Left atrial appendage clip occlusion: Early clinical results

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Objective: Atrial fibrillation puts patients at significant risk for embolic stroke originating from the left atrial appendage. Few means are available for safe, effective, and durable left atrial appendage occlusion. A new clip device was evaluated with regard to safety and effectiveness for epicardial left atrial appendage occlusion.

Methods: Patients with atrial fibrillation undergoing elective cardiac surgery through a median sternotomy were enrolled for concomitant epicardial clip placement. Early postoperative and 3-month follow-up computed tomography studies were used to assess clip stability and left atrial appendage perfusion.

Results: From September 2007 to December 2008, 34 patients underwent successful clip placement. No device-related complications occurred. Operative mortality was 8.8% and not study or device related. Deployment was rapid, and left atrial appendage occlusion was confirmed by intraoperative transesophageal echocardiography in all patients. In addition to excellent clinical outcomes (no stroke/transient ischemic attack), serial computed tomography demonstrated stable clip location and appendage perfusion at 3 months in all patients.

Conclusion: Safe, effective, and durable left atrial appendage occlusion can easily be achieved with this new clip. Further trials are necessary to evaluate the role of the left atrial appendage occlusion in stroke prevention. (J Thorac Cardiovasc Surg 2010;139:1269-74)

Atrial fibrillation (AF) is a common cardiac arrhythmia affecting many patients and is associated with increased mortality independently of other cardiac conditions and risk factors.^{1,2} The prevalence of AF and AF-related hospital admissions is constantly increasing.³ Thromboembolic origin in AF is often linked to the left atrial appendage (LAA).⁴ The gold standard for medical management of patients with AF remains oral anticoagulation with warfarin.^{5,6} Percutaneous device occlusion of the LAA remains challenging.⁷ The recent Protect AF trial has nevertheless showed noninferiority of LAA transcatheter device closure to oral anticoagulation in patients with AF.⁸ Surgical LAA occlusion is recommended in the latest AHA/ACC/ESC guidelines for surgical mitral valve disease⁶ but also lacks the desired effectiveness of an ideal therapy.⁹ With the advent of minimally invasive techniques to address AF, strategies to obtain LAA occlusion remain challenging and are

often traumatic to the LAA, even in expert hands.⁷ In addition, few data are available to determine the role of LAA occlusion in stroke prevention.¹⁰ This first human trial was designed to evaluate safety and effectiveness of a new clip¹¹ used for LAA occlusion in patients with AF undergoing cardiac surgery.

MATERIALS AND METHODS

From September 2007 to December 2008, patients were enrolled in this trial at the University Hospital Zurich. Primary inclusion criterion was elective cardiac surgery in adult patients with AF for whom an ablation procedure was planned. Patients undergoing a reoperation, with a known thrombus in the LAA, from the intensive care unit, with a history of pericarditis, who had a recent myocardial infarction (<90 days), and with a known allergy to the devices component were not allowed to participate (exclusion criteria). Intraoperative transesophageal echocardiography (TEE) was used to rule out LAA thrombus at baseline (exclusion criteria) and assess LAA perfusion at the end of the procedure. Patients returned to the University Hospital Zurich for serial follow-up after 3 months and yearly thereafter up to 3 years after surgery. Clinical follow-up included clinical status, laboratory examination, electrocardiogram, chest radiograph and computed tomography (CT) workup.

Research was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2000.¹² All patients gave informed written consent. The trial is registered at www.ClinicalTrials.gov (Reference: NCT00567515).

Device Description

The LAA clip system consists of a self-closing, sterile, implantable clip with a reusable deployment tool (Figure 1, A). The device is applied epicardially (Figure 1, B) and has been previously described.^{11,13} In addition, a disposable selection guide is used to choose the appropriate clip size. For human use, the clip is available in 4 sizes (35 mm, 40 mm, 45 mm, and 50 mm). When closed, the clip applies uniform pressure over the length of the 2 parallel branches to ensure consistent, reproducible, and secure occlusion of the LAA.

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Abbreviations and Acronyms

AF	= atrial fibrillation
CT	= computed tomography
LAA	= left atrial appendage
TEE	= transesophageal echocardiography

Computed Tomography Protocol

All scans were performed using a dual-source CT scanner system with nonionic contrast medium, standard scanning, and image reconstruction parameters.¹⁴ LAA neck diameter was preoperatively measured on curved multiplanar reformations through the LAA (Figure 2, A, B). The LAA patency was visually analyzed by 2 experienced independent readers in consensus. Clip stability was assessed using 2 different measures: (1) distance from the ostium of the circumflex artery to each end of the clip (Figure 2, C) and (2) angle between a line drawn along the posterior tips of the transverse processes of the spine and the long axis of the clip (Figure 2, D). Table 1 summarizes the CT findings.

Statistical Analysis

The Kruskal–Wallis test was used to test for significant changes between the parameters of average heart rate and heart rate variability during scanning, as well as the clip location (ie, distances and angles), LA diameters, and LV function parameters across the CT examinations at different dates. Statistical analysis was performed using commercially available software (SPSS, release 15.0, Chicago, Ill).

RESULTS

Summary

A total of 34 patients underwent cardiac surgery with concomitant LAA clip placement. Patients' median age was 71 ± 10 years, and 58% were men. Mean preoperative logistic EuroScore was $10\% \pm 3\%$, and mean left ventricular function was $58\% \pm 14\%$. Classification of AF was paroxysmal ($n = 14$, 42%), persistent ($n = 8$, 23%), or permanent ($n = 12$, 35%); the mean duration of AF before surgery was 4 ± 1.5 years. Procedures performed were mitral valve repair ($n = 11$), mitral and tricuspid valve repair (2), mitral repair and aortic valve replacement (3), aortic valve replacement with mitral and tricuspid repair (1), aortic valve replacement (5), composite graft (1), coronary artery bypass grafting (7), and combined valve and coronary artery bypass grafting (4). All patients underwent bipolar radiofrequency pulmonary vein isolation off pump, or if on-pump, before aortic crossclamping with intraoperative conduction block confirmation. In patients with paroxysmal AF addressed for isolated myocardial revascularization, a complete off-pump approach was used ($n = 5$). Patients requiring an aortic valve procedure underwent on-pump pulmonary vein isolation ($n = 8$). In the presence of persistent or permanent AF, cardiopulmonary bypass was used, and a complete left atrial lesion set was performed ($n = 21$, 62%). Left atrial lesions included a posterior connecting lesions to connect the epicardial pulmonary vein lesions, one connecting lesion to the LAA before clip placement and one line from the

FIGURE 1. LAA clip, deployment tool, and deployment. A, Reusable Miltex deployment tool as it was used in all cases. LAA clip is loaded onto the jaws of this tool. B, LAA mobilized within the clip (1), right pulmonary veins (2), and pulmonary artery (3), and operator's hand (4) gently mobilizing the heart to demonstrate the LAA and allow placement of the clip with the left hand.

atriotomy down to the mitral valve annulus. If a history of atrial flutter was present ($n = 7$), additional right-sided lesions were performed.

Operative mortality occurred in 3 patients (8.8%). Cause of death was iatrogenic lung bleed after chest tube injury (postoperative day 1), acute postoperative hepatic failure (postoperative day 16), and aortic tear at aortotomy suture line (postoperative day 20). There was 1 additional death after discharge that resulted from over-anticoagulation (international normalized ratio, 4.4) and subsequent out-of-hospital pericardial tamponade (postoperative day 24). Autopsy, institutional, and external review excluded any link to the device or study participation.

Clip Placement

TEE confirmed the absence of spontaneous echo contrast in all patients (exclusion criteria), as also seen on baseline CT scans. For clip placement, the heart was mobilized (Figure 1) to develop the base of the LAA, which was then assessed with the selection guide. Once the clip was loaded into the reusable deployment tool, while still mobilizing the heart, the primary surgeon placed the clip on the LAA, which was gently mobilized by the first assistant with an atraumatic forceps. When judged satisfactory, located at the base of the LAA, transversally to the roof of the left atrium, the clip was deployed (Figure 1, B). When performing a mitral valve replacement, the clip was applied before inserting the prosthesis. In all other cases with cardiopulmonary bypass, the clip was applied just before opening the aortic crossclamp. In the

FIGURE 2. CT imagery. A, Curved multiplanar CT reformation demonstrating the plane for measurements of the LAA neck diameter (arrow to black line). B, Oblique-transverse thick maximum intensity projection CT images showing the 2 distance measurements (arrow to thin white lines)

off-pump setting, the clip was applied after myocardial revascularization was completed to ensure sufficient coronary perfusion during cardiac mobilization. No clip repositioning was necessary. In all patients, satisfactory placement at the base of the LAA was achieved in a single attempt and swiftly. The pericardium was closed in all. Postoperatively, TEE confirmed LAA occlusion in all patients. Procedural success rate was 100%.

Postoperative Course

In regard to the device or study participation, no complications occurred. Anticoagulation and platelet aggregation were managed according to standard clinical practices, that is, all patients received Coumadin and Amiodarone for 6 months until sinus rhythm was documented on 24-hour Holter electrocardiogram. Patients were sent to the regular ward, at which time the first follow-up CT was performed ($n = 30$). Chest radiographs in both anteroposterior and lateral views ($n = 30$) were used to assess clip localization. A patient who had received a kidney transplant 5 years previously did not undergo any follow-up CT evaluation. In 3 of the 4 patients with fatal outcomes, no follow-up CT was performed. In 2 of these patients, TEE performed on the intensive care unit demonstrated no LAA perfusion, and chest radiographs showed stable clip localization.

Computed Tomography Findings

Despite AF at baseline ($n = 19$, 56% of patients) and high heart rate variability across all scans during scanning, the image quality of all examinations was diagnostic, that is, all measurements could be made in all patients. LAA neck diameter was on average 1.9 cm at its most narrow point, considered the “landing zone” of the clip (Table 1). After surgery, in all serial CT scans the LAA was completely occluded, and the clip appeared to remain stable (Figure 3). All measurements (ie, distances and angles) showed no significant changes across the serial examination dates (Table 1). Both left atrial and left ventricular function showed no significant changes when compared (Table 1).

Follow-up

Clinical follow-up was 100% complete at 3 months ($n = 30$). In several patients, no follow-up CT was performed, in which case serial chest radiographs were used to assess clip stability. Cardiac rhythm at 3 month follow-up was regular sinus rhythm in 21 patients (70%), AF in 6 patients (20%, all had permanent AF before surgery),

from the ostium of the circumflex artery to both ends of the LAA clip. C, Volume-rendered CT image demonstrating the measurement of the orientation of the LAA clip. The angle was measured between 2 lines drawn along the posterior tips of the transverse processes and along the LAA clip (arrow).

TABLE 1. Computed tomography findings before surgery, before discharge, and at 3-month follow-up

Time point N	Baseline 34	Before discharge 30	3-Month follow-up 26	P value*
Heart rate (beats/min)	68 ± 11 (52–103)	78 ± 15 (59–113)	71 ± 14 (58–100)	<.05
Variability	10 ± 8 (1–27)	9 ± 8 (1–33)	5 ± 4 (1–12)	.21
LAA patency	Patent, no thrombus	None	None	/
LAA neck (cm)	1.9 ± 0.4 (1.1–2.8)	/	/	/
LAA clip location				
First distance to CX (mm)	/	18 ± 5 (9–29)	17 ± 4 (12–29)	.49
Second distance to CX (mm)	/	32 ± 8 (20–49)	34 ± 8 (20–47)	.77
Angle (degrees)	/	39 ± 22 (11–96)	41 ± 16 (12–70)	.51
LA diameter (mm)				
LA systolic	48 ± 14 (27–90)	44 ± 9 (28–68)	47 ± 9 (33–68)	.65
LA diastolic	45 ± 15 (23–88)	41 ± 10 (20–64)	43 ± 9 (29–63)	.46
LV dimensions				
ESV	89 ± 57 (27–285)	82 ± 57 (22–297)	87 ± 52 (31–230)	.89
EDV	163 ± 74 (82–410)	148 ± 75 (63–410)	166 ± 63 (92–345)	.44
SV	74 ± 27 (23–139)	66 ± 29 (22–130)	72 ± 32 (15–134)	.60
LV function				
CO (L/min)	5.1 ± 2.0 (2.5–8.7)	5.0 ± 2.3 (1.7–9.8)	5.5 ± 1.9 (1.6–8.9)	.61
EF (%)	47 ± 14 (25–69)	47 ± 15 (22–69)	50 ± 16 (22–74)	.78
Myocardial mass (g)	181 ± 49 (112–270)	184 ± 52 (104–277)	170 ± 55 (22–236)	.87

LAA, Left atrial appendage; CX, circumflex coronary artery; LA, left atrium; LV, left ventricle; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; CO, cardiac output; EF, ejection fraction. *Kruskal–Wallis test.

de novo atrial flutter in 3 patients (10%), and pacemaker induced in 2 patients (6%). At follow-up, no stroke or transient ischemic attack had occurred in any patients (Table 2).

DISCUSSION

We report the first human application of a new epicardial clip for concomitant LAA occlusion during cardiac surgery in patients with AF. Clip placement through a median sternotomy was performed rapidly and in one attempt. There were no clip-related complications. CT provided proof of absence of LAA thrombus (baseline) and demonstrated durability and stability of clip occlusion after surgery and over time.

As part of the classic cut-and-sew Maze procedure, initially described by James Cox's group,¹⁵ surgical excision of both atrial appendages was first reported. After a mean follow-up of more than 5 years, only 1 patient in more than 200 had a stroke, despite the fact that most patients were not taking anticoagulation¹⁵; however, the causality of an effective procedure restoring sinus rhythm versus exclusion of atrial appendages remains uninvestigated. Since then, surgical epicardial occlusion was evaluated in the LAAOS trial¹⁶ in patients undergoing coronary artery bypass grafting with increased risk of stroke (CHADS score > 2). Seventy-seven patients were randomized to LAA occlusion, by staples or suture, or control. During surgery, there were 9 LAA injuries that were readily repaired. Pre-discharge LAA occlusion was effective in 45% using sutures and in 72% using a stapler. These results are similar to other reports,¹⁷ highlighting the main challenge faced when

attempting to eliminate the LAA safely from the circulation. This is stressed by a recent echocardiographic follow-up trial⁹ on 137 patients who underwent LAA closure by excision (n = 52) and exclusion by stapler or suture (n = 85) during cardiac surgery. In addition to an impressive learning curve affecting outcomes, the authors demonstrated only 40% of successful closures. Furthermore, LAA thrombus was found in 41% of patients with unsuccessful LAA exclusion versus none with excision. After 6 months, 6 patients with successful LAA closure (11%) and 12 patients with unsuccessful closure (15%) had evidence of stroke/transient ischemic attack. The authors concluded that there is a high occurrence of unsuccessful surgical LAA closure with severe neurologic consequences. The present study obtained 100% effective LAA occlusion with no learning curve, complications, or neurologic events during follow-up. Effective off-pump clip application was performed in 5 patients (15%) with paroxysmal AF requiring pulmonary vein isolation and off-pump coronary artery bypass grafting. In this setting, this device shows true promise, because LAA injury, especially in a minimally invasive setting, can be a serious complication. From preclinical^{11,13} and current experience, LAA injury during clip placement was never an issue.

Catheter-based approaches to closing the LAA have been reported but remain limited because of the inherent limitations of this approach. The Protect AF trial provides the first real evidence suggesting that closure of the LAA provides an alternative strategy to oral anticoagulation for stroke prevention in patients with nonvalvular AF. However, the

FIGURE 3. Multiple views to the heart in 3-dimensional volume showing clip placement technique preoperatively (A–C) and postoperatively (D–F).

limitations of this approach are once again highlighted by this trial as well.⁸ The authors conclude that a higher rate of adverse events mainly resulted of peri-procedural complications, as seen by other investigators.¹⁸ In addition, we believe that anatomic considerations such as the highly individual variability of the left atrial aperture at the base of the LAA,¹⁹ which we also documented in our preoperative CT imaging, may limit efficacious LAA occlusion from within. We encountered a very high individual anatomic variability of the LAA. It also appears that the CT measurements of the LAA neck were not at all correlated with the final intraoperative clip size chosen with the measuring device. This is mainly due to the variability of the neck, which is considered the landing zone for the clip. The dimension of the LAA neck in our series was on average 1.9 cm in diameter, varying from 0.8 to 2.9 cm (Table 1). In a recent series on LAA anatomy in patients with AF studied by magnetic resonance imaging, Heist and colleagues¹⁹ concluded that a significant heterogeneity in LAA size and dimension was present. The advantages of a standard epicardial approach for LAA closure are clear. The current clip is

available in 4 sizes. In our experience, we used the 2 smallest clip sizes (35 and 40 mm) in most cases. The positioning of the clip is the crucial part of the procedure, because it needs to be located as low as possible in the region of the LAA neck on the roof of the left atrium. In addition, we also

TABLE 2. Clinical follow-up data

N (%)	Baseline 34	Discharge 30	3 Mo 30 (100)	12 Mo 22 (73)*
Cardiac rhythm:				
Sinus rhythm	15 (44)	18 (60)	21 (70)	17 (77)
Atrial fibrillation	19 (56)	12 (40)	6 (20)	4 (18)
Atrial flutter	7† (21)		3 (10)	
Pacemaker		2 (0.6)	2 (0.6)	1 (5)
Medications:				
AAD‡	21 (62)	29 (97)	28 (93)	10 (45)
Coumadin	15 (44)	27 (90)	22 (73)	11 (50)
Clip stable§	34 (100)	30 (100)	30 (100)	22 (100)

AAD, Antiarrhythmic medication. *Follow-up not complete. †History of. ‡Beta-blocker or amiodarone. §On chest radiograph and/or computed tomography.

conducted a downsizing strategy when choosing the clip according to the measuring tool. We believe this minimized the surface of contact of this foreign body with the roof of the left atrium, which may have had a protective influence on outcomes after ablation procedures for AF. Our results compare well with those in the current literature in a dedicated AF setting. In our experience, LAA clip occlusion did not significantly affect LA diameters and left ventricular function, because these remained constant over time. Patients' well-being was not affected by trial participation.

LIMITATIONS

Because this was a pilot trial, no controls were enrolled. The trial was not powered to assess stroke prevention.

CONCLUSIONS

LAA clip occlusion is a safe and effective new therapy for patients with AF. Stroke prevention by LAA occlusions offers a new option for these patients.⁸ Thoracoscopic approaches, with or without an ablation procedure, might provide a new indication for cardiac surgeons. Further clinical trials are necessary to establish this new approach.

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