Technology Assessment Report No. 302

Economic Analysis of Left Atrial Appendage Closure for patients with atrial fibrillation, high stroke risk, and contraindicated to anticoagulants

Last updated May 2018

Summary of Proposal

Product	Percutaneous Left Atrial Appendage Closure (LAAC) devices including the WATCHMAN™ device (Boston Scientific) and the AMPLATZER™ Amulet™ (Abbott) device
Supplier	Boston Scientific, Abbott
Proposed Indication	Non-valvular atrial fibrillation, high stroke risk, and contraindicated to anticoagulants
Indicative Device Price	$7,900
Current Treatment	No treatment (contraindicated to available pharmaceutical therapy)

Executive Summary

Proposal under Assessment

In 2016, following earlier proposals by the Cardiac Society of New Zealand to the National Health Committee, PHARMAC considered a proposal for funding of Left Atrial Appendage Closure (LAAC) devices.

Objectives

This assessment considers the cost-effectiveness and budgetary impact of Left Atrial Appendage Closure (LAAC) for patients with non-valvular atrial fibrillation, at high risk of stroke, and contraindicated to oral anticoagulation. The perspective is that of the funder, including all device, procedure, and related health services costs as described in version 2 of the Prescription for Pharmacoeconomic Analysis (PFPA).

The assessment is a test case for a device using PHARMAC's PFPA and Factors for Consideration, and may be of assistance to DHBs interested in assessing the value of LAAC.

Clinical Effectiveness Review

People with Atrial Fibrillation (AF) are at increased risk of stroke, which can be up to five times that of a person without AF. The standard of care for most individuals at high risk of stroke is anticoagulation with warfarin or a novel anticoagulant therapy such as dabigatran or rivaroxaban. In high risk individuals for whom anticoagulation is not suitable treatment options are very limited. Left Atrial Appendage Closure is a potential treatment alternative for these individuals. LAAC is a percutaneous

cardiac intervention which leads to closure of the Left Atrial Appendage, preventing clot formation in the heart, and thereby reducing the risk of stroke.

Currently there is no regulatory approval process for medical devices in New Zealand. The Federal Drug Administration (FDA) approved the WATCHMAN™ device for marketing in 2015, with the FDA Panel voting 12 to 0 that the WATCHMAN™ LAA closure device was safe. A meta-analysis of randomised and non-randomised studies (n=2,779) reported the most frequent adverse events were major bleeding and pericardial effusions, occurring in 2.6% (95%CI: 1.5%, 3.6%) and 2.5% (95% CI: 1.8%, 3.2%) of patients undergoing LAAC, respectively.

Literature review has identified two randomised controlled trials, each comparing LAAC with warfarin, these being the PROTECT-AF and PREVAIL trials of the WATCHMAN™ device. No randomised controlled trials of LAAC have been completed in patients contraindicated to oral anticoagulation. Studies have extrapolated outcomes for patients contraindicated to oral anticoagulation by comparing stroke rates for LAAC with predicted stroke rates in untreated patients using stroke risk algorithms, principally the $CHADS_2$ or CHA_2DS_2-VASc scores.

The FDA and Boston Scientific undertook an imputed analysis of the WATCHMAN™ device in patients contraindicated to anticoagulation. The analysis reported a range of relative risks favouring LAAC over placebo. The base-case in this assessment uses the FDA's imputed analysis of the PREVAIL study, reporting a relative risk of stroke of 0.38 for people treated with LAAC, compared to placebo. Similarly, a meta-analysis of randomised and non-randomised studies (n=1,759) reported an (imputed) relative risk of stroke of 0.34 (95% CI, 0.25-0.46). Other studies indicate more favourable relative risk reductions which are tested in the sensitivity analysis of our economic appraisal.

Cost-Utility Analysis

A micro-simulation Markov model was constructed to model the different treatment strategies. The analysis was based on the methods described in version 2 of the Prescription for Pharmacoeconomic Analysis (PFPA), and was developed with clinical advice from the Interventional Cardiology Advisory Group (ICAG).

Key inputs in the model included: a relative risk of stroke of 0.38 with LAAC vs placebo, derived from the PREVAIL RCT; a CHA_2DS_2-VASc score of 4.37, based on the EWOLUTION study; 19% of strokes are assumed to result in death, 71% in non-disabling stoke and 10% in permanent disability, based on the PROTECT-AF RCT.

Costs were estimated from the perspective of the funder and include $7,900 for the device and $8,800 for the procedure and associated hospital costs, including: first and subsequent cardiology attendance, echocardiography and chest x-ray. The device cost is indicative only having not been subject PHARMAC's competitive processes. It includes the cost of the device, the delivery system, and the guidewire. The estimate was provided to PHARMAC, through clinical advice, for the Abbott Pharmaceutical's AMPLATZER™ Amulet™ LAAC system. The procedure cost is based on DRG F09C (other cardiothoracic procedures without cardiopulomonary bypass pump without complications and/or co-morbidities). Quality of life scores were based on a previous PHARMAC analysis of dabigatran for stroke prevention in AF patients. Costs and benefits were discounted using a discount rate of 3.5%.

The incremental cost-effectiveness of LAAC compared to placebo for treating non-valvular AF is estimated to be 75 QALYs per $ million or $13,000 per QALY. The procedure is most cost-effective in patients with the greatest life-time risk of stroke, tending towards younger patients with high stroke risk. The results are most sensitive to the magnitude of treatment effect and the cost of stroke. For a 60-year-old patient, changing the relative risk of stroke with LAAC, from the base-case of 0.38 to 0.17

(imputed from the Continued Access to PREOTECT-AF registry), improved cost-effectiveness from 63 to 123 QALYs per $ million. A 25% increase in the cost of stroke improves cost-effectiveness from 63 to 80 QALYs per $million; a 25% decrement in cost reduces cost-effectiveness to 50 QALYs per $million. The 2016 Medical Services Advisory Committee assessment of LAAC in Australia reported a cost-effectiveness result of 73 QALYs per $AUD million compared with placebo (or 67 QALYs per $NZ million at the current exchange rate of 0.92 AUD to NZD).

Contents

1 Context

1.1 Proposal Under Assessment

Product	Percutaneous Left Atrial Appendage Closure (LAAC) devices: WATCHMAN™ (Boston Scientific) and the AMPLATZER™ Amulet™ (Abbott)
Supplier	Boston Scientific, Abbott
Proposed Indication	Non-valvular atrial fibrillation, high stroke risk and contraindicated to anticoagulants
Indicative Device Price	$7,900
Current Treatment	No treatment (contraindicated to available pharmaceutical therapy)

In 2016, following earlier proposals by the Cardiac Society of New Zealand to the National Health Committee, PHARMAC considered a proposal for funding of Left Atrial Appendage Closure (LAAC) devices.

The proposal was reviewed by the Interventional Cardiology Advisory Committee (ICAG) on 17 February 2017 and again at ICAG's 23 August 2017 meeting.

This assessment considers the cost-effectiveness of LAAC for people with non-valvular atrial fibrillation, high stroke risk, and who are contraindicated to oral anticoagulants including novel agents. The assessment may inform PHARMAC's consideration of the proposal under the Factors for Consideration, especially in the areas of Health Benefits, Health Costs and Savings, and to some extent under Health Need and Suitability.

1.2 Description of Condition and Patient Population

1.2.1 Atrial Fibrillation

Atrial fibrillation (AF) is an irregular and rapid heart rate, and is the most common cardiac arrhythmia. People with atrial fibrillation are at increased risk of stroke, which can be up to five times that of a person without atrial fibrillation.(1) Non-valvular atrial fibrillation excludes atrial fibrillation from rheumatic mitral valve disease or a prosthetic heart valve.

The left atrial appendage (LAA) is a small pouch off the left atrium of the heart. During AF, blood can become stagnant and form clots in the LAA. These clots may travel to the brain, causing ischaemic stroke. The LAA is thought to be associated with up to 90% of strokes in patients with non-valvular atrial fibrillation. (2)

1.2.2 Stroke

The two broad categories of stroke, hemorrhagic and ischaemic stroke, are diametrically opposite: hemorrhagic stroke is characterized by bleeding within the closed cranial cavity, while ischaemic

stroke is characterized by too little blood supply (and associated oxygen and nutrients) to the brain.(3) About 87% of all strokes are ischaemic strokes.(4) Strokes due to the embolization of a clot from the left atrium or left atrial appendage in patients with AF is an ischaemic stroke.(5)

The Auckland Regional Community Stroke Study (ARCOS) collected population-based registry data across the Auckland region. For ischaemic stroke, ARCOS reports a 28-day case fatality rate of 18.8% between 2011-2012.(6)

Stroke is a leading cause of serious long-term disability.(7) A post-hoc analysis of the PROTECT-AF randomised controlled trial reported that 19% of strokes resulted in death, 5% in severe disability (Modified Rankin scale 4-5), 5% in moderate disability (MRS 3), and that 71% were non-disabling (MRS 0-2).(8)

1.2.3 Population with Atrial Fibrillation

1.2.4 Prevalence of Atrial Fibrillation

The 2016 European atrial fibrillation guidelines (ESC/EACTS) report an AF prevalence rate of 3% in adults aged 20 years or older.(9) That implies approximately 100,000 New Zealanders have non-valvular AF at any one time.

A retrospective study of 739,000 patients in 170 New Zealand general practices reported a prevalence rate of 1.7% (95% CI, 1.69–1.75%), implying about 80,000 New Zealanders have non-valvular AF. (10) As reported by the authors, the study likely underestimates true prevalence as diagnoses are not always comprehensively coded (using the GP diagnosis Read code) in New Zealand general practice.

Key findings include:

- Prevalence was highest amongst men, 2.1% vs 1.4% for women, $p<0.001$.
- Prevalence increased with age – for New Zealanders aged 44 years or younger AF prevalence was 0.1%, compared with 11.3% for those aged 75 years or older.
- Prevalence was higher in Māori than non-Māori - Māori had a relative risk of 1.74, compared with non- Māori, after adjusting for age and other risk factors.
- The mean age of individuals with AF was lower for Māori (66.2 years) and Pacific patients (66.2 years) than European patients (74.7years).
- Stroke risk (assessed using the CHA_2DS_2-VASc score) was higher for Māori and Pacific patients across all age groups.

As AF prevalence increases with age, and as New Zealand has an aging population, AF prevalence and incidence are expected to increase over time.

1.2.5 Incidence of AF

Overall AF incidence was estimated at 9.9 per 1000 person-years in a large European prospective study (n=6432, aged 55-years or older) with a mean follow up of 6.9 years.(11) The incidence rate increased with age, from 1.1/1000 person–years in the age group 55–59 years to 20.7/1000 person–years in the age group 80–84 years and stabilized in those aged 85 years and above.

1.2.6 Mortality with AF

AF is an independent risk factor for mortality. An UpToDate Overview of Atrial Fibrillation reported the following evidence:

- The Framingham Heart Study - AF was associated with a significant increased risk of death - odds ratio 1.9 for women and 1.5 for men - after adjustment for pre-existing cardiovascular disease.(12)

- A retrospective observational study of 272,186 AF patients matched with 544,344 AF-free controls - the adjusted relative risk of death for women and men aged under 65 years was 2.15 and 1.76, respectively; for 65 to 74 year olds the relative risk was 1.72 and 1.36; and for 75 to 85 year olds the relative risk was 1.44 and 1.24. All values were statistically significant ($P < 0.001$). (13)
- A post-hoc analysis of the Women's Health Study, including 34,772 women with a median age of 53 who were initially free of AF. The study reported approximately 3% of women developed AF at a median follow-up of 15.4 years. These women had a significantly increased risk of all-cause mortality compared with AF-free women - hazard ratio 2.14 (95% CI 1.64-2.77).(14)

The evidence is insufficient to label AF as causal since available data cannot rule out AF being a marker of a confounding factor.(15)

1.2.7 Population in recommended target group

ICAG has recommended the following patient selection criteria.(16)

Table 1: Patient selection criteria

INDICATION HIGH STROKE RISK	**AND**	**CONTRAINDICATION TO EITHER OAC OR NOAC**
CHA_2DS_2-VASc ≥ 6 **OR**		Bleeding Risk OR
CHA_2DS_2-VASc ≥ 2 **AND** **Cumulative Stroke Risk > 40 %**		Ineffective Anticoagulation OR Drug Intolerance

ICAG has defined the contraindications as follows:

Bleeding Risk:

- Previous life-threatening bleeding leading to hospital admission; or
- Chronic anaemia secondary to bleeding requiring blood transfusion; or
- Specialist assessment identifying relevant bleeding risk and confirming contraindication for either OAC or NOAC (most commonly intracranial bleeding risk).

Ineffective Anticoagulation:

- Stroke or embolic event or recurrent LAA thrombus; and (or rather despite of)
- Treatment with either OAC or NOAC.

Drug Intolerance:

- Intolerance affecting activities of daily living (ADL); and
- Sufficient trial of either OAC or NOAC.

ICAG noted in the February 2017 meeting that while the CHA_2DS_2-VASc score was not a perfect criterion, due to its age bias, it is the best tool available to evaluate stroke risk in patients. The Group recommended that the best indicator of high risk was a CHA_2DS_2-VASc score ≥6 or a score ≥ 2 with a (life-time) cumulative stroke risk >40%. Table 1 presents the recommended patient selection criteria. Note that the criteria are a slight modification of the original criteria proposed by the New Zealand Committee of the Cardiac Society of Australia and New Zealand.(17)

1.2.8 Prevalence and incidence of patients with AF contraindicated to OAC/NOAC

Contraindication to oral anticoagulation is not consistently defined in the clinical literature (18), however, the foremost concerns relate to a patient's risk or history of bleeding and haemorrhagic stroke.(19-22)

Eighty percent of patients in the discontinued Wellington LAAC registry were indicated for LAAC due to bleeding risk.(23) Of 26 patients identified for LAAC, indications for closure were bleeding risk (20), ineffective anticoagulation (5) and drug intolerance (1).

In the ASAP study of the WATCHMAN™ device for patients contraindicated to warfarin, history of haemorrhagic/bleeding tendencies was the most common reason for warfarin ineligibility - being reported in 93% of patients.(24) Other reasons for ineligibility were blood dyscrasia (7.3%), 'unsupervised senility/high fall risk' (4.0%) and other (5.3%).

A New Zealand general practice study of 12,712 individuals with AF reported 0.7% had recorded contraindications to warfarin, all of which involved prior evidence of haemorrhage.(10) PHARMAC staff contacted an author of the study for further information on contraindications. Contraindications to warfarin included previous: a) cerebral haemorrhage, b) subarachnoid haemorrhage, c) extra-dural or subdural haemorrhage d) haemorrhage unspecified, e) preretinal haemorrhages and f) vitreous haemorrhage. These data imply a prevalent pool contraindicated to warfarin of approximately 570 New Zealanders (100,000*82%*0.7%).

A United States study of 86,084 Medicare beneficiaries 65 years or older with atrial fibrillation reported 2.2% (1,868) being ineligible for any oral anticoagulation because of an absolute contraindication, most frequently a history of intracranial haemorrhage (60%).(25) All patients had an $CHA_2DS\text{-}VA_2Sc \geq 2$. Contraindications to any anticoagulation therapy were based on diagnoses of intracranial haemorrhage (ICD-9-CM 430, 431, 432.x), intracranial mass (ICD-9-CM 191.x, 225.x, 239.6, 198.3), or end-stage liver disease. This would imply a prevalent pool contraindicated to any oral anticoagulation of approximately 1,800 New Zealanders (100,000*82%*2.2%).

Incidence figures were not reported in the above studies, but may be roughly approximated assuming:

- an annual AF incidence of 1 new case for every 100 New Zealanders 55 years or older, for which there were 1.25 million in 2016. (See Section 1.2.5)
- 82% of cases having a $CHA_2DS_2VASc \geq 2$
- 0.7% to 2.2% of these cases being contraindicated to oral anticoagulation

This implies an annual incidence (new cases) of 88 (1.25 million*1%*0.82*0.7%) to 275 (1.25 million*1%*0.82*2.2%) patients.

1.3 Current Treatment in New Zealand

The aim of treatment is to reduce the risk of stroke.

The current standard of care in New Zealand for the prevention of stroke in patients at high risk is lifetime treatment with oral anticoagulation, warfarin, or a novel anticoagulant - dabigatran or rivaroxaban.(26)

However, some people are contra-indicated to both OACs and NOACs. Recent European guidelines have moved against recommending aspirin as an alternative treatment for patients contraindicated to oral anticoagulation.(9) In high risk patients for whom anticoagulation is not suitable treatment options are very limited.

At its February 2017 meeting, the ICAG was asked to advise on the preventive therapies used in New Zealand. The minute of the meeting states that:

- The Group noted that there is currently no evidence that mono- or dual-antiplatelet therapy with aspirin or clopidogrel has a stroke reduction benefit in the Target group, and noted that there are RCTs comparing aspirin to anticoagulants, which showed they were substantially less effective in AF patients. Mono- or dual-antiplatelet therapy with aspirin or OAC is not considered an alternative comparator to LAAC.

This assessment therefore assumes that the comparator is no active treatment.

Rivaroxaban

Rivaroxaban is an oral anticoagulant used for the prevention of strokes and the prevention or treatment of other blood clots. From 1 August 2018 rivaroxaban 10 mg, 15 mg and 20 mg tablets will be funded by PHARMAC. This will increase treatment options for people who require anticoagulation to prevent or treat the formation of blood clots. The current assessment is for patients contraindicated to warfarin or novel anticoagulant therapy, including rivaroxaban and dabigatran, noting:

- LAAC is proposed for patients with a significant risk of major bleeding, particularly intracranial bleeding (see sections 1.2.7 and 1.2.8), where a significant risk of major bleeding remains a contraindication for rivaroxaban (27)
- The Australian Medical Service Advisory Committee (MSAC) recommended LAAC consequent to an economic evaluation that considered patients contra-indicated to warfarin, rivaroxaban, apixaban and dabigatran (see section 2.8)
- The recommended AF patient pathway in the UK includes LAAC where NOAC's, including rivaroxaban, are contraindicated or not tolerated (see section 2.7).

1.4 Product Under Assessment

Left Atrial Appendage Closure is a percutaneous cardiac intervention which plugs off the Left Atrial Appendage (LAA) to prevent clot formation in the heart, and thereby reduce the risk of stroke. The procedure delivers a plug, a self-expandable nitinol cage, via the femoral artery to isolate the LAA. The procedure usually requires a general anaesthetic. This device is covered by a layer of permeable polyethylene terephthalate (PTFE) membrane, which is endothelialized within 45 days in animal models. (28) LAAC is not publicly funded in New Zealand, though the procedure is undertaken to a very limited extent in private practice. Globally the WATCHMAN™ device (Boston Scientific) and the AMPLATZER™ Cardiac Plug (Abbott) are the two most commonly used LAAC devices.(28) Both devices have previously been used in New Zealand.

ICAG considered that most LAAC patients would be monitored in an intensive care unit or cardiology wards for 1-day post-procedure, with a follow up echocardiogram then discharged on day 2. The Group considered that routine imaging to confirm the integrity of the closure, and no thrombus, would be performed 4-6 weeks post procedure, LAAC patients would then be discharged back to their GP without any need for further LAAC follow-up. The Group noted that LAAC patients do not require prophylactic antibiotic treatment pre- or post-procedure.

1.4.1 WATCHMAN™ device

The LAAC procedure for the WATCHMAN™ device is described by Boston Scientific as follows:

- The WATCHMAN™ implant procedure usually lasts about an hour and the patient is typically in the hospital for a day

- The WATCHMAN™ implant procedure is typically performed under general anaesthesia in a catheterization laboratory setting using a standard transseptal technique
- A transesophageal echocardiogram (TEE) is performed to measure the left atrial appendage (LAA) to determine which size WATCHMAN™ device to be implanted
- After the interatrial septum is crossed using a standard transseptal access system, the WATCHMAN™ access Sheath is advanced over a guidewire into the left atrium. The Access Sheath is then advanced into the distal portion of the LAA over a pigtail catheter
- The WATCHMAN™ Delivery System is prepped, inserted into the Access Sheath, and slowly advanced under fluoroscopic guidance. WATCHMAN™ is then deployed into the LAA. The device release criteria are confirmed via fluoroscopy and TEE prior to releasing the device

1.4.2 AMPLATZER™ device

The AMPLATZER™ Amulet™ cardiac plug (Abbott) is constructed of nitinol mesh, consisting of a proximal left atrial disk and a distal LAA lobe connected by a short waist. The device is shorter than the WATCHMAN™ device and is suggested to be more advantageous in individuals with short appendages.(28) ICAG considered that one advantage of the AMPLATZER™ Amulet™ over WATCHMAN™ is that it has a wider range of sizes available; which could offer better fit.

1.1. Regulatory Status

Currently there is no regulatory approval process for medical devices in New Zealand. For medical devices to be legally supplied, however, they must be notified to Medsafe's WAND database.

Globally the WATCHMAN™ device (Boston Scientific) and the AMPLATZER™ Cardiac Plug (Abbott) are the two most commonly used LAAC devices.(28)

The WATCHMAN™ device received marketing approval from the FDA, known as Premarket Approval (PMA), in March 2015.(29) FDA marketing approval was granted for patients who:

- have atrial fibrillation not related to heart valve disease.
- are at increased risk for a stroke.
- are recommended for blood thinning medicines.
- are suitable for warfarin
- have an appropriate reason to seek a non-drug alternative to warfarin.

The device is not approved for patients who:

- currently have a blood clot in their heart
- have had surgical repair of the wall between the upper chambers of the heart (atrial septum) or have a device placed in the atrial septum, or have a LAA that is too large or too small to fit the WATCHMAN™
- cannot tolerate blood thinning medicines including warfarin, clopidogrel, and aspirin
- have sensitivity to nickel or titanium (Nitinol) or any other material that is part of the device.(30)

The AMPLATZER™ Cardiac Plug first received a CE mark in 2008, and FDA Investigational Device Exemption (IDE) approval in 2010, but has not received FDA marketing approval.(31, 32)

2 Effectiveness Review

2.1 Literature Search Strategy

A literature search was conducted by PHARMAC staff for randomised controlled trials and meta-analyses of LAAC in patients with atrial fibrillation. The MEDLINE database was used with the following search terms: “left atrial appendage closure”, OR “left atrial appendage occlusion” AND “atrial fibrillation”.

The search was limited to papers referencing randomised controlled trials or meta-analyses with a date limit of January 2000 to August 2017. The search returned 26 articles. A title and abstract search identified two randomised control trials, the PROTECT-AF (33-35) and PREVAIL(36) RCTs and four meta-analyses.(37-40) Of these meta-analyses, one was for atrial fibrillation patients contraindicated to oral anticoagulation.(39) A further meta-analysis of LAAC for AF patients contraindicated to oral anticoagulation was identified through a non-systematic search of Google Scholar,(41) as well as a meta-analysis of major bleeding in patients undergoing LAAC.(42)

Separately the Cochrane Database of Systematic Reviews was searched using the search term “left atrial appendage” for systematic reviews of LAAC. One Cochrane systematic review protocol for LACC (versus oral anticoagulation) was identified, but no completed review.(43)

The search was supplemented by material provided by ICAG in its submission, scanning references in articles, and reviewing articles referenced in UpToDate: *Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation*. The following websites were also searched:

National Institute for Health and Care Excellence (UK): http://www.nice.org.uk/

The Australian Medical Services Advisory Committee: http://www.msac.gov.au/

The Centres for Medicare and Medicaid Services: https://www.cms.gov/

Federal Drug Agency (FDA): https://www.fda.gov/

Ontario Health Technology Advisory Committee: http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Ontario-Health-Technology-Advisory-Committee

Data relating to observational studies of LAAC were largely taken from UpToDate and recent health technology assessments by the Australian Medical Services Advisory Committee (MSAC) and the United States Centres for Medicare and Medicaid Services (CMS) and their reference lists. Data relating to the epidemiology of atrial fibrillation and stroke were identified largely from UpToDate review articles and their reference lists. As such these data are a convenience sample of the published epidemiological and observational trial data available rather than a systematic review.

Independent expert clinical advice was provided by ICAG.

2.2 Details of Key Clinical Evidence

PHARMAC staff are unaware of any published comparative prospective trial comparing LAAC to placebo in patients contraindicated to long term anticoagulation.

The FDA and Boston Scientific undertook an imputed analysis of the PREVAIL, PROTECT-AF, and the Continued Access PROTECT-AF (CAP) registry studies to compare WATCHMAN™ with placebo.

The analysis reported relative risk reductions for ischaemic stroke ranging from 62% in the PREVAIL study to 83% in the CAP registry. (44)

Table 2: FDA imputed placebo versus observed WATCHMAN™ ischaemic stroke rate

Study	Average $CHADS_2$ Score WATCHMAN™ Patients	Imputed Untreated Control Event Rate	Observed WATCHMAN™ Ischemic Stroke Rate (95% CI)	Relative Risk Reduction Stroke	RR
PROTECT-AF	2.2	5.6 to 5.7	1.3 (0.9,2.0)	77% (64%, 84%)	0.23
CAP	2.5	6.4	1.1 (0.8, 1.7)	83% (73%,88%)	0.17
PREVAIL*	2.6	6.6 to 6.7	2.5 (1.5,4.3)	62% (35%,77%)	0.38

* Though not specified, observed ischemic stroke rates appear to include systemic embolism (0.17%) in the PREVAIL-only data. CAP Continued Access to PROTECT AF registry

We note that these trials were designed to evaluate the safety and effectiveness of the WATCHMAN™ device in a warfarin-eligible population, not a warfarin-ineligible population. Accordingly, PHARMAC staff sort clinical advice from ICAG on the plausibility of these results (Section 2.6, below).

A network meta-analysis of randomised trials including 732 patients receiving the WATCHMAN™ device (including 1-year follow-up data from PREVAIL and 3.8-year follow-up data from PROTECT-AF) and 925 patients receiving placebo (including 3 studies with follow-up ranging from 1.3 to 2.3 years) reported a hazard ratio of 0.24 (95% CI 0.11, 0.52) for all strokes and systemic embolism, favouring LAAC over placebo.(41)

A meta-analysis of randomised and non-randomised studies (n=1,759) reported an imputed relative risk of stroke of 0.34 (95% CI, 0.25-0.46) compared with placebo. Mean follow-up was 23.2 months, with an average CHA_2DS_2-VASc score of 2.7 and an average patient age across studies ranging from 62 to 74 years.(39)

The single arm ASAP study (n=150) for patients contraindicated to warfarin (discussed below) reported a relative risk of ischaemic stroke of 0.23 compared with no therapy, with a mean follow-up of 14.4 months, (24) and 0.26 with a median follow-up of 55.4 months.(45)

A trial protocol for what PHARMAC staff understand is the first randomised control trial of LAAC in patients contraindicated to anticoagulation was published in July 2017.(46) The ASAP-TOO study is designed to establish the safety and effectiveness of the WATCHMAN™ in patients with nonvalvular AF who are deemed ineligible for OAC. The primary effectiveness end-point is the time to first occurrence of ischemic stroke or systemic embolism. The trial commenced in February 2017, estimated enrolment is 888 patients with a 5-year time frame.(47)

2.3 Effectiveness data

Table 3 presents mid-term event rates (per 100 patient years) for the WATCHMAN™ procedure in the PROTECT-AF and PREVAIL RCTs, two meta-analyses of PROTECT-AF and PREVAIL, and for the ASAP study.

Ischaemic stroke

With a mean 4 years of follow-up, ischaemic stroke rates were similar between WATCHMAN™ and warfarin in PROTECT-AF: 1.3 per 100 patient years (95% CI 0.86, 2.00) vs 1.1 (95% CI 0.51, 1.97), respectively.

With a mean 2.2 years of follow-up, ischaemic stroke rates were higher in the WATCHMAN™ arm compared with warfarin in PREVAIL [2.3 per 100PY (95% CI 1.23, 3.94) vs 0.34 per 100PY (95% CI 0.01, 1.87), respectively].

Holmes et al.'s (2015) pooled analysis of the PREVAIL and PROTECT-AF trials (with a 75% weighting to the PROTECT-AF results) reported a hazard ratio (HR) of 1.95; p=0.05 in favour of warfarin.

Ischaemic stroke rates in the ASAP study sit between those of the PROTECT-AF and PREVAIL studies, notwithstanding patients having a numerically greater risk of stroke (as measured by CHA_2DS_2-VASc).

Haemorrhagic stroke

Haemorrhagic stroke rates are numerically higher for warfarin compared with WATCHMAN™ in both the PROTECT-AF and PREVAIL studies, though confidence intervals overlap between WATCHMAN™ and warfarin in PREVAIL.

Holmes et al.'s (2015) pooled analysis reports higher haemorrhagic stroke rates for warfarin vs WATCHMAN™ HR: 0.22; p=0.004.

Haemorrhagic stroke rates in ASAP are similar to the rates reported in the PROTECT-AF and PREVAIL studies.

All-cause mortality

Although confidence intervals overlap, WATCHMAN™ has numerically lower all-cause mortality in PROTECT-AF and PREVAIL.

Holmes et al.'s (2015) pooled analysis reports lower all-cause mortality for WATCHMAN™, HR: 0.73; p=0.07, though not meeting statistically significance.

All-cause mortality is numerically higher for WATCHMAN™ in ASAP (4.6 per 100PY) compared with PROTECT-AF (3.8 per 100PY) and PREVAIL (3.3 per 100PY).

Table 3: Mid-term Results and meta-analyses for the WATCHMAN™ procedure (event rates per 100 patient years)

Study	Intervention	N	Age	CHA_2DS_2-VASc	Mean Follow-up	Ischaemic Stroke	Haemor-rhagic stroke	All-Cause Mortality	Major Bleeding	Major Bleeding Non-Procedural	Source
PREVAIL RCT	WATCHMAN™	269	74.0 ± 7.4	3.8 ± 1.2	2.2 years	2.3 (1.23, 3.94)	0.35 (0.04, 1.25)	3.8 (2.39, 5.76)	5.5 (3.8,7.9)	3.6 (2.3,5.6)	FDA 2014(44)
	Warfarin	138	74.9 ±7.2	3.9 ± 1.2		0.34 (0.01, 1.87)	0.67 (0.08, 2.41)	4.3 (2.31, 7.41)	5.0 (2.9,8.4)	5.0 (2.9,8.4)	
PROTECT- AF RCT	WATCHMAN™	463	71.7 [46-95]	3.5 ± 1.6	4 years	1.3 (0.86, 2.00)	0.2 (0.03, 0.48)	3.3 (2.5, 4.2)	2.9 (2.2,3.8)	1.3 (0.9,2.0)	FDA 2014
	Warfarin	244	72.7 [41-95]			1.1 (0.51, 1.97)	1.1 (0.52, 2.00)	4.6 (3.2, 5.8)	3.2 (2.2,4.6)	3.2 (2.2,4.6)	
Meta-analysis of PREVAIL and PROTECT-AF	WATCHMAN™				2.69 years	1.6	0.15				Holmes et al. 2015(37)
	Warfarin					0.9	0.96				
	WATCHMAN™ vs Warfarin					HR: 1.95; p=0.05	HR: 0.22; p=0.004	HR: 0.73; p=0.07	HR: 1.00; p = 0.95	HR: 0.51; p=0.02	
Meta-analysis of PREVAIL and PROTECT-AF (Major Bleeding)	WATCHMAN™				3.1 years				3.5	1.8	Price et al. 2015(42)
	Warfarin								3.6	3.6	
	WATCHMAN™ vs Warfarin								RR: 0.96; p=0.84	RR: 0.49; p = 0.001	
ASAP	WATCHMAN™	150	72.5 ± 7.4	4.4±1.7	4.6 years	1.8 (0.9 to 3.3)*	0.54 (0.1, 1.6)	4.6	1.8		Sharma et al. 2016(45); Reddy et al. 2013(24)
EWOLUTION registry	WATCHMAN™	1,025	73.4 ± 9	4.5 ± 1.6	12 months	1.1		9.8	2.6	2.3	Boersma et al. 2017(48)

* ASAP Ischaemic stroke rate includes systemic embolis

2.4 Limitations of Studies

PROTECT-AF

The FDA's 2009 review concluded that the PROTECT-AF study did not demonstrate a reasonable assurance of device safety and efficacy given:

- substantial, 31%, enrolment of patients with a low stroke risk, signified by a $CHADS_2$ score of one, who were eligible for enrolment per the study protocol but may have been acceptable candidates for aspirin therapy rather than anticoagulation;
- concomitant use of chronic clopidogrel therapy in both arms of the trial (51% of follow-up time in device subjects and 16% of follow-up time in control subjects);
- safety concerns regarding serious peri-procedural WATCHMAN™ device implantation adverse events including pericardial effusion and air embolism, and
- the selection of a non-inferiority event rate ratio for a primary effectiveness endpoint of 2.0, meaning that the WATCHMAN™ arm could be found non-inferior to warfarin with an event rate up to twice that observed in the control arm. (49, 50)

PREVAIL

To address the issues with PROTECT-AF, the PREVAIL RCT was mandated by the FDA to further evaluate the safety profile and confirm the efficacy of WATCHMAN™ for regulatory approval. PHARMAC staff reviewed PREVAIL noting:

- Patients and clinicians were not masked to treatment assignment
- Lack of information around loss to follow-up: at 12 months 53% of original LAAC group followed up (142/269)
- As with PROTECT-AF, it does not include patients on NOACs and does not provide direct evidence for patients contraindicated to OAC or NOAC

PREVAIL (Failure to meet primary endpoints)

The FDA noted that the WATCHMAN™ device did not meet non-inferiority vs. warfarin for the first or second primary endpoints of the trial

The primary endpoints were:

- The occurrence of stroke (including ischaemic and haemorrhagic stroke), cardiovascular death (cardiovascular and unexplained), and systemic embolism (18 month rates). Event rates were 0.064 in the device vs 0.063 for warfarin, rate ratio 1.07 (0.57 to 1.89). Where non-inferiority required that the upper CI did not exceed 1.75. At 2.2 years of follow-up the difference increased, rate ratio 1.21, in favour of the control group.
- The occurrence of late ischaemic stroke and systemic embolism [8 days' post-randomization and onward (i.e., excluding the first 7 days post randomization), 18 month rates]. Event rates were 0.0253 in the device vs 0.02 for warfarin, rate ratio 1.6 (0.5 to 4.2), achieving pre-specified non-inferiority. At 2.2 years of follow-up the difference increased, rate ratio 2.8 (0.9, 7.3), in favour of the control group. The FDA noted that the upper confidence interval of (7.3) of the 95% credible interval was not

lower than the non-inferiority margin of 2.0, and hence non-inferiority was not met. (44)

Holmes et al meta-analysis of PROTECT-AF and PREVAIL:

- Weighting to the PROTECT-AF RCT, which presents favourable results for WATCHMAN™, but has methodological flaws.
- All patients were candidates for warfarin, hence it does not indicate efficacy in warfarin intolerant patients
- Patients were not exposed to novel anticoagulants; hence it is not known how patients might have responded to dabigatran or rivaroxaban.
- Loss to follow up was not recorded, or if material, how it was adjusted for.

ASAP

Follow-up beyond 2 years was outside the study plan for ASAP and events were not centrally adjudicated. There was no independent neurologic adjudication of events. Patients received clopidogrel 6 months' post-implantation and 5 patients received OAC therapy during follow-up.

2.4.1 Comparison of devices

Although there are no head-to-head trials between the WATCHAMAN and AMPLATZER™ devices, ICAG noted that available data indicates similar performance and outcomes. ICAG noted that the WATCHMAN™ device may be preferred by New Zealand clinicians due to the better quality of clinical evidence available for the device (i.e. RCT data). But it also noted that the AMPLATZER™ Cardiac Plug comes with a wider range of sizes enabling a better fit and a lower incidence of peri-prosthetic leak. This assessment does not specify which device should be used.

2.4.2 FDA approval

The FDA approved the WATCHMAN™ device in March 2015 following its evaluation of four clinical studies, the PREVAIL and PROTECT-AF RCTs and their two associated continued access registries. Public summary information suggest the FDA approval was based on safety, the FDA Panel voted 12 to 0 that the WATCHMAN™ LAA closure device was safe (51), and efficacy compared with warfarin, although the FDA note higher rates of ischaemic stroke, haemorrhagic stroke was considered lower in WATCHAMN patients compared with warfarin.(52) They also note that the overall rate of serious bleeding is similar in WATCHMAN™ and warfarin patients. Hence for patients for whom blood thinning medicines (like warfarin) may have serious side effects, WATCHMAN™, may be considered an option.

2.5 Safety

Table 4 presents procedure-related event rates (events/subjects) for the WATCHMAN™ device across four studies and one registry. In brief, the PREVAIL and PROTECT-AF randomised controlled trials (RCTs) compared LAAC with warfarin in patients eligible for long-term anticoagulation. The ASAP trial is a single arm study that aimed to evaluate LAAC in patients with an absolute contraindication to warfarin. The ASAP study presents the longest-term data for patients contraindicated to warfarin. Of note, patients in the trial did not undergo short term anticoagulation after LAAC. The European EWOLUTION registry prospectively compiled short term clinical data for patients receiving the WATCHMAN™ device across 47 centres in 13 countries.

Rates of successful device implantation ranged between 91% and 98.5%. Procedure related major bleeding events were 4.5% and 6.0% in the PREVAIL and PROTECT-AF trials, respectively. Pericardial effusion rates requiring intervention appear to have declined between the PROTECT-AF (4.0%) and PREVAIL (1.9%) studies, and are numerically lower again in the ASAP (1.3%) and EWOLUTION (0.7%) studies. Across studies, event rates appear to be lowest in the recently published EWOLUTION registry.

2.5.1 PREVAIL composite short-term adverse events

The PREVAIL RCT included a composite endpoint to evaluate procedure-related adverse events for the WATCHMAN™ procedure which included occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair, occurring between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later. The FDA considered the result of this endpoint (2.2%, 6/269 subjects) met the pre-specified performance goal of 2.67%. (44)

2.5.2 Meta-analysis of adverse events

A network meta-analysis from randomised trials (41) reported no statistically significant differences for LAAC versus placebo for major bleeding, intracranial bleeding, and gastrointestinal bleeding:

- Major Bleeding events Hazard Ratio 2.33 (95% CI, 0.67-8.09).
    - 22 events / 463 subjects vs 8 events / 925 subjects for LACC and placebo, respectively.
- Intracranial bleeding HR 0.36 (95% CI 0.04 -1.88)
    - 4 events / 732 subjects vs 1 event / 925 subjects for LACC and placebo, respectively.
- Gastrointestinal bleeding HR 1.81 (95% CI 0.24-13.41)
    - 3 events / 722 subjects vs 1 event / 714 subjects

A meta-analysis of randomised and non-randomised studies (n=2,779) reported the most frequent adverse events being major bleeding and pericardial effusions, occurring in 2.6% (95%CI: 1.5%, 3.6%) and 2.5% (95% CI: 1.8%, 3.2%) of patients undergoing LAAC, respectively.(38)

2.5.3 Major bleeding events

Table 3 and Table 4 show that there were more major bleeding events in PREVAIL compared with PROTECT-AF across both arms of the studies. Overall rates of major bleeding were similar between warfarin and WATCHMAN™ in both studies, but there were fewer non-procedure related bleeding events for WATCHMAN™ than warfarin.

Holmes et al.'s (2015) pooled analysis reports lower non-procedure related bleeding rates for WATCHMAN™, HR: 0.51; p=0.02, as does Price et al.'s (2015) pooled analysis of the PREVAIL and PROTECT-AF trials, relative risk: 0.49; p = 0.001.

Over-all major bleeding events were numerically lower in ASAP for WATCHMAN™ (1.8 per 100PY) compared with PROTECT-AF (2.9 per 100PY) and PREVAIL (5.5 per 100PY).

An unpublished indirect comparison by MSAC reports that, excluding procedure related major bleeding events, there was no statistically significant difference in the proportion of patients experiencing a major bleeding event between LAAC and placebo. (53)

2.5.4 Device-related thrombus

A secondary analysis of the PROTECT-AF trial reported a device-related thrombus (DRT) rate of 5.7% (27/485) with 12-months of follow-up.(54) Primary efficacy events (ischemic stroke, peripheral embolism, and cardiovascular/unexplained death) in patients with DRT occurred at a rate of 3.4 per 100 patient-years of follow-up – which is between the event rates previously reported for the overall device and warfarin arms in PROTECT-AF.

A systematic review of randomised and non-randomised evidence across 34 studies reported a device related thrombus rate of 1% (95% CI: 0.01–0.02) at ≤ 12 months follow-up and 2% (95% CI: 0.01–0.03) > 12 months.(55)

Table 4: Short-term and procedure-related event rates (events/subjects) of the WATCHMAN™ procedure

Study	Intervention	N	Age	CHA_2DS_2-VASc	Implant success	Major bleeding	Pericardial effusion requiring intervention	Procedure-related strokes	Device embolization	All-cause mortality	Source
PREVAIL RCT	WATCHMAN ™	269	74.0 ± 7.4	3.8 ± 1.2	95.1%	4.5%	1.9%	0.7%	0.7%	-	FDA 2014 (12) & Holmes et al (2014) (13)
PROTECT-AF RCT	WATCHMAN ™	463	71.7 [46-95]	3.5 ± 1.6	90.9%	6.0%	4.0%	1.1%	0.4%	-	FDA 2014 & Holmes et al (2014)
ASAP	WATCHMAN ™	150	72.5 ± 7.4	4.4 ± 1.7	94.7%	2.7%	1.3%	0.7%	1.3%	-	Reddy et al 2013 (14) & Reddy et al 2015
EWOLUTION registry	WATCHMAN ™	1019	73 ± 9	4.5 ± 1.6	98.5%	1.7%	0.7%	0.3%	0.2%	0.7%	Boersma et al 2016 (15)
CAP	WATCHMAN ™	566	74.0 ± 8.3	2.4 ± 1.2	94.3%	3.2%	1.4%	0.0%	0.2%	-	FDA 2014 & Holmes et al (2014)

2.6 ICAG Evidence Review

ICAG met and discussed the evidence for LAAC at two separate meetings; the first meeting was held in February 2017 and the second in August 2017.

At the February 2017 meeting it was noted that:

> "(A)n important problem in interpreting the published evidence about LAAC in New Zealand and in applying it to a tightly defined subset of patients, was that all of the RCT evidence to date was from patients who were not contraindicated to anticoagulation, and there was no RCT evidence available for the specific patient group being assessed by PHARMAC. Members considered that the primary RCTs for the WATCHMAN™ PREVAIL trial (37) and PROTECT-AF trial (56) were of reasonable strength and moderate quality, but their relevance to the specific patient group being reviewed was low."

At the August 2017 meeting ICAG noted that:

> "There was no direct clinical trial evidence comparing LAAC to placebo for patients contraindicated to oral anticoagulation, and that for this reason indirect comparisons using historic controls or algorithms (such as the CHA_2DS_2-VASc) were required for the [economic] model."

ICAG appraised the EWOLUTION and Global, Prospective AMPLATZER™ Amulet™ observational studies.

Critical appraisal of 1-year follow-up of the EWOLUTION trial (48)

The Group rated the study as a 2B using the SIGN critical appraisal system, indicating a well-conducted cohort study directly applicable to the target population of interest.

The Group noted that:

- The study was a large (n=1025) observational longitudinal follow-up providing real-world experience of the WATCHMAN™ device in European centres.
- The data was collected prospectively and sequentially, with minimal loss to follow-up (13 patients), which reduces the risk of selection bias.
- All centres were monitored by an outside contract research organization. All centres were visited between 1 and 4 times, depending on the number of patients enrolled and compliance review. It was noted that this would reduce the risk of bias from reliance purely on self-reported data from the centres.
- Patients were high risk (mean CHA_2DS_2-VASc score 4.5) with most being contraindicated to oral anticoagulation. Patient selection criteria were reported to be consistent with European Society of Cardiology Guidelines, and the patient group was reasonably representative of the patient group proposed for intervention in New Zealand.
- Baseline patient characteristics showed that patients had high rates of prior stroke and heart failure. 34% had heart failure (with a third of these having >II NYHA class) and 46% had a prior history of stroke or TIA.
- Adverse events in the registry were considered more reflective of event rates likely to occur in the New Zealand setting, compared with earlier RCT data.

The Group considered that:

- The reported device failure rate of 1.5% observed in EWOLUTION was a more plausible estimate than the 4.9% reported in PREVAIL (37) and used in PHARMAC's initial economic assessment.
- The device thrombus rate observed in EWOLUTION of 7.9% at 6 weeks was high, but current evidence does not link device thrombus with subsequent strokes.

Global, Prospective AMPLATZER™ Amulet™ observational study (n =1,088) (57)

The Group considered that the paper reasonably reflected the proposed patient population in New Zealand, and noted that:

- 82.8% of patients were considered to have an absolute or relative contraindication to long-term anticoagulation
- revision procedures for LAAC were very infrequent
- 99% of patients were reported to have successful device implantation

Relative risk of stroke for LAAC vs Placebo

ICAG discussed the most appropriate relative risk of stroke for LAAC vs placebo for PHARMAC's cost-utility model. A two-thirds relative risk reduction for LAAC compared to placebo was considered reasonable, noting:

- clinical trials of oral anticoagulation compared with placebo showed a similar relative risk reduction
- PHARMAC had presented evidence in its economic appraisal from several imputed analyses of LAAC vs placebo (including the EWOLUTION study, (1) and the FDA analysis of the PROTECT-AF and its associated Continued Access registry which indicated much lower rates, but these were not considered clinically plausible. (2)
- The first-year all-cause mortality rate used in the model was considered too low due to the high-risk profile of the patients proposed for intervention. It was noted that the EWOLUTION study had a 1-year mortality rate of 9.8%. It was also noted that the proposed patient group would likely have an even higher all-cause mortality rate in the absence of LAAC.

2.7 International Recommendations

Table 5 presents recommendations from major international health technology assessment agencies with responsibility for assessing medical devices. Broadly speaking, where these agencies support LAAC it is for patients with contraindications to oral anticoagulation.

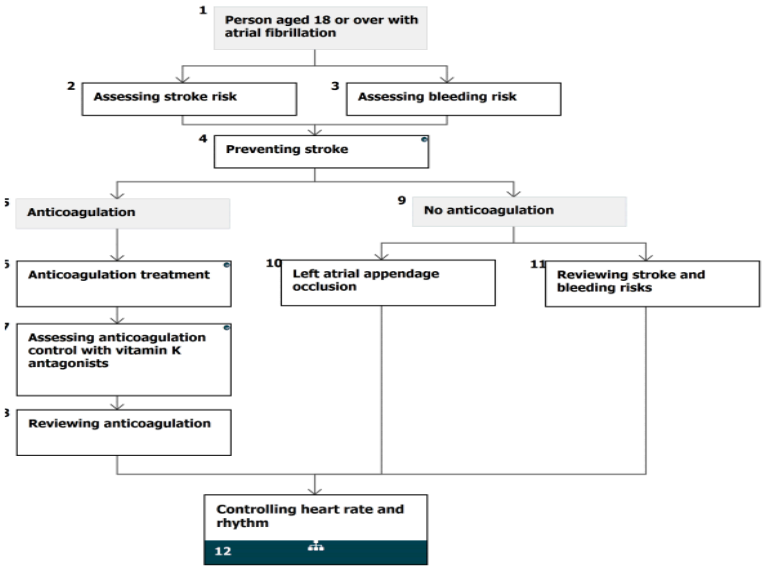
Table 5: Selected International Guidelines and Recommendations

Region	Year	Recommendation	Other comment
Australia	2016	**MSAC (53)**	When compared with best supportive care (placebo), LAAC has a reasonable safety profile and acceptable clinical and cost effectiveness.
		Supported in people with non-valvular AF at *moderate to high risk* of stroke and lifelong contraindications to both oral anticoagulation therapy and dual antiplatelet therapy	
UK	2010	**NICE (58)**	"The risk of life threatening complications is low"
		"Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated."	
USA	2015	**Centres for Medicare & Medicaid Services (18)**	$CHADS_2$ score ≥ 2 or CHA_2DS_2-VASc score ≥ 3. Patient selection requires input from an independent non-interventional physician. Patients must also be enrolled in a prospective national registry.
		Must be "Considered Suitability for short-term warfarin but deemed unable to take long term oral anticoagulation."	
Europe – ESC/EACTS	2016	**ESC/EACTS (9)**	"absolute contraindications to long-term OAC after a bleeding episode are rare"
		"LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause." Rec: class IIb	"**LAAO has not been compared with NOAC therapy in patients at risk for bleeding, or with thoracoscopic LAA clipping**"
			"The most common justification for LAA occlusion devices in clinical practice is a perceived high bleeding risk and, less often, contraindications for OAC. Unfortunately, LAA occluders have not been tested in such populations."
Ontario Canada	2017 (July)	The Ontario Health Technology Advisory Committee recommends that the left atrial appendage closure device with delivery system be publicly funded for patients with nonvalvular atrial fibrillation in whom all oral anticoagulants are contraindicated.(59)	"Moderate-quality evidence suggests that the LAAC device is as effective as novel oral anticoagulants in preventing stroke in people with nonvalvular atrial fibrillation. However, our results indicate that the LAAC device is cost-effective only in patients with contraindications to oral anticoagulants."

The recommended AF patient pathway in the UK is illustrated in Figure 1. In the pathway funded anticoagulation treatment includes warfarin, apixaban, dabigatran, rivaroxaban and edoxaban.

Left atrial appendage occlusion is recommended for preventing stroke risk if anticoagulation is contraindicated or not tolerated.

Figure 1: Preventing stroke in people with Atrial Fibrillation, NICE Pathways



2.8 Summary of International Economic Analyses

Published NICE guidelines do not include a cost-utility analysis for LAAC.

MSAC's 2016 review of LAAC for MBS listing in Australia concluded that LAAC had a reasonable safety profile and acceptable clinical and cost-effectiveness when compared with best supportive care (placebo). LAAC was found to incur an average lifetime cost of $AUD 27,481 and lead to a gain of 8.47 QALYs compared with $AUD8,310 and 7.07 QALYs for placebo, with a resulting Incremental Cost Effectiveness Ratio (ICER) of $AUD13,659 per QALY, or 73 QALY per $AUD million. MSAC's public summary document does not specify the line item costs, utilities, or baseline assumptions around clinical effectiveness (LAAC vs placebo) employed in the economic model. The analysis was not device specific. The CUA protocol included patients contraindicated to funded oral anti-coagulation including warfarin, rivaroxaban, apixaban and dabigatran.(60)

MSAC considered that the budgetary risk from indication creep would be mitigated with the use of multi-disciplinary heart teams in addition to appropriate training and accreditation of providers by site.

The Ontario Health Technology Advisory Committee's[1] 2017 review of LAAC concluded that the LAAC device was cost-effective only in patients with contraindications to oral anticoagulants. (59) OHTAC did not, however, conduct an economic evaluation of LAAC in patients contraindicated to oral anticoagulation, considering instead, that available clinical evidence, and two published economic evaluations in this population, were sufficient evidence for its recommendation. The referenced economic appraisals were:

[1] OHTAC is a health technology assessment advisory committee for the province of Ontario Canada

- A structured abstract of a cost utility analysis using the AMPLATZER™ Cardiac Plug in the Canadian Health care system for patients contraindicated to anticoagulation compared with Aspirin. The analysis found LAAC was the dominant option being more effective and less expensive, but did not report baseline patient characteristics, line item costs, utilities, or baseline assumptions around clinical effectiveness.(61)
- A cost utility analysis of LAAC versus placebo using the WATCHMAN™ device, from a US health payers' perspective, previously appraised by PHARMAC for ICAG's February 2017 meeting.(8)

3 Economic Analysis

3.1 Scope of Analysis

3.1.1 Decision Problem and Perspective

A cost-utility analysis was undertaken to estimate the cost-effectiveness of LAAC compared to no intervention, in individuals with atrial fibrillation at high risk of stroke and contraindicated to oral anticoagulants or novel anticoagulants.

This analysis was conducted from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

3.1.2 Target Population

The target population for this analysis was defined as set out in section 1.2.7 above.

The model has been set up to estimate the cost-utility for different sub-groups defined by their baseline stroke risk.

3.1.3 Comparator

The comparator used in the analysis was no active treatment.

Section 1.3 above summarises the evidence and clinical advice for AF patients contraindicated to OAC and NOAC therapy. These patients currently have no alternative treatments that would reduce their risk of future strokes.

3.2 Economic Model

A micro-simulation Markov model was constructed to model the different treatment strategies. Data was taken from the sources reviewed in sections 1 and 2 of this report. The baseline analysis uses effectiveness data from the PREVAIL study and stroke risk predicted by CHA_2DS_2-VASc score as reported in the FDA assessment of the WATCHMAN™ device. (44)

The model was implemented in TreeAge as a microsimulation, modelling the interventions and health outcomes for each of several thousand-representative people.

At the start of a model run, a person is assigned elements of the CHA_2DS_2-VASc risk score, including age, gender, congestive heart failure, hypertension history, stroke or TIA history, vascular disease history, and diabetes history. The Markov state-transition model tracks each such person through treatment until their death from stroke or other causes. Stroke risk is modelled as varying over time both from treatment and because of changes in the CHA_2DS_2-VASc risk factors. The cost-utility result for each sub-group of patients is an average over the set of people modelled.

The advantage of this model structure is that it can be used to assess the cost-effectiveness of the proposal in a wide range of different potential patient groups, as defined by age and other contributors to baseline and lifetime stroke risk.

3.2.1 Time Horizon

The model has a lifetime time-horizon: people enter the model at the time they are allocated to treatment with LAAC or otherwise, then followed until death from stroke or other causes.

Each Markov cycle is one year. The time horizon was chosen as the benefits of LAAC accumulate over the person's remaining lifetime; the one-year cycle length matches the risk equations available.

All costs and benefits were discounted at 3.5%, as specified in the PFPA v2.2.(62)

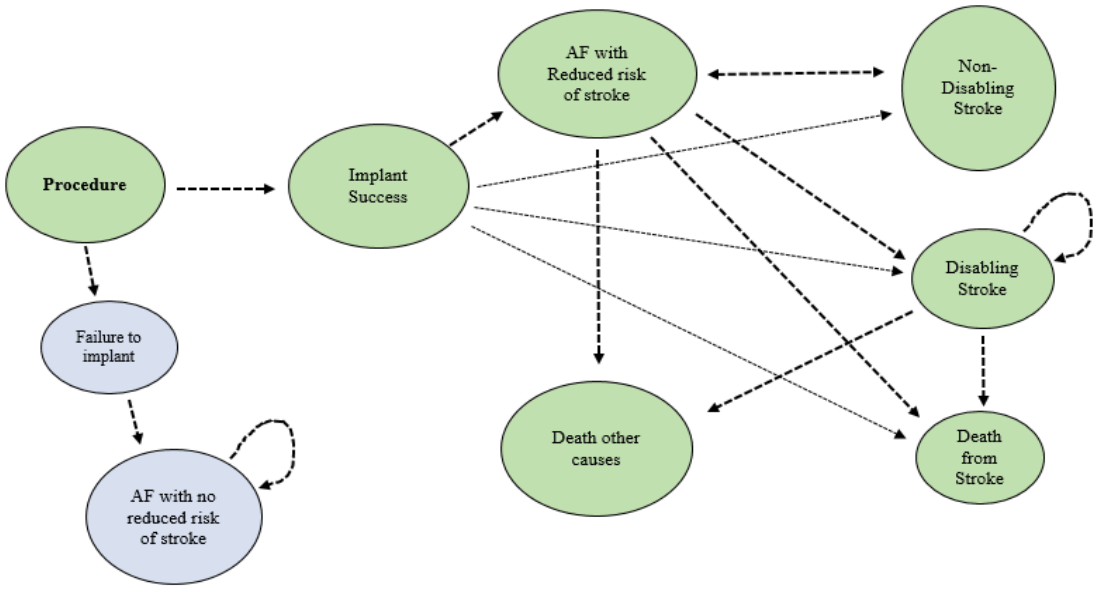
3.2.2 Model Structure

The key states in the model are:

- Procedure
- Post procedure with no stroke or non-disabling stroke
- Stroke disability
- Dead (stroke)
- Dead (other)

Figure 1 presents the model as a state transition diagram. The non-intervention arm is a clone (excluding failure to implant) of the intervention arm, with only costs and probabilities being different between the two.

Figure 1: Model Structure (Intervention Arm)



People enter the model at the procedure state. The procedure may result in a disabling stroke, a non-disabling stroke, death from stroke or other causes, or a successful procedure without any stroke. In each subsequent year, people may move from the 'successful' state to one of the three stroke states or to death from other causes. People who move to disabling stroke in any cycle will remain in that state until death. People who suffer a non-disabling stroke are assumed to have a term-limited disutility for 12 months, then return to the AF state.

The baseline utility for atrial fibrillation is 0.891, rewarded for each cycle unless overwritten by stroke or death.

For the no-treatment arm of the model the risk of stroke is determined by the CHA_2DS_2-VASc score. With a successful LAAC procedure the relative risk of stroke compared to no treatment is 0.38. After an unsuccessful procedure (ie failure to implant the device), the relative risk of stroke is 1 (ie the same as no treatment).

3.2.3 Key Assumptions and Inputs

Table 6: Base-case CUA Parameters

Parameter	Value	Source/Assumption
Patients	Atrial fibrillation and contraindicated to anticoagulation.	
CHA_2DS_2-VASc	4.37	EWOLUTION (average for patients aged 65-74)
Comparator	No treatment	Assuming mono or dual antiplatelet therapy (aspirin + clopidogrel) has no stroke reduction effect. ICAG advice
RR Stroke	0.38	FDA imputed placebo analysis of the PREVAIL RCT (In-line with ICAG's 2/3 estimated reduction in risk)
Outcomes of stroke		
Death (30-day)	19%	ARCOS and PROTECT-AF
% of strokes that are non-disabling	71%	PROTECT-AF
% of strokes that are disabling	10%	PROTECT-AF
First year all-cause mortality	9.8%	EWOULTION

3.2.3.1 Baseline Patient Characteristics

The baseline patient characteristics were modelled using the EWOLUTION study (Table 7). Relative to EWOLUTION, the model was simplified by assuming 100% of patients had hypertension (86.4% had hypertension in EWOLUTION).

Table 7: Baseline Patient Characteristics

Condition	Model Settings	CHA_2DS_2-VASc points	Average Points
CHF	34.2%	1	0.342
Hypertension	100%	1	1
Age ≥75	Varied	1	0
Diabetes	29.7%	1	0.297
Prior stroke	45.6%	2	0.912
Vascular disease	41.9%	1	0.419
Age≥65	Varied	1	1
Sex	40.1%	1	0.401
CHA_2DS_2-VASc		Aged 65-74	4.37

3.2.3.2 Stroke risk

The baseline risk of stroke with atrial fibrillation is defined by the CHA_2DS_2-VASc score, a 9-point score measured by summing up applicable points as follows:

Condition		Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

The sum of the points determine annual risk of stroke risk as follows.

Table 8: Predicted stroke risk

CHA_2DS_2-VASc Score	Patients (n=7329) Adapted from Lip et al**(63)**	Stroke Risk %
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	*82*	*6.7%*
9	14	15.2

Source: Chadvasc.org[2]

The algorithm is recommended by ICAG, the American College of Cardiology/American Heart Association (64) and the European Society of Cardiology (9). Of note, the small sample size in the scores from 7 to 9 may have contributed to some variability in stroke risk, where there is a marked decline in stroke risk for CHA_2DS_2-VASc score of 8 (6.7%) compared with 7 (9.6%).

The CUA models the transition probabilities of congestive heart failure, age, diabetes mellitus, vascular disease, and stroke. We adjusted Table 8 so that CHA_2DS_2-VASc score of 8 predicts a stroke risk of 12.4%, being the midpoint estimate between a CHA_2DS_2-VASc score of 7 and 9. No additional cost or disutility is modelled for the CHA_2DS_2-VASc risk factors other than stroke.

[2] http://www.chadsvasc.org/

Patients are attributed an additional point of risk at ages 65 and 75, an additional point for new onset diabetes, vascular disease or congestive heart failure, and an additional two points for surviving a stroke. Of note, points are only attributable once for any condition suffered. Therefore, subsequent strokes do not further increase the risk of stroke in the model.

For example, a 64-year-old male entering the model with a CHA_2DS_2-VASc of 2 and no prior stroke history, will have a score of 3 at age 65; a score of 4 at age 75; and a score of 6 if he then survives a stroke. In the model these CHA_2DS_2-VASc scores (2, 3, 4 and 6) correspond with 1.3%, 3.2%, 4.0% and 9.8% of patients suffering a stroke annually in the no treatment arm. Assuming a relative risk of 0.38, the corresponding annual rates of stroke in the LAAC arm are 38% lower.

3.2.3.3 Probability of developing congestive heart failure

CHA_2DS_2-VASc Definition: The presence of signs and symptoms of either right or left ventricular failure or both, confirmed by non-invasive measurements demonstrating objective evidence of cardiac dysfunction, e.g. LVEF < 40%.

In the Framingham Heart Study the incidence of developing CHF in AF patients was 33 per 1000 person-years.(65) The association between AF and the development of CHF was also analysed in a study of 3288 patients diagnosed with AF at the Mayo Clinic. With follow-up to 6.1 years, the study reported a spike in incidence with 7.8% of cases occurring within the first 12 months, and approximately 3% per year thereafter.(66, 67)

The CUA model assumes a 3% annual probability for patients developing CHF who do not already have the condition at baseline.

3.2.3.4 Probability of developing diabetes mellitus

CHA_2DS_2-VASc Definition: Fasting plasma glucose level >= 7.0 mmol/L (126 mg/dl) or treatment with oral hypoglycaemic agent and/or insulin.

The model assumes the risk of developing diabetes amongst AF patients is equivalent to the general population's. The risk of developing diabetes mellitus was calculated based on newly diagnosed rates observed in the United Kingdom between 2000 and 2013.(68)

Table 9 : Probability of developing diabetes mellitus

Age	Male Rate per 1000 PYAR	Female Rate per 1000 PYAR	Total Rate per 1000 PYAR	Transition Probability of developing type 2 Diabetes Mellitus
0-9	0.04	0.04	0.0	0.00%
10-19	0.11	0.28	0.2	0.02%
20-29	0.36	1.15	0.8	0.08%
30-39	1.36	1.91	1.6	0.16%
40-49	4.02	3.00	3.5	0.35%
50-59	7.86	5.43	6.6	0.66%
60-69	11.87	8.48	10.2	1.01%
70-79	12.68	10.32	11.5	1.14%
80-89	9.08	8.00	8.5	0.85%
90-99	5.96	4.55	5.3	0.52%

3.2.3.5 Probability of developing vascular disease

CHA_2DS_2-VASc Definition: Prior MI, angina pectoris, percutaneous coronary intervention or coronary bypass surgery. The presence of any the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic surgery, arterial and venous thrombosis.

The definition of congestive heart failure used in the CHA_2DS_2-VASc score is a composite of coronary artery disease (CAD) and peripheral artery disease (PAD). Noting intermittent claudication (IC) is the most prominent symptom of PAD, and is used to define its incidence and prevalence.(69)

Transition probabilities of developing vascular disease were estimated by combining risk rates in the Framingham Heart Study for CAD (70) and intermittent claudication (71). To avoid double counting we further assumed that 11% of patients with CAD also have PAD based on data in the International Reduction of Atherothrombotic for Continued Health (REACH) Registry.(72)

Table 10: Probability of developing vascular disease

Age group	10-year risk of CAD	4-year risk of Intermittent Claudication	Transition Probability of developing vascular disease
45-49	5%	0.65%	0.62%
50-54	8%	0.65%	0.91%
55-59	12%	1.65%	1.55%
60-64	12%	1.65%	1.55%
65-69	13%	2.00%	1.74%
70-74	14%	2.00%	1.84%
75-84	14%	1.50%	1.72%

Note: 10-year and 4-year rates are converted to annual rates r= -[ln(1-p)]/t, before being converted to transition probabilities p= 1-e^(-rt)

Although peripheral arterial disease and CAD share some of the same risk factors as atrial fibrillation, it is assumed that the risk of developing CAD and PAD are similar in an AF population as the general population.

- UpToDate notes that AF is not commonly associated with CAD unless it is complicated by acute myocardial infarction or heart failure.(73)
- PAD is an independent risk factor for incident AF but not vice versa.(74)

3.2.3.6 Disability Outcomes Following Stroke

For the purposes of this assessment, the outcomes following a stroke are full recovery (71%), disability stroke (10%), and death (19%).

The Auckland Regional Community Stroke Study (ARCOS) collects population-based registry data across the Auckland region. It reported a 28-day case fatality rate of 18.8% between 2011-2012. (6) 28-day mortality was defined as the proportion of people with stroke who died within 28 days of stroke onset among the total number of people with incident stroke.

Stroke disability outcomes were not reported in the ARCOS study nor have they been reported in the PREVAIL or ASAP trials. Reddy et al report an unpublished sub-group analysis of the PROTECT-AF data noting that 19% of strokes result in death, 5% in severe disability (Modified Rankin scale 4-5), and 5% in moderate disability (MRS 3); 71% were non-disabling (MRS 0-2).(8)

3.2.3.7 Durability of effect

IGAC advised that the effect of LAAC is expected to persist for the patient's lifetime. The model assumes a constant relative risk of stroke of 0.38 over time.

3.2.3.8 Learning Curve

The learning curve effect is tested in the model by varying the procedure failure rate. The PREVAIL RCT noted that implantation success was achieved in 95.1% overall, and in 96.3% with experienced operators, versus 93.2% with new operators (p = 0.256). There were no significant differences in complication rates between the 2 groups (36); the overall rate is used in the base-case of this assessment, while the other rates are used in a sensitivity analysis.

3.2.3.9 Non-stroke mortality

People with atrial fibrillation are more susceptible to other types of mortality events; they are more likely to die from non-stroke events than the general population. The background mortality rate has been adjusted to account for this. If standard population mortality rates were used, the model would overstate the benefit of LAAC. A meta-analysis comparing patients with atrial fibrillation to the general population reported the relative risk of mortality from stroke as 2.42 (95% CI 2.17 – 2.71) and from all causes as 1.46 (95% CI 1.39 – 1.53). (75)

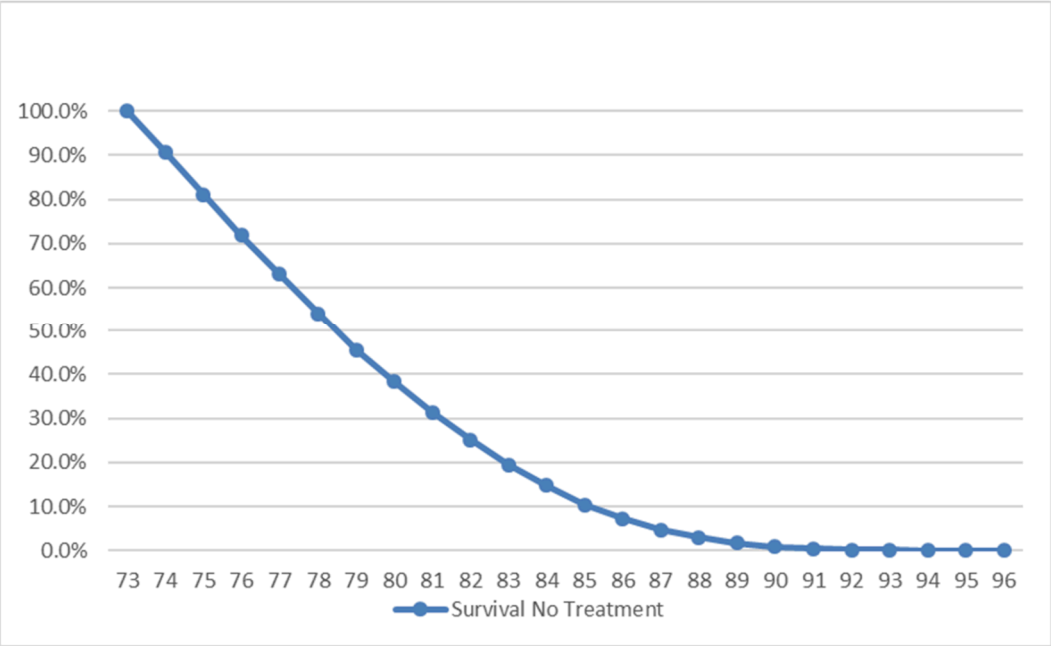
New Zealand mortality rates (76), by age and gender, have been applied to the relative risks above to determine the relative risk of death from non-stroke events. These relative risks were then applied to standard background mortality rates to determine background mortality rates for atrial fibrillation.

Table 11 Mortality parameters

All Mortality *(a)*	31,168
Stroke Mortality *(b)*	2,570
RR All-cause Mortality | AF *(c)*	1.46
RR Stroke | AF *(d)*	2.42
All Mortality | AF *(a*c)*	45,505
Stroke Mortality | AF *(b*d)*	6,219
Non-Stroke Mortality | AF *(a*c-b*d)*	39,286
Scale All Mortality to Non-Stroke Mortality | AF *(a*c-b*d)/(a)*	**1.26**

The above scaling approach was, however, considered too conservative by ICAG considering the high-risk profile of the patients proposed for intervention and the EWOLUTION study results. The EWOLUTION study reported a 1-year mortality rate of 9.8%. Accordingly, the all-cause mortality rate for high risk stroke patients was scaled up 3-fold, relative to the general population, to reflect an approximate 10% all-cause mortality rate in the first year (Figure 2). It was also noted that the proposed patient group would likely have an even higher all-cause mortality rate in the absence of LAAC.

Figure 2: Background mortality using baseline parameters in Table 7 and start age 73 years and CHA_2DS_2-VASc 4.37



3.3 Health-Related Quality of Life

The utility values included in the analysis were obtained using the New Zealand EQ-5D. Health state descriptions were informed by literature search and PHARMAC staff. NZ Tariff-2 EQ-5D weights were then applied to the generic health states to derive quality of life scores. These are outlined in the table below. The scores were validated by comparing to previous PHARMAC analyses, Global Burden of Disease study weights, and published cost utility analyses of LAAC in patients contraindicated to warfarin. These are outlined in the table below. ICAG reviewed the utility values noting they "were reasonably consistent with utility values collected in the ARCOS study using the 36-item Short Form Survey (SF36)."

Table 12: Health-Related Quality of Life weights

Health State	NZ EQ-5D	Utility	GBD Disability Weight	**Reddy et al** (8)
Atrial Fibrillation (AF)	11(1-2)11	0.891		0.82 for well patients with AF at age 70 years
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – First 3 months	(2-3)(2-3)(2-3)22	0.275		
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – 4 - 12 months	(1-2)22(1-2)1	0.634		
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – Recovered	*11(1-2)11*	0.891		

Health State	NZ EQ-5D	Utility	GBD Disability Weight	**Reddy et al** (8)
after 1 year				
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – Not Recovered after 1 year	(1-2)22(1-2)1	0.634	Permanent impairments Mild 0.64, Moderate 0.37, Severe 0.08	References a decrement for Ischemic and haemorrhagic stroke of 0.13850, but is not specified by severity, implying a utility of 0.682, using US EuroQol (EQ-5D) disability weights (77)

3.4 Costs

The combined cost of device procedure and associated costs is estimated to be $17,000; it is assumed that there are no additional ongoing costs associated with LAAC.

Table 13 lists the component costs. The analysis borrows from the MSAC assessment protocol for LAAC (60) and DLA-Piper's assessment for HEALTH-PACT in Australia.(78)

Table 13: Cost of LAAC procedure

Item	Cost	Source
Screening		
Cardiology - 1st attendance	$433	Purchase unit code M10002
Transoesophageal echocardiography	$330	C&C DHB and ADHB
Cardiology - Subsequent attendance	$279	Purchase unit code M10003
Procedure		
Device	$7,900	PHARMAC (indicative)
Procedure	$7,000	DRG F09C* Other cardiothoracic procedures without cardiopulmonary bypass pump without complications and/or co-morbidities.
Pre-discharge		
Chest X-Ray	$111	Pacific Radiology
Transoesophageal echocardiography	$330	C&C DHB and ADHB
Post-discharge		
Transoesophageal echocardiography	$330	C&C DHB and ADHB
Total Cost	$16,700	

*The DRG price was adjusted to remove average implant costs of approximately $1,200.

The device cost of $7,900 is indicative only having not been subject PHARMAC's competitive processes. It includes the cost of the device, the delivery system, and the guidewire. The

estimate was provided to PHARMAC, through clinical advice, for the Abbott Pharmaceutical's AMPLATZER™ Amulet™ LAAC system. DRG F09C was considered a suitable approximation of non-device procedure costs, where the average length of stay is 2.32 days. ICAG considered that most LAAC patients would be monitored in an intensive care unit or cardiology ward for 1-day post-procedure, with a follow up echocardiogram and then discharge on day 2. The Group considered that routine imaging to confirm the integrity of the closure, and no thrombus, would be performed 4-6 weeks post procedure, LAAC patients would then be discharged back to their GP without any need for further LAAC follow-up.

3.4.1 Cost of stroke

The cost of stroke includes health system costs including hospitalisations, age residential care and disability support services.

The first year cost of stroke is assumed to be $26,000; which was derived from a paper provided by CSANZ, based on the Auckland Regional Community Stroke Study.(79)

Death has a zero cost.

The out-year cost of stroke, $8,100 per annum, was derived from 5-year results of the Australian NEMESIS study.(80)[3] All costs were inflation adjusted to 2017 prices, and assumed to be constant in each remaining year of life.

The effect of these choices of parameter values are tested in sensitivity analysis below.

3.4.2 Cost of Complications

Additional to the costs above are the non-stroke costs of procedure-related complications, averaging to $381 per procedure. The costs are derived from New Zealand DRG codes and the rates from the PREVAIL RCT shown in Table 14. The average cost is calculated as the sum of the cost and probability of each complication type summarized below.

Table 14: Costs of complications

Complication type	Cost	Cost Reference	Probability
Device embolization	$5,186	MSAC (60), NZ DRG Costs 2015	0.7%
Major bleeding	$4,376	MSAC, NZ DRG Costs 2015	4.5%
Pericardial effusion	$7,797	MSAC, NZ DRG Costs 2015	1.9%

3.5 Results of the Economic Analysis

LAAC is estimated to generate 75 QALYs per $1 million invested (or $13,000 per QALY) compared with no treatment in patients with non-valvular AF at high risk of stroke and contraindicated to oral anticoagulation. Cost-effectiveness improves with life-time stroke risk and reduces with age.

[3] The North East Melbourne Stroke Incidence Study (NEMESIS) was used to model out-year costs by the authors of the New Zealand study provided by the applicant.

Table 15 shows the cost-effectiveness of LAAC using the patient selection criteria proposed by ICAG (section 1.2.7). In green are patients contraindicated to oral anticoagulation with a CHA_2DS_2-VASc score ≥ 2 and a cumulative risk of stroke (life-time risk) > 40%. In blue are patients contraindicated to oral anticoagulation with CHA_2DS_2-VASc ≥ 6. In grey are patients who do not meet the criteria. The average age of patients meeting the criteria is 76 years. The distribution of patients with an absolute contraindication to anticoagulation was estimated based on data provided to PHARMAC from the New Zealand general practice study stratifying patients contraindicated to anticoagulation by age and CHA_2DS_2-VASc score. (10)

Table 15: Cost-effectiveness of LAAC vs non-treatment in patients contraindicated to (N)OAC

QALYs per $m		Initial CHA2DS2-VASc ≥ 2								
		1	2	3	4	5	6	7	8	9
Start Age	50	31	60	108	163	498	-1061	2899		
	55	21	45	72	105	264	2311	818		
	60	15	32	48	77	149	345	666		
	65		11	23	33	61	107	139	342	
	70		7	14	20	35	49	71	171	
	75			4	9	14	23	22	44	65
	80			2	4	7	9	9	20	18
	85			0	1	2	4	4	7	8
	90			0	0	1	1	1	1	0

Negative signs indicate cost-saving with health gains

Table 16 shows the cost-effectiveness of LAAC including patients with a CHA_2DS_2-VASc ≥ 2 and a cumulative risk > 40%. The CHA_2DS_2-VASc ≥ 6 criterion has been removed. Mean weighted cost-effectiveness roughly doubles (145 QALYs per $m, not shown in table) while the patient population roughly halves (from 677 prevalent cases, to 349 cases, not displayed).

Table 16: Cost-Effectiveness of LAAC vs non-treatment in patients contraindicated (excluding CHA_2DS_2-VASc ≥ 6 criterion)

QALYs per $m		Initial CHA2DS2-VASc ≥ 2								
		1	2	3	4	5	6	7	8	9
Start Age	50	31	60	108	163	498	-1061	2899		
	55	21	45	72	105	264	2311	818		
	60	15	32	48	77	149	345	666		
	65		11	23	33	61	107	139	342	
	70		7	14	20	35	49	71	171	
	75			4	9	14	23	22	44	65
	80			2	4	7	9	9	20	18
	85			0	1	2	4	4	7	8
	90			0	0	1	1	1	1	0

Negative signs indicate cost-saving with health gains

3.6 Sensitivity Analyses

Sensitivity analyses find that the estimated cost-effectiveness of LAAC depends mostly on the effectiveness of treatment in reducing the risk of stroke. The cost-effectiveness estimate is relatively insensitive to the risk of complications or procedure failure across plausible ranges; to the cost of stroke; or to the health-related quality of life decrement attributed to stroke.

For computational efficiency the sensitivity analysis reports findings for a patient cohort contraindicated to (N)OAC aged 60-years with an average CHA_2DS_2-VASc of 3.37. Baseline characteristics for this patient population are shown in Table 17.

Table 17: Patient Characteristics Sensitivity Analysis

Condition	Model Settings	CHA_2DS_2-VASc Points	Average Points
CHF	34.2%	1	0.342
Hypertension	100%	1	1
Age ≥75	0%	1	0
Diabetes	29.7%	1	0.297
Prior stroke	45.6%	2	0.912
Vascular disease	41.9%	1	0.419
Age≥65	0%	1	0
Sex	40.1%	1	0.401
Total			**3.37**

The baseline cost-effectiveness of LAAC for this patient population is 63 QALYs per million.

Table 18: Cost-effectiveness of LAAC in a 60-year old (CHA_2DS_2-VASc 3.37) contraindicated to (N)OAC

Strategy	Modelled life-time cost per person (discounted)	Incremental Cost per person	QALY (per person, discounted)	Incremental QALYs gained per person	Cost per QALY (per person, discounted)	QALYs gained per $million
LAAC	$23,000	$9,000	8.34	0.55	$16,000	63
No Treatment	$14,000		7.79			

3.6.1 Complications

Probability of procedure-related complications are varied based on the highest results available from various studies. Table 19 suggests that the overall cost-effectiveness is moderately sensitive to procedure complication rates. ICAG advised that the adverse event rates observed in the EWOLUTION were more reflective of the event rates likely to occur in the New Zealand setting, compared with earlier RCT data.

Table 19: Sensitivity to complication rates

	Estimate	High
Probability of device embolization	0.2%	1.3%
Source	EWOLUTION	ASAP
Probability of major bleed	2.6%	6.0%
Source	EWOLUTION	PROTECT-AF
Probability of pericardial effusion	0.5%	4.0%
Source	EWOLUTION	PROTECT-AF
Probability of stroke	0.7%*	1.1%
Source	PREVAIL	ASAP
ICER (NZD per QALY gained)	$16,000	$23,000

* There were no reported procedural strokes in the EWOLUTION or CAP registries

3.6.2 Procedure failure rate

Probability of procedure failure is varied based on the highest results available from various studies. Cost-effectiveness is relatively insensitive to changes in the procedure failure rate.

Table 20 Sensitivity to procedure failure rate

	Estimate	High
Probability of unsuccessful procedure	1.5%	9.1%
Source	EWOLUTION	PROTECT-AF
ICER	$16,000	$18,500
QALYs per $million	63	54

3.6.3 Cost of stroke

The cost of stroke was tested across a range of +/- minus 25%, as this parameter is relatively uncertain. As would be expected the cost-effectiveness of LAAC improves if the cost of each stroke prevented is higher.

Table 21 Sensitivity to first year cost of stroke

	-25%	Estimate	25%
Cost in year of stroke	$19,500	$26,000	$32,500
Annual cost in years after stroke if no recovery	$6,075	$8,100	$10,125
ICER	$20,000	$16,000	$12,500
QALYs per $million	50	63	80

3.6.4 Treatment effectiveness

Relative risk of stroke with LAAC versus no treatment is varied based on the results from the FDA indirect placebo comparison. Table 22 shows that the overall cost-effectiveness of the proposal varies approximately in proportion to changes in the estimate of treatment effect size.

Table 22 Sensitivity to treatment effectiveness

	Estimate		
	CAP*	**PROTECT-AF**	**PREVAIL**
Relative risk of stroke with LAAC	17%	23%	38%
ICER	$7,700	$9,500	$16,000
QALYs per $million	123	105	63

*Similarly, the authors of the EWOLUTION study indicated a RR of 16% with 12 months of follow-up.

Using the results from the study most favourable to LAAC gives a value of 123 QALYs per $million invested, almost twice as much as for the PREVAIL analysis.

3.6.5 Health-related quality of life for stroke

The utility scores for stroke were varied between the lower and upper bounds estimates from TAR 165. Cost-effectiveness is very insensitive to changes in the utility values of stroke.

Table 23: Sensitivity of results to choice of HR-QOL weights for stroke at different times

State	Measure	Low	Base Case	High
0-3 months	EQ5D dimensions scores	3,3,3,2,2	(2-3),(2-3),(2-3),2,2	2,2,2,2,2
	HR-QOL	0.087	0.275	0.464
4-12 months AND disabling stroke	EQ5D dimensions scores	2,2,2,2,1	(1-2),2,2(1-2),1	1,2,2,1,1
	HR-QOL	0.556	0.636	0.711
	ICER	$15,000	16,000	17,000
	QALYs per $million	67	63	58

4 Budget Impact Analysis

4.1 Population

The numbers of AF patients contraindicated to oral anticoagulation are estimated in section 1.2.8 above. In brief, it appears that there are between 570 and 1800 people over the age of 65 who are contraindicated to (N)OAC. Incidence (the number of people newly reaching the treatment threshold) is between 88 and 275 patients per year.

4.2 Uptake

The initial proposal from CSANZ indicated that LAAC could be offered in five centres, each treating 20 patients in the first year and 40 in the second year. This would imply 100 procedures per annum in the first year and 200 procedures thereafter. On review, ICAG considered that

treatment volumes were likely to be less than this noting that “the long-term annual incidence may be lower than 200 per year, once the prevalent pool has been treated.” (ICAG, 2017-08-23)

The number of incident and prevalent cases that meet ICAG’s selection criteria is difficult to estimate. Noting that not all patients contraindicated to (N)OAC’s are eligible under the criteria. Based on ICAG’s advice, PHARMAC revised its patient volume estimate down to 100 patients in the first year, and 150 patients in subsequent years, with a limited growth path of an additional patient per annum. Total estimated patient volumes over 5-years are similar to estimated patient volumes in Australia, accounting for demographics. (Table 24)

Table 24 Patient Numbers

		Year					
		1	2	3	4	5	Total
Scenario	PHARMAC estimate	100	150	151	152	153	706
	Number of patients based on MSAC Public Summary Document	57	111	161	208	252	787

4.3 Budget impact

PHARMAC staff estimate the proposal has a 5-year budgetary impact to DHBs of $9 million. This assumes a procedure cost of $17,000, including a device cost of $7,900. Cost-savings are attributed to strokes prevented, $26,000 for each stroke patients in the first year, and $8,100 in subsequent years for each person suffering a disabling stroke.

Table 25: Budget Impact

Year	**1**	**2**	**3**	**4**	**5**	**NPV @8%**
Procedures	100	150	151	152	153	
Strokes Prevented	2	7	11	15	18	
Costs						
Device	$0.8m	$1.2m	$1.2m	$1.2m	$1.2m	
Procedure	$0.9m	$1.3m	$1.3m	$1.3m	$1.4m	
Complications	$16k	$24k	$25k	$25k	$25k	
Total	$1.7m	$2.5m	$2.6m	$2.6m	$2.6m	
Savings						
Strokes Prevented	-$50k	-$170k	-$300k	-$400k	-$500k	
Net Sector Cost	**$1.6m**	**$2.4m**	**$2.3m**	**$2.2m**	**$2.1m**	**$9.0m**

4.4 Sensitivity and Scenario Analyses – Budget Impact

This section tests how sensitive the predicted costs are to the key parameters in the budget impact analysis.

The budget impacts of the base case and an alternative scenario are given in Table 26 and Table 27.

Table 26: Base Case Budget Impact

Year	1	2	3	4	5	NPV @8%
Procedures	100	150	151	152	153	
Strokes Prevented	2	7	11	15	18	
Costs	$1.7m	$2.5m	$2.6m	$2.6m	$2.6m	
Savings	-$50k	-$170k	-$300k	-$400k	-$500k	
Net Sector Cost	**$1.6m**	**$2.4m**	**$2.3m**	**$2.2m**	**$2.1m**	**$9.0m**

Compared with the base-case, Australia's MSAC assumed lower procedure volumes in the first 2 years. The assumptions behind the uptake rate are not explained in publicly available information from MSAC. Total patient volumes, and the 5-year NPV, are similar under the two scenarios.

Table 27: Budget Impact – Australian take-up patterns

Year	1	2	3	4	5	NPV @8%
Procedures	57	111	161	208	252	
Strokes Prevented	1	5	12	21	30	
Costs	$1.0m	$1.9m	$2.7m	$3.5m	$4.3m	
Savings	-$30k	-$130k	-$300k	-$550k	-$800k	
Net Sector Cost	**$0.9m**	**$1.7m**	**$2.4m**	**$3.0m**	**$3.4m**	**$9.5m**

Table 28 presents the expected net health sector cost from changing the cost of the device from $6,000 to $10,000 (base-case $7,900) and changing the non-device procedure costs from $7,000 to $12,000 (base-case $9,000). All other costs, including complications and savings from strokes avoided are assumed to remain constant. These ranges are indicative only. The 5-year budgetary impact ranges from $6.8 million to $10.4 million under the low and high cost scenarios, respectively.

Table 28: Budget Impact – Sensitivity to Device and Procedure Costs

Year	**1**	**2**	**3**	**4**	**5**	**NPV @8%**
Procedures	100	150	151	152	153	
Base case						
Device	$0.8m	$1.2m	$1.2m	$1.2m	$1.2m	$4.8m
All other procedure related costs and savings	$0.8m	$1.2m	$1.1m	$1.0m	$0.9m	$4.2m
Net sector costs	$1.6m	$2.4m	$2.3m	$2.2m	$2.1m	**$9.0m**
Low cost estimate						
Device	$0.6m	$0.9m	$0.9m	$0.9m	$0.9m	$3.6m
All other procedure related costs and savings	$0.7m	$0.9m	$0.8m	$0.7m	$0.6m	$3.1m
Net sector costs	$1.3m	$1.8m	$1.7m	$1.6m	$1.5m	**$6.8m**
High cost estimate						
Device	$1.0m	$1.5m	$1.5m	$1.5m	$1.5m	$6.0m
All other procedure related costs and savings	$0.9m	$1.2m	$1.1m	$1.0m	$0.9m	$4.4m
Net sector costs	$1.9m	$2.7m	$2.6m	$2.5m	$2.4m	**$10.4m**

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.
2. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. The Annals of thoracic surgery. 1996;61(2):755-9.
3. R CL. Etiology, classification, and epidemiology of stroke. UpToDate. 2017.
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.
5. J MW. Stroke in patients with atrial fibrillation. UpToDate. 2017.
6. Feigin VL, Krishnamurthi RV, Barker-Collo S, McPherson KM, Barber PA, Parag V, et al. 30-year trends in stroke rates and outcome in Auckland, New Zealand (1981-2012): a multi-ethnic population-based series of studies. PloS one. 2015;10(8):e0134609.
7. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360.
8. Reddy VY, Akehurst RL, Armstrong SO, Amorosi SL, Brereton N, Hertz DS, et al. Cost effectiveness of left atrial appendage closure with the Watchman device for atrial fibrillation patients with absolute contraindications to warfarin. Europace. 2016:euv412.
9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). European Journal of Cardio-Thoracic Surgery. 2016:ezw313.
10. Tomlin AM, Lloyd HS, Tilyard MW. Atrial fibrillation in New Zealand primary care: Prevalence, risk factors for stroke and the management of thromboembolic risk. European Journal of Preventive Cardiology. 2016:2047487316674830.
11. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European heart journal. 2006;27(8):949-53.
12. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946-52.
13. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. European heart journal. 2013;34(14):1061-7.
14. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. Jama. 2011;305(20):2080-7.
15. Kapil K. Overview of atrial fibrillation. UpToDate. 2017.
16. ICAG. Record of the Interventional Cardiology Advisory Group meeting held at PHARMAC on 17 February 2017. 2017.
17. Sasse A, Matsis Phillip Proposal: LEFT ATRIAL APPENDAGE INTERVENTIONAL CLOSURE IN NEW ZEALAND - ON BEHALF OF THE NZ COMMITTEE OF CSANZ. PHARAMC internal link A959706. 2016.
18. CMS. Centre for Medicare and Medicaid Services. Decision Memo for Percutaneous Left Atrial Appendage (LAA) Closure Therapy (CAG-00445N. 2016.
19. GlaxoSmithKline. Marevan Tablets MedSafe Data Sheet. 2015.
20. Boehringer-Ingelheim. Medsafe Data Sheet Pradaxa (Dabigatran etexilate. 2015.
21. New_Zealand_Formulary. Dabigatran Etexilate. 2017.
22. New_Zealand_Formulary. Warfarin sodium. 2017.
23. Wilkins B, Matsis P, Sasse A. Left Atrial Appendage Closure. Experience from Wellington Regional Hospital. Heart, Lung and Circulation. 2016;25:S19.

24. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). Journal of the American College of Cardiology. 2013;61(25):2551-6.
25. Steinberg BA, Greiner MA, Hammill BG, Curtis LH, Benjamin EJ, Heckbert SR, et al. Contraindications to anticoagulation therapy and eligibility for novel anticoagulants in older patients with atrial fibrillation. Cardiovascular therapeutics. 2015;33(4):177-83.
26. BPAC. Management of atrial fibrillation in general practice 2011 [Available from: http://www.bpac.org.nz/BPJ/2011/october/af.aspx.
27. New_Zealand_Formulary. Rivaroxaban 2018 [Available from: https://nzf.org.nz/nzf_1508.
28. Hijazi ZM, Saw. Jacqueline Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation 2016 [Available from: https://www.uptodate.com/contents/nonpharmacologic-therapy-to-prevent-embolization-in-patients-with-atrial-fibrillation?source=search_result&search=Left%20Atrial%20Appendage%20Occlusion&selectedTitle=1~150.
29. SERVICES FDOHH. PMA Approval oder for the WATCHMAN LAA Closure Technology 2015 [Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013A.pdf.
30. FDA. WATCHMAN LAA Closure Technology - P130013 2015 [Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm440621.htm.
31. Saw J, Lempereur M. Percutaneous left atrial appendage closure: procedural techniques and outcomes. JACC: Cardiovascular Interventions. 2014;7(11):1205-20.
32. Business-Wire. AGA Medical Receives Conditional IDE Approval from FDA to Study Use of AMPLATZER® Cardiac Plug to Close the Left Atrial Appendage 2010 [Available from: http://www.businesswire.com/news/home/20100324006877/en/AGA-Medical-Receives-Conditional-IDE-Approval-FDA.
33. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. The Lancet. 2009;374(9689):534-42.
34. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation 2.3-year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. Circulation. 2013;127(6):720-9.
35. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Jama. 2014;312(19):1988-98.
36. Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.
37. Holmes DR, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: A patient-level meta-analysis. Journal of the American College of Cardiology. 2015;65(24):2614-23.
38. Xu H, Xie X, Wang B, Ma S, Wang F. Efficacy and Safety of Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Meta-analysis of Contemporary Studies. Heart, lung & circulation. 2016;25(11):1107-17.
39. Bode WD, Patel N, Gehi AK. Left atrial appendage occlusion for prevention of stroke in nonvalvular atrial fibrillation: a meta-analysis. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing. 2015;43(1):79-89.
40. Briceno DF, Villablanca P, Cyrille N, Massera D, Bader E, Manheimer E, et al. Left Atrial Appendage Occlusion Device and Novel Oral Anticoagulants Versus Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Circulation Arrhythmia and electrophysiology. 2015;8(5):1057-64.

41. Sahay S, Nombela-Franco L, Rodes-Cabau J, Jimenez-Quevedo P, Salinas P, Biagioni C, et al. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials. Heart. 2016:heartjnl-2016-309782.
42. Price MJ, Reddy VY, Valderrabano M, Halperin JL, Gibson DN, Gordon N, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN randomized trial experience. JACC: Cardiovascular Interventions. 2015;8(15):1925-32.
43. Murphy LA, Teljeur C, Moran PS, Harrington P, Ryan M, Williams D, et al. Left atrial appendage closure versus oral anticoagulation for preventing stroke in people with atrial fibrillation. The Cochrane Library.
44. FDA. FDA Executive Summary October 8, 2014 meeting of the Circulatory System Devices Panel, Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy, P130013 2014.
45. Sharma D, Reddy VY, Sandri M, Schulz P, Majunke N, Hala P, et al. Left Atrial Appendage Closure in Patients With Contraindications to Oral Anticoagulation. Journal of the American College of Cardiology. 2016;67(18):2190-2.
46. Holmes DR, Reddy VY, Buchbinder M, Stein K, Elletson M, Bergmann MW, et al. The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial. American Heart Journal. 2017;189:68-74.
47. ClinicalTrials.gov. NCT02928497: Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO). 2017.
48. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. Heart Rhythm. 2017.
49. Masoudi FA, Calkins H, Kavinsky CJ, Drozda JP, Gainsley P, Slotwiner DJ, et al. 2015 ACC/HRS/SCAI left atrial appendage occlusion device societal overview. Journal of the American College of Cardiology. 2015;66(13):1497-513.
50. FDA. FDA Executive Summary Prepared for the December 11, 2013 meeting of the Circulatory System Devices Panel 2013 [Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM377356.pdf.
51. Waksman R, Pendyala LK. Overview of the Food and Drug Administration circulatory system devices panel meetings on WATCHMAN left atrial appendage closure therapy. The American journal of cardiology. 2015;115(3):378-84.
52. FDA. WATCHMAN LAA Closure Technology - P130013. 2015.
53. MSAC. Public Summary Document. Application No. 1347.1 – Left Atrial Appendage Closure for stroke prevention in patients with non-valvular Atrial Fibrillation. 2016.
54. Main ML, Fan D, Reddy VY, Holmes DR, Gordon NT, Coggins TR, et al. Assessment of device-related thrombus and associated clinical outcomes with the WATCHMAN left atrial appendage closure device for embolic protection in patients with atrial fibrillation (from the PROTECT-AF trial). The American journal of cardiology. 2016;117(7):1127-34.
55. Wei Z, Zhang X, Wu H, Xie J, Dai Q, Wang L, et al. A meta-analysis for efficacy and safety evaluation of transcatheter left atrial appendage occlusion in patients with nonvalvular atrial fibrillation. Medicine. 2016;95(31).
56. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, Van Tassel R, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am Heart J. 2006;151(5):956-61.
57. Landmesser U, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2017;13(7):867-76.
58. NICE. Percutaneous occlusion of the left atrial ercutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for appendage in non-valvular atrial fibrillation for the pre the prev vention of thromboembolism (IPG349). 2010.

59. Ontario HQ. Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment. Ontario Health Technology Assessment Series. 2017;17(9):1.
60. MSAC. Final protocol to guide the assessment of transcatheter occlusion of the left atrial appendage for patients with non-valvular atrial fibrillation 2014.
61. Saw J, Bennell MC, Singh SM, Wijeysundera HC. Cost-effectiveness of left atrial appendage closure for stroke prevention in atrial fibrillation patients with contraindications to anticoagulation. Canadian Journal of Cardiology. 2016;32(11):1355. e9-. e14.
62. PHARMAC. Prescription for Pharmacoeconomic Analysis. Methods for cost-utility analysis. Version 2.2. 2015.
63. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation. Stroke. 2010;41(12):2731-8.
64. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2014:CIR. 0000000000000041.
65. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality. Circulation. 2003;107(23):2920-5.
66. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna W, et al. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. European heart journal. 2006:936-41.
67. Lubitz SA, Benjamin EJ, Ellinor PT. Atrial fibrillation in congestive heart failure. Heart failure clinics. 2010;6(2):187-200.
68. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ open. 2016;6(1):e010210.
69. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circulation research. 2015;116(9):1509-26.
70. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.
71. Murabito JM, D'agostino RB, Silbershatz H. Intermittent Claudication: A Risk Profile from the Framingham Heart Study. Journal of Vascular & Interventional Radiology. 1998;9(1):172.
72. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas J-L, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. Jama. 2006;295(2):180-9.
73. David S. Epidemiology of and risk factors for atrial fibrillation. Up-to-Date. 2017.
74. Lin Y-S, Tung T-H, Wang J, Chen Y-F, Chen T-H, Lin M-S, et al. Peripheral arterial disease and atrial fibrillation and risk of stroke, heart failure hospitalization and cardiovascular death: a nationwide cohort study. International journal of cardiology. 2016;203:204-11.
75. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. bmj. 2016;354:i4482.
76. Ministry_Of_Health. Mortality Data. 2013.
77. Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. Pharmacoeconomics. 2006;24(10):1021-33.
78. Piper D. NEW AND EMERGING CARDIAC TECHNOLOGIES IN AUSTRALIAN AND NEW ZEALAND PUBLIC HEALTH SERVICES OVER THE NEXT DECADE. 2013.
79. Te Ao BJ, Brown PM, Feigin VL, Anderson CS. Are stroke units cost effective? Evidence from a New Zealand stroke incidence and population-based study. International Journal of Stroke. 2012;7(8):623-30.
80. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Estimating the Long-Term Costs Of Ischemic and Hemorrhagic Stroke for Australia New Evidence Derived From the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2009;40(3):915-21.