

Effectiveness of Left Atrial Appendage Exclusion Procedures to Reduce the Risk of Stroke: A Systematic Review of the Evidence

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Background—Atrial fibrillation is an important cause of cardioembolic stroke. Oral anticoagulants (OAC) reduce stroke risk but increase the risk of serious bleeding. Left atrial appendage (LAA) procedures have been developed to isolate the LAA from circulating blood flow, as an alternative to OAC. We conducted a systematic review of the benefits and harms of surgical and percutaneous LAA exclusion procedures.

Methods and Results—We searched multiple data sources, including Ovid MEDLINE, Cochrane, and Embase, through January 7, 2015. Of 2567 citations, 20 primary studies met prespecified inclusion criteria. We abstracted data on patient characteristics, stroke, mortality, and adverse effects. We assessed study quality and graded the strength of evidence using published criteria. Trials found low-strength evidence that percutaneous LAA exclusion confers similar risks of stroke and mortality as continued OAC, but this evidence was limited to the Watchman device in patients eligible for long-term OAC. Observational studies found moderate-strength evidence of serious harms with a variety of percutaneous LAA procedures. There is low-strength evidence that surgical LAA exclusion does not add significant harm during heart surgery for another indication, but evidence on stroke reduction is insufficient.

Conclusions—There is limited evidence that the Watchman device may be noninferior to long-term OAC in selected patients. Data on effectiveness of LAA exclusion devices is lacking in patients ineligible for long-term OAC. Percutaneous LAA devices are associated with high rates of procedure-related harms. Although surgical LAA exclusion during heart surgery does not seem to add incremental harm, there is insufficient evidence of benefit. (*Circ Cardiovasc Qual Outcomes*. 2016;9:395-405. DOI: 10.1161/CIRCOUTCOMES.115.002539.)

Key Words: anticoagulants ■ atrial appendage ■ atrial fibrillation ■ hemorrhage ■ stroke

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 common comorbidities.

Cardioembolic strokes account for 14% to 36% of all ischemic strokes, and AF is the most important cause of cardioembolic stroke. In general, the risk of stroke in patients with nonvalvular AF is 2 to 7 times higher than in patients without AF.² Antithrombotic therapy with aspirin, warfarin, or one of several newer oral anticoagulants (OACs) has become the mainstay of stroke prevention in AF, but it is associated with an increased risk of bleeding.

The mechanism of thrombosis formation is stasis of blood in the left atrium, and it is currently thought that a high percentage of thromboemboli develop in the left atrial appendage (LAA).^{3,4} Given the high prevalence of AF, along with the potential risks

and inconvenience of long-term (LT) OAC therapy, there is a growing interest in LAA occlusion or removal as an alternative stroke risk reduction strategy. 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. Surgery was the only option for exclusion of the LAA before 2002, but several devices designed to occlude the LAA percutaneously have since been developed. The devices currently in use include the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device (Appriva Medical, Plymouth, MN), the Amplatzer device (AGA Medical Corporation/St. Jude Medical, Golden Valley, MN), the Watchman device (Boston Scientific, Natick, MA), and the LARIAT suture delivery device (SentreHeart, Redwood City, CA).

We conducted a systematic review of the benefits and harms of surgical or percutaneous LAA occlusion or removal. We use the general term LAA exclusion throughout the report

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WHAT IS KNOWN

- Anticoagulation is currently the standard of care to prevent cardioembolic stroke in patients with atrial fibrillation.
- The Watchman left atrial appendage closure device was found to be largely noninferior to standard therapy in patients with nonvalvular atrial fibrillation who are candidates for anticoagulation.

WHAT THE STUDY ADDS

- There is no evidence to recommend percutaneous left atrial appendage exclusion in patients with atrial fibrillation who are ineligible for therapeutic anticoagulation; randomized trials have not been performed.
- In the few published case series available, the overall risk of serious adverse events with percutaneous device therapy is ≈ 1 in 15 patients.
- Surgical left atrial appendage exclusion does not seem to be associated with increased harm when performed during cardiac surgery for another indication, but there is insufficient evidence to compare the efficacy of this procedure to anticoagulation therapy.

to refer to either removal or isolation of the LAA, except where otherwise specified.

Methods

A protocol describing the review plan was posted to a publicly accessible website before the study was initiated.⁵ The key questions and scope parameters that guided our review and synthesis of the literature is provided in Appendix I in the [Data Supplement](#).

To identify relevant articles, we searched Ovid MEDLINE, Embase, the Cochrane databases, and the FDA Devices database from database inception through January 7, 2015, using a search strategy that included terms for AF, cardiovascular procedures, and names of LAA devices and exclusion techniques (Appendix II in the [Data Supplement](#)). The search strategy was developed by 2 research librarians, using the instrument for Peer Review of Search Strategies.^{6,7} We further examined the bibliographies of relevant articles; consulted technical experts for additional studies; searched ClinicalTrials.gov, the Conference Abstracts database, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); and contacted device manufacturers (Appendix III in the [Data Supplement](#)) to identify in-progress or unpublished trial data. We reviewed titles and abstracts for relevance to the key questions using prespecified eligibility criteria. At the full-text screening stage, 2 independent reviewers concurred on final inclusion/exclusion decisions, with input from a third investigator to resolve questions and reach consensus.

We included controlled clinical trials to assess the effectiveness of percutaneous LAA exclusion procedures. In addition to controlled trials, cohort studies with or without a control population were included to examine harms of percutaneous interventions. After an initial survey of the literature, we found that there were several larger cohort studies providing harms data and, therefore, set a sample size cut off of ≥ 50 patients for inclusion.

Given that surgical 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 controlled clinical trials or cohort studies with a control population of patients who received heart surgery but no LAA exclusion to assess benefits and harms of surgical LAA exclusion. From each study, we abstracted study design, objectives, setting, subject eligibility

criteria, years of enrollment, sample size, population demographics and clinical characteristics, the study and comparator interventions, important cointerventions, duration of follow-up, health outcomes, and adverse events. A second author reviewed the entries for accuracy.

Two reviewers (among N.N., D.K., J.P., and M.F.) independently assessed study quality and assigned each trial, an overall rating of low, high, or unclear risk of bias, using a tool developed by the Cochrane Collaboration (Appendix IV in the [Data Supplement](#)).⁸ For evaluating cohort studies of surgical LAA interventions, we used the Newcastle-Ottawa criteria to assess methodological rigor and consider potential sources of bias⁹ but did not assign overall quality ratings because validated criteria are not currently available for rating observational studies.

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

We used a method developed by the Agency for Healthcare Research and Quality¹⁰ that considers the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies, to classify the overall strength of evidence for each outcome as follows: high, further research is 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 likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and insufficient, any estimate of effect is uncertain.

Results

We reviewed 2567 titles and abstracts, including 2469 from the electronic search and an additional 98 from reviewing reference lists and searching manually for recent, ongoing, or unpublished studies. We selected 207 articles for full-text review, of which 20 primary studies met our inclusion criteria (Figure). 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 III in the [Data Supplement](#)).

Percutaneous LAA Interventions

Two randomized controlled trials (RCTs) compared the Watchman Left Atrial Appendage Closure Device (Atritech, Inc, North Plymouth, MN) to warfarin therapy (Table 1). Both the trials were determined to have a low risk of bias. Inclusion into the Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF)¹²⁻¹⁴ trial required subjects to have nonvalvular AF and a CHADS₂²⁷ score of at least 1, whereas the Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL)¹¹ 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 interventions and 244 control patients with nonvalvular AF and excluded patients with low risk of stroke (CHADS₂=0). The device was successfully deployed in 88% (408/463) of patients, although it was not attempted in 14 patients. Successful closure was obtained in 92% (355/385) at 6 months and only 3.6% (14/385) of patients who underwent device implantation remained on warfarin after 3 months; warfarin was discontinued with complete closure or if residual peridevice flow was < 5 mm width on surveillance transesophageal echocardiogram (TEE).^{13,14} The control arm was within therapeutic international normalized ratio (INR) range 66% of the time.

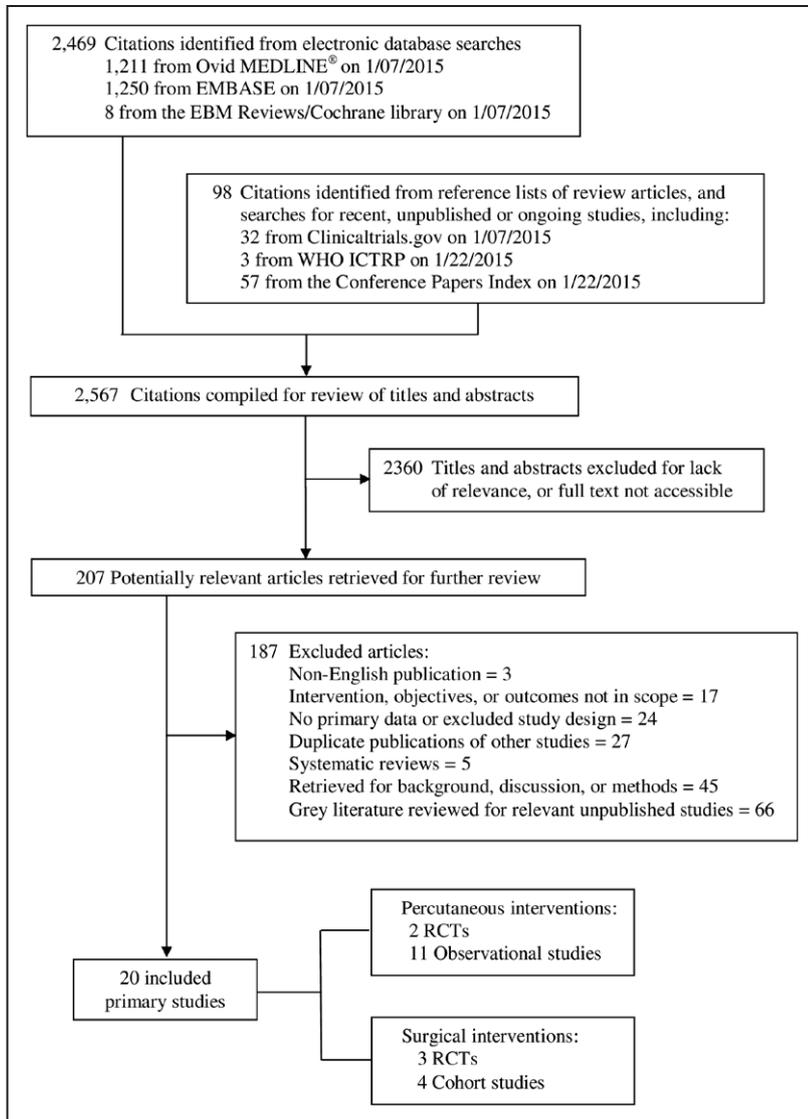


Figure. Literature flow diagram. RCT indicates randomized controlled trial.

There was no difference in a composite primary efficacy end point including ischemic/hemorrhagic stroke, cardiovascular/unexplained death, and systemic embolism with 3.0 (1.9–4.5) events per 100 patient-years in the LAA exclusion group versus 4.9 (2.8–7.1) events per 100 patient-years in the warfarin group (rate ratio, 0.62; 0.35–1.25). Cumulative events at 2.3 years of mean follow-up (SD, 1.1 years; median, 2.4; range, 0.5–9 years) were also similar with 3.0 (2.15–4.3) events per year in the LAA exclusion group versus 4.3 (2.6–5.9) events per year in the warfarin group. Overall, LAA exclusion was noninferior to warfarin therapy in patients who were candidates for anticoagulation in PROTECT-AF trial.^{13,14}

In a subset of patients in the PROTECT-AF trial, quality of life modestly improved in the intervention group on some subscales. 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 (SD, 5.8 months;

range, 0.03–25.9 months).¹¹ 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) of patients. At 6 months, device closure was demonstrated in 98.3% (235/239), although 11.2% (30/269) refused follow-up TEE.

The PREVAIL trial did not meet its target of noninferiority for overall efficacy, although event rates were low and numerically comparable to 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 in 2.9% of the warfarin group.¹¹

We found 2 trials and 11 observational studies reporting harms data (Table 1). Serious periprocedural adverse events were reported in 1.6% to 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.

Table 1. Health Outcomes, Adverse Effects, and Procedural Success in Trials and Observational Studies of Percutaneous LAA Exclusion Devices

| Study; Setting; Device; Mean Follow-Up | Patient Characteristics | Health Outcomes | Adverse Events | Procedural Success: Deployment, n (%) of Attempted; Closure, n (%) Assessed by TEE |
|---|--|---|--|--|
| Randomized controlled trials comparing the Watchman device vs warfarin therapy | | | | |
| PREVAIL ¹¹ ; 50 sites, USA Watchman; 11.8 mo | n patients: 269 vs 138, Mean age: 74.0 vs 74.9 y, Male: 67.7 vs 74.6%, CHADS ₂ mean: 2.6 vs 2.6, CHA ₂ DS ₂ -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=0.003), 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 (0.7%) of 269, Arteriovenous fistula: 1 (0.4%) of 269, Cardiac perforation: 1 (0.4%) of 269, Pericardial effusion requiring surgery: 1 (0.4%) of 269, Pericardial effusion with pericardiocentesis: 4 (1.5%) of 269, Major bleed requiring transfusion: 1 (0.4%) of 269, Procedure-related stroke: 1 (0.4%) of 269 | 252 (95.1%) successfully implanted of 265 attempted. Discontinuation of warfarin† among n assessed by TEE: 227 (92.2%) of 246 at 45 d, 235 (98.3%) of 239 at 6 mo, 141 (99.3%) of 142 at 12 mo |
| PROTECT-AF ¹²⁻¹⁴ ; 59 sites; USA, Europe Watchman, 12 mo | n patients: 463 vs 244, Mean age: 71.7 vs 72.9 y, Male: 70.4 vs 70.1%, CHADS ₂ mean: 2.2 vs 2.4 (P=0.0517), AF: 100 vs 100%, Stroke/TIA: 17.7 vs 20.1%, CAD: 39.6 vs 49.5% (P=0.0275), CHF: 26.8 vs 27.0, HTN: 90.9 vs 90.3, DM: 24.9 vs 30.6% | Ischemic stroke: 15 (3.0%) of 463 vs 6 (2.5%) of 244, Cardiovascular/unexplained death: 5 (1.1%) of 463 vs 10 (4.1%) of 244 (P<0.05), Hemorrhagic stroke: 1 (0.2%) of 463 vs 6 (2.5%) of 244, Systemic embolism: 2 (0.4%) of 463 vs 0 (0%) of 244, All strokes: 16 (3.4%) of 463 vs 12 (4.9%) of 244, All-cause mortality: 21 (4.5%) of 463 vs 18 (7.4%) of 244, QoL assessed by short form: 12 vs 2 mean change, baseline to 12 mo: Total physical score: +0.4 vs -0.2 (P=0.0015), Total mental score: 0.0 vs -0.9 (P=0.64); Physical functioning: +0.1 vs -3.0 (P=0.0005), Physical role limitation: +0.4 vs -2.35 (P=0.002), Pain: -0.1 vs -1.0 (P=0.57), General health: +0.8 vs -0.2 (P=0.06), Vitality: +0.2 vs -1.4 (P=0.1614), Social functioning: +0.5 vs -1.6 (P=0.07), Emotional role limitation: -0.3 vs -1.8, P=0.1115, Mental health: 0.0 vs -0.9, P=0.6780 | 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 (1.5%) of 463, Device embolization: 3 (0.6%) of 463, Major bleeding: 16 (3.4%) of 463, Procedure-related stroke: 6 (1.1%) of 463, Other: 2 (0.4%) of 463, 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 d: 348 (86%) of 401. 30 (7.5%) of 401 continued warfarin because of continued shunt. At 6 mo: 355 (92%) of 385. 14 (3.6%) of 385 continued warfarin because of continued shunt. Control arm was within therapeutic INR range 66% of the time. |
| Observational studies of percutaneous LAA exclusion devices | | | | |
| Bartus ¹⁵ ; Poland; Lariat, 1 y | n=89, ineligible for LT-OAC Mean age: 62 y, Male: 57%, CHADS ₂ mean: 1.9, CHA ₂ DS ₂ -VASc mean: 2.8, HAS-BLED mean: 2.4, Stroke/TIA: 25%, CAD: 4%, CHF: 12%, HTN: 94%, DM: 10% | At 3 mo, sudden cardiac death: 1 (1.2%) of 85, At 6 mo, hemorrhagic stroke: 1 (1.2%) of 85, At 1 y, lacunar stroke: 1 (1.2%) of 85 | Periprocedural AEs: pericarditis in 2 (2.4%) of 85, Longer-term harms: pericardial effusion in 1 (1.2%) of 85 | Deployment: 85 (95.5%) of 89, Closure: 1 d: 81 (95%) of 85, 30 d: 81 (95%) of 85, 90 d: 77 (95%) of 81, 1 y: 64 (98%) of 65 |
| Bayard ¹⁶ ; 18 centers, Europe; PLAATO; 9.6 mo | n=180, ineligible for LT-OAC Mean age: 70 y, Male: 66%, Mean CHADS ₂ score: 3.1, CHF: 42%, Stroke/TIA: 59%, HTN: 83%, DM: 29% | Stroke, at 129 patient-years follow-up: 2.3%, Cardiac death: 5 (3.1%) of 162 | Periprocedural AEs occurred in 8 (4.9%) of 162 Cardiac tamponade: 6 (3.7%) of 162, Cardiac death, procedure related: 2 (1.2%) of 162 | Deployment: 162 (90%) of 180, Closure at 2 mo: 126 (90%) of 140 |
| Block ¹⁷ ; USA; PLAATO; 5 y | n=64, ineligible for LT-OAC Mean age: 73 y, Male: 60.9%, CHADS ₂ score of 1, %: 23.4, CHADS ₂ score 2+, %: 76.6, CHF: 44%, Stroke/TIA: 69%, HTN: 77%, DM: 23.4% | Stroke: 8 of 64 (12.5%) | Periprocedural AEs occurred in 1 (1.6%) of 64: cardiac tamponade requiring surgery | Deployment: 61 (95.3%) of 64, Closure immediately after procedure: 55 (98.2%) of 56, Closure at 1 mo: 22 (100%) of 22 |
| CAP Registry ^{18,19} ; 26 centers; Watchman; 16 mo | n=566, eligible for LT-OAC Mean age: 74 y, 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% | ... | Periprocedural AEs occurred in 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%), Longer-term harms NR | Deployment: 437 (95.0%) of 460 Closure NR |

(Continued)

Table 1. Continued

| Study; Setting; Device; Mean Follow-Up | Patient Characteristics | Health Outcomes | Adverse Events | Procedural Success: Deployment, n (%) of Attempted; Closure, n (%) Assessed by TEE |
|--|---|---|--|--|
| Gafoor ²⁰ ; Single-center Retrospective case review, Single center, Germany; Watchman, n=26; ACP, n=27; PLAATO, n=13; Lariat, n=4; Coherex, n=4; 1 y | n=74, ineligible for LT-OAC Mean age: 83.4 y, Male: 53.3%, Mean CHADS ₂ : 3.3, Mean CHA ₂ DS ₂ -VASc: 5.2, Stroke: 21.3%, CAD: 41.3%, CHF: 36%, HTN: 96%, DM: 22.7% | Death due to renal failure: 1 (1.4%) of 74, Stroke: 1 (1.4%) of 74 | Periprocedural AEs occurred in 3 (4.1%) of 74 TIA: 1 (1.3%) of 74 Femoral bleeding (access site): 1 (1.3%) of 74 Device thrombus (patient not on anticoagulation): 1 (1.3%) of 74 | Deployment: 75 (100%) of 75, Closure at: 1 d: 68 (90.1%) of 75, 1 y: 97.4%, n with TEE not reported |
| Matsuo ²¹ ; Single center, Germany; Watchman or Amplatzer Cardiac Plug (ACP) device); 6 mo | n=179, ineligible for LT-OAC Mean age: 72.7 y, Male: 58.7%, Mean CHADS ₂ score: 2.9, Mean CHA ₂ DS ₂ -VASc: 4.3, Mean HAS-BLED: 3.9, Previous stroke/TIA: 27.9%, CHF: 39.1%, Vascular disease: 24.0%, HTN: 95.0%, DM: 44.7% | Stroke at 6 mo: 0 (0.0%) | Periprocedural AEs occurred in 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%), Longer-term harms: Thrombus: 7 (4.2%) of 165, Among 145 with 6-mo follow-up: Bleeding complications: 3 (2.0%), Upper GI bleeding: 2 (1.4%), Subdural hematoma: 1 (0.7%) | Deployment: Watchman: 163 (98.8%) of 165, ACP: 9 (90.0%) of 10, Closure at 45 d: 164 (99.4%) of 165, Discontinuation of OAC or Enoxaparine: 156 (94.5%) of 165 |
| Nietispach ²² ; Single center, Switzerland; Nondedicated LAA occlusion devices (off-label use of Amplatzer PFO, ASD, and VSD occluders), n=32 Amplatzer ACP, n=120; 32 mo | n=152, eligible for LT-OAC Mean age: 72 y, Male: 69%, Mean CHA ₂ DS ₂ -VASc: 3.46, Mean HAS-BLED score: 2.46, Stroke: 31%, HTN: 75%, DM: 23% | Ischemic stroke: 1 (0.7%) | Periprocedural AEs occurred in 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, Neurological events (2 TIA and 1 minor stroke): 3 (2.0%) of 152, GI bleeding resulting in death: 1 (0.7%) of 152, Longer-term harms: Embolization: 1 (0.7%) of 152, Bleeding: 13 (8.6%) of 152, 4 were major bleeds (2.6%); 2 intracerebral bleeds 2 subdural hematoma | Deployment: 146 (96.0%) of 152, Closure at 3–6 mo: 137 (93.8%) of 146 |
| Ostermayer ²³ ; Multisite: USA, Europe, and Canada; PLAATO; 9.8 mo | n=111, ineligible for LT-OAC Age≥65 y: 84%, Age>75 y: 35%, Male %: NR, mean CHADS ₂ : 2.5, Stroke/TIA: 38%, CAD: 41%, CHF or LVEF <40%: 39%, HTN: 72% | Stroke: 2 (1.8%) of 111 | Periprocedural AEs 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 | Deployment: 108 (97.3%) of 111, Closure at end of procedure: 86 (97.7%) of 88, 1 mo: 60 (100%) of 60, 6 mo: 49 (98.0%) of 50 |
| Park ²⁴ ; Single-center prospective registry, Germany; PLAATO; 2 y | n=73, ineligible for LT-OAC Age: 72.7 y, Male: 50.7%, CHADS ₂ mean score: 2.52; Stroke: 34.2%, CAD: 53.4%, HTN: 94.4%, DM: 36.1% | Stroke: 0 (0.0%) | Periprocedural AEs occurred in 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 | Deployment: 71 (97.2%) of 73, Closure at 3–6 mo: 52 (100%) of 52, 18 patients refused follow-up TEE |
| Price ²⁵ ; 8 sites; USA; Lariat; 112 d, median | n=154, no criteria for LT-OAC 60% on OAC at baseline, Mean age: 72 y, Male: 62%, CHADS ₂ mean: 2.8, CHA ₂ DS ₂ -VASc mean: 4.1, HAS-BLED mean: 3.2, CHF: 34%, Stroke/TIA: 38%, HTN: 81%, DM: 36% | NR | Periprocedural AEs occurred in 21 (13.6%) of 154: Major bleed: 14 (9.1%) of 154, Cardiac tamponade: 7 (4.5%) of 154, Longer term: thrombus formation in 4 (3%) of 134 with follow-up data | Deployment: 145 (94.2%) of 154, Closure at end of procedure: 133 (92%) of 145, Closure at follow-up: 50 (79%) of 63 |
| Reddy ²⁶ ; Multisite Germany, Czech Republic, and New York; Watchman; 14.4 mo | n=150, ineligible for LT-OAC Age, 72.5 y, Male: 64%, Mean CHADS ₂ score: 2.8, Mean CHA ₂ DS ₂ -VASc: 4.4, Stroke/TIA: 40.7%, CHF/ reduced LVEF: 28.7%, Vascular disease: 18%, HTN: 94.7%, DM: 32% | 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 | Periprocedural AEs 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, Longer-term harms: Device thrombus with ischemic stroke, 341 d post implant: 1 (0.7%) of 150 | Deployment: 142 (94.7%) of 150, Closure NR |

ACP indicates amplatzer cardiac plug; AE, adverse event; AF, atrial fibrillation; ASD, atrial septal defect; CAD, coronary artery disease; CHADS₂, stroke risk score in AF (congestive heart failure, hypertension, age 75+ years, 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; DM, diabetes mellitus; GI, gastrointestinal; HAS-BLED, score that estimates risk of major bleeding for patients on anticoagulation for atrial fibrillation; HTN, hypertension; INR, international normalized ratio; LAA, left atrial appendage; LT-OAC, long-term oral anticoagulation therapy; LVEF, left ventricular ejection fraction; n, number (of); NR, not reported; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; QoL, quality of life; TEE, transesophageal echocardiography; TIA, transient ischemic attack; VATS, video-assisted thoracoscopy; and VSD, ventricular septal defect.

*Total serious AEs in our report differs from primary source because we included procedure-related strokes and pericardial effusions requiring any intervention.

†Implies complete closure or residual peridevice flow <5 mm in width on TEE.

Two trials examined harms associated with placement of the Watchman device.^{11,13} In PROTECT-AF trial, 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.¹¹ Adverse event rates were similar in the single-center^{15,17,20–22,24} and the multicenter studies.^{18,23,25,26}

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 (Table 1). Currently, there is no RCT data available to compare deployment success, LAA exclusion achieved, or health outcome benefits among the different devices.

Over the LT in observational studies, patients had low rates of stroke and bleeding, and there were no reported technical device failures. However, data on longer-term safety from the observational studies are limited, in part, by high rates of attrition,²³ lack of information about the loss to follow-up,^{15,18–21} wide variation in follow-up duration (6 months to 5 years), and the lack of a consistent standard for adverse events reporting.

Although the 2 RCTs excluded patients who were ineligible to receive anticoagulant therapy, 7 of 11 observational studies included patients who were ineligible for LT-OAC therapy. In most of these studies, the LT rates of stroke were $\approx 2.1\%$ (12/565) during the course of 6 to 24 months of follow-up.^{15,20,23,24,26}

Surgical LAA Interventions

Three RCTs and 2 observational studies evaluated the effectiveness of surgical LAA exclusion compared with usual care (Table 2). Each of the randomized trials involved patients undergoing cardiac surgery and cardiopulmonary bypass for another indication (coronary artery bypass grafting or valve surgery) and were small studies designed to determine the safety and efficacy of the procedure.^{28–30} The RCTs, although at low risk of bias, were underpowered for determining the clinical effectiveness of this procedure. Both the observational studies demonstrated no significant difference in stroke-free survival during the course of their follow-up, but important data such as information about anticoagulation use among the groups was lacking.^{32,33}

One study evaluated success of surgical LAA closure as determined by postoperative TEE after a mean time of 8.1 ± 12 months.³¹ 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%, $P < 0.001$) than suture exclusion (23%, $P > 0.001$) or stapler exclusion (0%, $P = 0.002$). Another small study compared adverse events between anterior thoracotomy and video-assisted thorascopic surgery approaches to LAA exclusion and found no significant differences.³⁴

There were no significant differences in complication rates between the LAA exclusion and control groups in any of the surgical studies (Table 2).^{28–30,32,33}

Discussion

We systematically reviewed the literature and found 13 studies assessing the benefits and harms of percutaneous approaches to LAA exclusion and 7 studies assessing the benefits and harms of surgical LAA exclusion. The key findings and strength of evidence supporting these findings is listed in Table 3. Overall, there is limited evidence on 1 device that percutaneous LAA exclusion may be an effective alternative to LT oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained, although there are significant procedure-related harms. There is insufficient evidence to assess the benefits of surgical LAA exclusion, although these procedures do not seem to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed.

There is low-strength evidence that percutaneous LAA exclusion with the Watchman device is associated with a similar risk of LT stroke and mortality as continued oral anticoagulation therapy. Most patients who received the Watchman device were able to discontinue OAC therapy after undergoing a follow-up TEE showing persistent closure of the LAA at 3 to 6 months. However, there is moderate-strength evidence that a substantial proportion of patients experienced serious periprocedural harms. Overall, ≈ 1 in 15 patients experienced a serious adverse event during percutaneous LAA exclusion procedures. 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, although the data directly supporting the use in these circumstances is limited. First, LAA exclusion might be especially attractive for patients who are unable to take OACs. However, the trial data most closely apply to patients who do not have contraindications to LT-OAC therapy. In these trials, warfarin was used typically for 3 to 6 months until device endothelialization, and LAA closure was achieved.

Several observational studies included patients ineligible for LT-OAC therapy,^{17,20,21,23,24,26} and while most found low rates of stroke over 1 to 2 years of follow-up, at least 1 study found higher incidence of stroke during a longer follow-up period.¹⁷ 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 in the population of patients with AF 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.³⁵ It is notable that in a large study of warfarin versus dual antiplatelet therapy for prevention of stroke in AF, the risk of major bleeding was similar between the groups (2.21% annual risk of stroke versus 2.42%, respectively; RR, 1.10; 95% CI, 0.83–1.45; $P = 0.53$).³⁶ Thus, as long as the protocol for the use of LAA closure devices includes dual antiplatelet therapy for any significant length of time, it may not be an attractive option for patients who are at high risk for bleeding

Table 2. Studies of Cardiac Surgery With vs Without Concomitant LAA Occlusion or Removal, Stratified by Study Design

| Study, Setting, Surgery Performed | Technique; Length of Follow-Up | Sample Size and Patient Characteristics | Health Outcomes | Adverse Events | Procedural Success: Deployment, n (%) of attempted; Closure, n (%) Assessed by TEE |
|--|---|--|---|--|---|
| Randomized controlled trials | | | | | |
| Healey, ²⁸ Single site, Canada CABG | Sutures or stapler Mean, 13±7 mo | 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 wk postoperative: 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. Complete occlusion at 8 wk, suture vs stapler: 5/11 (45%) vs 24/33 (72%), <i>P</i> =0.14 |
| Naggal, ²⁹ Single center, Italy Mitral valve surgery | Suture Postoperative 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 (<i>P</i> =0.75) Mechanical ventilation time: 11.5 vs 8 h (<i>P</i> =0.078) Mean days in ICU: 2 vs 1 (<i>P</i> =0.56), Composite of AEs (respiratory failure, IABP, renal dysfunction, PPM, sepsis, mediastinitis, and reop for bleeding): 5/22 vs 7/21 | NR |
| Whitlock, ³⁰ 4 sites, Canada CABG and valve replacement | Sutures or stapler: 30 d (in-person); 1 y (telephone) | n: 26 suture vs 25 stapler Age, mean: 77.4 vs 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 (0.12–3.52) Stroke: 1/26 vs 3/25 RR (95% CI): 0.32 (0.03–2.88) | 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 |
| Cohort studies | | | | | |
| Kanderian ³¹ USA 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 mo | n: 52 excision vs 73 suture exclusion vs 12 stapler exclusion: Age: 64 vs 67 vs 37y 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 (<i>P</i> =NS) Stroke/TIA among patients with successful vs unsuccessful LAA closure: 6 (11%) vs 12 (15%; <i>P</i> =0.61) | ... | Excision: 38/52 (73%), <i>P</i> >0.001 Suture exclusion: 17/73 (23%), <i>P</i> >0.001 Stapler exclusion: 0/12, <i>P</i> =0.002, Total: 55/137 (40%) |
| Kim, ³² USA 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 y. | n: 631 vs 631 CHADS ₂ score: 2.25 vs 2.29 Age: 66.2 vs 65.7 y 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 CABG procedure, valve replacement, sex, age risk, Hx CHF, Hx HTN, Hx DM, and Hx CVA | After propensity score matching: postoperative AF: 22.9 vs 18.2% (<i>P</i> =0.037) Postoperative CVA: 1.0 vs 1.4% (<i>P</i> =0.44) Postoperative AF with CVA: 0 vs 1.1% (<i>P</i> =0.003) Among subjects with postoperative AF, n=145 vs 115: Postoperative CVA: 0 vs 6% (<i>P</i> =0.037) | ... | ... |

(Continued)

Table 2. Continued

| Study, Setting, Surgery Performed | Technique; Length of Follow-Up | Sample Size and Patient Characteristics | Health Outcomes | Adverse Events | Procedural Success: Deployment, n (%) of attempted; Closure, n (%) Assessed by TEE |
|---|---|---|---|--|---|
| Lee, ³³ Korea Mitral valve surgery with cryo-Maze procedure | Resection. Mean follow-up: 62.6 ± 44.0 mo. TEE at 1,3,6, and 12 mo; ECG at 1,3,6,12,24, and 36 mo | n: 119 vs 119 After propensity matching: Age: 53.4 vs 54.1 y 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 mo: Mortality: 0/119 vs 1/119, Stroke: 1/119 vs 1/119, After 6 mo: Mortality: 6/119 (5.0%) vs 10/119 (8.4%) RR: 0.60 (95% CI, 0.22–1.60) Stroke/TIA: 1/119 (0.8%) vs 2/119 (1.7%) RR: 0.50 (95% CI, 0.05–5.44) AF: 11/119 (9.2%) vs 9/119 (7.6%) | Total serious AEs: 35/119 (29.4%) vs 29/119 (24.4%) Reoperation because of 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, ³⁴ Saudi Arabia Anterior thoracotomy vs VATS | Anterior (open) thoracotomy vs VATS 2 y, by phone every 6 mo | n: 29 (open) vs 29 (VATS) Age: 62 y, Male: 60.3% HTN %: NR CHF %: NR DM %: NR | ... | Open vs VATS: Total serious AEs: 2 (6.9%) of 29 vs 0 (0.0%) of 29 Operative time (min): 77.3 vs 121.3 (<i>P</i> <0.001) Wound infection: 2/29 vs 0/29 Hospital stay, d: 11.3 vs 9.1 Duration of chest tube, d: 4.3 vs 3.7 | Occlusion was confirmed by intraoperative TEE, but postoperative or longer-term confirmation was not reported |

AE indicates adverse event; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CVA, cerebrovascular accident; DM, diabetes mellitus; GI, gastrointestinal; HTN, hypertension; Hx, history (of); IABP, intra-aortic balloon pump; LAA, left atrial appendage; MI, myocardial infarction; n, number (of); NR, not reported; NS, not significant; PSM, propensity score matching; RR, relative risk; TEE, transesophageal echocardiography; TIA, transient ischemic attack; and VATS, video-assisted thoracoscopy.

*Baseline characteristics were well balanced between the groups, with the exception that there was more valvular disease (*P*=0.01) and a trend toward more valve surgery (*P*=0.06) in the occlusion arm.³⁰

complications and who do not wish to take, or have contraindications to, warfarin.

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 OAC therapy over longer-time horizons. In the PROTECT-AF trial, most events in the LAA exclusion group accrued earlier in the study, whereas event rates in the control group increased steadily (although remained lower overall) during 3 years of follow-up.¹⁴ Theoretically, then, it is possible that the risks of LT 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 AF originate in the left atrial appendage, it is certainly possible that LT 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 LT 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 inadequate evidence that the efficacy and safety of each of these devices are similar enough to comfortably extrapolate data from 1 device and apply to the use of a different device. Although 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.

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% to 6% of patients had continued evidence of LAA blood flow at 6 months, and this may be an underestimate because 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.

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. However, data from 1 trial and 1 observational study suggest that a relatively high proportion of patients have persistent LAA blood flow detected on follow-up. Therefore, until more data become available, surgical LAA exclusion should likely not influence decision making about future OAC therapy.^{28,31}

Our findings corroborate and add to several recent systematic reviews.^{37–40} A recently published patient-level meta-analysis of the Watchman device⁴¹ similarly found no significant difference in risk of stroke between percutaneous LAA exclusion using the Watchman device and LT warfarin

Table 3. 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=1114) | No significant difference in mortality. RR (95% CI) in 2 RCTs: 1.20 (0.31–4.56) 0.62 (0.34–1.24) | Low | Limited applicability: only one device has been studied in 2 RCTs. Patients were eligible to receive LT-OAC. Low precision (wide CIs). |
| Stroke | Watchman 2 RCTs (n=1114) | No significant difference in risk of stroke. RR (95% CI) in 2 RCTs: 0.71 (0.35–1.64) 3.28 (0.37–25.31) | | |
| 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): 1.6–13.6 Overall, rate of serious adverse events within 7 d 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 1 event occurred in both groups: In 1 RCT: 7.7 vs 12% (P>0.05); RR (95% CI): 0.64 (0.12–3.52) In 1 cohort: 5.0 vs 8.4% (P>0.05) RR (95% CI): 0.60 (0.22–1.60) | 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 1 event occurred in both groups: In 1 RCT: 3.8 vs 12% (P>0.05); RR (95% CI): 0.32 (0.03–2.88) In 2 cohorts: 1.0 vs 1.4% (P=0.44) 0.84 vs 1.7% (P>0.05) | 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. |

ACP indicates amplatzer cardiac plug; CI, confidence interval; LAA, left atrial appendage; LT-OAC, long-term oral anticoagulation therapy; n, number (of); PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomized controlled trial; and RR, relative risk.

*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 follows¹⁰: high, further research is 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 likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and insufficient, any estimate of effect is uncertain.

therapy (hazard ratio, 1.02; 95% CI, 0.62–1.7), but did not examine harms of LAA exclusion more broadly.⁴¹ In contrast to previous reviews, we examined both percutaneous and surgical approaches to LAA exclusion. Also, we systematically examined data from trials and observational studies to assess harms, to better understand applicability to different patient populations (including those ineligible for LT-OAC therapy), and to identify patient or procedure-related factors that might modify benefits or harms of procedures. Although we, like others, have identified gaps in evidence, we think our explicit discussion about how the evidence does and does not apply to different devices and patient populations, along with a comprehensive description of harms will help inform shared decision-making discussions between patients and physicians contemplating increasingly available procedure-based therapies.

Although 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 empirical data, however, suggesting that reviews restricted to English language studies are largely concordant with reviews without language restrictions.⁴² 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 this article. Clearly, one of the biggest limitations is simply the relative paucity of methodologically rigorous studies examining the efficacy of percutaneous and surgical LAA exclusion. Trials of

percutaneous LAA interventions were limited to studies of the Watchman device in patients who were eligible for LT 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 interventions⁴³; studies of recently developed percutaneous devices (Lambre⁴⁴ and Occlutech⁴⁵); and a trial comparing Watchman with Apixaban in patients ineligible for warfarin therapy.⁴⁶

Conclusions

Overall, there is limited evidence that percutaneous LAA exclusion may be an effective alternative to LT oral anticoagulation in selected patients who are closely followed and in whom procedural success is sustained. However, only 1 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. Although surgical LAA exclusion does not seem 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 several ongoing studies that should add substantively to this body of evidence during the next several years.

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Effectiveness of Left Atrial Appendage Exclusion Procedures to Reduce the Risk of Stroke: A Systematic Review of the Evidence

North Noelck, Joel Papak, Michele Freeman, Robin Paynter, Allison Low, Makalapua Motu'apuaka, Karli Kondo and Devan Kansagara

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SUPPLEMENTAL MATERIAL

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APPENDIX C. LAA DEVICE MANUFACTURERS

APPENDIX D. QUALITY ASSESSMENT

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Supplemental Table 4. Quality assessment of trials of surgical LAA interventions

Supplemental Table 5. Quality assessment of cohort studies surgical LAA interventions

Newcastle-Ottawa criteria and code definitions used in Supplemental Table 5

REFERENCES

APPENDIX A. KEY QUESTIONS AND SCOPE PARAMETERS

Supplemental 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 | <ul style="list-style-type: none"> • 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 LAmbré™ Left Atrial Appendage Occluder <i>Device</i> (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: <ul style="list-style-type: none"> ▪ Stroke ▪ Mortality ▪ Cardiovascular morbidity ▪ Other reported health outcomes | <ul style="list-style-type: none"> ▪ Harms other than primary outcomes for KQ1 ▪ length of stay (hospital and ICU) ▪ bleeding ▪ infection ▪ need for surgical intervention | <ul style="list-style-type: none"> ▪ 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, or randomized controlled trials. For KQ2 and KQ3b, we will additionally include cohort and trial extension studies that report data on adverse events. <u>Exclude:</u> Non-systematic or narrative reviews, non-randomized trials, opinions, case studies, case series, and quasi-experimental studies. | | | |

Abbreviations: CT, computed tomography; ICU, intensive care unit; KQ, key question; LAA, left atrial appendage; MRI, magnetic resonance imaging; PICOTS, population, intervention, comparator, outcomes, timing, study design.

Supplemental 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 (i.e. Maze). | Patients undergoing surgical LAA exclusion. | Non-selected population of patients with atrial fibrillation |
| Intervention | <ul style="list-style-type: none"> • LAA occlusion/removal techniques that involve major surgery (sternotomy or thoracotomy), e.g.: <ul style="list-style-type: none"> ▪ 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 | <p>Primary outcomes:</p> <ul style="list-style-type: none"> ▪ Stroke ▪ Mortality ▪ Cardiovascular morbidity ▪ Other reported health outcomes | <ul style="list-style-type: none"> ▪ Harms other than primary outcomes for KQ1 ▪ length of stay (hospital and ICU) ▪ time on bypass ▪ bleeding ▪ ventilator days ▪ infection | <ul style="list-style-type: none"> ▪ Primary outcomes listed in KQ1 ▪ Other reported benefits and harms ▪ Rates of bleeding. | <p><u>Procedural outcome:</u> Successful closure/LAA removal, assessed by methods such as transesophageal echocardiogram; CT; MRI.</p> <p><u>Health outcomes:</u> Same as those listed for KQ1.</p> |
| Timing | Short- and long-term outcomes | | | |
| Study design | <p><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, e.g., propensity score matching</p> <p><u>Exclude:</u> Non-systematic or narrative reviews, opinions, case studies, case series, and quasi-experimental studies.</p> | | | |

Abbreviations: CHADS2, stroke risk score in AF (congestive heart failure, hypertension, age 75+, diabetes mellitus, and stroke/TIA); CT, computed tomography; ICU, intensive care unit; KQ, key question; LAA, left atrial appendage; MRI, magnetic resonance imaging; NOAC, new oral anticoagulants; PICOTS, population, intervention, comparator, outcomes, timing, study design.

APPENDIX B. 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 obliterate* 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 obliterated* OR ligation* OR ligat* OR sutur* OR exclusion* OR exclud* OR appendectomy* OR thoracoscopy* OR minithoracotomy* OR mini AND thoracotomy* OR stapling OR stapled OR stapler* OR sew OR sewn OR oversew* OR clamp* OR clip* OR atriclip OR 'gillinov cosgrove' OR ligation OR amputat* OR resect* OR removal OR remove* OR surgeon* OR surgical OR cabg OR maze OR avr OR sternotomy* 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 obliterated* or ligation* or ligat* or sutur* or exclusion* or exclud* or appendectomy* or thoracoscopy* or minithoracotomy* or mini-thoracotomy* or stapling or stapled or stapler* or sew or sewn or oversew* or clamp* or clip* or atriclip or Gillinov-Cosgrove or ligation or amputat* or resect* or removal or remove* or surgeon* or | 153735 |

| | | |
|---|---|----|
| | surgical or CABG or MAZE or AVR or sternotom* or percutaneous* or Watchman or Lariat or PLAATO or Amplatzer or Coherex or LAMBRE).mp. | |
| 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 obliterate* OR ligation* OR ligat* OR sutur* OR exclusion* OR exclude* OR appendectomy* OR thoracoscop* OR minithoracotomy* OR mini-thoracotomy* 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 C. LAA DEVICE MANUFACTURERS

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

| LAA exclusion device | Device manufacturer |
|---|--|
| <i>AMPLATZER™ Cardiac Plug, Cardiac Plug 2, Cardiac Plug 3, and Amulet™</i> | 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 |
| <i>ATRICLIP® PRO LAA Occlusion System</i> | ATRICURE, INC. ATTN.: Medical Information Officer 6217 Centre Park Drive West Chester, OH 45069 Email form: http://www.atricure.com/contact-atricure-usa |
| <i>WATCHMAN® Left Atrial Appendage Closure Device</i> | 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 |
| <i>COHEREX WAVECREST™ LAA Occluder System</i> | COHEREX MEDICAL, INC. ATTN: Medical Information Officer 3598 West 1820 South Salt Lake City, UT 84104 Online contact form: http://www.coherex.com/contact/ |
| <i>Lifetech LAmbre™ Left Atrial Appendage Occluder Device</i> | 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 |
| <i>LARIAT® Suture Delivery Device</i> | SENTRHEART, INC. ATTN: Medical Information Officer 300 Saginaw Drive Redwood City, CA 94063 Email: info@sentreheart.com |
| <i>LigaSure™</i> | COVIDIEN ATTN: Michael Tarnoff, MD FACS Corporate Chief Medical Officer Medical Devices/Medical Supplies 15 Hampshire Street Mansfield, MA 02048 |

APPENDIX D. QUALITY ASSESSMENT

Supplemental Table 3. 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 ¹ | 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 ² Holmes, 2009 ³ Reddy, 2013 ⁴ Viles-Gonzales, 2012 ⁵ | 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. |

Supplemental Table 4. 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 ⁶ 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 ⁷ 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 ⁸ 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 |

Abbreviations: ITT, intention-to-treat; KQ, key question; LAA, left atrial appendage; PI, principal investigator; QoL, quality of life.

Supplemental Table 5. 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 ⁹ | 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 ¹⁰ | 1 | 1 | 1 | 1 | 2 PSM model with 20 variables | 1 | 1 | 1 |
| Kanderian, 2008 ¹¹ | 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 ¹² | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |

Abbreviations: AF, atrial fibrillation; CVA, cerebrovascular accident; LAA, left atrial appendage; PSM, propensity score matching; TEE, transesophageal echocardiography.

Newcastle-Ottawa¹³ criteria and code definitions used in Supplemental Table 5:

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

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