QUERI

The Effectiveness of Procedures to Remove or Occlude the Left Atrial Appendage: A Systematic Review of the Evidence

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting between 2.7 and 6.1 million people in the United States. The prevalence of AF increases with age and is often associated with structural heart disease and co-morbidities that are common in the Veteran population. AF is the most important cause of cardioembolic stroke, which accounts for 14-36% of all ischemic strokes. While patients at highest risk for AF-related stroke also often have other independent risk factors for stroke secondary to atherosclerotic aortic or carotid disease, most cardiac sources of embolism are thought to be due to thrombus formation from blood stasis in the left atrium. Among patients with non-valvular AF more than 90% of thrombi develop in the left atrial appendage (LAA). Antithrombotic therapy with aspirin, warfarin, or one of several newer oral anticoagulants reduces the risk of stroke due to both atrial fibrillation and atherosclerotic disease but is associated with a risk of serious bleeding. As a potential alternative to long-term anticoagulant therapy, various LAA exclusion procedures have been developed in an attempt to isolate the LAA from circulating blood flow. These procedures, including both surgical occlusion and removal of the LAA and percutaneous catheter-based interventions to occlude the LAA, may be beneficial in reducing risk of cardioembolic stroke originating from the LAA.

The purpose of this report is to systematically review the literature to better understand the balance of benefits and harms of surgical or percutaneous LAA exclusion procedures.

METHODS

The research questions for this systematic review were developed in consultation with key stakeholders and content experts. The key questions (KQs) that this review sought to address were:

KQ1. What is the effectiveness of surgical or percutaneous LAA exclusion compared with usual care?

KQ2. What are the harms associated with surgical or percutaneous LAA exclusion?

KQ3. How do the benefits and harms of LAA exclusion vary in different subgroups?

KQ4. What are the comparative effects of different techniques (surgical and percutaneous) of LAA exclusion on rates of procedural success?

Data Sources and Searches

We developed search strategies in consultation with a research librarian, who conducted database searches in Ovid MEDLINE®, Embase®, the Cochrane databases, the FDA Devices database, ClinicalTrials.gov, the Conference Abstracts database, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from database inception through January 7, 2015. We reviewed the bibliographies of systematic reviews and other relevant articles for additional studies, and contacted device manufacturers to inquire for unpublished trial data.

Study Selection

We reviewed titles and abstracts using pre-specified inclusion/exclusion criteria. Potentially relevant full-text articles underwent independent review by at least 2 investigators for final decisions on inclusion/exclusion.

We included controlled clinical trials to assess the effectiveness of percutaneous LAA exclusion procedures. To assess the harms of percutaneous LAA procedures we also included cohort and registry studies with 50 or more patients.

We included cohort studies and controlled clinical trials to review both benefits and harms of surgical LAA procedures. Because LAA exclusion procedures were usually done in the context of heart surgery, and harms related to LAA exclusion are difficult to distinguish from those of the heart surgery itself, we only included cohort studies with a control group of patients who received heart surgery without LAA exclusion.

Data Abstraction and Quality Assessment

One author abstracted data from each study and a second author reviewed the entries for accuracy.

Two reviewers (among NN, DK, JP, and MF) independently assessed the quality of each study using published criteria. We graded the strength of evidence for each outcome using published criteria which consider the consistency, coherence, directness, and applicability of a body of evidence, as well as the internal validity of individual studies. We resolved disagreements through discussion.

Data Synthesis and Analysis

We qualitatively synthesized the evidence on the benefits and harms of LAA exclusion. Clinical heterogeneity and the small number of trials precluded the possibility of combining the findings in meta-analysis.

Peer Review

A draft version of this report was reviewed by 5 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix E.

SUMMARY OF FINDINGS

We reviewed 2,566 titles and abstracts from the combined searches. We selected 207 articles for full-text review, of which 20 studies contained primary data relevant to the effectiveness and/or harms of LAA interventions. We contacted 7 device companies to request information about unpublished studies but received no response.

Summary of Evidence

There is low-strength evidence that percutaneous LAA exclusion is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. This finding is based on trials of one device studied in patients without contraindications to oral anticoagulant therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant

therapy after undergoing follow-up transesophageal echocardiography (TEE) showing persistent closure of the LAA at 3-6 months. However, there is moderate strength evidence that a substantial proportion of patients undergoing various percutaneous LAA exclusion procedures experienced serious periprocedural harms. For example, patients undergoing placement of a Watchman device experienced 4.1-10.5% periprocedural adverse events. There is insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks. There is insufficient data to assess the balance of benefits and harms of percutaneous LAA exclusion procedures in patients who are ineligible for long-term oral anticoagulation therapy.

We found insufficient evidence to determine the efficacy of surgical LAA exclusion in reducing stroke. We found low-strength evidence that surgical LAA exclusion in the context of heart surgery done for another indication is unlikely to be associated with significant incremental harm. In 2 studies, successful closure of the LAA was demonstrated in follow-up in only 40-66% of patients.

Table 1 summarizes the evidence on percutaneous and surgical LAA exclusion interventions.

Research Gaps/Future Research

Trials of percutaneous LAA interventions were limited to studies of the Watchman device in patients who were eligible for long-term warfarin therapy. Trials of surgical LAA interventions were few and limited by sample size. Several studies that should add substantively to this body of evidence are underway, including a large RCT of surgical interventions with an estimated sample size of 4,700 patients, studies of recently developed percutaneous devices (LAmbre and Occlutech), and a trial comparing Watchman with Apixaban in patients ineligible for warfarin therapy.

Conclusions

Overall, there is limited evidence that percutaneous LAA exclusion using the Watchman device may be an effective alternative to long-term oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained. However, in many studies, percutaneous LAA exclusion has been associated with high rates of serious procedure-related harms. There is insufficient evidence to assess the benefits of surgical LAA exclusion. While surgical LAA exclusion does not appear to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed, rates of procedural success may be low. Overall, there is insufficient evidence to support the routine use of surgical LAA exclusion to reduce stroke risk or future need for anticoagulant therapy.

Table 1. Summary of evidence on the effectiveness of procedures to remove or occlude the left atrial appendage

Outcome	Device or procedure N studies (N=combined participants)	Findings	Strength of Evidence*	Comments
Percutaneous interventions				
Mortality	Watchman 2 RCTs (N=1,114)	No significant difference in mortality. RR (95% CI) in 2 RCTs: 1.20 (0.31 to 4.56) 0.62 (0.34 to 1.24)	Low	Limited applicability: only one device has been studied in 2 RCTs. Patients were eligible to receive LT-OAC. Low precision (wide confidence intervals).
Stroke	Watchman 2 RCTs (N=1,114)	No significant difference in risk of stroke. RR (95% CI): in 2 RCTs: 0.71 (0.35 to 1.64) 3.28 (0.37 to 25.31)		
Harms	ACP: 3 registries (N=147) Coherex: 1 registry (N=4) Lariat: 2 registries (N=93) PLAATO: 5 registries (n=441) Watchman: 2 RCTs + 4 registries (N=742) Device not specified: 2 registries (N=211)	Serious procedure- or device-related safety events (% of patients): 1.6 to 13.6. Overall, rate of serious adverse events within 7 days of device implantation was 6.5% (98/1506).	Moderate	A range of devices were examined among 2 trials and 11 observational studies. Strength of finding limited by wide range of event rates across studies, relatively small number of patients treated in each observational study.
Surgical interventions				
Mortality	Sutures or stapler in 3 RCTs (N=171) Various excision and exclusion techniques in 4 Cohort studies (N=1695)	No significant difference in mortality, among studies in which at least one event occurred in both groups: In 1 RCT: 7.7 vs 12% ($P > .05$) RR (95% CI) 0.64 (0.12, 3.52) In 1 cohort: 5.0 vs 8.4% ($P > .05$) RR (95% CI) 0.60 (0.22 to 1.60)	Insufficient	Trials too small and event rates too low to determine effectiveness of procedure.
Stroke	3 RCTs (N=171) 2 cohort studies (N=1500)	No significant difference in risk of stroke, among studies in which at least one event occurred in both groups: In 1 RCT: 3.8 vs 12% ($P > .05$); RR (95% CI) 0.32 (0.03 to 2.88) In 2 cohorts: 1.0 vs 1.4% ($P = .44$) 0.84 vs 1.7% ($P > .05$)	Insufficient	
Harms	3 RCTs (N=171) 1 cohort study (N=238)	Serious safety events: 6.9-32.0% of patients No significant differences in most major harms between cardiac surgery groups with and without LAA exclusion	Low	Limited number of studies and limited number of patients included.

Abbreviations: ACP = Amplatzer cardiac plug; CI = confidence interval; LT-OAC = long term oral anticoagulation; RCT = randomized controlled trial; PLAATO = percutaneous left atrial appendage transcatheter occlusion; RR = relative risk

ABBREVIATIONS

ACP	Amplatzer cardiac plug
AF	Atrial fibrillation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHADS2	Stroke risk score in AF (congestive heart failure, hypertension, age 75+, diabetes mellitus, and stroke/TIA)
CHA2DS2-VASc	Stroke risk score in AF that includes CHADS2 with age in 2 categories and vascular disease
CHF	Congestive heart failure
CI	Confidence interval
CT	Computerized tomography
DM	Diabetes mellitus
HAS-BLED	Score that estimates risk of major bleeding for patients on anticoagulation for atrial fibrillation
HR	Hazard ratio
HTN	Hypertension
Hx	History (of)
INR	International normalized ratio
LAA	Left atrial appendage
LT-OAC	Long-term oral anticoagulation therapy
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Study Design
PLAATO	Percutaneous Left Atrial Appendage Transcatheter Occlusion
PSM	Propensity score matching
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
VATS	Video assisted thoracoscopy
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

EVIDENCE REPORT

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting between 2.7 and 6.1 million people in the United States.[1] The prevalence of AF increases with age and is often associated with structural heart disease and co-morbidities that are common in the Veteran population. Complications related to AF can be classified as hemodynamic or thromboembolic.

Cardioembolic strokes account for 14-36% of all ischemic strokes, and AF is the most important cause of cardioembolic stroke. In general, the risk of stroke in patients with non-valvular AF is 2 to 7 times higher than patients without AF.[2] Antithrombotic therapy with aspirin, warfarin, or one of several newer oral anticoagulants have been the mainstay of stroke prevention in atrial fibrillation, but may be cumbersome and are associated with an increased risk of bleeding.

The mechanism of thrombosis formation is stasis of blood in the left atrium and it is currently believed that a high percentage of thromboemboli develop in the left atrial appendage (LAA).[3,4] Thus, various procedures have been developed that attempt to isolate the LAA from circulating blood flow in an effort to reduce the risk of thromboembolic stroke. These methods include surgical occlusion or removal of the LAA, and percutaneous, catheter-based approaches to occlude the LAA. The LAA is, however, only one potential source of strokes and patients at the highest risk of stroke related to AF frequently have associated risk factors for stroke that are independent of AF. These risk factors – including hypertension, diabetes, and advanced age – increase a patient's likelihood of an ischemic stroke secondary to atherosclerotic aortic or carotid disease which would not be addressed by exclusion or removal of the LAA.

Prior to 2002, surgery was the only option for exclusion of the LAA. This could be done in conjunction with surgery being performed for other reasons, such as coronary artery bypass grafting (CABG) or valve replacement in patients who also have or are at risk for AF, or as part of a mini-thoracotomy typically in association with a maze procedure. Surgical approaches to LAA exclusion include simple suture ligation, oversewing the base without excision, excising the appendage and oversewing the base, or surgical stapling and excision.[1]

More recently, a number of devices designed to occlude the LAA percutaneously have been developed. The devices currently in use include the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device (Appriva Medical, Plymouth, Minnesota), the Amplatzer device (AGA Medical Corporation/St. Jude Medical, Golden Valley, Minnesota), the Watchman device (Boston Scientific, Natick, Massachusetts), and the LARIAT suture delivery device (SentreHeart, Redwood City, California). Given the high prevalence of atrial fibrillation in the general and Veteran population, along with the potential risks and inconvenience of long-term oral anticoagulant therapy, there is a growing interest in LAA occlusion or removal as an alternative stroke risk reduction strategy. The purpose of this report is to systematically review the literature to better understand the balance of benefits and harms of surgical or percutaneous LAA occlusion or removal. We use the general term LAA exclusion throughout the report to refer to either removal or isolation of the LAA, except where otherwise specified.

METHODS

TOPIC DEVELOPMENT

The topic of this review was nominated by Dr. Alaa Shalaby, a member of the VHA Cardiology Field Advisory Committee and Director of Cardiac Electrophysiology at the VA Pittsburgh Healthcare System. Dr. William Gunnar, National Director of Surgery for the Veterans Health Administration, also served as an operational partner.

The research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, consultation with internal partners and investigators, and consultation with content experts and key stakeholders. The key questions (KQs) that this review sought to address are as follows:

KQ1. What is the effectiveness of surgical or percutaneous LAA exclusion compared with usual care?

KQ2. What are the harms associated with surgical or percutaneous LAA exclusion?

KQ3. How do the benefits and harms of LAA exclusion vary in different subgroups?

KQ4. What are the comparative effects of different techniques (surgical and percutaneous) of LAA exclusion on rates of procedural success?

A protocol describing the review plan was posted to a publicly accessible website before the study was initiated.[5]

SEARCH STRATEGY

Search strategy was developed in consultation with a research librarian, and was peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS).[6,7] To identify relevant articles, we searched Ovid MEDLINE®, Embase®, the Cochrane databases, and the FDA Devices database from database inception through January 7, 2015. We further reviewed the bibliographies of systematic reviews and other relevant articles for additional studies. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov, the Conference Abstracts database, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and contacted device manufacturers to inquire for unpublished trial data.

Using pre-specified inclusion/exclusion criteria, we reviewed titles and abstracts for relevance to the key questions. At the full-text screening stage, 2 independent reviewers concurred on final inclusion/exclusion decisions, with input from a third investigator when needed to resolve questions and reach consensus. Articles meeting eligibility criteria were included for data abstraction.

STUDY SELECTION

The criteria for patient population, intervention, comparator, outcome, timing parameters, and study designs (PICOTS) that apply to each key question are specified in Table 1 (percutaneous procedures) and Table 2 (surgical procedures). Given the availability of larger-scale trials of percutaneous procedures, along with recent systematic reviews of percutaneous approaches to LAA exclusion, we only included controlled clinical trials to assess the effectiveness of percutaneous LAA exclusion procedures. On the other hand, we included cohort studies with or without a control population to examine harms of percutaneous interventions.[8] After an initial survey of the literature, we found there were a number of larger cohort studies providing harms data and therefore set a sample size cut-off of 50 or more patients for inclusion.

We included cohort studies in addition to controlled clinical trials for all key questions examining benefits and harms of surgical procedures.[8] However, given that the LAA exclusion procedures were usually done in the context of heart surgery and that the harms related to LAA exclusion would be difficult to distinguish from those of the heart surgery itself, we only included cohort studies with a control population of patients who received heart surgery but no LAA exclusion.

Table 1. PICOTS and Key Questions for Percutaneous LAA Interventions

Key Question	**KQ1.** What is the effectiveness of LAA exclusion interventions compared with usual care?	**KQ2.** What are the harms associated with LAA exclusion?	**KQ3a.** How do the benefits LAA exclusion vary in different subgroups? **KQ3b.** How do the harms of LAA exclusion vary in different subgroups?	**KQ4.** What are the comparative effects of different techniques on rates of procedural success?
Population	Patients with atrial fibrillation who are eligible for percutaneous LAA exclusion			
Intervention	· AMPLATZER™ Cardiac Plug (company: AGA Medical, Corp., North Plymouth, MN, USA) · WATCHMAN® Left Atrial Appendage Closure Technology/Device/System (company: Atritech, Inc., North Plymouth, MN, USA) · PLAATO™ Percutaneous Left Atrial Appendage Transcatheter Occlusion (company: Appriva Medical, Inc., Sunnyvale, CA) · Coherex WaveCrest™ LAA Occluder System (company: Coherex Medical, Inc., Salt Lake City, Utah, USA) · LARIAT suture delivery device (SentreHeart, Redwood City, California) · Lifetech LAmbre™ Left Atrial Appendage Occluder *Device (*Lifetech Scientific Co., Ltd) Nanshan District, Shenzhen, PEOPLE'S REPUBLIC OF CHINA			
Comparator	Usual care without LAA exclusion			Compares percutaneous intervention to another LAA closure technique (surgical, thoracoscopic, or percutaneous)
Outcomes	Primary outcomes: § Stroke § Mortality § Cardiovascular morbidity § Other reported health outcomes	§ Harms other than primary outcomes for KQ1 § length of stay (hospital and ICU) § bleeding § infection § need for surgical intervention	§ Primary outcomes listed in KQ1 § Other reported benefits and harms § Rates of bleeding.	Procedural outcome: Successful closure/LAA removal, assessed by methods such as transesophageal echocardiogram; CT; MRI. Health outcomes: Same as those listed for KQ1.
Timing	Short- and long-term outcomes			
Study design	Include: Systematic reviews, meta-analyses, or randomized controlled trials. For KQ2 and KQ3b, we will additionally include cohort and trial extension studies that report data on adverse events. Exclude: Non-systematic or narrative reviews, non-randomized trials, opinions, case studies, case series, and quasi-experimental studies.			

Table 2. PICOTS and Key Questions for Surgical LAA Interventions

Key Question	**KQ1.** What is the effectiveness of LAA exclusion interventions compared with usual care?	**KQ2.** What are the harms associated with LAA exclusion?	**KQ3.** How do the benefits and harms of LAA exclusion vary in different subgroups?	**KQ4.** What are the comparative effects of different techniques on health outcomes and rates of procedural success?
Population	Patients undergoing cardiac surgery: coronary bypass surgery; valvular surgery; or both bypass and valve surgery.	Patients undergoing surgical LAA occlusion/removal in combination with surgery for atrial fibrillation (*ie*, MAZE).	Patients undergoing surgical LAA exclusion.	Non-selected population of patients with atrial fibrillation
Intervention	· LAA occlusion/removal techniques that involve major surgery (sternotomy or thoracotomy), *eg*: § specific devices such as AtriClip, or § techniques such as stapling or suturing · LAA occlusion/removal via thoracoscopic surgery · Minimally invasive Maze procedures if there are data about the incremental effects of concomitant LAA exclusion.			
Comparator	Cardiac surgery without LAA removal or occlusion.	Surgery for atrial fibrillation without LAA removal.	Non-surgical/usual care for thromboembolic stroke prevention, such as aspirin for patients with CHADS2 of 0 or 1, and antithrombotic therapy with warfarin or a NOAC (apixiban, dabigatran, rivaroxaban) for CHADS2 of >=1.	Compares surgical intervention to another LAA closure technique (surgical, thoracoscopic, or percutaneous)
Outcomes	Primary outcomes: § Stroke § Mortality § Cardiovascular morbidity § Other reported health outcomes	§ Harms other than primary outcomes for KQ1 § length of stay (hospital and ICU) § time on bypass § bleeding § ventilator days § infection	§ Primary outcomes listed in KQ1 § Other reported benefits and harms § Rates of bleeding.	<u>Procedural outcome:</u> Successful closure/LAA removal, assessed by methods such as transesophageal echocardiogram; CT; MRI. <u>Health outcomes:</u> Same as those listed for KQ1.
Timing	Short- and long-term outcomes			
Study design	<u>Include:</u> Systematic reviews, meta-analyses, controlled clinical trials (randomized or non-randomized), and methodologically rigorous observational studies (case control/cohort studies) that adjust for important confounders, *eg*, propensity score matching <u>Exclude:</u> Non-systematic or narrative reviews, opinions, case studies, case series, and quasi-experimental studies.			

DATA ABSTRACTION

One investigator (among NN, JP, and MF) abstracted data from published reports into a customized database, and entries were confirmed by a second reviewer. From each study, we abstracted study design, objectives, setting, population characteristics (including sex, age, race/ethnicity), subject eligibility and exclusion criteria, number of subjects, years of enrollment, duration of follow-up, the study and comparator interventions, important co-interventions, health outcomes, and adverse events. A second author reviewed the entries for accuracy.

QUALITY ASSESSMENT

Two reviewers (among NN, DK, JP, and MF) independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration (Appendix C).[9] We assigned each trial an overall summary assessment of low, high, or unclear risk of bias.

For evaluating cohort studies of surgical LAA interventions, we used the Newcastle-Ottawa criteria to assess methodological rigor and consider potential sources of bias.[10] We did not assign overall quality ratings, however, as validated criteria for ranking observational studies are not currently available.

DATA SYNTHESIS

We qualitatively synthesized the evidence on the benefits and harms of LAA exclusion. Clinical heterogeneity and the small number of trials precluded the possibility of combining the findings in meta-analysis.

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for each outcome using a method developed by the Agency for Healthcare Research and Quality (AHRQ).[11] We considered the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies, to classify the strength of evidence for each outcome as follows:

High = Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Any estimate of effect is very uncertain.

PEER REVIEW

A draft version of this report was reviewed by 5 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix E.

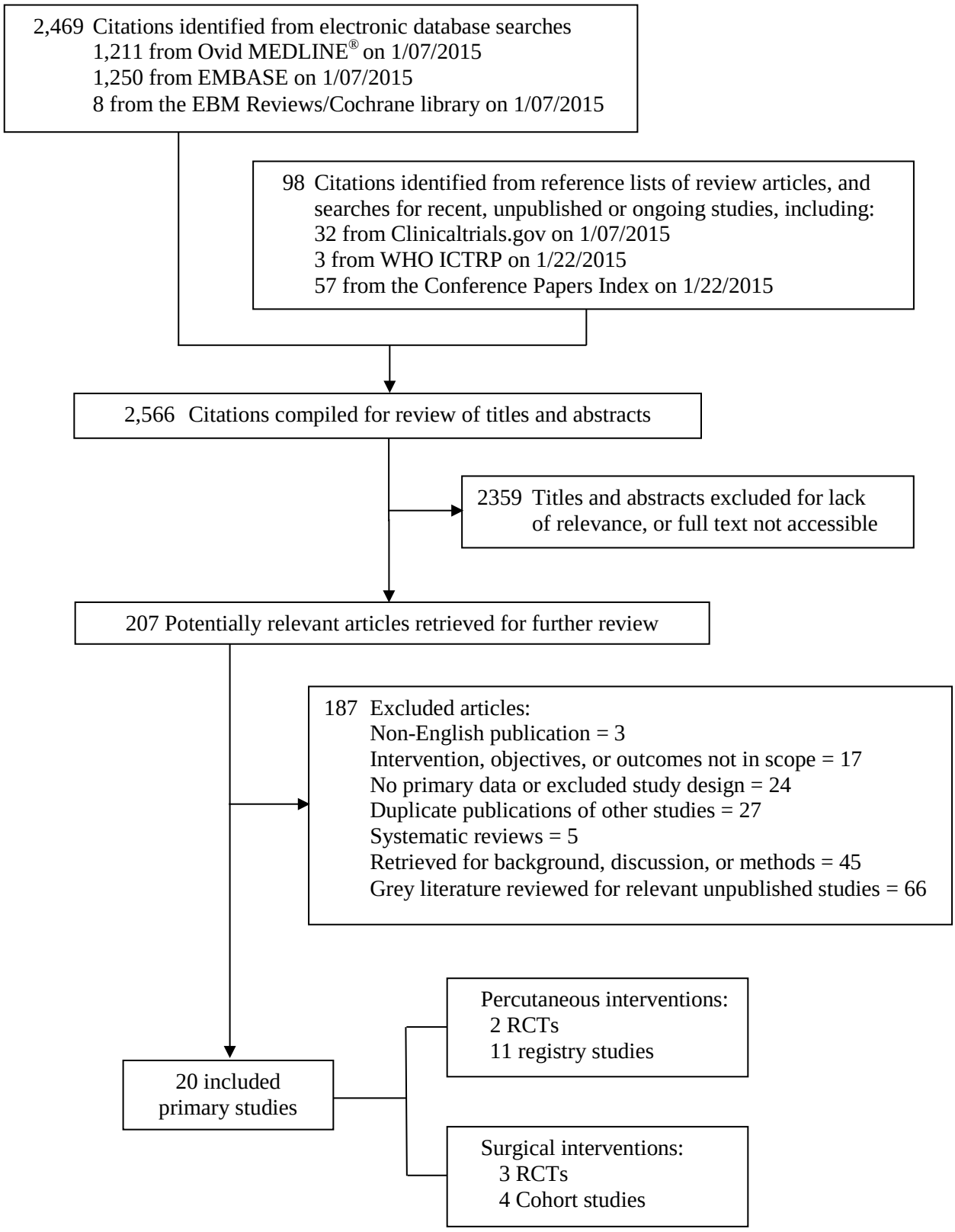
RESULTS

We reviewed 2,566 titles and abstracts, including 2,469 from the electronic search and an additional 98 from reviewing reference lists and performing manual searches for recently published and unpublished or ongoing studies. After applying inclusion/exclusion criteria at the abstract level, we reviewed 207 full-text articles from which we found 20 primary studies that met our inclusion criteria. We also identified 5 systematic reviews of the effectiveness of percutaneous LAA devices. We contacted 7 device companies to request information about unpublished studies but received no response (Appendix D).

LITERATURE FLOW

The diagram on the following page shows the yield of citations from database searches and other sources, the numbers of excluded abstracts and full-text articles, and the final yield of included studies (Figure 1).

Figure 1. Literature flow diagram



PERCUTANEOUS LAA INTERVENTIONS

KQ1: What is the effectiveness of LAA exclusion interventions compared with usual care?

We found 2 randomized controlled trials (RCTs) with low risk of bias, both of which compared the Watchman(R) Left Atrial Appendage Closure Device (Atritech, Inc., North Plymouth, MN, USA) to medical therapy with warfarin (Table 3). Inclusion into the PROTECT-AF[12-14] trial required subjects to have non-valvular atrial fibrillation (NVAF) and a CHADS2[15] score of at least 1, while the PREVAIL[16] trial enrolled subjects with higher risk of stroke; patients were excluded from these trials if they had contraindication to warfarin therapy, recent stroke, or a patent foramen ovale/atrial septal defect.

The PROTECT-AF trial included 463 intervention and 244 control patients with non-valvular atrial fibrillation, and excluded patients with low stroke risk (CHADS2 of 0). The device was successfully deployed in 88% (408/463) of patients, though it was not attempted in 14 patients. Successful closure was obtained in 86% (348/401) of patients at 45 days and in 92% (355/385) at 6 months. Warfarin was typically discontinued with complete closure or if residual peri-device flow was less than 5 mm width on surveillance transesophageal echocardiogram (TEE). At 6 months, successful closure was demonstrated in 92% (355/385), although 5.6% (23/408) refused follow-up TEE. Most patients were able to stop warfarin therapy (7.5% (30/401), 3.6% (14/385), and 2.7% (10/370) of subjects in the LAA exclusion group remained on warfarin therapy at 45 days, 6 months, and 2 years respectively.[13,14] The control arm was within therapeutic international normalized ratio (INR) range 66% of the time.

There was no difference in a composite primary efficacy endpoint including ischemic/hemorrhagic stroke, cardiovascular/unexplained death, and systemic embolism with 3.0 (1.9 to 4.5) events per 100 patient-years in the LAA exclusion group versus 4.9 (2.8 to 7.1) events per 100 patient-years in the warfarin group (rate ratio 0.62, 0.35 to 1.25). Cumulative events at 2.3 years mean follow up (standard deviation 1.1 years, median 2.4, range 0.5 to 9 years) were also similar with 3.0 (2.15 to 4.3) events per year in the LAA exclusion group versus 4.3 (2.6 to 5.9) events per year in the warfarin group. Overall, there was >99.9% posterior probability for non-inferiority for the LAA exclusion group compared to the warfarin treated group.[13,14] Additionally, there was no statistically significant difference in mortality between the 2 groups.

In a subset of patients in the PROTECT-AF trial, quality of life on some subscales was modestly improved in the intervention group. However, the absolute differences were small and the findings subject to bias given lack of patient blinding and differential rates of follow-up in each group.[12]

The PREVAIL trial enrolled 407 subjects (269 assigned to LAA exclusion and 138 assigned to warfarin therapy) and followed them for an average of 11.8 months (standard deviation 5.8 months, median 12 months, range 0.03 to 25.9 months).[16] Patients were slightly older and had a higher risk of stroke than the population included in the PROTECT-AF trial. Device deployment was successful in 95.1% (252/269) patients. At 6 months, device closure was demonstrated in 98.3% (235/239), though 11.2% (30/269) refused follow-up TEE.

The PREVAIL trial did not meet its target of non-inferiority for overall efficacy, although event rates were low and numerically comparable for both arms. Overall mortality was 2.6% in the LAA exclusion group versus 2.2% in the warfarin group. A composite outcome of death, ischemic/hemorrhagic stroke, or systemic embolism occurred in 5.2% of the LAA exclusion group and 2.9% of the warfarin group. On the other hand, the rate of events adjusted for person-time of observation months was similar: 18 month rate ratio of composite events was 1.07 (credible interval 0.57 to 1.89).[16] The discrepancy in the reported results may be related to a later occurrence of outcomes in the device group.

KQ2: What are the harms associated with LAA exclusion?

We found 2 trials and 11 observational studies reporting harms data (Tables 3 and 4). Serious periprocedural adverse events were reported in 1.6-13.6% of patients. Overall, the rate of periprocedural harms occurring within 7 days of device placement was 6.5% (98/1506). The types of periprocedural events most commonly reported included pericardial effusions with and without associated tamponade, bleeding, device thrombus, and device embolization.

Two trials examined harms associated with placement of the Watchman device.[13,16] In PROTECT-AF 10.6% (49/463) of patients experienced a safety event with 55.1% (27/49) of those occurring on the day of the procedure. Significant pericardial effusion followed by major bleeding accounted for most of these events. The authors note the rate of pericardial effusion declined with operator experience. In contrast, the safety event rate was much lower (2.2%) in the more recently conducted PREVAIL trial.[16] Adverse event rates were similar in the single center[17-22] and the multicenter studies.[23-26]

We did not find robust comparative effectiveness data to directly assess the relative rates of serious safety events according to the device used. However, there were serious periprocedural events including death or need for emergent surgery reported for all included devices.

Overall, patients had low rates of stroke and bleeding and there were no reported technical device failures over the long term. Data on longer-term safety from the observational studies is limited in part by either high rates of attrition[24] or lack of information about the loss to follow-up.[17,21,22,26,27] Additionally, the duration of follow-up ranged from 6 months to 5 years and there was no clear standard for which events were reported.

KQ3a: How do the benefits of LAA exclusion vary in different subgroups?

The evidence for use of LAA exclusion devices in different subgroups is limited to retrospective analysis of a single randomized controlled trial of the Watchman device. In PROTECT-AF the use of the Watchman appeared equally effective in men and women and was non-inferior to warfarin in patients with CHADS2 score greater than 1, patients who are greater than or equal to 75 years old, patients with normal and reduced left ventricular ejection fraction (LVEF), patients with prior stroke, and in those with higher CHADS2.[25] Findings were also consistent in patients with paroxysmal and permanent atrial fibrillation.[25] However, the strength of these findings should be considered low because of the post-hoc nature of these analyses and the relatively wide confidence intervals associated with the findings.

KQ3b: How do the harms of LAA exclusion vary in different subgroups?

The PROTECT-AF and PREVAIL trials of the Watchman device did not address harms in different subgroups.[13,14,16] The observational studies did not directly compare rates of harms across patient subgroups. In these studies, there were a substantial proportion of older patients with higher stroke risk and the rates and types of periprocedural harms were similar across the studies.

While the 2 RCTs excluded patients who were ineligible to receive anticoagulant therapy, 7 of 11 observational studies included patients who were ineligible for long-term oral anticoagulant therapy. In most of these studies, the long-term rates of stroke were low – 2.1% (12/565) over the course of 6-24 months of follow-up.[17,19,21,24,25] One study of the PLAATO device found a higher incidence of stroke (12.5%) during a follow-up period which lasted up to 5 years,[20] though the annual rate of stroke is similar to studies with shorter follow-up periods. Long-term complications were not reported as part of the CAP Registry.[26,27]

KQ4: What are the comparative effects of different techniques on health outcomes and rates of procedural success?

Given that RCT data is limited to a single device, the Watchman, and a single technique, it is impossible to compare the effectiveness of different techniques. The PREVAIL trial included analysis of the learning curve for implantation of the Watchman by requiring a minimum of 20% of participants from centers that had not previously participated in LAA exclusion trials with this device, as well as a requirement that a minimum of 25% of randomized patients be treated by new operators. The study found an overall implantation success of 95.1%., with no statistically significant difference in successful deployment when comparing experienced operators (96.3%) to new operators (93.2%; $P = .256$).[16] Similarly, there were no significant differences in complication rates between experienced and new operators.

A number of different devices were represented among the observational studies; however, the Watchman and PLAATO devices were the most frequently studied. In these studies, the device was successfully deployed in most patients selected to undergo the procedure, regardless of the device used. In one study, device deployment rates were similar in the Watchman device (98.8%, 165 of 167) and the Amplatzer Cardiac Plug (ACP) device (90%, 9 of 10).[22] Rates of device closure as determined by follow-up TEE were high among studies of different devices reporting this outcome, but there was substantial variation in the timing of follow-up, and a substantial proportion of patients did not undergo follow-up TEE.

Table 3. Health outcomes, adverse effects, and procedural success in trials comparing percutaneous LAAO to warfarin therapy

Study, Setting, Mean follow-up time	Patient characteristics, T vs C	KQ1. Health outcome effects, T vs C	KQ2. Harms associated with LAA exclusion, T vs C	KQ4. Rates of procedural success, T vs C
PREVAIL[16] 50 sites, USA 11.8 months	N patients: 269 vs 138 Mean age: 74.0 vs 74.9 Male %: 67.7 vs 74.6 CHADS2 mean: 2.6 vs 2.6 CHA2DS2-VASc mean: 3.8 vs 3.9 AF %: 100 vs 100 Stroke %: 27.5 vs 28.3 CHF %: 23.4 vs 23.2 HTN %: 88.5 vs 97.1 (P = .003) DM %: 33.8 vs 29.7	Ischemic stroke: 5 of 269 (1.9%) vs 1 of 138 (0.7%) Hemorrhagic stroke: 1 of 269 (0.4%) vs 0 of 138 (0.0%) Death (cardiovascular/unexplained): 7 of 269 (2.6%) vs 3 of 138 (2.2%) Systemic embolism: 1 of 269 (0.4%) vs 0 of 138 (0.0%)	Total serious AEs: 11 (4.1%) of 269** Device embolization: 2 of 269 (0.7%) Arteriovenous fistula: 1 of 269 (0.4%) Cardiac perforation: 1 of 269 (0.4%) Pericardial effusion requiring surgery: 1 of 269 (0.4%) Pericardial effusion with pericardiocentesis: 4 of 269 (1.5%) Major bleed requiring transfusion: 1 of 269 (0.4%) Procedure-related stroke: 1 of 269 (0.4%)	252 (95.1%) successfully implanted of 265 attempted. Discontinuation of warfarin*, among N assessed by TEE: 227 (92.2%) of 246 at 45 days 235 (98.3%) of 239 at 6 months 141 (99.3%) of 142 at 12 months
PROTECT AF[12-14] 59 sites USA, Europe 12 months	N patients: 463 vs 244 Mean age: 71.7 vs 72.9 Male %: 70.4 vs 70.1 Mean CHADS: 2.2 vs 2.4 (P = .0517) AF %: 100 vs 100 Stroke/TIA %: 17.7 vs 20.1 CAD %: 39.6 vs 49.5 (P = .0275) CHF %: 26.8 vs 27.0 HTN %: 90.9 vs 90.3 DM %: 24.9 vs 30.6	Ischemic stroke: 15 of 463 (3.0%) vs 6 of 244 (2.5%) Cardiovascular/unexplained death: 5 of 463 (1.1%) vs 10 of 244 (4.1%), P <.05 Hemorrhagic stroke: 1 of 463 (0.2%) vs 6 of 244 (2.5%) Systemic embolism: 2 of 463 (0.4%) vs 0 of 244 (0%) All strokes: 16 of 463 (3.4%) vs 12 of 244 (4.9%) All-cause mortality: 21 of 463 (4.5%) vs 18 of 244 (7.4%) Quality of Life (QoL) assessed by Short-Form 12 vs 2, Mean change from baseline to 12 months: Total physical score: +0.4 vs -0.2, P = .0015 Total mental score: 0.0 vs -0.9, P = .6400 Physical functioning: +0.1 vs -3.0, P = .0005 Physical role limitation: +0.4 vs -2.35, P = .0021 Pain: -0.1 vs -1.0, P = .5668 General health: +0.8 vs -0.2, P = .0606 Vitality: +0.2 vs -1.4, P = .1614 Social functioning: +0.5 vs -1.6, P = .0650 Emotional role limitation: -0.3 vs -1.8, P = .1115 Mental health: 0.0 vs -0.9, P = .6780	Total serious AEs: 49 (10.5%) of 463 vs 20 (8.2%) of 244 Pericardial effusion requiring surgery: 15 of 463 (3.2%) Pericardial effusion with pericardiocentesis: 7 of 463 (1.5%) Device embolization: 3 of 463 (0.6%) Major bleeding: 16 of 463 (3.4%) Procedure-related stroke: 6 of 463 (1.1%) Other: 2 of 463 (0.4%) 27 (55%) of 49 primary safety events occurred on the day of the procedure. Timing of specific AEs not otherwise stated.	408 (91%) successfully implanted of 449 attempted. Discontinuation of warfarin*, among N assessed by TEE: At 45 days: 348 (86%) of 401. 30 (7.5%) of 401 continued warfarin due to continued shunt At 6 months: 355 (92%) of 385. 14 (3.6%) of 385 continued warfarin due to continued shunt Control arm was within therapeutic INR range 66% of the time.

*Implies complete closure or residual peri-device flow <5mm in width on TEE.
**Total serious AEs in our report differs from primary source as we included procedure related strokes and pericardial effusions requiring any intervention.

Table 4. Procedural success, harms, and long-term stroke risk in registry studies of percutaneous LAA exclusion

Study, Setting	Device; Mean follow-up; N patients; Eligible/ineligible for LT-OAC	Patient characteristics	Periprocedural harms occurring within 7 days	Longer-term harms	Procedural success: Deployment, N (%) of attempted Closure, N (%) of patients assessed by TEE
Bartus, 2013[17] Poland	Lariat 1 year N=89 Ineligible for LT-OAC	Mean age: 62 Male %: 57 CHADS2 mean: 1.9 CHA2DS2-VASc mean: 2.8 HAS-BLED mean: 2.4 Stroke/TIA %: 25 CAD %: 4 CHF %: 12 HTN %: 94 DM %: 10	Serious procedure- or device-related safety events: Pericarditis: 2 (2.4%) of 85	Pericardial effusion: 1 (1.2%) of 85 At 3 months, sudden cardiac death: 1 (1.2%) of 85 At 6 months, hemorrhagic stroke: 1 (1.2%) of 85 At 1 year, lacunar stroke: 1 (1.2%) of 85	Deployment: 85 (95.5%) of 89 Closure:: 1 day: 81 (95%) of 85 30 days: 81 (95%) of 85 90 days: 77 (95%) of 81 1 year: 64 (98%)of 65
Price, 2014[23] 8 sites USA	Lariat 112 days, median N=154 No criteria for LT-OAC; 60% were using an OAC at baseline	Mean age: 72 Male %: 62 CHADS 2 mean: 2.8 Cha2DS2-VASc mean: 4.1 HAS-BLED mean: 3.2 CHF %: 34 Stroke/TIA %: 38 HTN %: 81 DM %: 36	Serious procedure- or device-related safety events occurred in 21 (13.6%) of 154 Major bleed: 14 (9.1%) of 154 Cardiac tamponade: 7 (4.5%) of 154	Thrombus formation: 4 (3%) of 134 with follow-up available	Deployment: 145 (94.2%) of 154 Closure at end of procedure: 133 (92%) of 145 Closure at follow-up: 50 (79%) of 63
Nietlispach, 2013[18] Single center Switzerland	Nondedicated LAA occlusion devices (off-label use of Amplatzer PFO, ASD and VSD occluders), N=32 Amplatzer ACP, N=120 32 months Eligible for LT-OAC	Mean age 72 Male %: 69 Mean CHA2DS2-Vasc: 3.46 Mean HASBLED score: 2.46 Stroke %: 31 HTN %: 75 DM %: 23	Serious procedure- or device-related safety events: 19 (12.5%) of 152 Cardiac tamponade: 4 (2.6%) of 152 Device embolizations: 6 (4.0%) of 152 Device dislocations: 3 (1.7%) of 179 Pericardial effusion: 2 (1.1%) of 179 Neurologic events (2 TIA and 1 minor stroke): 3 (2.0%) of 152 GI bleeding resulting in death: 1 (0.7%) of 152	Embolization: 1 (0.7%) of 152 Bleeding: 13 (8.6%) of 152 4 were major bleeds (2.6%): 2 intracerebral bleeds 2 subdural hematoma Ischemic stroke: 1 (0.7%)	Deployment: 146 (96.0%) of 152 Closure at 3-6 months: 137 (93.8%) of 146

Study, Setting	Device; Mean follow-up; N patients; Eligible/ineligible for LT-OAC	Patient characteristics	Periprocedural harms occurring within 7 days	Longer-term harms	Procedural success: Deployment, N (%) of attempted Closure, N (%) of patients assessed by TEE
Bayard, 2010[28] 18 centers Europe	PLAATO N=180 9.6 months Ineligible for LT-OAC	Mean age: 70 Male %: 66 Mean CHADS2 score: 3.1 CHF %: 42 Stroke/TIA %: 59 HTN %: 83 DM %: 29	Serious procedure- or device-related safety events: 8 (4.9%) of 162 Cardiac tamponade: 6 (3.7%) of 162 Cardiac death, procedure related: 2 (1.2%) of 162	Stroke (at 129 patient-years follow-up): 2.3% Cardiac death: 5 (3.1%) of 162	Deployment: 162 (90%) of 180 Closure at 2 months: 126 (90%) of 140
Block, 2009[20] USA	PLAATO 5 years N=64 Ineligible for LT-OAC	Mean age: 73 Male %: 60.9 CHADS2 score of 1, %: 23.4 CHADS2 score 2+, %: 76.6 CHF %: 44 Stroke/TIA %: 69 HTN %: 77 DM %: 23.4	Serious procedure- or device-related safety events: 1 (1.6%) of 64 (cardiac tamponade requiring surgery)	Stroke: 8 of 64 (12.5%)	Deployment: 61 (95.3%) of 64 Closure immediately after procedure: 55 (98.2%) of 56 Closure at 1 month: 22 (100%) of 22
Park, 2009[19] Single-center prospective registry, Germany	PLAATO 2 years N=73 Ineligible for LT-OAC	Age 72.7 Male %: 50.7 CHADS2 mean score: 2.52 Stroke: 34.2 CAD %: 53.4 HTN%: 94.4 DM %: 36.1	Serious procedure- or device-related safety events: 4 (5.5%) of 73 Pericardial effusion: 1 (1.4%) of 73 Device embolization resulting in sudden cardiac death 1 (1.4%) of 73 Stroke: 1 (1.4%) of 73 Device instability, explanted by open-heart surgery to avoid device embolization: 1 (1.4%) of 73	Stroke: 0 (0.0%)	Deployment: 71 (97.2%) of 73 Closure at 3-6 months: 52 (100%) of 52 18 patients refused follow-up TEE
Ostermayer, 2005[24] Multisite: USA, Europe, Canada	PLAATO 9.8 months N=111 Ineligible for LT-OAC	Age >= 65 yrs: 84% Age >75 yrs: 35% Male %: NR Mean CHADS2: 2.5 Stroke/TIA: 38% CAD: 41% CHF or LVEF <40%: 39% HTN: 72%	Serious procedure- or device-related safety events occurred in 7 (6.3%) of 111 Respiratory failure: 1 (0.9%) of 111 Pericardial effusion: 2 (1.8%) of 111; only 1 required pericardiocentesis Cardiac Tamponade: 2 (1.8%) of 111; both had pericardiocentesis Hemothorax: 1 (0.9%) of 111	Stroke: 2 of 111 (1.8%)	Deployment: 108 (97.3%) of 111 Closure at end of procedure: 86 (97.7%) of 88 1 month: 60 (100%) of 60 6 months: 49 (98.0%) of 50

Study, Setting	Device; Mean follow-up; N patients; Eligible/ineligible for LT-OAC	Patient characteristics	Periprocedural harms occurring within 7 days	Longer-term harms	Procedural success: Deployment, N (%) of attempted Closure, N (%) of patients assessed by TEE
Reddy, 2013[25] Multisite Germany, Czech Republic, New York	Watchman 14.4 months N=150 Ineligible for LT-OAC	Age 72.5 Male %: 64 Mean CHADS2 score: 2.8 Mean CHAD2DS2-VASC score: 4.4 Stroke/TIA %: 40.7 CHF/reduced LVEF %: 28.7 Vascular disease %: 18 HTN %: 94.7 DM %: 32	Serious procedure- or device-related safety events occurred in 13 (8.7%) of 150 Pericardial effusion (with/without tamponade): 5 (3.3%) of 150 Device embolization: 2 (1.3%) of 150 Device thrombus: 6 (1.0%) of 150	Device thrombus with ischemic stroke, 341 days post-implant: 1 (0.7%) of 150 All-cause stroke or systemic embolism: 4 (2.7%) of 150 Ischemic stroke: 3 (2.0%) of 150 Hemorrhagic stroke: 1 (0.7%) of 150	Deployment: 142 (94.7%) of 150 Closure NR
CAP Registry[26,27] 26 centers	Watchman 16 months N=566 Eligible for LT-OAC	Mean age: 74 Male %: 65.5 CHADS mean: 2.4 CHADS score 1 = 25% CHADS score 2+ = 76% Stroke/TIA; 30.6% CHF %: 18.9 HTN %: 88.3 DM %: 24.7	Serious procedure/device-related safety AE: 17 (3.7%) of 460 Serious pericardial effusion: 10 of 460 (2.2%) Bleeding: 3 of 460 (0.7%) Respiratory failure: 2 of 460 (0.4%)	NR	Deployment: 437 (95.0%) of 460 Closure NR
Gafoor, 2014[21] Single center Retrospec-tive case review, single center Germany	Watchman, n=26 ACP, n=27 PLAATO, n=13 Lariat, n=4 Coherex, n=4 1 year Ineligible for LT-OAC	Mean age: 83.4 Male %: 53.3 Mean CHADS2 = 3.3 Mean CHA2DS-VASc = 5.2 Stroke %: 21.3 CAD %: 41.3 CHF %: 36 HTN %: 96 DM %: 22.7	Serious procedure- or device-related safety events occurred in 3 of 74 (4.1%) TIA: 1 of 74 (1.3%) Femoral bleeding (access site): 1 of 74 (1.3%) Device thrombus (patient not on anticoagulation): 1 of 74 (1.3%)	Death due to renal failure: 1 (1.4%) of 74 Stroke: 1 (1.4%) of 74	Deployment: 75 (100%) of 75 Closure at: 1 day: 68 (90.1% of 75 1 year: 97.4%, N with TEE not reported

Study, Setting	Device; Mean follow-up; N patients; Eligible/ineligible for LT-OAC	Patient characteristics	Periprocedural harms occurring within 7 days	Longer-term harms	Procedural success: Deployment, N (%) of attempted Closure, N (%) of patients assessed by TEE
Matsuo, 2014[22] Single center Germany	Watchman® or Amplatzer Cardiac Plug (ACP®) device) 6 months N=179 Ineligible for LT-OAC	Mean age 72.7 Male %: 58.7 Mean CHADS2 score = 2.9 Mean CHA2DS2VASC = 4.3 Mean HASBLED = 3.9 Prior stroke/TIA %: 27.9 CHF %: 39.1 Vascular disease %: 24.0 HTN %: 95.0 DM %: 44.7	Serious procedure- or device-related safety events: 13 (7.3%) of 179 Cardiac tamponade: 2 (1.1%) Device dislocations: 3 (1.7%) Pericardial effusion: 2 (1.1%) Air embolization: 3 (1.7%) Device thrombus: 3 (1.7%)	Thrombus: 7 (4.2%) of 165 Among 145 with follow-up data at 6-months: Bleeding complications: 3 (2.0%) Upper GI bleeding: 2 (1.4%) Subdural hematoma: 1 (0.7%) Stroke: 0 (0.0%)	Deployment: Watchman: 163 (98.8%) of 165 ACP: 9 (90.0%) of 10 Closure at 45 days: 164 (99.4%) of 165 Discontinuation of OAC or Enoxaparine: 156 (94.5%) of 165

Abbreviations are found on page 5.

SURGICAL LAA INTERVENTIONS

KQ1: What is the effectiveness of LAA exclusion interventions compared with usual care?

Three randomized controlled trials and 2 observational studies evaluated the effectiveness of surgical LAA exclusion compared with usual care (Table 5).

In one trial of 43 patients undergoing open mitral valve surgery randomized to either LAA exclusion or control,[29] no postoperative death or stroke occurred in either group. The composite outcome of death, stroke or transient ischemic attack (TIA), and myocardial infarction (MI) in the postoperative period was also not significantly different (9.1% vs 4.5%, *P* = 1.00).

The LAAOS trial randomized 77 patients at risk for stroke undergoing elective coronary artery bypass grafting (CABG) without concomitant valve surgery to either LAA exclusion or control.[30] Two patients in the LAA exclusion group had perioperative stroke or TIA (2.6% vs 0%, *P*-value not reported). After being followed for an average of 13 +/- 7 months, no additional patients had stroke.

The LAAOS II trial randomized 51 patients with AF and increased stroke risk undergoing cardiac surgery using cardiopulmonary bypass to LAA exclusion or no occlusion with oral anticoagulation.[31] At one year of follow-up there was no significant difference in the primary composite efficacy outcome of rate of death, MI, stroke, non-CNS embolism, and major bleeding (RR 0.7, 95% CI 0.2 to 2.7).

The 3 randomized controlled trials were found to have a low risk of bias. However, all were small pilot studies conducted to assess the safety and feasibility of larger trials and therefore were not powered and did not have adequate follow-up to detect clinically significant outcomes.

The 2 observational studies used propensity score matching to create comparator groups. One study reviewed 119 pairs of patients who underwent surgical ablation of AF over a mean follow-up of 3.1 +/- 2.8 years and found no significant differences in stroke-free survival (*P* = .88) and freedom from AF while off antiarrhythmic drugs (*P* = .46) between the 2 groups.[32]

The other study reviewed 631 pairs of patients who had undergone a variety of cardiac surgical procedures and found that while the rate of postoperative atrial fibrillation was higher in the LAA exclusion group (23% vs 18%, *P* = .037), fewer of these patients had stroke through postoperative day 30 (0.0% vs 6.1%, *P* = .003).[33] However, there were more strokes in the LAA ligation group among patients without postoperative atrial fibrillation, so the overall rate of cerebrovascular accident (CVA) was not significantly different between the 2 groups (*P* = .44). All patients in this study underwent surgery by the same cardiothoracic surgeon, whose practices changed over the course of 10 years from performing no LAA exclusion to routine LAA exclusion during cardiac surgery. Other concurrent changes over time, such as changes in anticoagulation strategy in patients developing AF, may confound the findings of this study.

KQ2: What are the harms associated with LAA exclusion?

The same 3 randomized controlled trials and 2 observational studies evaluated the harms of surgical LAA exclusion (Tables 5 and 6).

One RCT found a trend towards longer median mechanical ventilation time in the LAA exclusion group (11.5 h vs 8 h, $P = .078$).[29] There was no significant difference in the composite of 10 major complications (death, cerebrovascular events, MI, respiratory failure, intra-aortic balloon pump, renal dysfunction, permanent pacemaker, septicemia, mediastinitis, and re-operation for bleeding) between the exclusion and control groups (32% vs 38%, $P = .75$).

The LAAOS trial found more intraoperative tears involving the left atrial appendage or the left atrium in the LAA exclusion group than the control group (15% vs 4%, *P*-value not reported).[30] However, performance of LAA occlusion did not significantly prolong cardiopulmonary bypass time ($P = .63$) and did not increase perioperative bleeding ($P = .53$), the occurrence of postoperative AF ($P = .56$), or diuretic use ($P = .87$).

The LAAOS II trial found no significant difference between the LAA exclusion and control groups for rates major bleeding (RR 0.4, 95% CI 0.0 to 4.6) or reoperation for bleeding (RR 1.9, 95% CI 0.2 to 19.9) and neither of the 2 reoperations in the LAA occlusion group was deemed secondary to bleeding at the LAA occlusion site.[31] No significant difference was found for the total bypass time or cross-clamp time between the 2 groups.

Only one observational study reported harms associated with LAA exclusion and found no significant difference in early operative complications including reoperation due to bleeding (10.9% vs 5.0%, $P = .17$), requirement for dialysis (7.6% vs 8.4%, $P > 0.99$), permanent pacemaker insertion (3.4% vs 1.7%, $P = .63$), mediastinitis (0% vs 0.8%, $P > 0.99$), wound revision (0.8% vs 1.7%, $P > 0.99$) or pericardial effusion (6.7% vs 5.0%, $P = .77$).[32]

KQ3: How do the benefits and harms of LAA exclusion vary in different subgroups?

We identified no trials evaluating subgroup differences in the benefits and harms of surgical LAA exclusion.

KQ4: What are the comparative effects of different techniques on health outcomes and rates of procedural success?

Two observational studies reported the comparative effects of different surgical techniques for LAA exclusion.

One study evaluated success of surgical LAA closure as determined by postoperative TEE after a mean time of 8.1 +/- 12 months.[34] Of 137 patients who underwent surgical excision, only 40% of all closures were successful. Successful LAA exclusion was found to be more common with excision (73%, $P < .001$) than suture exclusion (23%, $P > .001$) or stapler exclusion (0%, $P = .002$).

Another study compared anterior thoracotomy to video-assisted thoracoscopy (VATS) for LAA exclusion in 58 patients with chronic nonrheumatic AF. While there was no significant

difference between the groups for hospital stay (11.3 vs 9.1 days, $P = .61$) or duration of chest tube (4.3 vs 3.7 days, $P = .11$), there was a significant increase in operative time (77.3 vs 121.3 min, $P > .001$) in the VATS group.[35]

Table 5. Characteristics and findings of trials of cardiac surgery with vs without concomitant LAA occlusion or removal

Study, Setting, Surgery performed	Technique; length of follow-up	Sample size and patient characteristics, T vs C	KQ1. Health outcome effects, T vs C	KQ2. Harms associated with LAA exclusion, T vs C	KQ4. Rates of procedural success, T vs C
Healey, 2005[30] Single site, Canada CABG	Sutures or stapler Mean 13 +/- 7 months	N: 52 vs 25 Age, mean: 72 vs 71 Male %: 73 vs 72 History of AF %: 17 vs 8 Stroke %: 17 vs 0 HTN %: 75 vs 92 DM %: NR	Mortality: 0 vs 0 Postoperative AF: 12/52 vs 4/25 Intraoperative ischemic stroke: 1/52 vs 0/25 TIA: 1/52 vs 0/25	Total serious AEs: 10 (19.2%) of 52 vs 1 (4%) of 25 Cross-clamp time (min): 72 vs 75 Intraoperative LAA tears: 8/52 vs 1/25 LAA tears in Tx group: Stapler: 4 Forceps: 2 Suture: 1 Not specified: 1 Perioperative stroke/TIA: 2 (2.6%) vs 0	TEE at 8 weeks postop: 29/44 (66%) with occlusion defined as no flow beyond the line of occlusion and a residual stump of <1 cm. 8 patients refused follow-up TEE. % with complete occlusion at 8 weeks, suture vs stapler (*P* = .14): 5/11 (45%) vs 24/33 (72%) Complete occlusion, stapling device vs sutures alone (*P* = .14.): 24 (72%) of 33 vs 5 (45%) of 11
Nagpal, 2009[29] Single center Italy Mitral valve surgery	Suture Postop period	N: 22 vs 21 Age, mean: 57.8 vs 59.2 Male %: 50 vs 57.1 AF %: 18.2 vs 19 TIA/stroke %: 0 vs 4.8 CAD %: 0 vs 0 DM %: 4.5 vs 0	Mortality: 0/22 vs 0/21 Stroke: 0/22 vs 0/21 TIA: 1/22 vs 1/21 MI: 1/22 vs 0/21	Total serious AEs: 7 (32%) of 22 vs 8 (38%) of 21 (*P* = .75) Mechanical ventilation time: 11.5 h vs 8 h (*P* = .078) Mean days in ICU: 2 vs 1 (*P* = .56) Composite of AEs (respiratory failure, IABP, renal dysfunction, PPM, sepsis, mediastinitis, re-op for bleeding): 5/22 vs 7/21	NR
Whitlock, 2013[31] 4 sites, Canada CABG and/or valve replacement	Sutures or stapler 30 days (in person); 1 year (telephone)	N: 26 vs 25 Age, mean: 77.4 v 74.6 Male %: 76.92 vs 76 AF %: 100 vs 100 CVA %: 23 vs 20 TIA %: 12 vs 24 CAD %: 81 vs 84 CHF %: 27 vs 40 Valvular heart disease %: 81 vs 48* HTN %: 92 vs 92 DM %: 27 vs 28	Mortality: 2/26 vs 3/25 RR (95% CI): 0.64 (0.12 to 3.52) Stroke: 1/26 vs 3/25 RR (95% CI): 0.32 (0.03 to 2.88)	Total serious AEs: 4 (15.4%) of 26 vs 5 (20.0%) of 25 Major GI bleeding: 1/26 vs 2/25 Re-op for bleeding: 2/26 vs 1/25	NR

*"Baseline characteristics were well-balanced between the groups, with the exception that there was more valvular disease (*P* = .01) and a trend toward more valve surgery (*P* = .06) in the occlusion arm"[31]

Table 6. Characteristics and findings of cohort studies of cardiac surgery with vs without concomitant LAA occlusion or removal

Study, Setting, Surgery performed	Technique; length of follow-up	Sample size and patient characteristics, T vs C	KQ1. Health outcome effects, T vs C	KQ2. Harms associated with LAA exclusion, T vs C	KQ4. Rates of procedural success, T vs C
Kanderian, 2008[34] U.S.A. Valve surgery: 62% CABG + valve surgery: 31% Maze surgery: 39%	Excision (via scissors or an amputating stapling device) vs Exclusion (via suture or stapler exclusion with the LAA remaining attached). Mean time to TEE was 8.1 +/- 12 months	N: 52 excision vs 73 suture exclusion vs 12 stapler exclusion: Age: 64 vs 67 vs37 Male %: 67 vs 48 vs 75 AF %: 54 vs 30 vs 8 HTN %: 58 vs 70 vs 50 Stroke %: 17 vs 14 vs 8 CHF %: 54 vs 73 vs 25 DM %: NR Warfarin use %: 69 vs 51 vs 33 Valve surgery %: 62 vs 59 vs 75 CABG + Valve surgery %: 20 vs 41 vs 25 Maze surgery %: 67 vs 22 vs 25	Stroke/TIA: 18 (13.1%) of 137: 6 with LAA excision 11 with suture exclusion, and 1 with stapler exclusion, (*P* = NS). Stroke/TIA among patients with successful vs unsuccessful LAA closure: 6 (11%) vs 12 (15%) (*P* = .61)	---	Excision: 38/52 (73%), *P* > .001 Suture exclusion: 17/73 (23%), *P* > .001 Stapler exclusion: 0/12, *P* = .002 Total: 55/137 (40%)
Kim, 2013[33] U.S.A. CABG %: 82.1 Valve surgery: 8.8% Combined CABG + valve surgery % = 8.6	LAA techniques varied over time: ligation; excision and oversewn; stapled. Retrospective chart review spanning 10 years.	N: 631 vs 631 CHADS2 score: 2.25 vs 2.29 Age: 66.2 vs 65.7 After propensity score matching: Male %: 68 vs 68 Hx stroke: 5 vs 5 CHF %: 81 vs 81 HTN %: 75 vs 75 DM %: 34 vs 34 PSM model included CA BG procedure, valve replacement, gender, age risk, Hx CHF, Hx HTN, Hx DM, and Hx CVA.	After propensity score matching: Postop AF %: 22.9 vs 18.2 (*P* = .037) Postop CVA %: 1.0 vs 1.4 (*P* = .44) Postop AF with CVA %: 0 vs 1.1 (*P* = .003) Among subjects with postop AF, N=145 vs 115: Postop CVA %: 0 vs 6% (*P* = .037)	---	---

Study, Setting, Surgery performed	Technique; length of follow-up	Sample size and patient characteristics, T vs C	KQ1. Health outcome effects, T vs C	KQ2. Harms associated with LAA exclusion, T vs C	KQ4. Rates of procedural success, T vs C
Lee, 2014[32] Korea Mitral valve surgery with cryo-Maze procedure	Resection. Mean follow-up: 62.6 +/- 44.0 months. TEE at 1,3,6, and 12 months; ECG at 1,3,6,12,24, and 36 months.	N: 119 vs 119 After propensity matching: Age: 53.4 vs 54.1 Male %: 37.8 vs 41.2 HTN %: 18.5 vs 19.3 CHF %: 55.5 vs 53.8 DM %: 7.6 vs 7.6 Hx stroke: 5.0 vs 5.9 Hx cardiac surgery: 6.7 vs 4.2	Within 6 months: Mortality: 0/119 vs 1/119 Stroke: 1/119 vs 1/119 After 6 months: Mortality: 6/119 (5.0%) vs 10/119 (8.4%), RR (95% CI) 0.60 (0.22 to 1.60) Stroke/TIA 1/119 (0.8%) vs 2/119 (1.7%), RR (95% CI) 0.50 (0.05 to 5.44) AF: 11/119 vs 9/119	Total serious AEs: 35 (29.4%) of 119 vs 29 (24.4%) of 119 Reoperation due to bleeding: 13/119 vs 6/119 Requirement for dialysis: 9/119 vs 10/119 Permanent pacemaker insertion 4/119 vs 2/119 Mediastinitis: 0/119 vs 1/119 Wound revision: 1/119 vs 2/119 Pericardial effusion 8/119 vs 6/119	---
Muhammad, 2014[35] Saudi Arabia Anterior thoracotomy versus video-assisted thoracoscopy (VATS)	Anterior thoracotomy (open) vs VATS 2 years, by phone every 6 months	N: 29 (open) vs 29 (VATS) Age: 62 Male %: 60.3 HTN %: NR CHF %: NR DM %: NR	---	Total serious AEs: 2 (6.9%) of 29 vs 0 (0.0%) of 29	Open thoracotomy vs VATS: Operative time (min): 77.3 vs 121.3 ($P < .001$) Wound infection: 2/29 vs 0/29 Hospital stay, days: 11.3 vs 9.1 Duration of chest tube, days: 4.3 vs 3.7

SUMMARY AND DISCUSSION

Interest in mechanical exclusion of the LAA to reduce the risk of stroke in patients with atrial fibrillation has grown rapidly in recent years. We systematically reviewed the literature and found 12 studies assessing the benefits and harms of percutaneous approaches to LAA exclusion, and 7 studies assessing the benefits and harms of surgical LAA exclusion. Overall, there is limited evidence that one specific approach to percutaneous LAA exclusion may be an effective alternative to long-term oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained, though there are significant procedure-related harms. There is insufficient evidence to assess the benefits of surgical LAA exclusion, though these procedures do not appear to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed (Table 7).

Our findings corroborate and add to several recent systematic reviews,[36-39] A recently published patient-level meta-analysis[40] similarly found no significant difference in risk of stroke between percutaneous LAA exclusion using the Watchman device and long-term warfarin therapy (HR 1.02, 95% CI 0.62 to 1.7).[40] In contrast to prior reviews we examined both percutaneous and surgical approaches to LAA exclusion. Also, we systematically examined both trial and observational study data.

Percutaneous LAA exclusion

There is low-strength evidence that percutaneous LAA exclusion with the Watchman device is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant therapy after undergoing a follow-up TEE showing persistent closure of the LAA at 3-6 months. However, there is moderate-strength evidence that a substantial proportion of patients experienced serious periprocedural harms. There is insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks.

There are several clinical situations in which percutaneous LAA exclusion may be a potentially attractive option, though the data directly supporting use in these circumstances is limited. First, LAA exclusion might be especially attractive for patients unable to take oral anticoagulants. However, the trial data most closely apply to patients who do not have contraindications to long-term oral anticoagulant therapy. In these trials, warfarin was used typically for 3-6 months until device endothelialization and LAA closure was achieved.

A number of observational studies included patients ineligible for long-term oral anticoagulant therapy,[19-22,24,25] and while most found low rates of stroke over 1-2 years of follow-up, at least one study found higher incidence of stroke over a longer follow-up period.[20] Of note, even though warfarin was not used, patients in most of these studies used dual antiplatelet therapy for a duration ranging from 4 weeks to 6 months. Dual antiplatelet therapy (DAPT) in the population of patients with atrial fibrillation who have increased risk of stroke and for whom vitamin-K antagonists are unsuitable is associated with a 2.0% risk of major bleeding annually.[41] It is notable that in a large study of warfarin versus DAPT for prevention of stroke in AF the risk of major bleeding was similar between groups (respectively 2.21% annual risk of stroke vs 2.42%,

RR 1.10, 95% CI 0.83-1.45, *P* = .53). Minor bleeding and overall bleeding was increased in patients taking DAPT compared to warfarin (15.4% risk per year vs 13.2%, RR 1.21, 95% CI 1.08-1.35, *P* = .001).[42] Thus as long as the protocol for the use of LAA closure devices includes DAPT for any significant length of time it may not be an attractive option for patients who are high risk for bleeding complications and who do not wish to take, or have contraindications to, warfarin.

The clinical circumstances which contribute to anticoagulant ineligibility could also contribute to one's risk of suffering a periprocedural harm. While we do not have data to directly compare rates of periprocedural harms in patients eligible and ineligible for anticoagulant therapy, up to 8.7% of patients experienced a serious periprocedural safety event among 8 observational studies in patients ineligible for oral anticoagulant therapy.[17,19-22,24,25,28]

The second clinical circumstance in which LAA exclusion might provide a useful alternative is for patients who might otherwise accrue a more substantial bleeding risk from oral anticoagulant therapy over longer time horizons. Take, for example, a 70 year-old woman with a history of atrial fibrillation, hypertension, and a prior stroke who is living independently and is a candidate for OAC. She has an annual stroke risk of 6.7% (based on CHADS2-VASC = 5)[1] and would be expected to have a significant benefit from OAC. This same patient would be considered at high risk of major bleed (HAS-BLED = 3) with an expected 3.7 bleeds per 100 patient-years of follow-up while on OAC.[43] She will experience these annual risks of bleeding for the duration of her OAC therapy. In the PROTECT-AF trial, most events in the LAA exclusion group accrued earlier on in the study, while event rates in the control group increased steadily (though remained lower overall) over 3 years of follow-up.[14] Theoretically, then, it is possible that the risks of long-term anticoagulation might eventually offset the near-term risks of LAA exclusion device placement. However, this has not been tested empirically and, given that not all cardioembolic strokes in atrial fibrillation originate in the left atrial appendage, it is certainly possible that long-term stroke risk in patients receiving a device who remain off anticoagulation may increase.

Third, some patients may simply prefer the placement of an LAA exclusion device over the inconvenience of long-term OAC. Policy makers will need to consider whether routine availability of periprocedural LAA exclusion for preference-sensitive indications is warranted.

There are a variety of devices being used for LAA exclusion, but there is not adequate evidence that the efficacy and safety of each of these devices is similar enough to comfortably extrapolate data from one device and apply to the use of a different device. While the techniques used for many of the devices are similar, there are still important differences, perhaps most notably for the Lariat device which takes an epicardial approach to snaring and externally excluding the LAA. For the time being, the evidence for device efficacy applies most closely to the Watchman device and there is insufficient evidence to determine the efficacy of other devices.

There is enough variation in the reported safety of percutaneous exclusion devices that, if the VHA does choose to pursue more widespread use of LAA exclusion procedures, an outcomes registry carefully tracking periprocedural and longer term harms should be established first, with results reviewed at periodic intervals. The finding that the multicenter observational studies often reported fairly high rates of serious periprocedural harms is troubling though the reasons for this

finding are not clear. It is possible that patient selection may be less restrictive and operator experience more variable with broader adoption of a procedure.

Finally, it should be noted that the decision to discontinue anticoagulant therapy in the included studies was based on demonstrated LAA closure on follow-up TEE. Up to 4-6% of patients had continued evidence of LAA blood flow at 6 months, and this may be an underestimate as these figures do not account for the proportion of patients in trials and observational studies who refused follow-up TEE. The benefits and harms of percutaneous LAA exclusion in patients for whom TEE monitoring is infeasible remain essentially unknown.

Surgical LAA exclusion

We found insufficient evidence to determine the efficacy of surgical LAA exclusion in reducing stroke. We found low strength evidence that surgical LAA exclusion in the context of heart surgery performed for another indication is unlikely to be associated with significant incremental harm.

While surgical LAA exclusion might seem analogous to performing an appendectomy during an exploratory laparotomy, the clinical implications may be quite different. The promise of surgical LAA exclusion is to reduce long-term risk of stroke and, possibly, to obviate the need for long-term oral anticoagulant therapy. However, we do not have sufficient evidence to determine whether prophylactic surgical LAA exclusion actually does reduce stroke. In the meantime, there is at least the theoretic possibility that surgical LAA exclusion may offer false reassurance to patients who then decide to discontinue oral anticoagulant therapy.

Limited data from one trial and one observational study suggest that a relatively high proportion of patients have persistent LAA blood flow detected on follow-up TEE.[30,34] Given the lack of robust efficacy data, and the relatively low rates of long-term procedural success, patients who do undergo LAA exclusion during heart surgery should likely not discontinue long-term oral anticoagulant therapy.

Table 7. Summary of the evidence on percutaneous and surgical interventions to occlude or remove the LAA

Outcome	Device or procedure N studies (N=combined participants)	Findings	Strength of Evidence*	Comments
Percutaneous interventions				
Mortality	Watchman 2 RCTs (N=1,114)	No significant difference in mortality. RR (95% CI) in 2 RCTs: 1.20 (0.31 to 4.56) 0.62 (0.34 to 1.24)	Low	Limited applicability: only one device has been studied in 2 RCTs. Patients were eligible to receive LT-OAC. Low precision (wide confidence intervals).
Stroke	Watchman 2 RCTs (N=1,114)	No significant difference in risk of stroke. RR (95% CI): in 2 RCTs: 0.71 (0.35 to 1.64) 3.28 (0.37 to 25.31)		
Harms	ACP: 3 registries (N=147) Coherex: 1 registry (N=4) Lariat: 2 registries (N=93) PLAATO: 5 registries (N=441) Watchman: 2 RCTs + 4 registries (N=742) Device not specified: 2 registries (N=211)	Serious procedure- or device-related safety events (% of patients): 1.6 to 13.6 Overall, rate of serious adverse events within 7 days of device implantation was 6.5% (98/1506).	Moderate	Various devices were examined among 2 trials and 11 observational studies. Wide range of event rates across studies and relatively small number of patients treated in each observational study limited strength of findings.
Surgical interventions				
Mortality	Sutures or stapler in 3 RCTs (N=171) Various excision and exclusion techniques in 4 Cohort studies (N=1695)	No significant difference in mortality, among studies in which at least one event occurred in both groups: In 1 RCT: 7.7 vs 12% ($P > .05$) RR (95% CI) 0.64 (0.12, 3.52) In 1 cohort: 5.0 vs 8.4% ($P > .05$) RR (95% CI) 0.60 (0.22 to 1.60)	Insufficient	Trials too small and event rates too low to determine effectiveness of procedure.
Stroke	3 RCTs (N=171) 2 cohort studies (N=1500)	No significant difference in risk of stroke, among studies where at least one event occurred in both groups: In 1 RCT: 3.8 vs 12% ($P > .05$); RR (95% CI) 0.32 (0.03 to 2.88) In 2 cohorts: 1.0 vs 1.4% ($P = .44$) 0.84 vs 1.7% ($P > .05$)	Insufficient	
Harms	3 RCTs (N=171) 1 cohort study (N=238)	Serious safety events: 6.9-32.0% of patients No significant differences in most major harms between cardiac surgery groups with and without LAA exclusion	Low	Limited number of studies and limited number of patients included.

*The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[11]

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

LIMITATIONS

While we adhered to published standards for systematic review conduct, there are several potential methodologic limitations to note. First, we excluded non-English language studies. There is empiric data, however, suggesting that reviews restricted to English-language studies are largely concordant with reviews without language restrictions.[44] Second, we excluded observational studies enrolling fewer than 50 participants. However, we felt that these typically single-center studies with very small denominators were unlikely to yield reliable information about rates of harms or procedural success.

There are significant limitations in this body of evidence as a whole, and these are noted throughout our report. Clearly, one of the biggest limitations is simply the relative paucity of methodologically rigorous studies examining the efficacy of percutaneous and surgical LAA exclusion.

RESEARCH GAPS/FUTURE RESEARCH

Trials of percutaneous LAA interventions were limited to studies of the Watchman device in patients who were eligible for long-term warfarin therapy. Trials of surgical LAA interventions were few and limited by sample size. Several studies that should add substantively to this body of evidence are underway (Table 8), including a large RCT of surgical interventions with an estimated sample size of 4,700 patients; studies of recently developed percutaneous devices (LAmbre and Occlutech); and a trial comparing Watchman with Apixaban in patients ineligible for warfarin therapy.

Table 8. Ongoing studies of percutaneous and surgical LAA interventions

Study title; Clinicaltrials.gov ID	Device or technique vs control	Study design; Estimated enrollment; Status; Estimated completion date	Country; Funding source	Comment
Percutaneous interventions				
Feasibility and Safety Study of LAmbre Left Atrial Appendage Occluder; NCT01920412	LAmbre	Single-group, open-label N=20 Recruiting as of Aug 2013; Est. completion: Sept 2014	China; Lifetech Scientific (Shenzhen) Co., Ltd.	First-in-man study
Safety and Efficacy Study of LAmbre LAA Closure Device for Treating AF Patients Who Cannot Take Warfarin; NCT02029014	LAmbre	Single group, open-label N=154 Recruiting as of Mar 2014; Est. completion: Jul 2016	China; Lifetech Scientific (Shenzhen) Co., Ltd.	Includes patients who cannot be treated long-term with Warfarin
Prospective, Non-randomized, Safety and Efficacy Study of a New Occluder Design for Minimally Invasive Closure of the Left Atrial Appendage (LAA) in Patients With Atrial Fibrillation (OLAAC); NCT02105584	Occlutech	Single group, open-label N=105 Recruiting as of Apr 2014; Est. completion: Apr 2016	Germany Occlutech International AB	Includes patients eligible or non-eligible for long-term oral anticoagulation therapy

Study title; Clinicaltrials.gov ID	Device or technique vs control	Study design; Estimated enrollment; Status; Estimated completion date	Country; Funding source	Comment
Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17); NCT02426944	Watchman vs Apixaban	RCT, open-label N=400 Ongoing not recruiting as of April 2015; Est. completion: May 2020	Czech Republic; Charles University and Ministry of Health	Includes patients with significant bleeding during warfarin treatment
Surgical interventions				
Left Atrial Appendage Occlusion Study III (LAAOS III); NCT01561651	Cardiac surgery with vs without LAA occlusion via suture and/ or surgical stapler	RCT, double-blinded N=4700 Recruiting as of May 2014; Est. completion: May 2019	Canada; Population Health Research Institute	Estimated mean follow-up of 4 years
Left Atrial Appendage CLOSURE for the Prevention of Thromboembolisms in Patients Undergoing Aortic Bioprosthesis Surgery (LAA-CLOSURE); NCT02321137	Valve surgery with vs without surgical LAA closure	RCT, open-label N=1040 Recruiting as of Dec 2014; Est. completion: Dec 2027	Finland and Netherlands; 5 regional/ university hospitals	Includes patients with no indication for long-term anticoagulation

CONCLUSIONS

Overall, there is limited evidence that percutaneous LAA exclusion may be an effective alternative to long-term oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained. However, only one percutaneous device has been studied rigorously in trials, and percutaneous LAA exclusion has been associated with high rates of serious procedure-related harms in many studies. There is insufficient evidence to assess the benefits of surgical LAA exclusion. While surgical LAA exclusion does not appear to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed, rates of procedural success may be low. Overall, there is insufficient evidence to support the routine use of surgical LAA exclusion to reduce stroke risk or future need for anticoagulant therapy. There are a number of ongoing studies that should add substantively to this body of evidence over the next several years.

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45. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. *J Am Coll Cardiol.* Mar 6 2012;59(10):923-929.

APPENDIX A. SEARCH STRATEGIES

Database Strategy:

- Medline (Ovid)
- Embase (Elsevier)
- Cochrane Library (EBM Reviews)
- Conference Papers Index (ProQuest)

Grey Literature Sources

- Clinicaltrials.gov
- WHO ICTRP
- ISRCTN Registry
- US FDA medical devices website: Advisory Committee/Panel Meetings (CDRH); Premarket Approvals (PMA); Premarket Notifications (510(k)s)
- Device manufacturer scientific information request

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946-November Week 3 2014,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 06, 2015
Searched: January 7, 2015

1	atrial appendage/ and left.ti,ab.	1060
2	(left adj1 ((atrial or atrium or auricular) adj1 appendage*)).ti,ab.	2410
3	1 or 2	2552
4	Atrial Fibrillation/su or exp cardiovascular surgical procedures/ or ligation/ or thoracic surgical procedures/ or sternotomy/ or thoracoscopy/ or thoracic surgery, video-assisted/ or thoracotomy/ or (excis* or excision* or occlude* or occlusion* or closure* or destruction or obliterat* or ligation* or ligat* or sutur* or exclusion* or exclud* or appendectom* or thoracoscop* or minithoracotom* or mini-thoracotom* or stapling or stapled or stapler* or sew or sewn or oversew* or clamp* or clip* or atriclip or Gillinov-Cosgrove or ligasure or amputat* or resect* or removal or remove* or surger* or surgical or CABG or MAZE or AVR or sternotom* or percutaneous* or Watchman or Lariat or PLAATO or Amplatzer or Coherex or LAmbre).ti,ab.	2716235
5	3 and 4	1457
6	remove duplicates from 5	1421
7	limit 6 to "all child (0 to 18 years)"	145
8	limit 7 to "all adult (19 plus years)"	48
9	7 not 8	97
10	6 not 9	1324
11	animals/ not humans/	4025968
12	10 not 11	1213

ELSEVIER EMBASE.COM : 1950-present
Searched: January 7, 2015

#13	#9 NOT #12	2,164
#12	#10 NOT #11	373
#11	#10 AND ({young adult}/lim OR {adult}/lim OR {middle aged}/lim OR {aged}/lim OR {very elderly}/lim)	68
#10	#9 AND ({newborn}/lim OR {infant}/lim OR {child}/lim OR {preschool}/lim OR {school}/lim OR {adolescent}/lim OR {animal experiment}/lim OR {animal model}/lim)	441
#9	#7 OR #8	2,537
#8	'left atrial appendage closure device'/exp	184
#7	#3 AND #6	2,485
#6	#4 OR #5	4,435,729
#5	'heart atrium fibrillation'/exp AND 'surgery'/lnk OR 'cardiovascular surgery'/de OR 'ligation'/de OR 'thorax surgery'/de OR 'sternotomy'/de OR 'thoracoscopy'/de OR 'thoracotomy'/de	110,162
#4	excis* OR excision* OR occlude* OR occlusion* OR closure* OR destruction OR obliterat* OR ligation* OR ligat* OR sutur* OR exclusion* OR exclud* OR appendectom* OR thoracoscop* OR minithoracotom* OR mini AND thoractom* OR stapling OR stapled OR stapler* OR sew OR sewn OR oversew* OR clamp* OR clip* OR atriclip OR 'gillinov cosgrove' OR ligasure OR amputat* OR resect* OR removal OR remove* OR surger* OR surgical OR cabg OR maze OR avr OR sternotom* OR percutaneous* OR watchman OR lariat OR plaato OR amplatzer OR coherex OR lambre.ti,ab.	4,421,880
#3	#1 OR #2	4,759
#2	((atrial OR atrium OR auricular) NEXT/1 appendage*):ab,ti	4,553
#1	'heart atrium appendage'/exp AND left:ab,ti	2,855

Ovid EBM Reviews:

- Cochrane Central Register of Controlled Trials: 1991-**November 2014**
- Cochrane Database of Systematic Reviews: **2005-November 2014**
- Database of Abstracts of Reviews of Effects: 1991-**4th Quarter 2014**
- Health Technology Assessment: 2001-**4th Quarter 2014**
- NHS Economic Evaluation Database: 1995-**4th Quarter 2014**

Searched: January 7, 2015

1	(left adj1 ((atrial or atrium or auricular) adj1 appendage*)).mp.	79
2	(excis* or excision* or occlude* or occlusion* or closure* or destruction or obliterat* or ligation* or ligat* or sutur* or exclusion* or exclud* or appendectom* or thoracoscop* or minithoracotom* or mini-thoracotom* or stapling or stapled or stapler* or sew or sewn or oversew* or clamp* or clip* or atriclip or Gillinov-Cosgrove or ligasure or amputat* or resect* or removal or remove* or surger* or surgical or CABG or MAZE or AVR or sternotom* or percutaneous* or Watchman or Lariat or PLAATO or Amplatzer or Coherex or LAmbre).mp.	153735
3	And/1-2	45

ProQuest COS Conference Papers Index
Searched: January 22, 2015

(left atrial appendage* OR left atrium appendage* OR left auricular appendage*) AND (excis* OR excision* OR occlude* OR occlusion* OR closure* OR destruction OR obliterat* OR ligation* OR ligat* OR sutur* OR exclusion* OR exclud* OR appendectom* OR thoracoscop* OR minithoracotom* OR mini-thoracotom* OR stapling OR stapled OR stapler* OR sew OR sewn OR oversew* OR clamp* OR clip* OR atriclip OR Gillinov-Cosgrove OR ligasure OR amputat* OR resect* OR removal OR remove* OR surger* OR surgical OR CABG OR MAZE OR AVR OR sternotom* OR percutaneous* OR Watchman OR Lariat OR PLAATO OR Amplatzer OR Coherex or Lambre) [Search field=anywhere; document type=conference, conference papers; dates=all dates] Results=57

ClinicalTrials.gov
https://www.clinicaltrials.gov/ct2/search/advanced
Searched: July 28, 2015
Search terms = "left atrial appendage" OR "left atrium appendage" OR "left auricular appendage"
Study type = Interventional Studies
Results = 58

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
http://apps.who.int/trialsearch/
Searched: January 22, 2015
Search terms: Watchman OR Amplatzer OR Coherex OR Wavecrest OR Ligasure OR Lambre OR PLAATO OR Atriclip OR Lariat OR left atrial appendage OR left atrium appendage OR left auricular appendage
Results = 3

ISRCTN Registry
http://www.isrctn.com/editAdvancedSearch?q=plaato&filters=&searchType=advanced-search
Searched: January 22, 2015
Searched each of the following terms/phrases separately in the text search field:

> Watchman OR Amplatzer OR Coherex OR WaveCrest OR Ligasure OR Lambre OR PLAATO OR Atriclip OR Lariat OR left atrial appendage OR left atrium appendage OR left auricular appendage

Results = 0

APPENDIX B. STUDY SELECTION

Code	Definition	KQ1. What is the effectiveness of LAA exclusion interventions compared with usual care?	KQ2. What are the harms associated with LAA exclusion?	KQ3a. How do the benefits LAA exclusion vary in different subgroups? KQ3b. How do the harms of LAA exclusion vary in different subgroups?	KQ4. What are the comparative effects of different techniques on health outcomes and rates of procedural success?
I – Surg	Addresses KQ1, KQ2, or KQ3: Primary trial or cohort study that compares surgical LAA technique with usual care, and reports outcomes of interest.	<u>Included surgical interventions:</u> · LAA occlusion/removal techniques that involve major surgery (sternotomy or thoracotomy), *eg*: § specific devices such as AtriClip, or § techniques such as stapling or suturing. · LAA occlusion/removal via thoracoscopic surgery, *eg*: § Thoracoscopic Left Appendage Total Obliteration No cardiac Invasion (LAPTONI) procedure · Minimally invasive Maze procedures if there are data about the incremental effects of concomitant LAA exclusion.			
I – Perc	Addresses KQ1, KQ2, or KQ3: · For all KQs, include RCTs that compare percutaneous LAA technique with usual care, and reports outcomes of interest. · For KQ2 and KQ3b, may also include cohort, registry, trial extension, or post market surveillance studies that report harms data and have a sample size >50.	<u>Included percutaneous interventions:</u> · AMPLATZER™ Cardiac Plug (company: AGA Medical, Corp., North Plymouth, MN, USA) a.k.a. "Amulet" · WATCHMAN® Left Atrial Appendage Closure Technology/Device/System (company: Atritech, Inc., North Plymouth, MN, USA) · PLAATO™ Percutaneous Left Atrial Appendage Transcatheter Occlusion (company: Appriva Medical, Inc., Sunnyvale, CA) · Coherex WaveCrest™ LAA Occluder System (company: Coherex Medical, Inc., Salt Lake City, Utah, USA) · LARIAT suture delivery device (SentreHeart, Redwood City, California) · Lifetech LAmbre™ Left Atrial Appendage Occluder ***Device (***Lifetech Scientific Co., Ltd., Shenzhen, CHINA)			
I4 – Surg	Addresses KQ4: Primary trial or cohort study that compares different surgical techniques to close LAA, and reports either procedural or health outcomes.	<u>Included outcomes for KQ4:</u> · Procedural outcomes: successful closure/LAA removal, assessed by methods such as transesophageal echocardiogram; CT; MRI. · Health outcomes: stroke, mortality, cardiovascular morbidity, or other reported health outcomes			
I4 – Perc	Addresses KQ4: Include RCTs only. Study compares different percutaneous LAA techniques, and reports either procedural or health outcomes.				
I–SR	Systematic review or meta-analysis of surgical / percutaneous techniques that addresses any of the 4 KQs				

APPENDIX C. QUALITY ASSESSMENT

Table 9. Quality assessment of trials of percutaneous LAA interventions

Study	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Study was funded by
PREVAIL Holmes, 2014[16]	Yes: "computer-generated randomization" for most of the subjects: 407 were enrolled thru randomization; the remaining 68 were enrolled through "roll-in process"	Yes Centralized system performed block randomization stratified by clinical center; password protected; accessed by PI and study coordinator	No: Participants and clinicians were not masked to treatment assignment	Yes, presumably: "All follow-up information from the post-182-day period was used in the final hazards analysis in the model, contributing to the calculation of the probability of 18-month events."	Yes	Yes	Low	Atritech/Boston Scientific.
PROTECT AF Alli, 2013[12] Holmes, 2009[13] Reddy, 2013[14] Viles-Gonzales, 2012[45]	Yes: "randomly assigned by a computer-generated randomization sequence" in a 2:1 intervention:control ratio	Yes Centralized system performed block randomization stratified by clinical center; password protected; accessed by PI and study coordinator	No: Participants and clinicians were not masked to treatment assignment	Yes. Reports "Analyses were performed on randomized subjects for those with a paired mental and physical component score at baseline and 12 months, or in subjects who died before 1 year of follow-up irrespective of actual treatment received, following the intention-to-treat principle." Caveat: patients with unsuccessful implantation were censored at 45 days and, therefore, did not have 12 month reported QoL data and were excluded.	Yes	Yes	Low; High for QOL outcomes owing to lack of blinding, subjective nature of the outcome, and differential rates of follow-up for this outcome.	Atritech, Inc.

Table 10. Quality assessment of trials of surgical LAA interventions

Study; Setting	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias
Nagpal, 2009[29] Single center Italy	Yes: "Simple randomization, stratified by presence of preoperative atrial fibrillation, was carried out using a computer program"	Yes: "sealed-envelope technique was used to assign each patient to a treatment group"	Yes: "sealed-envelope"	Yes: ITT analysis	Yes	Yes	Low
Whitlock, 2013[31] LAAOS II	Yes "participants were randomly assigned to either the occlusion arm or the no-occlusion arm by a central 24-hour automated interactive voice-activated randomization system. Treatment allocation was performed according to a computer-generated randomization list and was stratified based on preoperative OAC use."	Yes	Yes "Treatment was not blinded" but unlikely that outcomes measured would be influenced by lack of blinding. "Although the study will not be blinded, the following steps will be taken to reduce the risk of bias in the assessment of outcome events. Patients will be assessed by standardized questionnaire at each visit. All reported outcome events will be reviewed by an adjudication committee blinded to treatment allocation. All hospital admissions occurring during the study will be reported, including all admission and discharge diagnoses, to detect possible stroke."	Yes "Assessment of the secondary clinical outcomes was based on the intention-to-treat principle, in which all participants are included in their assigned treatment groups regardless of actual surgical procedure performed." "One-year data were available for 100% of the patients enrolled in the LAAOS II trial."	Yes	Yes	Low

Study; Setting	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias
Healey, 2005[30] LAAOS	Yes "consecutively ordered, opaque, sealed envelope" "randomized, using sealed envelopes, to undergo LAA occlusion or serve as a control. Patients were randomized 2:1, favoring occlusion."	Yes	Yes "Treatment was not blinded" but unlikely that outcomes measured would be influenced by lack of blinding. "Although the study will not be blinded, the following steps will be taken to reduce the risk of bias in the assessment of outcome events. Patients will be assessed by standardized questionnaire at each visit. All reported outcome events will be reviewed by an adjudication committee blinded to treatment allocation. All hospital admissions occurring during the study will be reported, including all admission and discharge diagnoses, to detect possible stroke."	Yes no missing outcome data for KQ2	Yes prespecified outcomes (Crystal 2003) all reported	Yes	Low risk of bias

Table 11. Quality assessment of cohort studies surgical LAA interventions

Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
Kim, 2013[33]	1 all patients who underwent surgery with a single cardiothoracic surgeon over the course of 10 years	1	1	1	2 study controls for 8 variables in PSM model	1	1? only looks at 30 days post-op, difficult to say how this would change the data. Could see more of a benefit in decreased CVA in the LAA ligation group with longer follow-up, however may have also seen more harm from the increased incidence of post-op AF.	1 A total of 2078 patients underwent cardiac surgery during the 10-year study time period. Eleven patients were excluded from the study (10 patients died and 1 patient had an incomplete medical record because of transfer to another facility on postoperative day 1), leaving a sample size of 2067.
Lee, 2014[32]	1	1	1	1	2 PSM model with 20 variables	1	1	1
Kanderian, 2008[34]	0 only 173 of 1,546 who underwent surgical LAA closure (follow-up complete TEE with color Doppler interrogation of LAA)	1	1	1	0	1	1	1
Muhammad, 2014[35]	0	1	1	1	0	0	1	1

Newcastle-Ottawa[10] criteria and code definitions used in Table 10:

Representativeness of the exposed cohort
1 = truly representative of the average pt in the community
1 = somewhat representative of the average pt in the community
0 = selected group of users eg nurses, volunteers
0 = no description of the derivation of the cohort

Selection of the non exposed cohort
1 = drawn from the same community as the exposed cohort
0 = drawn from a different source
0 = no description of the derivation of the non exposed cohort

Ascertainment of exposure
1 = secure record (eg surgical records)
1 = structured interview
0 = written self-report
0 = no description

Demonstration that outcome of interest was not present at start of study
1= yes
0 = no

Comparability of cohorts on the basis of the design or analysis
Add points: Minimum 0 , Maximum 2
1 = study controls for ___ (select most important factor)
1 = study controls for any additional factor (a second important factor)
0 = no adjustment for potential confounders

Assessment of outcome
1 = independent blind assessment
1 = record linkage
0 = self-report
0 = no description

Was follow-up long enough for outcomes to occur?
1 = yes (need to define adequate follow up period for outcome of interest)
0 = no

Adequacy of follow up of cohorts
1 = complete follow up; all subjects accounted for.
1 = subjects lost to follow up unlikely to introduce bias; small number (define %) lost, or description was provided of those lost.
0 = follow up rate < ____% (define adequate %) and no description of those lost.
0 = no statement

APPENDIX D. LAA DEVICE MANUFACTURERS

Scientific information requests were sent January 17, 2015, to the companies listed below.

LAA exclusion device	Device manufacturer
AMPLATZER™ Cardiac Plug, Cardiac Plug 2, Cardiac Plug 3, and Amulet™	**ST. JUDE MEDICAL, INC.** ATTN: Medical Information Officer St. Jude Medical, Inc. One St. Jude Medical Drive St. Paul, MN 55117-9983 Email form: http://sjm.com/corporate/data/forms/email-us
ATRICLIP® PRO LAA Occlusion System	**ATRICURE, INC.** ATTN.: Medical Information Officer 6217 Centre Park Drive West Chester, OH 45069 Email form: http://www.atricure.com/contact-atricure-usa
WATCHMAN® Left Atrial Appendage Closure Device	**BOSTON SCIENTIFIC, CORP.** ATTN: Medical Information Officer 100 Boston Scientific Way Marlborough, MA 01752 Online form (scroll to bottom right): https://www.bostonscientific.com/en-US/contact-us.html
COHEREX WAVECREST™ LAA Occluder System	**COHEREX MEDICAL, INC.** ATTN: Medical Information Officer 3598 West 1820 South Salt Lake City, UT 84104 Online contact form: http://www.coherex.com/contact/
Lifetech LAmbre™ Left Atrial Appendage Occluder Device	**LIFETECH SCIENTIFIC (SHENZHEN) CO., LTD.** ATTN.: Medical Information Officer Cybio Electronic Building, Langshan 2nd Street, Nanshan District, Shenzhen 518057, PEOPLE'S REPUBLIC OF CHINA Email: lifetechmed@lifetechmed.com
LARIAT® Suture Delivery Device	**SENTREHEART, INC.** ATTN: Medical Information Officer 300 Saginaw Drive Redwood City, CA 94063 Email: info@sentreheart.com
LigaSure™	**COVIDIEN** ATTN: Michael Tarnoff, MD FACS Corporate Chief Medical Officer Medical Devices/Medical Supplies 15 Hampshire Street Mansfield, MA 02048

APPENDIX E. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

Question	Reviewer	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	Noted.
	2	Yes	Noted.
	3	Yes	Noted.
	4	Yes	Noted.
	5	Yes	Noted.
Is there any indication of bias in our synthesis of the evidence?	1	No	Noted.
	2	No	Noted.
	3	Yes - The method section clearly identifies the process for evidence collection and synthesis.	Noted.
	4	No	Noted.
	5	No	Noted.
Are there any published or unpublished studies that we may have overlooked?	1	Yes - Medtronic sponsored and run The Cardioblate Closure Device Study (FDA IDE G080156) “An evaluation of the Cardioblate Closure Device in Facilitating Occlusion of the Left Atrial Appendage". Enrollment was suspended in 2009. The data was not published but is available by the FDA.	We came across this study in our search for trials in clinicaltrials.gov. We decided not to include it because the study was terminated due to a Medtronic business decision, and no study results were posted. We were unable to find the study on the FDA website.
	2	No	Noted.
	3	No	Noted.
	4	No	Noted.
	5	No	Noted.
Additional suggestions or comments can be provided below. If applicable,	1		No comment.
	2	This analysis of the safety and efficacy of procedures to occlude or remove the left atrial appendage is comprehensive, informative, and well written. The conclusions are well supported and though the paper does not provide definitive guidance on the role of LAA exclusion in reducing the risk of AF associated stroke it will be very useful for clinicians and policy makers.	Noted, thank you.

Question	Reviewer	Comment	Response
please indicate the page and line numbers from the draft report.		I have a minor disagreement with the point in the introduction that since 90% of thrombi that develop in the atrium are in the appendage it would make sense that elimination of the appendage would reduce the risk of stroke. This point is certainly true but a more nuanced discussion of the etiology on stroke in AF would be helpful in understanding why exclusion of the appendage may not eliminate the risk of stroke in AF. It is worth mentioning that the appendage is not the only source of strokes in AF patients. The patients at highest risk AF associated stroke have risk factors for stoke that are independent of AF such as hypertension, diabetes, and advanced age. Each of these puts patients at risk for mechanisms of stroke that are not related to AF such as aortic and carotid atherosclerosis. I do not know if it is really known what percentage of strokes in patients with AF are from appendage thrombus versus other mechanisms. Thus the point is that though 90% of clots in the heart are in the appendage it is not known what percentage of AF associated strokes are due to the embolism of clots from the appendage. This is especially true as one does more extensive monitoring for occult AF in stroke patients.	Edits made to reflect our uncertainty regarding source of thrombi in the introduction of the executive summary and evidence report.
		Minor points: Maze is not consistently capitalized (single or all caps) in the manuscript	Corrected. We will use “all caps” MAZE.
		Page 10 Table 2 (and elsewhere): There is some inconsistency in whether the CHADS2 score or the CHA2DS2-VASC is used for risk stratification. If possible the CHA2DS2-VASC should be used though I understand that not all studies will report it.	We will continue to use CHADS2 and CHADS2-VASC as appropriate for individual studies, however, when making general comments/summary statements we will use low risk (CHADS2 <2 or CHADS2-Vasc <2) when patients/providers have been given the option of aspirin versus warfarin therapy.
		In the PREVAIL trial statistical methods it states, “Data on endpoints from PROTECT AF subjects meeting the inclusion/exclusion criteria for PREVAIL were used in a historical previous distribution, with 50% discounting to reduce the influence of the earlier data. “ To me this sounds that some patients acted as controls in both PROTECT and PRVAIL. Was this taken into account in your analysis? Should it be?	The PREVAIL study used the data from PROTECT in power calculations to determine the study size. Patients from PREVAIL were not included in the PREVAIL trial.
		Page 15: It does not seem to make sense to me that the composite endpoint would be 5.2% in the LAA exclusion group and 2.9% in the warfarin group but that the 18 month composite event rate ration was only 1.07.	We agree this is confusing, and have added wording to clarify the % vs rate ratio which is based on person-time of observation. It is likely because the event rates are reported for the total duration of the study (longer than 18 months) and some of the events in the device group occurred later in the study.
		Table 3: The PROTECT AF quality of life data is suspect in my mind in that the study was unblinded and one group had a complex procedure. Such a procedure it would seem to me could have a profound placebo effect that might influence the patient’s assessment of quality of life.	We agree, and have rated the ROB for QOL outcomes as follows: High for QOL outcomes owing to lack of blinding, subjective nature of the outcome, and differential rates of follow-up for this outcome.

Question	Reviewer	Comment	Response
		Page 29: It might be worth mentioning that in one large study of warfarin versus aspirin and clopidogrel for AF associated stroke prevention the risk of major bleeding was similar between with warfarin compared to the combination of ASA and clopidogrel and that minor bleeding and overall bleeding were higher with ASA and clopidogrel compared to warfarin. Thus as long as the protocol for the use of the watchman device requires that drug combination for up to 6 months it will not be an attractive device for patients that are at high risk for bleeding complications and do not want to take warfarin.	We appreciate this point and have added it to our discussion.
		There is a very wide range of reported % rate of stroke in various studies reported in the manuscript. I believe some of this variation is due to variable follow-up time and differing risk stroke factor profiles. There probably is no easy way to correct for these factors and make the numbers comparable across studies but it would be nice if possible. Perhaps as you have done just having follow-up time and risk factors in the tables is the best you can do.	Challenging. This represents that variable populations which were enrolled and different follow-up time. We hope to provide the data in a clear format so that the differences are relatively clear.
	3	The report is overall very well-conceived and written. I am not clear why the RCTs that are listed in appendix C while satisfying most of the questions are still considered low quality evidence. I did not find enough support for that determination in the narrative as well.	Low = Low risk of bias.
	4	In the summary of evidence (page 2) please expand the statement pertaining to LAA percutaneous LAA exclusion (line 51) to include comment for all devices not just Watchman.	We agree and have made the suggested change.
		I am unclear as to the statements made regarding surgical ablation of the LAA during routine cardiac procedures (page 30, lines 4-27). Specifically, why could the clinician not avoid anticoagulation if the patient had a prior LAA ablation (whether open surgical or percutaneous)? Please consider clarifying that no evidence exists to evaluate whether prophylactic LAA oblation prevents or minimizes stroke risk associated with later onset AF.	We have edited this to reflect the uncertainty of the literature regarding reduction in stroke risk from surgical LAA exclusion.

Question	Reviewer	Comment	Response
	5	Noelck and colleagues from the ESP Center performed a systematic review of the effectiveness and harms of percutaneous catheter-based and surgical interventions to occlude, exclude, or remove the left atrial appendage (LAA). They were charged with addressing 4 key questions regarding effectiveness compared to usual care (*ie* anticoagulation or antiplatelet agents), harms, variance of effects among subgroups, and comparative effects of different techniques. They concluded that the Watchman device may be an effective alternative to long-term oral anticoagulation in selected patients, though the evidence (for efficacy) was deemed low-strength, and high rates of serious procedure-related harms were noted in many studies. Specific comparisons between devices or patient groups was not possible due to insufficient evidence; most notably this included the subgroup of patients who are ineligible for long-term oral anticoagulation. Though additional harms appeared low with surgical procedures for LAA exclusion/resection, there was insufficient evidence to evaluate efficacy, with some studies suggesting low procedural success. For this reason the routine use of surgical LAA exclusion for the purpose of stroke prevention or cessation of anticoagulation could not be recommended. Dr. Noelck and team should be congratulated for an exhaustive and fair review. Some specific comments follow.	Thank you.
		Major: 1. Perhaps due to the structure of the key questions there is no direct comparison of risks of intervention versus standard of care (long-term oral anticoagulation). Within key question #1 the harms of stroke or death are addressed in a comparative fashion. Key question #2 primarily examines all other harms only on the side of intervention. This may bias the reader's resulting assessment of the risks and benefits between intervention and anticoagulation. I do agree with the assessment that percutaneous intervention on the LAA has had high rates of serious procedure-related harms in many studies (perhaps lessening with experience, as the authors mentioned). Given the indefinite nature of the risks of anticoagulation though, if a patient has a reasonable life expectancy, this risk will likely eventually be equaled and surpassed. A bit more detailed statement of risks on the standard of care side of the equation, other than the brief mention of its "cumbersome" nature in the introduction would seem to be appropriate.	Addressed in discussion (page 36).
		Minor: 1. Might be reasonable to add a sentence to the findings in the harms row of the table on 3 in the executive summary that pertains to harms found specifically with Watchman device (even if only to say percentages fit in range above), since that is the only percutaneous intervention in which efficacy was addressed, *ie*, the most relevant.	Added Watchman example of periprocedural event rates (from RCTs PROTECT & PREVAIL) to executive summary of findings.

Question	Reviewer	Comment	Response
		2. In Table 1 p9 PICOTS and key questions for percutaneous LAA interventions time on bypass is listed as an outcome for KQ2, presumably for symmetry with Table 2. Might favor listing need for surgical intervention instead. Ventilator days also probably is less relevant for percutaneous intervention category, whereas device migration or emboli formation could potentially be included.	Agree. Revised as suggested.
		3. In Table 2 p10 PICOT and key questions for surgical LAA interventions the comparator for KQ2 is listed as surgery for atrial fibrillation without LAA removal. To my review, studies included in this comparison were primarily CABG and/or valve surgeries with or without LAA intervention. It would be surprising to find a study of surgery for AF only/specifically that did not include intervention on the LAA.	We agree, we searched more broadly but did not find any studies on these.
		4. In Table 3 p17, might consider adding DM statistics to patient characteristics as all other aspects of CHADS score already included. Is it of interest to add race as well?	Agree, and we have added data on DM. Information on race was mostly unreported among both RCTs and observational studies.
		5. KQ4 text on p22 addresses comparison of surgical techniques. Ref 28, Healey et al, also reported comparison numbers between stapler and suture technique, which were different. Is there a reason this data / inconsistency was not mentioned?	While this study reported results for both stapler and suture LAA occlusion, the surgical technique was not randomized. Over time the percentage of surgeries performed using staplers increased, making it difficult to determine whether it was increasing surgeon experience or change to stapler technique that led to higher rates of successful LAA occlusion.