Australian Government

Department of Health

RATIFIED PICO

Application 1615:

Transcatheter occlusion of the left atrial appendage, for patients with non-valvular atrial fibrillation

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	<u>Population 1:</u> Patients with non-valvular atrial fibrillation (NVAF) assessed by a non-interventional and interventional cardiologist as having **absolute** contraindication to life-long oral anticoagulation therapy (OAT), and being at increased risk of thromboembolism demonstrated by: a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or b) at least 2 of the following risk factors: i. an age of 65 years or more; ii. hypertension; iii. diabetes mellitus; iv. heart failure or left ventricular ejection fraction of 35% or less (or both); v. vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) An **absolute** contraindication to lifelong anticoagulation is defined as (expanding existing definition of 'absolute' contraindication defined in MBS item 3827 to include iv. and v. below): i. a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy, or ii. a blood dyscrasia, or iii. a vascular abnormality predisposing to potentially life threatening haemorrhage or iv. unacceptably high bleeding risk due to: a. decompensated liver disease b. advanced renal failure c. intracranial conditions with high bleeding risk (amyloid, cerebral microbleeds) v. end stage renal disease. <u>Population 2:</u> Patients with NVAF assessed by a non-interventional and interventional physician as having **relative** contraindication to life-long OAT, and being at increased risk of thromboembolism demonstrated by: a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or b) at least 2 of the following risk factors: i. an age of 65 years or more; ii. hypertension; iii. diabetes mellitus; iv. heart failure or left ventricular ejection fraction of 35% or less (or both); v. vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque).

Component	Description
	A **relative** contraindication to lifelong anticoagulation is defined as: i. a previous major bleeding complication, or ii. bleeding diathesis, or iii. anaemia, or iv. prior gastrointestinal bleed, or v. thrombocytopenia, or vi. haematological malignancy, or vii. traumatic intracranial haemorrhage, or viii. hypersensitivity to registered anticoagulant(s) – per the product information for each registered DOAC, or ix. high falls risk, or x. cognitive impairment such as dementia.
Intervention	Percutaneous insertion of a left atrial appendage closure (LAAC) device to occlude the left atrial appendage (LAA)
Comparator	Population 1: Placebo or standard of care Population 2: Preferred: Direct oral anticoagulants (DOAC) on the Australian Register of Therapeutic Goods, noting evidence comparing agents not registered in Australia is not directly relevant Alternative: warfarin
Outcomes	**Efficacy/effectiveness** <u>Primary effectiveness</u> • Stroke incidence rate (ischaemic (embolic) stroke and haemorrhagic stroke) • Visceral/limb emboli , noting not all emboli will end up in cerebral circulation • All-cause mortality • Cardiovascular mortality • Health-related quality of life (HRQoL) <u>Secondary effectiveness</u> • Procedure success i.e. successful transcatheter occlusion of LAA **Safety** • Major bleeding events (procedural and post-procedural) • Procedural adverse events with LAAC • Post procedural adverse events with LAAC vs comparators **Healthcare resources** • Cost to deliver intervention **Total Australian Government Healthcare costs** • Total cost to the Medicare Benefits Schedule (MBS) • Total cost to other healthcare services

POPULATION

This is an application to amend the current patient population under existing MBS item 38276, which has been listed on the Medicare Benefits Schedule (MBS) since 1 November 2017.

PASC noted the purpose of this application was to amend MBS item 38276 to expand the definition of contraindication to lifelong oral anticoagulation therapy (OAT) to include 'relative' contraindications to OAT.

PASC recalled that MBS item 38276 was listed on the MBS on 1/11/2017 following support of application 1347.1 for a population with 'absolute' contraindication to OAT defined as a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy; or a blood dyscrasia; or a vascular abnormality predisposing to potentially life threatening haemorrhage. Compared with ***placebo,*** *MSAC concluded that there was evidence of reasonable safety, improved clinical outcomes and cost-effectiveness in high need population.*

The proposed population for transcatheter occlusion of the left atrial appendage is patients with non-valvular atrial fibrillation (NVAF), assessed by a non-interventional and interventional cardiologist as having a contraindication to life-long oral anticoagulation therapy (OAT), and being at increased risk of thromboembolism.

Increased risk of thromboembolism is demonstrated by:

a) a prior stroke (whether of ischaemic or unknown type), transient ischaemic attack, or non-central nervous system systemic embolism; or
b) at least two (2) of the following risk factors:
    i. aged 65 years or more;
    ii. hypertension;
    iii. diabetes mellitus;
    iv. heart failure or left ventricular ejection fraction of 35% or less (or both);
    v. vascular disease (prior myocardial infarction; peripheral artery disease; or aortic plaque)

A contraindication to lifelong anticoagulation is defined as:

i. a previous major bleeding complication, or
ii. bleeding diathesis, or
iii. a blood dyscrasia, or
iv. a vascular abnormality predisposing to potentially life-threatening haemorrhage, or
v. anaemia, or
vi. prior gastrointestinal bleed, or
vii. thrombocytopenia, or
viii. haematological malignancy, or
ix. traumatic intracranial haemorrhage, or
x. hypersensitivity to Australian-registered therapies

PASC noted that in the pre-PASC response to the current application, the applicant requested revising the PICO into two patient populations. The Summary PICO criteria above have been updated accordingly.

Population 1

*Patients with non-valvular atrial fibrillation (NVAF) assessed by a non-interventional and interventional cardiologist as having **absolute** contraindication to life-long OAT, and being at increased risk of thromboembolism demonstrated by:*

a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or
b) at least 2 of the following risk factors:
  i. an age of 65 years or more;
  ii. hypertension;
  iii. diabetes mellitus;
  iv. heart failure or left ventricular ejection fraction of 35% or less (or both);
  v. vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque).

*An **absolute** contraindication to lifelong anticoagulation is defined as:*

i. a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy, or
ii. a blood dyscrasia, or
iii. a vascular abnormality predisposing to potentially life threatening haemorrhage or
iv. unacceptably high bleeding risk due to:
  a. decompensated liver disease
  b. advanced renal failure
  c. intracranial conditions with high bleeding risk (amyloid, cerebral microbleeds)
v. endstage renal disease.

Population 2

*Patients with NVAF assessed by a non-interventional and interventional cardiologist as having **relative** contraindication to life-long OAT, and being at increased risk of thromboembolism demonstrated by:*

a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or
b) at least 2 of the following risk factors:
  i. an age of 65 years or more;
  ii. hypertension;
  iii. diabetes mellitus;
  iv. heart failure or left ventricular ejection fraction of 35% or less (or both);
  v. vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque).

*A **relative** contraindication to lifelong anticoagulation is defined as:*

i. a previous major bleeding complication, or
ii. bleeding diathesis, or
iii. anaemia, or
iv. prior gastrointestinal bleed, or

v. *thrombocytopenia, or*
vi. *haematological malignancy, or*
vii. *traumatic intracranial haemorrhage, or*
viii. *hypersensitivity to registered anticoagulant(s) – per the product information for each registered DOAC, or*
ix. *high falls risk, or*
x. *cognitive impairment such as dementia.*

PASC noted that by proposing the two populations, the applicant was now requesting:

1. *to expand the existing definition of 'absolute' contraindication to OAT defined in MBS item 38276 to include iv. and v. (Population 1) and*
2. *a new patient population with 'relative' contraindication to OAT (Population 2).*

PASC noted the applicant's claim to expand the definition of 'absolute' contraindications in the existing MBS item 38276 (Population 1) is based upon application 1347.1 and that the new patient population with 'relative' contraindications to OAT (Population 2) will be supported by new evidence not previously considered by MSAC.

*PASC advised that the applicant's request to amend the list of **absolute** contraindications currently stated within MBS item 38276 (Population 1) should be presented along with a budget impact analysis, to the MSAC Executive for consideration and that only Population 2 should be the focus of this application.*

PASC advised that that the 'relative' contraindications will need to be well defined. PASC advised that 'prior gastrointestinal bleed' (for which there was no correctional basis) required further clarification and suggested using the definitions for the "absolute contraindications" for this item be aligned with the contraindications for DOACs as per the TGA approved product information (PI) across the class of agents. Accordingly, the "relative contraindications" can be defined as the "cautions for use" described in the PIs across the class of DOACs.

Background

Atrial fibrillation (AF) is a condition characterised by disorganised atrial activity without discrete p-waves on a 12 lead electrocardiogram. 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% of AF is described as non-valvular atrial fibrillation (NVAF) (Ang et al 1998). AF is associated with substantial morbidity and mortality from heart failure, stroke, and other thromboembolic complications (Lip 2003). 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 (Savelieva 2001).

The death rate from atrial fibrillation has seen a steady increase in the last decade with a total of 1552 Australians having lost their lives due to atrial fibrillation in 2009 increasing to a total of 2953 lives lost in 2018 (Australian Bureau of Statistics [ABS] 2018). These figures do not account for deaths caused by AF related conditions (such as stroke, heart failure), thus are likely to underestimate the

true numbers. Costs of AF to the Australian economy are at least $1.25 billion (AUD) per annum through medical costs, costs of long-term care for those with a disability, and lost productivity (Price Waterhouse Coopers 2010).

In 2015, 1.7% of the Australian population (~397,000) had experienced a stroke at some time in their life (Australian Institute in Health of Health and Welfare [AIHW]: cardiovascular disease 2019). 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%) (AIHW: Heart, stroke and vascular diseases 2004).

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% of people with AF have no symptoms; many of these people are not diagnosed and thus do not receive appropriate treatment for stroke risk (Department of Health and Ageing (DoHA): review of anticoagulation therapies in atrial fibrillation 2012).

Based on the Australian National Heart Foundation (NHF) and Cardiac Society of Australia and New Zealand (CSANZ) clinical guidelines for diagnosis and management of AF (2018), the stroke risk of patients with NVAF in Australia is assessed using a modified version of the CHA_2DS_2-VAS score, namely CHA_2DS_2-VA. This does not take into account sex (the former gives one point for female sex).

The sexless score is recommended to avoid the cumbersome practice of selecting different thresholds for males and females when recommending anticoagulation. The definition and points in the CHA_2DS_2-VA are provided in Table 1.

Table 1 Definition and points in the CHA_2DS_2-VA score

Score	Points	Definition
C	1	Congestive heart failure—recent signs, symptoms or admission for decompensated heart failure; this includes both HFrEF and HFpEF, or moderately to severely reduced systolic left ventricular function, whether or not there is a history of heart failure
H	1	History of hypertension, whether or not BP is currently elevated
A2	2	Age ≥ 75 years
D	1	Diabetes
S2	2	History of prior stroke or TIA or systemic thromboembolism
V	1	Vascular disease, defined as prior myocardial infarction or peripheral arterial disease or complex aortic atheroma or plaque on imaging (if performed)
A	1	Age 65–74 years

AF=atrial fibrillation; BP=blood pressure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; TIA=transient ischaemic attack.
Source: National Heart Foundation (NHF) of Australia and Cardiac Society of Australia and New Zealand (CSANZ) Guidelines (2018) Table 3 pg. 1235.

Work-up of patients with NVAF

In the Australian NHF and CSANZ Guidelines for AF (2018), the CHA_2DS_2-VA score is recommended for predicting stroke risk in AF, which determines the management of patients. In patients with a score of zero, oral anticoagulation or antiplatelet agents are not recommended. Rather, these patients will be re-evaluated annually, to review their score. Patients with a CHA_2DS_2-VA score of 1 are considered for OAT, to prevent stroke and systemic embolism (note the Guidelines refer to oral

anticoagulant [OAC], which is interchangeable with OAT). The Guidelines specifically recommend that "when oral anticoagulation is initiated in patients with NVAF, a DOAC – apixaban, dabigatran, or rivaroxaban – is recommended in preference to warfarin" (p.1237). Antiplatelet agents are not recommended for stroke prevention of NVAF patients, irrespective of their CHA_2DS_2-VA score.

For patients with a CHA_2DS_2-VA score of ≥ 2 who are not contraindicated for anticoagulation, OAT is recommended, with direct oral anticoagulants (DOACs) being preferred. For patients with clear contraindications to OAT, LAAC may be considered. This pathway is consistent with the MBS listing for LAAC, with the Guidelines citing MSAC Application 1347.1, with reference to effectiveness and cost-effectiveness of LAAC versus placebo, to support this positioning of LAAC.

Prevalence of NVAF

The prevalence of NVAF and stroke risk distribution is substantiated by a relatively robust set of epidemiological inputs derived from Australian epidemiological studies. According to the report by the Department of Health and Ageing (DoHA) in 2012, the prevalence of AF in Australia is 1–2% (DoHA: review of anticoagulation therapies in atrial fibrillation 2012, Section 5.2; Go et al 2001; Miyasaka et al 2006; Sturm et al 2002), although prevalence estimates sharply increase with age, and the number of people with stroke is also expected to increase significantly as the population ages.

Rationale

Currently, to be eligible for LAAC on the MBS, patients must have NVAF and be at increased risk of stroke (CHA_2DS_2-VA ≥ 2) and have a contraindication to lifelong oral anticoagulation (OAT), here referred to as 'absolute' contraindication to OAT. The proposed patient population in this application is the same as those who are currently eligible for LAAC on the MBS with the exception that patients have '**relative'** contraindication to OAT, rather than 'absolute' contraindication to lifelong OAT. Eligibility criteria for MBS item 38276 is as follows, with contraindications to life-long anticoagulation defined in Explanatory Note TN.8.132:

A contraindication to lifelong anticoagulation is defined as:

i) a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy,
ii) a blood dyscrasia, or
iii) a vascular abnormality predisposing to potentially life-threatening haemorrhage.

The use of OAT for prevention of stroke in NVAF patients is based on a patient's stroke risk, relative to any comorbid conditions that might carry significant risk of bleeding. Such characteristics are referred to as relative contraindications. Relative contraindications represent patient characteristics that put them at higher risk for bleeding and may result in withholding OAT, given the balance of risk to benefit of treatment (Steinberg et al 2015).

The 'absolute' contraindication to lifelong anticoagulation as per explanatory note (TN.8.132) were defined in the Stakeholder meeting for Application 1347 (MSAC Application 1347 Stakeholder meeting minutes 5 June 2015). This stakeholder meeting "considered that relative contraindications were more difficult to establish particularly whether there was true intolerance to therapy or just reflected patient preference" (p.2). To mitigate this, the Applicant has sought local expert advice to formulate a specific list of contraindications that do not reflect patient preference.

The study by Steinberg et al (2015) defines relative contraindications as advanced age (85 years or older), evidence of dementia, gastrointestinal haemorrhage, thrombocytopenia, anaemia, haematological malignancy and traumatic intracranial haemorrhage. Other sources are broadly similar, however also include recent history of recurrent iatrogenic falls in patient at higher bleeding risk as a relative contraindication, whilst acknowledging that risk of fall is not a contraindication to OAT per se (Buckinghamshire Formulary NHS[1]). The definitions used by Steinberg et al (2015) were adapted based on local expert advice, to ensure only contraindications pertaining to patients bleeding risk were included. As such, age ≥ 85 years and dementia were not considered specific to patients bleeding risk per se and were not included in the list.

INTERVENTION

The intervention for the proposed medical service is percutaneous insertion of a left atrial appendage closure (LAAC) device, to occlude the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation (NVAF). The left atrial appendage is the primary source for thromboembolism in patients with NVAF. The percutaneous insertion of an implantable device to occlude the LAA may be performed to reduce thromboembolism in patients with NVAF. The procedure aims at preventing stroke and systemic thromboembolism, by closing off the LAA permanently to avoid formation and migration of emboli to the brain.

PASC confirmed the intervention as stated in the PICO.

Surgical procedure

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 measurements should be taken and the appropriate size device selected as per the directions for use (DFUs) of the respective devices.

The procedure is performed under local or 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:

- Pre-service component: 5—10 min. The cardiologist 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 (Reddy et al 2013).
- Post-service component: 5 minutes. This may include procedures notes.

The implantation procedure uses standard transseptal techniques. 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. The device is unsheathed when in the appropriate position. Several criteria are assessed prior to final release of the device including position, seal and device stability. A

[1] http://www.bucksformulary.nhs.uk/docs/ContraindicationsOralAnticoag%26Anti-plateletsAFPrimaryCare.pdf (accessed 28 October 2019)

device can be repositioned or removed prior to its final release if criteria for permanent placement are not met.

Setting

The proposed medical service is provided in a public or private hospital. 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 transthoracic echocardiogram [TTE]). Accessibility to the LAAC procedure is limited by referral to an interventional cardiologist or cardiac electrophysiologist, availability of an accredited operator and equipped facility including a catheterisation laboratory.

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

- Proficiency in trans-septal skills and left sided procedures
- 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 a cardiologist experienced in LAAC and/or a clinical specialist. To be considered an independent treating cardiologist, both the trainee and proctor must agree that there is an appropriate level of skill in implanting the device which is normally achieved following the successful completion of 5-10 procedures under supervision pending skill set.

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

Postoperative care

Postoperatively, patients should begin antiplatelet medication to achieve optimal results. The appropriate dose and duration of antiplatelet therapy post-procedure is manufacturer specific. In general terms, patients will be managed on dual antiplatelet therapy for a minimum of 3 months (aspirin and clopidogrel) and maintained on aspirin for at least 12 months. Follow up examination with a TOE is performed at six weeks to evaluate the LAA seal. A cardiologist may choose to perform additional TOE procedures if any complications are suspected.

Devices

There are currently four devices registered for use to perform the LAAC procedure in Australia, WATCHMAN™ (Boston Scientific), the AMPLATZER™ Cardiac Plug (St Jude Medical), the AMPLATZER™ Amulet (St Jude Medical) and the Coherex WaveCrest™ (Johnson and Johnson).

The intervention for the purpose of this resubmission is transcatheter occlusion of the LAA. In the Final Protocol for MSAC Application 1347, PASC agreed that from a clinical perspective, all LAA occlusion devices are similar and for the purposes of the assessment report, it is appropriate to

group all technologies in a generic approach. Indeed, in the PSD, MSAC "noted that there was insufficient basis to compare across available LAAC devices in terms of their comparative safety and comparative effectiveness (MSAC Application 1347 PSD November 2014).

While the WATCHMAN, AMPLATZER Cardiac Plug and AMPLATZER Amulet devices are listed on the Prostheses List, the Coherex WaveCrest device is not. For completeness, details of all four devices are provided below.

WATCHMAN™

The WATCHMAN LAA Closure Technology consists of the Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and LAA Closure Device). The Access System and Delivery System permit device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium. The WATCHMAN device is a self-expanding nitinol structure with a porous membrane on the proximal face (Figure 11). The device is constrained within the Delivery System until deployment in the LAA. The device is available in 5 sizes from 21 to 33 mm.

The WATCHMAN LAA Closure device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA.

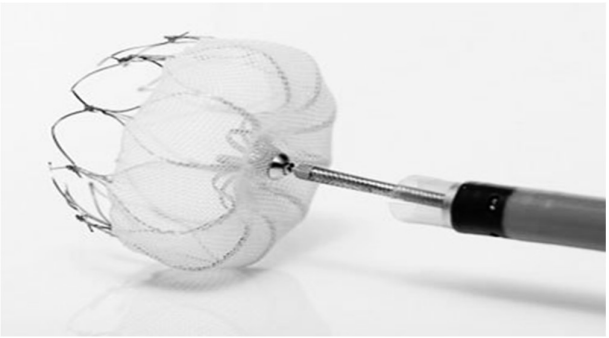

Figure 1 WATCHMAN™ LAA occluder
Source: Cardiac Rhythm News <www.CardiacRhythmNews.com>

AMPLATZER Cardiac Plug™

The AMPLATZER Cardiac Plug™ (Abbott Australia Pty Ltd) is a transcatheter self-expanding nitinol device for use in cardiac structures. The AMPLATZER™ Cardiac Plug™ consists of a small proximal disc, a central polyester patch, and a larger disc with hooks to anchor the device in the LAA. (Figure 22). The device is constrained within the Delivery System until deployment in the LAA.

The lobe has stabilising wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cables. The device has radiopaque markers at each end and at the stabilising wires which permit visibility during fluoroscopy to facilitate accurate device placement.

It is designed to provide optimal occlusion with full cross-sectional orifice coverage of the LAA, regardless of the LAA anatomy and is delivered via AMPLATZER™ TORQVUE™ Delivery systems designed specifically for use with this device.

The AMPLATZER Cardiac Plug™ device is available in eight different sizes (16mm to 30mm) to accommodate the size of the LAA. The AMPLATZER™ Cardiac Plug is intended for use in cardiac

structures that do not involve the septal wall, but which require closure or occlusion. The AMPLATZER™ Cardiac Plug is intended to prevent thrombus embolization from the LAA in patients with NVAF.

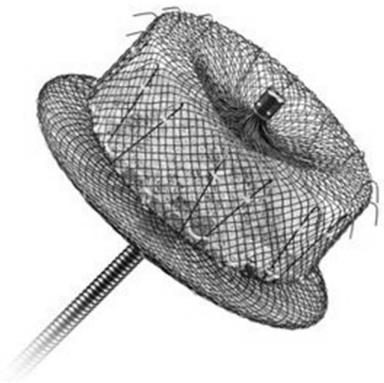

Figure 2 AMPLATZER Cardiac Plug™ LAA occluder
Source: Cardiac Rhythm News <www.CardiacRhythmNews.com>

AMPLATZER Amulet™

The AMPLATZER Amulet™ Left Atrial Appendage Occluder is a percutaneous transcatheter device intended to prevent thrombus embolization from the LAA in patients who have NVAF.

The device is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist. Polyester patches are sewn into both the lobe and disc to facilitate occlusion. The lobe has stabilising wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cables. The device has radiopaque markers at each end and at the stabilising wires that permit visibility during fluoroscopy to facilitate accurate device placement. The device is constrained within the Delivery System until deployment in the LAA.

It is designed to provide optimal occlusion with full cross-sectional orifice coverage of the LAA, regardless of the LAA anatomy and is delivered via AMPLATZER™ TORQVUE™ Delivery systems designed specifically for use with this device. The AMPLATZER Amulet™ device is available in eight different sizes (16mm to 34mm) to accommodate the size of the LAA.

Coherex WaveCrest™

The Coherex WaveCrest Left Atrial Appendage Occlusion System (Johnston and Johnston) is intended to be used for occlusion of the left atrial appendage in patients who have all of the following: non-valvular paroxysmal, persistent, or permanent AF, LAA anatomy amenable to treatment by percutaneous techniques, and risk factors for potential thrombus formation in the LAA (Figure 3).

The system consists of the following components: 1) the occluder, 2) the anchors, and 3) the delivery system. The system is designed to be used exclusively with the Coherex WaveCrest Left Atrial Appendage Occlusion System Delivery Sheath, which is packaged and delivered separately. The occluder and anchors comprise the implantable components of the system and together for the

Coherex WaveCrest Implant. The delivery system for the implant consists of a delivery catheter with a loading device and a proximal control handle. The control handle is designed to actuate the anchors through the catheter and to detach the implant from the system.

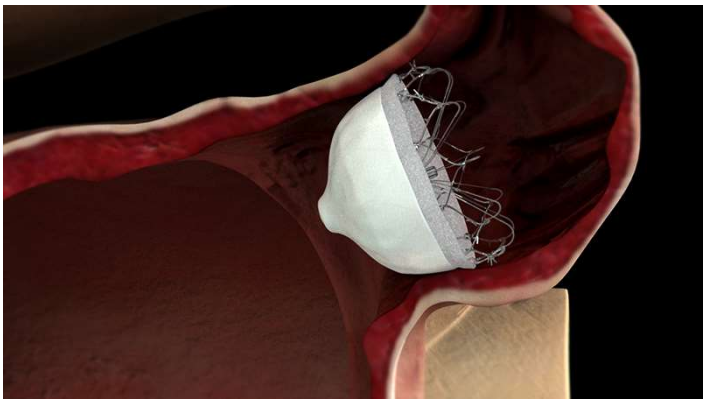

Figure 3 Coherex WaveCrest ™ LAA occluder

Current use and reimbursement of LAA occluder prostheses

The proposed medical service, LAAC, using LAA occluder prostheses, is currently used and reimbursed for patients with NVAF on the MBS. Thus, the procedure does not represent a new approach towards managing patients with NVAF as such, however, the proposal for funding would allow a subgroup of patients who currently don't have access to the procedure to undergo LAAC. That is, it is proposed that patients with relative contraindications to OAT who are currently not eligible for LAAC will be able to access the procedure.

Rationale

Devices such as AtriClip (Australian Register of Therapeutic Goods (ARTG) 175070) are also used for LAA exclusion. However, the procedures associated with these devices are not comparable with the 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 resubmission, as specified in the Final Protocol for Application 1347 and consistent with Application 1347.1.

PASC noted that there are four medical devices listed on the Australian Register of Therapeutic Goods (ARTG) relevant to this medical procedure and that these cost approximately $11,400.

PASC noted that the actual utilisation of the intervention under the current MBS item 38276 for patients with NVAF who have an 'absolute' contraindication to OAT is lower than was originally predicted but is increasing. PASC noted that the application estimated the utilisation of the intervention will increase approximately 10-fold with the proposed addition of the 'relative' contraindications to OAT. PASC advised that robust estimates of population size with sensitivity analyses will be required as part of the evaluation.

COMPARATOR

The proposed main comparator for LAAC in patients with NVAF with relative contraindication to OAT is direct oral anticoagulants (DOAC) as these agents are the preferred treatment option in the proposed patient population. Warfarin is an alternate treatment option in these patients, thus is included as an additional comparator.

Warfarin has a general listing on the pharmaceutical benefits scheme (PBS) whereas the DOACs are restricted to stroke prevention in NVAF patients with CHA_2DS_2-VA ≥ 1. There are three DOACs listed on the PBS for stroke prevention in NVAF: apixaban, dabigatran and rivaroxaban, restriction provided in Table 2. Rivaroxaban was listed on a cost-effectiveness basis versus warfarin, with apixaban and dabigatran cost-minimised to rivaroxaban.

PASC confirmed the following comparators for Population 2:

- *Direct oral anticoagulants (DOACs) e.g. apixaban, dabigatran, rivaroxaban*
- *Additional comparator: Warfarin (general listing).*

Table 2 PBS restriction for DOACs for prevention of stroke

PBS restriction for DOACs
Prevention of stroke or systemic embolism Patient must have non-valvular atrial fibrillation Patient must have one or more risk factors for developing stroke or systemic embolism: 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.

OUTCOMES

The applicant claims that, relative to the comparators, DOACs and warfarin, LAAC is associated with superior safety (in terms of bleeding), and superior effectiveness in terms of cardiovascular mortality.

PASC confirmed the following outcomes were relevant to the application and recommended the addition of further outcomes, included in italics below.

Primary effectiveness

- Stroke incidence rate (ischaemic stroke and haemorrhagic stroke)
- Visceral or Limb embolism (noting not all emboli will end up in cerebral circulation
- All-cause mortality
- Cardiovascular mortality
- Health-related quality of life (HRQoL)

Secondary effectiveness

- Procedure success i.e. successful transcatheter occlusion of LAA
- *Discontinuation of therapy*

Safety

- Major bleeding events (procedural and post-procedural)
- Procedural adverse events with LAAC
- Post procedural adverse events with LAAC vs comparators

Healthcare resources

- Cost to deliver intervention *(including follow up/monitoring for both intervention and comparator arms)*
- *PBS costs*

Total Australian Government Healthcare costs

- Total cost to the Medicare Benefits Schedule (MBS)
- Total cost to other healthcare services *(including cost of prostheses)*

Current and proposed clinical management algorithms for the identified population

PASC advised that updated current and proposed clinical algorithms need to be provided that reflect Population 2 and the updated relative contraindications.

Current clinical management algorithm

The current clinical management pathways that patients follow after they receive the comparator treatments is provided in

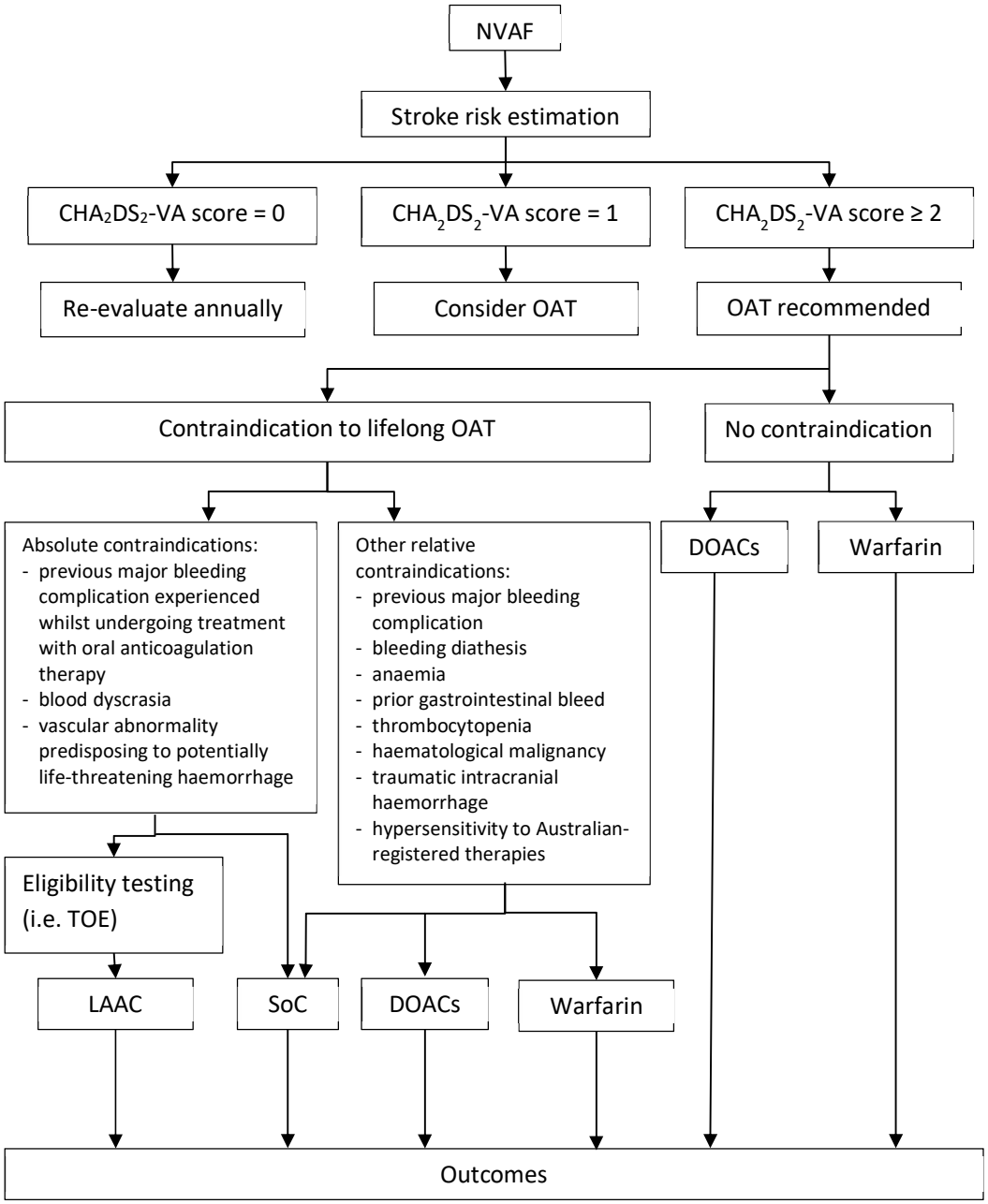

Figure 4. The main health care resources consumed from the point of receiving the comparator is monitoring of bleeding risk and treatment adherences.

According to the Australian NHF and CSANZ Guidelines for AF (2018), patients prescribed pharmacotherapy including OAT should have their treatment adherence and persistence regularly monitored, although the Guidelines do not specify the time interval at which patients should be monitored. Non-compliance with DOACs is a particular concern given the rapid offset of action, thus potentially increasing the risk of stroke in these patients (Australian NHF and CSANZ Guidelines 2018).

While patients treated with DOACs do not require specific monitoring in terms of bleeding risk, patients treated with warfarin require regular monitoring of their international normalised ratio (INR) to ensure adequate anticoagulation whilst balancing the risk of bleeding.

Patients with relative contraindication to OAT treated with DOACs or warfarin may experience a major bleeding complication, a blood dyscrasia or develop a vascular abnormality predisposing them to potentially life-threatening haemorrhage, thus becoming eligible for LAAC based on the current MBS reimbursement).

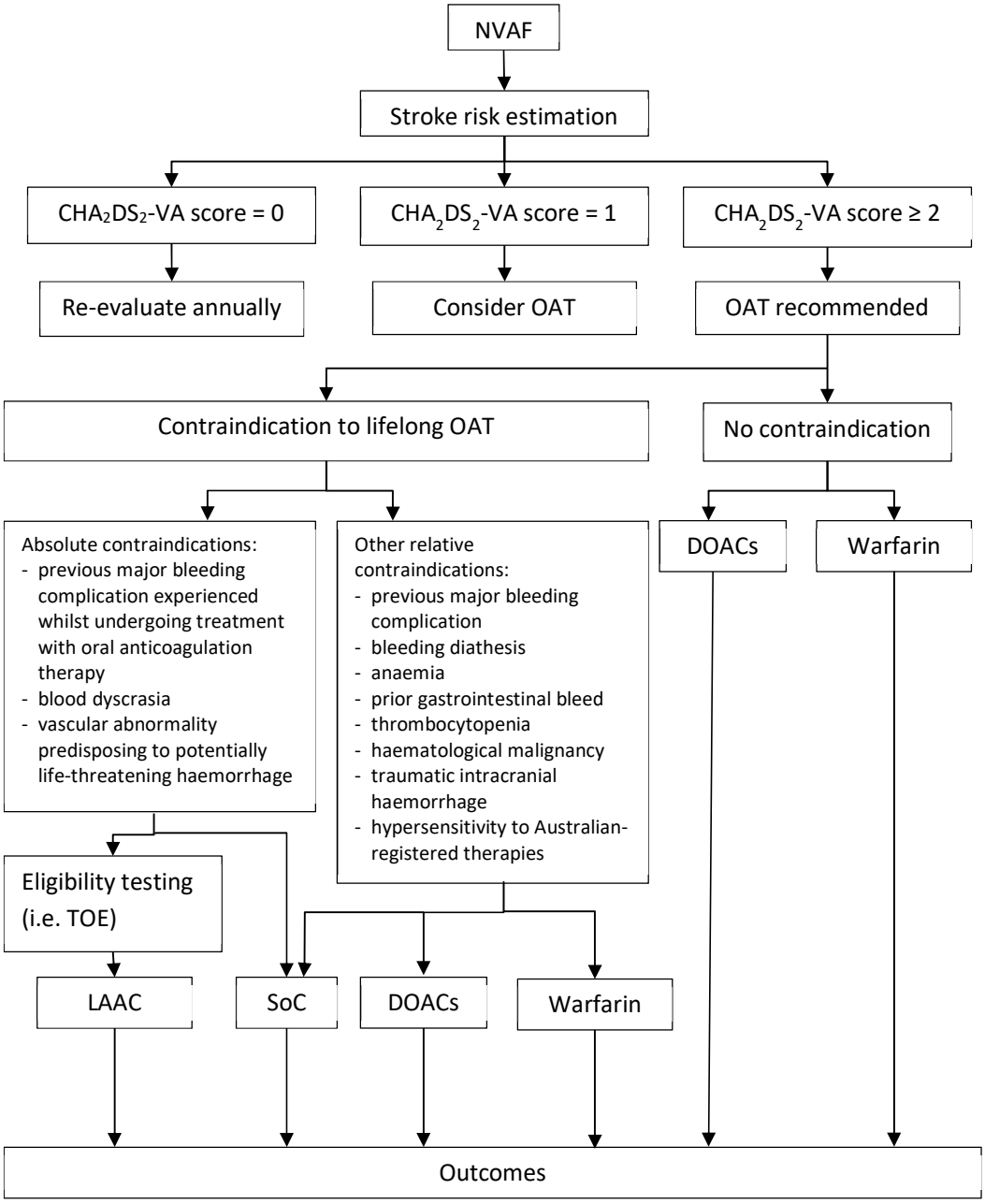

Figure 4 Current management pathway

LAAC=left atrial appendage closure; DOACs=direct oral anticoagulants; NVAF=non-valvular atrial fibrillation; OAT=oral anticoagulant therapy; SoC=Standard of Care; TOE=transoesophageal echocardiogram.

INR monitoring

Given the narrow therapeutic window of warfarin, regular monitoring of INR is required to ensure adequate anticoagulation, whilst minimising the risk of bleeding. According to warfarin product information (PI) (Coumadin), the therapeutic range is INR 2-3, with bleeding risk increasing significantly with an INR of 4.

The bleeding risk of INR 2-3 is 1.3% (De Caterina et al 2007). Thus, regular INR measurement is required for the duration of warfarin therapy. The approaches to monitoring in Australia include:

- General practitioner (GP)-led management
- Anticoagulation clinic
- Pathology service-led care (using validated computerised dosing algorithms)
- Point of care (POC) testing (including patient self-management using coagulometers (Australian NHF and CSANZ Guidelines 2018).

When commencing treatment, patients treated with warfarin are recommended to have daily checks of prothrombin time (PT), until the patient is stable and a therapeutic range is reached (Warfarin PI). The PT is used to calculate the INR. Patients maintained on warfarin require continuous monitoring, at an interval of every 1-4 weeks (Warfarin PI).

POC devices using finger-prick capillary blood sampling allows convenient and efficient INR measurement in the clinical practice setting, as well as self-management in the patient's home.

POC devices (i.e. coagulometers) and required consumables (e.g. test strips) are not reimbursed via the MBS, with those costs being borne by the practice/clinic or patient. The healthcare resources required for INR measurement of patients treated with warfarin depend on the model of care used. There are several coagulometers registered for use in Australia. POC testing is generally most relevant in the on-going monitoring of patients who are stable.

Costs associated with INR monitoring (when warfarin is prescribed) include pathology collection and testing, and general practitioner consultations (reimbursed through the MBS). It is estimated the annual cost of monitoring INR (to ensure a patient sits in the therapeutic target range) is $445 per patient per year.

Alternatively, POC monitoring by the patient would mean purchasing the coagulometer, such as CoaguChek (estimated at $700 per device), together with test strips (estimated at $150 per 24 strips). Devices and consumables are not reimbursed through the MBS.

Proposed clinical management algorithm

Listing LAAC for the proposed patients (with relative contraindications to OAT) provides patients and cardiologists with a 'one procedure' treatment alternative to DOACs and warfarin. The main differences (in terms of

healthcare resources) from the point of service in using LAAC, rather than DOACs and warfarin, are illustrated in

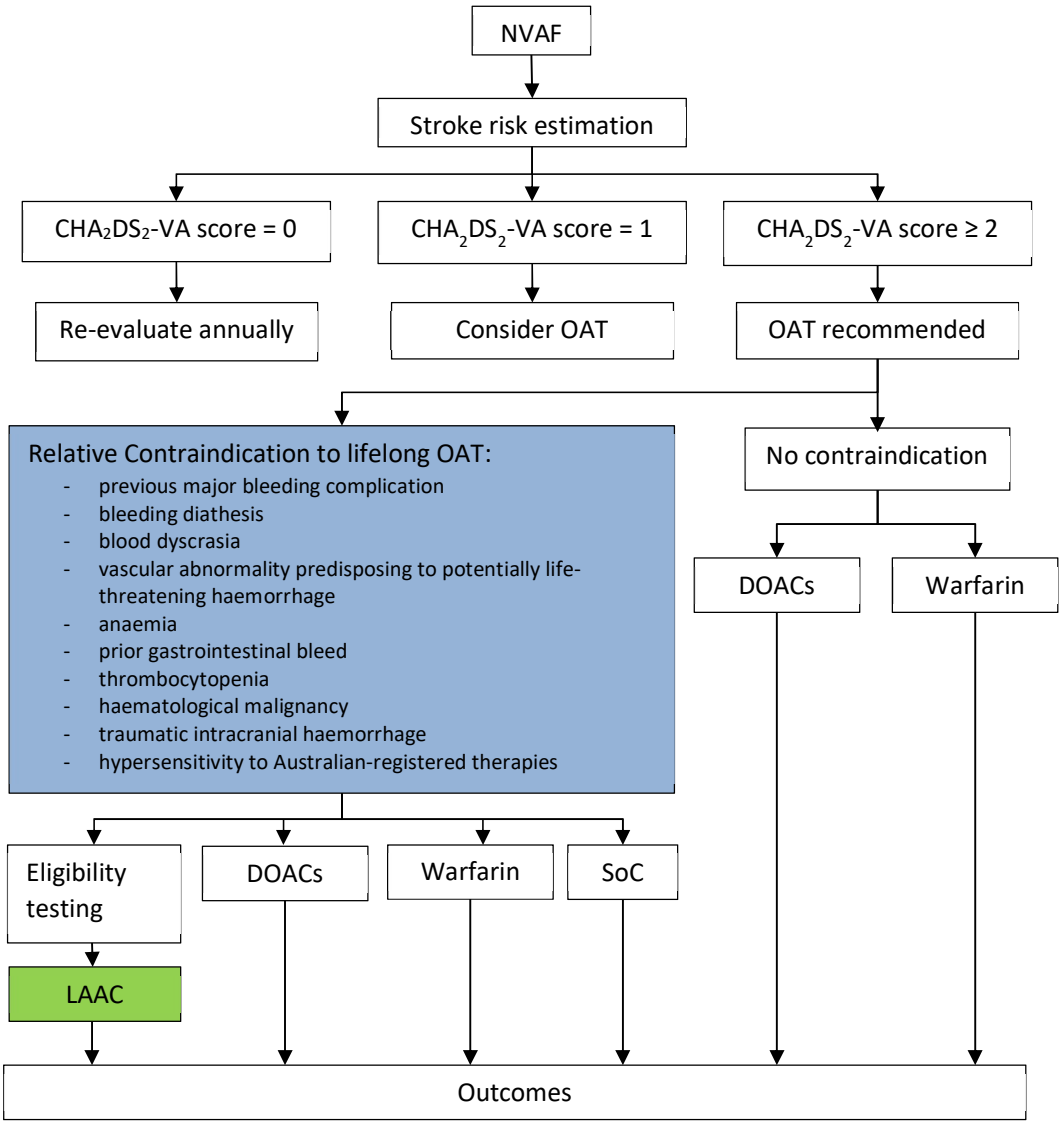

Figure 5 and include:

- Monitoring of adherence is not required. DOACs and warfarin require long-term treatment, with effectiveness dependent on adherence. In contrast, LAAC is a once-off procedure, thus effectiveness is not dependent on compliance.
- Monitoring of INR is not required. Regular, ongoing INR monitoring is relevant to all patients prescribed warfarin, to ensure adequate coagulation whilst balancing the risk of bleeding. Monitoring will continue for as long as the patient is treated with warfarin.
- Reduction in major bleeding events and improved survival with LAAC, relative to OAT (Reddy et al 2017), providing superior outcomes to patients.
- Patients undergoing LAAC have the potential of experiencing procedural complications, such as procedure-related cardiac perforation or pericardial tamponade. However, based on key clinical evidence, the rates of procedure-related events are relatively low.

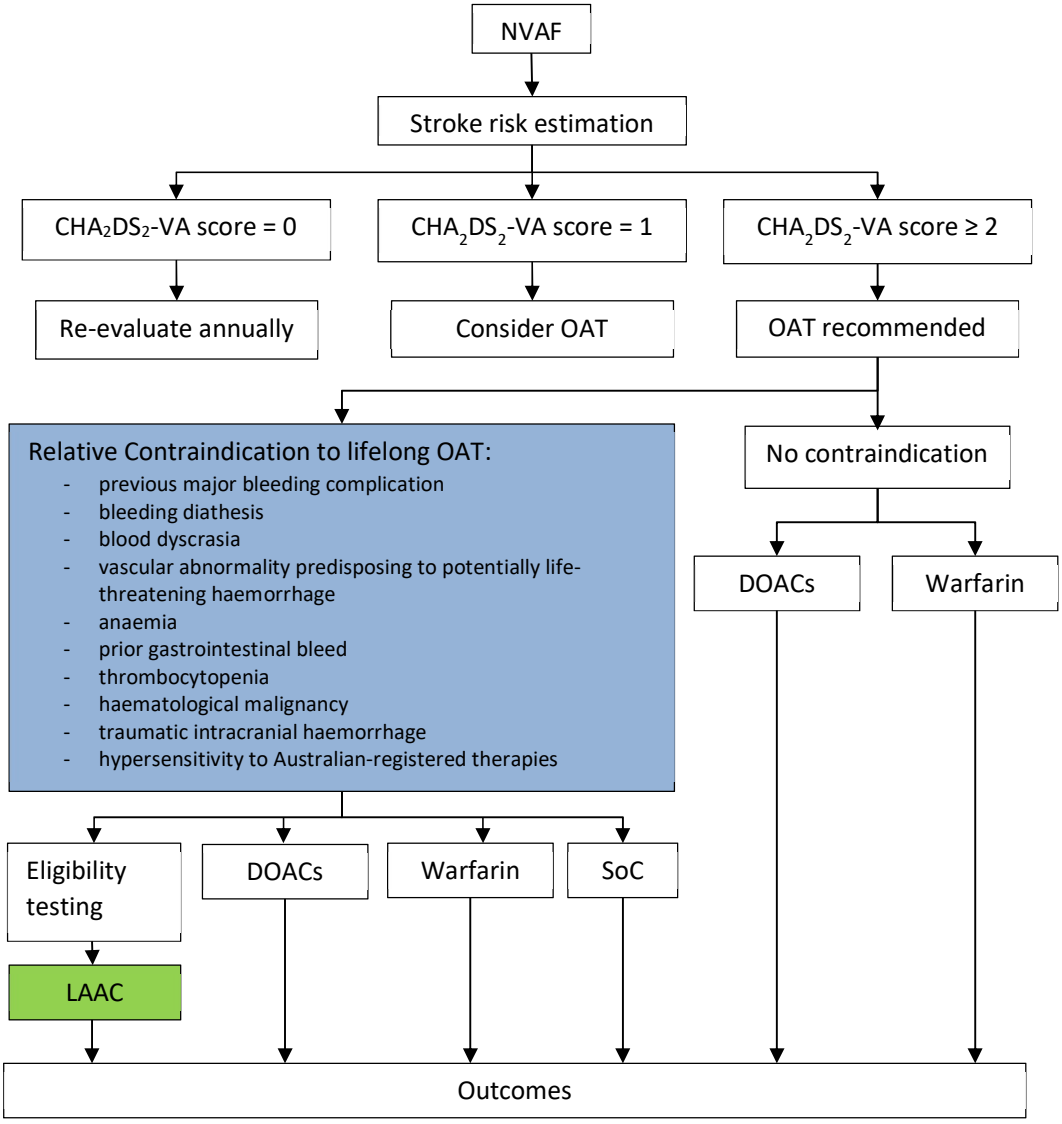

Figure 5 Proposed management pathway from the point of receiving the comparators and proposed service

LAAC=left atrial appendage closure; DOACs=direct oral anticoagulants; NVAF=non-valvular atrial fibrillation; OAT=oral anticoagulant therapy; SoC=Standard of Care.
Proposed expansion of absolute contraindications to include the other relative contraindications is marked in blue in the algorithm.
Proposed service is marked in green in the algorithm.

Proposed economic evaluation

The clinical claim is that LAAC is superior in clinical effectiveness to the comparators (DOACs and warfarin). According to the Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative, the required economic analysis is therefore a cost-utility or a cost-effectiveness analysis. However, if the evidence does not prove superiority, then a cost-consequence model may be more appropriate.

PASC noted that as there is a claim of LAAC superiority in clinical effectiveness a cost-utility or cost-effectiveness analysis is appropriate. Should superiority not be demonstrated, cost-consequences may be appropriate.

Proposed MBS item descriptor and MBS fee

The existing/proposed MBS item descriptor and proposed associated explanatory note for the LAAC procedure is provided in Table 3. The proposed MBS fee and item descriptor is identical to the current MBS item for LAAC. The proposed changes relate to the definition of contraindication in the explanatory note.

The existing explanatory note to the current MBS item descriptor stipulates patients must have (absolute) contraindications to lifelong OAT, defined as: i) a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy; ii) a blood dyscrasia; or iii) a vascular abnormality, predisposing to potentially life-threatening haemorrhage.

The proposed note update stipulates that patients must have a relative contraindication to lifelong OAT as defined in Table 3.

Table 3 MBS item descriptor and proposed explanatory note changes for LAAC *

Category 3 – THERAPEUTIC PROCEDURE
MBS item 38276 ***Proposed item descriptor (identical to existing item descriptor):*** Transcatheter occlusion of left atrial appendage, and cardiac catheterisation performed by the same practitioner, for stroke prevention in a patient who has non-valvular atrial fibrillation and a contraindication to life-long oral anticoagulation therapy, and is at increased risk of thromboembolism demonstrated by: (a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or (b) at least 2 of the following risk factors: (i) an age of 65 years or more; (ii) hypertension; (iii) diabetes mellitus; (iv) heart failure or left ventricular ejection fraction of 35% or less (or both); (v) vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) MBS Fee: $926.90 Benefit: 75% = $695.20 (in-hospital / admitted patient only)
Existing Explanatory Note TN.8.132 ***(with proposed changes indicated by 'strikethrough' and red text)*** Transcatheter occlusion of left atrial appendage for stroke prevention (MBS item 38276) **Explanatory Note** A contraindication to lifelong anticoagulation is defined as: i) a previous major bleeding complication ~~experienced whilst undergoing treatment with oral anticoagulation therapy~~, or ii) Bleeding diathesis, or iii) a blood dyscrasia, or iv) a vascular abnormality predisposing to potentially life-threatening haemorrhage, or

v) anaemia, or
vi) prior gastrointestinal bleed, or
vii) thrombocytopenia, or
viii) haematological malignancy, or
ix) traumatic intracranial haemorrhage, or
x) hypersensitivity to registered anticoagulant(s)

The procedure is performed as a hospital service.

*MBS item descriptor has not been amended to include PASC's advice (see below).

PASC noted that the proposed MBS item in the PICO will need to be revised to be consistent with the revised Population 2 (see Population). PASC noted that all contraindications will need to be clearly defined.

PASC noted that in the draft PICO, determining eligibility for the intervention required both a non-interventional and interventional cardiologist to assess contraindications to life-long OAT and risk of thromboembolism. However, the proposed MBS item, based on the current MBS item 38276, does not include the requirement for a non-interventional and interventional cardiologist to determine eligibility. PASC noted that in the pre-PASC response, the applicant claimed the populations were well defined and that having a non-interventional and interventional cardiologist determine eligibility is most likely redundant. However, the applicant acknowledged that should the definition of 'relative' contraindications for Population 2 include ix. high falls risk and x. cognitive impairment such as dementia, then both a non-interventional and interventional cardiologist would be required to determine eligibility. PASC considered an interventional and non-interventional cardiologist should be required to determine eligibility in both populations.

PASC advised that the issue of whether MBS item 38276 should be amended to include Population 2 or whether Population 2 should be a separate MBS item can be resolved during the evaluation phase.

Consultation feedback

PASC noted the following feedback:

- *A health care funding body noted the cost of the prosthesis ($11,400) relative to the cost of one of the common medications for AF (PBS list price of $21) along with risk of over-servicing.*
- *A consumer group was supportive, noting the bleeding risk with anticoagulation and that some patients "have trouble taking or staying on medicines".*

Next steps

PASC advised that the two patient populations proposed by the applicant in the pre-PASC response be progressed separately. PASC advised that Population 1, expanding the 'absolute' contraindications to OAT in the current MBS item 38276, be presented along with a budget impact analyses to the MSAC Executive for consideration.

PASC advised that, upon ratification of the post-PASC PICO, the application for Population 2 can proceed to Evaluation Sub-Committee (ESC).

PASC noted the applicant elected to progress its application as an ADAR (applicant-developed assessment report) and therefore a contracted commentary of the ADAR will be presented to the ESC.

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