Left Atrial Appendage Occlusion: Lessons Learned From Surgical and Transcatheter Experiences

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Since the 1950s, the pathophysiologic role of the left atrial appendage (LAA) has been known in thromboembolic disease. A variety of surgical techniques have been described to close the LAA, with various degrees of efficacy. Today, transcatheter devices for LAA occlusion may offer a less invasive solution. This review looks at the surgical experience with LAA occlusion, with a focus on the techniques of closure, the prospects for stroke reduction, and the percutaneous trials completed so far, to formulate some meaningful conclusions about the status of LAA closure today.

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The left atrial appendage (LAA) is well recognized as a source for thromboembolism (TE) in valvular heart disease and in atrial fibrillation (AF). In a review of operative, autopsy, and transesophageal echocardiographic (TEE) studies, Blackshear and Odell [1] identified the LAA as the source of up to 90% of left atrial thrombi in nonvalvular AF and 57% in valvular AF. Efforts to ligate or remove the LAA during operations began early in the development of valve surgical techniques to reduce the incidence of TE. Despite consensus favoring LAA ligation or removal, there is little agreement or analysis to define a best method for obliteration of the LAA. This review examines the history of LAA occlusion, the efficacy of various surgical techniques, and the prospects of newer, less invasive surgical methods and transcatheter technologies.

AF affects more than 2.5 million Americans and is thought to be responsible for 17% of all strokes (or 135,000 annually), which are primarily due to the formation and embolization of left atrial thrombus [2, 3]. There is a fivefold increase in stroke in nonvalvular AF compared with patients in sinus rhythm, with an overall rate of ischemic stroke averaging 5% per year. This increases sharply with age, and the risk of stroke for an individual is as high as 35% over 10 years [4]. Stroke associated with AF is more lethal and disabling than stroke in patients without AF [5].

Warfarin anticoagulation has reduced the risk of stroke by 60% to 70% in AF patients. Put into practical perspective and assuming a baseline risk of 51 ischemic stroke events/1,000 person-years, estimates show standard-dose warfarin for AF could prevent 28 ischemic strokes at the expense of 11 major or fatal bleeding episodes [6]. Pooled studies, however, indicate that only 50% to 60% of patients who should be prescribed warfarin are actually taking warfarin [7]. This is due to multiple factors, including patient frailty with fall risk, difficulty in achieving the narrow therapeutic window for warfarin use, patient refusal due to lifestyle demands, or discontinuation because of a recent stroke. Indeed, long-term oral anticoagulation is contraindicated in 14% to 44% of AF patients who are at risk of stroke [8]. Recent studies demonstrate that warfarin carries a 1.8% annual risk of life-threatening bleeding [9]. Although several newer, direct antithrombin agents are available that do not require international normalized ratio monitoring, bleeding complications and discontinuation rates that are comparable to warfarin make it likely that the fundamental problems associated with warfarin anticoagulation will still persist.

Material and Methods

An English language literature search was performed using OVID, Medline, and the Cochrane Library for all studies from 1948 to April 2011. The medical subject heading terms and keywords included combinations of "left atrial appendage," "surgery for left atrial appendage," "left auricular appendage," "stroke prevention," and "percutaneous closure left atrial appendage." The "related articles" feature and additional references in identified articles were used to expand the search.

LAA Anatomy and Physiology

The 2-cm to 4-cm-long tubular LAA usually forms a narrow junction with the LA and angles downward from

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its origin; in contrast, the right atrial appendage is more broad-based and triangular, forming a wide junction to the right atrium at an upward angle that makes stasis less likely [10]. Clinical studies using TEE [11] and magnetic resonance angiography [12] demonstrate significant heterogeneity among AF patients in LAA size, wall thickness, and morphology. The LAA is located on the lateral wall of the heart close to the circumflex artery, which is relevant for surgical occlusion. On the epicardial surface, it is near the great cardiac vein; on the endocardial surface, it is within 1 cm of the mitral valve (MV) annulus and the orifice of the left superior pulmonary vein [13].

Animal studies demonstrate that the LAA contains stretch receptors that mediate thirst. Its endocrine function is shown by a 40-fold higher concentration of atrial natriuretic peptide compared with other areas of the heart, and it contributes to brain natriuretic peptide [14]. The LAA may have a role in the regulation of LA pressure–volume relationships in fluid homeostasis such that LAA occlusion may lead to altered LA compliance [15]. Although water retention is observed after bilateral atrial appendectomy [16], sparing the right atrial appendage attenuates this effect [17].

The fibrillating LA results in stretching and dilatation, leading to stasis and LAA thrombus formation. Stöllberger and colleagues [14] used casting models to demonstrate a threefold increase in LAA size and loss of the fine branching structure in AF, making stasis and thromboembolism more likely. Dense, spontaneous echo contrast or "smoke" is a precursor to thrombus formation and was noted in the LAA of 20% of the patients in the Stroke Prevention in Atrial Fibrillation (SPAF) III Trial, with a threefold increase in stroke [18].

An underappreciated role of the LAA is as a trigger for recurrent AF after catheter ablation, as was seen in 27% of patients in a large review of 987 cases [19]. This area deserves further study and recognition that ultimately successful management of the LAA may also provide electrical isolation of the LAA and make the AF ablation procedure more successful and durable [20].

History of LAA Exclusion and Removal

Belcher and Somerville [21] noted the relationship between rheumatic MV disease, systemic embolism, and the LAA in observing that LAA thrombus was present in 64% of these patients who presented with TE events compared with 16% in those who did not. LAA obliteration was first suggested as an adjunct to mitral valvotomy before the advent of cardiopulmonary bypass. Madden (1949) [22] published one of the first reports of LAA removal in 2 patients. Interestingly, he reviewed three reports from the 1940s and observed that the LAA was the source of 92% of TE, accurately predicting Blackshear and Odell's observation nearly 4 decades later. The results of LAA obliteration in 8 patients involving ligation and appendectomy were reviewed by Leonard and Cogan [23], who noted a high complication rate, including 3 deaths, 1 paraplegia, and 3 peripheral emboli and recommended that the procedure "should be abandoned."

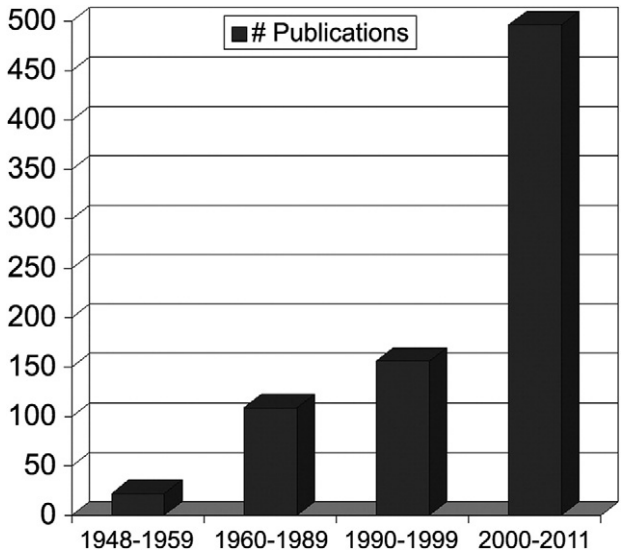

Fig 1. Number of left atrial appendage publications in various periods from 1948 to 2011.

Growing interest in LAA ligation is highlighted in Figure 1 by comparing the sharp recent increase in the medical literature from 1948 to 2011. In the 1990s, interest was likely increased by two developments: First, Cox developed the Maze procedure, which was the first reliable operation for the treatment of atrial fibrillation, in 1987 and included atrial appendage removal [24]. Second, the widespread use of TEE demonstrated the success or failure of surgical LAA closure techniques. In the last decade, interest in the LAA has been driven by the development in percutaneous occlusion devices.

Surgical Techniques for LAA Occlusion

Johnson and colleagues [25] described the LAA as "our most lethal human attachment" in a report of prophylactic LAA excision in 437 patients from 1995 to 1997. In this group, there were 21 perioperative cerebrovascular accidents, but there were no later strokes or demonstrable thrombus seen by TEE. Consequently, the authors recommended an aggressive strategy of LAA excision in patients undergoing heart operations. There have been a number of techniques for management of the LAA. Broadly, they fall into two categories: (1) exclusion and (2) excision.

Within the exclusion method are running or mattressed sutures, with and without felt pledgets. Specifically, the ligation occurs on the epicardial surface (Fig 2A) or more commonly, from the endocardial surface (Fig 2B). The most common techniques within the excision method include a stapled excision (Fig 2C) or removal

and oversew. DiSesa and colleagues [26] reported the use of an automatic surgical stapler for LAA removal at the time of MV operations in 1988, and Gillinov and colleagues [27] reported the use of a stapler with pericardial buttressing strips in 2005.

Although each of the techniques is being used today, it has been our surgical practice to perform LAA excision with simple removal and oversew in AF patients undergoing their first cardiac operation. After the heart has been arrested, the lateral wall of the heart is brought up into position. The LAA is excised with scissors or electrocautery, leaving a 1-cm cuff. A 3–0 polypropylene suture is used in a 2-layer closure flush with the heart surface (Fig 2D). This closure, which takes less than 5 minutes, is inspected for hemostasis, with a remnant of no more than 2 to 3 mm. The rest of the surgical procedure is then completed. Confirmation of closure is seen on TEE (Fig 2E) and by operative view of the endocardial (Fig 2F) surface. In our experience, this method is quick, inexpensive (the only cost is the suture), reliable, and safe. In rare cases a LAA will appear too friable for closure, but we have not experienced any instances of bleeding after the procedure in more than 120 procedures since 2007.

Results With Various Surgical Techniques

The surgical literature on LAA closure consists primarily of retrospective case series of patients who had LAA occlusion and then later presented with new findings warranting TEE evaluation. As such, there is a selection bias because only a small segment of the treated population is studied. Nevertheless, it is possible to gather some meaningful insights. It is important in each of these prior reports to focus on the technique used for surgical obliteration of the LAA.

One randomized trial examined the efficacy of prophylactic occlusion of the LAA in prevention of stroke in coronary artery bypass grafting patients [28]. The LAA Occlusion Study (LAAOS) randomized 77 patients in a 2:1 fashion to occlusion (epicardial suture or stapler) or no occlusion, with core laboratory TEE follow-up 14 months later. The TEE definition of success was no Doppler flow and a residual remnant length of less than 1 cm. The 1-cm criterion was based on the observation that because the mean width of the LAA was 2 cm, the assumption was that a 50% reduction would be necessary to prevent recurrent thrombus formation in the residual stump. Overall, closure success was 43% in the suture group and 72% in the stapled group.

The pattern of failure was interesting. The epicardial suture group failed due to persistent Doppler flow into the appendage, suggesting an inadequate technical closure. The stapled group failed for residual remnant size. Even though the failures in the stapled group showed a remnant greater than 1 cm, there was no demonstrable thrombus present. In this study, prophylactic LAA occlusion did not reduce the risk of neurologic events between the occlusion and control groups. However, in a comparison with a screened but unenrolled nonrandomized group, the perioperative stroke rate in the occlusion group was 2.6% (2 of 77), which compared favorably with the higher stroke (5.6%) and transient ischemic attack (6%) rate at 12 months in the unenrolled patients, suggesting a benefit to LAA occlusion.

Kanderian and colleagues [29] looked at 137 patients who had LAA closure and later had TEE for various reasons. This is the largest study to look at the relationship between closure technique and results [29]. This group represented 5.4% of the total population of patients (137 of 2,546) who had a LAA occlusion procedure. The LAA was excluded in 52 (38%), and 85 (62%) had exclusion by endocardial suture ligation or stapling. Moreover, of the LAA excision group, 80% had scissor excision and oversew and 20% had cutting stapler excision. Overall, successful closure, defined as no persistent Doppler flow and a remnant of less than 1 cm, was 40%. In a pattern very similar to the LAAOS Study, 60% of suture exclusions failed due to persistent flow on TEE, and 60% of the stapled exclusion failed for large remnant.

Despite the 27% failure rate of the excision group, it is likely that this was largely influenced by the 20% of excision patients managed with a cutting stapler. The stapler's known limitation is difficulty achieving a remnant of less than 1 cm. The scissor excision group may have demonstrated a higher success rate. The importance of successful closure is highlighted by the fact that 41% of the patients with an unsuccessful closure had LAA thrombus compared with 0% in the successful closure group and none in the entire excision group.

Katz and colleagues looked at 50 patients who all had concomitant MV operations with LAA ligation [30]. In this group 70% had MV replacement and 30% had MV repair. Endocardial suture exclusion with a double row of 4–0 polypropylene suture was the closure technique. This study demonstrated that 36% of LAA ligations were incomplete. The results were not influenced by LA size, degree of mitral regurgitation, or the type of MV procedure; moreover, it found a similar incidence of incomplete ligation immediately postoperatively and at various times afterwards. This suggests that rather than gradual suture dehiscence over time, failure was immediate from a technically inadequate closure during the operation. Emphasizing the importance of incomplete closure was that 50% of the unsuccessful closures had spontaneous echo contrast or thrombus in the LAA and 22% had TE events.

Garcia-Fernandez and colleagues [31] looked retrospectively at 205 patients after MV operations. The LAA was ligated in 58 patients and was not ligated in 147 [31]. They found that no LAA occlusion (odds ratio, 6.7) and an incomplete LAA occlusion (odds ratio, 11.9) were the major risk factors for the development of TE sequelae over a mean follow-up of 69 months. In this series, an incomplete LAA occlusion was more dangerous than no LAA occlusion at all. This study was cited in the 2006 American College of Cardiology/American Heart Association Valve Guidelines [32] to recommend amputation of the LAA at the time of MV procedures to reduce TE events.

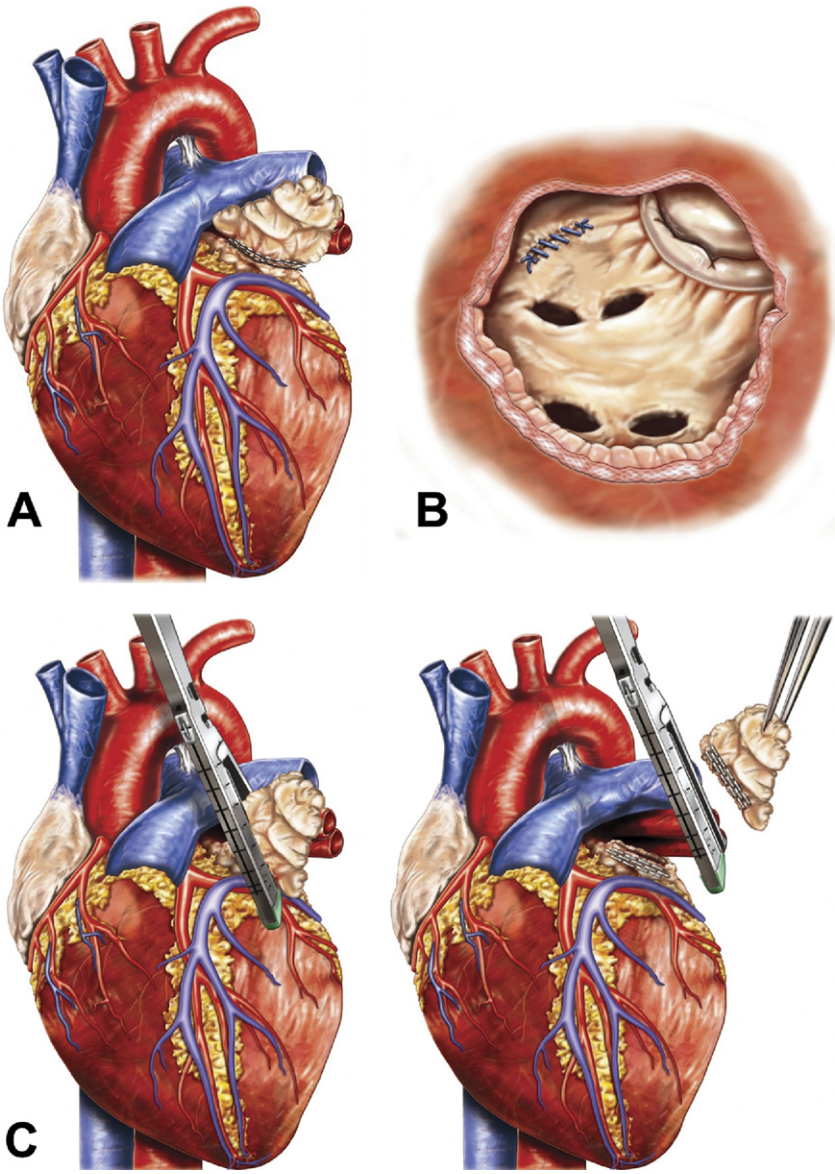

Fig 2. Surgical techniques of left atrial appendage (LAA) closure. (A) Epicardial suture exclusion. (B) Endocardial suture exclusion. (C) Stapled excision. (Left panel) Stapler positioned across the base of the LAA; (Right panel) LAA removed with intact stump. Studies suggest the residual stump may be too large. (D) Excision by removal and oversew. (Left panel) Lateral wall of the heart is elevated to bring the LAA into view; (Middle panel) Removal of the LAA by scissors (pictured) or electrocautery with a < 1 cm stump for closure; (Right panel) Two-layer suture closure of the LAA stump flush with the heart surface. (E) Transesophageal echocardiogram shows no flow after removal and oversew. (F) View from inside the left atrium after removal and oversew demonstrates complete closure.

Bakhtiary and colleagues [33] used a Derra clamp at the base of the LAA in an arrested heart, placed two 2–0 nonabsorbable ligatures around the stump, and then removed the clamp. They reported a series of 259 consecutive patients with AF or for prophylaxis in cardiac operations. Two patients (0.7%) returned for bleeding from the LAA. There was no TEE evidence of incomplete closure. New postoperative neurologic deficits were seen in 7 patients. Although the follow-up period was not specified to define the stroke prevention benefit against historical AF patients not taking warfarin, the data are encouraging for an epicardial ligation and near excision technique.

Summary of Surgical Techniques

The echocardiography literature has numerous additional examples of failure of endocardial suture closure [34] and epicardial closure [35]. A closer examination of the efficacy of the various closure techniques is reported in Table 1. It is apparent that endocardial ligation alone appears to be an inferior method of closure compared

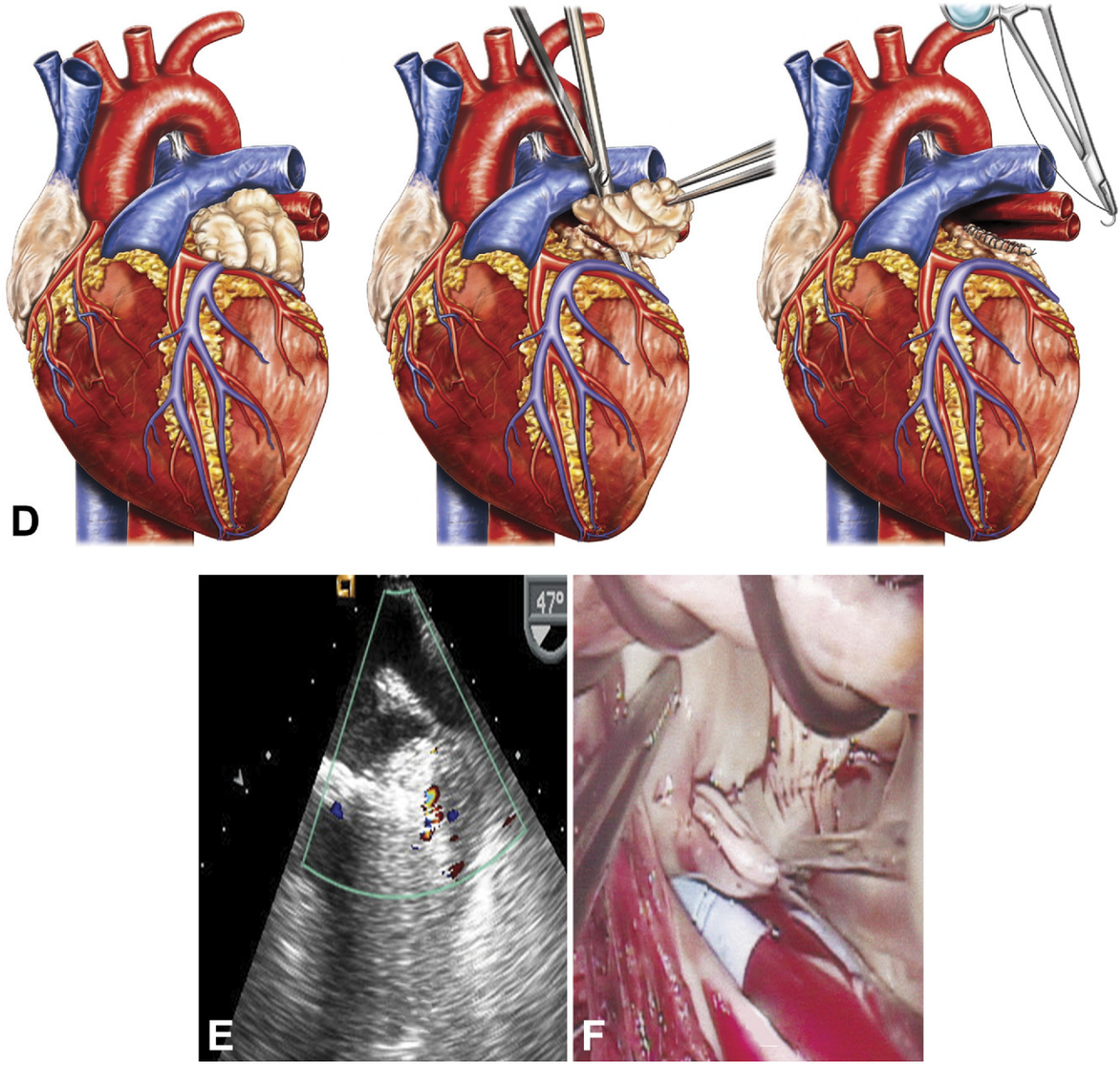

Fig 2. Continued

with stapling. The main limitation to stapling is the large (>1 cm) remnant that is left behind, although two studies [28, 29] found no thrombus on TEE even if there was a remnant exceeding 1 cm. Removal with oversew appears to be the most successful technique. As a practical matter, it cannot be performed in off-pump operations or in minimally invasive procedures. Our review is mixed about whether there is a benefit in stroke reduction with LAA occlusion, as seen in Table 1. Although excision appears to demonstrate a positive benefit compared with other techniques, any meaningful evaluation of surgical results must account for the closure technique.

Finally, successful removal of the LAA may make the Maze procedure for AF more successful by eliminating a source of recurrent AF. In many surgical AF series, however, the method of LAA occlusion is not defined, making it difficult to determine the effect of LAA occlusion on the efficacy of AF treatment and on the stroke rate. Despite doing a LAA excision, it is likely that the 98% freedom from AF at 11 years explains the 0.7% stroke rate success of the Cox-Maze III procedure [36]. There does not appear to be a study in the surgical AF literature showing that a failed Maze procedure (back in AF) with LAA ligation has a lower stroke rate than with the LAA intact.

Why is it that a large percentage of a seemingly simple technical procedure—LAA suture ligation from inside the left atrium—is incomplete? The most likely explanation is that shallow suture bites are used to avoid the adjacent circumflex artery. It may also result from failure

Table 1. Comparison of Surgical Left Atrial Appendage Closure Techniques

First Author, Year	Country	No. Studied	Method of Closure	Closure Success Rate,[a] %	Effect of LAA Closure on Stroke Prevention
Johnson, 2000 [25]	USA	437	Excision	100	Positive
Katz, 2000 [30]	USA	50	Endocardial suture	64	None
Garcia-Fernandez, 2003 [31]	Spain	205	Endocardial suture	90	Positive
Bando, 2003 [38]	Japan	812	Endocardial suture	Not measured	Negative
Blackshear, 2003 [45]	USA	15	Thoracoscopic epicardial pursestring	93[b]	Positive
Pennec, 2003 [40]	France	30	Endocardial	70–80	Negative
			Excision	100	Positive
Schneider, 2005 [41]	Germany	6	Endocardial suture	17	Negative
Healey, 2005 [28]	Canada	77	Epicardial suture	45	Positive
			Stapler	72	
Kanderian, 2008 [29]	USA	137	Excision	73 (20% stapler)	Positive trend
			Suture exclusion	23	
			Stapler	0	
Bakhtiary, 2008 [33]	Germany	259	Clamp and epicardial suture	100[b]	Positive

[a] As assessed by transesophageal echocardiography. [b] Remnant size not measured.

LAA = left atrial appendage.

to extend the running suture lines to the most distal edge of the LAA orifice. This may be more problematic when a MV annuloplasty ring or MV prosthesis is already in place. Multislice computed tomography angiography demonstrates that the LAA orifice is in a 3-dimensional spiral configuration and not a single circular ostium, which may pose a technical challenge to closure [37]. Incomplete LAA closure may be worse than no closure. Dawson and colleagues [42] reviewed the LAA occlusion literature and concluded that prophylactic LAA exclusion "is not warranted and may be harmful."

Newer Surgical Techniques

Pericardial reinforced techniques [43] or an inversion and excision method [44] are other alternative excision techniques. Each method might offer satisfactory results, although an advantage over the simple oversew is unlikely. In an effort to offer a less invasive LAA occlusion, Blackshear and colleagues [45] described successful thoracoscopic obliteration of the LAA using a stapled or snare technique. The procedure was completed in 14 of 15 patients, with one conversion to thoracotomy for bleeding. At a mean follow-up of 42 months, there were two strokes and two deaths. The TEE results were not reported. The stroke rate (5.2%/year) in the 11 patients with previous TE events was lower than in aspirin-treated patients from the SPAF trials (13%/year) [46]. Because of the concern for bleeding requiring urgent thoracotomy, the natural tendency would be to accept a larger residual LAA remnant, which may compromise the efficacy of the LAA closure.

Several surgical devices designed specifically to provide reliable LAA occlusion are available and in various stages of development. Atricure (West Chester, OH) has developed the Atriclip Gillinov-Cosgrove Left Atrial Appendage (LAA) Exclusion system device, which has been on the market since 2010. Studies of this LAA epicardial exclusion device show good elimination of LA flow. Its ability to achieve closure with a remnant smaller than 1 cm is not reported [47]. In addition, it may be used through a minimally invasive thoracoscopic approach. Publication of the recently concluded Exclusion of Left Atrial Appendage with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery (EXCLUDE) registry trial to demonstrate safety and efficacy is anticipated soon. A thoracoscopic expandable silicone band, the Occlusion developed by Medtronic Inc (Minneapolis, MN), was successful in 15 dogs [48]. After 40 patients, further enrollment was stopped. A communication was identified between the LA and LAA in a small number of patients, and no further device development is planned. Each of the thoracoscopic approaches requires left thoracoscopic access for LAA removal.

Transcatheter Closure Devices

During the last decade, several transcatheter devices have been developed for the management of the LAA in AF patients. Three devices have been investigated: the Percutaneous LAA Transcatheter Occlusion or PLAATO System (eV3, Plymouth, MN), the Amplatzer Cardiac Plug (St. Jude Medical, Minneapolis, MN), and the Watchman (Boston Scientific, Maple Grove, MN) device.

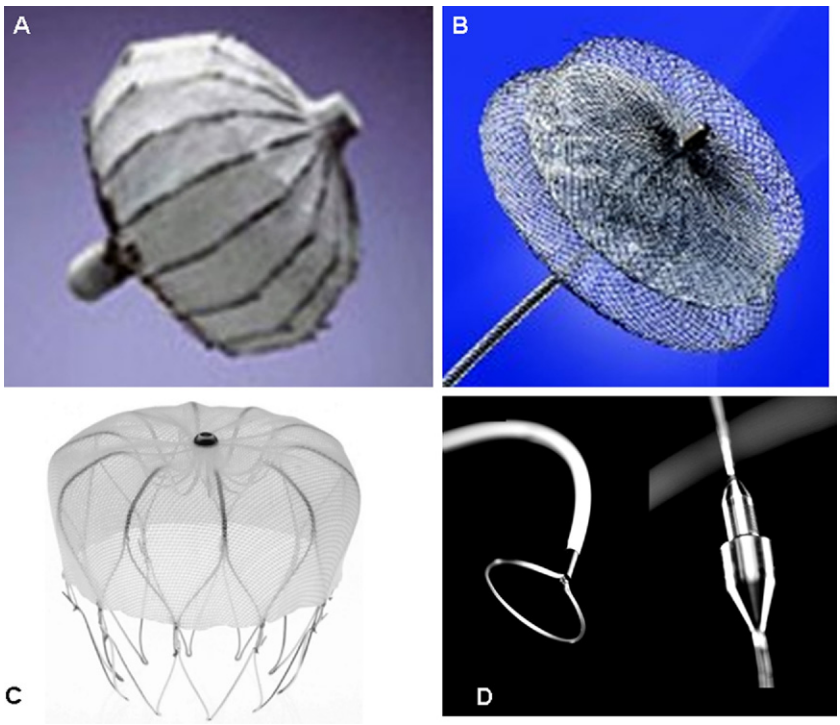

Fig 3. New left atrial appendage closure devices: (A) PLAATO, (B) Amplatzer Cardiac Plug, (C) Watchman, and (D) Lariat.

All are delivered percutaneously through transseptal access to the LA [49]. Preprocedural evaluation of the LA and LAA, exclusion of thrombus, verification of placement, and evaluation of postprocedural pericardial effusion requires skilled fluoroscopic and TEE coordination [50].

The PLAATO System (Fig 3A) is a self-expandable nitinol cage with a polytetrafluoroethylene membrane and was the first device developed specifically for LAA occlusion. Although it is no longer available, data from early experience with this first-in-class device are instructive. Preliminary success in canine models was demonstrated in the late 1990s and the first implant in a patient was in 2001. Its initial evaluation involved an international multicenter registry of 111 patients with contraindication to oral anticoagulation [51]. In this cohort, device implantation was 97% successful, and LAA occlusion was documented in 98% of patients at the 6-month follow-up TEE. There were seven major adverse events, including one death and two strokes, at a mean follow-up of 9.8 months. Overall, the stroke rate of 2.2%/year compared with the estimated annual stroke rate of 6.3% for this population represented a 65% relative reduction in stroke.

The 5-year North American results consisted of 64 AF patients who were similarly at high risk of stroke (mean congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack [$CHADS_2$] score = 2.6) and were not oral anticoagulation candidates [52]. Device implantation success was 100%, with 98% success by core laboratory TEE. In comparison with historical controls, with an expected 6.6% stroke rate, the PLAATO device in this trial showed a 3.8% stroke rate, or a 42% relative risk reduction.

Several hundred PLAATO systems have been implanted worldwide. The PLAATO experience showed that in a nonrandomized cohort, device implantation is feasible and safe, and compared with the stroke risk estimated using the $CHADS_2$ score, cut the stroke rate by 40% to 65% in higher risk AF patients.

The Amplatzer septal occluder (ASO, AGA Medical/St. Jude Medical, St. Paul, MN) has been in use for almost 15 years, with extensive success in patent foramen ovale and atrial septal defect closure. This device is not designed for LAA occlusion, but has been used off-label. The first human clinical application in LAA occlusion was in 2002. In a series of 16 patients, LAA occlusion was successful in 15, with one instance of device embolization requiring surgical intervention [53].

Subsequently, the Amplatzer Cardiac Plug (ACP, AGA Medical; Fig 3B) was developed specifically for LAA occlusion. It consists of a self-expanding flexible nitinol mesh with a distal lobe with retaining hooks, a proximal disk, and a central polyester patch. The mechanism of the lobe and disk for sealing the LAA orifice has being termed the "pacifier principle." In the initial European experience, the device was successfully implanted in 96% of patients [54]. Serious complications occurred in 10 patients (7.0%), as outlined in Table 2. The ACP does not require warfarin anticoagulation, and patients are maintained on dual antiplatelet therapy, with 1 month of clopidogrel and 6 months of aspirin. The ACP received the Conformité Européene mark in 2008 with almost no human implant data. Implantations with the device have been done in more than 1,200 patients worldwide. It is currently in phase I United States clinical trials.

The Watchman device (Boston Scientific, Natick, MA; Fig

Table 2. Adverse Event Comparison of Current Transcatheter Closure Devices

Study	Device	Pts in Study (No.)	Age, Years (Mean ± SD)	Procedural Stroke No. (%)	Device Embolization No. (%)	Major Pericardial Effusion or Tamponade No. (%)	Bleeding No. (%)
Initial European experience [54]	Amplatzer Cardiac Plug	143	74 ± 9	3 (2)	2 (1)[a]	5 (4)	NR
PROTECT-AF [55]	Watchman	463	72 ± 9	5 (1)	3 (0.6)[b]	22 (5)	16 (4)
CAP Registry [39]	Watchman	460	74 ± 8	0 (0)	0 (0)	10 (2)	3 (1)

[a] Both retrieved percutaneously. [b] One percutaneous and two surgical retrievals.

AF = atrial fibrillation; CAP = Continued Access Protocol; NR = not reported; PROTECT-AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF; SD = standard deviation.

3C) has a porous polyethylene membrane on the proximal face of a self-expanding nitinol cage with fixation barbs for secure implantation within the LAA. Unlike the ACP device, the fabric of the Watchman is blood permeable and requires warfarin for 6 weeks until TEE demonstrates sealing of the LAA. The first human implantation was in 2002.

The only randomized clinical trial with any percutaneous LAA occlusion device is the landmark Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial. The population was at lower risk than the PLAATO studies, with 68% having a $CHADS_2$ score of 1 or 2 (mean, 2.17). The study randomized 707 patients with nonvalvular AF from 59 sites worldwide 2:1 to the WATCHMAN device to determine device noninferiority for efficacy [55]. The control group was maintained on warfarin therapy and the WATCHMAN group received warfarin for 45 days. Efficacy was assessed by a primary composite end point of stroke, cardiovascular death, and systemic embolism. Implant success was 91%. If the TEE at 45 days showed less than minimal flow in the LAA and no thrombus or clinical end points, then warfarin was discontinued with aspirin/clopidogrel to 6 months, followed by aspirin alone. At 45 days, 86% of the Watchman patients were able to stop warfarin. Core laboratory echocardiography documented successful closure in 92% by 6 months.

The primary end point for safety was serious adverse events, which included major bleeding, pericardial effusion, and device embolization. In the Watchman group, there was a 38% reduction in primary efficacy, 29% in stroke, and 38% in death compared with the warfarin control group. Meanwhile, there was a 77% increase in primary safety events in the Watchman group. Specifically, procedural complications occurred in 49 of 453 (10.6%) of the Watchman group, as outlined in Table 2. The control group on warfarin had a 6.6% (16 of 244) adverse event rate, which consisted of major bleeding (4.3%) and hemorrhagic stroke (2.5%).

The PROTECT-AF study successfully demonstrated the noninferiority of the Watchman device compared with standard therapy with warfarin. The frequency of device-related safety events in the first 30 days was considered high. Most of the safety events occurred in the first week after implant due to periprocedural complications associated with the learning curve.

As with most procedures, with experience come better results. In a recent analysis comparing the PROTECT AF Trial with the subsequent Continued Access Protocol (CAP) Registry, Reddy and colleagues [39] found that procedure-related and device-related adverse events were greater in the first half of PROTECT AF than in the second half. The continued improvement in the CAP Registry is summarized in Table 2. At this time, more than 1,500 devices have been implanted worldwide. Currently, the PREVAIL study (Prospective Randomized EVAluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Version Long Term Warfarin Therapy) is underway to seek Food and Drug Administration approval in the United States.

Two additional devices in various stages of development involve a transcatheter transpericardial technique. First, the Epitek (Minneapolis, MN) Anchorage Closure System uses a subxiphoid approach combined with an endoscope and an LAA forceps-like grasper. The appendage is grasped, and a snare advanced over it with a pretied suture and to ligate the LAA. Second, the LARIAT Suture Delivery Device (SentreHEART Inc, Palo Alto, CA) uses a combination of transseptal placement of a temporary balloon in the LAA, magnet-tipped guidewires inserted into the LAA and the pericardial space, and a closure snare device. A 40-mm pretied radiopaque suture loop is used to ligate the LAA (Fig 3D). This device demonstrated successful LAA closure in a canine model [56]. More than 100 patients have been treated in a registry, with promising early safety results and complete LAA obliteration on 30-day echocardiograms. The LARIAT is approved in Europe and was approved by the Food and Drug Administration in 2009.

Percutaneous closure devices are promising and offer patients a genuine alternative to warfarin. There are procedural-related and device-related challenges, including the risk of over-sizing or under-sizing, device migration, dislodgment or embolization, and hemopericardium or cardiac perforation.

In conclusion, when a patient with AF has a LAA occlusion procedure, what are the clinical implications based on this review? First, the success of the closure is highly dependent on the technique of closure, with the excision and oversew technique demonstrating the best results. Second, an incomplete closure is more thrombogenic and worse than no closure at all. It is important for surgeons to appreciate that despite a high successful

closure rate by the percutaneous devices of 90% to 95%, which exceeds most surgical series, the stroke risk reduction is more modest (40% to 65% reduction). Thus, when patients or referring physicians ask if an AF patient, despite LAA removal or exclusion, should still be anticoagulated, the answer is still yes. The results of these controlled trials show that a highly reliable surgical closure technique would likely cut the stroke risk in half. This is likely due to other causes of stroke in AF, such as cerebrovascular disease, complex aortic plaque, or a hypercoagulable state. Blackshear and Odell's observation that 90% of LA thrombus is found in the LAA is not the same as stating that 90% of strokes in AF come from the LAA.

A post hoc analysis of the SPAF I-III trials showed that of the strokes that could be classified, 32% were noncardioembolic [57]. Moreover, Blackshear and colleagues [58] performed an echocardiographic analysis on 770 patients in the SPAF III trial and found that 57% of patients had aortic plaque and 25% had complex aortic plaque. Interestingly, the single greatest predictor of aortic plaque by multivariate analysis in this series was LA or LAA thrombus.

Finally, AF is also associated with a systemic hypercoagulable state. Increased plasma levels of β-thromboglobulin and platelet factor 4 reveal enhanced platelet function [59]. Systemic markers of activation of the coagulation cascade are increased, including thrombin-antithrombin II complex, D-dimers, fibrinogen, and prothrombin factors 1 and 2 [60]. Thus, there will always be a rationale for the continued use of anticoagulation in AF, regardless of the method (suture excision, minimally invasive epicardial occlusion device, or transcatheter closure device) of LAA closure. Although warfarin alternatives such as dabigatran (Pradaxa, Boehringer Ingelheim, Ingelheim am Rhein, Germany) are now available, the expectation would be to reduce AF strokes by one-third (31% relative risk reduction), although the bleeding risk would be similar to warfarin [9].

Transcatheter devices must maintain a very high level of closure success along with a favorable safety profile. It will be difficult to design surgical LAA trials that are randomized or as rigorous as percutaneous device trials with core laboratory and longitudinal follow-up. Because most surgeons believe that something should be done to the LAA at the time of an AF procedure, it may be difficult to randomize surgical patients to a no-intervention group in the comparison of a surgical technique or new device. Historical $CHADS_2$ controls or the percutaneous trial control groups may provide the only comparative reference.

The importance of the LAA has been known for a half century, with multiple closure techniques used in time. Today, the opportunity for reliable closure exists. The simplest prospect for surgical closure is removal and oversew. Minimally invasive surgical techniques may lead to reliable closure devices for epicardial LAA occlusion. Finally, the field of percutaneous devices is promising, with safe and effective devices likely to be available in the very near future.

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