Australian Government

Department of Health

MSAC Application 1700

Totally thoracoscopic exclusion of the left atrial appendage for patients with non-valvular atrial fibrillation

Ratified
PICO Confirmation

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

Table 1 PICO for totally thoracoscopic exclusion of the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation (NVAF): PICO Set 1

Component	Description
Population	Patients with non-valvular atrial fibrillation (NVAF) who have an absolute contraindication to life-long oral anticoagulant therapy, at risk of stroke based on a CHA_2DS_2-VA* score of ≥2.
Intervention	Totally thoracoscopic implantation of an epicardial clip device to exclude the left atrial appendage (LAA)
Comparator/s	Percutaneous insertion of a LAA closure (LAAC) device to occlude the LAA
Outcomes	• Safety o Major bleeding events (procedural and post-procedural) o Procedural adverse events related to totally thoracoscopic LAA exclusion o Procedural adverse events with percutaneous LAAC *versus* totally thoracoscopic LAA exclusion o Post-procedural adverse events of percutaneous LAAC *versus* totally thoracoscopic LAA exclusion, including infection • Clinical effectiveness: Primary outcomes: o Procedural success, i.e., successful occlusion of LAA as confirmed by ultrasound or computed tomography imaging o Stroke incidence: i. Ischaemic/embolic stroke ii. Haemorrhagic stroke o Systemic embolism, noting not all emboli will end up in cerebral circulation o Cardiovascular and all-cause mortality o Failure rate and re-intervention rate Secondary outcomes: o Health-related quality of life (HRQoL) • Cost-effectiveness: o Cost per life-year gained o Cost per quality-adjusted life year (QALY) gained • Healthcare resources: o Cost to deliver intervention o Cost associated with changes in clinical management (e.g., follow-up, dual antiplatelet therapy) • Total Australian Government healthcare costs: o Total cost to the Medicare Benefits Schedule (MBS) o Total cost to other healthcare services.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of totally thoracoscopic LAA exclusion versus percutaneous LAAC in persons with NVAF who have an absolute contraindication to life-long oral anticoagulant therapy?

*Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years; Brieger et al. (2018)

Note: Absolute contraindication as defined in Explanatory note for MBS item 38276, TN.8.132.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of totally thoracoscopic implantation of an epicardial clip device to exclude the left atrial appendage (LAA) for patients with non-valvular atrial fibrillation (NVAF) who have an absolute contraindication to life-long oral anticoagulant therapy was received from AtriCure Inc by the Department of Health.

The clinical claim is that the use of totally thoracoscopic LAA exclusion results in superior health outcomes compared to the comparator, percutaneous insertion of a LAA closure (LAAC) device. The applicant claims that the proposed service results in a higher LAA closure rate with decreased risk of adverse events and the requirement for ongoing antiplatelet therapy.

PICO criteria

Population

Proposed patient population

The proposed population are patients with NVAF who have an absolute contraindication to life-long oral anticoagulation therapy, and at increased risk for thromboembolism based on a CHA_2DS_2-VA[1] score of ≥2. Although the application form included both patients with absolute or relative contraindication to life-long oral anticoagulation therapy, the applicant subsequently confirmed that the proposed population is to be the same population that is eligible for occlusion of the LAA for stroke prevention under MBS item 38276 (i.e. patients with an absolute contraindication to life-long oral anticoagulation therapy only).

Increased risk of thromboembolism is demonstrated by:

(i) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or

(ii) at least 2 of the following risk factors:

(A) an age of 65 years or more;

(B) hypertension;

(C) diabetes mellitus;

(D) heart failure or left ventricular ejection fraction of 35% or less (or both);

(E) vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque).

The patient's absolute and permanent contraindication to oral anticoagulation must be confirmed and documented by a medical practitioner, independent of the practitioner rendering the service.

As per the explanatory note for MBS item 38276, TN.8.132, the following list provides examples of the conditions that are considered an absolute and permanent contraindication to oral coagulation for which MBS item 38276 and the population proposed in this application is intended:

i) a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy without remedial cause, or

ii) history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, or

iii) chronic, irreversible, recurrent gastrointestinal bleeding of any cause (e.g., radiation proctitis, gut angiodysplasia, hereditary haemorrhagic telangiectasia, gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy, refractory radiation proctitis, obscure source), or

[1] Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years; Brieger et al. (2018)

iv) life-long spontaneous impairment of haemostasis, or
v) a vascular abnormality predisposing to potentially life threatening haemorrhage, or
vi) irreversible hepatic disease with coagulopathy and increased bleeding risk (Child Pugh B and C), or
vii) receiving concomitant medications with strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp), or
viii) severe renal impairment defined as creatinine clearance (CrCL) < 15 ml/min or undergoing dialysis and where warfarin is inappropriate, or
ix) known hypersensitivity to the direct oral anticoagulant (DOAC) or to any of the excipients.

Consistent with MBS item 38276, the proposed population is not intended to include patients with a relative contraindication to oral anticoagulation.

PASC noted the population of interest for totally thoracoscopic LAA exclusion was the same as the population currently eligible for percutaneous LAAC. These patients have NVAF, an increased risk of stroke, and an absolute contraindication for life-long oral anticoagulation. PASC noted that there is no need for antiplatelet therapy following totally thoracoscopic LAA exclusion, but that following percutaneous LAAC, 4-12 weeks of dual antiplatelet therapy and then potentially ongoing single antiplatelet therapy is currently recommended.

PASC noted that some patients may have contraindications for the proposed procedure, e.g., patients with pericardial adhesions due to prior cardiothoracic surgery and patients with unsuitable atrial appendage anatomy (for example, snaring is difficult in circumstances where the atrial appendage is extremely small, and in other circumstances the atrial appendage may be too large for the size of the device, an atrial clip). The applicant clarified that it is unlikely that the LAA would be too big for a 50mm clip (the largest available size). The applicant also stated that, unlike in percutaneous LAAC, variations in LAA morphology do not affect the patients' suitability for the atrial clip.

Epidemiology of atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia. NVAF is atrial fibrillation in the absence of moderate to severe mitral stenosis or mechanical heart valve (National Heart Foundation of Australia, 2019). The symptoms of atrial fibrillation include palpitations, dizziness, chest pain and shortness of breath, often noticed as an inability to tolerate exercise. However, approximately 10-30% of people with atrial fibrillation have no symptoms (Australian Department of Health and Ageing (DoHA), 2012).

Atrial fibrillation is recognized as a key risk factor for ischaemic strokes. Stroke occurs when a blood vessel supplying blood to the brain either suddenly becomes blocked (ischaemic stroke) or ruptures and begins to bleed (haemorrhagic stroke). Either may result in part of the brain dying, leading to sudden impairment that can affect a number of functions. Stroke often causes paralysis of parts of the body normally controlled by the area of the brain affected by the stroke, or speech problems and other symptoms, such as difficulties with swallowing, vision and thinking.

Thrombus may form when blood becomes trapped in the LAA due to the fibrillation effectively causing intermittent stasis of the blood. This thrombus is able to enter the systemic circulation upstream of the cerebral vasculature, creating the risk of it migrating to the cerebral circulation and causing ischaemic stroke via occlusion of one or more cerebral arteries. Ischaemic strokes are often devastating to the patient, with sequalae including but not limited: to hemi-paralysis, speech deficits, dysphasia, and death.

The presence of atrial fibrillation is a strong independent predictor of stroke incidence. The 1991 Framingham study showed the risk of ischaemic stroke to be near fivefold when atrial fibrillation was present ($p<0.001$) (Kirchhof et al., 2016; Yaghi et al., 2015). The Framingham study also concluded attributable risk of stroke for all cardiovascular contributors decreased with age except for atrial

fibrillation, for which the attributable risk increased significantly ($p<0.001$), with stroke risk for those aged 85 years and older being ~23% in the presence of atrial fibrillation.

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%) (Australian Institute of Health and Welfare (AIHW), 2004).

Because up to one third of people with atrial fibrillation are asymptomatic, many of them are not diagnosed and thus do not receive appropriate preventive treatment for stroke (Australian Department of Health and Ageing (DoHA), 2012). A definitive diagnosis of atrial fibrillation is obtained from ECG monitoring, management of both the atrial fibrillation and associated stroke risk performed by a cardiologist. A certain proportion of patients with atrial fibrillation are at a higher risk of embolic stroke, as defined by their respective CHA_2DS_2-VA score. The CHA_2DS_2-VA score risk indicative score can be calculated from patient attributes obtained in routine clinical evaluation (Brieger, 2018).

In 2018, an estimated 387,000 people—214,000 males and 173,000 females—had had a stroke at some time in their lives, based on self-reported data from the Australian Bureau of Statistics 2018 Survey of Disability, Ageing and Carers (Australian Bureau of Statistics (ABS), 2019; Australian Institute of Health and Welfare (AIHW), 2020). In 2018, stroke was recorded as the underlying cause of 8,400 deaths, accounting for 5.3% of all deaths in Australia (Australian Institute of Health and Welfare (AIHW), 2020). Although the mortality rate from stroke continues to improve—between 1980 and 2018, overall death rates for stroke have fallen by three-quarters (75%), or 3.5% a year—the impact of stroke on Australian society is still profound.

Utilisation estimates

According to a 2012 report from the Department of Health and Ageing (DoHA), the prevalence of atrial fibrillation in Australia is 1-2% (Australian Department of Health and Ageing (DoHA), 2012).

O'Brien et al. (2014) reported rates of contraindications in 10,130 patients from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) between June 2010 and August 2011. This study reported an overall contraindication rate of 13.1% (both event- and patient-related contraindications).

Table 2 Inputs for estimate of prevalence of patients with non-valvular atrial fibrillation at high risk of stroke in the Australian population

Parameter	Estimate	Predicted Patient Numbers	Source
AF prevalence	1-2%	250,000 – 500,000	AF Prevalence: Australian Department of Health and Ageing (DoHA) (2012); Sturm et al. (2002) Australian Bureau of Statistics -National, state and territory population, September 2021
NVAF proportion	88.7%	221,750 – 443,500	Bista et al. (2017)
Contraindicated to OAT	13.1%	29,049 – 58,099	O'Brien et al. (2014)
Patients referred to cardiac surgeon for LAA exclusion	10%	2,905 – 5,810	Assumption
Patients anatomically suitable for proposed service	50%	1,453 – 2,905	Applicant elicited consensus expert opinion

Source: Adapted from Figure 6 of MSAC 1700 Application Form
AF=atrial fibrillation; LAA=left atrial appendage; NVAF=non-valvular atrial fibrillation; OAT=oral anticoagulant therapy

The comparator, percutaneous LAAC (MBS item number 38276), was listed on the MBS in November 2017, with an amendment to the approval being granted in 2021 to expand the list of absolute contraindications; the comparator offers the service to the same patient population. The number of reimbursed MBS services for the LAAC procedure over time since its listing is provided in **Figure 1**.

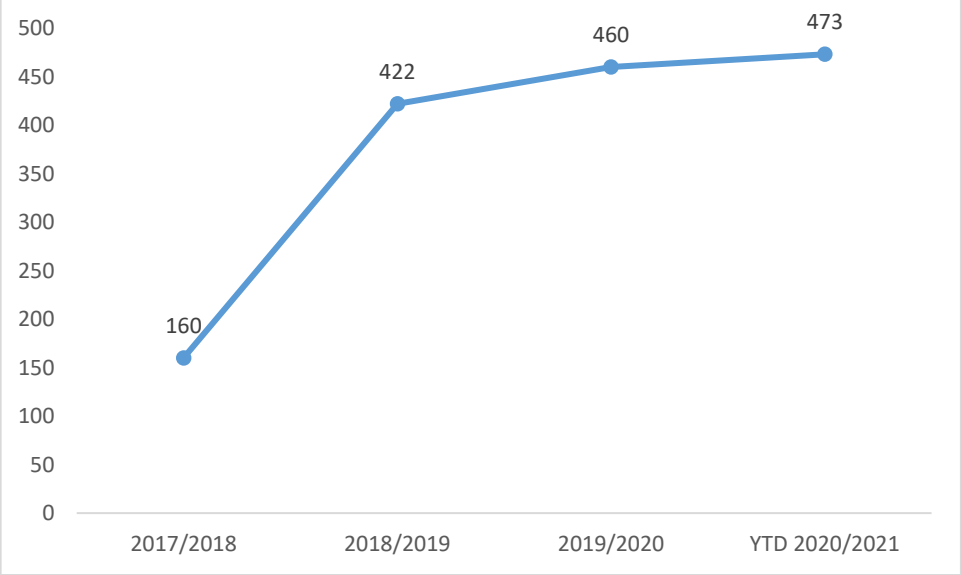

Figure 1 Utilization of comparator service

Source: Medicare Item Reports, http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp

The applicant anticipates that the uptake of the proposed medical service (estimated in **Table 3** below) will be significantly less than the eligible population (

Table 2 above) and less than the uptake observed by the comparator medical service (**Figure 1** above), due to the following constraints:

- limited number of cardiothoracic surgeons with total thoracoscopy skills relative to number cardiologists with interventional skills (interventional cardiologists and electrophysiologist)
- limited number of sites with cardiothoracic surgery relative to number of sites with interventional cardiology
- referral pathway currently does not involve consultation with cardiothoracic surgeon
- patients with previous cardiac surgery that has resulted in pericardial adhesions which prevent access to the LAA are contraindicated for the proposed service.

The applicant estimated that there are currently five centres and seven operators, inclusive of public and private, in Australia performing the proposed service. While acknowledging there is potential to increase capacity within existing centres and expand to new centres, the applicant considered that the number of centres and operators performing the proposed service is likely to limit access to the procedure.

Table 3 Estimated utilisation of the proposed medical service in the first three years

Year	Estimated sites	Estimated total count of service
1	4	40
2	6	72
3	8	160

Source: pg24 of MSAC 1700 Application Form

The applicant considered that it was unlikely there would be significant 'leakage' to populations not indicated for the proposed service as the patients must be referred by a cardiologist, and also seen by a non-interventionist who both have decided the patient is suitable for the proposed service.

PASC noted that the predicted utilisation of totally thoracoscopic LAA exclusion would be initially limited by a small number of providers, i.e., cardiothoracic surgeons with experience in video-assisted thoracoscopic approach, performing the procedure. PASC noted that there are currently five centres and seven operators in public and private settings that perform the proposed service.

PASC acknowledged that growth in utilisation of the comparator procedure (percutaneous LAAC) has been relatively slow, with 460 cases in 2019-20 rising to 520 cases in 2020-21. PASC considered that referrals for the proposed procedure, performed by cardiothoracic surgeons, were likely to be lower than for the percutaneous LAAC, performed by interventional cardiologists. PASC noted there was a concern that totally thoracoscopic LAA exclusion may be a more attractive procedure because, unlike percutaneous LAAC, it does not require post-procedure antiplatelet therapy. However, PASC considered that in clinical practice, not all patients continue life-long antiplatelet therapy after percutaneous LAAC.

Overall, given access limitations, PASC considered that the patient population would likely only expand by a small number.

PASC noted that there may be barriers to access for people in rural and remote areas.

Intervention

The proposed medical service is exclusion of the LAA via implantation of an epicardial clip via totally thoracoscopic access. The LAA is sized via direct measurement under view of the thorascope to determine the appropriate size of the epicardial LAA exclusion device to be used, this device is then positioned and deployed under thorascope visualization at the base of the LAA. The result is electrical and haemodynamic isolation of the LAA from the left atrium. The implantation procedure, assuming no pathology or abnormal

anatomy which limits the ability of the surgeon to safely place the closure device at the base of the LAA, normally takes 20-40 minutes to complete.

PASC noted the intervention is LAA exclusion using a clip implanted via a totally thoracoscopic approach, performed by a cardiothoracic surgeon under general anaesthesia and using single-lung ventilation. The procedure requires an overnight to two-night hospital stay.

The applicant claimed that the proposed intervention takes 30-60 minutes, however, PASC noted that studies in the literature indicated duration of 60-90 minutes. The applicant's clinical expert clarified that in their experience the procedure takes 20-30 minutes (around 60 minutes in total when accounting time for general anaesthesia). As such, PASC concluded that the duration of the thoracoscopic LAA exclusion is most likely comparable to percutaneous LAAC.

The delivery of the service is limited to qualified and accredited cardiothoracic surgeons. The cardiothoracic surgeon must be skilled in performing video-assisted thoracoscopic surgery. Patients would be treated in an inpatient setting in both the public and private system.

AtriClip Device

AtriClip PRO2 device consists of a disposable clip applicator preloaded with a Gillinov-Cosgrove LAA Clip (Clip) for exclusion of the heart's LAA shown in **Figure 2**. The Clip is a self-closing, sterile, implantable clip that is made of two parallel rigid titanium tubes with elastic nitinol springs and covered with a knit-braided polyester sheath. It comes in four clip sizes: 35 mm, 40 mm, 45 mm, and 50 mm. The AtriClip PRO2 device is listed on the Australian Register of Therapeutic Goods (ARTG; number 308864) for epicardial exclusion of the LAA.

Figure 2 Image of AtriClip PRO2 device

Source: Atricure website accessed 22 March 2022 - https://www.atricure.com/healthcare-professionals/therapies/LAAM/atriclip-exclusion-system/atriclip-pro2-device

The AtriClip LAA Exclusion System device (application + clip) comes in several models that are indicated for use either concomitant to open cardiac surgery or as stand-alone minimally invasive surgery. **Table 4** details the various AtriClip models and their regulatory status in Australia.

Table 4 Regulatory status of all AtriClip devices

Concomitant	ARTG	Date included on ARTG	GMDN	Device
Open cardiac surgery	Not listed[1]	N/A	35649	AtriClip LAA Exclusion System (ACH1)
	308862	31/08/2018	35649	AtriClip FLEX (ACH2)[2]
	354171	03/02/2021	35649	AtriClip FLEX V (FLEXV)
	Not listed	N/A	N/A	AtriClip Long
Minimally invasive cardiac surgery	308863	31/08/2018	35649	AtriClip PRO (PRO)
	308864	31/08/2018	35649	AtriClip PRO 2 (PRO2)[3]
	354170	03/02/2021	35649	AtriClip PRO V (PROV)

Sources: AtriClip webpage, ARTG website accessed 22/3/2022.
ARTG=Australian Register of Therapeutic Goods; GMDN=Global Medical Device Nomenclature
1 Was previously listed under ARTG 175070
2 Subject of MSAC application 1666
3 Subject of MSAC application 1700 (this application)

Procedure details

Prior to the procedure, angiographic computed tomography (CT) procedure is performed to assess the patient's eligibility for totally thoracoscopic LAA (e.g. assess the size and orientation of the LAA).

Conditions that may preclude implantation are the size and orientation of the LAA, previous cardiothoracic surgery that has resulted in pericardial adhesions, and the presence of LAA thrombus, as outlined in the AtriClip PRO2 contraindications. These contraindications would be most frequently detected during pre-procedure imaging, although in rare cases they may only be detected once total thoracoscopic access is gained.

A recent review by Collado et al. (2018), noted that transesophageal echocardiography (TOE) is the gold standard in preprocedural assessment of the LAA but that CT is also widely used for preprocedural assessment of the LAA. CT is less invasive than TOE with less interoperator variability. A standard CT analysis includes an assessment of the LAA anatomy in the sagittal, axial, and coronal planes. The perimeter, maximal, and minimal diameters of the LAA ostium and landing zone are standard measurements in cardiac CT analysis of the LAA.

PASC noted the pre-PASC response clarified that the only required pre-implantation screening for the proposed service is cardiac CT. While surgeons may order a TOE for further evaluation, the applicant confirmed that there was no scope for intracardiac echography (ICE) before or during the proposed intervention. PASC considered that the current pre-procedure standard of practice for the comparator is CT only, with TOE performed at the time of the percutaneous LAAC, therefore, the pre-implantation screening is the same for the intervention and the comparator.

After initiating eligible patients on general anaesthesia, three thoracoscopic access ports are created on the left side of the patient chest and carbon dioxide (CO_2) is insufflated into the left thoracic cavity to deflate the left lung.

After entering the chest cavity with the camera, all structures are visualized and two additional accesses are gained under direct endocavitary view. The second port (camera port) is placed at least 4 cm caudally along the posterior axillary line (5th intercostal space) and the lowest port is placed in the intercostal space at the intersection between a sagittal line crossing the xiphoid and line between the anterior and midaxillary line (7th intercostal space).

Under video guidance, an incision is made on the pericardium on the anterior lateral surface, exposing the LAA. The LAA is measured with a sizing device to confirm which size of epicardial clip is appropriate. During the pre-PASC meeting with the applicant, the applicant advised that the size and orientation is assessed during angiographic CT but that in very rare circumstances, upon accessing the LAA it may then be identified that the LAA size/orientation is not suitable. The device is placed on the epicardial surface at the base of the LAA. Consistent atraumatic force is equalized over tissue variations and trabeculation of the LAA via parallel titanium crossbars which apply pressure without crushing or damaging tissue. The device position is assessed via trans-oesophageal echocardiography to ensure complete haemodynamic exclusion of the LAA. The device is then deployed leaving the LAA permanently hemodynamically and electrically isolated from the left atrium.

PASC noted the statement from the applicant's expert that the pericardium is not closed following placement of the epicardial clip, therefore reducing the risk of post-procedure pericardial effusion, a known complication in the comparator service.

The health care resources delivered at the same time as the proposed medical service are general anaesthesia, TOE imaging, video-assisted thoracoscopic devices to facilitate totally thoracoscopic access, and a procedure room with video-assisted thoracoscopic display capabilities (**Table 5**). The duration of the procedure is estimated at 20-40 minutes, assuming no issues in accessing the pericardial space.

Table 5 Estimated recourses required for the proposed medical service

Resource	Provide of resource	Price per unit of resource	Quantity	Source
Medical services – screening prior to intervention				
Computed tomography - angiography	Radiologist	$522.30	1	MBS item 57352[1]
Cardiology consultation	Cardiologist	79.75	1	MBS item 116
Cardiothoracic consultation	Cardiac surgeon	$79.75	1	MBS Item 116
Medical services – intervention				
Totally thoracoscopic exclusion of LAA	Cardiac surgeon	$1698.30	1	Proposed service
Intra-operative transesophageal echocardiography	Anaesthetist	$412.00	1	MBS item 20560
Initiation of management of anaesthesia for open procedures on the heart, pericardium or great vessels of the chest	Anaesthetist	$144.20	1	MBS item 21941
Intra-arterial cannulation when performed in association with the administration of anaesthesia	Anaesthetist	$82.40	1	MBS item 22025
Prosthesis cost				
Epicardial clip	Prosthesis	REDACTED	1	
Hospital services				
Other cardiothoracic procedures without CPB pump, Minor complexity	Hospital	$11,396.00	1	DRG F09C – Prosthesis cost
Total cost of service per patient		REDACTED		

Source: Adapted from information on page 25 of MSAC 1700 Application Form and MBS online website
CPB=cardiopulmonary bypass; LAA=left atrial appendage
1 Note the application referenced MBS item 57351 which does not currently exist and was therefore corrected to MBS 57352.

Comparator

Currently patients with NVAF who have an absolute contraindication to life-long oral anticoagulant therapy and at risk of stroke based on a CHA_2DS_2-VA score of ≥2 are treated via transcatheter implantation of an occlusion device. The comparator service, also referred to as percutaneous LAAC, was listed on the MBS (MBS item 38276) following consideration and support by MSAC (MSAC applications 1347 and 1615). The most recent MSAC consideration of LAAC (MSAC 1615) was in April 2021. At that time MSAC advised the Minster that after considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness:

- MSAC supported amendment of MBS item 38276 to expand the list of absolute contraindications to oral anticoagulation therapy (Population 1). MSAC advised that the MBS item should require formal documentation of the absolute contraindication by an independent specialist/medical practitioner and recommended utilisation of this item be monitored to inform a review 2 years after this amendment is implemented.
- MSAC did not support amendment of MBS item 38276 to include relative contraindications to oral anticoagulation therapy (Population 2). MSAC considered that the evidence did not demonstrate comparative safety and clinical effectiveness of left atrial appendage closure for stroke prevention in this population where there is an effective alternative treatment option.

LAA occluders listed on the ARTG and on the Prostheses List are summarised in **Table 6**.

Table 6 LAA occluders and associated delivery kits listed on the ARTG

ARTG number	GMDN / Product category	Product name	Sponsor	PL billing code
340173	45418 cardiac occluder / Medical Device Class III	WATCHMAN FLX™ LAA Closure Device with Delivery System – Cardiac occluder	Boston Scientific Pty Ltd	BS384
310680	45419 cardiac occlude delivery kit/ Medical Device Class III	WATCHMAN™ TruSeal Access System – Cardiac occlude delivery kit	Boston Scientific Pty Ltd	-
216398	45418 cardiac occluder/ Medical Device Class III	AMPLATZER Amulet LAA Occluder – Cardiac occluder	Abbott Medical Australia Pty Ltd	SJ395
345210	45418 cardiac occluder/ Medical Device Class III	AMPLATZER Amulet LAA Occluder – Cardiac occluder	Abbott Medical Australia Pty Ltd	
230575	45418 cardiac occluder/ Medical Device Class III	Coherex WaveCrest™ Left Atrial Appendage Occlusion System - Cardiac occluder	Johnson & Johnson Medical Pty Ltd	-
230576	45419 cardiac occlude delivery kit / Medical Device Class III	Coherex WaveCrest™ LAA Occlusion System Delivery Sheath - Cardiac occluder delivery kit	Johnson & Johnson Medical Pty Ltd	-
340173	45418 / Medical Device Class III	WATCHMAN LAA Closure Device Delivery System – Cardiac occluder	Boston Scientific Pty Ltd	BS332
310680	45419 / Medical Device Class III	WATCHMAN Access System – Cardiac occluder delivery kit	Boston Scientific Pty Ltd	-
366090	45418 / Medical Device Class III	The AMPLATZER Cardiac Plug		-

Source: ARTG website (accessed on 17 March 2022)
ARTG=Australian Register of Therapeutic Goods; GMDN=Global Medical Device Nomenclature; LAA=left atrial appendage; PL=Prostheses List

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. 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 transoesophageal echocardiography. The procedure takes approximately 60 minutes.

PASC confirmed that the comparator is percutaneous LAAC, which is currently MBS-funded and being performed in Australia by cardiologists using Watchman or Amulet devices, both included on the ARTG and the Prostheses List. PASC agreed that the percutaneous LAAC procedure is widely accepted and performed in Australia. The duration of the procedure is around 30-60 minutes, it is performed under general anaesthesia, and is performed either as a day procedure or with a single overnight hospital stay. The standard of care for confirming the procedural success (i.e., LAA exclusion) is TOE 45-90 days post procedure.

The applicant noted that because of the endocardial positioning of the LAAC device, the devices used for the comparator medical service (percutaneous LAAC), patients may require a period of oral anticoagulation therapy and/or ongoing dual antiplatelet therapy post the LAAC procedure. However, as the proposed population for this application are patients with an absolute contraindication to oral anticoagulant therapy, these patients would not receive oral anticoagulation therapy but may receive dual antiplatelet therapy.

PASC noted that the standard of care after percutaneous LAAC is dual antiplatelet therapy for 4-12 weeks and single-agent antiplatelet therapy thereafter, not to prevent the formation of thrombus in the atrium or to prevent a stroke, but to prevent the formation of thrombus on the occluder device itself. PASC acknowledged that for the atrial clip, there is potentially no need for antiplatelet therapy post-procedure because the device is implanted epicardially, and therefore it is not exposed to the circulation. PASC also noted that in clinical practice, many patients do not require life-long antiplatelet therapy following percutaneous LAAC.

PASC discussed whether stapler obliteration may be a potential comparator based on a 2021 publication in the New England Journal of Medicine (Whitlock et al., N Engl J Med 2021; 384:2081-2091) where surgeons were at liberty to choose between surgical amputation and closure, stapler closure, double-layer linear closure, or closure with an approved surgical occlusion device (percutaneous LAAC or purse-string closure were not permitted). The trial did not find any differences in the incidence of bleeding or other major adverse events between the procedures. The applicant stated that, in addition to the technical difficulty of using stapler for this indication and thoracoscopic approach, there is also a risk of bleeding associated with the stapling procedure. In comparison, thoracoscopic LAA exclusion does not involve suture line or stapling, therefore, the risk of bleeding is almost zero. Furthermore, using a stapler on a beating heart is associated with considerable trauma, particularly without the backup of a bypass machine. PASC noted that the NEJM study was performed on patients undergoing open heart cardiac surgery for other reasons and was not restricted to patients with NVAF, and therefore does not align with the population considered in this application. As such, PASC confirmed that stapling is not an appropriate comparator.

Another potential comparator, the LARIAT device (not included on the ARTG), was also discussed. However, PASC considered that the trial results of this device, a combination of endocardial and epicardial procedure, were not as beneficial as expected, and that the proposed atrial clip procedure is simpler.

Outcomes

Safety:

- Major bleeding events (procedural and post-procedural)
- Procedural adverse events related to totally thoracoscopic LAA exclusion
- Procedural adverse events of percutaneous LAAC *versus* totally thoracoscopic LAA exclusion
- Post-procedural adverse events of percutaneous LAAC *versus* totally thoracoscopic LAA exclusion, including infection

Clinical effectiveness:

Primary outcomes:

- Procedural success, i.e., successful occlusion of LAA as confirmed by ultrasound or computed tomography imaging
- Stroke incidence:
    - Ischaemic/embolic stroke
    - Haemorrhagic stroke
- Systemic embolism, noting not all emboli will end up in cerebral circulation
- Cardiovascular and all-cause mortality
- Failure rate and re-intervention rate

Secondary outcomes:

- Health-related quality of life (HRQoL)

Cost-effectiveness:

- Cost per life-year gained
- Cost per quality-adjusted life year (QALY) gained

Healthcare resources:

- Cost to deliver intervention
- Cost associated with changes in clinical management (e.g., follow-up, antiplatelet dual therapy)

Total Australian Government healthcare costs:

- Total cost to the Medicare Benefits Schedule (MBS)
- Total cost to other healthcare services.

PASC confirmed the outcomes listed in the PICO were appropriate.

Clinical management algorithms

The current clinical management pathway for stroke prevention in atrial fibrillation, based on the National Heart Foundation of Australia (NHF) and the Cardiac Society of Australia and New Zealand (CSANZ) Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018 (Brieger et al., 2018), is provided in **Figure 3**. The pathway considers both NVAF and valvular atrial fibrillation, however, the focus of this application is NVAF.

The CHA_2DS_2-VA score is recommended for predicting stroke risk in atrial fibrillation and determines management. According to the Guidelines, patients with a CHA_2DS_2-VA score of ≥2 and contraindications to oral anticoagulant therapy should be considered for occlusion of the LAA (Brieger et al., 2018).

PASC noted that patients with NVAF are assessed using a stroke risk score. It was noted that while the CHA2DS2-VA score is the most widely used risk assessment instrument, there are other tools that can be used as well.

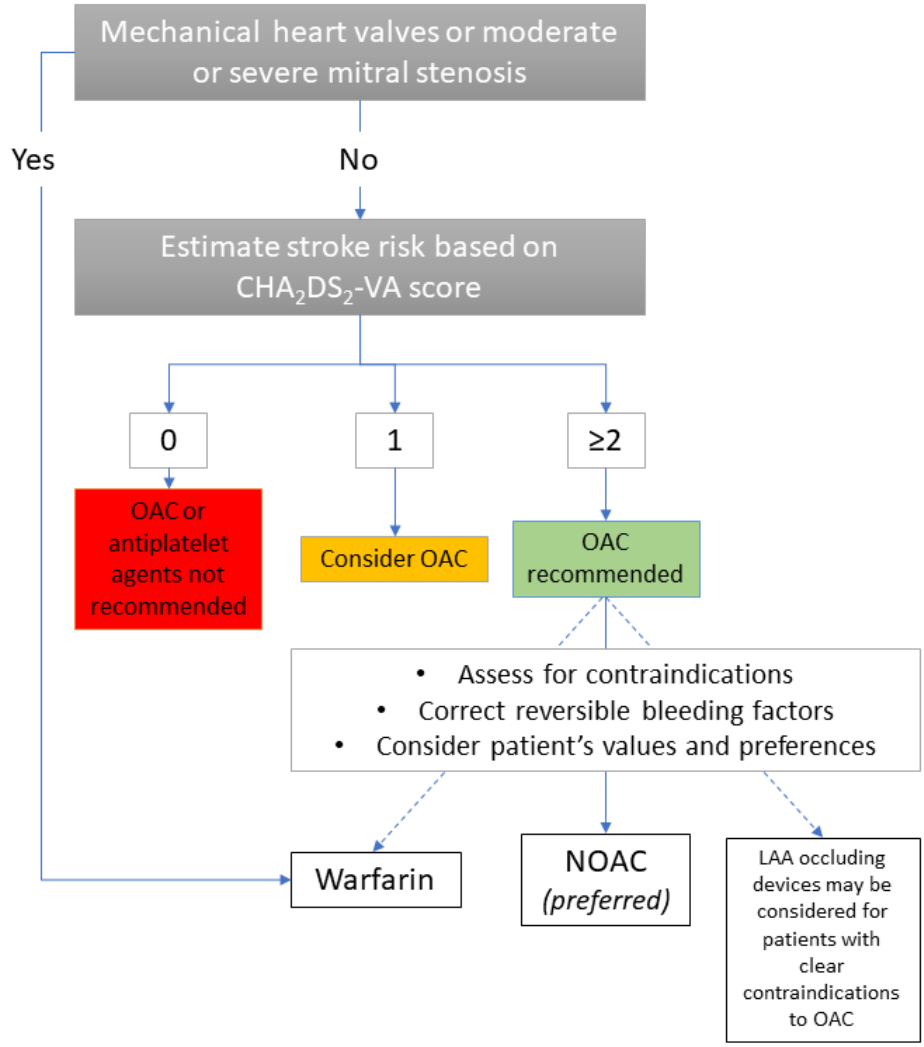

Figure 3 Management of stroke prevention in atrial fibrillation

OAC=oral anticoagulants; LAA left atrial appendage; NOAC=non-vitamin K oral anticoagulants
Source: Brieger et al. (2018), p 1238 Figure 6.

The current clinical management algorithm for patients with NVAF, a CHA_2DS_2-VA score of ≥2 and contraindications to oral anticoagulant therapy is depicted in **Figure 4**.

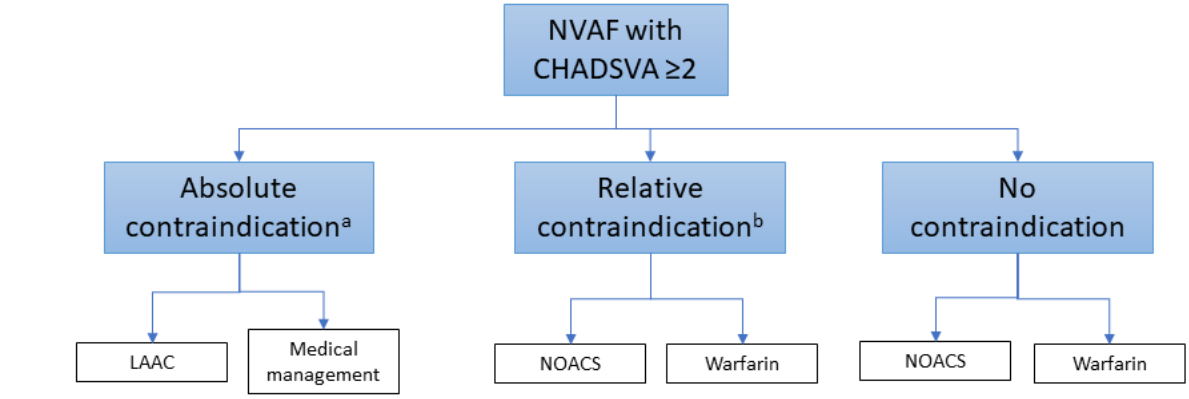

Figure 4 Current clinical management pathway for stroke prevention in patients with non-valvular atrial fibrillation

LAAC=left atrial appendage closure; NOACS=non-vitamin K antagonist oral anticoagulants

[a]Absolute contraindications = contraindication to life-long anticoagulation as defined in Explanatory Note TN.8.132 of MBS item 38276

[b]Relative contraindication defined as: i) a previous major bleeding complication, or ii) a blood dyscrasia, or iii) a vascular abnormality predisposing to potentially life-threatening haemorrhage, or iv) anaemia, or v) prior gastrointestinal bleed, or vi) thrombocytopenia, or vii) haematological malignancy, or viii) traumatic intracranial haemorrhage.

The proposed clinical management pathway for stroke prevention in atrial fibrillation is provided in **Figure 5**. Percutaneous devices come with the risk of technical issues and failures, along with the need for antiplatelet therapy, which presents a problem in patients with a high HAS-BLED score. Totally thoracoscopic LAA exclusion would provide an alternative to percutaneous LAAC in patients with absolute contraindications to life-long oral anticoagulant therapy.

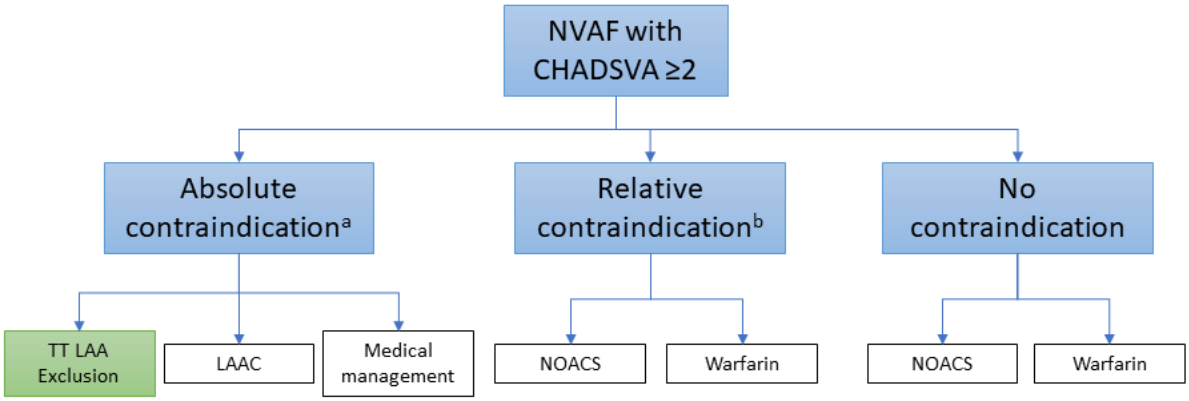

Figure 5 Proposed clinical management pathway for stroke prevention in patients with non-valvular atrial fibrillation

LAAC=left atrial appendage closure; NOACS=non-vitamin K antagonist oral anticoagulants; TT LAA=totally thoracoscopic left atrial appendage

[a]Absolute contraindications = contraindication to life-long anticoagulation as defined in Explanatory Note TN.8.132 of MBS item 38276

[b]Relative contraindication defined as: i) a previous major bleeding complication, or ii) a blood dyscrasia, or iii) a vascular abnormality predisposing to potentially life-threatening haemorrhage, or iv) anaemia, or v) prior gastrointestinal bleed, or vi) thrombocytopenia, or vii) haematological malignancy, or viii) traumatic intracranial haemorrhage.

PASC acknowledged the proposed clinical management algorithm was accurate, with the only change to the current clinical management being the addition of thoracoscopic LAA exclusion as an alternative to the percutaneous LAAC procedure.

The proposed medical service is expected to provide an alternative service for patients who are eligible for the comparator. The applicant claims that the proposed procedure has the following advantages over the comparator:

- lack of requirement for post-procedure dual antiplatelet therapy,
- the electrical isolation of the LAA which is known to be a source of triggers for atrial fibrillation.

PASC discussed whether the claim regarding the electrical isolation of the LAA was relevant and that the application form did not include an outcome related to this claim. Although PASC noted that the proposed procedure (i.e., exclusion of the LAA using AtriClip PRO2 device) may potentially isolate the LAA, PASC considered that the role and importance of electrical isolation in relation to stroke reduction is unclear and is unlikely to improve primary or secondary outcomes.

The comparator service (LAAC) would not be replaced by totally thoracoscopic LAA exclusion in the following cases:

- the patient is not suitable for the proposed service (totally thoracoscopic LAA exclusion), or
- the proposed service cannot be provided to the patient due to lack of clinician capability (i.e., no trained cardiothoracic surgeon available).

The changes to current clinical management pathway in terms of health care resources from the point of delivery of the proposed medical service onwards include:

- no requirement for antiplatelet therapy after totally thoracoscopic LAA exclusion delivery, compared to LAAC.

The application form also claimed that unlike the comparator, there is no requirement for oral anticoagulation therapy after totally thoracoscopic LAA exclusion. However, as the proposed population are patients with an absolute contraindication to oral anticoagulation therapy, and no longer includes patients with a relative contraindication to oral anticoagulation therapy, this claim is not appropriate for the proposed population.

Proposed economic evaluation

The applicant claims that the proposed medical service results in a higher LAA closure rate with a decreased risk of adverse events and no requirement for ongoing antiplatelet therapy after totally thoracoscopic LAA exclusion.

Based on a clinical claim of superior clinical effectiveness and superior safety of totally thoracoscopic LAA exclusion for stroke prevention in patients with NVAF who are absolutely contrainidcated to life-long oral anticoagulants compared to percutanous LAAC, the appropriate economic evaluation is a cost-effectiveness or cost-utility analysis (Table 7).

PASC noted the applicant intends to claim a superior outcome in terms of both clinical effectiveness and safety, based on a higher achieved exclusion rate of the proposed intervention and the fact that no antiplatelet treatment may be required post-procedure. As such, PASC confirmed that the appropriate economic evaluation would be a cost-utility analysis (CUA). However, PASC advised that a non-inferiority claim may be more appropriate because there may be more peri-procedural complications given the totally thoracoscopic surgical approach is more invasive than the percutaneous approach. These complications may offset the reduction in peri-procedural need for the dual antiplatelet agents.

It should be noted that the application does not reference any comparative evidence to support the clinical claim. Scoping searches performed by the Assessment Group did not identify any relevant comparative evidence, either. In a pre-PASC meeting, the applicant confirmed they were not aware of any direct comparative evidence for totally thoracoscopic LAA exclusion versus LAAC for treatment of NVAF, and that they intended to pursue an indirect comparison methodology for the assessment.

PASC noted that there was insufficient evidence for a direct comparison between thoracoscopic LAA exclusion and percutaneous LAAC. Published data is limited, and no randomised controlled trials are available comparing thoracoscopic LAA exclusion and percutaneous LAAC, as confirmed by a literature search. The largest study identified is a meta-analysis published in 2019, but only a small proportion of patients had an isolated thoracoscopic LAA exclusion procedure, while most were concomitant with other surgery or ablation. PASC considered that the applicability of this study was therefore limited.

Table 7 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The applicant proposed creation of a new MBS item for the proposed therapeutic medical service based on the MBS item 38276 for percutaneous LAAC but with a higher fee. No justification for the higher proposed fee was provided by the applicant. The proposed MBS item also seeks to allow access to the MBS for a specific health practitioner group (i.e., cardiothoracic surgeons).

The service relies on an implantable medical device to achieve its intended effect: a single-use consumable AtriClip PRO2 LAA Exclusion System, a class III device manufactured by AtriCure Inc and sponsored by AA-Med Pty Ltd and included on the ARTG by the Therapeutic Goods Administration (TGA) under ARTG 308864. The AtriClip LAA Exclusion System is indicated for the exclusion of the heart's LAA. No other sponsors and/or manufacturers have a similar medical device for epicardial use in the Australian marketplace (although there are similar medical endocardial devices, i.e., cardiac occluders as described in the Comparator section and with MBS funding under item 32876 that achieve a similar outcome).

Table 8 Proposed MBS item for totally thoracoscopic exclusion of the LAA for patients with NVAF with an absolute contraindication to oral anticoagulation therapy and at risk of stroke based on a CHA2DS2-VA score of ≥ 2.

Category 3 – THERAPEUTIC PROCEDURES GroupT8 - Surgical Operations
MBS item XXXX Totally thoracoscopic exclusion of the left atrial appendage for patients with non-valvular atrial fibrillation, if: (a) the patient is at increased risk of thromboembolism demonstrated by: (i) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or (ii) at least 2 of the following risk factors: (A) an age of 65 years or more; (B) hypertension; (C) diabetes mellitus; (D) heart failure or left ventricular ejection fraction of 35% or less (or both); (E) vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque); and (b) the patient has an absolute and permanent contraindication to oral anticoagulation (confirmed by written documentation that is provided by a medical practitioner, independent of the practitioner rendering the service); and (c) the service is not associated with a service to which item 38200, 38203, 38206 or 38254 applies (H) Multiple Operation Rule (Anaes.) (Assist.) (See para TN.8.YYY of explanatory notes to this Category)
Fee: $1698.30 Benefit: 75% = $1273.73
Explanatory note TN.8.YYY Totally thoracoscopic exclusion of the left atrial appendage for stroke prevention (item xxxxx) **Eligibility requirements for Item xxxx** This item is intended for use in patients where an independent medical practitioner has documented an absolute and permanent contraindication to oral coagulation. The medical practitioner who has documented this contraindication should not have been involved in any decision to provide the service or the actual provision of the service, and is not engaged in the same or a similar group of practitioners. The following list provides examples of the conditions for which this item is intended: i. A previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy without remedial cause, or ii. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, or iii. Chronic, irreversible, recurrent gastrointestinal bleeding of any cause (eg, radiation proctitis, gut angiodysplasia, hereditary haemorrhagic telangiectasia, gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy, refractory radiation proctitis, obscure source), or iv. Life-long spontaneous impairment of haemostasis, or v. A vascular abnormality predisposing to potentially life threatening haemorrhage, or vi. Irreversible hepatic disease with coagulopathy and increased bleeding risk (Child Pugh B and C), or vii. Receiving concomitant medications with strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp), or viii. Severe renal impairment defined as creatinine clearance (CrCL) < 15 ml/min or undergoing dialysis and where warfarin is inappropriate, or ix. Known hypersensitivity to the direct oral anticoagulant (DOAC) or to any of the excipients. This item is not intended for use in patients with a relative contraindication to oral anticoagulation. The procedure is performed as a hospital service.

Source: MSAC 1700 Application form with modifications to align with updated MBS item 38276

PASC noted that the proposed MBS item aligns with the percutaneous LAAC procedure, with an almost identical wording. PASC acknowledged that the proposed MBS fee of $1,698 is considerably higher than the MBS fee for the percutaneous LAAC procedure ($949.25). PASC noted that the pre-PASC response confirmed that the fee was proposed after consultation with the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS), and that while this procedure was short in duration, it required significant skill and investment of time in thoracoscopic training. PASC considered that the training requirements for percutaneous LAAC procedure are also extensive and that they would not be significantly different between the two procedures.

PASC concluded that the fee difference would need to be carefully considered by the applicant to support their justification within the given context.

PASC discussed the question of restricting the service to cardiothoracic surgeons with training in video-assisted thoracoscopic surgery. PASC noted that there was no specific restriction on the percutaneous LAAC procedure, although several other MBS procedures did currently have specific training requirements. PASC concluded that specific training was required to perform the proposed procedure and that MSAC would need to consider whether this should be defined as cardiothoracic surgeons with training in video-assisted thoracoscopic surgery.

According to the applicant, there is a potential for co-claiming with radiofrequency ablation for atrial fibrillation (thoracoscopic maze procedure, a minimally invasive surgical ablation procedure that uses an energy source to form a maze of scar tissue over the heart to cure atrial fibrillation) with MBS items 38512 and 38515. The applicant estimates around 80% of all procedures would be stand-alone and 20% combined with radiofrequency ablation.

PASC noted that the pre-PASC response advised that the estimated proportion of standalone cases of totally thoracoscopic LAA exclusion should be revised to 70%, noting that surgeons may at times choose to perform the proposed procedure concomitant to mini thoracotomy valve surgery.

The service is delivered once per lifetime of a patient.

PASC also discussed possible leakage and advised that it is unlikely the proposed intervention would be used outside the proposed patient population noting it is the same population currently eligible for percutaneous LAAC and the patient's absolute contraindication to life-long oral anticoagulation must be documented by an independent medical practitioner.

Private health insurance

The AtriClip PRO2 device (ARTG 308864) is not currently included on the Prostheses List and an application for listing on the Prostheses List has not yet been submitted to the Prostheses List Advisory Committee (PLAC). However, the applicant is planning to submit an application for listing on the Prostheses List. The cost of the AtriClip PRO2 epicardial clip is currently proposed to be $ REDACTED (**Table 5**).

A similar AtriClip, the AtriClip FLEX epicardial clip used during open heart surgery is currently listed on the Prostheses List at $1,097 (as at July 2021). The applicant has submitted an application requesting listing of the AtriClip FLEX device on the Prostheses List with a benefit of $2,450 for patients undergoing open cardiac surgery with a documented history of atrial fibrillation (AF) (see MSAC application 1666).

PASC noted the applicant's pre-PASC response to the query regarding the price difference between AtriClip PRO2 and AtriClip FLEX, used during open-heart surgery. The applicant clarified that AtriClip PRO2 was a more complicated and expensive to manufacture device than AtriClip FLEX. The AtriClip PRO2 has active

articulation levers providing pitch and yaw articulation of the clip, as well as rapid release mechanism and a hoopless end effector.

PASC concluded that the price difference would need to be carefully considered by the applicant to support their justification within the given context.

Summary of public consultation input

Consultation feedback was received from one (1) professional organisation and one (1) consumer organisation:

- the Australia New Zealand Society for Vascular Surgery (ANZSVS), and
- Hearts4Heart.

The consultation feedback was supportive of public funding for totally thoracoscopic LAA exclusion for patients with non-valvular atrial fibrillation who have an absolute contraindication to life-long oral anticoagulant therapy and are at risk of stroke.

Clinical need and public health significance

The main benefits of publicly funding the totally thoracoscopic LAA procedure noted in the consultation feedback included:

- improved management of the embolic risk for patients with atrial fibrillation where patients are considered too high risk for standard therapy, resulting in decreased number of patients with embolic complications from atrial fibrillation;
- safe, effective occlusion of the LAA;
- providing an option for patients who are not suited to taking blood thinning medications and is recommended for patients who have had a stroke previously;
- the short duration of the procedure, and no need for the patient to take blood thinning medication post-procedure.

The main disadvantages of the totally thoracoscopic LAA procedure identified in the consultation feedback were the possible complications from intra-thoracic surgery.

Cost information for the proposed medical service

The ANZSVS agreed with the proposed service descriptor, but it considered that the proposed service fee appeared significantly higher than the equivalent endovascular procedure.

PASC acknowledged that the ANZSVS was generally supportive of the thoracoscopic LAA exclusion procedure, however, they did not support a greater fee than for percutaneous LAAC.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).

Applicant comment on the ratified PICO Confirmation

Population

The applicant stated that they wish to change the clinical claim to non-inferiority.

Proposed economic evaluation

The applicant stated that they wish to change the claim to non-inferior clinical effectiveness.

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