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.