Healthcare Improvement Scotland | SHTG Advice on health technologies

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In response to an enquiry from the National Advisory Committee for Heart Disease

Left atrial appendage occlusion (LAAO) in patients with atrial fibrillation who have contraindications to oral anticoagulation

Advice for NHSScotland

Left atrial appendage occlusion (LAAO) may be offered to patients with non-valvular atrial fibrillation deemed to be at high risk of ischaemic stroke, who have absolute contraindications to oral anticoagulation with warfarin and direct oral anticoagulants. Prior to undergoing the LAAO procedure, an individual patient risk assessment must be carried out by a multidisciplinary team. The potential future benefits of LAAO, the risks associated with the procedure, and the need for long-term antiplatelet therapy, should be discussed with each patient prior to making a treatment decision.

LAAO procedure volume per centre should be maximised to support optimal patient outcomes and ensure clinical experience is achieved and retained.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

What were we asked to look at?

The National Advisory Committee for Heart Disease asked us to look at a percutaneous intervention, left atrial appendage occlusion (LAAO), in patients with atrial fibrillation and contraindications to oral anticoagulation.

Why is this important?

Patients with atrial fibrillation have a substantially increased risk of ischaemic stroke compared with the general population. The standard of care for ischaemic stroke prevention in patients with atrial fibrillation is long-term anticoagulant therapy with warfarin or a direct oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban). However, some patients with atrial fibrillation have contraindications to oral anticoagulation, meaning they cannot receive this treatment and hence remain at increased risk of having an ischaemic stroke. LAAO involves inserting a device designed to block the left atrial appendage of the heart where many of the blood clots that lead to ischaemic stroke in atrial fibrillation patients are thought to form. LAAO may therefore be an option for patients with atrial fibrillation and contraindications to oral anticoagulation.

What was our approach?

We produced SHTG Advice based on a rapid review of published evidence on the clinical effectiveness, cost effectiveness and safety of LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation. Information on our SHTG Advice product can be found here.

What next?

The National Services Division will use the SHTG Advice when considering inclusion of LAAO in the National Percutaneous Mitral Valve and Related Interventions Service. The National Advisory Committee for Heart Disease will also consider the SHTG Advice on this topic.

Key points from the evidence review

- The presence of atrial fibrillation increases the risk of ischaemic stroke by up to 5-fold compared with the general population. Prevalence of atrial fibrillation increases from approximately 4% of people aged over 60, to 10% of those aged 80 or older.
- Clinical effectiveness evidence for left atrial appendage occlusion (LAAO) in patients with atrial fibrillation and contraindications to oral anticoagulation is limited to single-arm cohort and registry studies.
    - Peri-procedure ischaemic stroke and mortality rates ranged from 0% to 1% of patients treated with LAAO.
    - Ischaemic stroke during 12 months follow-up ranged from 0.6% to 6% of patients.
    - Seven studies, with a median of 12 months follow-up, compared observed ischaemic stroke rates during follow-up with predicted annual ischaemic stroke rates based on mean baseline CHA_2DS_2-VASc scores (similar to an historical cohort comparison). These studies reported ischaemic stroke risk reductions of 57% to 84% in patients treated with LAAO. These results should be interpreted with caution given the limitations of studies that use historical cohorts as comparator groups.
- A composite of all major adverse events was reported in six studies, with event rates ranging from 0% to 5.5%. All three studies reporting peri-procedure cardiac tamponade (a cardiac emergency) had an associated event rate of 0.9%.
- Higher annual volume of LAAO procedures within a hospital (≥18 per annum) was associated with a significant decrease in a composite of mortality and safety compared with hospitals performing <3 procedures per annum. Operator experience of performing the procedure was also associated with significant reductions in complication rates.
- LAAO occlusive devices cost approximately £4,000 per unit (plus VAT). English registry-based estimates for the complete LAAO procedure range from £9,500 to £13,300 per patient. Based on these estimates, LAAO was found to be cost incurring from an NHS perspective. When social care costs, such as home care or nursing home care for patients with stroke-related impairment of daily activities, were added to NHS perspective, LAAO became cost-neutral with a small per-patient saving.
- In 2018 NHS England agreed to routinely fund LAAO for patients with atrial fibrillation, an elevated stroke risk, and pre-specified, physician-assessed contraindications to oral anticoagulation (see Organisational Issues on page 27 for details). Initial case volume in England is estimated at 400 LAAO procedures per annum, increasing to 1,000 per annum in 5 years' time.

SHTG Committee considerations

- LAAO is a prophylactic procedure and therefore confers no immediate clinical or symptomatic benefit. There is an immediate risk of significant complications, including mortality, and this should form part of the doctor-patient discussion.
- A range of adverse events were noted as being associated with the LAAO procedure. The Committee made particular reference to the proportion of serious adverse events relating to LAAO and how this should be considered during shared decision-making.
- Patients in Scotland are currently selected for LAAO based on a CHA_2DS_2-VASC score ≥3, high surgical risk or inoperable, absolute contraindications to oral anticoagulation, and a minimum post-procedure life expectancy of 2 years. It was agreed that this level of rigour in selection of potential candidates for LAAO should continue in future.
- There were three percutaneous LAAO procedures in Scotland April 2017 to March 2018. The Committee discussed the very low numbers of patients currently undergoing LAAO in Scotland and noted that numbers may rise in future, should the procedure be commissioned nationally.
- The Committee had reservations about reaching conclusions based on the lack of high quality research data, since there are no RCTs that assess LAAO in the specific population of interest – patients with atrial fibrillation and contraindications to oral anticoagulation.

Contents

Definitions

Cardiac tamponade: an accumulation of fluid, blood, pus, or air within the pericardial space surrounding the heart. This creates an increase in intra-pericardial pressure, restricting cardiac filling and decreasing cardiac output. Cardiac tamponade is a cardiac emergency that can be fatal if not quickly diagnosed and treated[1].

CHA_2DS_2-VASc score: a clinical prediction rule for estimating annual stroke risk in patients with atrial fibrillation. The score is calculated based on gender, age, and history of vascular disease, congestive heart failure, hypertension, diabetes and stroke[2].

Ischaemic stroke: when the blood supply to the brain is blocked by a blood clot resulting in the brain being starved of oxygen and brain cells becoming damaged[3].

Pericardial effusion: excess fluid collecting in the pericardial sac surrounding the heart[4]. Pericardial effusion with sufficient pressure to adversely affect heart function is called cardiac tamponade.

Peri-procedure: for the purposes of this review peri-procedure was defined as events occurring during the LAAO procedure, in hospital (index hospitalisation) or within 7 days of the procedure.

Literature search

A recent systematic review by Baman *et al* (2018)[5], which assessed the use of left atrial appendage occlusion (LAAO) in the correct patient population, was identified during initial scoping work for this project. Consequently the literature search described below was limited to primary studies published after the search dates in the systematic review.

The primary literature was systematically searched on 11 Jan 2019 using the Medline and Embase databases. Search results for clinical effectiveness and safety outcomes were limited to English language studies published after April 2017 (date of search in Baman *et al*, 2018). No restrictions were applied for study type. Studies were selected for inclusion if they were prospective studies that recruited a minimum of 100 patients. These criteria were not imposed on studies on cost effectiveness, volume-outcome, or learning curve.

Concepts used in all searches included: left atrial/atrium appendage and closure, occlusion, excision, removal, procedure, implant, suture. A full list of resources searched and terms used are available on request.

Introduction

Atrial fibrillation is the most common cardiac arrhythmia with an estimated population prevalence in England of between 1.5% and 5% depending on the source data used[6-8]. The prevalence in Scotland is assumed to be similar. People with atrial fibrillation have an irregular and often abnormally fast heart rate[9].

The presence of atrial fibrillation is an independent risk factor for ischaemic stroke since the irregular heart beat can cause the chambers of the heart to not empty completely, resulting in blood clots

forming in the blood left behind. Approximately 90% of intra-cardiac blood clots in patients with atrial fibrillation are thought to form in the left atrial appendage[5]. The left atrial appendage is a small opening off the side wall of the left atrium. This appendage varies in shape, length (16-51mm), volume (0.7-19.2ml), and diameter (5-40mm)[10]. An estimated 50% of ischaemic strokes that occur in patients with atrial fibrillation are thought to be a consequence of blood clots becoming detached from the atrial appendage, entering the circulation and blocking a blood vessel in the brain[11]. The presence of atrial fibrillation increases the risk of ischaemic stroke by up to 5-fold compared with the general population[5] and at least 15-20% of all ischaemic strokes are associated with atrial fibrillation[10].

Most patients with atrial fibrillation are treated with long-term oral anticoagulant therapy to reduce the risk of ischaemic stroke by limiting blood clot formation[10]. However, a proportion of patients with atrial fibrillation have relative or absolute contraindications to oral anticoagulation. Although the term 'contraindication' is open to interpretation, the most commonly accepted contraindications to oral anticoagulation are a history of major bleeding while taking an oral anticoagulant or a recent history of intracranial haemorrhage/bleeding (Dr D Northridge, Consultant Cardiologist, NHS Lothian. Personal communication, 24 Jan 2019). These patients are currently largely unprotected from the increased risk of stroke associated with atrial fibrillation as the alternative treatment, antiplatelet therapy, is less effective for stroke prevention (Prof. K Muir, SINAPSE Professor of Clinical Imaging & Consultant Neurologist, University of Glasgow. Personal communication, 29 Mar 2019)[12]. LAAO is a prophylactic percutaneous intervention that could potentially reduce the risk of stroke in patients with atrial fibrillation who have contraindications to oral anticoagulation[10].

Research question

What is the clinical effectiveness, safety and cost effectiveness of LAAO in patients with atrial fibrillation at high risk of ischaemic stroke who have relative or absolute contraindications to oral anticoagulation?

Health technology description

LAAO is a percutaneous interventional procedure. The patient is given a general anaesthetic, or a local anaesthetic plus sedation, then a guide sheath is inserted through a large vein in the groin and passed up to the right atrium of the heart[13]. The sheath is then moved into the left atrium of the heart, either through a naturally existing hole in the atrium wall or through a small incision made by the cardiologist. The sheath is manoeuvred to the mouth of the left atrial appendage and an occlusive device is delivered through the sheath into the appendage. Once the device is in place (covering the entrance to the left atrial appendage) the sheath is removed.

There are a number of occlusive devices available for use in LAAO procedures:

- WATCHMAN™ (Boston Scientific)
- AMPLATZER™ Cardiac Plug (St Jude Medical Inc.)
- AMPLATZER™ Amulet (Abbott)

- Ultraseal/Ultrasept (Cardia Inc.)
- LAmbre™ LAA Closure System (Lifetech Scientific)
- WaveCrest® (Biosense Webster Inc.)

Each occlusive device looks slightly different but all have common features including a sheath delivery system, a mesh or fabric covered surface for occluding the appendage orifice, and hooks or barbs to hold the device in place[14]. Most occlusive devices come in a range of sizes to allow for variations in individual patient anatomy.

In the NHS England Commissioning through Evaluation (CtE) registry, patients with atrial fibrillation and contraindications to oral anticoagulation underwent LAAO using the AMPLATZER™ Amulet (46.9%), WATCHMAN™ (38.1%) and AMPLATZER™ Cardiac Plug (7.7%) devices[15].

Epidemiology

Atrial fibrillation

Scotland-specific data on atrial fibrillation and contraindication to oral anticoagulation was not available. Prevalence estimates for atrial fibrillation in England vary between 1.5% and 5% depending on the source data used[6-8]. It is assumed prevalence in Scotland would be similar. In a recent commissioning report the prevalence of diagnosed atrial fibrillation in the English population was estimated as 1.7% using data from the Quality and Outcomes Framework for general practice[12]. Based on this estimate, atrial fibrillation affects approximately 800,000 people in England, with 664,000 patients having a risk profile indicating the need for treatment[12].

The prevalence of atrial fibrillation increases with age. Over the age of 60, atrial fibrillation affects approximately 4% of the Scottish population and this rises to 10% of those aged 80 or older[16]. Atrial fibrillation is more common in women than men across all ages[7].

Atrial fibrillation and stroke

The risk of stroke in patients with atrial fibrillation is up to five times higher than in the general population, and 15-20% of all ischaemic strokes occur in patients with atrial fibrillation[10]. Strokes in patients with atrial fibrillation also tend to be more severe, and associated with higher mortality and morbidity, compared with strokes in people without atrial fibrillation[10, 16]. In 2017 there were 9,345 confirmed hospital admissions for stroke in Scotland, 87% of which were for ischaemic stroke[16]. This gives a crude rate of 150.5 ischaemic strokes per 100,000 population per year in Scotland[16].

Contraindications to oral anticoagulation

Owing to variation in the criteria used to define 'contraindications' in relation to oral anticoagulation, estimates of the proportion of patients with atrial fibrillation that fall into this category are highly variable[12]. An Italian consensus statement estimated that 20% of atrial fibrillation patients have contraindications to oral anticoagulation[10]. This is considerably higher than the UK-based estimate of 6% of patients diagnosed atrial fibrillation[12, 17]. Based on the lower, UK-specific, estimate approximately 40,000 patients with atrial fibrillation in England have one or more contraindications to oral anticoagulation (Dr D Northridge, Consultant Cardiologist, NHS Lothian.

Personal communication, 24 Jan 2019)[12]. Estimates of the number of patients in Scotland with atrial fibrillation and one or more contraindications to oral anticoagulation are approximately 4,000 to 5,500[a].

A cross-sectional study in the UK indicated that in 2015 an estimated 67.2% (95% confidence interval (CI) 65.6% to 68.8%) of patients with atrial fibrillation and contraindications to oral anticoagulation were still being prescribed these medications[6].

Guidelines

Three guidelines were identified that contained recommendations on the use of LAAO in patients with atrial fibrillation[8, 18, 19]. These guidelines all recommend use of LAAO only in patients with atrial fibrillation and contraindications to oral anticoagulation (table 1). The NICE guidance specifically recommends LAAO should not be offered as an alternative to oral anticoagulation in patients who have no contraindications to these medications.

Table 1: guideline recommendations on LAAO in patients with atrial fibrillation

Guideline	Recommendations
American College of Cardiology, American Heart Association & the Heart Rhythm Society (2019)[19]	LAAO may be considered in patients with atrial fibrillation at increased risk of stroke who have contraindications to long-term anticoagulation.
European Society of Cardiology (2016)[18]	LAAO may be considered in patients with atrial fibrillation and contraindications to long-term anticoagulant therapy, such as a previous life-threatening bleed without a reversible cause.
NICE (2014)[8]	Consider LAAO if anticoagulation is contraindicated or not tolerated, and discuss the benefits and risks of LAAO with the person. Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.

Clinical effectiveness

Two randomised controlled trials (RCTs) have been conducted on LAAO in patients with atrial fibrillation: the PREVAIL and PROTECT-AF trials[20, 21]. In both studies the WATCHMAN™ occlusive device was compared with warfarin (an oral anticoagulant) and patients with contraindications to

[a] Based on the estimated number of patients in this category in England there would be approximately 4,000 patients in Scotland with atrial fibrillation and one or more contraindications to oral anticoagulation. If published prevalence estimates are used, approximately 5,500 patients in Scotland would have atrial fibrillation and contraindications to oral anticoagulation: prevalence of atrial fibrillation 1.7%; contraindications to oral anticoagulation 6%; Scotland population 5.4 million.

oral anticoagulation were excluded. The relevant evidence for this rapid review therefore consists of one systematic review of single-arm studies[5], eight single-arm primary studies published after the search inclusion dates of the systematic review[14, 22-28], and data from the CtE registry in England which were included alongside the published primary literature[15, 29].

The systematic review incorporated 12 registry studies that related to LAAO[5]. Three additional registries in the systematic review evaluated the LARIAT® suture delivery system for atrial appendage closure; data from these studies were not used in this evidence review as LARIAT® was considered to be a different procedure (Dr D Northridge, Consultant Cardiologist, NHS Lothian. Personal communication, 24 Jan 2019).

The systematic review contained potential methodological flaws and there were concerns about the quality of the analyses. The pooled weighted analysis reported in the systematic review was unclear as to which studies had been included, how the pooled estimates were calculated, and whether the results were based on peri-procedure or long-term follow-up data. For these reasons, data from the included primary studies were extracted. Baseline patient characteristics from the 12 relevant studies extracted from the systematic review are reported in table 2. Although the review authors state that they included studies in "*patients with atrial fibrillation for whom anticoagulation is contraindicated and for whom percutaneous LAA* [left atrial appendage] *occlusion/closure may be indicated*"[5], three of the registry studies involved an unspecified proportion of patients eligible for oral anticoagulation.

Baseline characteristics for the nine primary cohort studies/registry published after the systematic review are also presented in table 2. Overall, the baseline characteristics of patients recruited into these primary studies indicate that the majority of patients with atrial fibrillation enrolled in each study had contraindications to oral anticoagulation and a mean CHA_2DS_2-VASc score ≥3. In summary:

- The most common indications for LAAO were a patient history of major bleeding, high risk of bleeding and a history of bleeding or stroke while taking oral anticoagulants. Between 11% and 65% of study participants had a prior history of stroke and 61% to 90% had a history of bleeding (appendix 2). As shown in table 2 however, the definition and interpretation of contraindications to oral anticoagulation varied across studies.

- A total of 11,482 patients were included in the studies in this rapid review, with individual studies recruiting between 101 and 3,822 patients. Two studies were single centre[14, 26]. Patients were from England, the USA, Canada, Europe, China and Korea.

- Mean age of study participants ranged from 64.2 (standard deviation (SD) 8.6) years to 77.6 (SD 8.9) years, and 50% to 72.2% of patients were male. The mean CHA_2DS_2-VASc score ranged from 3.6 (SD 1.5) to 5.0 (SD 2.0) indicating that study participants generally had a high baseline risk of ischaemic stroke.

One of the main risks of bias in single-arm observational studies comes from selection of patients for inclusion in the study. Of the primary studies in this rapid review, five specifically stated that they minimised selection bias by recruiting consecutive patients[14, 15, 22, 24, 28]. In one study, patient selection at each participating centre was based on international guidelines, with 83% of institutions recruiting consecutive patients[25]. Another study stated it recruited 'all comers' but did not specify if that meant consecutive patients[27]. The study by Regueiro *et al* (2018) appears to have only reported

results for patients where the LAAO procedure was successful which may have biased the study findings[23].

Given the inherent risk of bias in single-arm studies with no control group, large cohorts are preferable as they are likely to provide more accurate estimates of effect. Three recent primary studies were identified that recruited more than 200 patients[15, 25, 27]. One of these studies is the 1-year follow-up from the EWOLUTION registry that is contained in the systematic review by Baman *et al* (2018), therefore only long-term outcomes were extracted from this paper[25]. An additional six studies in the systematic review recruited more than 200 patients; five of these studies included at least a proportion of patients who were eligible for oral anticoagulation.

There was variation between primary studies in type and duration of anticoagulant or antiplatelet therapy patients received following LAAO which may have affected outcomes (appendix 2); anticoagulant and antiplatelet regimens also varied between centres within individual studies. Additional variation between studies was noted for outcome definitions. For example, major bleeding was variously defined using the Bleeding Academic Research Consortium (BARC) definition, the Munich consensus, ISO criteria, or the need for invasive treatment or blood transfusion. Two primary studies reported having an event adjudication committee which should reduce observer bias, however one of these committees appears to have consisted of representatives from the study sponsor (device manufacturer)[25, 27].

Clinical effectiveness results from all studies, including those extracted from the systematic review, are reported in table 3. In summary:

- Five studies in the systematic review and four of the primary studies published separately evaluated the WATCHMAN™ device[5, 14, 25, 26, 30]. One study in the systematic review and two studies published separately assessed the AMPLATZER™ Amulet[5, 14, 27]. Three studies in the systematic review and two studies published separately included multiple occlusive devices[5, 14, 15]. In total, two studies considered the LAmbre™ system[14, 22] and one study evaluated the Ultraseal/Ultrasept device[28]. The AMPLATZER™ Cardiac Plug device was only assessed in studies within the systematic review (3 studies)[5].

- Peri-procedure stroke rates ranged from 0% to 1% of patients treated with LAAO. No peri-procedure strokes were reported in studies using the AMPLATZER™ Amulet device[5, 14, 27].

- Peri-procedure mortality ranged from 0% to 1% of patients treated with LAAO. Large studies (n>1,000) reported peri-procedure mortality rates ≤0.6%.

- Ischaemic stroke rates during follow-up ranged from 0% to 6.9% of patients treated with LAAO. These stroke rates may be misleading as the mean follow-up period ranged from 6 months to 50.4 (SD 15.6) months. When considering only studies with a mean or median follow-up of approximately 12 months (six studies), the ischaemic stroke rate during follow-up ranged from 0.9% to 6.0%. The highest stroke rate during follow-up was reported in a small study (n=50) of the AMPLATZER™ Amulet device contained within the systematic review[5].

Table 2: baseline patient characteristics extracted from primary studies in the systematic review by Baman *et al* (2018)[5] and studies published after the review

Study	Device	N	Mean age (SD)	% Male	Mean CHA_2DS_2-VASc score (SD)	Anticoagulant contraindications
Asmarats (2018)[28]	Ultraseal/ Ultrasept	126	75.0 (8.0)	57.0	5.0 (2.0)	93.0% ineligible: 44.5% absolute, 48.4% relative. 78.0% history of bleeding
Baman (2018)[5] *Systematic review*	WATCHMAN™	6,032	73.7	–	4.5	–
	AMPLATZER™ Cardiac Plug	1,266	74.6	–	4.5	–
	AMPLATZER™ Amulet	50	76.1	–	5.2	–
	Mixed	709	72.0	–	4.2	–
Boersma (2017)[25]	WATCHMAN™	1,025	73.4 (8.9)	59.9	4.5 (1.6)	73.3% contraindicated
Chen (2018)[14]	LAmbre™	30	77.6 (8.9)	50.0	3.9 (1.5)	All contraindicated due to anticoagulant bleeding events, intolerance or refusal
	AMPLATZER™ Amulet	74	76.0 (7.9)	66.2	3.9 (1.5)	
	WATCHMAN™	36	75.3 (8.8)	72.2	3.6 (1.5)	
CtE (2018)[15]	Mixed	525	74.5 (8.0)	68.7	4.3 (1.5)	61.1% bleeding or embolic event on anticoagulation; 23.4% history of bleeding; 7.1% high bleeding risk; 6.9% intolerance
Huang (2017)[22]	LAmbre™	153	69.3 (9.4)	56.2	4.0 (1.7)	All contraindicated: history of cerebrovascular or gastrointestinal bleeding, poor compliance, warfarin allergy

Huang (2017)[26]	WATCHMAN™	106	64.2 (8.6)	59.4	3.6 (1.6)	77.3% failed to tolerate warfarin; 18.9% history of haemorrhage or embolism
Landmesser (2018)[27]	AMPLATZER™ Amulet	1,088	75.0 (9.0)	65.0	4.2 (1.6)	83.0% absolute or relative. 72.0% history of major bleeding
Regueiro (2018)[23]	Mixed	101	Median 76.0 (IQR 69.0 to 80.0)	57.4	4.8 (1.6)	All contraindicated: history of bleeding, blood disorder, unsupervised patients with senility and/or high fall risk, other (including warfarin hypersensitivity)
Saw (2107)[24]	WATCHMAN™	106	74.8 (7.7)	62.3	4.3 (1.5)	89.6% history of prior bleeding; 9.4% high risk of bleeding; 0.9% stroke on warfarin

IQR = inter-quartile range

Table 3: clinical outcomes for LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation

Study	N	Peri-procedure stroke	Peri-procedure mortality	Follow-up (months)	Ischaemic/embolic stroke during follow-up
WATCHMAN™					
Baman (2018)[5*] *Systematic review*	6,092	0.1% (1 per 1,000)	0.05% (0.5 per 1,000)	Mean 11.1	0.9% (9 per 1,000)
Boersma (2017)[25]	1,020	–	–	12	1.1% (11 per 1,000)
Chen (2018)[14]	36	0	0	6	0
Huang (2017)[26]	106	0.9% (9 per 1,000)	0	12	1.9% (19 per 1,000)
Saw (2107)[24]	106	0	0.9% (9 per 1,000)	Mean 7.0 (SD 6.0)	0
AMPLATZER™ Cardiac Plug					
Baman (2018)[*5] *Systematic review*	1,266	0.7% (7 per 1,000)	0.6% (6 per 1,000)	Mean 20.2	1.3% (13 per 1,000)
AMPLATZER™ Amulet					
Baman (2018)[*] *Systematic review*	50	0	0	12	6.0% (60 per 1000)
Chen (2018)[14]	74	0	0	6	0
Landmesser (2018)[27]	1,088	–	0.3% (3 per 1,000)	Mean 11.1 (SD 2.6)	2.5% (25 per 1,000)
LAmbre™					
Chen (2018)[14]	30	0	0	6	0
Huang (2017)[22]	153	0.7% (7 per 1,000)	0	12	1.3% (13 per 1,000)

Ultraseal/Ultrasept					
Asmarats (2018)[28]	126	0.8% (8 per 1,000)	0	Median 6	Stroke or TIA 1.6% (16 per 1,000) Systemic embolism 0
Mix of devices (undifferentiated)					
Baman (2018)[5*] *Systematic review*	709	0.7% (7 per 1,000)	0.4% (4 per 1,000)	Mean 11.1	1.1% (11 per 1,000)
CtE (2018)[15]	525	–	1.0% (10 per 1,000)	Maximum 24	1.9% (19 per 1,000)
Regueiro (2018)[23]	101	1.0% (10 per 1,000)	–	Mean 50.4 (SD 15.6)	5.9% (59 per 1,000)

*Outcome rates from the Baman *et al* (2018) systematic review were calculated based on data in table 2 of the published review[5]. The results for each outcome were calculated as Number of events in all studies of that device/Total number of patients in all studies of that device x 100.

TIA=transient ischaemic attack

Seven primary studies compared observed ischaemic stroke rate with predicted ischaemic stroke/thromboembolic event rates based on mean baseline CHA_2DS_2-VASc scores[22-25, 27, 28]. Two studies did not report how they calculated the predicted stroke rate for the baseline CHA_2DS_2-VASc score in their patient cohort[23, 27]. Three studies based predicted stroke rate estimates on the results of the same large cohort study (Friberg *et al*, 2012)[24, 25, 28, 31]. The CtE report used stroke risk estimates from Danish registry data[15]. The remaining study based the predicted ischaemic stroke rate on a different published study (Lip *et al*, 2010)[22, 32]. The estimated reduction in ischaemic stroke risk in the seven studies ranged from 57% to 84% following LAAO (table 4). These estimates should be treated with some caution for the following reasons:

- The predicted ischaemic stroke rate was based on previously published studies – effectively a historical cohort – in patients that may have differed in baseline characteristics, underlying stroke risk, treatment or lifestyle factors.
- It is unclear whether the CHA_2DS_2-VASc score is accurate for predicting annual stroke risk in patients with atrial fibrillation and contraindications to oral anticoagulation. In the study by Friberg *et al* (2012) the CHA_2DS_2-VASc score had only moderate discriminative ability[31]. The predictive performance of the CHA_2DS_2-VASc score may also be sensitive to absolute population stroke rates, therefore stroke risk in a historical cohort may not generalise to more recent cohorts.
- A single consistent source of stroke risk estimates for patients with a particular mean CHA_2DS_2-VASc score was not used in all seven studies. This means that even when based on similar mean CHA_2DS_2-VASc scores, study cohorts had different predicted stroke risks (table 4).

Table 4: predicted and observed ischaemic stroke rates in seven primary studies

Study	N	Mean CHA_2DS_2-VASc score (SD)	Predicted ischaemic stroke rate	Observed ischaemic stroke rate	Estimated risk reduction
Asmarats* (2018)[28]	126	5.0 (2.0)	7.2% (72 per 1000)	2.5% (25 per 1,000)	65%
Boersma (2017)[25]	1,025	4.5 (1.6)	7.2% (72 per 1000)	1.1% (11 per 1,000)	84%
CtE# (2018)[15]	525	4.3 (1.5)	6.7% (67 per 1000)	2.6% (26 per 1,000)	61%
Huang# (2017)[22]	153	4.0 (1.7)	5.2% (52 per 1000)	1.3% (13 per 1,000)	75%
Landmesser (2018)[27]	1,088	4.2 (1.6)	6.7% (67 per 1000)	2.9% (29 per 1,000)	57%
Regueiro# (2018)[23]	101	4.8 (1.6)	6.2% (62 per 1000)	1.7% (17 per 1,000)	73%
Saw# (2017)[24]	106	4.3(1.5)	8.1% (81 per 1000)	3.3% (33 per 1,000)	59%

*Predicted risk and estimated risk reduction were re-calculated based on the Friberg *et al* (2018)[31] study as this appears to have been misread by Asmarats *et al* (2018)[28]
#predicted and observed risk of thromboembolic events (stroke, transient ischaemic attack, systemic embolism)

Ongoing studies

Five RCTs are currently recruiting patients with atrial fibrillation and contraindications to oral anticoagulation to evaluate LAAO (table 5).

Table 5: RCTs on LAAO recruiting atrial fibrillation patients with contraindications to oral anticoagulation

Study	Patients and comparison	Estimated completion date
NCT03463317 Left atrial appendage CLOSURE in patients with atrial fibrillation compared to medical therapy (CLOSURE-AF)	Atrial fibrillation patients with a high risk of bleeding on oral anticoagulation or contraindications to anticoagulant therapy LAAO (any device) vs. best medical care	Feb 2023
NCT02928497 Assessment of the WATCHMAN™ device in patients unsuitable for oral anticoagulation (ASAP-TOO)	Atrial fibrillation patients deemed by two physicians to be unsuitable for oral anticoagulation WATCHMAN™ vs. single antiplatelet therapy or no therapy	Dec 2023
NCT02879448 AMPLATZER™ Amulet LAA occluder trial (Amulet IDE)	Atrial fibrillation patients with an appropriate rationale for seeking an alternative to anticoagulation and deemed by investigators to be unable to take long-term oral anticoagulation AMPLATZER™ Amulet vs. WATCHMAN™	Dec 2023
NCT03302494 WAveCrest vs. Watchman transseptal LAA closure to reduce AF-mediated stroke 2 (WAVECREST2)	Atrial fibrillation patients with an appropriate rationale for seeking an alternative to oral anticoagulation WaveCrest® vs. WATCHMAN™	Dec 2025
NCT02830152 Prevention of stroke by left atrial appendage closure in atrial fibrillation patients after intracerebral haemorrhage	Atrial fibrillation patients with an intracerebral haemorrhage within 6 months of enrollment AMPLATZER™ Amulet vs. best medical therapy	May 2030

Safety

Complications and adverse events relating to LAAO include pericardial effusion, cardiac tamponade, major bleeding, peri-procedure stroke (which is covered in the clinical effectiveness section), device embolisation, and device-related thrombi where the blood clot forms on the occlusive device[10]. Some of these safety outcomes are procedure-related, for example pericardial effusion, while others are device-related.

Safety outcome from the two RCTs excluded from the clinical effectiveness section (PROTECT AF and PREVAIL)[20, 21] were included here on the basis that adverse events could be expected to be similar or lower in patients in these trials compared with patients who cannot receive oral anticoagulation. Both trials recruited patients eligible for oral anticoagulation and performed LAAO procedures using the WATCHMAN™ device (PROTECT AF n=463; PREVAIL n=269). Safety results in these RCTs were as follows:

- Serious pericardial effusion was reported in 4.8% of patients in the PROTECT AF trial. In the PREVAIL trial, pericardial effusion with cardiac tamponade was observed in 0.4% of patients.
- Major bleeding was reported in 3.5% of patients in the PROTECT AF trial and 0.4% of patients in the PREVAIL trial.
- Device embolisation occurred in 0.6% of patients in the PROTECT AF trial and 0.7% of patients in the PREVAIL trial.

It is unclear why the serious pericardial effusion and major bleeding rates reported in the PROTECT AF trial were so much higher than in the PREVAIL trial. It is possible that this relates to the PROTECT AF study being conducted earlier in the learning curve for LAAO.

Safety outcomes for LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation were also extracted from the studies used in the clinical effectiveness section[5, 14, 15, 22-24, 26-28] (table 6). The primary study by Boersma *et al* (2017)[25] was not included in the safety section because it reported long-term outcomes from a study in the systematic review. In summary:

- The rate of peri-operative pericardial effusion with or without cardiac tamponade ranged from 0% to 7.5% of patients treated with LAAO. The highest event rate was described as 'minor effusion' in a single study[26]. In large studies (n>1,000) pericardial effusion with or without tamponade occurred in 1.3% to 1.6% of patients[5, 27]. All three studies that reported cardiac tamponade separately recorded an event rate of 0.9%[24, 26, 27].
- Major bleeding, the definition of which varied between studies, was recorded in 0% to 4.9% of patients treated with LAAO. In studies with over 1,000 participants the major bleeding event rate ranged from 0.2% to 2.8%[5, 27].
- Device embolisation, where the occlusive device comes loose from the atrial appendage and may cause a blockage in the circulation, was reported in 0% to 2.0% of patients. The highest rate of device embolisation was in a small study (n=50) evaluating the AMPLATZER™ Amulet device[5]. In studies with more than 1,000 participants device embolisation rates were 0.2% to 0.9%[5, 27].

- Device-related thrombi during follow-up were reported for 0% to 5.6% of patients treated with LAAO. Variation in length of follow-up may partly explain the range for this outcome. In two studies with 12 months follow-up, device-related thrombi occurred in 1.7% and 1.9% of patients[26, 27]. The highest rate of device-related thrombi during follow-up (5.6%) was reported at 6 months follow-up in the only study assessing the Ultraseal device[28].
- A composite of all major adverse events was reported in six studies, with event rates ranging from 0% to 5.5%[14, 15, 22, 24, 26, 28]. There was between-study variation in how this outcome was defined and it was not reported in any of the studies with more than 1,000 participants.

Table 6: adverse event rates in atrial fibrillation patients with high stroke risk and contraindications for oral anticoagulation

Study	N	PERI-PROCEDURE ADVERSE EVENTS				Device related thrombi during follow up
		Pericardial effusion (with or without cardiac tamponade)	Major bleeding	Device embolisation	All major adverse events	
WATCHMAN™						
Baman (2018)[*5] *Systematic review*	6,092	1.4% (14 per 1,000)	0.2% (2 per 1,000)	0.2% (2 per 1,000)	–	–
Chen (2018)[14]	36	2.8% (28 per 1,000)	–	0	2.8% (28 per 1,000)	0 at 6 months
Huang (2017b)[26]	106	7.5% minor effusion (75 per 1,000) 0.9% tamponade (9 per 1,000)	0	0	1.9% (19 per 1,000)	1.9% (19 per 1,000) at 12 months
Saw (2107)[24]	106	0.9% tamponade (9 per 1,000) 1.9% effusion (19 per 1,000)	–	0.9% (9 per 1,000)	2.8% (28 per 1,000)	0.9% (9 per 1,000) at mean 7.0 (± 6.0) months
AMPLATZER™ Cardiac Plug™						
Baman (2018)[*5] *Systematic review*	1,815	1.3% (13 per 1,000)	1.3% (13 per 1,000)	0.9% (9 per 1,000)	–	–
AMPLATZER™ Amulet™						
Baman (2018)[*5] *Systematic review*	50	4.0% (40 per 1,000)	–	2.0% (20 per 1,000)	–	–

Chen (2018)[14]	74	0	–	0	0	0 at 6 months
Landmesser (2018)[27]	1,078	0.9% tamponade (9 per 1,000) 0.7% effusion (7 per 1,000)	2.8% (28 per 1,000)	0.2% (2 per 1,000)	–	1.7% (17 per 1,000) at 12 months
LAmbre™						
Chen (2018)[14]	30	0	–	0	0	3.3% (33 per 1,000) at 6 months
Huang (2017a)[22]	153	2.0% (20 per 1,000)	0.7% (7 per 1,000)	–	3.3% (33 per 1,000)	1.3% (13 per 1,000) at 3 months
Ultraseal/Ultrasept						
Asmarats (2018)[28]	126	0.8% (8 per 1,000)	1.6% (16 per 1,000)	0.8% (8 per 1,000)	2.4% (24 per 1,000)	5.6% (56 per 1,000) at 6 months
Mixed (undifferentiated)						
Baman (2018)[*5] *Systematic review*	709	6.5% (65 per 1,000)	2.8% (28 per 1,000)	1.6% (16 per 1,000)	–	–
CtE (2018)[15]	525	2.1% major (21 per 1,000) 1.1% minor (11 per 1,000)	1.9% (19 per 1,000)	0.8% (8 per 1,000)	5.5% (55 per 1,000)	–
Regueiro (2018)[23]	101	–	4.9% (49 per 1,000)	2.0% (20 per 1,000)	–	2.5% (25 per 1,000) at mean 50.4 months

*Outcome rates from the Baman *et al* (2018) systematic review were calculated based on data in table 2 of the published review[5]. The results for each outcome were calculated as Number of events in all studies of that device/Total number of patients in all studies of that device x 100.

Cost effectiveness

The NHS England CtE report on LAAO contained a cost consequence analysis which is summarised in this section and is likely to generalise to the Scottish context[15]. In addition, two published economic evaluations were identified that explored the cost effectiveness of LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation[30, 33]. Neither of the published economic evaluations were conducted in the UK, therefore the results may not generalise to Scotland.

CtE cost consequence analysis

The CtE cost consequence analysis compared LAAO plus medical therapy (antiplatelet drugs) with medical therapy alone in patients with atrial fibrillation and contraindications to oral anticoagulation[15]. The analysis was conducted from both an NHS perspective and an NHS plus social care perspective since approximately 60% of costs relating to management of stroke patients are incurred in social care. An economic model was developed to estimate cost consequences using a decision tree and Markov model for a cohort of 1,000 patients over a 15 year time horizon. In the decision tree, patients undergoing LAAO could have a successful or unsuccessful procedure and could develop major and/or minor complications. The Markov model consisted of three health states: stroke-free, a neurological event (ischaemic or haemorrhagic stroke, transient ischaemic attack (TIA)), and death. Patients entered the model at age 75 and could experience multiple neurological events. The probability of death increased with the occurrence of each neurological event. The risk of ischaemic stroke and bleeding events in the medical therapy group were estimated according to baseline CHA_2DS_2-VASc and HAS-BLED scores, while these risks were based on observed data from the CtE registry for patients in the LAAO group.

Key costs incorporated into the analysis included LAAO procedure costs, NHS and social care costs relating to management of patients following a stroke or TIA, medication costs and costs associated with bleeding events. NHS costs (hospital care, primary care, prescribing, and rehabilitation) and social care costs associated with stroke management were derived from the Sentinel Stroke National Audit Programme. Social care costs included home care and nursing home care for patients with impairments affecting activities of daily living following a stroke. Other costs were derived from NHS national datasets and English national cost sources. NHS Supply Chain overheads of 3% were included in the LAAO procedure cost, as was a further 15% overhead cost for NHS procurement. All costs were discounted at 3.5% per annum.

The best estimate of the cost of the LAAO procedure was £11,600, with a range of £9,500 to £13,300 in low and high cost scenarios respectively. The majority of these costs were incurred peri-operatively. In the NHS-only analysis, the estimated cost per patient in the LAAO plus medical therapy group was £14,963 compared with £8,392 in the medical therapy group over a 15 year time horizon (table 7). LAAO therefore incurred an additional cost of £6,571 per person. Compared to medical therapy alone, the model predicted 343 fewer strokes per 1,000 patients treated with LAAO. Cost savings from avoided strokes and medication costs were estimated at £5,050 per person, which did not completely offset the initial LAAO procedure cost. As there is no standard threshold for cost consequence analysis, it was not possible for the CtE authors to say whether LAAO was cost effective from an NHS perspective. From the NHS plus social care perspective LAAO was cost neutral compared with medical therapy; £17,835 per patient in the LAAO group compared with £17,905 per patient in the medical therapy group, leading to a small cost saving of £70 per person. LAAO therefore appeared to be cost effective from an NHS plus social care perspective.

Table 7: NHS costs per patient treated with LAAO plus medical therapy compared with medical therapy alone over a 15 year time horizon[15]

	Discounted cost per patient		
	LAAO	Medical therapy	Difference
Procedure & bleeds	£11,621	£0	£11,621
Medication	£1,131	£1,561	-£429
Ischaemic stroke (NHS)	£1,419	£4,514	-£3,096
Haemorrhagic stroke (NHS)	£516	£1,669	-£1,153
Transient ischaemic attack (TIA)	£45	£160	-£115
Bleeding	£231	£488	-£257
Total	**£14,963**	**£8,392**	**£6,571**

The main drivers in the analysis were LAAO procedure costs and the cost associated with managing stroke in the NHS and social care. If the 15% overhead costs for NHS Procurement were removed from the LAAO model, the estimated savings in the analysis from an NHS plus social care perspective rose to £960 per patient. However, LAAO was no longer cost saving if there were small changes in the procedure cost or annual stroke risk following surgery, and became cost incurring if a shorter time horizon was used. Key uncertainties identified by the CtE authors include the validity of using CHA_2DS_2-VASc scores from the literature to estimate stroke rates in the medical therapy group, extrapolating observed stroke risk reductions from a 2 year follow-up period to a 15 year time horizon, and extrapolating stroke costs over 15 years for a patient population that entered the model at age 75.

Published economic analyses

A published economic evaluation from Canada compared LAAO plus long-term aspirin with long-term aspirin alone in patients with atrial fibrillation who were ineligible for oral anticoagulation[30]. The study took a third party public payer perspective (Ontario Health Ministry) and used a lifetime time horizon. A Markov microsimulation model was developed using clinical input values derived from published RCTs and Canadian healthcare costs. In the model, patients could either be 'well' or experience one of five events: death, stroke, systemic embolism, myocardial infarction, or bleeding. The mean age of patients in the model was 74, with a range of 66 to 88 years used in sensitivity analyses. Women made up 57.7% of patients in the model and 90% of patients had a baseline CHA_2DS_2-VASc score ≥3. These and other baseline patient characteristics were derived from Canadian multicenter LAAO experience. Direct medical costs were incorporated into the model, including medication costs, device costs, hospitalisation costs, and physician services. The cost of the LAAO device was assumed to be CAD$8,500 (£5,000) with a total procedural cost estimate of CAD$13,334 (£7,800). All costs were in 2015 Canadian dollars and discounted by 5% annually.

In the base case analysis, LAAO dominated aspirin (was both less expensive and more effective in terms of quality adjusted life years (QALYS)): treatment with aspirin only was associated with

incremental costs of CAD$8,226 (£4,816) and 0.41 fewer QALYS compared with LAAO. The incremental costs were a result of higher cumulative risk of developing clinical events for patients on aspirin only. The model predicted lifetime risks of 74% for total stroke, 42% for major stroke, 27% for minor stroke and 37% for TIA in patients on aspirin alone. This compared to lifetime risks of 66% for total stroke, 21% for major stroke, 13% for minor stroke and 18% for TIA in LAAO patients. In probabilistic sensitivity analyses, LAAO was the preferred option in more than 90% of cases using a willingness-to-pay threshold of CAD$50,000 (approximately £29,000). This analysis was conservative as it did not take into account costs or consequences of LAAO patients experiencing a reduced risk of disabling stroke (as reported in RCTs) and used a lower LAAO efficacy estimate compared to registry data. A potential source of uncertainty in the model was the assumption that patients undergoing LAAO would receive dual antiplatelet therapy for one month post-procedure and aspirin monotherapy thereafter. The duration of dual antiplatelet therapy following LAAO has not been agreed internationally and a longer duration may increase post-LAAO costs and bleeding risks.

The second published economic evaluation compared LAAO using the WATCHMAN™ device with long-term aspirin or long-term apixaban (a direct oral anticoagulant) in patients with atrial fibrillation and absolute contraindications to oral anticoagulation with warfarin[33]. This analysis used a German healthcare system perspective and a 20 year time horizon. Clinical inputs for event probabilities were obtained from published meta-analyses, RCTs and registry studies. Clinical events captured by the Markov model included different types of stroke, systemic embolism, major or minor bleeding and myocardial infarction. The model allowed for patients experiencing a clinical event to return to the 'well' state, incur a level of disability, or die. The model assumed that patients were 70 years old at baseline with a $CHADS_2$ score of 3, which is equivalent to a CHA_2DS_2-VASc score of 5-6, and an estimated annual stroke risk of 8.6%. Discontinuation of treatment was also incorporated in the model: LAAO patients were assumed to be treated with aspirin if the procedure failed, apixaban patients were assumed to transition to aspirin if they discontinued apixaban, and aspirin patients that discontinued treatment were assumed to receive no further intervention. Direct medical costs and long-term disability care costs were included in the analysis, and collated from German healthcare data sources. The combined LAAO device and procedure cost as per the German tariff was €9,136 (£8,000). Costs were reported in 2014 Euros. All costs and QALYs were discounted at an annual rate of 3.5%.

LAAO was cost effective compared with aspirin after 5 years (incremental cost effectiveness ratio (ICER) €16,971/£14,898) and apixaban after 7 years (ICER €9,040/£7,936). After 8 years LAAO dominated aspirin (25% less expensive and 0.6 additional QALYs) and after 10 years it dominated apixaban (15% less expensive and 0.2 additional QALYs). The results of the economic model at 10 years for patients with three different baseline risk profiles are presented in table 8. In probabilistic sensitivity analyses LAAO was cost saving in 94% of scenarios, and resulted in increased life-years and QALYs in 99% of cases. One-way sensitivity analysis showed the model to be most sensitive to variation in the baseline risk of stroke, cost of LAAO and implantation success rate. This economic evaluation was specific to the WATCHMAN™ device and may therefore not generalise to other devices. It should also be noted that the analysis and the publication was funded by the manufacturer who directly employed or paid as a consultant all of the study authors.

Table 8: cost effectiveness at 10 years for LAAO in patients with three different baseline risk profiles in a comparison of LAAO using the WATCHMAN™ device, long-term apixaban and long-term aspirin[33]

	LAAO	Apixaban	Aspirin
Base case (annual stroke risk 8.6%, annual bleeding risk 3.7%)			
Total costs	€15,837 (£13,923)	€18,869 (£16,589)	€21,077 (£18,530)
Incremental costs (vs. aspirin)	Cost saving	Cost saving	–
Incremental QALYs (vs. aspirin)	0.61	0.38	–
ICER (vs. aspirin)	Dominant	Dominant	–
ICER (vs. apixaban)	Dominant	–	Dominated
Low risk (annual stroke risk 2.2%, annual bleeding risk 1.9%)			
Total costs	€12,529 (£11,015)	€10,382 (£9,127)	€6,653 (£5,849)
Incremental costs (vs. aspirin)	€5,876 (£5,166)	€3,729 (£3,279)	–
Incremental QALYs (vs. aspirin)	0.13	0.09	–
ICER (vs. aspirin)	€46,562 (£40,938)	€44,012 (£38,696)	–
ICER (vs. apixaban)	€51,771 (£45,518)	–	–
High risk (annual stroke risk 10.9%, annual bleeding risk 12.5%)			
Total costs	€19,236 (£16,910)	€25,596 (£22,501)	€29,021 (£25,512)
Incremental costs (vs. aspirin)	Cost saving	Cost saving	–
Incremental QALYs (vs. aspirin)	0.75	0.38	–
ICER (vs. aspirin)	Dominant	Dominant	–
ICER (vs. apixaban)	Dominant	–	Dominated

Volume-outcome

Published evidence on the relationship between operator or hospital volume and patient outcomes for LAAO was limited to one administrative database study[34]. This study was not restricted to atrial fibrillation patients with contraindications to oral anticoagulation. Badheka *et al* (2015) gathered data on 268 atrial fibrillation patients who had undergone LAAO between 2006 and 2010. Data were retrieved from the National Inpatient Sample database which contains 20% of inpatient records from 1,051 hospitals in the USA. These data have limitations as they do not include detailed information on important patient characteristics that may influence outcomes. The database also does not

contain information on cardiologist experience with the procedure or how many teams within each hospital performed the procedure.

The study authors looked at the relationship between annual hospital volume (number of LAAO procedures) and in-hospital complications, in-hospital mortality and length of hospital stay. Hospitals were divided into tertiles based on the number of LAAO procedures performed per year: <3 procedures, 3-17 procedures and ≥18 procedures. Patients with atrial fibrillation identified from the database as having had a LAAO procedure had a mean age of 70 (SD 12) years and 67.8% were male. The rate of procedural complications was 24.3%. This included diverse events such as pressure ulcers, kidney injury and respiratory complications. In-hospital mortality was 2.3%, which is higher than in the studies reported in the clinical effectiveness section. It is possible that the high rates of in-hospital mortality and adverse events reflect early clinical experience with performing LAAO in patients with atrial fibrillation.

In a meta-regression analysis, increased annual LAAO procedure volume was associated with statistically significant reductions in a composite of complications and mortality: odds ratio (OR) 0.89, 95% CI 0.85 to 0.94, p<0.001. Increasing hospital volume was also associated with a statistically significant reduction in length of hospital stay: hazard ratio (HR) 0.95, 95% CI 0.92 to 0.98, p<0.001. The composite outcome and length of hospital stay were statistically significantly lower in hospitals performing ≥18 LAAO procedures per year compared with hospitals conducting less than three LAAO procedures per year (table 9). There were no statistically significant differences in these outcomes between hospitals performing 3-17 LAAO procedures per annum and hospitals performing fewer than three procedures per year.

Table 9: effect of annual hospital LAAO volume on patient outcomes[34]

	Composite of complications and mortality OR (95% CI)	Length of hospital stay OR (95% CI)
First tertile (<3 procedures)	Reference	Reference
Second tertile (3-17 procedures)	0.69 (0.16 to 2.86) p=0.6	0.66 (0.39 to 1.10) p=0.11
Third tertile (≥18 procedures)	0.002 (0 to 0.027) p<0.001	0.22 (0.11 to 0.45) p<0.001

Learning curve

Two studies were identified that explored the learning curve for LAAO[35, 36]. Only one of these studies was restricted to atrial fibrillation patients with contraindications to oral anticoagulation[35].

In the study that recruited patients with atrial fibrillation, a CHA_2DS_2-VASc score ≥2 and contraindications to oral anticoagulation, 31 consecutive patients were prospectively treated with the AMPLATZER™ Cardiac Plug or WATCHMAN™ devices[35]. Three patient groups were created: 10 patients undergoing LAAO using the AMPLATZER™ Cardiac Plug (2009-2010); 11 patients receiving the AMPLATZER™ Cardiac Plug between 2011 and 2013; and 10 patients implanted with the

WATCHMAN™ device (2012-2013). The same operator performed all of the procedures and decided whether patients treated after 2010 would receive the AMPLATZER™ Cardiac Plug or WATCHMAN™ device. The primary outcome was a composite safety endpoint of pericardial effusion/tamponade, procedure-related stroke, device embolisation and bleeding events requiring a transfusion.

Mean age of study participants was 76.7 (SD 7.2) years, 61.3% were male and the mean CHA_2DS_2-VASc score was 3.52 (SD 0.72). The only instances of the composite endpoint were recorded in the first 10 patients who were all treated with the AMPLATZER™ Cardiac Plug: 3 events versus 0 events versus 0 events, p=0.04. These safety events were one pericardial effusion, one air embolism, and one ischaemic stroke within 24-hours of surgery. There were no statistically significant differences in operating time: 63.6 (SD 29) minutes versus 61.4 (SD 21) minutes versus 59.6 (SD 19) minutes, p=0.4. The study authors concluded that complications associated with the LAAO procedure decrease significantly with increasing operator experience, and initial experience gained with one LAAO device may generalise to other devices. However, it should be noted that this conclusion is based on a small sample of patients treated by a single operator with an unknown level of prior experience of percutaneous cardiac procedures.

The second study explored the learning curve for LAAO in 90 consecutive patients with atrial fibrillation who were treated with the WATCHMAN™ device, regardless of whether they were eligible for oral anticoagulation[36]. Study participants were divided into three sequential groups based on time of treatment: patients 1-30 in group 1, patients 31-60 in group two and patients 61-90 in group 3. All procedures were performed by a single operator who was supervised by a proctor for the first three patients. It is therefore assumed that the operator had limited, if any, prior experience with this procedure.

Participants in this study had a mean age of 77 years, 62% were male and the median CHA_2DS_2-VASc score was 5 (inter-quartile range (IQR) 3 to 5). There was no statistically significant difference in implantation success rate between groups: 87% versus 90% versus 93%, p=0.69. Procedure time was significantly reduced with increasing operator experience: 75 minutes (IQR 62 to 108) versus 50 minutes (IQR 43 to 66) versus 47 minutes (IQR 41 to 61), p<0.0001. Results for the primary safety outcome in this study ('in-hospital complications') appears to have been reported incorrectly at some point in the published paper as the results presented in the text, tables and figures are not consistent. This appears to be an error of magnitude rather than relative effect. Within their text, the authors report that device and procedure-related complications reduced from 20% in group 1 to 7% in group 2 and 0% in group 3 (p=0.021). In the table of complications in their published paper, there were 12 events (40%) in group 1, 4 events (13.3%) in group 2 and 0 events in group 3: in other words approximately double the percentage reported in the text for each group. No strokes, systemic embolisms or device embolisations were reported for any of the groups. The authors of this study, contrary to the previous study, conclude that the results may not generalise to cohorts using devices other than the WATCHMAN™.

Organisational issues/context

In 2018, NHS England agreed to routinely fund LAAO for patients with non-valvular atrial fibrillation, a CHA_2DS_2-VASc score ≥2 and physician-assessed contraindications to oral anticoagulation with warfarin and direct oral anticoagulants[12]. Contraindications were defined as a history of severe/major haemorrhage, high risk of bleeding or an acquired bleeding disorder, documented

contraindications, a Rockwood frailty score <6, and history of a thromboembolic event or ischaemic stroke despite oral anticoagulation. The decision to commission this procedure in NHS England was based on results from the CtE registry and a review of 14 published registry or single-arm observational studies. Initial case volume in England was estimated as 400 LAAO procedures per annum, increasing to 1,000 per annum over 5 years.

Although there is potentially a relatively large Scottish population who have atrial fibrillation and are ineligible for oral anticoagulation, many patients may not be suitable for LAAO due to high bleeding risk, frailty or comorbidities[6]. There were three percutaneous LAAO procedures in Scotland between 1 April 2017 and 31 March 2018 (Mr G Clark, Senior Information Analyst, NHS National Services Scotland. Personal communication, 29 March 2019).

Conclusion

When assessing the evidence on using LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation, a number of factors need to be considered. Firstly, effective options for reducing ischaemic stroke risk in this patient group are limited. Secondly, LAAO is a prophylactic intervention so any adverse events or harms caused by the procedure need to be measured against potential future benefits from reducing the risk of ischaemic stroke, rather than an immediate treatment benefit. As with any prophylactic intervention, any harm caused by the procedure or device is an added burden for the patient who would not otherwise have been exposed to this risk. Thirdly, patients eligible for LAAO will have a high baseline risk for bleeding and stroke due to their age, comorbidities, and medical history. Finally, patients referred for LAAO will need to be capable of taking long-term antiplatelet therapy following the procedure.

Based on 21 single-arm prospective registry/cohort studies LAAO appears to be associated with peri-operative stroke and mortality rates approximating ≤1% of patients treated. Ischaemic stroke rates within 12 months of a LAAO procedure were estimated to be ≤2% of patients treated. Compared with historical cohorts of atrial fibrillation patients, which may not be suitable comparison groups, this may represent a substantial reduction (57% to 84%) in the risk of ischaemic stroke in patients with atrial fibrillation who undergo a LAAO procedure. As noted previously, these perceived future benefits of LAAO in reducing ischaemic stroke and bleeding risk need to be balanced against adverse events associated with the procedure or device. In six studies, a composite of major adverse events was reported to affect a median of 2.8% of patients treated with LAAO. The most serious adverse event, cardiac tamponade, was recorded in 0.9% of patients treated. These risks need to be thoroughly discussed with patients alongside the potential benefits of this procedure. Future decisions on the use of LAAO in patients with contraindications to oral anticoagulation should ideally be based on RCT evidence once it becomes available (from 2023 onwards).

Based on economic evidence and registry data from NHS England, LAAO would appear to be cost effective/cost-neutral compared with standard medical therapy from an NHS and social care perspective. Published economic evaluations from the perspective of non-UK healthcare systems found LAAO to be cost saving and more effective than aspirin or direct oral anticoagulants (apixaban).

Since patient outcomes relating to safety and mortality were significantly lower in hospitals with an annual volume of LAAO procedures ≥18 compared with hospitals performing <3 per year,

consolidating LAAO services at a small number of centres in Scotland to ensure sufficient patient numbers may be indicated. Consolidating LAAO services within a limited number of hospitals would also ensure interventional cardiologists obtain sufficient experience with LAAO to develop and maintain competence with this procedure, further improving patient outcomes.

Identified research gaps

Current evidence on LAAO in patients with atrial fibrillation and contraindications to oral anticoagulation appears to be at stage 2b 'exploration' of the IDEAL framework for surgical innovation. Future research (some of which is already underway) should focus on RCTs comparing LAAO with standard medical therapy in this patient group.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Appendix 1: abbreviations

BARC	Bleeding Academic Research Consortium
DOAC	direct oral anticoagulant
CAD	Canadian dollars
CI	confidence interval
CtE	Commissioning through Evaluation
GI	gastrointestinal
HR	hazard ratio
ICER	incremental cost effectiveness ratio
ICH	intracranial haemorrhage
IQR	inter-quartile range
ISO	International Organisation for Standardisation
LAA	left atrial appendage
LAAO	left atrial appendage occlusion
NICE	National Institute for Health and Care Excellence
OAC	oral anticoagulant
OR	odds ratio
QALY	quality adjusted life years
RCT	randomised controlled trial
SD	standard deviation
TIA	transient ischaemic attack
VAT	value added tax

Appendix 2: additional data extracted from included primary studies

Study	N	Prior stroke/TIA	Prior bleeding	Antiplatelet regimen	Post-procedure stroke
WATCHMAN™					
Chen (2018)[14]	36	16.7%	58.3% (GI and non-GI)	OAC + aspirin for 6 weeks; clopidogrel + aspirin for 6 months; lifelong aspirin monotherapy	No strokes reported at 6 months follow-up
Huang (2017)[26]	106	38.7%	–	Warfarin for 45 days; aspirin (100mg) + clopidogrel (75mg) for 6 months; aspirin monotherapy indefinitely	1 in-hospital stroke: no negative consequences at discharge. 1 ischaemic stroke: all symptoms resolved within 12 weeks with warfarin
Saw (2107)[24]	106	28.3%	89.6% (29.2% ICH)	At physician discretion. Most commonly: aspirin + clopidogrel for 1-6 months; aspirin monotherapy indefinitely. If suitable for OAC: warfarin/DOAC for 45 days; dual antiplatelet therapy for 6 months; aspirin alone indefinitely	No strokes reported at a mean of 7 months follow-up
AMPLATZER™ Amulet					
Chen (2018)[14]	74	21.6%	60.8% (GI and non-GI)	Clopidogrel + aspirin for 3-6 months followed by antiplatelet monotherapy. Reduced/shortened antithrombotic if high bleeding risk on dual therapy	No strokes reported at 6 months follow-up
Landmesser (2018)[27]	1,088	11%	72% (major)	At discharge: 57.6% on dual antiplatelets; 16.8% aspirin; 5.7% clopidogrel/other At 12 months: 9.3% dual antiplatelets; 55.7% aspirin; 7.3% clopidogrel/other	5 ischaemic stroke deaths (29 total ischaemic strokes in 27 patients) at a mean of 11.1 months follow-up
LAmbre™					

Chen (2018)[14]	30	13.3%	70.0% (GI and non-GI)	Clopidogrel + aspirin for 3-6 months followed by aspirin monotherapy. Reduced/shortened antithrombotic if high bleeding risk on dual therapy	No strokes reported at 6 months follow-up
Huang (2017)[22]	153	64.7%	–	Clopidogrel (75mg) + aspirin (100mg) for 3 months; aspirin monotherapy indefinitely	1 ischaemic stroke managed with conservative treatment. 2 ischaemic stroke during 12 months follow-up in patients with a history of stroke
Ultraseal/Ultrasept					
Asmarats (2018)[28]	126	27.0%	77.8%	Dual antiplatelet therapy for 3 months; lifelong aspirin monotherapy (straight to antiplatelet monotherapy if high bleeding risk om dual therapy)	–
Mixed (undifferentiated)					
CtE (2018)[15]	525	49.7% (cerebrovascular accident)	39.3% (major)	–	–
Regueiro (2018)[23]	101	36.6%	82.2%	At physician discretion: 71.3% dual antiplatelet therapy; 28.7% single antiplatelet (aspirin or clopidogrel). No indication of duration of treatment.	7 major strokes – 3 died during follow-up consequent to stroke – at a mean of 50.4 months follow-up

TIA = transient ischaemic attack; GI = gastrointestinal; OAC = oral anticoagulant; DOAC = direct oral anticoagulant; ICH = intracranial haemorrhage