adverse Event	$2,996	NHCDC Rd 14 (2009—10) Public Sector - F65B-Peripheral vascular disorders w/o CC
Cost of disability in first year after stroke	Hospital episode	Adverse Event	$13,127	PWC, June 2010
Resources provided following the comparator to deliver the current intervention (from Step 7, e.g., resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions conditioned on the results of the proposed intervention). *Identify variations where there may be more than one comparator or where these may vary across different decision options.*				
Incident Cost of Major Bleeding	Hospital episode	Adverse Event	$6,020	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG =G61A, Gi Haemorrhage A>64/+CSCC]
Incident Cost of Minor Bleeding	Hospital episode	Adverse Event	$2,436	NHCDC Rd 14 (2009—10)Public Sector - Avg direct cost per DRG [DRG =G61B, Gi Haemorrhage A<65 - CSCC]
Incident Cost of Haemorrhagic stroke	Hospital episode	Adverse Event	$9,920	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = B70B, Stroke +SCC]
Incident Cost of Ischaemic Stroke	Hospital episode	Adverse Event	$9,920	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = B70B, Stroke +SCC]
Incident Cost of Pericardial Effusion	Hospital episode	Adverse Event	$8,781	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = F21B, Oth Circ Sys OR Pr -CCC]
Incident Cost of Systemic Embolism with Catastrophic Complications or Comorbidities	Hospital episode	Adverse Event	$12,067	NHCDC Rd 14 (2009—10) Public Sector - Avg direct cost per DRG [DRG = E61A, Pulmonary Embolism + CSCC]
Incident Cost of	Hospital episode	Adverse Event	$5,879	NHCDC Rd 14 (2009—10) Public

Resource	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units[a]
Systemic Embolism with Catastrophic Complications or Comorbidities				Sector - Avg direct cost per DRG [DRG = E61B, Pulmonary Embolism - CSCC]
Cost of femoral pseudoaneurysm	Hospital episode	Adverse Event	$2,996	NHCDC Rd 14 (2009—10) Public Sector - F65B-Peripheral vascular disorders w/o CC
Cost of disability in first year after stroke	Hospital episode	Adverse Event	$13,127	PWC, June 2010

AR-DRG: Australian refined diagnosis-related groups; DRG: diagnosis-related groups; LAA: left atrial appendage; TBC: to be confirmed; TOE: transoesophageal echocardiography; PBS: pharmaceutical benefits scheme; DPMQ: dispensed price for maximum quantity; MBS: Medicare Benefits Schedule; NHCDC: National Hospital Cost Data Collection; PWC: PricewaterhouseCoopers Australia.

a Possible sources include experimental or trial data, observational data such as epidemiological data or utilisation data from Medicare Australia, survey data, expert opinion.

b Performed before discharge and at six week or six months. Repeated imaging would be required, if post procedural adverse events are suspected.

Costs relevant to the transcatheter occlusion of LAA compared to antiplatelet therapy should be included in the final model, and all costs to be validated and updated at the time of model development.

Proposed structure of economic evaluation (decision-analytic)

Table 8: Summary of extended PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients who: -have NVAF; -have one or more risk factors for stroke[a]; and -are contraindicated for oral anticoagulation therapy (i.e. warfarin and NOAC)[c]	Transcatheter occlusion of LAA[b]	Antiplatelet therapy	<u>Effectiveness:</u> Primary effectiveness -Stroke rate (including ischaemic stroke vs. haemorrhagic stroke) -All-cause mortality -Health-related quality of life (HRQoL) Secondary effectiveness Procedure success i.e. successful placement of a LAA occluder <u>Safety:</u> Any adverse event or complications that occur following the use of the intervention	Refer to 'Health care resources' Table 7. <u>Resources:</u> Consider time taken for the procedure, requirement of an assistant and length of hospital stay into consideration when related resources are calculated.

LAA: left atrial appendage; LVEF: left ventricular ejection fraction; NOAC: Novel oral anticoagulation; NVAF: non-valvular atrial fibrillation; TIA: transient ischaemic attack.
a Stroke risk can be assessed by CHADS1, CHADS2 or CHA2DS2-VASc scoring system. Based on CHADS2, risk factors for stroke are: history of stroke or transient ischaemic attack, cardiac failure and/or LVEF ⩽35%, hypertension, diabetes mellitus and age ⩾75 years. Clinical judgement will play a major role in the final decision of identifying patients with high stroke risk, once they have any of these risk factors for stroke.
b Transcatheter LAA occlusion devices include WATCHMAN™ (Boston Scientific), AMPLATZER Cardiac Plug™ (St Jude Medical) and WAVECREST™ (Coherex Medical).
c Contraindications to oral anticoagulation therapy include absolute and relative contraindications (see Table 2).

In this context, a patient could have contraindications to OAT due to: adverse reactions; inability to tolerate or adhere to OAT; or having failed OAT. PASC recognised that a minority of patients would be considered to have contraindications to OAT even if they have not received these drugs (eg patient refusal). Clinical judgement will play a major role in the final decision of identifying patients for the proposed intervention.

PASC has agreed that from a clinical perspective all LAA occlusion devices are similar and for the purposes of the protocol and the subsequent assessment report that it is appropriate to group all technologies in a generic approach to the assessment.

Research questions for public funding

Primary research question

- In patients with NVAF and a risk of stroke who are contraindicated for oral anticoagulation therapy: what is the safety, effectiveness, and cost-effectiveness of transcatheter occlusion of LAA compared with medical treatment with antiplatelet therapy?

Appendix A: Stroke risk and bleeding risk assessments

Table 9 $CHADS_2$ stroke risk score[26]

Risk Factors	Score
Cardiac failure	1
Hypertension	1
Age of 75 years or over	1
Diabetes mellitus	1
Prior stroke or transient ischaemic attack	2
Maximum	6

Table 10 CHA_2DS_2-VASc stroke risk score[26]

Risk Factors	Score
Cardiac failure	1
Hypertension	1
Age of 75 years or over	2
Diabetes mellitus	1
Prior stroke or transient ischaemic attack	2
Vascular disease	1
Age 65—74 years	1
Female	1
Maximum	9

Table 11 Stroke risk as a function of CHADS2 score[26]

$CHADS_2$ score	Adjusted stroke rate (% per year without antithrombotic treatment)[a]	Stroke risk
0	1.9	Low
1	2.8	Moderate
2	4.0	High
3	5.9	High
4	8.5	High
5	12.5	High
6	18.2	High

a The European Society of Cardiology explained the adjusted stroke rate as being 'derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalised AF patients, published in 2001, with low numbers in those with a $CHADS_2$ score of 5 and 6 to allow an accurate judgment of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalized cohorts may also vary from these estimates'.

Source: Adapted from Gage et al (2001)[18], Lip et al (2010)[19] and the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (2010)[20]

Table 12 Stroke risk as a function of CHA_2DS_2-VACs score[26]

$CHA_{27}DS_2$–VASc score	Adjusted stroke rate (% per year without antithrombotic treatment)[a]	Stroke risk
0	0.0	Low
1	1.3	Moderate
2	2.2	High
3	3.2	High
4	4.0	High
5	6.7	High
6	9.8	High
7	9.6	High
8	6.7	High
9	15.2	High

a These are the theoretical thromboembolic event rates without therapy, assuming that warfarin provides a 64% reduction in thromboembolic event risk.

Source: Adapted from Lip et al (2010)[19] and the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (2010)[20]

Figure 8 Clinical characteristics comprising the HAS-BLED bleeding risk score[6]

HASBLED

	Condition	Points
H	Hypertension	1
A	Abnormal liver and renal function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2

Bleeding Risk

Score	Bleeding Risk
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7

^Bleeds per 100 patient years as determined by bleeding within one year in patients with AF enrolled in the Euro Heart Survey

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