NHS England

Evidence review: Clinical and Cost-Effectiveness and Adverse Events Associated with Left Atrial Appendage Occlusion in Patients for Whom Anticoagulation Therapy is Contraindicated

First published: December 2017

Updated: Not applicable

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Contents

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia (abnormal heart rhythm) seen in clinical practice. Some patients with AF may not experience symptoms relating to their arrhythmia whilst others may experience dizziness, shortness of breath or notice palpitations. AF is associated with around a 4-5 times increased risk of stroke, rising to 23.5% for those aged 80-89 years (Kannel and Benjamin 2008).

The risk of AF-associated stroke can be greatly mitigated using systemic pharmacotherapy, including warfarin, and direct oral anticoagulants (DOACs), also known as novel oral anticoagulants (NOACs), such as dabigatran, apixaban, edoxaban and rivaroxaban. However, warfarin has a narrow therapeutic window and interacts with food and drink, requiring frequent monitoring of international normalized ratio for effective and safe anti-coagulation, and is associated with an increased risk of bleeding including serious intracranial bleeding. Although NOACs may reduce this risk a little, they do not eliminate it. As a consequence, a proportion of people who are predisposed to bleeding, or have had a serious bleed on anticoagulation, are not suitable for long term oral anticoagulation therapy. Additionally, the adverse effects of anticoagulant medication are variably tolerated, have a negative impact on quality of life, and there are consequently issues with compliance. A high proportion of patients voluntarily stop their anticoagulant medication as a result. These patients remain at high risk of stroke and have no treatment option available.

The National Institute for Health and Care Excellence (NICE) reviewed the clinical and safety evidence associated with percutaneous Left Atrial Appendage Occlusion (LAAO) and recommended its use if anticoagulation therapy is contraindicated or not tolerated (CG 180). This interventional procedure can be used to reduce the risk of thromboembolic stroke in patients with AF by physically closing the LAA with a specifically designed implantable device (Perrotta et al. 2014).

Currently, broadly three methods of LAAO are practiced. These are occlusion or removal of the appendage through open surgery, percutaneous closure using an epicardial approach (for example using LARIAT system) and percutaneous closure using an endocardial route. Several LAAO closure devices are currently available for use by the NHS. This review focuses ONLY on percutaneous closure using an endocardial route in accordance with the research questions set out by NHS England.

The percutaneous approach for LAAO is via the femoral vein into the right atrium and then into the left atrium via a transseptal puncture. The location of the LAA is confirmed using angiography and transoesophageal echocardiography (TOE). Then a LAAO closure device of the appropriate size can be implanted.

In 2010, a review of the use of LAAO in patients with AF at high risk of thromboembolic stroke was conducted to inform the NICE Interventional Procedures guidance [IPG349] (National Institute for Health and Care Excellence 2010). Drawing on this experience, NHS England has commissioned a new evidence review in accordance with NHS England Evidence Review Guidance (NHS England 2017).

The objective of this evidence review is to address the following primary research question

(using a new search strategy):

1. What are the clinical outcomes, cost-effectiveness, and adverse events, of left atrial appendage occlusion (LAAO) in patients with atrial fibrillation (AF) for whom anticoagulation therapy is relatively or absolutely contraindicated?

In terms of adverse events, this evidence review sought to address any safety concerns of LAAO in the prevention of stroke, and to describe complications associated with the insertion of the LAAO device at different time points.

This review also addressed a number of secondary sub-questions *based on studies that met the inclusion criteria for the primary research question above*:

2. What were the contraindications for insertion of the device in studies?
3. What are the patient eligibility criteria for the LAAO device in the studies?
4. What were the reasons for oral anti-coagulation drugs being contraindicated in studies?
5. What health care resources are associated with their management and treatment?
6. What is the duration of the initial learning curve to undertaken the procedure and impact of experience on the reduction of complications?
7. Are there any service quality indicators for patient assessment and selection, procedure and follow –up intervals?
8. What anti-antiplatelet drug regimens should be used post-procedure, at discharge, and at follow up after LAAO?

2. Summary of results

Fourteen studies (presented in 20 publications) met the inclusion criteria for **clinical effectiveness and adverse events** (Berti et al. 2016, Betts et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b, Figini et al. 2017, Koskinas et al. 2016, Lopez Minguez et al. 2015, Reddy et al. 2013, Santoro et al. 2016, Seeger et al. 2016, Tzikas et al. 2016, Bergmann et al. 2017, Boersma et al. 2017, Freixa et al. 2016, Huang et al. 2017, Lempereur et al. 2017b, Meerkin et al. 2013, Murarka et al. 2017, Saw et al. 2017, Tzikas et al. 2017). All of these studies were registry or observational studies; no randomised controlled studied were identified that met the inclusion criteria.

Two further studies informed our analysis of **cost effectiveness** (Panikker et al. 2016, Reddy et al. 2016).

Please note this evidence review was restricted to peer-reviewed publications with studies of any design as long as they had a sample size of 100 or above, as well as registry studies that included over 50% patients for whom anticoagulation therapy was contraindicated. Thus, studies with fewer than 100 participants or those only published in conference abstracts were not eligible for inclusion (see section 9).

Clinical effectiveness and adverse events:

The 14 included registry or observational studies ranged in size from 100 to 1,047 patients. These studies reported on various procedure and device-related adverse events (typically ≤ 7 days), as well as follow-up complications and adverse events (with a follow-up duration that ranged from 210.3 [SD 182.2] days to 30 [SD 12] months [264 patient-years] across the studies).

These studies show that LAAO with various devices (Watchman, ACP, Amulet) is associated with a moderate number of peri-procedural complications and low adverse events. The most frequent peri-procedural events were minor pericardial effusion and bleeding. The most frequent complications associated with LAAO devices in the long-term included stroke, bleeding, device-related thrombus and leaks. The percentages of patients with various complications and adverse events is described in detail in Section 4 below.

In terms of stroke, the percentage of patients who experienced peri-procedural stroke was reported in eleven studies and ranged from 0% to 1.2% across these studies. Three studies reported on ischaemic stroke, which ranged from 0% to 1%. The remaining studies did not report on peri-procedural stroke.

All-cause stroke or embolism at follow-up was reported in six studies and ranged from 0% (reported at a mean follow-up of 210.3 ± 182.2 days) to 4.5% (reported at a mean follow-up of 30 ± 12 months). Rates ranged from 1.6 per 100 patient-years to 2.3% per year. Eight studies reported on ischaemic or haemorrhagic stroke. The percentages of patients with ischaemic stroke ranged from 0% (reported at a mean follow-up of 448 (167-793) days) to 2% (reported at a mean follow-up of 400 days). Rates of ischaemic stroke ranged from 0.57 per 100 patient-years to 2.2% per year and rates of haemorrhagic stroke ranged from 0.28 per 100 patient-years to 0.6% per year.

Many of the authors of these registry and observational studies concluded that LAAO appeared to be safe and effective in patients for whom anticoagulation therapy is contraindicated. However, given that these studies are inherently limited by the lack of a control group and had other methodological issues, the results presented by the study authors (as summarised in this evidence review) should be considered with caution and need to be confirmed with data from randomised controlled trials.

Cost-effectiveness:

Results from both studies suggest that LAAC provides long-term clinical and economic benefits when compared with aspirin; one study (Panikker et al. 2016) found that LAAO was also cost saving after year 7 compared with no therapy.

The Panikker (2016) study was a high quality cost study set in England, with good internal validity but poor external validity. The second, slightly weaker study, set in Germany, also lacked external validity (Reddy et al. 2016).

3. Methodology

Identifying Clinical Studies

NHS England's Policy Working Group prepared Population, Intervention, Comparison and Outcomes (PICO) definitions for this review (see section 9 for PICO).

Search strategy

The following bibliographic databases were searched from inception to July 2017: MEDLINE, PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Database of Systematic Reviews (CDSR), NHS EED, CEA Registry, CEA Registry, National Guidelines Clearinghouse, Guidelines International Network: International Guideline Library National Institute for Health and Care Excellence. We also checked the reference lists of relevant systematic reviews and guidelines published in the last three years for any eligible studies that might have been missed by the database searches.

Study selection and extraction

One reviewer screened the titles and abstracts and a second reviewer independently screened 40% of these records. Two reviewers working independently screened the full texts of potentially relevant full papers meeting the review's eligibility criteria.

One reviewer extracted data from all of the eligible documents and recorded the data in evidence summary tables. Studies were quality assessed using the NHS England guidance for conducting evidence reviews (see sections 7 and 8 below). A second reviewer checked 45% of the documents, all of which were full publications.

Synthesis and analysis

The data were synthesised separately for each of the outcomes using a narrative summary and tables (see sections 4 and 8 below). As this was not a full systematic review, we were only able to present a broad overview of the study results from each study. Further synthesis of the data could be conducted in a full systematic review.

Identifying Health Economics Studies

The same PICO criteria were applied to identify economic as well as clinical studies. For economic studies an additional criterion was agreed with NHS England: included studies must be set in the UK or a similar healthcare setting.

4. Results

At the first stage of this evidence review, we screened 3169 titles and abstracts. From these, 262 records were identified as potentially relevant and full papers were obtained and

screened for relevance. Fourteen studies (presented in 20 publications) met the inclusion criteria for clinical effectiveness and adverse events, and a further two studies (presented in two publications) met the inclusion criteria for the cost-effectiveness review. We excluded 240 documents.

During the screening process, we identified the following potentially relevant ongoing trials of clinical-effectiveness, but since no published results are yet available from these trials they could not be included in this evidence review:

- Osmancik P, Tousek P, Herman D, Neuzil P, Hala P, Stasek J, et al. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). Am Heart J. 2017;183:108-14. (NCT02426944)
- 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. Am Heart J. 2017;189:68-74. (NCT02928497)
- AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial (NCT02879448)

Results of the Clinical Studies

The following 14 studies (reported in 20 papers) assessed clinical effectiveness and adverse events (*please note studies are only described as registries if explicitly reported by the study authors*):

- ASAP study (Reddy et al. 2013)
- ACP registry (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)
- EWOLUTION Registry (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)
- UK observational study (Betts et al. 2017)
- Swiss Registry (Koskinas et al. 2016)
- German observational study (Seeger et al. 2016)
- Italian registry Study (Berti et al. 2016)
- Italian observational study 1 (Figini et al. 2017)
- Italian observational study 2 (Santoro et al. 2016)
- Iberian registry (Lopez Minguez et al. 2015)
- Israeli observational study (Meerkin et al. 2013)
- Canadian observational study (Saw et al. 2017)
- American observational study (Murarka et al. 2017)
- Chinese observational study (Huang et al. 2017)

Of the studies that evaluated clinical effectiveness and adverse events, all but two of the studies included only patients for whom anticoagulation therapy was contraindicated, or were characterised by absolute or relative contraindications. The EWOLUTION Registry included 74% of patients for whom long-term anticoagulation

therapy was contraindicated, and another study included 95% patients for whom anticoagulation therapy was contraindicated (Betts et al. 2017).

Mean age ranged between 64 (SD 8.6) to 77 (SD 6) years, and the majority of patients were males ranging from 55% to 89% across the studies. Where reported, the mean $CHADS_2$ score ranged between 2.6 (SD 1.2) and 3.2 (SD 1.2), the mean $CHA2DS_2VASC$ score ranged between 3.6 (SD 1.6) and 4.6 (SD 1.4), and the mean HAS-BLED score ranged between 2.3 (SD 1.2) and 4.2 (SD 1.3).

Five studies evaluated only the Watchman device (ASAP Study; EWOLUTION Registry, Canadian observational study by Saw et al. 2017, American Registry by Murarka et al. 2017; Chinese observational study by Huang et al. 2017). Four studies only evaluated the Amplatzer Cardiac Plug (ACP) (ACP Registry; Italian observational study by Santoro et al. 2016; Iberian registry by López Minguez et al. 2015; Israeli observational study by Meerkin et al. 2013). Two studies evaluated Amplatzer devices (ACP, Amulet) (Switzerland registry study by Koskinas et al. 2016; Italy Registry Study by Berti et al. 2016), two studies evaluated the Watchman and Amplatzer devices (German observational study by Seeger et al. 2016; Italian observational study by Figini et al. 2017). One study conducted in the UK evaluated several devices (Watchman [63%], ACP [35%], Lariat [1.7%], and Coherex WaveCrest [0.6%]) (Betts et al. 2017).

Procedural success was high in all of the included studies and ranged from 88.3% to 100%.

Further details of these 14 studies are presented in Table 7a.

What are the clinical outcomes and adverse events, of left atrial appendage occlusion (LAAO) in patients with atrial fibrillation for whom anticoagulation therapy is relatively or absolutely contraindicated?

As the majority of the studies reported on peri-procedural adverse events and follow-up complications, we have also summarised the results in this same format. Although some studies also dichotomised peri-procedural events as major and minor, not all studies have done so, and studies are not all defined in the same way. Therefore, we have not attempted to make this distinction in this evidence review. As this review is not a full systematic review, we have only presented a broad summary of the findings.

PROCEDURE AND DEVICE-RELATED EVENTS

Procedure and device-related events were typically reported to have occurred within 7 days after LAAO, however, the studies did not always report the time frame. There were 15 types of procedure and device-related outcomes:

1. Procedure and device-related adverse events: Stroke

Eleven studies reported on peri-procedural stroke, which ranged from 0% to 1.2% across the studies. Three studies reported only on ischaemic stroke (ASAP; Seeger et al. 2016;

Figini et al. 2017) which ranged from 0% to 1%. The remaining three studies did not report on peri-procedural stroke.

2. Procedure and device-related adverse events: Overall major and minor peri-procedural events

Eleven studies reported on overall major peri-procedural adverse events. These ranged from 2% to 9%, but the definition of a major adverse event appears to differ slightly among the studies (or may also just reflect how the data were reported in the studies). Many of the studies also reported minor adverse events, ranging from 3% to 4.5% across the studies.

3. Procedure and device-related adverse events: Death

Ten studies reported on peri-procedural deaths, which ranged from 0% to 0.9% across the studies. The remaining four studies did not report on peri-procedural deaths.

4. Procedure and device-related adverse events: Device embolism

Eleven studies reported on peri-procedural device embolism, which ranged from 0% to 2% across the studies. In some studies, the authors reported results separately for device embolisation requiring surgery (ranging from 0.09% to 0.8%) and device embolism snared (ranging from 0.1% to 0.9%). The remaining three studies did not report on peri-procedural device embolism.

5. Procedure and device-related adverse events: Systemic embolism

Five studies reported on peri-procedural systemic embolism. None of the patients in these studies experienced this outcome. The remaining nine studies did not report on peri-procedural systemic embolism.

6. Procedure and device-related adverse events: Pericardial effusion

Nine studies reported on peri-procedural pericardial effusion. Where reported separately, minor pericardial effusion ranged from 0.2% to 8% and major pericardial effusion (requiring an intervention) ranged from 0.3% to 3.2% across the studies. The remaining five studies did not report on pericardial effusion, but some did report on cardiac tamponade (see below) which may have followed pericardial effusion in some patients, but possibly not in others i.e. if cardiac tamponade was used to resolve LAA perforation. *If not explicitly reported as tamponade following pericardial effusion by the study authors, we did not include it here.*

7. Procedure and device-related adverse events: Cardiac tamponade

Twelve studies reported on cardiac tamponade, which ranged from 0.3% to 2.7% across the studies.

8. Procedure and device-related adverse events: Transient ischaemic attack (TIA)

Six studies reported on peri-procedural TIA which ranged from 0% to 1.2% across the studies. The remaining eight studies did not report on peri-procedural TIA.

9. Procedure and device-related adverse events: TIA/Stroke/Embolisation

Two studies reported a combined outcome: TIA/strokes (0.5% in Betts et al. 2017) or TIA/stroke/systemic embolisation (0% in Saw et al. 2017).

10. Procedure and device-related adverse events: Myocardial infarction (MI)

Six studies reported on peri-procedural myocardial infarction, which ranged from 0% to 0.7% across the studies. The remaining eight studies did not report on peri-procedural MI.

11. Procedure and device-related adverse events: Bleeding

Eleven studies reported on peri-procedural bleeding. Minor bleeding ranged from 0% to 11.4% and major bleeding ranged from 0% to 5.8% across the studies. The remaining three studies did not report on bleeding, but one (López Minguez et al. 2015) did also report on vascular complications.

12. Procedure and device-related adverse events: Vascular complications

Eight studies reported on peri-procedural vascular complications. When reported, minor vascular complications ranged from 1.2% to 4.4% and major vascular complications ranged from 0% to 2.2% across the studies.

13. Procedure and device-related adverse events: Air embolisation

Six studies reported on peri-procedural air embolisation, which ranged from 0% to 0.6% across the studies. The remaining eight studies did not report on peri-procedural air embolisation.

14. Procedure and device-related adverse events: Device-related thrombus

Two studies reported on device-related thrombus, which was 0.3% in one study and 0.7% in the other study. The remaining twelve studies did not report on device-related thrombus.

15. Procedure and device-related adverse events: Other peri-procedural events

Eight studies reported 'other' peri-procedural events. The percentage of these events (i.e. oral bleeding, hypotension, need for surgery, re-interventions due to incomplete seal, adverse reaction to anaesthesia, bailout cardiovascular surgery, cardiopulmonary resuscitation, device dislocation, device migration, acute respiratory distress with pulmonary oedema) were generally very low (ranging from 0% to 1.4%). The highest event rates reported were asymptomatic blood pressure drop (transfusions) at 1.9% (Saw et al. 2017) and bailout transcatheter intervention at 2.0% (Koskinas et al. 2016).

FOLLOW-UP COMPLICATIONS AND ADVERSE EVENTS

Follow-up complications and adverse events were reported in twelve of the included studies. Mean follow-up duration ranged from 210.3 (SD 182.2) days to 30 (SD 12) months (264 patient-years). There were 12 types of follow-up and adverse events described below:

1. Follow-up complications and adverse events: All-cause stroke or embolism

Six studies reported on all-cause stroke or embolism during follow-up. The percentage of patients who had an all-cause stroke ranged from 0% (reported at a mean follow-up of 210.3 ± 182.2 days) to 4.5% (reported at a mean follow-up of 30 ± 12 months). When reported, rates ranged from 1.6 per 100 patient-years to 2.3% per year. The remaining six studies did not report on all-cause stroke during follow-up, but one study did report clear percentages for *both* ischaemic and haemorrhagic stroke (Figini et al. 2017). The other studies largely reported on annual rates of ischaemic and/or haemorrhagic stroke (see below).

2. **Follow-up complications and adverse events: Ischaemic or haemorrhagic stroke**

Eight studies reported on ischaemic or haemorrhagic stroke during follow-up. When reported, percentages of ischaemic stroke ranged from 0% (reported at a mean follow-up of 448 (167-793) days) to 2% (reported at a mean follow-up of 400 days). Rates of ischaemic stroke ranged from 0.57 per 100 patient-years to 2.2% per year. Rates of haemorrhagic stroke ranged from 0.28 per 100 patient-years to 0.6% per year.

3. Follow-up complications and adverse events: Overall events

Five studies reported on overall event rates during follow-up. These ranged from 5% to 19.0%, but the events evaluated differed among the studies (or was not specified). The ASAP study reported data by patient-years (Reddy et al. 2013). In this study, the overall events consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism, which occurred at a rate of 4.6% per year.

4. Follow-up complications and adverse events: Death

Ten studies reported on death. Some reported on the peri-procedural period plus follow-up, and others reported only on the follow-up period. The percentage of patients who died ranged from 0% (reported at 12 months follow-up) to 12% (reported at a mean follow-up of 30 ± 12 months). When reported, rates ranged from 1.84 per 100 patient-years to 5.8% per year. The percentage of patients with cardiovascular deaths ranged from 1.6% (reported at a mean follow-up of 680 ± 351 days) to 2.4% (reported at a mean follow-up of 1.3 years). The remaining two studies did not report on death during follow-up.

5. Follow-up complications and adverse events: Device embolism

One study reported on device embolisation (Huang et al. 2017). In this study, device embolisation occurred in 2% of patients during 12 months of follow-up (none occurred within the peri-procedural period).

6. Follow-up complications and adverse events: Systemic embolism

Four studies reported on systemic embolism during follow-up. Two studies reported that no patients experienced systemic embolism, one reported an annual rate of 2.3% (ACP Registry), and one reported a rate of 0.14 per 100 patient-years (Betts et al. 2017). The remaining eight studies did not report on systemic embolism during follow-up.

7. Follow-up complications and adverse events: Transient ischaemic attack (TIA)

Six studies reported on TIA during follow-up, which ranged from 0.7% to 2.3% across the studies. The remaining six studies did not report on TIA during follow-up.

8. Follow-up complications and adverse events: TIA/Stroke/Embolism

Two studies reported on TIA/strokes/embolism during follow-up. One reported a rate of 0.85 per 100 patient-years (Betts et al. 2017) and the other reported an annual rate of 1.5% (EWOLUTION Registry).

9. Follow-up complications and adverse events: Myocardial infarction (MI)

Four studies reported on myocardial infarction (MI) during follow-up, which ranged from 0% to 1.6% across the studies. The remaining ten studies did not report on MI during follow-up.

10. Follow-up complications and adverse events: Bleeding

Ten studies reported on bleeding during follow-up. Four studies reported the percentages of patients who had minor bleeding, which ranged between 0% (at 12 months follow-up) to 4.6% (reported at a mean follow-up of 448 (167-793) days). Five studies reported the percentages of patients who had major bleeding and this ranged between 1% (at 12 months follow-up) to 5.7% (reported at a mean follow-up of 24 months (290 patient-years). Five studies reported the annual rate of major bleeding, which ranged from 1.3% to 4.7%. Three studies reported the annual rate of total bleeding, which ranged from 0.42% to 5.5%.

11. Follow-up complications during follow-up echocardiography: Device-related thrombus

Eleven studies reported on device-related thrombus during follow-up echocardiography. The percentage of patients with device thrombosis ranged from 0% to 8.2%.

12. Follow-up complications during follow-up echocardiography: Leaks

Nine studies reported on leaks identified during follow-up echocardiography. When reported, the percentage of patients with leaks ranged from 11.6% to 37%. Some studies also reported further details by size.

FURTHER RESEARCH QUESTIONS

In addition to assessing the clinical and adverse events of LAAO in patients for whom anticoagulation therapy is contraindicated, this evidence review aimed to address the following questions *based on information presented in the included studies*:

- ***What were the contraindications for insertion of the device in studies?***

Indications for LAAO included both relative and absolute contraindications. These are detailed below (see the third research question). Generally, the most common contraindication for oral anticoagulants (and also indications for LAAO) were previous major bleeding/high risk of bleeding. In some of the included studies, patients also appear to have undergone LAAO in order to avoid triple anticoagulation after LAAO, or were treated for secondary prevention due to a previous stroke on warfarin, or preferred an alternative to OAC, or were non-compliant to OAC. See below for further reasons.

- ***What are the patient eligibility criteria for the LAAO device in the studies?***

Very few of the included studies reported any detailed patient eligibility criteria for inclusion in a study - and thus for LAAO device insertion. The majority of the studies only reported the study population characteristics in their results section (i.e. after inclusion).

Of those studies that reported clear criteria, age was one factor with patients being aged over 18 years of age ((Huang et al. 2017); EWOLUTION Registry (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b); ASAP Study - Reddy et al. 2013). Other criteria cited were that patients had non-valvular atrial fibrillation (Huang et al. 2017; Koskinas et al. 2016; ASAP Study (Reddy et al. 2013); (Seeger et al. 2016, Saw et al. 2017)), a high risk of stroke (Seeger et al. 2016), a $CHADS_2$ or score ≥ 1 (ASAP Study (Reddy et al. 2013); (Santoro et al. 2016); (Saw et al. 2017)), CHA_2DS_2-VASc ≥ 1 ((Seeger et al. 2016, Santoro et al. 2016)), or CHA_2DS_2-VASc ≥ 2 ((Huang et al. 2017, Saw et al. 2017)), or high bleeding risk (HAS-BLED Score >3) (Seeger et al. 2016), eligibility for 6 months of treatment with a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin (ASAP Study (Reddy et al. 2013)) as well as contraindication for oral anticoagulation therapy (ASAP Study (Reddy et al. 2013); (Huang et al. 2017, Koskinas et al. 2016, Seeger et al. 2016, Santoro et al. 2016, Saw et al. 2017)). Criteria reported in single studies were failed OAC (with recurrent thromboembolic events on OAC) (Saw et al. 2017) and patients unwilling to accept long-term OACs (Huang et al. 2017).

The EWOLUTION Registry also specified that patients were eligible for a device "according to current international and local guidelines and per physician discretion", and if the patient was willing and capable of providing informed consent. The US registry

study (Murarka et al. 2017) only stated that "the indications for LAAO were in concurrence with the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) approved criteria that included a heart team decision with shared decision-making by a treating non-implanting physician, patient and implanting physician".

- ***What were the reasons for oral anti-coagulation drugs being contraindicated in studies and the frequencies of specific contraindications?***

The following reasons for contraindication to oral anticoagulation drug (or indications for LAAO) were reported in the included studies:

1. ASAP Study (Reddy et al. 2013):
- History of hemorrhagic/bleeding tendencies: 140 (93.0%);
- Blood dyscrasia: 11 (7.3%);
- Unsupervised senility/high fall risk: 6 (4.0%);
- Other: 8 (5.3%).

2. ACP Registry (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016):
- Previous major bleeding: (47%);
- High risk for bleeding: (35%);
- Coronary stenting mandating triple therapy: (22%);
- In 16% of patients, one of the indications was stroke occurrence despite oral anticoagulant (OAC) treatment.

3. EWOLUTION registry (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b):
- History of major bleeding: (31.3%);
- History of major bleeding or predisposition to bleeding: (38.7%) *(reasons for contraindications were not fully reported*)

4. UK observational study (Betts et al. 2017):
- Embolic event despite therapeutic OACs: (3.5%);
- High risk of bleeding on OAC: 65 (17.6%);
- Intolerance of OACs: 19 (5.1%);
- Lifestyle choice: 20 (5.4%);
- Poor control/labile INR: 12 (3.2%);
- Previous bleed on OACs: 196 (52.8%);
- Previous bleed off OACs: 45 (12.1%).

5. Swiss registry study (Koskinas et al. 2016):
- Frequencies not specified

6. German observational study (Seeger et al. 2016):
- Gastrointestinal bleeding: (41%);
- Intracranial bleeding: (14 %);
- Epistaxis with syncope and need for transfusion: (8%);

- Fall tendency with ≥10 documented falls per 6 months, cerebral ataxia or peroneal nerve paresis (percentage not reported).

7. Italian registry study (Berti et al. 2016):
- Previous bleeding: (77.3%);
- Intracranial haemorrhage: (21.8%);
- Gastrointestinal bleeding: (33.6%);
- Spontaneous haematoma: (0.9%);
- Other (urinary, genital or respiratory tract): (20.9%);
- International normalised ratio (INR) lability: (27.3%);
- Risk of fall: (3.6%);
- Warfarin allergy: (2.7%).

8. Italian observational study (Figini et al. 2017):
- History of severe bleeding: (60%);
- Previous intracranial haemorrhage: (21.2%);
- Coagulopathy (14.7%);
- Increased expected haemorrhagic risk (2.4%);
- Other reasons for LAA closure included: development of LAA thrombosis while being treated with anticoagulant therapy (11.5%) or (presumed) thromboembolic stroke despite adequate treatment (9.7%); indication for DAPT and oral anticoagulation ("triple antithrombotic therapy" 6.1%) or patient preference (4.2%).

9. Italian observational study (Santoro et al. 2016):
- Major (40%) and minor (25%) bleeds occurred in 11% of patients while on OAC, with 56% of the major bleeds being due to intracranial bleeding.

10. Iberian Registry (Lopez Minguez et al. 2015):
- Gastrointestinal haemorrhage: (30.5%);
- Cranial haemorrhage: (22.8%);
- Other haemorrhages: (16.8%);
- Cerebrovascular accident (CVA)/embolism with OAC: (7.2%);
- High risk of bleeding: (4.2%);
- Others: (19.2%).

11. Israeli observational study (Meerkin et al. 2013):
- Bleeding: (67%);
- Gastrointestinal: (40%);
- Intracranial: (15%);
- Ocular: (2%);
- Other sources (epistaxis/respiratory etc.): (11%);
- Compliance: (14%);
- Falls: (9%);
- Sundry: (11%).

12. Canadian observational study (Saw et al. 2017):
- Previous bleeding: (89.6%);

- Major bleeding: (82.1%);
- Minor bleeding: (28.3%);
- High fall risk: 13 (12.3%);
- Recurrent stroke on anticoagulation: 1 (0.9%);
- Other reasons: 10 (9.4%).

13. US registry study (Murarka et al. 2017):
- Frequencies not specified

14. Chinese observational study (Huang et al. 2017):
- Failure to administer or not tolerate with warfarin intake: (77%);
- Haemorrhage: (11%);
- Recurrent embolism under anticoagulant therapy: (8%);
- Poor compliance or other contraindication for anticoagulant therapy: 4 (4%).

- ***What health care resources are associated with their management and treatment?***

None of the included studies reported outcomes that could be used address this question.

- ***What is the duration of the initial learning curve to undertake the procedure and impact of experience on the reduction of complications?***

Two of the included studies provided data that could be used to partly address this question (Betts et al. 2017, Figini et al. 2017).

Betts et al. (2017) compared the first 185 LAAO procedures conducted (Group A) with the last 186 procedures (Group B) in order to examine temporal trends and procedural outcomes. The authors reported a higher rate of procedure success (89.2% vs 95.7%; p=0.018) was observed in Group B, because of a significant reduction of procedures terminated before any attempt to deploy the device (12 vs 1). They also reported a significant reduction in acute major adverse events (6.5% vs 0.5%; p=0.001), due to a reduction of pericardial effusions, major bleeding and vascular complications requiring intervention. In-hospital stay was also shorter in Group B (1.5 ± 1.92 vs 1.1 ± 0.92 days; p=0.040). No significant difference in the acute thromboembolic events rate was observed between the two groups (0.54% vs 0.54%; p=ns), while a significantly lower acute bleeding event rate was seen in Group B (4.32% vs 1.07%; p=0.001). Overall, the authors stated that procedural success and safety increased with operator and centre experience.

Figini et al. (2017) reported that there 'was a (non-statistically significant) trend toward a reduction in incidence of leak in the procedures performed in the second half of the study period (OR 0.509 for leaks >1 mm; 95% CI: 0.211 to 1.228; P = 0.133), indicating a possible positive effect associated with the learning curve (other outcomes were not analysed to evaluate a learning curve).'

- ***Are there any service quality indicators for patient assessment and selection, procedure and follow –up intervals?***

None of the included studies reported outcomes that could be used address this question.

- ***What anti-antiplatelet drug regimens should be used post – procedure, at discharge and follow-up after LAAO?***

Many of the included studies reported medications provided after LAAO, and sometimes also at baseline and in the long-term. This information is not, however, enough to assess what anti-antiplatelet drug regimens *should* be used. Further detailed analyses are beyond the scope of this evidence review. The following three studies provided some additional analyses or recommendations:

The EWOLUTION study (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b) evaluated outcomes (bleeding, ischaemic stroke, device thrombus) stratified by post-procedural medication regimens, but found no statistical differences between these outcomes, and made no recommendations.

Seeger et al. (2016) compared six months of dual antiplatelet therapy with three months' therapy and reported that bleeding events were higher in the six month group (16.2%) compared with the three months group (3.0%) ($p < 0.05$). There was no significant difference between the groups in residual flow or incidence of stroke, but the authors did not make definitive recommendations.

In contrast, Figini et al. (2017) reported that "a therapeutic regimen including dual antiplatelet therapy for the first months, followed by aspirin alone if TEE confirms absence of significant leaks and thrombosis, appears an acceptable management strategy, but should be tailored according to individual risk profile."

Table 7a shows the drug regimens used after LAAO for each study.

Results of the Health Economics Studies

Following record selection using titles and abstracts only, 262 documents were assessed for relevance. Two health economics studies were eligible (Panikker et al. 2016, Reddy et al. 2016). 260 publications were excluded.

Panikker et al. (2016) reported the results of a cost-impact analysis, together with a LAAC registry study conducted in England, outcomes of which informed parts of the cost analysis. Relevant comparators were patients managed on aspirin and those on no therapy. Clinical outcomes for these arms came from a network meta-analysis of medicines for non-valvular AF (Dogliotti et al. 2014). Resource use came from hospital records and unit costs from English national tariff datasets (National Tariff Payment System) and other published sources. The model had a 10 year time horizon.

Reddy et al. (2016) reported the results of a cost-effectiveness model, which compared LAAO with aspirin and clopidogrel therapy, over a 20-year time horizon. Clinical inputs were drawn from several sources and no attempt was made to adjust for differences in the patients included in the various studies. Resource usage was poorly reported but seemed to include resources used in social care settings to manage patients with disabilities. Unit costs

were from German national datasets. Benefits were measured in quality-adjusted life years (QALYs) and results expressed as an incremental cost-effectiveness ratio (ICER).

Evidence tables and quality assessment findings are provided in Section 7 and Appendix B respectively.

What is the cost-effectiveness of LAAO in patients for whom anticoagulation therapy is contraindicated?

Results from both studies suggest that LAAC provides long-term clinical and economic benefits when compared with antiplatelet therapy in patients unable to be managed on oral anticoagulants. The Panikker et al (2016) results and sensitivity analyses reported cost-savings with LAAC against aspirin and no therapy by year 7 following the LAAO procedure. At year 10, forecast savings with LAAO were reported as £5,387 per person compared to no therapy and £3,857 per person compared to treatment with aspirin. Reddy et al. (2016) also reported LAAO was cost saving by year 7 compared with aspirin and clopidogrel; estimated savings were 5,240€ (about £4,200 in 2014 prices) at 10 years following the procedure.

5. Discussion

Discussion of Clinical Studies

Fourteen studies provided evidence on clinical effectiveness and adverse events. These studies show that LAAO with various devices (Watchman, ACP, Amulet) is associated with a moderate number of peri-procedural complications and low adverse events. The most frequent peri-procedural events were minor pericardial effusion and bleeding. The most frequent complications associated with LAAO devices in the long-term included stroke, bleeding, device-related thrombus and leaks.

There were a number of issues with how the studies reported data, which means that the percentages reported for the outcomes may not always be directly comparable across the studies. For example, some of the included studies presented overall complications or adverse events using different criteria. In addition, some of the authors reported follow-up data without also including the peri-procedural outcomes, whereas other authors reported both together. Sometimes authors did not clearly differentiate between percentages calculated from events or patients. Lastly, a number of studies did not consistently report all potential complications or adverse events. The studies may not also be directly comparable given different baseline characteristics, different LAAO devices implanted, and different medication regimens after LAAO.

More research is needed to confirm the current results of these registry studies and their results should be interpreted with caution. Some resolution may become apparent when the results from the ongoing trials identified above are published (i.e. NCT02426944; NCT02928497; NCT02879448).

Discussion of Health Economics Studies

The Panikker (2016) study was scored as 8/10, having good internal validity but poor external validity; whilst Reddy et al. (2016) was also of reasonable quality, scoring 7/10, with the main concern also being external validity. Both studies identified conflicts of interest. With Panikker (2016), 2 authors received research grants from Boston Scientific, whilst it provided financial support to Reddy et al. (2016). This company manufactures the WATCHMAN device.

Results from both studies suggest that LAAC provides long-term clinical and economic benefits when compared with aspirin; one study (Panikker et al. 2016) found LAAO was also cost saving after year 7 compared with no therapy.

The use of German costs is the key limitation with Reddy et al. (2016). The key limitation with the Panikker (2016) study is the assumed device and procedure cost per patient of £6,334 which was taken from an existing NHS tariff adjusted by 30%. This is materially lower than the cost obtained by the EAC when undertaking a bottom-up costing, using resource use information from the NHSE LAAO registry. This estimated procedure costs of £11,600 per patient. If one adopts the higher cost of £11,600 per patient then, at 10 years after the procedure, LAAO would have similar costs to no therapy but higher costs than those managed on aspirin.

6. Conclusion

Clinical Studies

Many of the authors of these registry and observational studies concluded that LAAO appeared to be safe and effective in patients for whom anticoagulation therapy is contraindicated. However, given that these studies are inherently limited by the lack of a control group and had other methodological issues, the results presented by the study authors (as summarised in this evidence review) should be considered with caution and need to be confirmed with data from randomised controlled trials.

Health Economics Studies

The review of health economics studies identified one high quality cost study set in England (Panikker et al. 2016) and a second, slightly weaker study, set in Germany, which lacked external validity (Reddy et al. 2016). The Panikker (2016) study identified that LAAO was cost saving after 7 years compared with aspirin or no therapy but there are major concerns about the procedure costs used. A simple, crude adjustment to the LAAO procedure costs suggests LAAO has similar costs to patients unable to be managed on any therapy. However, a new cost study is required to provide robust information for decision making purposes.

7. a. Evidence Summary Table for Clinical Studies

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
ASAP Study (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) *Paper*: (Reddy et al. 2013)	Multicentre, prospective non-randomised study 4 centres in 3 countries (USA, Germany, Czech Republic) between Jan 2009 and Nov 2011	N=150 patients 'with contraindication for oral anticoagulation' Mean age: 72.5 (SD 7.4) years; Male 96 (64.0%) Stroke risk factors: Heart failure or reduced LVEF: 43 (28.7%); Hypertension: 142 (94.7%); Age ≥75 years: 64 (42.7%); Diabetes mellitus: 48 (32.0%); Prior stroke or TIA: 61 (40.7%); Vascular disease: 27 (18.0%) Age 65 to 74 years: 64 (42.7%); Female 54 (36.0%) CHADS2 score: 1: 22 (14.7%); 2: 39 (26.0%); 3: 52 (34.7%);	Intervention: Percutaneous closure using the **WATCHMAN** device. Following implantation, patients were treated with 6 months of thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin **Reasons for warfarin ineligibility:** History of haemorrhagic/bleeding tendencies: 140 (93.0%); Blood dyscrasia: 11 (7.3%); Unsupervised senility/high fall risk: 6 (4.0%); Other 8 (5.3%) **Procedural success:** 142/150 patients (94.7%)	**Procedure and device related adverse events** (timeframe not reported)	Procedure and device-related serious adverse events: 13/150 (8.7%) Device embolism: 2/150 (1.3%) Pericardial effusion with tamponade (percutaneous drainage): 2 (1.3%) Pericardial effusion, no tamponade (no intervention required): 3 (2.0%) Device thrombus with ischemic stroke* 1 (0.7%) Femoral pseudoaneurysm (surgically repaired): 1 (0.7%) Femoral haematoma/bleeding: 2 (1.3%) Other: 3 (2.0%) (oral bleeding, n=1; intraprocedural hypotension, n=2) *Device thrombus and stroke occurred in a single patient, but was counted as 2 adverse events	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Directly applicable	Inherently limited by the absence of a control; prone to selection bias An independent clinical events committee adjudicated all adverse events The authors determined a sample size of 150 based on feasibility (not statistically calculated)
				Follow-up complications and adverse events	Mean follow up 14.4 ± 8.6 months (176.9 patient-years follow-up): Composite endpoint*: 8/175 patient-years (4.6% per year) All-cause stroke or embolism: 4/176.0 patient-years (2.3% per year) Ischaemic stroke: 3/ 176.9 patient-years (1.7% per year) Haemorrhagic stroke: 1/179 patient-years (0.6% per year) Death: 9/180 patient-years (5.0% per year). None were considered to be device			

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		4: 23 (15.3%); 5: 13 (8.7%); 6: 1 (0.7%). Mean CHADS2 score: 2.8 (SD 1.2) CHA2DS2-VASC scores: 1: 7 (4.7%); 2: 12 (8.0%); 3: 25 (16.7%); 4: 42 (28.0%); 5: 28 (18.7%); 6: 18 (12.0%); 7: 13 (8.7%); 8: 5 (3.3%); 9: 0 (0.0%). Mean CHA2DS2-VASC score: 4.4 (SD 1.7)			or procedure related *Composite endpoint (primary efficacy endpoint) that consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism There were 6/150 cases (4%) of device-related thrombus on the device face, but only 1 resulted in clinical sequela (an ischemic stroke). The remaining 5 thrombi were detected during routine TEE screening			
Amplatzer Cardiac Plug (ACP) Multicenter Registry *Papers*: (Freixa et al. 2016) (Tzikas et al. 2016) (Tzikas et al. 2017)	Multicentre, retrospective non-randomised study 22 centres between Dec 2008 and Nov 2013	N=1,047 'mostly characterised by an absolute or relative contraindication to oral anticoagulation' Mean age:75 (SD 8) years; >65 years: 939 (90%); >75 years: 577 (55%) Male: 648 (62%);	Intervention: Percutaneous closure using **Amplatzer** Cardiac Plug (ACP). Dual-antiplatelet therapy (DAPT) was the most common antithrombotic therapy after LAAO with an average duration of 3.8 months **Main indication for LAAO**: Previous major	**Peri-procedure major adverse events (0-7 days)**	Peri-procedural major adverse events*: 51/1047 (4.97%) (*reported as n=52 in Tzikas et al. 2015*) Procedure-related deaths: 8 (0.8%) Stroke: 9 (0.9%) Transient ischaemic attack (TIA): 4 (0.4%) Systemic embolism: 0 (0.0%) Myocardial infarction: 1 (0.1%) Cardiac tamponade: 12 (1.2%) (*reported as 13 in Tzikas et al. 2015*) Major bleeding: 13 (1.3%) Minor bleeding: 25 (2.4%) Device embolisation: 8 (0.8%) (1 requiring surgery and 7 device embolization snared) (*reported as 10 in Lempereur et al. 2017 and Tzikas et al. 2015; Tzikas reported that 2 resulted in death, one required surgery, and 7 were snared*) Need for surgery: 0 (0%) (apart from	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score	Directly applicable	Inherently limited by the absence of a control There was no independent adjudication for events and the follow-up of the total cohort was not done by neurologists Large sample size

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Lempereur et al. 2017b)		Atrial fibrillation, Permanent: 594 (57%); Paroxysmal/persistent: 453 (43%); Heart failure: 274 (26%); Arterial hypertension: 909 (87%); Diabetes mellitus: 306 (29%); Previous stroke/TIA: 404 (39%); Carotid disease: 87 (8%); Coronary artery disease: 367 (36%); Myocardial infarction: 164 (16%); Percutaneous coronary intervention: 228 (22%); Peripheral embolization: 56 (5%); Labile INR: 141 (13%). CHADS2 score: 2.8 (SD 1.3); CHA2DS2-VASc score: 4.5 (SD 1.6); CHA2DS2-VASc	bleeding (47%), followed by high risk for bleeding (35%) and coronary stenting mandating triple therapy (22%). In 16% of patients, one of the indications was stroke occurrence despite oral anticoagulant (OAC) treatment **Procedural success:** 1,019 of 1,047 patients (97.3%)		device embolisation) Tamponade: 16 (1.5%) Air embolisation: 5 (0.5%) Device-related thrombus: 3 (0.3%) Other complications: 15 (1.4%) *consisted of death, myocardial infarction, stroke, transient ischemic attacks (TIAs), systemic embolisation, air embolisation, device embolization, significant pericardial effusion or cardiac tamponade, and major bleeding (requiring surgery or transfusion)	of 1). Total score: 7		
				Follow-up complications and adverse events	Adverse events during *total* follow-up (mean 1.3 years [1,349 patient years]): Major adverse events (stroke, TIA, major bleeding, death): 107 (10.2%) Death: 80 (7.6%) Cardiovascular death: 24 (2.4%) Stroke: 16 (1.6%) Transient ischaemic attack (TIA): 13 (1.3%) Major bleeding: 27 (2.7%) Intracranial haemorrhage: 0 (0.0%) Device-related thrombus: 28/632 patients (with complete clinical follow-up) (4.4%) (*Tzikas et al. 2015 reported data for follow-up period only, not peri-procedural + follow-up)* One-year all-cause mortality rate was 4.3% Stroke (procedure + follow-up): 1.6 per 100 patient-years Ischaemic stroke (procedure + follow-up): 1.5 per 100 patient-years Annual rate of systemic thromboembolism (procedure + follow-up): 2.3% (31/1,349 patient-years)			

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		score ≥3: 742 (72%); HAS-BLED score: 3.1 (SD 1.2)			Annual rate of major bleeding (procedure + follow-up): 2.1% (28/1,349 patient-years) A peri-device leak was found in 73 patients (11.6%). The leak was trivial, mild, and significant in 27 (4.3%), 34 (5.4%), and 12 (1.9%) patients, respectively			
EWOLUTION Registry *Papers*: (Boersma et al. 2016b) (registry design) (Boersma et al. 2016a) (peri-procedural outcomes up to 30 days) (Bergman n et al. 2017) (3-month data) (Boersma et al. 2017) (per-procedure and 1-year	Multicentre, prospective non-randomised study 47 centres in 13 countries between Oct 2013 and May 2015	N=1025 patients of which '73.5% were deemed contraindicated for long-term oral anti-coagulation therapy' *Data as presented in most recent publication (earlier publication info slightly differs)* Mean age at the time of consent: 73.4 (SD 8.9) years; ≥75 years: 520/1025 (50.7%) Female: 411/1025 (40.1%) CHA_2D_2-VASc score: 4.5 (SD 1.6); ≤1: 19/1024 (1.9%);	Intervention: Percutaneous closure using the **WATCHMAN** device. Following implantation, 16% received a vitamin K antagonist (VKA); 11% received non-oral anticoagulation (dabigatran, rivaroxaban, apixaban), 60% received dual antiplatelet therapy, 7% received single antiplatelet therapy, and 6% did not receive anticoagulation. During follow-up, discontinuation of clopidogrel and (N)OAC occurred, resulting in 84% of patients receiving anti-platelet therapy (55% single and 28% dual) and 9% had no medications. The average time	**Procedure and device related serious adverse events (≤ 7 days and up to 30 days)**	**(≤ 7 days):** Major adverse cardiac events*: 18/1020 (1.8%) *Percentages have been calculated below:* All deaths (0–7 days): 4 (0.4%) Major bleeding: 9 (0.9%) Cardiac tamponade/significant pericardial effusion: 3 (0.3%) Device embolisation requiring surgery: 1 (0.1%) Device embolisation snared: 1 (0.1%) Stroke: 0 (0%) Systemic embolism: 0 (0%) Myocardial infarction: 0 (0%) Other events requiring surgery/major intervention: 0 (0%) *Major cardiac adverse events include 5 events (3 deaths and 2 major bleeding events) that are deemed unrelated to the procedure Other peri-procedural serious adverse events: 15/1020 (1.5%) *Percentages have been calculated below:* Vascular complications @ groin: 4 (0.4%) Air embolism (coronary): 2 (0.2%) Minor pericardial effusion (untreated): 2 (0.2%) Re-interventions due to incomplete seal: 2 (0.2%) Minor bleeding (untreated)/haematoma: 2 (0.2%) Transient ischaemic attack (TIA): 1 (0.1%)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 1); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 6	Somewhat applicable (74% patients contraindicated)	Inherently limited by the absence of a control The study authors also noted that detailed information on the management and resolution of device thrombus was not systematically captured in the study database. All centres were monitored by an outside contract research organisation; events and relevant source documents were reviewed by the Sponsor Medical Safety Group. Sample size was estimated to obtain sufficiently precise estimates

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
follow-up)		2–3: 257/1024 (25.1%); ≥4: 748/1024 (73.0%); HAS-BLED score: 2.3 (SD 1.2); <3: 614/1024 (60.0%); ≥3: 410/1024 (40.0%) Congestive heart failure: 350/1024 (34.2%) New York Hearth Association (NYHA) class: I: 36/348 (10.3%); II: 194/348 (55.7%); III: 111/348 (31.9%); IV: 7/348 (2.0%) Left ventricle ejection fraction (LVEF) ≤40%: 135/1022 (13.2%) Vascular disease: 429/1024 (41.9%) Abnormal renal	to discontinue dual antiplatelet therapy was 6 months, but a large proportion of subjects (25%) used a short dual antiplatelet therapy regimen (≤3 months) **Contraindicated**: 751/1024 (73.3%); History of major bleeding: 320/1024 (31.3%); History of major bleeding or predisposition to bleeding: 396/1024 (38.7%) *(reasons for contraindications not fully reported*) **Procedural success:** 1,004 of 1,019 patients (98.5%)		Hypotension: 1 (0.1%) Adverse reaction to anaesthesia: 1 (0.1%) Procedure-and or device related SAEs within 7 days: 2.8% event rate (95% CI: 1.9% to 4.0%) *Subgroup post hoc analysis was also conducted on OAT ineligible vs OAT eligible patients; serious procedure-/device related events through 7 days were 2.2% vs. 3.8% (p=0.129)* **Up to 30 days** (n=1019): Device-/procedure related SAEs: 34 (in 32 patients) *(there were also 50 unrelated serious adverse events for a total of 84 adverse events in 73 patients)* Major bleeding requiring transfusion: 8 Other bleeding complications (haematoma, haemoptysis, haematuria, and anaemia requiring transfusion): 2 Pericardial effusion (requiring subxphoidal or surgical pericardiocentesis): 3 Cardiac tamponade: 2 Strokes: 1 Suspected transient ischaemic attack (TIA): 0 Pulmonary embolism: 0 Air embolism: 3 Device embolisation: 2 Adverse reaction to anaesthesia: 2 Reintervention due to incomplete seal: 2 Vascular damage at puncture site: 5 Hypotension: 1 Other cardiovascular conditions: 1 Other non-cardiac conditions: 2 Procedure-and or device related SAEs within 30 days: 3.6% event rate (95% CI:			of rare events 1020/1025 completed the study; 5 patients were withdrawn from the study and did not have the implant The subgroup data are considered exploratory The authors stated that the final end-point is two-year follow up – but these data have not yet been published Some sample sizes and results differ or are not clear in the various publications, so difficult to know which results are correct [1]none of the possible sample sizes (denominators) reported in text work with the percentages presented (data not clearly

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		function: 162/1024 (15.8%); Abnormal liver function: 44/1024 (4.3%); Hypertension: 885/1024 (86.4%); Diabetes: 304/1024 (29.7%); Previous ischemic stroke/TIA: 312/1024 (30.5%); Previous haemorrhagic stroke: 155/1024 (15.1%)			2.5% to 4.9%) Overall 30 day mortality rate: 0.7% *Subgroup post hoc analysis was also conducted on OAT ineligible vs OAT eligible patients; serious procedure-/device related events through 30 days were 2.9% vs. 4.7% (p=0.148)*			reported)
				Follow-up complications and adverse events	**3 months** (n=943) (*calculated based on the authors stating that 1005 patients were implanted, and the three month data represented 94% of study population*): All deaths: 24 (percentage not reported) All bleeding complications: 40 (4.1%)* Major bleeding SAE: 25 (2.6%)* Major bleeding SAE excluding procedural: 17 (1.8%)* Ischaemic stroke SAE: 4 (0.4%)* Device thrombus: 20 (2.6%)* *reported as percentages based on Kaplan-Meier estimation **1 year follow-up** (n=893): Death rate: 91/n?[1] (9.8%) (*reported as n=98 in abstract and n=91 in text*). The authors stated that cause of death was known in 77 of 91 patients; none were considered to be complications of the device. Haemorrhagic stroke: 0 (0%) Annual rate of ischaemic stroke: 15/1325 patient-years (1.1% per year) Annual rate of ischaemic stroke/TIA/thromboembolism: 20/1318 patient-years (1.5% per year) Annual rate of major bleeding: 34/1303 patient-years (2.6% per year) (the majority occurred outside of the peri-procedural period) Device thrombus: 28/n?[1] (3.7%)			

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					No leaks >5mm: 1002/1005 (99.7%)			
Observational study - UK *Paper*: (Betts et al. 2017)	Multicentre, retrospective non-randomised study 8 centres in the UK between Jul 2009 and Nov 2014	N=371 patients 'the majority [94.6%] with contraindications to oral anticoagulation' Mean age: 72.9 (SD 8.26) years; Male: 330 (88.9%); History of atrial fibrillation: Paroxysmal: 105 (28.3%); Persistent: 76 (20.5%); Permanent: 190 (51.2%); Left ventricular ejection fraction - Normal (>55%): 315 (84.9%); Moderately impaired (30–55%): 48 (13%); Severely impaired (<30%): 8 (2.1%); Risks factors for stroke - History of heart failure:	Intervention: LAAO using **WATCHMAN** (63%), **ACP** (35%), **Lariat** (1.7%), **Coherex WaveCrest** (0.6%) Peri- and early post-procedural (until first follow-up visit) antithrombotic regimen: Single antiplatelet therapy (APT) (aspirin-clopidogrel): 40 (10.8%); Dual APT: 186 (50.1%); Anticoagulation (AC) (warfarin, non-vitamin K antagonist oral anticoagulants, low molecular weight heparin): 76 (20.5%); AC plus single APT: 69 (18.6%). **Indication for LAAO:** Embolic event despite therapeutic OACs: 13 (3.5%); High	**Acute adverse events** (timeframe not reported)	Acute major events:* 13/371 (3.5%) Pericardial effusions with tamponade (pericardial drain/surgery): 2 (0.5%) Device embolisations (percutaneous/surgical retrieval): 3 (0.8%) Major bleedings (fatal): 5 (1.4%) TIA/strokes (ischemic/haemorrhagic): 2 (0.5%) Vascular complications requiring intervention; 5 (1.4%) Death: 1 (0.3%) (procedure-related) Systemic embolism: 0 (0%). * Acute major adverse events were defined as those resulting in death or requiring intervention or prolonged hospital stay (i.e., pericardial effusions requiring percutaneous drain or surgery, device embolization requiring percutaneous or surgical retrieval, neurological events, bleeding requiring transfusion or surgical intervention, vascular complications requiring surgical treatment). Acute minor complications* (no intervention required): 11/371 (3.0%) Pericardial effusions not requiring intervention: 8 (2.2%) Minor bleeding: 3 (0.8%) * Acute minor adverse events were defined as those not requiring intervention or prolonging hospital stay (small pericardial effusions requiring no treatment, minor hematomas). All ischemic	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Somewhat applicable (95% with contraindications and 98% devices eligible for inclusion in this review)	Inherently limited by the absence of a control This study included different devices, including Lariat (2%)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		71 (19.1%); Hypertension: 277 (74.7%); Diabetes: 70 (18.9%); Previous TIA/stroke: 184 (49.6%); History of Ischaemic heart disease: 335 (90.3%); Peripheral vascular disease: 93 (25%); Age ≥75 years: 170 (45.8%); Age 65–74 years: 138 (37.2%) $CHADS_2$ score: 2.63 (SD 1.24); 0: 11 (3%); 1: 62 (16.7%); 2: 101 (27.2%); 3: 100 (27%); 4: 74 (19.9%); 5: 22 (5.9%); 6: 1 (0.3); CHA_2DS_2-Vasc score: 4.22 (SD 1.56); 1: 10 (2.7%); 2: 51 (13.8%); 3: 62 (16.7%); 4: 90 (24.3%); 5: 74 (19.9%); 6: 58 (15.6%); 7: 22 (5.9%);	risk of bleeding on OACs; 65 (17.6%); Intolerance of OACs: 19 (5.1%); Lifestyle choice: 20 (5.4%); Poor control/labile INR: 12 (3.2%); Previous bleed on OACs: 196 (52.8%); Previous bleed off OACs: 45 (12.1%) **Procedural success:** 343 of 371 patients (92.5%)		neurological events were considered as strokes (without distinction between strokes and transient ischemic attacks (TIAs)).			
				Follow-up complications and adverse events	Follow-up at 24.7 ± 16.07 months (706 patient-years): Deaths: 13 (1.84 per 100 patient-years) Cardiovascular deaths: 10 (1.42 per 100 patient-years) (Haemorrhagic strokes): (2) (0.28 per 100 patient-years) Non-cardiovascular deaths: 3 (0.42 per 100 patient-years) TIAs/strokes: 6 (0.85 per 100 patient-years) Haemorrhagic stroke: 2 (both fatal) (0.28 per 100 patient-years) Ischaemic strokes: 4 (0.57 per 100 patient-years) Systemic embolism: 1 (0.14 per 100 patient-years) TIAs/strokes/systemic embolism: 7 (0.99 per 100 patient-years) Myocardial infarction: 1 (0.14 per 100 patient-years) Major bleedings: 3 (2 fatal) (0.42 per 100 patient-years) Minor bleedings: 7 (0.99 per 100 patient-years) Total bleeding: 10 (1.42 per 100 patient-years). Annual ischaemic stroke rate: 0.57% (4/706 patient-years) Annual thromboembolic (TIA, ischaemic stroke, or systemic embolism) event rate: 0.71% (5/706 patient-years)			

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		8: 4 (1.1%) HAS-BLED score: 3.34 (SD 1.17); 0: 2 (0.5%); 1: 17 (4.6%); 2: 64 (17.2%); 3: 126 (34%); 4: 106 (28.6%); 5: 46 (12.4%); 6: 8 (2.2%); 7: 2 (0.5%)			Annual bleeding rate: 0.42% (3/706 patient-years)			
Registry study - SWITZERLAND *Paper*: (Koskinas et al. 2016)	Multicentre, prospective non-randomised study 2 centres in Switzerland between 2009 and 2014 (month not stated)	N=500 patients 'who had absolute or relative contraindications to oral anticoagulation treatment [and] were deemed by their physicians to be at high risk for OAC treatment, or preferred an alternative OAC' Mean age: 73.9 (SD 10.1) years; Female: 152 (30.4%); Cardiac risk factors: Diabetes mellitus: 116 (23.2%); Arterial hypertension:	Intervention: Percutaneous closure using **Amplatzer** devices (ACP, Amulet). OAC was discontinued immediately following successful LAAC, and dual-antiplatelet therapy was initiated, consisting of aspirin 100 mg for at least 5 months and clopidogrel 75 mg for 1 to 6 months **Indication for LAAC**: was absolute or relative contraindication to OAC in 419	**Procedure- and device-related major adverse events** (within 7 days)	Major adverse events*: 29 (5.8%) Death: 2 (0.4%) Stroke: 5 (1.0%) Major/disabling: 1 (0.2%) Pericardial effusion: 33 (6.6%) Serious pericardial effusion**: 16 (3.2%) Bailout cardiovascular surgery: 5 (1.0%) Bailout transcatheter intervention: 10 (2.0%) Cardiopulmonary resuscitation: 7 (1.4%) Vascular access complication related to LAAC: Major: 0 (0%) Minor: 22 (4.4%) Vascular access complication unrelated to LAAC: 8 (1.6%) Bleeding related to LAA: Life-threatening: 16 (3.2%) Major: 1 (0.2%) Minor: 57 (11.4%) Bleeding unrelated to LAAC: 8 (1.6%) Device embolisation: 10 (2.0%) Air embolisation not resulting in stroke: 3 (0.6%) *Composite of death, stroke, Valve Academic Research Consortium major or life-threatening bleeding, major access	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Directly applicable	Inherently limited by the absence of a control All events were adjudicated, and relatedness to the device or procedure was determined by an independent clinical events committee. No independent monitoring was conducted No long-term outcomes presented

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		441 (88.2%); Coronary artery disease: 305 (61%); Previous PCI/CABG: 291 (58.2%); Previous myocardial infarction: 116/467 (24.85); History of systemic embolization: 137 (27.4%); Previous stroke: 151 (30.1%); Ischemic stroke: 116 (23.2%): eGFR (ml/min/1.73 m^2): 69.6 (SD 33.1); eGFR <60 ml/min/1.73m^2: 217 (43.4%); Atrial fibrillation Permanent/ Paroxysmal: 253 (50.6%); LVEF (%): 54.9 (SD 11.5); LVEF ≤30%: 35 (7%); HAS-BLED score: 2.95 (SD 1.12); HAS-BLED score ≥3: 334 (66.8%); $CHADS_2$ score: 2.57 (SD 1.31);	patients (**84%**) and LAAC as an alternative to OAC in 81 patients (16%) **Procedural success:** 489 of 500 patients (97.8%)		vessel complication, device embolisation, need for cardiovascular surgery, cardiopulmonary resuscitation, and serious pericardial effusion **Hemodynamically significant pericardial effusion requiring drainage or prolonging hospitalization			

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		$CHADS_2$ score ≥3 251 (50.2%); CHA_2DS_2-VASc score: 4.33 (SD 1.66)						
Observational study - GERMANY *Paper*: (Seeger et al. 2016)	Prospective, non-randomised study Number of centes and dates not reported	N=101 patients 'with contraindications to long-term oral anticoagulation or at high risk of bleeding' Mean age: 74.7 ± 7.5 years; Female: 43 (43%) Atrial fibrillation – Paroxysmal: 41 (41%); Persistent: 22 (22%); Permanent: 38 (38%); CHA2DS2-VASc Score: 4.4 ± 1.6; HAS-BLED-Score: 4.2 ± 1.3; LVEF, %: 48.7 ± 13.0; Diabetes: 34 (34%);	Intervention: Percutaneous closure using the **WATCHMAN** (38%) or **AMPLATZER (63%)** devices**.** During procedure, heparin was administered. Dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg was recommended for 6 months (n = 68; 67 %) followed by a recommendation for 3 months (n = 33; 33 %) after device implantation, followed by long-term antiplatelet therapy with aspirin 100 mg daily. No oral anticoagulation	**Procedure-related serious complications** (timeframe not reported)	Procedure-related serious complications: 3 (3%) Pericardial tamponade (requiring pericardiocentesis): 2 (2%) Ischaemic stroke: 1 (1%)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 0); the results are generalisable (score of 1). Total score: 6	Directly applicable	Inherently limited by the absence of a control The authors stated that only first generation devices were used so may not be translated to the newest generation of devices Very few outcomes presented
				Follow-up complications and adverse events	Mean follow-up (400 days) (*follow-up only*) (n=101): Transient ischemic attack (TIA): 1 (1%) Ischaemic stroke: 2 (2%) Bleeding events: 14 (14%) Device thrombus: 2 (2%) Three months post-device implantation, there was residual flow <5 mm in 15 % (14/94). Twelve months post-device implantation, 14 % of patients showed residual flow <5 mm.			

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		History of TIA/ischemic stroke: 22 (22%); Renal insufficiency:53 (53%); Coronary artery disease: 63 (63%)	was recommended after device implantation **Indication for LAAO and contraindication for long-term OAC**: Gastrointestinal bleeding: 41%; intracranial bleeding: 14 %; epistaxis with syncope and need for transfusion: 8 %; Fall tendency with ≥10 documented falls per 6 months, cerebral ataxia or peroneal nerve paresis (% not reported). **Procedural success:** NR (implantation success was 100%)					

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Registry study - ITALY *Paper*: (Berti et al. 2016)	Single centre, prospective non-randomised study 1 centre in Italy between Jan 2009 and June 2014	N=110 patients 'with contraindications to oral anticoagulants' Mean age: 77± 6 years (range 65–94); Men: 68 (61.8%); Atrial fibrillation type: Paroxysmal: 22 (20%); Persistent: 17 (15.5%); Permanent:71 (64.5%); Arterial hypertension: 99 (90%); Diabetes mellitus: 34 (30.9%); Previous thromboembolic events: Stroke: 26 (23.6%); Transient ischaemic attack (TIA): 7 (6.4%); Peripheral embolism: 2 (1.8%); Heart failure: 14 (12.7%); Coronary artery disease: 31 (28.2%); Renal	Intervention: Percutaneous closure using **ACP** (91%) or **Amulet** (19%) devices. No anticoagulation therapy was administered after the procedure. As a general rule, dual antiplatelet therapy with aspirin (250 mg intravenous load, followed by 100 mg daily) plus clopidogrel (300 or 600 mg load, followed by 75 mg daily) was given for 3 months after the procedure, with subsequent single antiplatelet therapy **Reasons for contraindication to anticoagulation therapy:** Previous bleeding: 85 (77.3%); Intracranial haemorrhage: 24 (21.8%); Gastrointestinal bleeding: 37 (33.6%); Spontaneous haematoma: 1 (0.9%); Other	**Peri-procedure major adverse events** (timeframe not reported)	Pericardial tamponade: 3 (2.7%) Major bleeding*: 1 (0.9%) Stroke: 0 (0%) Transient ischaemic attack (TIA): 1 (0.9%) Device embolisation: 0 (0%) Myocardial infarction: 0 (0%) Systemic embolism: 0 (0%) Death 0 (0%) *Due to access site haematoma	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Directly applicable	Inherently limited by the absence of a control The authors stated that imaging follow-up was performed only once in the majority of patients, which may limit diagnostic accuracy
				Follow-up complications and adverse events	Mean follow-up 30±12 months (264 patient-years) (n=110): *(follow-up only)* Device embolisation: 0 (0%) Cardiac tamponade: 0 (0%) Major bleeding: 3 (2.7%) Stroke: 5 (4.5%) Transient ischaemic attack (TIA): 1 (0.9%) Systemic embolism: 0 (0%) Death: 14 (12%) Cardiovascular or neurological death:* 3 (2.7%) Annual rates of ischaemic stroke: 2.2% Annual rates of other thromboembolic events: 0% Annual rate of bleeding: 1.1% * One sudden cardiac death in hypertrophic cardiomyopathy (HCM), one massive stroke in patient in therapy with growth factors for haematological disorders, one haemorrhagic stroke, 27 days after procedure in patient in DAPT. DAPT, double antiplatelet therapy. Leak: 4/20 (20%) Device thrombus: 0 (0%)			

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		insufficiency: 21 (19.1%); Previous bleeding: 85 (77.3%); International normalised ratio (INR) lability: 30 (27.3%); CHA_2DS_2-VASc score: 4.3±1.3 (2–7); HAS-BLED 3.4±1 (1–6).	(urinary, genital or respiratory tract): 23 (20.9%); INR lability: 30 (27.3%); Risk of fall: 4 (3.6%); Warfarin allergy: 3 (2.7%). **Procedural success:** 106 of 110 patients (96.4%)					
Observational study - ITALY *Paper*: (Figini et al. 2017)	Single centre, retrospective non-randomised study 1 centre in Italy between June 2009 and May 2015	N=165 patients of which 'the main indication for the procedure was contraindication anticoagulants' Mean age: 72 (SD 9) years; Female: 56 (34%); CHA2DS2-VASc: 3.9 (SD 1.7); HAS-BLED: 3.6 (SD 1.4); Ischemic heart disease: 46 (27.9%); Previous stroke: 48 (29.1%); Previous intracranial bleeding: 35 (21.2%); Renal failure: 41	Intervention: Percutaneous closure using **ACP or Amulet (**60%) or **WATCHMAN** (40%) devices. The protocol at the study institution was to discharge patients on dual antiplatelet therapy (DAPT) and to switch to single antiplatelet drug after 1–3 months if follow-up TEE shows absence of leaks >5 mm or thrombosis. Therapy at hospital discharge: Dual antiplatelet therapy (DAPT): 121 (73.3%); Low molecular	**In-hospital events** (days of hospitalisation: 2 (1–3))	Serious in-hospital events*: 8 (4.8%) Death: 0 (0%) Haemorrhagic stroke: 2 (1.2%) Ischaemic stroke: 0 (0%) Transient ischaemic attack (TIA): 0 (0%) Pericardial tamponade: 1 (0.6%) Any pericardial effusion: 4 (2.4%) Air embolisation: 1 (0.6%) Device dislocation: 0 (0%) Life threatening bleeds: 2 (1.2%) Major bleeding: 3 (1.8%) Minor bleeding: 2 (1.2%) Major vascular compl.: 1 (0.6%) Minor vascular compl.: 2 (1.2%) *Death, any stroke, major bleeding, major vascular complication, air embolisation, pericardial tamponade	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Directly applicable	Inherently limited by the absence of a control The authors stated that the lack of systematic TEE and dedicated questionnaire for stroke assessment at follow-up is a limitation of the study The authors also stated that 25% of patients were not contacted within 3 months of the manuscript preparation, so that there is also the possibility that some events, including strokes, will not have been
				Follow-up complications and adverse events	Mean follow-up of 448 (167-793) days (n=152): Death: 5 (2 were cardiac) (3.3%) Cardiovascular death: 2 (1.3%) Haemorrhagic stroke (non-fatal): 1 (0.7%) Ischaemic stroke: 0 (0%) Transient ischaemic attack (TIA): 1 (0.7%)			

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		(24.8%); Dialysis: 7 (4.2%)	weight heparin (LMWH): 16 (9.7%); Warfarin 15 (9.1%); Single antiplatelet Rx: 11 (6.7%); Warfarin + Aspirin: 6 (3.6%); None: 2 (1.2%); Warfarin + Dual antiplatelet therapy (DAPT): 1 (0.6%) **Indication for LAAO**: Presence of a contraindication to anticoagulation (history of severe bleeding: 60% of the overall population, previous intracranial haemorrhage: 21.2%), coagulopathy (14.7%) or increased expected haemorrhagic risk (2.4%). Other reasons for LAA closure included: development of LAA thrombosis		Life threatening bleeding: 1 (0.7%) Major bleeding: 2 (1.3%) Minor bleeding: 7 (4.6%) Leaks: 32/114 (28%) Device thrombus: 1 (0.7%) (*the authors stated that one case of thrombosis was identified on an Amulet device*)			recognised

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			while treated with anticoagulant therapy (11.5%) or (presumed) thromboembolic stroke despite adequate treatment (9.7%); indication for DAPT and oral anticoagulation ("triple antithrombotic therapy," 6.1%) or patient preference (4.2%). **Procedural success:** 164 of 165 patients (99.4%)					
Observational study - ITALY *Paper*: (Santoro et al. 2016) (we note that many of the authors are also authors of the Berti et	Multicentre, retrospective, non-randomised study 2 centres in Italy between Jan 2009 and Dec	N=134 patients 'with long-term anticoagulation contraindication' Mean age: 76.6±7.6 years; Male 80 (59.7%); CHA_2DS_2 – VASc: Median (interquartile range) 4 (2-5); $CHADS_2$: Median	Intervention: Percutaneous closure using the **Amplatzer Cardic Plug** (ACP). Short term dual antiplatelet therapy (one to three months) and subsequent indefinite single antiplatelet therapy were prescribed after successful device implantation.	**Procedure-related complications** (timeframe not reported)	Major complications: 3 (2.2%) Pericardial effusion*: 1 Cardiac tamponade: 2 Stroke: 0 Systemic embolism: 0 Major bleeding (except tamponade/effusion): 0 Device embolisation: 0 Minor complications: 6 Transient ischaemic attack (TIA): 1 Non-significant pericardial effusion: 3 Minor bleeding**: 2 *requiring drainage, transfusion and/or surgery; **femoral access haematoma	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are	Directly applicable	Inherently limited by the absence of a control The authors stated that maging follow-up was performed in 69% of the patients so that real rated of post-implant leaks and thrombosis may have been underestimated

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al. paper, but Santoro does not mention this parallel paper which may include some of the same patients?)	2012	(interquartile range) 3 (2-3.75); HAS-BLED: Median (interquartile range) 3 (2-3); Atrial fibrillation type: Paroxysmal: 28 (20.9%); Persistent: 15 (11.2%); Permanent: 91 (67.9%)	**Reason for LAAO**: Major (40%) and minor (25%) bleeds occurring in 11% patients while on OAC, with 56% of the major bleedings being due to intracranial bleeding. **Procedural success:** 125 of 134 patients (93.3%)	**Follow-up complications and adverse events**	Follow-up at 680±351 days (238 patient-years (n=128): CV-related events: 23 Ischaemic stroke: 2 Transient ischaemic attack (TIA): 3 Haemorrhagic complications - Subdural haematoma: 1 Other major bleeding: 2 Minor bleeding: 4 Myocardial infarction: 2 Sudden cardiac death: 1 Other: 8 (pericardial tamponade (n=1), cardiac arrest/hypokalaemia (n=1), coronary artery disease (n=3), pulmonary embolism (n=1), (pleuro-) pericarditis (n=2) Non-Cardiovascular-related events: 10 Cancer: 4 Hepatic insufficiency: 1 Pneumonia: 3 Femoral fracture: 1 Head trauma: 1 Deaths: 8; CV-related: 2; Non-CV-related: 6. All deaths were confirmed to be unrelated to the implanted device and implantation procedure. Annual rate of major bleeding: 1.3% TEE imaging was performed on 67 patients with mean implant duration at imaging of 9.7 months; one major residual leak was observed (1.4%) and non-significant leaks were observed in 6 patients. Device thrombosis: 1 (1.4%)	generalisable (score of 1). Total score: 7		

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Iberian Registry *Paper*: (Lopez Minguez et al. 2015)	Multicentre, prospective, non-randomised study 12 hospitals in Spain and Portugal between Mar 2009 and early 2013	N=167 patients 'contraindicated for oral anticoagulants' Mean age: 74.68 ± 8.58 years; ≥75 years: 84 (53.2%); ≥78 years: 63 (39.9%); Men: 102 (61.1%); $CHADS_2$: median 3 (2–4); CHA_2DS_2-VASC: median 4 (3–6); HAS-BLED: median 3 (3–4)	Intervention: Percutaneous closure using the **ACP** device. Following implantation, a loading dose (600 mg) of clopidogrel was administered, and treatment was started with 300 mg aspirin (ASA) on the first day and 100 mg daily thereafter. Clopidogrel was maintained for 3–6 months, barring haemorrhagic complications, and ASA for 6–12 months. If thrombus occurred, subcutaneous enoxaparin in a therapeutic dose was added for 2 weeks, clopidogrel was prolonged and the transoesophageal echocardiogram (TOE) was repeated to check for disappearance. If the result was negative, the decision to prolong the treatment for another week or hospitalise the	**Procedure-associated events** (timeframe not reported)	Procedural complications: 9 (5.4%) Transient ischaemic attack (TIA): 2 (1.2%) Vascular complication: 4 (2.4%) Cardiac tamponade: 2 (1.2%) Device migration (percutaneously snared): 1 (0.6%)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 7	Directly applicable	Inherently limited by the absence of a control Most hospital sites started and included cases under a common monitor (which the authors believed ensured homogeneity)
				Follow-up complications and adverse events	Mean follow-up 24 months (290 patient-years) (n=158): Death: 17 (10.8%) Major bleeding: 9 (5.7%) Minor relevant bleeding: 7 (4.4%) Total bleeding events: 16 (10.1%) Stroke/TIA: 7 (4.4%) Some event 30 (19.0%) Annual death rate: 5.8% Annual rate of major bleeding: 3.1% Annual rate of total bleeding: 5.5% Annual rate of stroke/TIA: 2.4% Leak: 13 (8.2%). Device thrombus: 13 (8.2%)			

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			patient and begin treatment with intravenous heparin was evaluated. **Reasons for LAAO:** Gastrointestinal haemorrhage: 51 (30.5%); Cranial haemorrhage: 38 (22.8%); Other haemorrhages: 28 (16.8%); cerebrovascular accident (CVA)/embolism with OAC: 12 (7.2%); High risk of bleeding: 7 (4.2%); Others: 32 (19.2%) **Procedural success:** 100 of 100 patients (100%)					
Observational study - ISRAEL *Paper*: (Meerkin et al. 2013)	Single centre, retrospective, non-randomised study 1 centre in Israel between June	N=100 'anticoagulant ineligible patients' Mean age: 73 ± 9.95 years; Male: 55; $CHADS_2$ score: 3.21 ± 1.23: $CHADS_2$ score 0 (n): 0;	Intervention: Percutaneous closure using the **ACP** device. All had a loading dose of 300 mg of aspirin and 300 mg of clopidogrel post-procedure followed by a lifelong recommendation of 100 mg aspirin	**Procedural and in-hospital outcomes** (mean 2.4 [SD 4.1] days)	*Percentages calculated* Death: 0/100 (0%) Stroke: 0/100 (0%) Myocardial infarction: 0/100 (0%) Air embolism: 0/100 (0%) Device embolism: 0/100 (0%) Pericardial effusion with tamponade: 1/100 (1%) Other (acute respiratory distress with pulmonary oedema): 1/100 (1%)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 1); the data is adequate to support	Directly applicable	Inherently limited by the absence of a control This report only focuses on acute results The authors stated "Major adverse events were defined as death, stroke, systemic

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	2009 and Mar 2012	1: 7; 2: 24; 3: 30; 4: 21; 5: 16; 6: 2; Congestive heart failure: 49 Hypertension: 94; Age >75 years: 48; Diabetes mellitus: 25; Previous embolic neurological event: 53; Atrial fibrillation pattern: Paroxysmal: 26; Persistent: 16; Permanent: 58	daily with 75 mg of clopidogrel recommended to be continued for one month only **Contraindications to OAC:** (n): Bleeding: 67; Gastrointestinal: 40; Intracranial: 15; Ocular: 2; Other sources (epistaxis/respiratory etc.): 11; Compliance: 14; Falls: 9; Sundry: 11. **Procedural success:** 142/150 patients (94.7%)			the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 6		embolism, device embolization, pericardial bleeding requiring an intervention (cardiac tamponade) or other major bleeding requiring invasive treatment or blood transfusion occurring during index hospital admission", however, details of these *all* outcomes are not reported
Observational study - CANADA *Paper*: (Saw et al. 2017)	Multicentre, prospective non-randomised study (patient-level pooled analysis) 4 centres in Canada	N=106 patients 'with contraindications to long-term oral anticoagulation' Mean age: 74.8 ± 7.7 years; Male: 66 (62.3%); AF paroxysmal: 34 (32.1%); AF chronic: 72 (67.9%);	Intervention: Percutaneous closure using the **WATCHMAN** device. The most common antithrombotic regimen post-LAA closure consisted of dual antiplatelet therapy (DAPT: aspirin + clopidogrel) for 1–6 months, followed by aspirin alone indefinitely.	**Peri-procedure major adverse events** (within 7 days)	Composite Major Safety Events: 2 (1.9%) Death†: 1 (0.9%) Stroke/TIA/systemic embolisation: 0 (0%) Myocardial infarction: 0 (0%) Cardiac tamponade†: 1 (0.9%) Device embolisation (snared): 1 (0.9%) †Required surgical repair, died 5 days later from sepsis. Other in-hospital events - Pericardial effusion (small, no drainage): 2 (1.9%) Asymptomatic blood pressure drop (transfusions): 2 (1.9%) Minor bleed (haematoma): 1 (0.9%)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data is adequate to support the authors' interpretation (score of 1); the results are	Directly applicable	Inherently limited by the absence of a control The authors stated that the sample size is relatively small, and that the events and imaging results were not adjucated

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	between May 2013 and Oct 2005	History stroke/TIA: 30 (28.3%); CAD: 48 (45.3%); CHF: 32 (30.2%); Diabetes mellitus: 38 (35.8%); Hypertension: 87 (82.1%); Cirrhosis: 6 (5.7%); Renal failure (Cr>200): 12 (11.3%); $CHADS_2$ score: 2.8 ± 1.2; CHA_2DS_2-VASc score: 4.3 ± 1.5; HASBLED score: 3.2 ± 1.2	Patients deemed acceptable for short-term OAC post-procedure were discharged on warfarin or direct OAC (DOAC) for 45 days, followed by DAPT till 6 months, and subsequently aspirin alone indefinitely **Indications for LAA closure**: Previous bleeding: 95 (89.6%) – Major bleeding 87 (82.1%); Minor bleeding: 30 (28.3%); High fall risk: 13 (12.3%); Recurrent stroke on anticoagulation: 1 (0.9%); Other reasons: 10 (9.4%) **Procedural success:** 103/106 patients (97.2%)		Pseudoaneurysm (thrombin injection): 1 (0.9%)	generalisable (score of 1). Total score: 7		
				Follow-up complications and adverse events	The mean follow-up duration was 210.3 ± 182.2 days (n=106): CV death: 2 (1.9%) Non-CV death: 2 (1.9%) Stroke 0 (0%) TIA: 2 (1.9%) Systemic embolisation: 0 (0%) Myocardial infarction: 1 (1.0%) Major bleeding: 5 (4.7%); Major bleeding event rate: 4.7% Follow-up device surveillance imaging was performed in 73 with TEE and 31 with cardiac CT angiography. There was only one device-associated thrombus that was identified, and this patient was treated with OAC without sequela. TEE showed peri-device leak in 28 of 76 (37.0%) Device-associated thrombus: 1 (1.0%)			

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Registry study - USA *Paper*: (Murarka et al. 2017)	Single centre, prospective non-randomised study 1 centre USA between Jan 2015 and Aug 2016	N=137 patients 'who had absolute or relative contraindications to long-term oral anticoagulants'. Mean age: 75.4 ± 8.6 years; Male: 76 (55.5%) CHADSVASC: 4.56 ± 1.42; HASBLED: 3.98 ± 0.86; Diabetes mellitus: 49 (35.8%); Hypertension: 130 (94.9%); Stroke: 36 (26.3%); Vascular disease: 70 (51.1%); LVEF: 53.9 ± 9.2; CHADSVASC > 2: 128 (93.4%); HASBLED > 4:	Intervention: Percutaneous closure using the **WATCHMAN** device. After the procedure, the OAC regimen was left to the discretion of the operators. All patients were treated with OAC for 45 days as specified in the PROTECT-AF study and a follow up TEE was performed at 45 days. If no device thrombus was noted and LAAO was complete then the OAC or NOAC was discontinued in most of the patients and antiplatelet therapy resumed for 6 months. **Reasons for LAAO:** Not	**Procedure-related major adverse cardiac and cerebral events** (during the index hospitalization or within 45 days' post-procedure)	Procedural mortality: 1/137 (0.7%) Peri-procedural strokes: 0/137 (0%) Device embolisation: 0/137 (0%) Vascular complication rate: 6/137 (4.4%) Minor vascular complications (groin haematomas): 3 (2.2%) Major vascular complications: 3 (2.2%) (2 femoral artery pseudoaneurysms and one large haematoma requiring surgical excision and drainage) Life threatening and major bleeding: 8/137 (5.8%) The study's pre-specified primary endpoint was "freedom from procedure-related major adverse cardiac and cerebral events (MACCE's) during the index hospitalisation or within 45 days' post-procedure, whichever occurred later." MACCE's were defined to include death, stroke, procedure related major or life-threatening bleeding, device embolization, major vascular complication, need for cardiovascular surgery, need for cardiopulmonary resuscitation, and significant pericardial effusion (i.e., hemodynamically significant effusion prompting surgical or endovascular intervention or resulting in prolonged hospitalisation) The authors stated that the primary endpoint was reached in 5.8% of patients, *but this does not make sense give the results presented;; it also appears the results are adverse events, not patients without these adverse events?*	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 1); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 6	Directly applicable	Inherently limited by the absence of a control All events were adjudicated and independent clinical events committee determined relatedness to the device or procedure The authors stated that these observations may not be extrapolated to populations with different OACs at baseline or different peri-procedural antithrombotic treatments Study results not clearly presented

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		35 (25.5%)	explicity reported; **Procedural success:** 121/137 patients (88.3%)	**Follow-up complications and adverse events**	Follow-up (at 45 days) (n=131): Device thrombus: 2 (1.5%)			
Observational study – CHINA *Paper*: (Huang et al. 2017)	Single centre, prospective non-randomised study 1 centre in China between Apr 2014 and May 2015	N=106 patients 'who either had ccontraindication or were unwilling to accept long-term oral anticoagulants' Mean age: 64.2 ± 8.6 years; Male: 63 (59.4%); Persistent or permanent atrial fibrillation: 100 (94.3%); CHA_2 DS_2 -VASc score: 3.6 ± 1.6; LVEF (%): 51.8	Intervention: Percutaneous closure using the **WATCHMAN** device. After the procedure, all patients received warfarin (target international normalized ratio [INR]: 2.0–3.0) for 45 days. All patients discontinued warfarin after confirmation of adequate LAA sealing. If residual leak was > 5 mm, warfarin was continued. After warfarin treatment	**Procedure/in-hospital events** (timeframe not reported)	Major* procedural in-hospital events: 2/100 (2%) Cardiac tamponade: 1 Stroke (ischaemic/haemorrhagic): 1 Myocardial infarction: 0 Air embolisation: 0 Device embolisation: 0 Minor bleeding: 0 Major bleeding: 0 Procedure/device-related death: 0 Minor pericardial effusion: 8 *Major adverse events included death, transient myocardial ischemia/TIA/stroke, tamponade, device embolization, air/systemic embolism, myocardial infarction, major bleeding requiring intervention or transfusion, other complication requiring surgery. Minor complications included minor pericardial effusions and vascular complications.	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 1); the data is adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). Total score: 6	Directly applicable	Inherently limited by the absence of a control Relatively small sample size

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated								
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		± 5.2; Diabetes: 12 (11.3%); Hypertension: 66 (62.3%); History of Transient ischaemic attack (TIA)/ischaemic stroke: 41 (38.7%); Coronary heart disease: 32 (30.2%); Hypertrophic cardiomyopathy: 3 (2.8%); Dilated cardiomyopathy: 4 (3.8%); Congenital heart disease: 5 (4.7%).	was stopped, once-daily low-dose aspirin (100 mg) and clopidogrel (75 mg) were prescribed until completion of 6-month follow-up visit, and then aspirin alone was continued indefinitely **Reasons for LAAO:** Failure to administer or not tolerate with warfarin intake: 82 (77%); haemorrhage: 12 (11%); recurrent embolism under anticoagulant therapy: 8 (8%); poor compliance or other contraindication for anticoagulant therapy: 4 (4%). **Procedural success:** 100/106 patients (94.3%)	**Follow-up complications and adverse events**	12 months follow-up (n=95): (*follow-up period only)* Stroke (ischaemic/haemorrhagic): 2 Myocardial infarction: 0 Air embolisation: 0 Device embolisation: 2 Minor bleeding: 0 Major bleeding: 1 Annual rate of ischaemic stroke: 2.0% Leak: 34 patients presented with small residual leak (≤5 mm), and no large residual leak (>5 mm) Device thrombus: 2/95 (2.1%) 12 month freedom from major adverse events (secondary endpoint): 95/100 (95%)			

7. b. Evidence Summary Table for Economic Studies

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Panikker et al. 2016). Only results for relevant comparators are reported in this table.	An existing cost model developed by Amorosi, et al. 2014 was used to estimate long-term costs and clinical outcomes. An NHS commissioner perspective was adopted, with a 10-year time horizon. Costs and tariffs were reported in 2015 British pounds and were discounted at an annual rate of 3.5%.	Baseline characteristics of Royal Brompton & Harefield Hospitals (RBHH) cohort of 110 patients were: age 71.3 years; females 45%; $CHADS_2$ median 3. Outcomes for other arms reflect the patients included in the 20 clinical studies used. Baseline characteristics for the modelled population and subgroups were matched for age, $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, and anticoagulation suitability. No details of how this was achieved was provided.	LAAC with the WATCHMAN device was compared with - warfarin, - dabigatran --rivaroxaban, - apixaban for patients able to take oral anticoagulants; and - aspirin monotherapy - no antithrombotic therapy for those unable to take oral anticoagulants.	Clinical inputs for LAAO were taken from the PROTECT AF study (Holmes et al. 2009) and from the RBHH LAAC cohort. Inputs for aspirin and no therapy were from a published network meta-analysis (Dogliotti et al. 2014). The key modelling assumption was that of continued benefit with LAAC. The cost of clinical events were from the 2014/15 National Tariff Payment System, drug costs were from the NHS Drug Tariff and stroke costs from a UK population-based study of acute- and long-term care costs after stroke in patients with AF.	Event rates reported at 10 years for LAAO and comparators were: **Stroke** RBHH LAAO 10.2% PROTECT AF LAAO 17.1% Aspirin 41.2% No therapy 49.0%. **Major bleeding** RBHH LAAO 13.3% No therapy 23.8% Aspirin 38.0% **All-cause mortality** PROTECT AF LAAC 20.3% RBHH LAAC 25.7% Aspirin 40.6% No therapy 48.2%. **Costs.** Over a 10-year period, Estimated cost-savings with LAAO versus no medical therapy were £5,387 and £3,855 compared with aspirin. Results were most sensitive to the LAAO stroke rates.	The research questions, aims and design are clearly stated (score of 2). The research design is appropriate for the aims and objectives of the research (score of 2). Methods are well-described particularly in the supplementary materials (score 2). Assumptions and data used are transparent and provide sufficient information to give confidence that these support the authors' interpretation/conclusions (score 2). Results likely to generalise to NHS perspective if cost of LAAO is valid – see Applicability (score 0). Total score 8/10.	The main concern is cost of LAAO and related procedure. The unit cost used in the study was £6,334. This compares to a bottom-up cost, using registry data from the centres undertaking the procedure of £11,600 at current prices. The cost used in the study is not broken down but may not include pre- and post-operative costs plus cost of investigations. There is also no evidence supporting the assumed continued benefit from LAAO, particularly in terms of reducing stroke risk for the period beyond 2 years.	This is a well planned and executed study. The populations, interventions, health effects and costs, other than device costs are relevant to the NHS. Clinical inputs results rely heavily on results from a published network analysis and the quality of that has not been investigated. We also have little information on the conduct of the RBHH registry. The registry was not randomised and thus is weaker evidence than the RCTs. The main weakness relates to the cost of the LAAO device and procedure. This study was partly funded by Boston Scientific Inc and supported by the NIHR Cardiovascular Biomedical Research Unit at the Royal

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
								Brompton & Harefield NHS Foundation Trust and Imperial College London. Identification, design, conduct, and reporting of the registry study and economic analysis were independent of the funders. 2 authors had received research grants from Boston Scientific and a third was a consultant to Boston Scientific.
(Reddy et al. 2016) Note evidence table excludes data pertaining to comparison of LAAO with apixiban.	A Markov model was constructed using 3-month cycles and a 20 year time horizon. Within each cycle, patients could experience clinical events leading to death, disability, and/or primary therapy discontinuation and incur associated costs and quality of life adjustments.	Patients were assumed to be 70 years old, with a CHADS2 score of 3 (annual stroke risk 8.6%) and a HASBLED score of 3 (annual haemorrhage risk 3.74%). Risks of stroke were assumed to increase with age. Patients who experienced an ischaemic event had a 2.6 times increase in the probability of experiencing a second ischaemic event	LAAC with the WATCHMAN device was compared with aspirin and clopidogrel.	Clinical inputs for events were from several sources. For LAAO, event probabilities were from the ASAP study (Reddy et al 2013), For the aspirin arm, the relative risk of stroke was taken from a meta-analysis of multiple trials of stroke prevention in AF. (Hart et al 2007). All other event probabilities	Results were presented for 3 risk profiles at 10 years. For high risk group and the base case, LAAO arm had lower costs and higher quality of life and hence dominated aspirin. For the low risk cohort aspirin was cheaper (6,653€ vs 12,529€) but had fewer QALYs, given an ICER of 46,562€. For the base case, the costs of LAAO were lower	The research questions, aims and design are clearly stated (score of 2). The research design is appropriate for the aims and objectives of the research (score of 2). Methods are not clearly described particularly resource use in social care setting (score 1). Assumptions and data used are transparent and provide sufficient information to give confidence that these support the authors' interpretation/conclusions (score 2). Results unlikely to generalise to NHS (score 0). Total score 7/10	Costs unlikely to generalise to NHS England setting. For example model used a cost for LAAO procedure of 9,136€ (2014 prices), about £7,310 using a currency conversion of £1 = 1.25€ (rate from HM Revenue and Customs). The estimated cost for the procedure in 2017 was £11,600.	Intervention, population and total costs are relevant. Clinical inputs results for aspirin are taken from a published meta-analysis and the quality of that has not been investigated. Cost of clopidogrel now materially less as drug is generic. The ASAP study was a prospective single-arm, non-randomised study and thus is weaker evidence than the RCTs. No

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				were taken from ACTIVE A study (Active Investigators, 2009). Baseline stroke risk was based on CHADS2 scores and bleeding risk based on HASBLED scores. Costs from German national datasets.	than for aspirin from year 8.			attempt was made to check for heterogeneity across ASAP and the patients receiving aspirin. Cost of LAAO understated. This study was supported by Boston Scientific Inc.

8. Grade of evidence tables

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Procedure and device-related adverse events: **Stroke**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Device thrombus with ischaemic stroke: 1/150 (0.7%)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Stroke: 9/1047 (0.9%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Stroke: 0/1020 (0%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Stroke: 5/500 (1.0%) Major/disabling: 1/500 (0.2%)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Ischaemic stroke: 1/101 (1%)
	Registry study – ITALY - (Berti et al. 2016)	7	Direct		Stroke: 0/110 (0%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Haemorrhagic stroke: 2/165 (1.2%) Ischaemic stroke: 0/165 (0%)

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Stroke: 0/134 (0%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		Stroke: 0/100 (0%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		Stroke: 0/137 (0%)
	Observational study –CHINA- (Huang et al. 2017)	6	Direct		Stroke (ischaemic/haemorrhagic): 1/100 (1%)
Interpretation of Evidence	Eleven studies reported on peri-procedural stroke, which ranged from 0% to 1.2% across the studies. Three studies reported only on ischaemic stroke (ASAP – Reddy et al. 2013; Seeger et al. 2016; Figini et al. 2017) which ranged from 0% to 1%. The remaining three studies did not report on peri-procedural stroke. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Overall peri-procedural adverse events** *Notes:* *The adverse events that make up an overall score*	ASAP Study (Reddy et al. 2013)	7	Direct	A	13/150 (8.7%) (included device embolism, pericardial effusion [with and without tamponade], device thrombus with ischaemic stroke, femoral pseudoaneurysm, femoral haematoma/bleeding, other)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		51/1047 (4.97%) (*reported as 52 in Tzikas et al. 2015*) (consisted of death, myocardial infarction, stroke, transient ischemic attacks (TIAs), systemic embolisation, air embolisation, device embolization, significant pericardial effusion or cardiac tamponade, and major bleeding (requiring surgery or transfusion)
	EWOLUTION Registry - (Bergmann	6	Somewhat direct (74%		18/1020 (1.8%) (major cardiac events that consisted of death, major

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
slightly differ between studies. *In some studies, it appears that the authors only reported what types of events occurred, and did not report the types of events that could have occurred but did not, i.e. it was not always clear if other serious adverse events were considered, but were not reported because of negative findings.* *If authors did not report a total score, we did not attempt to calculate it.*	et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)		patients for whom anticoagulation therapy was contraindicated)		bleeding, cardiac tamponade/significant pericardial effusion, device embolisation, stroke, systemic embolism, myocardial infarction, and other events requiring surgery/major intervention); *5 events - 3 deaths and 2 major bleeding events were deemed unrelated to the procedure* 15/1020 (1.5%) (other peri-procedural serious adverse events that included vascular complications @ groin, air embolism, minor pericardial effusion (untreated), re-interventions due to incomplete seal, minor bleeding (untreated)/haematoma, TIA, hypotension, and adverse reaction to anaesthesia) Procedure-and or device related SAEs within 7 days: 2.8% event rate (95% CI: 1.9% to 4.0%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% patients for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		13/371 (3.5%) (acute major events defined as those resulting in death or requiring intervention or prolonged hospital stay (i.e., pericardial effusions requiring percutaneous drain or surgery, device embolization requiring percutaneous or surgical retrieval, neurological events, bleeding requiring transfusion or surgical intervention, vascular complications requiring surgical treatment). 11/371 (3.0%) (acute minor complications - no intervention required, defined as those not requiring intervention or prolonging hospital stay (small pericardial effusions requiring no treatment, minor hematomas). All ischemic neurological events were considered as strokes (without distinction between strokes and transient ischemic attacks (TIAs)).
	Registry study – SWITZERLAND -	7	Direct		29/500 (5.8%) (major adverse events was a composite of death, stroke, Valve Academic Research Consortium major or life-threatening

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	(Koskinas et al. 2016)				bleeding, major access vessel complication, device embolisation, need for cardiovascular surgery, cardiopulmonary resuscitation, and serious pericardial effusion)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Procedure-related serious complications: 3 (3%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Serious in-hospital events: 8/165 (4.8%) (included death, any stroke, major bleeding, major vascular complication, air embolisation, pericardial tamponade)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Major complications: 3/134 (2.2%) (assessments of pericardial effusion, cardiac tamponade, stroke, systemic embolism, major bleeding, device embolisation) Minor complications: 6/134 (4.5%) (assessments of transient ischaemic attack, non-significant peri-cardial effusion, minor bleeding)
	Iberian Registry -(Lopez Minguez et al. 2015)	7	Direct		Procedural complications: 9/167 (5.4%) (included TIA, vascular complications, cardiac tamponade and device migration [percutaneously snared])
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Peri-procedure major safety events: 2/106 (1.9%) (major procedural safety events in-hospital or within 7 days (whichever is longer) included death, stroke, transient ischemic attack (TIA), systemic embolisation, myocardial infarction (MI), cardiac tamponade requiring intervention, and device embolisation)
	Observational study – CHINA- (Huang et al. 2017)	6	Direct		Major procedural in-hospital events: 2/100 (2%) (included death, transient myocardial ischemia/TIA/stroke, tamponade, device embolization, air/systemic embolism, myocardial infarction, major

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
					bleeding requiring intervention or transfusion, other complication requiring surgery)
Interpretation of Evidence	Eleven studies reported on overall major peri-procedural adverse events. These ranged from 2% to 9%, but the definition of a major adverse event appears to differ slightly among the studies (or may also just reflect how the data were reported in the studies). Many of the studies also reported minor adverse events and rates ranged from 3% to 4.5% across the studies. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Deaths**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	8/1047 (0.8%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		4/1020 (0.4%)
	Observational study – UK - Betts et al. 2017	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		1/371 (0.3%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		2/500 (0.4%)
	Registry study – ITALY -	7	Direct		0/110 (0%)

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	(Berti et al. 2016)				
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		0/165 (0%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		0/100 (0%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		1/106 (0.9%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		1/137 (0.7%)
	Observational study – CHINA- (Huang et al. 2017)	6	Direct		0/100 (0%)
Interpretation of Evidence	Ten studies reported on peri-procedural deaths, which ranged from 0% to 0.9% across the studies. The remaining four studies did not report on peri-procedural deaths. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Device embolism**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	2/150 (1.3%)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		8/1047 (0.8%) (1 requiring surgery and 7 device embolisation snared) (*reported as 10 in Lempereur et al. 2017 and Tzikas et al. 2015; Tzikas reported that 2 resulted in death, one required surgery, and 7 were snared*)
	EWOLUTION Registry - (Bergmann	6	Somewhat direct (74%		Device embolisation requiring surgery: 1/1020 (0.1%)

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)		patients for whom anticoagulation therapy was contraindicated)		Device embolisation snared: 1/1020 (0.1%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		10/500 (2.0%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Device embolisation (percutaneous/surgical retrieval): 3/371 (0.8%)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Device embolisation: 0/110 (0%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Device embolisation: 0/134 (0%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		Device embolism: 0/100 (0%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Device embolisation (snared): 1/106 (0.9%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		Device embolisation: 0/137 (0%)
	Observational study – CHINA-	6	Direct		Device embolisation: 0/100 (0%)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	(Huang et al. 2017)				
Interpretation of Evidence	Eleven studies reported on peri-procedural device embolism, which ranged from 0% to 2% across the studies. In some studies, the authors reported results separately for device embolisation requiring surgery (ranging from 0.09% to 0.8%) and device embolism snared (ranging from 0.1% to 0.9%). The remaining three studies did not report on peri-procedural device embolism. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Systemic embolism**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	0/150 (0%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		0/1020 (0%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		0/371 (0%)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		0/110 (0%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		0//134 (0%)
Interpretation of Evidence	Five studies reported on peri-procedural systemic embolism. None of the patients in these studies experienced this outcome. The remaining nine studies did not report on peri-procedural systemic embolism. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be				

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Pericardial effusion**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Pericardial effusion with tamponade (percutaneous drainage): 2/150 (1.3%) Pericardial effusion, no tamponade (no intervention required): 3/150 (2.0%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Cardiac tamponade/significant pericardial effusion: 3/1020 (0.3%) Minor pericardial effusion (untreated): 2/1020 (0.2%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Pericardial effusions with tamponade (pericardial drain/surgery): 2/371 (0.5%) Pericardial effusions not requiring intervention: 8/371 (2.2%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Pericardial effusion: 33/500 (6.6%) Serious pericardial effusion**: 16/500 (3.2%) ** Hemodynamically significant pericardial effusion requiring drainage or prolonging hospitalization
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Any pericardial effusion: 4/165 (2.4%) Pericardial tamponade: 1/165 (0.6%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Pericardial effusion (requiring drainage, transfusion and/or surgery: 1/134 (0.7%) Non-significant pericardial effusion: 3/134 (2.2%)

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	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		Pericardial effusion with tamponade: 1/100 (1%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Pericardial effusion (small, no drainage): 2/106 (1.9%)
	Observational study – (Huang et al. 2017)	6	Direct		Minor pericardial effusion: 8/100 (8%)
Interpretation of Evidence	Nine studies reported on peri-procedural pericardial effusion. Where reported separately, minor pericardial effusion ranged from 0.2% to 8% and major pericardial effusion (requiring an intervention) ranged from 0.3% to 3.2% across the studies. The remaining five studies did not report on pericardial effusion, but some did report on cardiac tamponade (see below) which may have followed pericardial effusion in some patients, but possibly not in others i.e. if cardiac tamponade was used to resolve LAA perforation. *If not explicitly reported as tamponade following pericardial effusion by the study authors, we did not include it here.* All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Cardiac tamponade**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Pericardial effusion with tamponade (percutaneous drainage): 2/150 (1.3%)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		12/1047 (1.2%) (*reported as 13 in Tzikas et al. 2015 and reported as 16/1047 (1.5%) in Lempereur et al. 2017*)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Cardiac tamponade/significant pericardial effusion: 3/1020 (0.3%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation		Pericardial effusions with tamponade (pericardial drain/surgery): 2/371 (0.5%)

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			therapy was contraindicated and 98% with eligible devices)		
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Pericardial tamponade (requiring pericardiocentesis): 2/101 (2%)
	Registry study – ITALY - (Berti et al. 2016)	7	Direct		Pericardial tamponade: 3/110 (2.7%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Pericardial tamponade: 1/165 (0.6%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Cardiac tamponade: 2/134 (1.5%)
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Cardiac tamponade: 2/167 (1.2%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		Pericardial effusion with tamponade: 1/100 (1%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Cardiac tamponade: 1/106 (0.9%) (Required surgical repair, died 5 days later from sepsis)
	Observational study – CHINA- (Huang et al. 2017)	6	Direct		Cardiac tamponade: 1/100 (1%)
Interpretation of Evidence	Twelve studies reported on cardiac tamponade, which ranged from 0.3% to 2.7% across the studies. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Procedure and device-related adverse events: **Transient ischaemic attack (TIA)**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	4/1047 (0.4%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		1/1020 (0.1%)
	Registry study – ITALY - (Berti et al. 2016)	7	Direct		1/110 (0.9%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		0/165 (0%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		1/134 (0.7%)
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		2/167 (1.2%)
Interpretation of Evidence	Six studies reported on peri-procedural TIA, whichranged from 0% to 1.2% across the studies. The remaining eight studies did not report on peri-procedural TIA. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **TIA/Stroke/embolisation**	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)	A	TIA/strokes (ischaemic/haemorrhagic): 2/371 (0.5%)
	Observational study – CANADA -	7	Direct		TIA/stroke/systemic embolisation: 0/106 (0%)

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	(Saw et al. 2017)				
Interpretation of Evidence	Two studies reported a combined outcome: TIA/strokes (0.5% in Betts et al. 2017) or TIA/stroke/systemic embolisation (0% in Saw et al. 2017). All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Myocardial infarction (MI)**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	1/1047 (0.1%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		0/1020 (0%)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		0/110 (0%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		0/100 (0%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		0/106 (0%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		0/100 (0%)
Interpretation of Evidence	Six studies reported on peri-procedural myocardial infarction, which ranged from 0% to 0.7% across the studies. The remaining eight studies did not report on peri-procedural MI. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				

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Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Procedure and device-related adverse events: **Bleeding**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	2/150 (1.3%) (femoral haematoma/bleeding)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Major bleeding: 13/1047 (1.3%) Minor bleeding: 25/1047 (2.4%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Major bleeding: 9/1020 (0.9%) Minor bleeding (untreated)/haematoma: 2/1020 (0.2%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Major bleedings (fatal): 5/371 (1.4%) Minor bleeding: 3/371 (0.8%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Life-threatening: 16/500 (3.2%) Major: 1/500 (0.2%) Minor: 57/500 (11.4%)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Major bleeding: 1 (0.9%) (due to access site haematoma)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Life threatening bleeds: 2/165 (1.2%) Major bleeding: 3/165 (1.8%) Minor bleeding: 2/165 (1.2%)
	Observational study – ITALY-	7	Direct		Major bleeding (except tamponade/effusion): 0/134 (0%)

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	(Santoro et al. 2016)				Minor bleeding: 2/134 (1.5%) (femoral access haematoma)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Minor bleed (haematoma): 1/106 (0.9%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		Life threatening and major bleeding: 8/137 (5.8%) Minor vascular complications (groin haematomas): 3 (2.2%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		Minor bleeding: 0/100 (0%) Major bleeding: 0/100 (0%)
Interpretation of Evidence	Eleven studies reported on peri-procedural bleeding. Minor bleeding ranged from 0% to 11.4% and major bleeding ranged from 0% to 5.8% across the studies. The remaining three studies did not report on bleeding, but one (López Minguez et al. 2015) did also report on vascular complications. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Vascular complications**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Femoral pseudoaneurysm (surgically repaired): 1/150 (0.7%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Vascular complications @ groin: 4/1020 (0.4%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Vascular complications requiring intervention; 5/371 (1.4%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Vascular access complication related to LAAC: Major: 0/500 (0%) Minor: 22/500 (4.4%)

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	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Major vascular complication: 1/165 (0.6%) Minor vascular complication: 2/165 (1.2%)
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Vascular complication: 4/167 (2.4%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Pseudoaneurysm (thrombin injection): 1/106 (0.9%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		Vascular complication rate: 6/137 (4.4%) Minor vascular complications (groin haematomas): 3 (2.2%) Major vascular complications: 3 (2.2%) (2 femoral artery pseudoaneurysms and one large haematoma requiring surgical excision and drainage)
Interpretation of Evidence	Eight studies reported on peri-procedural vascular complications. When reported, minor vascular complications ranged from 1.2% to 4.4% and major vascular complications ranged from 0% to 2.2% across the studies. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Air embolisation**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	5/1047 (0.5%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Air embolism (coronary): 2/1020 (0.2%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Air embolisation not resulting in stroke: 3 (0.6%)

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	Observational study – ITALY – (Figini et al. 2017)	7	Direct		1/165 (0.6%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		0/100 (0%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		0/100 (0%)
Interpretation of Evidence	Six studies reported on peri-procedural air embolisation, which ranged from 0% to 0.6% across the studies. The remaining eight studies did not report on peri-procedural air embolisation. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events: **Device-related thrombus**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Device thrombus with ischaemic stroke: 1/150 (0.7%)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		3/1047 (0.3%)
Interpretation of Evidence	Two studies reported on device-related thrombus, which was 0.3% in one study and 0.7% in the other study. The remaining twelve studies did not report on device-related thrombus. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Procedure and device-related adverse events:	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Other: 3/150 (2.0%) (oral bleeding, n=1; intraprocedural hypotension, n=2)
	ACP Registry - (Freixa et al. 2016,	7	Direct		Need for surgery: 0/1047 (0%) (apart from device embolisation)

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Other events	Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)				Other complications: 15/1047 (1.4%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Other events requiring surgery/major intervention: 0/1020 (0%) Re-interventions due to incomplete seal: 2/1020 (0.2%) Hypotension: 1/1020 (0.1%) Adverse reaction to anaesthesia: 1/1020 (0.1%)
	Registry study – SWITZERLAND - (Koskinas et al. 2016)	7	Direct		Bailout cardiovascular surgery: 5/500 (1.0%) Bailout transcatheter intervention: 1/500 (2.0%) Cardiopulmonary resuscitation: 7/500 (1.4%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Device dislocation: 0/165 (0%)
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Device migration (percutaneously snared): 1/167 (0.6%)
	Observational study – ISRAEL- (Meerkin et al. 2013)	6	Direct		Other (acute respiratory distress with pulmonary oedema): 1/100 (1%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Asymptomatic blood pressure drop (transfusions): 2/106 (1.9%)
Interpretation of Evidence	Eight studies reported 'other' peri-procedural events. The percentage of these events (i.e. oral bleeding, hypotension, need for surgery, re-interventions due to incomplete seal, adverse reaction to anaesthesia, bailout cardiovascular surgery, cardiopulmonary resuscitation, device dislocation, device migration, acute respiratory distress with pulmonary oedema) were generally very low (ranging from 0% to 1.4%). The highest event rates reported were asymptomatic bloos pressure drop (transfusions) at 1.9% (Saw et al. 2017) and bailout transcatheter intervention at 2.0% (Koskinas et al. 2016). All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications	ASAP Study - (Reddy et al. 2013)	7	Direct	A	4/170 patient-years (2.3% per year)

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and adverse events: **All-cause stroke or embolism** *Note:* *For this evidence review, we did not calculate all-cause stroke (based on data presented on ischaemic and haemorrhagic stroke) if not reported by the study authors*	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Mean follow-up 1.3 years (1,349 patient years); Stroke: 16/1047 (1.6%) Stroke (procedure + follow-up): 1.6 per 100 patient-years
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Mean follow-up 30 ± 12 months (264 patient-years): Stroke 5/110 (4.5%) *(follow-up only)*
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Mean follow-up 24 months (290 patient-years): Stroke/TIA: 7/158 (4.4%) Annual rate of stroke/TIA: 2.4%
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up at 210.3 ± 182.2 days: 0/106 (0%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		12 months follow-up: (*follow-up period only)* Stroke (ischaemic/haemorrhagic): 2/95 (2%) Annual rate of ischaemic stroke: 2.0%
Interpretation of Evidence	Six studies reported on all-cause stroke or embolism during follow-up. The percentage of patients who had an all-cause stroke ranged from 0% (reported at a mean follow-up of 210.3 ± 182.2 days) to 4.5% (reported at a mean follow-up of 30 ± 12 months). When reported, rates ranged from 1.6 per 100 patient-years to 2.3% per year. The remaining six studies did not report on all-cause stroke during follow-up, but one study did report clear percentages for *both* ischaemic and haemorrhagic stroke (Figini et al. 2017). The other studies largely reported on annual rates of ischaemic and/or haemorrhagic stroke (see below). All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **Ischaemic and haemorrhagic stroke**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Ischaemic stroke: 3/176.9 patient-years (1.7% per year) Haemorrhagic stroke: 1/179 patient-years (0.6% per year)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Ischaemic stroke: 1.5 per 100 patient-years Haemorrhagic stroke: mean 1.3 years (1,349 patient years); 3 /1047 (1.3%)

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	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Annual rate of ischaemic stroke: 15/1325 patient-years (1.1% per year) Haemorrhagic stroke: 1 year follow up: 0/893 (0%)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Ischaemic stroke: 4 events at mean follow-up 24.7 ± 16.07 months (0.57 per 100 patient-years) Annual rate of ischaemic stroke: 0.57% (4/706 patient-years) Haemorrhagic stroke: 2 events (both fatal) at mean follow-up 24.7 ± 16.07 months (0.28 per 100 patient-years)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Mean follow-up 400 days: Ischaemic stroke: 2/101 (2%) (*follow-up only*)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Annual rates of ischaemic stroke: 2.2%
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Mean follow-up of 448 (167-793) days: Ischaemic stroke: 0/152 (0%) Non-fatal haemorrhagic stroke: 1/152 (0.7%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Mean follow-up at 680 ± 351 days (238 patient-years): Ischaemic stroke: 2/128 (1.6%)
Interpretation of Evidence	Eight studies reported on ischaemic or haemorrhagic stroke during follow-up. When reported, percentages of ischaemic stroke ranged from 0% (reported at a mean follow-up of 448 (167-793) days) to 2% (reported at a mean follow-up of 400 days). Rates of ischaemic stroke ranged from 0.57 per 100 patient-years to 2.2% per year. Rates of haemorrhagic stroke ranged from 0.28 per 100 patient-years to 0.6% per year. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
	ASAP Study - (Reddy et al. 2013)	7	Direct	A	8/175 patient-years (4.6% per year) (primary efficacy endpoint that

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Follow-up complications and adverse events: **Overall events** *Notes:* *The events that make up the overall score slightly differ between studies.*					consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Mean 1.3 years (1,349 patient years): Major adverse events (stroke, TIA, major bleeding, death): 107/1047 (10.2%)
	Observational study – ITALY-	7	Direct		Follow-up at 680 ± 351 days (238 patient-years): Cardiovascular related events: 23/128 (18.0%) (consisted of ischaemic stroke, TIA, subdural haematoma, other major bleeding, minor bleeding, myocardial infarction, sudden cardiac death, pericardial tamponade, cardiac arrest/hypokalaemia, coronary artery disease, pulmonary embolism), (pleuro-) pericarditis)
	(Santoro et al. 2016)	7	Direct		Mean follow-up 24 months (290 patient-years): Some event 30/158 (19.0%) (not specified)
	Iberian Registry - (Lopez Minguez et al. 2015)	6	Direct		12 month freedom from major adverse events (secondary endpoint): 95/100 (95%)
Interpretation of Evidence	Five studies reported on overall event rates during follow-up. These ranged from 5% to 19.0%, but the events evaluated differed among the studies (or was not specified). The ASAP study reported data by patient-years (Reddy et al. 2013). In this study, the overall events consisted of the occurrence of stroke (including ischaemic or haemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism, which occurred at a rate of 4.6% per year. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **Death and cardiovascular**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Death: 9/180 patient-years (5.0% per year) (none were considered to be device or procedure related) One-year all-cause mortality rate was 4.3%

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
death *Notes:* *For this evidence review, we did not attempt to calculate an overall rate if studies reported data for follow-up period separately from the peri-procedural period.*	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Mean 1.3 years (1,349 patient years): Death: 80/1047 (7.6%) Cardiovascular death: 24/1047 (2.4%)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		After 1 year follow-up, death rate reported as 9.8% *The authors stated that cause of death was known in 77 of 91 patients; none were considered to be complications of the device.*
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Deaths (overall): 13 (1.84 per 100 patient-years) Non-cardiovascular deaths: 3 (0.42 per 100 patient-years) Cardiovascular deaths: 10 (1.42 per 100 patient-years)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Mean follow-up 30 ± 12 months (264 patient-years): Deaths: 14 /110 (12%) *(follow-up period only)* Cardiovascular or neurological death: 3/110 (2.7%) *(follow-up period only)* (one sudden cardiac death in hypertrophic cardiomyopathy (HCM), one massive stroke in patient in therapy with growth factors for haematological disorders, one haemorrhagic stroke, 27 days after procedure in patient with double antiplatelet therapy)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Mean follow-up of 448 (167-793) days: Death: 5/152 (3.3%) Cardiovascular deaths: 2/152 (1.3%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Follow-up at 680 ± 351 days (238 patient-years): Deaths (overall): 8/128 (6.3%)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
					Cardiovascular deaths: 2/128 (1.6%) All deaths were unrelated to the implanted device and implantation procedure.
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Mean follow-up 24 months (290 patient-years): Deaths: 17/158 (10.8%) Annual death rate: 5.8%
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up 210.3 ± 182.2 days: Deaths (overall): 4/106 (3.7%) Cardiovascular deaths: 2/106 (1.9%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		12 months follow-up: (*follow-up period only)* 0/95 (0%)
Interpretation of Evidence	Ten studies reported on death. Some studies reported on the peri-procedural period plus follow-up, and others reported only on the follow-up period. The percentage of patients who died ranged from 0% (reported at 12 months follow-up) to 12% (reported at a mean follow-up of 30 ± 12 months). When reported, rates ranged from 1.84 per 100 patient-years to 5.8% per year. The percentage of patients with cardiovascular deaths ranged from 1.6% (reported at a mean follow-up of 680 ± 351 days) to 2.4% (reported at a mean follow-up of 1.3 years). The remaining two studies did not report on death during follow-up. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **Device embolism**	Observational study – CHINA - (Huang et al. 2017)	6	Direct	B	12 months follow-up: (*follow-up period only)* Device embolisation: 2/95 (2%)
Interpretation of Evidence	One study reported on device embolisation (Huang et al. 2017). In this study, device embolisation occurred in 2% of patients during 12 months of follow-up (none occurred within the peri-procedural period). This study is inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Follow-up complications and adverse events: **Systemic embolism**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	Annual rate of systemic thromboembolism: 2.3% (31/1,349 patient-years)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		Systemic embolism: 1 (0.14 per 100 patient-years)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Mean follow-up 30 ± 12 months (264 patient-years): Systemic embolism 0/110 (0%) *(follow-up only)*
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up 210.3 ± 182.2 days: Systemic embolism: 0/106 (0%)
Interpretation of Evidence	Four studies reported on systemic embolism during follow-up. Two studies reported that no patients experienced systemic embolism, one reported an annual rate of 2.3% (ACP Registry), and one reported a rate of 0.14 per 100 patient-years (Betts et al. 2017). The remaining eight studies did not report on systemic embolism during follow-up. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **Transient ischaemic attack (TIA)**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	Mean follow-up at 1.3 years (1,349 patient years); 13 /1047 (1.3%)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Mean follow-up (400 days): 1/101 (1%) (*follow-up only*)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Mean follow-up 30 ± 12 months (264 patient-years): 1/110 (0.9%) *(follow-up only)*
	Observational study – ITALY –	7	Direct		Mean follow-up of 448 (167-793) days:

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	(Figini et al. 2017)				1/152 (0.7%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Follow-up at 680 ± 351 days (238 patient-years): 3/128 (2.3%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up 210.3 ± 182.2 days: 2/106 (1.9%)
Interpretation of Evidence	Six studies reported on TIA during follow-up, which ranged from 0.7% to 2.3% across the studies. The remaining six studies did not report on TIA during follow-up. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **TIAs/strokes/embolism**	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)	B	Annual rate of ischaemic stroke/TIA/thromboembolism: 20/1318 patient-years (1.5% per year)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated and 98% with eligible devices)		TIAs/strokes/systemic embolism: 7 events (0.99 per 100 patient-years) Annual thromboembolic (TIA, ischaemic stroke, or systemic embolism) event rate: 0.71% (5/706 patient-years) (*does not include haemorrhagic stroke*) TIAs/strokes: 6 events (0.85 per 100 patient-years)
Interpretation of Evidence	Two studies reported on TIA/strokes/embolism during follow-up. One reported a rate of 0.85 per 100 patient-years (Betts et al. 2017) and the other reported an annual rate of 1.5% (EWOLUTION Registry). Both studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events:	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation	A	1 (0.14 per 100 patient-years)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
Myocardial infarction:			therapy was contraindicated and 98% with eligible devices)		
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Follow-up at 680 ± 351 days (238 patient-years): 2/128 (1.6%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up 210.3 ± 182.2 days: 1/106 (1%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		12 months follow-up: (*follow-up period only)* 0/95 (0%)
Interpretation of Evidence	Four studies reported on myocardial infarction (MI) during follow-up, which ranged from 0% to 1.6% across the studies. The remaining eight studies did not report on MI during follow-up. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications and adverse events: **Bleeding or haemorrhage**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	Mean follow-up 1.3 years (1,349 patient years); Major bleeding: 27/1047 (2.7%) Intracranial haemorrhage: 0/1047 (0.0%) Annual rate of major bleeding: 2.1% (28/1,349 patient-years)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		Annual rate of major bleeding: 34/1303 patient-years (2.6% per year) (the majority occurred outside of the peri-procedural period)
	Observational study – UK - (Betts et al. 2017)	7	Somewhat direct (95% for whom anticoagulation therapy was contraindicated		Major bleedings: 3 events (2 fatal) (0.42 per 100 patient-years) Minor bleedings: 7 events (0.99 per 100 patient-years) Total bleeding: 10 events (1.42 per 100 patient-years)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
			and 98% with eligible devices)		Annual bleeding rate: 0.42% (3/706 patient-years)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Mean follow-up (400 days): 14/101 (14%) (*follow-up only*)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Mean follow-up 30 ± 12 months (264 patient-years): 3/110 (2.7%) *(follow-up only)* Annual rate of bleeding: 1.1%
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Mean follow-up of 448 (167-793) days: Life threatening bleeding: 1/152 (0.7%) Major bleeding: 2/152 (1.3%) Minor bleeding: 7/152 (4.6%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		Follow-up at 680 ± 351 days (238 patient-years): Haemorrhagic complications - Subdural haematoma: 1/128 (0.8%) Other major bleeding: 2/128 (1.6%) Minor bleeding: 4/128 (3.1%) Annual rate of major bleeding: 1.3%
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Mean follow-up 24 months (290 patient-years): Major bleeding: 9/158 (5.7%) Minor relevant bleeding: 7/158 (4.4%) Total bleeding events: 16 (10.1%) Annual rate of major bleeding: 3.1% Annual rate of total bleeding: 5.5%
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Mean follow-up 210.3 ± 182.2 days: 5/106 (4.7%) Major bleeding event rate: 4.7%

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		12 months follow-up: (*follow-up period only)* Minor bleeding: 0/95 (0%) Major bleeding: 1/95 (1%)
Interpretation of Evidence	Ten studies reported on bleeding during follow-up. Four studies reported the percentage of patients who had minor bleeding which ranged from 0% (at 12 months follow-up) to 4.6% (reported at a mean follow-up of 448 (167-793) days). Five studies reported the percentage of patients who had major bleeding, which ranged from 1% (at 12 months follow-up) to 5.7% (reported at a mean follow-up of 24 months (290 patient-years). Five studies reported the annual rate of major bleeding, which ranged from 1.3% to 4.7%. Three studies reported an annual rate of total bleeding, which ranged from 0.42% to 5.5%. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications: **Device-related thrombus**	ASAP Study - (Reddy et al. 2013)	7	Direct	A	Device thrombus (at TEE): 5/150 (3.3%)
	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct		Mean follow-up 1.3 years (1,349 patient years): 28/632 (4.4%) (with complete clinical follow-up)
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		At 1 year follow-up, device thrombus rate was 3.7% (sample size not clear)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Device thrombus: 2/101 (2%)
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Device thrombus: 0/110 (0%)
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Device thrombus: 1 (0.7%) (*the authors stated that one case of thrombosis was identified on an Amulet device*)
	Observational study – ITALY-	7	Direct		Device thrombosis: 1/67 (1.4%)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	(Santoro et al. 2016)				
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Device thrombus: 13/158 (8.2%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Device-associated thrombus: 1/106 (1.0%)
	Registry study – USA - (Murarka et al. 2017)	6	Direct		Device thrombus: 2/131 (1.5%) (at 45 days) (possibly considered peri-procedural?)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		12 months follow-up: (*follow-up period only)* Device thrombus: 2/95 (2.1%)
Interpretation of Evidence	Eleven studies reported on device-related thrombus during follow-up echocardiography. The percentage of patients with device thrombosis ranged from 0% to 8.2%. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
Follow-up complications: **Leaks**	ACP Registry - (Freixa et al. 2016, Lempereur et al. 2017b, Tzikas et al. 2017, Tzikas et al. 2016)	7	Direct	A	A peri-device leak was found in 73/632 patients (11.6%). The leak was trivial, mild, and significant in 27 (4.3%), 34 (5.4%), and 12 (1.9%) patients, respectively
	EWOLUTION Registry - (Bergmann et al. 2017, Boersma et al. 2017, Boersma et al. 2016a, Boersma et al. 2016b)	6	Somewhat direct (74% patients for whom anticoagulation therapy was contraindicated)		At one year follow-up: No leaks >5mm: 1002/1005 (99.7%)
	Observational study – GERMANY - (Seeger et al. 2016)	6	Direct		Three months post-device implantation, there was residual flow <5 mm in 15% (14/94). Twelve months post-device implantation, 14% of patients showed residual flow <5 mm.
	Registry study – ITALY -(Berti et al. 2016)	7	Direct		Leak: 4/20 (20%)

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
	Observational study – ITALY – (Figini et al. 2017)	7	Direct		Leak: 32/114 (28%)
	Observational study – ITALY- (Santoro et al. 2016)	7	Direct		TEE imaging was performed on 67 patients with mean implant duration at imaging of 9.7 months; one major residual leak was observed (1.4%) and non-significant leaks were observed in 6 patients (8.9%)
	Iberian Registry - (Lopez Minguez et al. 2015)	7	Direct		Leak: 13/158 (8.2%)
	Observational study – CANADA - (Saw et al. 2017)	7	Direct		Leak: 28/76 (37%)
	Observational study – CHINA - (Huang et al. 2017)	6	Direct		Leak: 34/95 (36%) patients presented with small residual leak (≤5 mm), and no large residual leak (>5 mm)
Interpretation of Evidence	Nine studies reported on leaks identified during follow-up echocardiography. When reported, the percentage of patients with leaks ranged from 11.6% to 37%. Some studies also reported further details by size. All of these studies are registry or observational studies that are inherently limited by the lack of a control group. The results should be considered with caution and need to be confirmed with randomised controlled trials.				
					Summary and Interpretation of Evidence
Hospitalisation or other health care resources	No studies provided detailed information on health care resource use or length of stay.				
Cost-effectiveness	(Panikker et al. 2016)	8	Concerns with external validity	B	The study had good internal validity and identified conflicts of interest. LAAC provides long-term clinical and economic benefits when compared with aspirin and was cost saving after year 7 compared with no therapy. The key limitation of this study is the assumed cost of the device is much lower than that obtained by the NICE EAC. If one

Use of Percutaneous LAAO in Patients for Whom Anticoagulant therapy is Contraindicated					
Outcome Measure	**Reference (*only described as a registry study if explicitly reported in paper)***	**Quality of Evidence Score (out of 10) **please note that the included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases inherent to registry and observational studies***	**Applicability**	**Grade of Evidence**	**Summary**
					adopts the higher cost of £11,600 per patient then, at 10 years after the procedure, LAAO would have similar costs to no therapy but higher costs than those managed on aspirin.
	(Reddy et al. 2016)	7	Costs unlikely to generalise to NHS England setting	B	This study was of reasonable quality although with concerns about external validity and reported conflicts of interest. LAAC provides long-term clinical and economic benefits when compared with aspirin, but the costs used are for Germany.

9. Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults with paroxysmal, persistent or permanent atrial fibrillation with a risk of stroke (CHA2DS2VASC score of 2 or higher) for whom long-term anticoagulation therapy is contraindicated. Registry studies that included **over 50% patients for whom anticoagulation therapy was contraindicated, were included**. For other study types, data had to be reported separately for patients contraindicated to anticoagulation therapy to be eligible for inclusion. This subgroup data was to be considered separately from the other studies. Studies that included patients with an average CHA_2DS_2VASC score of 2 or higher were also included. Studies were not be eligible for inclusion if they were conducted in: • Patients who were previously treated with a surgical LAA ligation; • Patients undergoing cardiac surgery.
I – Intervention Which intervention, treatment or approach should be used?	LAAO Device/s (local/mechanical therapy) for the prevention of cardio-embolic stroke. The LAAO method of interest was limited to **percutaneous closure** using an endocardial route. These devices were expected to include WATCHMAN, ACP, Amulet, WaveCrest, Occlutech LAA Occluder, Sideris Transcatheter Patch, LAambre, Pfm, Utrasept devices amongst others. Studies that aimed to evaluate a peri-procedural or post-procedural OAC were included (NOACs, warfarin etc.) As PLAATO is no longer on the market, studies that evaluated this device were excluded. Occlusion or removal of the appendage through open surgery (including LAAO using the named devices), or closure using an epicardial approach (using the Lariat device) were not be eligible for inclusion. In addition, studies that combined LAAO with other interventions (e.g. MitraClip, ablation plus LAAO) were not eligible for inclusion.
C – Comparison	Depending on the study design, comparators may not be observed. For those studies that included a comparator, LAAO had to be compared with medical therapy.

What is/are the main alternative/s to compare with the intervention being considered?	Studies that compared different devices, and studies that compared different generations (i.e. first and second generation) of the same device were excluded.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	All outcomes reported by the studies that meet other inclusion criteria were considered. Outcome of interest are listed below, however, this is not an exhaustive list: *Critical to decision-making:* • Stroke/embolism (total, haemorrhagic, ischaemic); • Death (all-cause, cardiovascular mortality, treatment related mortality) • Non-procedure-related bleeding; *Important to decision-making:* • Major bleeding; • The number of adverse events and number of serious adverse events; • Treatment-related morbidity - procedure related complications (and time point that they occur) including cardiac perforation, pericardial effusion with tamponade, device embolisation, device thrombosis; • Interventions following complications, including open heart surgery for open pericardiocentesis or device retrieval; pericardiocentesis; vascular surgery for device retrieval or femoral vessel damage; device snare and retrieval; blood transfusion; • Hospitalisation, health care resources associated with the management and treatment of complications; • Economic outcomes: summary health outcomes (Quality-adjusted Life Years (QALYs)) and incremental cost-effectiveness ratios (ICER); • Cost analyses. • Additional information will be collected from studies that meet the PICO criteria including contraindications for device insertion, learning curves, service quality indicators, anti- thrombotic regimens post-procedure.
S - Study design	Studies with any study design will be eligible if they include a **sample size of 100 or above**.

	The following study designs were not data extracted: • Systematic reviews and guidelines published in the last three years (but screened for references). Studies that combined data from a RCT and a registry were not eligible for inclusion as data from any relevant RCTs and registries will have already be eligible for inclusion separately.
Assumptions / limits applied to search	
Inclusion Criteria	Only peer-reviewed publications in the English-language **published in the last 10 years** will be eligible for inclusion. For cost-effectiveness studies, only those which report on the UK or European countries.
Exclusion Criteria	As reported in each section above. Also, economic evaluations/budget impact analyses conducted in countries outside of Europe were excluded.

10. Search Strategy

The literature search was designed to identify studies reporting on clinical effectiveness, cost effectiveness, or adverse events associated with LAAO.

The strategy was developed for MEDLINE (Ovid interface) and is presented in Figure 10.1. It comprised 2 concepts which were combined using the Boolean AND:

- AF (search lines 1 - 4);
- LAAO (search lines 5 – 14).

The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReMiner tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi).

The terms for the LAAO concept included device trade name terms (lines 12 – 13). These device trade name terms were also combined with LAA terms in a stand-alone search section; the terms were not combined with the AF terms (lines 16-17). These lines were designed to act as an additional, focused search to capture records which include a device name, but where the AF context is not made explicit in the record.

Animal studies were excluded from MEDLINE using a standard algorithm. The strategy was not restricted by study design, but publication types which were unlikely to yield relevant study reports (news, comments, editorials, letter, case reports) and records with the phrase 'case report' in the title field were excluded. The search is limited to English language studies, published in the last ten years (2007 to current) as per the eligibility criteria.

The MEDLINE strategy was translated appropriately for other databases. Full strategies (including search dates) for all sources searched are included in Appendix A.

Figure 10.1: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 Atrial Fibrillation/ (46672)
2 ((atrial or atrium or auricular or heart or cardiac) adj3 (fibrillat$ or tachycardia$ or tachyarrhythmia$)).ti,ab,kf. (66206)
3 (AF or A-Fib or PAF).ti,ab,kf. (42540)
4 or/1-3 (96761)
5 Atrial Appendage/su (850)
6 Atrial Appendage/ and ("Prostheses and Implants"/ or Cardiovascular Surgical Procedures/ or Prosthesis Implantation/ or Ligation/) (240)
7 Atrial Appendage/ and (clos$ or occlus$ or occulus$ or occlud$ or clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$ or device$1).ti,ab,kf. (1153)

8 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (occlus$ or occulus$ or occlud$ or clos$)).ti,ab,kf. (1120)
9 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$)).ti,ab,kf. (803)
10 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 device$1).ti,ab,kf. (451)
11 (laao or plaao or laac or plaac).ti,ab,kf. (257)
12 (acp$2 or acp2$2).ti,ab,kf. (11954)
13 (aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kf. (5444)
14 or/5-13 (19165)
15 4 and 14 (1748)
16 Atrial Appendage/ and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kf. (335)
17 ((atrial appendage$1 or LAA) and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2)).ti,ab,kf. (495)
18 or/15-17 (1799)
19 exp animals/ not humans/ (4441809)
20 (news or comment or editorial or letter or case reports).pt. or case report.ti. (3513449)
21 18 not (19 or 20) (1223)
22 limit 21 to (english language and yr="2007 -Current") (997)
23 remove duplicates from 22 (921)

Key to syntax:

$	unlimited truncation symbol; words beginning with the specified stem
$N	limited right-hand truncation - restricts the number of characters following the word to N
?	wildcard symbol; identifies any character or no character
adjN	finds terms within N terms of each other, in either direction
.ti,ab,kf.	search terms in the title ,abstract or author keywords
.pt	search terms in the publication type field
/	subject heading search
exp	exploded subject heading
*	focused subject heading
or/1-4	combine search lines 1-16 with Boolean OR

The literature search was conducted in a range of relevant bibliographic databases appropriate to the context outlined in NHS England Guidance on conducting evidence reviews for Specialised Services Commissioning Products.

We also checked the reference lists of any relevant systematic reviews and guidelines published in 2016 and 2017 (Hanif et al. 2017, Lempereur et al. 2017a, Sahay et al. 2017, Li et al. 2016, Noelck et al. 2016, Sohaib and Fox 2015, Safavi-Naeini et al. 2015, Bajaj et al. 2016b, Xu et al. 2016, Wei et al. 2016, Holmes and Reddy 2016, Koifman et al. 2016, Zhou et al. 2016, Chatterjee et al. 2015, Bode et al. 2015, Aminian et al. 2015c, Yerasi et al. 2017, Franco et al. 2016, Lempereur et al. 2016a, Lempereur et al. 2016b, Bajaj et al. 2016a, Parashar et al. 2016, Briceno et al. 2015c, Koifman et al. 2015, Hanif et al. 2015, Aminian et al. 2015a, Gangireddy et al. 2015, Briceno et al. 2015b, Aminian et al. 2015b, Kanmanthareddy et al. 2015, Bajaj et al. 2015, Briceno et al. 2015a, Noelck et al. 2015, New Zealand National Health Committee 2015) for any eligible studies that may have been missed by the database searches.

No further relevant studies were identified.

The databases and information sources searched are shown in Table 10.1.

Table 10.1: Databases and information sources searched

Database / information source	Interface / URL
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Embase	OvidSP
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley
Health Technology Assessment Database (HTA)	Cochrane Library / Wiley
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
National Guidelines Clearinghouse	http://www.guideline.gov/index.aspx
Guidelines International Network: International Guideline Library	http://www.g-i-n.net/library/international-guidelines-library
National Institute for Health and Care Excellence	https://www.nice.org.uk/

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms. Where result format did not facilitate loading into EndNote, Word documents or Excel spreadsheets were used as appropriate.

Literature Search Results

The searches identified 4302 records (Table 10.2). Following deduplication 3169 records were assessed for relevance.

Table 10.2: Literature search results

Resource	Number of records identified
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	921
PubMed	252
Embase	2856
Cochrane Central Register of Controlled Trials (CENTRAL)	136
Database of Abstracts of Reviews of Effects (DARE)	4
Health Technology Assessment Database (HTA)	11
Cochrane Database of Systematic Reviews (CDSR)	2
NHS Economic Evaluation Database (NHS EED)	3
CEA Registry	5
National Guidelines Clearinghouse	17
Guidelines International Network: International Guideline Library	14
National Institute for Health and Care Excellence	8
Records found via review reference checking	73
Total number of records retrieved	**4302**
Total number of records after deduplication	**3169**

11. Evidence selection

- Total number of publications reviewed: 3169 titles and abstracts.
- Total number of publications considered relevant: 262 records were identified as potentially relevant and full papers were obtained and screened for relevance.
- Total number of publications selected for inclusion in this briefing: 22. 20 documents were included for clinical effectiveness and adverse events (reporting on a total of 14 studies) and two documents were included for economic data (reporting on a total of two studies).

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Appendix A: Full Search Strategies

A.1: Source: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Interface / URL: Ovid SP
Database coverage dates: 1946 to current. Updated daily.
Search date: 19/07/17
Retrieved records: 921
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Atrial Fibrillation/ (46672)
2 ((atrial or atrium or auricular or heart or cardiac) adj3 (fibrillat$ or tachycardia$ or tachyarrhythmia$)).ti,ab,kf. (66206)
3 (AF or A-Fib or PAF).ti,ab,kf. (42540)
4 or/1-3 (96761)
5 Atrial Appendage/su (850)
6 Atrial Appendage/ and ("Prostheses and Implants"/ or Cardiovascular Surgical Procedures/ or Prosthesis Implantation/ or Ligation/) (240)
7 Atrial Appendage/ and (clos$ or occlus$ or occulus$ or occlud$ or clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$ or device$1).ti,ab,kf. (1153)
8 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (occlus$ or occulus$ or occlud$ or clos$)).ti,ab,kf. (1120)
9 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$)).ti,ab,kf. (803)
10 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 device$1).ti,ab,kf. (451)
11 (laao or plaao or laac or plaac).ti,ab,kf. (257)
12 (acp$2 or acp2$2).ti,ab,kf. (11954)
13 (aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kf. (5444)
14 or/5-13 (19165)
15 4 and 14 (1748)
16 Atrial Appendage/ and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-

tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kf. (335)
17 ((atrial appendage$1 or LAA) and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2)).ti,ab,kf. (495)
18 or/15-17 (1799)
19 exp animals/ not humans/ (4441809)
20 (news or comment or editorial or letter or case reports).pt. or case report.ti. (3513449)
21 18 not (19 or 20) (1223)
22 limit 21 to (english language and yr="2007 -Current") (997)
23 remove duplicates from 22 (921)

A.2: Source: PubMed

Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed/
Database coverage dates: 1940s to current. Updated daily.
Search date:
Retrieved records: 252
Search strategy:

Search Query Items found
#25 Search (#23 NOT #24) 252
#24 Search medline[sb] 24152103
#23 Search (#18 NOT (#19 OR #20)) Filters: Publication date from 2007/01/01 to 2017/12/31; English 962
#22 Search (#18 NOT (#19 OR #20)) Filters: Publication date from 2007/01/01 to 2017/12/31 1019
#21 Search (#18 NOT (#19 OR #20)) 1247
#20 Search (news[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR case reports[pt]) OR case report[ti] 3417460
#19 Search animals[mh] NOT humans[mh:noexp] 4348558
#18 Search (#15 OR #16 OR #17) 1844
#17 Search (atrial appendage*[tiab] OR LAA[tiab]) AND (acp*[tiab] OR acp2*[tiab] OR aegis*[tiab] OR amplatzer*[tiab] OR amulet*[tiab] OR atriclip*[tiab] OR atri-clip*[tiab] OR cardioblate*[tiab] OR cardio-blate*[tiab] OR coherex*[tiab] OR endoloop*[tiab] OR endo-loop*[tiab] OR lambre*[tiab] OR lariat*[tiab] OR ligasure*[tiab] OR liga-sure*[tiab] OR occlutech*[tiab] OR occlu-tech*[tiab] OR (pfm[tiab] AND occluder*[tiab]) OR plaato*[tiab] OR tigerpaw*[tiab] OR tiger-paw*[tiab] OR ultraseal*[tiab] OR ultra-seal*[tiab] OR ultrasept*[tiab] OR ultra-sept*[tiab] OR watchman*[tiab] OR watch-man*[tiab] OR wavecrest*[tiab] OR "wave-crest" [tiab]) 455
#16 Search "Atrial Appendage"[Mesh:NoExp] AND (acp*[tiab] OR acp2*[tiab] OR aegis*[tiab] OR amplatzer*[tiab] OR amulet*[tiab] OR atriclip*[tiab] OR atri-clip*[tiab] OR

cardioblate*[tiab] OR cardio-blate*[tiab] OR coherex*[tiab] OR endoloop*[tiab] OR endo-loop*[tiab] OR lambre*[tiab] OR lariat*[tiab] OR ligasure*[tiab] OR liga-sure*[tiab] OR occlutech*[tiab] OR occlu-tech*[tiab] OR (pfm[tiab] AND occluder*[tiab]) OR plaato*[tiab] OR tigerpaw*[tiab] OR tiger-paw*[tiab] OR ultraseal*[tiab] OR ultra-seal*[tiab] OR ultrasept*[tiab] OR ultra-sept*[tiab] OR watchman*[tiab] OR watch-man*[tiab] OR wavecrest*[tiab] OR "wave-crest" [tiab]) 299

#15 Search (#4 AND #14) 1710

#14 Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) 20059

#13 Search aegis*[tiab] OR amplatzer*[tiab] OR amulet*[tiab] OR atriclip*[tiab] OR atri-clip*[tiab] OR cardioblate*[tiab] OR cardio-blate*[tiab] OR coherex*[tiab] OR endoloop*[tiab] OR endo-loop*[tiab] OR lambre*[tiab] OR lariat*[tiab] OR ligasure*[tiab] OR liga-sure*[tiab] OR occlutech*[tiab] OR occlu-tech*[tiab] OR (pfm[tiab] AND occluder*[tiab]) OR plaato*[tiab] OR tigerpaw*[tiab] OR tiger-paw*[tiab] OR ultraseal*[tiab] OR ultra-seal*[tiab] OR ultrasept*[tiab] OR ultra-sept*[tiab] OR watchman*[tiab] OR watch-man*[tiab] OR wavecrest*[tiab] OR "wave-crest" [tiab] 5280

#12 Search acp*[tiab] OR acp2*[tiab] 12223

#11 Search laao[tiab] OR plaao[tiab] OR laac[tiab] OR plaac[tiab] 220

#10 Search (atrial appendage*[tiab] OR laa[tiab]) AND (device[tiab] OR devices[tiab]) 766

#9 Search (atrial appendage*[tiab] OR laa[tiab]) AND (clip*[tiab] OR sutur*[tiab] OR ligat*[tiab] OR plug*[tiab] OR stapl*[tiab] OR block*[tiab] OR remov*[tiab] OR isolat*[tiab] OR amputat*[tiab] OR obliterat*[tiab] OR excis*[tiab] OR exclu*[tiab] OR invaginat*[tiab]) 1750

#8 Search (atrial appendage*[tiab] OR laa[tiab]) AND (occlus*[tiab] OR occulus*[tiab] OR occlud*[tiab] OR close[tiab] OR closed[tiab] OR closes[tiab] OR closure*[tiab] OR closing[tiab]) 1360

#7 Search "Atrial Appendage"[mesh:noexp] AND ("Prostheses and Implants"[mesh:noexp] OR "Cardiovascular Surgical Procedures"[mesh:noexp] OR "Prosthesis Implantation"[mesh:noexp] OR "Ligation"[mesh:noexp]) 219

#6 Search "Atrial Appendage"[Mesh:NoExp] AND (clos*[tiab] OR occlus*[tiab] OR occulus*[tiab] OR occlud*[tiab] OR clip*[tiab] OR sutur*[tiab] OR ligat*[tiab] OR plug*[tiab] OR stapl*[tiab] OR block*[tiab] OR remov*[tiab] OR isolat*[tiab] OR amputat*[tiab] OR obliterat*[tiab] OR excis*[tiab] OR exclu*[tiab] OR invaginat*[tiab] OR device*[tiab]) 1060

#5 Search "Atrial Appendage/surgery"[Mesh:NoExp] 781

#4 Search #1 OR #2 OR #3 101377

#3 Search (AF[tiab] OR A-Fib[tiab] OR PAF[tiab]) 40414

#2 Search (atrial[tiab] OR atrium[tiab] OR auricular[tiab] OR heart[tiab] OR cardiac[tiab]) AND (fibrillate*[tiab] OR tachycardia*[tiab] OR tachyarrhythmia*[tiab]) 36643

#1 Search "Atrial Fibrillation"[mesh:noexp] 43526

A.3: Source: Embase

Interface / URL: Ovid SP

Database coverage dates: 1974 to 18 July 2017

Search date: 19/07/17

Retrieved records: 2856
Search strategy:

Database: Embase <1974 to 2017 July 18>
Search Strategy:
---
1 exp atrial fibrillation/ (28962)
2 ((atrial or atrium or auricular or heart or cardiac) adj3 (fibrillat$ or tachycardia$ or tachyarrhythmia$)).ti,ab,kw. (103739)
3 (AF or A-Fib or PAF).ti,ab,kw. (67352)
4 or/1-3 (140298)
5 heart atrium appendage/su (39)
6 left atrial appendage closure device/ (695)
7 heart atrium appendage/ and (exp implant/ or exp "prostheses and orthoses"/ or prosthesis implantation/ or cardiovascular surgery/ or interventional cardiovascular procedure/ or ligation/) (1353)
8 heart atrium appendage/ and (clos$ or occlus$ or occulus$ or occlud$ or clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$ or device$1).ti,ab,kw. (3156)
9 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (occlus$ or occulus$ or occlud$ or clos$)).ti,ab,kw. (1940)
10 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 (clip$ or sutur$ or ligat$ or plug$ or stapl$ or block$ or remov$ or isolat$ or amputat$ or obliterat$ or excis$ or exclu$ or invaginat$)).ti,ab,kw. (1407)
11 ((left atrial appendage$1 or atrial appendage$1 or laa) adj5 device$1).ti,ab,kw. (855)
12 (laao or plaao or laac or plaac).ti,ab,kw. (437)
13 (acp$2 or acp2$2).ti,ab,kw. (15088)
14 (aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kw. (8767)
15 or/5-14 (27290)
16 4 and 15 (3445)
17 heart atrium appendage/ and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2).ti,ab,kw. (788)
18 ((atrial appendage$1 or LAA) and (acp$2 or acp2$2 or aegis$2 or amplatzer$2 or amulet$2 or atriclip$2 or atri-clip$2 or cardioblate$2 or cardio-blate$2 or coherex$2 or endoloop$2 or endo-loop$1 or lambre$2 or lariat$2 or ligasure$2 or liga-sure$2 or occlutech$2 or occlu-tech$2 or pfm occluder$2 or plaato$2 or tigerpaw$2 or tiger-paw$2 or

ultraseal$2 or ultra-seal$2 or ultrasept$2 or ultra-sept$2 or ultraseptor$2 or ultra-septor$2 or watchman$2 or watch-man$2 or wavecrest$2 or wave-crest$2)).ti,ab,kw. (1049)
19 or/16-18 (3612)
20 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5714017)
21 (editorial or letter or note).pt. (2206914)
22 19 not (20 or 21) (3293)
23 limit 22 to (english language and yr="2007 -Current") (2947)
24 remove duplicates from 23 (2856)

A.4: Source: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface / URL: Cochrane Library
Database coverage dates: Issue 6 of 12, June 2017
Search date: 20/07/17
Retrieved records: 136
Search strategy:

ID Search Hits
#1 [mh ^"Atrial Fibrillation"] 3409
#2 (atrial or atrium or auricular or heart or cardiac) near/3 (fibrillat* or tachycardia* or tachyarrhythmia*) 9548
#3 AF or A-Fib or PAF 10197
#4 #1 or #2 or #3 16477
#5 MeSH descriptor: [Atrial Appendage] this term only and with qualifier(s): [Surgery - SU] 24
#6 [mh ^"Atrial Appendage"] 67
#7 [mh ^"Prostheses and Implants"] or [mh ^"Cardiovascular Surgical Procedures"] or [mh ^"Prosthesis Implantation"] or [mh ^Ligation] 1915
#8 clos* or occlus* or occulus* or occlud* or clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat* or device* 201307
#9 #6 and (#7 or #8) 47
#10 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (occlus* or occulus* or occlud* or clos*) 118
#11 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat*) 49
#12 (left next atrial next appendage* or atrial next appendage* or laa) near/5 device* 64
#13 laao or plaao or laac or plaac 30
#14 acp* or aegis* or amplatzer* or amulet* or atriclip* or atri next clip* or cardioblate* or cardio next blate* or coherex* or endoloop* or endo next loop* or lambre* or lariat* or ligasure* or liga next sure* or occlutech* or occlu next tech* or pfm next occluder* or plaato* or tigerpaw* or tiger next paw* or ultraseal* or ultra next seal* or ultrasept* or ultra next sept* or watchman* or watch next man* or wavecrest* or wave next crest* 2111
#15 #5 or #9 or #10 or #11 or #12 or #13 or #14 2217

#16 #4 and #15 206
#17 #6 and #14 15
#18 atrial next appendage* or LAA 359
#19 #18 and #14 62
#20 #16 or #17 or #19 211
#21 #20 Publication Year from 2007 to 2017 136

A.5: Source: Database of Abstracts of Reviews of Effect (DARE)
Interface / URL: Cochrane Library
Database coverage dates: Issue 2 of 4, April 2015
Search date: 20/07/17
Retrieved records: 4
Search strategy:

ID Search Hits
#1 [mh ^"Atrial Fibrillation"] 3409
#2 (atrial or atrium or auricular or heart or cardiac) near/3 (fibrillat* or tachycardia* or tachyarrhythmia*) 9548
#3 AF or A-Fib or PAF 10197
#4 #1 or #2 or #3 16477
#5 MeSH descriptor: [Atrial Appendage] this term only and with qualifier(s): [Surgery - SU] 24
#6 [mh ^"Atrial Appendage"] 67
#7 [mh ^"Prostheses and Implants"] or [mh ^"Cardiovascular Surgical Procedures"] or [mh ^"Prosthesis Implantation"] or [mh ^Ligation] 1915
#8 clos* or occlus* or occulus* or occlud* or clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat* or device* 201307
#9 #6 and (#7 or #8) 47
#10 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (occlus* or occulus* or occlud* or clos*) 118
#11 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat*) 49
#12 (left next atrial next appendage* or atrial next appendage* or laa) near/5 device* 64
#13 laao or plaao or laac or plaac 30
#14 acp* or aegis* or amplatzer* or amulet* or atriclip* or atri next clip* or cardioblate* or cardio next blate* or coherex* or endoloop* or endo next loop* or lambre* or lariat* or ligasure* or liga next sure* or occlutech* or occlu next tech* or pfm next occluder* or plaato* or tigerpaw* or tiger next paw* or ultraseal* or ultra next seal* or ultrasept* or ultra next sept* or watchman* or watch next man* or wavecrest* or wave next crest* 2111
#15 #5 or #9 or #10 or #11 or #12 or #13 or #14 2217
#16 #4 and #15 206
#17 #6 and #14 15
#18 atrial next appendage* or LAA 359

#19 #18 and #14 62
#20 #16 or #17 or #19 211
#21 #20 Publication Year from 2007 to 2017, in Other Reviews 4

A.6: Source: Health Technology Assessment Database (HTA Database)
Interface / URL: Cochrane Library
Database coverage dates: Issue 4 of 4, October 2016
Search date: 20/7/17
Retrieved records: 11
Search strategy:

ID Search Hits
#1 [mh ^"Atrial Fibrillation"] 3409
#2 (atrial or atrium or auricular or heart or cardiac) near/3 (fibrillat* or tachycardia* or tachyarrhythmia*) 9548
#3 AF or A-Fib or PAF 10197
#4 #1 or #2 or #3 16477
#5 MeSH descriptor: [Atrial Appendage] this term only and with qualifier(s): [Surgery - SU] 24
#6 [mh ^"Atrial Appendage"] 67
#7 [mh ^"Prostheses and Implants"] or [mh ^"Cardiovascular Surgical Procedures"] or [mh ^"Prosthesis Implantation"] or [mh ^Ligation] 1915
#8 clos* or occlus* or occulus* or occlud* or clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat* or device* 201307
#9 #6 and (#7 or #8) 47
#10 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (occlus* or occulus* or occlud* or clos*) 118
#11 (left next atrial next appendage* or atrial next appendage* or laa) near/5 (clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat*) 49
#12 (left next atrial next appendage* or atrial next appendage* or laa) near/5 device* 64
#13 laao or plaao or laac or plaac 30
#14 acp* or aegis* or amplatzer* or amulet* or atriclip* or atri next clip* or cardioblate* or cardio next blate* or coherex* or endoloop* or endo next loop* or lambre* or lariat* or ligasure* or liga next sure* or occlutech* or occlu next tech* or pfm next occluder* or plaato* or tigerpaw* or tiger next paw* or ultraseal* or ultra next seal* or ultrasept* or ultra next sept* or watchman* or watch next man* or wavecrest* or wave next crest* 2111
#15 #5 or #9 or #10 or #11 or #12 or #13 or #14 2217
#16 #4 and #15 206
#17 #6 and #14 15
#18 atrial next appendage* or LAA 359
#19 #18 and #14 62
#20 #16 or #17 or #19 211
#21 #20 Publication Year from 2007 to 2017, in Technology Assessments 11

A.7: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library

Database coverage dates: Issue 7 of 12, July 2017

Search date: 20/07/17

Retrieved records: 2

Search strategy:

ID	Search	Hits
#1	[mh ^"Atrial Fibrillation"]	3409
#2	((atrial or atrium or auricular or heart or cardiac) near/3 (fibrillat* or tachycardia* or tachyarrhythmia*)):ti,ab,kw	9003
#3	(AF or A-Fib or PAF):ti,ab,kw	4057
#4	#1 or #2 or #3	9987
#5	MeSH descriptor: [Atrial Appendage] this term only and with qualifier(s): [Surgery - SU]	24
#6	[mh ^"Atrial Appendage"]	67
#7	[mh ^"Prostheses and Implants"] or [mh ^"Cardiovascular Surgical Procedures"] or [mh ^"Prosthesis Implantation"] or [mh ^Ligation]	1915
#8	(clos* or occlus* or occulus* or occlud* or clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat* or device*):ti,ab,kw	173162
#9	#6 and (#7 or #8)	47
#10	((left next atrial next appendage* or atrial next appendage* or laa) near/5 (occlus* or occulus* or occlud* or clos*)):ti,ab,kw	116
#11	((left next atrial next appendage* or atrial next appendage* or laa) near/5 (clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat*)):ti,ab,kw	49
#12	((left next atrial next appendage* or atrial next appendage* or laa) near/5 device*):ti,ab,kw	62
#13	(laao or plaao or laac or plaac):ti,ab,kw	28
#14	(acp* or aegis* or amplatzer* or amulet* or atriclip* or atri next clip* or cardioblate* or cardio next blate* or coherex* or endoloop* or endo next loop* or lambre* or lariat* or ligasure* or liga next sure* or occlutech* or occlu next tech* or pfm next occluder* or plaato* or tigerpaw* or tiger next paw* or ultraseal* or ultra next seal* or ultrasept* or ultra next sept* or watchman* or watch next man* or wavecrest* or wave next crest*):ti,ab,kw	1023
#15	#5 or #9 or #10 or #11 or #12 or #13 or #14	1130
#16	#4 and #15	155
#17	#6 and #14	14
#18	(atrial next appendage* or LAA):ti,ab,kw	336
#19	#18 and #14	59
#20	#16 or #17 or #19	160
#21	#20 Publication Year from 2007 to 2017, in Cochrane Reviews (Reviews and Protocols)	2

A.8: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: Cochrane Library

Database coverage dates: Issue 2 of 4, April 2015

Search date: 20/07/17

Retrieved records: 3

Search strategy:

ID	Search	Hits
#1	[mh ^"Atrial Fibrillation"]	3409
#2	(atrial or atrium or auricular or heart or cardiac) near/3 (fibrillat* or tachycardia* or tachyarrhythmia*)	9548
#3	AF or A-Fib or PAF	10197
#4	#1 or #2 or #3	16477
#5	MeSH descriptor: [Atrial Appendage] this term only and with qualifier(s): [Surgery - SU]	24
#6	[mh ^"Atrial Appendage"]	67
#7	[mh ^"Prostheses and Implants"] or [mh ^"Cardiovascular Surgical Procedures"] or [mh ^"Prosthesis Implantation"] or [mh ^Ligation]	1915
#8	clos* or occlus* or occulus* or occlud* or clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat* or device*	201307
#9	#6 and (#7 or #8)	47
#10	(left next atrial next appendage* or atrial next appendage* or laa) near/5 (occlus* or occulus* or occlud* or clos*)	118
#11	(left next atrial next appendage* or atrial next appendage* or laa) near/5 (clip* or sutur* or ligat* or plug* or stapl* or block* or remov* or isolat* or amputat* or obliterat* or excis* or exclu* or invaginat*)	49
#12	(left next atrial next appendage* or atrial next appendage* or laa) near/5 device*	64
#13	laao or plaao or laac or plaac	30
#14	acp* or aegis* or amplatzer* or amulet* or atriclip* or atri next clip* or cardioblate* or cardio next blate* or coherex* or endoloop* or endo next loop* or lambre* or lariat* or ligasure* or liga next sure* or occlutech* or occlu next tech* or pfm next occluder* or plaato* or tigerpaw* or tiger next paw* or ultraseal* or ultra next seal* or ultrasept* or ultra next sept* or watchman* or watch next man* or wavecrest* or wave next crest*	2111
#15	#5 or #9 or #10 or #11 or #12 or #13 or #14	2217
#16	#4 and #15	206
#17	#6 and #14	15
#18	atrial next appendage* or LAA	359
#19	#18 and #14	62
#20	#16 or #17 or #19	211
#21	#20 Publication Year from 2007 to 2017, in Economic Evaluations	3

A.9: Source: CEA Registry

Interface / URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx

Database coverage dates: Not reported. Data for 2015 is available and updates for 2016 data are ongoing.

Search date: 20/07/17

Retrieved records: 5

Search strategy:

Very basic search functionality – Boolean not supported and no option to export results.

Each term below searched for individually. The results were scanned by the Information Specialist and only potentially relevant, non duplicate records published in or since 2007 were selected (5 in total).

atrial appendage 5 results
atrial appendages 0 results
laa 41 results
laao 1 result
plaao 0 results
laac 2 results
plaac 0 results
acp 3 results
acp2 0 results
aegis 0 results
amplatzer 0 results
amulet 0 results
atriclip 0 results
atri-clip 0 results
cardioblate 0 results
cardio-blate 0 results
coherex 0 results
endoloop 0 results
endo-loop 0 results
lambre 1 result
lariat 0 results
ligasure 0 results
liga-sure 0 results
occlutech 0 results
occlu-tech 0 results
pfm occlude 0 results
plaato 0 results
tigerpaw 0 results
tiger-paw 0 results
ultraseal 0 results
ultra-seal 0 results
ultrasept 0 results

ultra-sept 0 results
ultraseptor 0 results
ultra-septor 0 results
watchman 2 results
watch-man 0 result
wavecrest 0 results
wave-crest 0 results

A.10: Source: National Guideline Clearing House

Interface / URL: https://www.guideline.gov/
Database coverage dates: N/A
Search date: 20/07/17
Retrieved records: 17
Search strategy:

Search using MeSH tag – Atrial Fibrillation – 17 records
Keyword search - atrial appendage* OR LAA OR LAAO OR PLAAO OR LAAC OR PLAAC – 81 records. Results were scanned by the Information Specialist and only potentially relevant, non duplicate records were selected (0)

A.11: Source: International Guideline Library-Guidelines International Network (GIN)

Interface / URL: http://www.g-i-n.net/library/international-guidelines-library/international-guidelines-library
Database coverage dates: N/A
Search date: 20/07/17
Retrieved records: 14
Search strategy:

No advanced search limiters/options selected.

Atrial Fibrillation – 14 records
atrial appendage* OR LAA OR LAAO OR PLAAO OR LAAC OR PLAAC – 0 results

A.12: Source: National Institute for Health and Care Excellence (NICE) webpages

Interface / URL: https://www.nice.org.uk/
Database coverage dates: N/A
Search date: 20/07/17
Retrieved records: 8
Search strategy:

All results were scanned by the Information Specialist and only potentially relevant, non duplicate records were selected

Browse Guidance: Conditions and Diseases: Cardiovascular Conditions: Heart Rhythm Conditions
AND
Browse Guidance: Conditions and Diseases: Cardiovascular Conditions: Embolism and thrombosis

1 record selected.

Site-wide search for the following terms, each searched individually as Boolean is not supported. Results limited to Guidance OR NICE Advice.

atrial appendage
atrial appendages
laa
laao
plaao
laac
plaac
acp 3 results
acp2
aegis
amplatzer
amulet
atriclip
atri-clip
cardioblate
cardio-blate
coherex
endoloop
endo-loop
lambre
lariat
ligasure
liga-sure
occlutech
occlu-tech
pfm occlude
plaato
tigerpaw
tiger-paw
ultraseal
ultra-seal
ultrasept
ultra-sept
ultraseptor

ultra-septor
watchman
watch-man 0 result
wavecrest
wave-crest

7 records selected

Appendix B: Quality assessment of included economic studies

(Panikker et al. 2016)	
Each quality item is scored as follows: Yes= 2; In part = 1; No= 0	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**2**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**2**
5. Are the results generalizable?	**0**
Total	**8/10**

Source: Department of Health. The National Service Framework for Long Term Conditions. March 2005. Available at https://www.gov.uk/government/publications/quality-standards-for-supporting-people-with-long-term-conditions

(Reddy et al. 2016)	
Each quality item is scored as follows: Yes= 2; In part = 1; No= 0	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**2**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**2**
5. Are the results generalizable?	**0**
Total	**7/10**

Source: Department of Health. The National Service Framework for Long Term Conditions. March 2005. Available at https://www.gov.uk/government/publications/quality-standards-for-supporting-people-with-long-term-conditions