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Thoracoscopic Left Atrial Appendage Clipping: a multicenter cohort analysis

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Short Title: Left atrial appendage clipping

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Abstract

Objectives: To document the closure rate, safety and stroke rate after thoracoscopic left atrial appendage (LAA) clipping.

Background: The LAA is the main source of stroke in patients with AF and thoracoscopic clipping may provide a durable and safe closure technique.

Methods: We studied consecutive patients undergoing clipping as part of a thoracoscopic maze procedure in 4 referral centers (Netherlands and USA; 2012-2016). Completeness of LAA closure was assessed by either computed tomography (n=100) or transesophageal echocardiography (n=122). The primary outcome was complete LAA closure (absence of residual LAA flow and pouch <10 mm). Secondary outcomes were 30-day complications; the composite of ischemic stroke, hemorrhagic stroke or transient ischemic attack (TIA); and all-cause mortality.

Results: 222 Patients were included, with a mean age of 66±9 years and 68.5% male. The mean CHA_2DS_2-VASc score was 2.3±1.0. Complete LAA closure was achieved in 95.0% of patients. There were no intraoperative or clip-related complications and the overall 30-day freedom from any complication was 96.4%. Freedom from cerebrovascular events after surgery was 99.1% after median follow-up of 20 months (interquartile range 14-25; 369 patient-years of follow-up) and overall survival was 98.6%. The observed rate of cerebrovascular events after LAA clipping was low (0.5 per 100-patient-years).

Conclusions: LAA clipping during thoracoscopic ablation is a feasible and safe technique for closure of the LAA in patients with AF. The lower than expected rate of cerebrovascular events after deployment was likely multifactorial, including not only LAA closure, but also the effect of oral anticoagulation and rhythm control.

Keywords: atrial fibrillation; left atrial appendage; left atrial appendage closure; thoracoscopic; stroke; outcomes

Condensed Abstract (100 words)

Our objective was to provide cardiologists, surgeons and the multidisciplinary atrial fibrillation (AF) team with adequate information about thoracoscopic left atrial appendage (LAA) clipping in order to make appropriate decisions on stroke prevention. We studied 222 consecutive patients undergoing clipping as part of a thoracoscopic ablation procedure (TT-maze) in 4 referral centers. We observed high LAA closure rates (95.0%) without clip related complications, high overall 30-day freedom from any complication (96.4%) and a low stroke rate (0.5 per 100-patient-years). This suggest that thoracoscopic LAA clipping is a feasible and safe technique for closure of the LAA in patients with AF.

Abbreviations

AF: atrial fibrillation

CT: computed tomography

LA: Left atrium/left atrial

LAA: left atrial appendage

NOAC: non-vitamin-K-dependent oral anticoagulants

TEE: transesophageal echocardiography

TIA: transient ischemic attack

TT-Maze: totally thoracoscopic maze

Introduction

Atrial fibrillation (AF) is a common condition with a prevalence around 3% in adults which is expected to rapidly increase in the next few decades.[1–3] AF is an independent risk factor for stroke and rates are three to five-fold higher compared to the general population.[1–3] The left atrial appendage (LAA) is thought to be the main source of stroke and emboli in AF patients and hence a variety of techniques have been developed to occlude or close this structure. Various surgical techniques have been described, such as suture ligation, stapling and surgical excision. However, these techniques often result in incomplete occlusion or residual pouches of the LAA that may contribute to thrombus formation and ongoing risk of stroke. [4,5,6]

A few small studies have shown promising results of LAA closure by using a clip during either open-heart surgery [7] or thoracoscopic surgery. [8,9] In some centers, LAA clipping is routinely performed in combination with thoracoscopic AF ablation as part of the totally thoracoscopic maze procedure (TT-maze).[10,11] However, we currently lack systematic data about the efficacy of this procedure in terms of successful closure rates, or the safety of this approach. In this multicenter study, we evaluated both procedural success and complications of thoracoscopic clipping in consecutive patients undergoing either TT-maze or hybrid endocardial and epicardial ablation. The purpose of the study was to provide cardiologists, surgeons and the multidisciplinary AF care team with adequate information about this new technique. We hypothesize that thoracoscopic clipping would be an effective and durable approach for closure of the LAA.

Methods

This study has a prospective observational cohort design and was approved by the local ethical committee at the St. Antonius Hospital, Nieuwegein, the Catharina Hospital, Eindhoven, St. Helena Hospital, St. Helena and Sutter Medical Center, Sacramento (reference number: W15.077).

Patient selection

Consecutive patients who underwent thoracoscopic LAA clipping between February 2012 and March 2016 in 4 major referral centers in the Netherlands and USA were included. All patients were suffering from symptomatic, drug-refractory AF and were discussed by the multidisciplinary AF care team (the AF Heart Team) consisting of dedicated cardiac surgeons and electrophysiologists.

Study endpoints

The primary outcome for this study was complete LAA closure defined as absence of residual flow in the LAA after clipping, combined with a residual LAA pouch of less than 10 mm revealed by either computed tomography (CT) or transesophageal echocardiography (TEE). CT and TEE were performed in all patients according to local operating procedures, approximately 6 months after surgery (some patients earlier or later depending on clinical need). Complete LAA closure also implied successful introduction of the clip into the chest cavity, positioning and release of the clip and removal of the steering tool.

The secondary outcomes were: (1) 30-day freedom from complications; (2) freedom from the combined clinical endpoint of ischemic stroke, hemorrhagic stroke or transient ischemic attack (TIA); and (3) all-cause mortality. The following operative complications were classified as clip related: signs of cardiac ischemia and bleeding related to the introduction of the clip into the chest cavity, clip positioning and release, and conversion to (mini)thoracotomy or sternotomy.

Data collection

All patient data were prospectively gathered as each patient went through their surgery and hospital admission; we used medical and operative charts and records, including data on complications (surgical, bleeding and others) and medication usage (including prescription charts for anticoagulation and antiarrhythmic drug therapy).

Complications after surgery were extracted from these records using a standardized list of potential complications.[11] When patients were referred from other centers, these centers were contacted to assess if any complications from the standardized list occurred between discharge from our hospital and 30 days postoperatively. Survival data were obtained from hospital and national registry data. Stroke data and medication history at latest follow-up were obtained by telephone interviews with all individual patients. Patients were interviewed according to the Questionnaire for Verifying Stroke-Free Status.[12] Additionally we contacted the neurologists at local hospitals to check for confirmation of any diagnosis of a cerebrovascular event. Neurologic events in this series were confirmed by MRI-scan according to local clinical protocols.

Device

Details of the clip (AtriClip™, AtriCure, Inc. Mason, Ohio, USA) have been described previously.[13] In brief, the clip is composed of two parallel titanium crossbars covered with a woven polyester sheath. Nitinol springs at each end provides, dynamic, parallel pressure on the tissue causing tissue necrosis. The clip can be easily repositioned prior to being deployed if required.

Surgical Procedure

An extensive and video-guided description of the TT-maze has been published previously.[10] In brief, the TT-maze consists of an epicardial pulmonary vein isolation with creation of a box through bilateral video-assisted thoracoscopic surgery using the AtriCure Isolator Synergy ablation clamp (AtriCure Inc) and the Cool rail pen (AtriCure Inc). The box is connected with the base of the LAA and furthermore with the left fibrous trigone. The endpoint of the ablation is sinus rhythm and bidirectional block confirmation of the pulmonary veins and box. Clipping of the LAA is performed in all patients immediately after ablation as a routine part of the TT-maze procedure. First, the length of the base of the LAA is measured with a sizer. The appropriate clip is then introduced and directed parallel to the base of the LAA. The clip is opened and manipulated over the LAA assisted by a blunt suction device. The clip is then closed after direct thoracoscopic confirmation of correct positioning fully against the LAA base. The clip is opened and repositioned in case of a suboptimal position and/or a residual pouch revealed by TEE or by direct thoracoscopic view. After conformation of an appropriate position of the clip, release of the clip from the steering tool is delayed for 30 seconds to rule out electrocardiographic ST-segment changes and wall motion disturbances on TEE.

Postoperative care and follow-up

Oral anticoagulation was initiated on the first postoperative day with either non-vitamin-K-dependent oral anticoagulants (NOAC), or vitamin-K-antagonists and low-molecular-weight heparin injections until an International Normalized Ratio level of ≥ 2 was achieved. The next day, anti-arrhythmic drugs were restarted depending on heart rate and rhythm. After discharge management of oral anticoagulation and anti-arrhythmic drugs were left to the discretion of the referring cardiologist.

Computed tomography-scan

CT-scans were performed according to the local protocol. A dual-source CT scanner system, 256-or 356-slice CT scanner with non-ionic contrast medium was used. Three-dimensional reconstructions were created. The base of the LAA was defined as the line that starts 3 mm peripheral from the circumflex vein or artery on the coronal sections. From this point, an imaginary line is directed towards the sharp angle representing the border between the LAA and the epicardium. The distance between the mid part of this imaginary line and the clip, was systematically measured and defined as residual pouch length (Figure 1). All CT-scans were adjudicated by an independent radiologist (HWVE).

Transesophageal echocardiography

TEE imaging of the LAA was systematically performed by an independent cardiologist according to the local protocol. Starting with the high mid-oesophageal view at 0 degrees, followed by views at 45, 60, 90 and 105 degrees from the top of the mitral valve annulus, with further views as necessary for optimal imaging, including a 3D and en-face view of the LAA orifice.

Statistics

Descriptive statistics were used to report patients' characteristics. Continuous variables were reported as mean ± standard deviation. Percentages were used to report categorical variables. The estimated event-free survival probabilities were calculated using Kaplan–Meier analysis. Data were analyzed using SPSS version 22 and Stata version 14.2.

Results

Patient characteristics

Patient characteristics are outlined in Table 1. In total 222 patients were included in our analysis: St. Antonius Hospital (n=67, 2 operating surgeons), the Catharina Hospital (n=33, 1 operating surgeon), St. Helena Hospital (n=66, 1 operating surgeon) and Sutter Medical Center (n=56, 1 operating surgeon). 70.3% (n=156) underwent thoracoscopic LAA clipping as part of a standalone TT-maze and 29.7% (n=66) as part of thoracoscopic procedure followed by a planned second stage catheter ablation (hybrid maze procedure including epicardial then endocardial ablation after 6 weeks). The mean age of the patients was 66±9 years and 68.5% (n=152) were male. Paroxysmal AF was present in 17.3% (n=38), persistent AF in 28.6% (n=63), longstanding persistent in 52.7% (n=116) and atypical atrial flutter in 1.4% (n=3). Mean arrhythmia duration prior to surgery was 8±8 years. Previous catheter ablation was performed in 45.5% (n=101) and a documented prior history of ischemic stroke was reported in 9.9% (n=22). Mild or moderate mitral regurgitation was present in 36.6% (n=81) and left ventricular ejection fraction < 50% in 23.5% (n=52). The mean CHA_2DS_2-VASc score was 2.3±1.5, the mean $CHADS_2$ score was 1.3±1.1 and the median hospital stay was 4 days (interquartile range 3-6 days). No patients were lost to follow-up.

Primary outcome

Complete closure was achieved in 95.0% (211/222) as assessed with CT-scan or TEE after a median period of 6 months after the LAA clipping procedure (interquartile range 3-8 months).
In those with a follow-up CT-scan, complete closure of the LAA was obtained in 93.0% (93/100). Absence of residual flow or contrast peripheral to the clip was confirmed in all patients. A residual pouch of more than 10 mm was present in 7 patients and the overall mean size of the residual pouch was 14±3 mm [range: 11-19 mm]. In 2 patients a residual pouch could not be measured because of poor quality of the CT-scan. In 1 patient the LAA was clipped partially and repositioning was not possible. Therefore a second clip was introduced and positioned over the first clip into an adequate position at the base of the LAA.
In those patients with a follow-up TEE, complete closure of the LAA was obtained in 96.7% (118/122). Absence of residual flow peripheral to the clip was confirmed in all patients. A residual pouch of more

than 10 mm was observed in 4 patients and the overall mean size of the pouch was 16±5 mm [range: 10-21 mm].

Secondary outcomes

Surgical complications: No intraoperative complications occurred and there were no clip-related complications seen. No patients died during 30-day follow-up. Overall freedom from any 30-day complication was 96.4%. All complications that occurred are listed in Tables 2 and 3. The 30-day major complication rate was 0.9% (n=2) and minor complication rate was 4.5% (n=10).

Cerebrovascular events: The freedom from the combined endpoint of ischemic stroke, hemorrhagic stroke or TIA was 99.1% over 369 patient-years of follow-up (median length of follow-up 20 months; interquartile range 14-25 months); Figure 2A. The observed cerebrovascular event rate was low at 0.5 per 100 patient-years, with 57% of patients not on oral anticoagulation therapy at latest follow-up. In detail, one patient had an ischemic stroke confirmed on MRI 24 months after TT-maze (CHA_2DS_2-VASc score 3, on oral anticoagulation therapy and in sinus rhythm at the time), and another patient had a TIA 30 months after TT-maze (CHA_2DS_2-VASc score 1 and off oral anticoagulation therapy).

All-cause mortality: 3 patients died during median follow-up of 14 months (interquartile range 9-22 months), all of non-cardiac causes; Figure 2B.

Discussion

Stroke prevention is one of the cornerstones of AF treatment. The LAA is the main source of thrombo-embolism in AF patients, due to blood stasis and coagulation, fulfilling the main conditions of Virchow's triad.[14–18] Oral anticoagulation is the mainstay of stroke prevention in AF, but other strategies are now available and can complement interventional approaches to rhythm control. This is the first observational multicenter cohort study evaluating procedural success and complications of thoracoscopic LAA clipping. We observed high LAA closure rates (95.0%), the absence of clip related complications, and a low rate of cerebrovascular events at 0.5 per 100 patient years. To put into context for a CHA_2DS_2-VASc score of 2 in large population databases, the event rate in non-anticoagulated patients is approximately 2.0 per 100 patient years, 1.2 per 100 patient years for those with a similar rate of anticoagulation as observed in our cohort, and 0.7 per 100 patient years for those fully anticoagulated (Table 4). [19–22]

Surgical LAA closure

Various surgical techniques of LAA closure have been described, such as suture ligation, stapling and surgical excision. These techniques are associated with incomplete LAA closure rates of 40-60%.[5,6] Depending on the morphology after incomplete closure, these remnant LAA may present an ongoing risk of thrombus formation and embolisation. [23,24] Our data on LAA clipping have shown a complete closure rate of 95.0% based on a large cohort of consecutive patients in 4 different referral centers, consistent with published data from a smaller single center cohort.[25] Put together, these data suggest that thoracoscopic LAA clipping has overcome the problems of reproducibility seen in other surgical techniques. Interestingly, long-term follow-up data from LAA clipping in patients undergoing sternotomy showed stable closure rates of 100% after 5 years.[7] We speculate that the closure rate in our patient group will also remain stable, since the clips used in our study were similar.

The primary outcome in this study, complete closure rate, depends on the applied definition of complete closure. Earlier papers from LAA clipping randomly used a cut-off value of 10 mm for the definition of complete closure without a clear anatomic description of how the LAA pouch was assessed. [9,26,27] We therefore decided to accept the fairly liberal cut-off point of 10 mm as the second condition for the definition of complete closure. Absence of any contrast peripherally from the clip in all patients in this series seems to be a beneficial difference compared to significant (≥ 3-5 mm) or not-significant (≤ 3-5 mm) peridevice leaks described for the percutaneous closure devices.

Percutaneous transcatheter LAA occlusion

Percutaneous transcatheter LAA occlusion, including the WATCHMAN device (Boston Scientific Inc, Marlborough, USA) the Amplatzer (St. Jude Medical, Minneapolis, USA) and the Lariat LAA exclusion system (SentreHeart Inc, Redwood City, California, USA) are associated with closure rates varying from 91-98.5%.[28–34] However, the definition of success included peri-device leakage of ≤ 3-5 mm in diameter for WATCHMAN and Amplatzer (8-13% of the patients [30,31,33]) and 2 mm in diameter for Lariat (n=13, 1.8%).[34] Although these remnant orifices are small, the clinical relevance is unknown and might possibly explain why the overall stroke rate after 5 years is non-inferior to warfarin therapy only. No comparison studies between percutaneous LAA closure and NOAC therapy are as yet available. Another potential challenge of percutaneous devices is the risk of device related thrombus.[33] The event rate for the composite endpoint of stroke and systemic embolism was 1.0% (mean $CHADS_2$ score 2.4) and 1.6% (mean $CHADS_2$ score 2.2) per year for Lariat (SentreHeart Inc) and WATCHMAN (Boston Scientific Inc) respectively. [35,36]

Although the 30-day complication rate in our study (5.4%) was not directly clip related, it is in line with the device related complication rates described after percutaneous devices (8.7%) and Lariat implantation (5.3%).[29,36,37] The recently published EWOLUTION trial showed a 30-day device and procedure-related complication rate of 3.6%, indicating a learning-curve effect for percutaneous devices,[33] which is also likely to apply to thoracoscopic LAA clipping. In contrast to the WATCHMAN, Amplatzer and Lariat system which are all restricted to ostial size, LAA size or morphology, thoracoscopic LAA clipping is performed under direct view irrespective of LAA size, anatomy or atrial dilatation.

Current guidelines

Current guidelines suggest continuation of anticoagulation therapy in patients at risk for stroke after closure or exclusion of the LAA, even after successful ablation. [1] This can be explained by several reasons: that successful ablation does not guarantee maintenance of sinus rhythm, (recurrent) AF is often asymptomatic, and that the LAA is not the only source of stroke. Adequately powered randomized controlled trials investigating the effect of LAA closure on stroke reduction are not available, [38] and we await results from the Left Atrial Appendage Occlusion Study III (LAAOS III) comparing cardiac surgery with and without LAA closure in AF patients. However, many clinicians tend to stop anticoagulation therapy after successful ablation and/or closure or exclusion of the LAA despite elevated stroke risk. This approach can only be condoned after appropriate trials have demonstrated safety, in particular the comparison between LAA closure/exclusion and NOAC therapy. Even with anticoagulation, there is a residual risk of stroke in patients with AF that should be considered and discussed with patients.[1,39]

Limitations

Although this is the first multicenter study reporting on the efficacy and safety of LAA clipping, it is an observational study with potential risk of selection bias. As described in our methods section, patients eligible for TT-maze were first discussed and referred by the multidisciplinary AF care team. They are not representative of an ''average'' AF population since 46% had prior catheter ablation. Furthermore, the low event rate of cerebrovascular events was likely multifactorial including not only the LAA clip, but also the effect of oral anticoagulation and rhythm control. Although we report on the number of patients taking anticoagulation at the end of follow-up, periods on and off anticoagulation, and the time in therapeutic range for those on vitamin-K-antagonists, was not collected. The follow-up time was relatively short and patient numbers limited, and therefore no definite conclusions regarding stroke reduction can be made. Although we provide a detailed overview of 30-day complications, long-term events (aside from cerebrovascular events and mortality) were not studied.

Conclusion

Thoracoscopic LAA clipping is a feasible and safe LAA closure approach with lower than expected rates of stroke after deployment. Randomized trials are required to directly compare this approach with and without cessation of NOAC therapy to assess the place of thoracoscopic LAA clipping for stroke prevention in AF.

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Table 1. Patient characteristics

Results	**Total** **N=222**
Age, years	66±9
Male gender	152 (68.5%)
Mean duration of AF, years	8±8
Type of AF	
Paroxysmal AF	38 (17.3%)
Persistent AF	63 (28.6%)
Longstanding persistent AF	116 (52.7%)
Atrial flutter	3 (1.4%)
Left ventricular ejection fraction	
> 50%	169 (76.5%)
< 50%	52 (23.5%)
Mitral regurgitation	
None	65 (29.4%)
Trace	74 (33.5%)
Mild	61 (27.6%)
Moderate	20 (9.0%)
Moderately severe	1 (0.5%)
CHA_2DS_2-VASc score	2.3±1
$CHADS_2$ score	1.2±1
Prior catheter ablation	100 (45.5%)
Of which > 1 procedure	63 (28.8%)
History of ischemic stroke	22 (9.9%)

Table 2. Intraoperative complications

Complication	N (%)
Mortality	0 (0.0)
Stroke	0 (0.0)
Sternotomy for bleeding	0 (0.0)
Mini-sternotomy for bleeding	0 (0.0)
Mini-thoracotomy for bleeding	0 (0.0)
Bleeding with discontinuation of procedure	0 (0.0)
Total number of intraoperative complications, n (%)	**0 (0.0)**

Standardized reporting of intraoperative complications is presented according to published criteria.[40]

Table 3. Postoperative complications

Major	**N (%)**
Clip related complications	0 (0.0)
Death	0 (0.0)
Reinterventions*:	
Hemothorax	0 (0.0)
Pericardial effusion/tamponade	0 (0.0)
Empyema	1 (0.5)
Re-intubation to hemodynamic instability	1 (0.5)
Re-intubation without hemodynamic instability	0 (0.0)
Venous lung Infarction	0 (0.0)
Lung emboli	0 (0.0)
Permanent phrenic nerve paralysis	0 (0.0)
Stroke	0 (0.0)
Transient Ischemic Attack	0 (0.0)
Atrium-esophagus fistula	0 (0.0)
Myocardial infarction	0 (0.0)
Total number of patients with ≥1 major complication	***2 (0.9)***
Total number of major complications	***2 (0.9)***
Minor	
Pericardial fluid necessitating pericardiocentesis	0 (0.0)
Permanent pacemaker implantation	2 (0.9)
Thoracostomy drain for:	
Pneumothorax	0 (0.0)

Pleural effusion	3 (1.4)
Hematothorax	1 (0.5)
Infections:	
Airway infection	1 (0.5)
Urinary tract infection	2 (0.9)
Superficial wound infection	0 (0.0)
Delirium	1 (0.5)
Gastrointestinal bleeding	0 (0.0)
Total number of patients with ≥1 minor complication	***8 (3.6)***
Total number of minor complications	***10 (4.5)***
Overall freedom from 30-day complications	***96.4%***

Standardized reporting of postoperative complications is presented according to published criteria.[40]

[*]Including thoracotomy, sternotomy or Video-Assisted-Thoracoscopic Surgery.

Table 4: Indirect comparison of events with a CHA_2DS_2-VASc score of 2

Study	Oral anticoagulation use (%)	CHA_2DS_2-VASc	Outcome	Person-years of follow-up	Rate per 100 person-years	Description study
Nielsen[21]	0%	2	Ischemic stroke and systemic embolism	114,034	2.0	Danish nationwide observational study of hospitalized AF patients not receiving anticoagulation
Van de Ham[22]	0%	2	Ischemic stroke	21,500	1.9	UK observational general practice electronic health record database of AF patients not receiving anticoagulation
Allen et al[20]	43%	2	Ischemic stroke	37,750	1.2	UK observational general practice electronic health record database of AF patients with and without anticoagulation
THIS STUDY	43%	Mean 2.3	Ischemic stroke and transient ischemic attack	369	0.5	US and Netherlands observational study of patients undergoing LAA clipping during thoracoscopic AF ablation
Yao et al[19]	100%	2 to 3	Ischemic stroke and systemic embolism	26,250	0.7	US commercial insurance database of AF patients initiated on anticoagulation