Ministero della Salute

Agenzia Nazionale per i Servizi Sanitari Regionali

Appendices to the Rapid HTA Report:

Epicardial clip for the left atrial appendage closure

February 2018

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APPENDIX 1 - The Agenas adaptation of the EUnetHTA Core Model ®

Health Technology Assessment (HTA) is the multidisciplinary evaluation of one or more health interventions in their context of use. Since 2006 Agenas has been involved in the E uropean HTA network EUnetHTA (http://www.eunethta.eu/contactus/all/356/all). EUnetHTA's main aim is to increase collaboration and avoid inefficiencies and duplications by using shared, standardised and agreed methods. These in a continuous development cycle. One of the methods produced and used is the HTA Core Model ® (http://meka.thl.fi/htacore/BrowseModel.aspx). The idea behind the Model is the provision of a standard method for HTA evidence synthesis, structuring and presenting in a standard format to facilitate its use by network agencies and others.

The Core Model is divided into domains which represent the various aspects of the assessment of health technologies' research. Each domain contains a series of research questions or Assessment Elements (AEs). Ver 2.0 of the EUnetHTA Core Model is divided into domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

While using the Core Model in both Joint Actions 1 and 2 with the European Commission, Agenas identified some recurring common problems with the Core Model requiring further development work if the Model were to be used in the production of Health Technology Assessment reports in Italy.

The problems are mainly AEs repetition, partial or complete overlap of AE content and likely answers, as well as lack of definition and clarity.

As a consequence Agenas undertook its own review of the Model to streamline its use and increase its relevance to everyday work of both HTA doers and HTA users. The Model basis for the review was version 2.0, medical and surgical intervention application.

The review process included a visual inspection of the 104 AEs with linked clarifications to identify any likely overlaps. The second phase consisted in grouping all AEs related to a unique concept (such as informed consent, technology and comparator(s) descriptions, regulatory information, mortality as a burden of illness measure, mortality as an outcome measure) into the likeliest domain of relevance. Agenas also attempted to link some of the text of each AE's clarification note more closely with the AE and corrected any English syntax problems. In addition a single AE containing multiple questions was divided into sub questions. All original AE identifiers were maintained to denote the origin of the AE. To make identification of the information quicker and unpack some domains, Agenas also introduced two new domains REG or Regulatory Information and HAZ or Environmental Hazard for the assessment of possible harms not directly caused to the technology's recipient.

Agenas started using its Core Model adaptation for the 2014-2015 crop of Agenas HTA reports. Although some Agenas HTA reports are adaptations to Italy of up to date reports produced elsewhere or updates of previous Agenas work. In these cases the Agenas Core Model adaptation use will be partial. Agenas plans to evaluate and develop the Model further.

APPENDIX 2 – List of selected Assessment Elements (AEs)

Assessment Element ID	Research question
Health problem and current use of technology (CUR)	
A0001a	For which health condition is the technology proposed?
A0001b	Which group of patients represents the target population for the technology?
A0001c	For what purposes is the technology used?
A0002	What is the health condition in the scope of this assessment?
A0003	What are the known risk factors for the health condition?
A0004	What is the natural course of the health condition?
A0005	What are the symptoms for the patient at different stages of the health condition?
A0006	What are the statistics of incidence, prevalence, morbidity, and mortality of the health condition?
A0011	What is the diffusion of the technology in Italy?
B0001b	What is(are) the comparator(s)?
B0005b	In what context and level of care is the comparator used?
G0009a	Who decides which people are eligible for the technology?
G0009b	On what basis is the eligibility for the technology decided?
Description of technology (TEC)	
B0001	What is this technology?
B0003	What is the phase of development of the technology?
B0004	How is the technology used?
B0005	In which setting and level of care is the technology used?
B0007	Does the technology require additional/special equipment/tools or accommodation?
B0009	What disposables and supplies are needed to use the technology?
F0001	F0001a: Is the technology new/innovative? F0001b: Is the technology an add-on, a replacement or a modification of the standard mode of care?
Regulatory aspects (REG)	
A0020	What is the marketing authorisation status of the technology?
A0021	What is the reimbursement status of the technology across the country?
Effectiveness (EFF)	
D0006	D0006a; How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥2) and unsuitable for long term anticoagulant treatment affect the progression of the target condition? D0006b: How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥2) and unsuitable for long term anticoagulant treatment affect the recurrence of the target condition?

Safety (SAF)	
C0001	What harms are associated with the use of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥2) and unsuitable for long term anticoagulant treatment?
Costs and economic evaluation (ECO)	
E0001	Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?
E0005	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?

APPENDIX 3 – Questions for the manufacturer/distributor

Agenzia Nazionale per i Servizi Sanitari Regionali

RIHTA Rete Italiana Health Technology Assessment

Agenas is carrying out a Rapid HTA report on the epicardial clip for the left atrial appendage (LAA) closure. You are receiving this request in order to integrate information and data relative to the AtriClip system (all models) to be used in our report for the Italian Ministry of Health (MoH). This will be a public document, so we ask you not to release any confidential information. Please also be aware that the aim of our HTA activities is to conduct a factual assessment of the performance of this class of devices. We are interested in the factual accuracy of the document but the interpretation of those facts is our role. Thank you for your support.

Your contribution will be acknowledged, according to your indications, in the final report that will be published, after the public consultation phase, on the MoH and Agenas websites.

Manufacturer/Distributor:_____

Name of technology: :_____

Contact Person: :_____

Questions for the manufacturer/distributor

1. Which group(s) of patients represents the target population for AtriClip system (all models)?
2. Which other devices or therapies can be considered as the main comparators[1] of AtriClip system (all models)?
3. Are there specific ICD9-CM (ICD10-CM) codes that identify the use of the AtriClip system (all models) (and comparators) in the hospital discharge database?
4. At today, how many of your AtriClip system (all models) have been used in Italy? How many around the world?
5. At today, how many Italian hospitals use your technology? (Please specify if private or public providers).
6. What is the current phase of development of the models on the market?
7. How many versions/evolutions of these models have been launched to the last version?

[1] Comparator is the standard intervention against which the intervention under assessment is compared. The comparator can be no intervention, for example best supportive care.

8. [In case of two or more versions] Could you describe the differences between the [n] generations of AtriClip system?
9. Which is the risk class of the AtriClip system? (Only applicable for medical devices)
10. Could you describe the mechanism of action and the main characteristics of the AtriClip system (all models)?
11. What is/are the indication(s) of use of the AtriClip system (all models)?
12. What are the warnings, precautions, contraindications for the use of the AtriClip system (all models)?
13. What disposables and supplies are needed to use the AtriClip system (all models) ?
14. Does the technology require specific equipment/tools? If yes, please provide descriptions and Classificazione Nazionale Dispositivi (CND) codes for all of them.
15. Are there similar devices/therapies/procedures that can be considered as "competitors" of the AtriClip system (all models)? (Please specify device names and manufacturers).
16. Do you have any report about the durability of the clip, once implanted? (Please, report full reference
17. Has the AtriClip system obtained the CE mark? If yes, When? (Please report month and year for all the AtriClip models).
18. Has the AtriClip system (any model) been approved by the FDA?
    18.a If yes, when? (Please report month and year)

    18.b If not, please report details on the FDA approval status (if any).

19. When was AtriClip system (all models) launched in Italy? In addition, which are the registration numbers on the medical devices' repertory of the Italian Ministry of Health?
20. What is the reimbursement status of the AtriClip system in Italy? (Please, provide possible DRGs for the procedure).
21. Are you aware of any difference in the reimbursement of the AtriClip system across the Italian regions? If yes, please provide specific regional reimbursement status.
22. Are you aware of any difference in the reimbursement of the AtriClip system across Europe? If yes, please provide specific national reimbursement status.
23. Does the technology require further specific regulations (eg. environmental safety) ?
24. Are there comparative clinical studies (on humans) published/ongoing aimed to compare your device versus other treatments? (if yes, please report full references)
25. Are there non-comparative clinical studies (on humans) published/ongoing aimed to report on effectiveness and safety of your device? (if yes, please report full references)
26. Is there any register for data collection and patient's follow-up? If yes, who runs it? (please specify web-link and/or key-person name and e-mail address)
27. Can you specify the ID number(s) of the ongoing trial(s)?
28. What is the list price of AtriClip system? (please, indicate the price, VAT excluded, for all the equipment needed for the implantation procedure)
29. Please fill the table below with all the relevant items for a single procedure:

Item	Number of units	Price per unit (VAT excluded)

30. What is the real cost of AtriClip system (VAT excluded)?
31. Are there economic evaluation studies published/ongoing on AtriClip system? (if yes, please report full references).
32. Which professionals decide on the use of the [technology]?
33. Which professionals (nurses, doctors, and other professionals) use the [technology]? Describe the staff involved in terms of skills and number of units.
34. Is there the need of training for the staff members?
    34.a If yes, who provides it?

    34.b How much does this training cost and who funds it?

35. Do you have any report about the learning curve of the procedure? (please report full reference).
36. How does the procedure using your device differ from the standard of care in terms of need of additional/special equipment/tool, complexity, dedicated human resources?

APPENDIX 4 – Literature search strategy

Pubmed: **61 articles** (16/06/2017)

Recent queries in pubmed	
Search,Query,Items found,Time	
#1,"Search ((""atrial appendage""[MeSH Terms]) OR atrial appendage OR (atrial function, left[MeSH Terms]) OR atrial function, left OR laa OR LAA*)",30304,10:54:39	
#2,"Search (occlu* OR clos* OR sutur* OR exclu* OR remov* OR isola* OR amputat*)",3637738,10:16:36	
#3,"Search (clip* OR atriclip OR *clip)",54171,10:18:04	
#1 AND #2 AND #3	#4,"Search (((((""atrial appendage""[MeSH Terms]) OR atrial appendage OR (atrial function, left[MeSH Terms]) OR atrial function, left OR laa OR LAA*))) AND ((occlu* OR clos* OR sutur* OR exclu* OR remov* OR isola* OR amputat*))) AND ((clip* OR atriclip OR *clip))",61,10:59:37

CRD database: **19 articles** (19/06/2017)

"MeSH DESCRIPTOR Atrial Appendage EXPLODE ALL TREES"

Clinical trial.gov: **7 trial** (19/06/2017)

"atricure AND Left Atrial Appendage"

EMBASE: **176 articles** (13/07/2017)

Embase Search Queries	
Id.	**Query; Results Date**
#1	atrial AND appendage OR (left AND atrial AND appendage) OR (left AND atrial AND function) OR laa; 32,020 13 Jul 2017
#2	occlu* OR clos* OR sutur* OR exclu* OR remov* OR isola* OR amputat*; 4,191,834 13 Jul 2017
#3	clip* OR atriclip; 40,602 13 Jul 2017
#1 AND #2 AND #3	#4. (atrial AND appendage OR (left AND atrial AND appendage) OR (left AND atrial AND function) OR laa) AND (occlu* OR clos* OR sutur* OR exclu* OR remov* OR isola* OR amputat*) AND (clip* OR atriclip); 176 13 Jul 2017

APPENDIX 5 – Included/Excluded/Not retrieved (full text screening)

REFERENCE	INCLUDED (I) /EXCLUDED (E) *with motivation*/FULL TEXT NOT RETREIVED (NR)
INCLUDED	
Salzberg SP, Plass A, Emmert MY, et al. Left atrial appendage clip occlusion: early clinical results. *The Journal of thoracic and cardiovascular surgery* 2010;139(5):1269-74. doi: 10.1016/j.jtcvs.2009.06.033 [published Online First: 2009/11/03]	I *same study
Starck CT, Steffel J, Emmert MY, et al. Epicardial left atrial appendage clip occlusion also provides the electrical isolation of the left atrial appendage. *Interactive cardiovascular and thoracic surgery* 2012;15(3):416-8. doi: 10.1093/icvts/ivs136 [published Online First: 2012/06/01]	I *same study
Emmert MY, Puippe G, Alkadhi H, et al. Left atrial appendage clip occlusion: Long term results. *Thoracic and Cardiovascular Surgeon* 2013;61 doi: 10.1055/s-0032-1332669	I*Early online publication of Emmert 2014*
Salzberg SP, Plass A, Emmert MY, et al. One year results after left atrial appendage clip occlusion. *Thoracic and Cardiovascular Surgeon* 2011;58 doi: 10.1055/s-0029-1246929	I *same study ; NR
Emmert MY, Puippe G, Baumuller S, et al. Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term results from a prospective device trial. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2014;45(1):126-31. doi: 10.1093/ejcts/ezt204 [published Online First: 2013/05/10]	I *same study Note: this is the most updated article relative to this study.
Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: Early results of a multicenter trial. *Journal of Thoracic and Cardiovascular Surgery* 2011;142(5):1002-09.e1. doi: 10.1016/j.jtcvs.2011.07.052	I
Kurfirst V, Mokracek A, Bulava A, et al. Two-staged hybrid treatment of persistent atrial fibrillation: short-term single-centre results. *Interactive cardiovascular and thoracic surgery* 2014;18(4):451-6. doi: 10.1093/icvts/ivt538 [published Online First: 2014/01/15]	I **same study
Mokracek A, Kurfirst V, Bulava A, et al. Thoracoscopic Occlusion of the Left Atrial Appendage. *Innovations (Philadelphia, Pa)* 2015;10(3):179-82. doi: 10.1097/imi.0000000000000169 [published Online First: 2015/07/17]	I **same study
Kurfirst V, Mokráček A, Čanádyová J, et al. Effectivity of left atrial appendage occlusion with AtriClip in 155 consecutive patients - Single center study. *Cor et Vasa* 2017 doi: 10.1016/j.crvasa.2017.05.015	I **same study Note: this is the most updated article relative to this study.
Kurfirst V, Mokracek A, Canadyova J, et al. Epicardial clip occlusion of the left atrial appendage during cardiac surgery provides optimal surgical results and long-term stabilitydagger. *Interactive cardiovascular and thoracic surgery* 2017 doi: 10.1093/icvts/ivx065 [published Online First: 2017/04/04]	I **same study
	I **same study

Mokracek A, Kurfirst V, Bulava A, et al. [Closure of the left atrial appendage by means of the AtriClip System]. *Vnitrni lekarstvi* 2017;63(1):31-35. [published Online First: 2017/02/23]	NR
Ad N, Massimiano PS, Shuman DJ, et al. New Approach to Exclude the Left Atrial Appendage During Minimally Invasive Cryothermic Surgical Ablation. *Innovations (Philadelphia, Pa)* 2015;10(5):323-7. doi: 10.1097/imi.0000000000000179 [published Online First: 2015/11/03]	I
Alqaqa A, Martin S, Hamdan A, et al. Concomitant Left Atrial Appendage Clipping During Minimally Invasive Mitral Valve Surgery: Technically Feasible and Safe. *Journal of atrial fibrillation* 2016;9(1):1407. doi: 10.4022/jafib.1407 [published Online First: 2016/12/03]	I
EXCLUDED	
Salzberg SP, Emmert MY, Gruenenfelder J, et al. Excellent clinical outcome 1 year after left atrial appendage clip occlusion. *European Heart Journal* 2010;31:513. doi: 10.1093/eurheartj/ehq288	E; poster abstract
Tsai YC, Phan K, Munkholm-Larsen S, et al. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. European Journal of Cardio-Thoracic Surgery, 2014:epub.	E; intervention does not include atriclip
Gómez-Echeverri CA, Ramos-Hurtado LF. Devices for percutaneous appendage occlusion in the prevention of embolism in atrial fibrillation. *Revista Colombiana de Cardiologia* 2016;23:165-69. doi: 10.1016/j.rccar.2016.10.026	E; review article
G.Suwalski et al. Early operative comparison of two epicardial left atrial appendage occluding system applied during off-pump coronary revascularization in patients with persistent atrial fibrillation. Kardiochirurgia I Torakochirurgia Polska 2016; 13(1): 10-14.	E; Comparative arm : TigerPaw System which has been withdrawn from the market.
Haensig M, Rastan AJ, Holzhey DM, et al. Surgical therapy of atrial fibrillation. Cardiology Research and Practice 2012;1(1) doi: 10.1155/2012/149503	E; review article
Masoudi FA, Calkins H, Kavinsky CJ, et al. 2015 ACC/HRS/SCAI left atrial appendage occlusion device societal overview: A professional societal overview from the American college of cardiology, heart rhythm society, and society for cardiovascular angiography and interventions. Catheterization and Cardiovascular Interventions 2015;86(5):791-807. doi: 10.1002/ccd.26170	E; review article
Lin AC, Knight BP. Left Atrial Appendage Closure. *Progress in Cardiovascular Diseases* 2015;58(2):195-201. doi: 10.1016/j.pcad.2015.07.009	E; review article
Salzberg SP, Grünenfelder J, Emmert MY. Left atrial appendage closure to prevent stroke in patients with atrial fibrillation: A call for the heart team approach. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2015;17(12):1885-86. doi: 10.1093/europace/euu402	E; commentary
Bedeir K, Holmes DR, Cox JL, et al. Left atrial appendage exclusion: An alternative to anticoagulation in nonvalvular atrial fibrillation. *Journal of Thoracic and Cardiovascular Surgery* 2017;153(5):1097-105. doi: 10.1016/j.jtcvs.2016.12.040	E; review article
6. Jazayeri MA, Vuddanda V, Parikh V, et al. Percutaneous left atrial appendage closure: current state of the art. *Current opinion in cardiology* 2017;32(1):27-38. doi: 10.1097/hco.0000000000000367 [published Online First: 2016/11/30]	E; Intervention does not include atriclip
Noheria A, Syed FF, De Simone CV, et al. Optimization of stroke prophylaxis strategies in nonvalvular AF - Drugs, devices or both? Journal of atrial fibrillation 2015;8(2):71-80.	E; review article
Patti G, Pengo V, Marcucci R, et al. The left atrial appendage: From embryology	E; review article

to prevention of thromboembolism. *European Heart Journal* 2017;38(12):877-87. doi: 10.1093/eurheartj/ehw159	
Barekatain A, Rasekh A, Massumi A. Exclusion of the left atrial appendage: To prevent stroke in cases of atrial fibrillation. *Texas Heart Institute Journal* 2012;39(4):535-37.	E; review article
Aznaurov SG, Ball SK, Ellis CR. Thoracoscopic Atriclip Closure of Left Atrial Appendage After Failed Ligation via LARIAT. *JACC Cardiovascular interventions* 2015;8(15):e265-7. doi: 10.1016/j.jcin.2015.08.025 [published Online First: 2015/12/03]	E; case report
Sakellaridis T, Argiriou M, Charitos C, et al. Left atrial appendage exclusion-where do we stand? Journal of Thoracic Disease 2014;6(SUPPL1):S70-S77. doi: 10.3978/j.issn.2072-1439.2013.10.24	E; review article
Gasbarri T, Arena G, Gilmanov D, et al. Minimally invasive hybrid sequential approach to persistent and long-standing persistent lone atrial fibrillation. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery* 2014;9(3):194. doi: 10.1097/IMI.0000000000000069	E; poster
Zoffoli G, Venturini A, Asta A, et al. Total thoracospic approach for surgical treatment of atrial fibrillation. *Giornale Italiano di Cardiologia* 2014;15(4):e45. doi: 10.1714/1501.16521	E; poster
Suwalski P, Witkowska A, Drobinski D, et al. Stand-alone totally thoracoscopic left atrial appendage exclusion using a novel clipping system in patients with high risk of stroke - initial experience and literature review. *Kardiochirurgia i torakochirurgia polska = Polish journal of cardio-thoracic surgery* 2015;12(4):298-303. doi: 10.5114/kitp.2015.56777 [published Online First: 2016/02/09]	E; technical paper
Lewis RS, Wang L, Spinelli KJ, et al. Surgical occlusion of the left atrial appendage and thromboembolic complications in patients with left ventricular assist devices. *Journal of Heart and Lung Transplantation* 2017;36(5):586-88. doi: 10.1016/j.healun.2017.01.1297	E, the relusts are not diveded between atriclip and tigerpaw.
Lewis RS, Mangum M, Wang L, et al. Impact of left atrial appendage occlusion on thromboembolic complications in patients supported by the heartmate ii left ventricular assist device. *Journal of Heart and Lung Transplantation* 2016;35(4):S129-S30.	E; poster
Caliskan IE, Sahin A, Yilmaz M, et al. Epicardial left atrial appendage occlusion provides first evidence on stroke reduction in patients with atrial fibrillation undergoing cardiac surgery. *European Heart Journal* 2016;37:890. doi: 10.1093/eurheartj/ehw433	E; poster
Lakkireddy DR, Rajasingh J, Iskandar S, et al. Does left atrial appendage exclusion using an epicardial system reduce systemic blood pressures?-The dawn of a new frontier. *Heart rhythm* 2016;13(5):S29.	E; results are not devided by device
Mohanty S, Gianni C, Gokoglan Y, et al. Does the open smooth antrum of the left atrial appendage serve as a nidus for thrombus formation in patients with atrial fibrillation and surgical appendage clip in situ? *European Heart Journal* 2016;37:890. doi: 10.1093/eurheartj/ehw433	E; poster
Smith NE, Joseph J, Morgan J, et al. Initial Experience With Minimally Invasive Surgical Exclusion of the Left Atrial Appendage With an Epicardial Clip. *Innovations (Philadelphia, Pa)* 2017;12(1):28-32. doi: 10.1097/imi.0000000000000339 [published Online First: 2017/01/28]	E; poster
Kaiser D, Pierce C, Liem LB, et al. Hybrid ablation plus left atrial appendage closure using the atriclip exclusion device successfully reduces the rate of thromboembolic events in patients with atrial fibrillation and may be a safe alternative to anticoagulant therapy. *Heart rhythm* 2017;14(5):S530.	E; poster
Alam T, Clyne CA, White CM. Pharmacologic and nonpharmacologic	E; to our knowledge there are no

thromboprophylactic strategies in atrial fibrillation. *Journal of Comparative Effectiveness Research* 2012;1(3):225-39. doi: 10.2217/cer.12.21	concluded RCT of our interest
Gdkoglan Y, Mohanty S, Gianni C, et al. Characteristics of the open smooth vestibule of the left atrial appendage and its role in thrombus formation in patients with atrial fibrillation and surgical appendage clip in situ. *Heart rhythm* 2016;13(5):S31.	E; poster

APPENDIX 6 - Data extraction of included articles

Study	Objective	Population	Intervention	Outcomes	Conlusions/limitations
Kurfirst V, Mokráček A, Čanádyová J, et al. Effectivity of left atrial appendage occlusion with AtriClip in 155 consecutive patients - Single center study. Cor et Vasa 2017 doi: 10.1016/j.crvasa.2017.05.015 **NOTE**: This study has previous publications [Kurfirst 2017 Interactive..; Mokraceck 2015; Kurfirst 2014; Mokraceck 2017 (full text not retrieved)], we extracted the most recent and checked that they analyzed similar issues.	The purpose of the study was to evaluate the efficiency (no cul de sac, no flow through the clip) and safety (no revision or bleeding due to the clip implantation) of AtriClip implantation.	155 patients undergoing cardiac surgery procedures with epicardial AtriClip exclusion of the LAA were enrolled in the study. Average CHA2DS2-VASc score was 2.7 21.9% of patients had suffered from TIA/CVA preoperatively.	AtriClip placed via a sternotomy, thoracotomy or from a thoracoscopic approach. Device: AtriClip, or the second generation – AtriClip Pro (AtriCure, West Chester, OH, USA). Period: July 2012-September 2016	Perioperative characteristics: CABG 32 (20.6%) Valve procedure 39 (25.2%) Combined procedure 6 (3.9%) Thoracoscopic AF ablation + AtriClip 71 (45.8%) AtriClip as a lone procedure 7 (4.5%) CABG, coronary artery bypass grafting. Periprocedural success rate. Variables No. = 155 Complete LAA occlusion 152 (98.0%) LAA leak 0 (0%) LAA residual stump >1 cm 3 (1.9%) LAA, left atrial appendage Postoperative characteristics Revision for bleeding 10 (6.4%) TIA 0 (0%) CVA 1 (0.6%) ICU stay (days) 4.1 3.8 Hospital stay (days) 12.1 5.2 TIA, transitory ischemic attack; CVA, cerebrovascular event	*Limitations:* It is a single center observational study without any control group. *Conclusions:* Epicardial clip exclusion of the LAA appears to be a reproducible and safe surgical method with a high success rate. Our follow-up confirmed clip stability, complete occlusion of the LAA, and absence of any AF-related thromboembolic events. These results support regular usage of AtriClip during LAA closure.

				Patients' follow-up. Variables No. = 142 TIA 4 (2.8%) CVA 1 (0.7%) Antiaggregation usage 62 (43.7%) Warfarin usage 55 (38.7%) NOAC usage 20 (14.1%) LMWH usage 5 (3.5%) TIA, transitory ischemic attack; CVA, cerebrovascular event; NOAC,	
Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: Early results of a multicenter trial. Journal of Thoracic and Cardiovascular Surgery 2011;142(5):1002-09.e1. doi: 10.1016/j.jtcvs.2011.07.052	The Exclusion of Left Atrial Appendage with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery EXCLUDE trial	71 patients Enrolled The majority of patients were white (97.2%) and in functional New York Heart Association class II or III.	Atricliip insertion in patients undergoing elective cardiac surgery via median sternotomy AtriClip (Atricure Inc, Westchester, Ohio)(35, 40, 45, and 50 mm) October 2008, and the last patient was enrolled in June 2009. The last 12-month follow-up visit was in June 2010	Surgical procedure: Total%(n) (N¼71) N¼71%(n/N) CABG 77.5%(55) Mitral valve 23.9%(17) Repair 16.9%(12) Replacement 7.0%(5) Tricuspid valve 5.6%(4) Repair 5.6%(4) Aortic valve 40.8%(29) Replacement 40.8%(29) ASD/PFO closure 0.0%(0) Surgical (ablation or cut-and sew) Maze procedure 35.2%(25) CABG,Coronary artery bypass grafting;ASD,atrial septal defect;PFO,patent foramen ovale *Efficacy end points %(n/N)* Procedural success 95.7 (67/70)	*Limitations:* This study is limited in the short-term imaging follow-up of only 3 months, although clinical follow-up extends to 12 months. This is a relatively small cohort of patients. Longer follow-up is needed to evaluate for evidence of device migration. This study was not designed to assess reduction in stroke risk. Late neurologic events developed in 2 patients, which did not appear to be related to the LAA to the best of our knowledge. A significantly larger randomized study would be required with longer-term follow-up to document any efficacy in stroke prophylaxis.

				by visual assessment 97.1 (68/70) by TEE 95.7 (67/70) 3-mo success (CT or TEE) 98.4 (60/61) (95–100 95%1-sided Bayesian credible Interval) *By method of assessment* CT evaluation by core laboratory 98.2 (55/56) TEE evaluation by site 100 (5/5) Composite end point success (primary end point) 95.1 (58/61) (90–100 95%1-sided Bayesian credible Interval) TEE,Transesophageal echocardiography;CT,computed tomography. No reported adverse events were attributable to LAA exclusion or the device (results are reported at 3 and 6 months follow up). The most common events included postoperative hemorrhage, pleural effusion,heart block, and congestive heart failure. No event was thought to be due to the AtriClip device or LAA closure.	*Conclusions:* In this small study, safe and atraumatic exclusion of the left atrial appendage can be performed during open cardiac surgery with the AtriClip device with greater than 95%success and appears to be durable in the short term by imaging. Long-term studies are needed to evaluate the efficacy in the prevention of stroke.
Emmert MY, Puippe G, Baumuller S, et al. Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term	Long-term safety and efficacy data on LAA closure using a novel epicardial LAA clip device in patients undergoing	40 patients with AF for which a concomitant ablation procedure was	Concomitant ablation procedure Device: LAA Clip	LAA occlusion was total and complete in all patients (32 of 32, 100%) No residual LAA perfusion or	This was a surgical trial designed to evaluate this new device as a concomitant therapy option in patients undergoing cardiac

results from a prospective device trial. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2014;45(1):126-31. doi: 10.1093/ejcts/ezt204 [published Online First: 2013/05/10] **NOTE:** This study has previous publications [Emmert 2013; Starck 2012; Salzberg 2010 Journal of thoracic…; salzberg 2011 (full text not retrieved)], we extracted the most recent and checked that they analyzed similar issues.	cardiac surgery The trial is registered at www.ClinicalTrials.gov, reference: NCT00567515.	planned mean CHA2DS2 -VASC Score of the entire study cohort (n= 40) was 3.7 ± 1.7 points	System (Atriclip, Atricure, Dayton, OH, USA) Date: September 2007 - July 2009	LAA stump > 1cm at 3 years follow up. Intracardial thrombi were not seen, and none of the LAAs were reperfused. Only one transient ischaemic attack (TIA) occurred in one patient 2 years after surgery (78-year old patient, CHA2DS-VASC = 4) in the setting of documented sinus rhythm with only aspirin and discontinued statins. On CT and TEE, the LAA was occluded and no intracavitary thrombi were seen. *Adverse events:* Number of patients (n= 36) Overall mortality 4 (10.8%) Device-related mortality 0 (0%) Stroke 0 (0%) Transient ischaemic attack 1 (2.7%) Myocardial infarction 1 (2.7%) Heart failure 1 (2.7%) Arrhythmia 1 (2.7%) Endocarditis 1 (2.7%) Renal failure 1 (2.7%) Pulmonary failure 0 (0%) Liver failure 1 (2.7%) Pneumonia 2 (5.2%) Malignancy 1 (2.7%)	surgery. The real potential for impact comes in the setting of the treatment for lone AF even in a stroke-prevention scenario, where stand-alone LAA therapies might effectively impact medicine. Conclusions: This is thefirst prospective trial in which concomitant epicardial LAA occlusion using this novel epicardial LAA clip device is 100% effective, safe and durable in the long term. Closure of the LAA by epicardial clipping is applicable to all-comers regardless of LAA morphology. Minimal access epicardial LAA clip closure may become an interesting therapeutic option for patients in AF who are not amenable to anticoagulation and/or catheter closure; *Limitations*: This was a surgical trial designed to evaluate this new device as a concomitant therapy option in patients undergoing cardiac surgery. The real potential for impact comes in the setting of the treatment for lone AF

				At 3 years, 22 patients were in sinus rhythm (22 of 32, 68.8%) and of the 10 in AF (10 of 32, 31.2%), only 3 (3 of 10, 30.0%) were still being anticoagulated with warfarin. On CT, LAA clips were found to be stable, showing no secondary dislocation. .	even in a stroke-prevention scenario. Further data are necessary to establish LAA occlusion as a true and viable therapy for stroke prevention.
Alqaqa A, Martin S, Hamdan A, et al. Concomitant Left Atrial Appendage Clipping During Minimally Invasive Mitral Valve Surgery: Technically Feasible and Safe. Journal of atrial fibrillation 2016;9(1):1407. doi: 10.4022/jafib.1407 [published Online First: 2016/12/03]	the study used only preexisting post-operative records/ case series We assessed the safety and efficacy of a new surgical approach to apply the AtriClip PRO and exclude the LAA through right minithoracotomy and transverse sinus.	Total of 22 patients(50% males) were included in the study median age was 66.0 years All consecutive patients who had no previous history of cardiac surgery and had minimally invasive mitral valve surgery with concomitant LAA exclusion using The	minimally invasive mitral valve surgery with concomitant LAA clipping *Period:* December 2012 and February 2014	Eight(36%) had mitral valve replacement and the rest had mitral repair surgery. All patients had concomitant LAA clipping as recommended by the ACC guidelines.All patients were on-pump during the surgery. All patients had minimally invasive mitral valve surgery through right minithoracotomy incision. All patients had successful clipping of the LAA from the first time and no repositioning was needed. Five(23%) patients needed blood product transfusion during the surgery.	*Limits:* This is a small retrospective study, which should be replicated using a prospective design of a larger number. It is not powered to evaluate stroke prevention and no outpatient follow up was done. There was also no subsequent follow-up of the success of the procedure by either TEE or CT post-operatively. *Conclusions:* During minimally invasive mitral valve surgery, Concomitant exclusion of the left atrial appendage using AtriClip® can be performed rapidly and safely.

		AtriClip® LAA Exclusion System (Cincinnati, Ohio, AtriCure®) were included.		Two patients had re-operation to evacuate chest wall hematoma. No clip related bleeding was observed and no perioperative mortality was recorded	
Ad N, Massimiano PS, Shuman DJ, et al. New Approach to Exclude the Left Atrial Appendage During Minimally Invasive Cryothermic Surgical Ablation. Innovations (Philadelphia, Pa) 2015;10(5):323-7. doi: 10.1097/imi.0000000000000179 [published Online First: 2015/11/03]	We assessed the safety and efficacy of a new surgical approach to apply the AtriClip PRO and exclude the LAA through right minithoracotomy and transverse sinus.	24 patients mean EuroSCORE II was 1.4% The mean (SD) age of the patients was 64.5 (8.6) years, and 88% were male.	patients who underwent surgical ablation for AF through a right minithoracotomy using a fibrillatory arrest technique and the transverse sinus using the AtriClip PRO Period: November 2012 and May 2014	Intraoperative transesophageal echocardiography was used to exclude LAA thrombi at baseline and evaluate LAA perfusion and residual neck postoperatively./ Elective status 24 (100) Stand-alone procedure 15 (63) Mitral valve repair 9 (37) no strokes or TIAs, no acute renal failure, no pneumonia, no operative deaths (<30 days), and only two readmissions within 30 days (8%), which were unrelated to LAA closure. After application of the AtriClip PRO device, there was no remaining LAA neck in 71% of the patients, and in only three patients (13%) was the size of the remaining neck greater than 1 mm but not greater than 4 mm.	Intraoperative transesophageal echocardiography was used to exclude LAA thrombi at baseline and evaluate LAA perfusion and residual neck postoperatively./ This study demonstrated that application of the AtriClip PRO through a right minithoracotomy and the transverse sinus is feasible. This approach ensures good control of the LAA. In none of the cases was a residual base of more than 10 mm captured, and the device was stable over time. Indeed, the only contraindications for this specific approach are significant epicardial adhesions, poor visualization, and LAA thrombi.

			During the hospital stay, 33% of the patients experienced recurrent AF, but by discharge, almost all patients were in sinus rhythm. The median length of stay was 5.5 days (range, 4Y7days), and the majority of the patients (79%) were able to be discharged home. Mean follow-up of 12.3 months, there were no deaths, strokes/TIAs, major bleeding events, or new pacemaker implantations. Follow-up catheter ablation was performed in one patient, and cardioversion in two patients; in all TEE revealed stable closure and no remaining LAA neck

APPENDIX 7 - Quality Assessment Tool for Case Series Studies

Criteria (§)	Ailwadi 2011	Kurfirst 2017	Emmert 2014	Alqaqa 2016	AD 2015
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	No	No	No	Yes	Yes
4. Were the subjects comparable?	No	No	Yes	Yes	Yes
5. Was the intervention clearly described?	Yes	Yes	yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	yes	Yes	Yes
7. Was the length of follow-up adequate?	CD	CD	CD	CD	Yes
8. Were the statistical methods well-described?	Yes	NO	Yes	Yes	No
9. Were the results well-described?	Yes	Yes	Yes	Yes	Yes
Rating Quality Rating (Good, Fair, or Poor)	Fair	Fair	Fair	Good	Fair
Notes on COI/funding	Funding provided by Atricure Inc, West Chester, Ohio. Disclosures: Authors have nothing to disclose with regard to commercial support	"No funding was provided for this work./None of the authors have a conflict of interest regarding this paper."	This research was funded by an unrestricted research grant from Atricure. Conflict of interest: Sacha P. Salzberg is a consultant for Atricure and has received speaker fees.	Disclosure none/ funding not reported	Disclosures: Niv Ad, MD, is a consultant for AtriCure, Inc, West Chester, OH USA, and is coowner of Left Atrial Appendage Occlusion, LLC, North Bethesda, MD USA. Paul S. Massimiano, MD, Deborah J. Shuman, BS, Graciela Pritchard, BS, and Sari D. Holmes, PhD, declare no conflicts of interest.

(§) Quality Assessment Tool for Case Series Studies developed by National Lung Heart Blood Institute (NLHBI https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series)

*CD, cannot determine; NA, not applicable; NR, not reported