Aetna considers left atrial appendage closure (LAAC) devices medically necessary for nonvalvular atrial fibrillation (NVAF) when the device has received U.S. Food and Drug Administration (FDA) Premarket Approval (PMA) for that device’s FDA-approved indication and meet all of the conditions specified below:

- The member must have: A CHADS2 score ≥ 2 (congestive heart failure, hypertension, age >75, diabetes, stroke/transient ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3 (congestive heart failure, hypertension, age ≥ 65, diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, sex category); and
- A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in persons with NVAF prior to LAAC. Additionally, the shared decision making interaction must be documented in the medical record; and
- A suitability for short-term warfarin (i.e., the member is able to take short-term warfarin) and long-term aspirin but deemed unable to take long term oral anticoagulation for one or more of the following reasons, following the conclusion of shared decision making.

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
making, as LAAC is only considered medically necessary as a second line therapy to oral anticoagulants:

- Member has thromboembolism while on an oral anticoagulant (i.e., while INR is in therapeutic range); or
- Member has major bleed (intracranial bleed, significant gastrointestinal bleeding (not just guaiac positive stools) while on an oral anticoagulant (i.e., while INR is in therapeutic range); or
- Member has elevated risk of bleeding on oral anticoagulant with a HAS-BLED score of 3 or more; or
- Member has other absolute contraindication to long-term anticoagulation; and

- The member (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team (MDT) of medical professionals; and
- The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program; and
- The procedure must be performed by an interventional cardiologist(s), electrophysiologist(s) or cardiovascular surgeon(s) that meet the following criteria:

  - Has received training prescribed by the manufacturer on the safe and effective use of the device prior to performing LAAC; and
  - Has performed ≥ 25 interventional cardiac procedures that involve transeptal puncture through an intact septum; and
  - Continues to perform ≥ 25 interventional cardiac procedures that involve transeptal puncture through an intact septum, of which at least 12 are LAAC, over a two year period.

**Aetna considers cardiac devices for occlusion of the left atrial appendage experimental and investigational for all other indications.**

**Background**
Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and a leading cause of stroke. Individuals with AF have a higher risk for stroke due to the possibility of thrombus (blood clot) formation in coronary arteries. The left atrial appendage (LAA) of the heart was previously considered to have little purpose or activity; however, due to the shape of the appendage and lack of blood flow in the area, it is believed that thrombi could develop in certain individuals. While current standard treatment for non-valvular AF focuses on anticoagulation; it is suggested that closure by exclusion or occlusion of the LAA may reduce the risk for embolic stroke from atrial thrombi. Exclusion of the LAA may be performed at the same time as another open cardiac surgical procedure.

Stroke is one of the leading causes of death and disability in developed countries. Atrial fibrillation (AF), one of the most common cardiac arrhythmias, is a well-known predisposing factor for stroke, raising the risk significantly. Patients with AF have a 5-fold increased risk for stroke due to the possibility of thrombus (blood clot) formation in coronary arteries. The left atrial appendage (LAA) of the heart was previously considered to have little purpose or activity; however, due to the shape of the appendage and lack of blood flow in the area, it is believed that thrombi could develop in certain individuals. While current standard treatment for non-valvular AF focuses on anticoagulation; it is suggested that closure by exclusion or occlusion of the LAA may reduce the risk for embolic stroke from atrial thrombi.

Oral anti-coagulation (OAC) with warfarin is currently the most effective therapy for stroke risk reduction; however, this therapy increases the risk of bleeding and is often underutilized, contraindicated, or when administered, often subtherapeutic. It has been documented that the left atrial appendage (LAA) is the main source of left atrial thrombus, especially in nonrheumatic AF. Meta-analyses have shown that more than 90 % of atrial thrombi in patients with non-rheumatic AF originate in the LAA. Thus, LAA exclusion may reduce the risk of stroke in AF, and retrospective surgical data have demonstrated a reduced risk of embolic events if surgical LAA exclusion was also performed during mitral valve replacement. Recently, several less invasive percutaneous transcatheter techniques of LAA exclusion -- the PLAATO device, the Watchman device, and the Amplatzer Septal Occluder -- have been employed with initially encouraging results. These cardiac devices are designed to seal
LAA and avoid risk of clot migration in the blood stream. There is currently an ongoing randomized trial comparing percutaneous LAA exclusion to long-term OAC. Until such data are available, however, OAC should remain the standard of care for stroke prevention in patients with AF (Onalan and Crystal, 2007; Chiam and Ruiz, 2008).

Exclusion of the LAA may be performed at the same time as another open cardiac surgical procedure, or may be attempted using a less invasive transcatheter-based method. Generally, a catheter to deliver the device is inserted through a vein in the individual’s leg, and advanced to the right atrium of the heart. After an opening is made between the right and left atrium; the device is advanced via catheter to the LAA, where it purportedly opens and creates an occlusion of the appendage. After approximately 45 days, the area supposedly develops a thin layer of tissue which inhibits future clot formation. Examples of devices used for this procedure include; but are not limited to, the Amplatzer Cardiac Plug, Lariat Suture Delivery Device or WATCHMAN LAA Closure Technology. Currently, only the WATCHMAN has gained approval by the US Food and Drug Administration (FDA) for occlusion of the LAA. Following implantation of the WATCHMAN device, the individual must be able to tolerate anticoagulation medication for approximately 45 days post-procedure.

Sievert et al (2002) evaluated the feasibility and safety of implanting a novel device for percutaneous LAA transcatheter occlusion (PLAATO). Occlusion of the LAA using the PLAATO system was attempted in 15 patients with chronic AF at high-risk for stroke, who are poor candidates for long-term warfarin therapy. The implant consists of a self-expanding nitinol cage covered with a polymeric membrane. The LAA was successfully occluded in 15/15 patients (100 %). Angiography as well as trans-esophageal echocardiography (TEE) during the procedure showed that the device was well-seated in all patients and that there was no evidence of perforation, device embolization, or interference with surrounding structures. In 1 patient, the first procedure was complicated by a hemopericardium, which occurred during LAA access. A second attempt 30 days later was successful with no untoward sequela. No other complications occurred. At 1-month follow-up, chest fluoroscopy and TEE revealed continued stable implant position with smooth atrial-facing surface and no evidence of thrombus. The authors concluded that
transcatheter closure of the LAA is feasible in humans. The PLAATO system may be appropriate for patients with AF who are not suitable candidates for anti-coagulation therapy. Moreover, they noted that further trials are needed to show the long-term safety and its effectiveness in reducing stroke.

Ostermayer et al (2005) evaluated the feasibility of percutaneous LAA occlusion using the PLAATO system. Within 2 prospective, multi-center trials, LAA occlusion was attempted in 111 patients (age of 71 +/- 9 years). All patients had a contraindication for anti-coagulation therapy and at least 1 additional risk factor for stroke. The primary end point was incidence of major adverse events (MAEs), a composite of stroke, cardiac or neurological death, myocardial infarction, and requirement for procedure-related cardiovascular surgery within the 1st month. Implantation was successful in 108 of 111 patients (97.3 %, 95 % confidence interval [CI]: 92.3 % to 99.4 %) who underwent 113 procedures. One patient (0.9 %, 95 % CI: 0.02 % to 4.9 %) experienced 2 MAEs within the first 30 days: need for cardiovascular surgery and in-hospital neurological death; 3 other patients underwent in-hospital pericardiocentesis due to a hemopericardium. Average follow-up was 9.8 months; 2 patients experienced stroke. No migration or mobile thrombus was noted on TEE at 1 and 6 months after device implantation. The authors concluded that closing the LAA using the PLAATO system is feasible and can be performed at acceptable risk. It may become an alternative in patients with AF and a contraindication for lifelong anti-coagulation treatment.

Himbert and colleagues (2006) reported the results of a series of 11 consecutive AF patients (7 men and 4 women, mean age of 72 +/- 9 years) in whom percutaneous exclusion of the LAA by the PLAATO System was employed to prevent stroke. Subjects had AF for over 3 months, were at high-risk and had contraindications to OAC. The implantation of the prosthesis was performed after treatment with aspirin and clopidogrel, under general anesthesia radioscopy and TEE guidance with success in 9 cases (1 implantation refused in the catheter laboratory and 1 failure). The only complication observed was transient ST elevation treated by emergency angioplasty. The echographical and angiographical criteria of success of LAA exclusion were fulfilled in all implanted patients. The hospital course was uncomplicated. One
recurrence of stroke was observed at the 2nd month: TEE confirmed the absence of thrombosis, of migration of the prosthesis and its impermeability in all patients. After 7 +/- 5 months’ follow-up, no other adverse event was observed. The authors concluded that the PLAATO system is technically feasible. Moreover, they noted that despite encouraging results, its long-term effectiveness in the prevention of thrombo-embolic complications of AF remains to be demonstrated.

The Watchman LAA occluder is a parachute-shaped device designed to mechanically block the opening between the atrial appendage and the left atrium, preventing clots formed in the LAA from entering the main atrial cavity. It is composed of a nitinol (a self-expanding metal) frame covered with a polyester mesh and comes in several sizes (i.e., 21 mm, 24 mm, 27 mm, 30 mm, and 33 mm) to accommodate differences in anatomy. The Watchman occluder is implanted within or just behind the opening of the LAA during a percutaneous transcather procedure. Once deployed, it is anchored in place by means of fixation barbs on the nitinol frame, with its convex top bowing out toward the atrial chamber. The device becomes fully endothelialized within 9 months of implantation.

The Watchman LAA occluder is implanted percutaneously using standard cardiac catheterization techniques. The device is contained within the catheter and expands when implanted in the LAA. If repositioning is necessary, the device can be pulled back into the catheter and maneuvered to the correct position. This procedure requires a minimum 24-hour hospital stay, and regular follow-up for up to 1 year after implantation (Ingenix, 2009).

Fountain et al (2006) stated that the Watchman LAA occluder device is currently being tested in a Food and Drug Administration (FDA)-approved clinical trial, the PROTECT AF trial, for patients who are diagnosed with paroxysmal, persistent, or permanent non-valvular AF (NVAF). However, rigorous screening and the study design have resulted in the exclusion of a large number of patients. These researchers assessed the potential utility of this device among those who were eligible but excluded for trial criteria and the reasons for exclusion. Screening logs from the respective sites participating in the PROTECT AF trial were collected and analyzed for potential utilization outside of a research trial. Only 31 patients were enrolled into the research trial from the screening of 1,798 patients. Information from excluded patients was examined and it was determined
that 79% of these patients would be eligible for the device outside the research trial. Twenty-one percent of patients were not able to receive the device because of long-term warfarin need, contraindications to warfarin, unsuitable anatomy as determined by echocardiography, or the inability to take short-term aspirin and clopidogrel for protocol requirements. The authors concluded that should a device like the Watchman LAA occluder be approved, approximately 79% of all patients with AF would be eligible for device placement.

Sick et al (2007) evaluated the feasibility of implanting a device in the LAA in patients with AF to prevent thrombo-embolic stroke. The investigators explained that the Watchman LAA System is a nitinol device implanted percutaneously to seal the LAA. Patients were followed by clinical and TEE at 45 days and 6 months with annual clinical follow-up thereafter. A total of 66 patients underwent device implantation. Mean follow-up was 740 +/- 341 days. At 45 days, 93% (54 of 58) devices showed successful sealing of LAA according to protocol. Two patients experienced device embolization, both successfully retrieved percutaneously. No embolizations occurred in 53 patients enrolled after modification of fixation barbs. There were 2 cardiac tamponades, 1 air embolism, and 1 delivery wire fracture (1st generation) with surgical explantation but no long-term sequelae for the patient. Four patients developed a flat thrombus layer on the device at 6 months that resolved with additional anti-coagulation. Two patients experienced transient ischemic attack, 1 without visible thrombus. There were 2 deaths, neither device-related. Autopsy documented a stable, fully endothelialized device 9 months after implantation. No strokes occurred during follow-up despite greater than 90% of patients with discontinuation of anti-coagulation. The authors concluded that preliminary data suggest LAA occlusion with the Watchman System to be safe and feasible. They stated that a randomized study is ongoing comparing OAC with percutaneous closure.

In April 2009, the FDA’s advisory panel on circulatory systems devices voted 7 to 5 to recommend that the FDA approve the pre-market application for the Watchman LAA embolic protection device, subject to certain conditions.
Maisel (2009) noted that implantation of the Watchman LAA occluder is associated with significant procedural risk. After 449 attempted implantations, the Watchman device was successfully inserted in 408 patients (90.9%). Overall, 12.3% of patients had serious procedural complications, including peri-cardial effusion requiring drainage or surgery in about 5% as well as acute ischemic stroke due to air or thromboemboli in 1.1%. Four patients had to have the device removed because of device embolization or post-implantation sepsis. In total, 2.2% of attempted implantations resulted in cardiovascular surgical intervention because of device-related complications. In addition, the substantial learning curve associated with device implantation (the rate of serious peri-cardial effusion was 50% higher at less-experienced centers) has important implications for provider training. Also, although discontinuing warfarin therapy is appealing to many patients with AF, anyone who has a Watchman occluder must receive ongoing anti-coagulation therapy, anti-platelet therapy, or both. Studies in animals in which anti-platelet therapy was withheld showed acute thrombus formation on the device surface; the use of aspirin and clopidogrel in subsequent studies reduced the quantity of thrombus.

Maisel (2009) stated that routine implantation does not appear to be warranted, though the device is promising and may be a reasonable option for selected patients with a particularly high-risk of bleeding complications. Nevertheless, the lessons learned from the well-publicized recent problems with other cardiovascular devices (e.g., drug-eluting stents and implantable defibrillator leads) should be heeded. In those cases, large numbers of patients were rapidly exposed to a new device on which there were limited performance data. The concerns about procedural safety and the need for long-term follow-up should be addressed before the Watchman device is deployed widely.

It is interesting to note that Dr. Maisel was acting chair of the FDA’s circulatory system medical device advisory panel, which reviewed data related to the Watchman LAA device and voted 7 to 5 in favor of approval with conditions. As acting panel chair, Dr. Maisel did not vote at the meeting.
The Amplatzer PFO (patent foramen ovale) Occluder is a mesh-covered, nitinol pair of disks containing a radiopaque marker implanted percutaneously. It is FDA-approved for repairing defects in the atrial septum. In limited cases, the Amplatzer has also been used to occlude the LAA, however it is not approved by the FDA for this purpose (Ingenix, 2009).

Cruz-Gonzalez et al (2009) stated that although the Amplatzer septal occluder device was not originally intended to occlude the LAA, it has been used with success in the authors’ institution for this purpose. They presented an illustrative case of a patient with AF no longer suitable for chronic OCA referred for percutaneous exclusion of the LAA. She was treated successfully with an Amplatzer septal occluder. Although the authors’ experience with this device holds promise, future trials are needed to explore this strategy.

Syed and Halperin (2007) stated that percutaneous LAA occlusion devices have shown some initial successes, but additional safety and effectiveness data are required before this approach can be routinely considered. Lerakis and Synetos (2008) stated that the PLAATO System and the Watchman LAA system are currently the 2 devices specifically designed for LAA occlusion. Although available data are still limited, LAA occlusion is technically feasible, with good intermediate results, but its long-term safety and ability to reduce stroke incidence remains unproven. They stated that randomized studies will clarify the usefulness of LAA occlusion devices as an alternative treatment strategy to long-term anti-coagulation.

Mobius-Winkler et al (2008) reviewed the different devices for stroke prevention in patients with AF. Recently, 2 devices developed for percutaneous transcatheter occlusion of the LAA have been studied: (i) the PLAATO device, and (ii) the Watchman device. Safety and feasibility data are available for both devices. About 200 patients have received a PLAATO device. These patients were at high-risk for thrombo-embolic stroke and were not candidates for OAC therapy. The Watchman device was implanted in 75 patients who were eligible for long-term anti-coagulation therapy with a moderate-risk for thrombo-embolic stroke due to NVAF. The authors concluded that for both devices, a reduction in the
risk of stroke was documented, and device implantation was shown to be safe and feasible. Provided the ongoing trials show non-inferiority to OAC, another therapeutic option will become available to prevent ischemic strokes. In addition, Franke and colleagues (2009) stated that techniques to prevent cardio-embolic stroke by percutaneous occlusion of the LAA in patients with AF are emerging.

The American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines’ report on the management of patients with AF (2006), as well as the Institute for Clinical Systems Improvement’s guideline on AF (2007) did not mention the use of occluder devices to prevent thrombo-embolic stroke in the LAA of patients with AF.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2006) concluded: "Current evidence on the safety and efficacy of percutaneous occlusion of the left atrial appendage (LAA) for atrial fibrillation does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research."

Furthermore, the Australian Safety and Efficacy Registrar of New Interventional Procedures - Surgical assessment on percutaneous LAA transcatheter occlusion (PLAATO) system (Lee, 2007) noted that despite promising results, no randomized controlled trials have been conducted at the time of writing and the long-term effectiveness of the PLAATO system remains unknown. Due to the limited evidence available, the Australian agency recommended the monitoring of this technology.

Holmes et al (2009) evaluated the safety and effectiveness of percutaneous closure of the LAA for prevention of stroke compared with warfarin treatment in patients with AF. Adult patients with NVAF were eligible for inclusion in this multi-center, randomized non-inferiority trial if they had at least 1 of the following: previous stroke or transient ischemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. A total of 707 eligible patients were randomly assigned in a 2:1 ratio by computer-generated randomization sequence to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n = 463) or to warfarin treatment with a target international normalized ratio between 2.0 and 3.0 (control; n = 244). Effectiveness
was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. These investigators selected a 1-sided probability criterion of non-inferiority for the intervention of at least 97.5 %, by use of a 2-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. Analysis was by intention-to-treat. At 1,065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years (95 % credible interval [CrI]: 1.9 to 4.5) in the intervention group and 4.9 per 100 patient-years (2.8 to 7.1) in the control group (rate ratio [RR] 0.62, 95 % CrI: 0.35 to 1.25). The probability of non-inferiority of the intervention was more than 99.9 %. Primary safety events were more frequent in the intervention group than in the control group (7.4 per 100 patient-years, 95 % CrI: 5.5 to 9.7, versus 4.4 per 100 patient-years, 95 % CrI: 2.5 to 6.7; RR 1.69, 1.01 to 3.19). The authors concluded that the effectiveness of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of peri-procedural complications. They noted that closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with NVAF.

In a commentary on the afore-mentioned study by Holmes et al, Sobieraj-Teague and Eikelboom (2009) stated that major safety concerns need to be overcome and efficacy needs to be better established before the device can be considered as an alternative to warfarin anti-coagulation in patients with AF. Furthermore, Whitlock et al (2009) noted that although recent results with the percutaneous closure device are promising, the evidence of efficacy and safety is insufficient to recommend this approach for any patients other than those in whom long-term warfarin is absolutely contraindicated. They stated that more large randomized controlled trials of the device and surgical approaches should be done. At present, anti-thrombotic medications will remain the standard treatments to prevent stroke in patients with AF.

Dawson et al (2010) examined if patients undergoing cardiac surgery with AF should have LAA exclusion? Altogether 310 papers were found using the reported search, of which 12 represented the best evidence to answer the clinical question. The authors, journal, date and country of
Cardiac Devices and Procedures for Occlusion of the Left Atrial Appendage

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Publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. These investigators concluded that despite finding 5 clinical trials including 1 randomized controlled trial, that studied around 1,400 patients who underwent LAA occlusion, the results of these studies do not clearly show a benefit for appendage occlusion. Indeed of the 5 studies, only 1 showed a statistical benefit for LAA occlusion, with 3 giving neutral results, and in fact 1 study demonstrating a significantly increased risk. One reason for this may be the inability to achieve acceptably high rates of successful occlusion on echocardiography when attempting to perform this procedure. The highest success rate was only 93% but most studies reported only a 55 to 66% successful occlusion rate when attempting closure in a variety of methods including stapling, ligation and amputation. Currently, the evidence is insufficient to support LAA occlusion and may indeed cause harm especially if incomplete exclusion occurs.

The American College of Cardiology Foundation Task Force on expert consensus document on cardiovascular magnetic resonance (Hundley et al, 2010) stated that standardization of protocols and further studies are needed to determine if cardiovascular magnetic resonance provides a reliable effective method for detecting thrombi in LAA in patients with AF.

Bartus et al (2011) examined the feasibility of a closed-chest surgical suture ligation of the LAA in man. A total of 13 patients undergoing either mitral valve surgery (n = 2) or electrophysiological study and radiofrequency catheter ablation for AF (n = 11) underwent ligation of the LAA with the Lariat snare device. In patients having an ablation procedure, peri-cardial access was obtained prior to the patients undergoing radiofrequency catheter ablation. After trans-septal catheterization, endocardial and epicardial magnet-tipped guide wires were positioned under fluoroscopic guidance to stabilize the LAA. Trans-esophageal echocardiography was used as guidance for positioning a marker balloon at the ostium of the LAA. An over-the-wire approach was used to guide the Lariat snare device over the LAA to allow closure and suture ligation of the LAA. Contrast fluoroscopy and TEE were used to confirm acute closure of the LAA. Both mitral valve replacement (MVR) patients had complete closure of the LAA determined by visual inspection; 10 of 11 patients having ablation underwent a successful closed-chest LAA ligation procedure with TEE and contrast fluoroscopy.
verification of closure of the LAA. Only 1 of 11 procedures was terminated owing to the lack of echocardiography guidance of the snare over the marker balloon. One patient with pectus excavatum did have ligation of his LAA; however, a thorascopic procedure was required to remove the snare from the LAA owing to compression of the Lariat by the concave sternum. There were no other significant complications. The authors concluded that catheter-based surgical suture ligation of the LAA is feasible in humans. They noted that this novel catheter approach may be appropriate for patients with AF who are ineligible for anti-coagulation therapy. Moreover, they stated that further investigation is needed to demonstrate the long-term safety and effectiveness of LAA closure.

Ailawadi et al (2011) reported the initial results of a multi-center FDA trial to assess the safety and effectiveness of a novel LAA exclusion clip (the AtriClip, Atricure Inc, Westchester, OH). Patients undergoing elective cardiac surgery via median sternotomy with AF or a congestive heart failure, hypertension, age greater than 75 Years, diabetes mellitus, stroke score greater than 2 were eligible for concomitant AtriClip device insertion. Device insertion (35, 40, 45, and 50 mm) was performed at any point after sternotomy on or off cardio-pulmonary bypass. Safety was assessed at 30 days, and effectiveness of LAA exclusion was assessed at operation (by TEE) and 3-month follow-up (by computed tomography angiography or TEE). A total of 71 patients (mean age of 73 years) undergoing open cardiac surgery at 7 U.S. centers were enrolled in the study. The LAA in 1 patient was too small and did not meet eligibility criteria; the remaining 70 patients had successful placement of an AtriClip device. Intra-procedural successful LAA exclusion was confirmed in 67 of 70 patients (95.7 %). Although significant adverse events occurred in 34 of 70 patients (48.6 %), there were no adverse events related to the device and no peri-operative mortality. At 3-month follow-up, 1 patient died and 65 of 70 patients (92.9 %) were available for assessment. Of the patients who underwent imaging, 60 of 61 patients (98.4 %) had successful LAA exclusion by computed tomography angiography or TEE imaging. The authors concluded that in this small study, safe and atraumatic exclusion of the LAA 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. Moreover, they stated that long-term studies are needed to evaluate the effectiveness of the AtriClip in the prevention of stroke.
Montenegro et al (2012) determined the feasibility of percutaneous occlusion of the LAA in patients at high-risk of embolic events and limitations to the use of anti-coagulation. These investigators reported their initial experience with the Amplatzer Cardiac Plug (St. Jude Medical Inc., Saint Paul, Estados Unidos) in patients with NVAF. They selected patients at high-risk of thrombo-embolism, major bleeding, contraindications to the use or major instability in response to the anti-coagulant. The procedures were performed percutaneously under general anesthesia and TEE. The primary outcome was the presence of peri-procedural complications and follow-up program included clinical and echocardiographic review within 30 days and by telephone contact after 9 months. In 5 selected patients it was possible to occlude the LAA without peri-procedural complications. There were no clinical events in follow-up. The authors concluded that controlled clinical trials are needed before percutaneous closure of the LAA should be considered an alternative to anti-coagulation in NVAF. But the device has shown to be promising in patients at high-risk of embolism and restrictions on the use of anti-coagulants. This is in agreement with the observations of Weglarz et al (2012) who stated that percutaneous closure of the LAA seems to be a promising tool to prevent AF-related strokes in a selected group of patients.

Lam and colleagues (2012) reported the initial safety, feasibility, and 1-year clinical outcomes following AMPLATZER cardiac plug (ACP) implantation. A total of 20 NVAF patients (16 males, age 68 +/- 9 years) with high-risk for developing cardio-embolic stroke (CHADS(2) score: 2.3 +/- 1.3) and contraindications to warfarin received ACP implants from June 2009 to May 2010. Patients received general anesthesia (n = 9) or controlled propofol sedation (n = 11) and the procedures were guided by fluoroscopy and TEE. Clinical follow-up was arranged at 1 month and then every 3 months after implantation, whereas, a TEE was scheduled at 1 month upon completion of dual anti-platelet therapy. The LAA was successfully occluded in 19/20 patients (95 %). One procedure was abandoned because of catheter-related thrombus formation. Other complications included coronary artery air embolism (n = 1) and TEE-attributed esophageal injury (n = 1). The median procedural and fluoroscopic times were 79 (IQR: 59 to 100) and 18 (IQR 12 to 27) minutes, respectively. The mean size of implant was 23.6 +/- 3.1 mm. The average hospital stay was 1.8 +/- 1.1 days. Follow-up TEE showed
all the LAA orifices were sealed without device-related thrombus formation. No stroke or death occurred at a mean follow-up of 12.7 +/- 3.1 months. The authors concluded that these preliminary findings suggested LAA closure with ACP is safe, feasible with encouraging 1-year clinical outcomes. They stated that further large-scaled trials are needed to confirm the effectiveness of this device.

Aryana et al (2012) stated that evidence suggests that at least 90% of left atrial thrombi discovered in patients with AF are localized to the LAA. Surgical ligation or excision of the LAA is considered the standard of care in patients who undergo mitral valve surgery or as an adjunct to a surgical Maze procedure for treatment of AF. In addition, in selected patients with AF and an elevated risk of thrombo-embolic events, particularly in those with contraindication to OAC therapy, it is reasonable to consider LAA exclusion to offer protection against ischemic stroke and other embolic complications. This can be achieved through a number of different strategies, including surgical amputation or ligation of the LAA, percutaneous endocardial occlusion of the LAA by deployment of occlusive devices, and also ligation of the LAA via a closed-chest, percutaneous, epicardial catheter-based approach in select patients. Although results from several recent percutaneous LAA closure and ligation studies are highly promising, the evidence for long-term safety and effectiveness is insufficient to presently recommend this approach to all patients other than those in whom long-term OAC is contraindicated. The authors concluded that future randomized studies are needed to further address the long-term safety and effectiveness of these therapeutic options.

Bai et al (2012) stated that transcatheter LAA closure with the Watchman device has become one of the therapeutic options in AF patients who are at high risk for ischemic stroke. However, the incidence and evolution of incomplete occlusion of the LAA during and after placement of the Watchman device has not been reported. A total of 58 consecutive patients who had undergone Watchman device implant were included in the study. Intra-procedural, 45-day and 12-month TEE images were reviewed and analyzed. Peri-device gap was noted in 16 (27.6 %), 17 (29.3 %), and 20 (34.5 %) patients across the 3 time points. Intra-procedural gaps are more likely to be persistent until 12 months and become larger in size over time. New gap also occurs during follow-up
even if the LAA was completely sealed at implantation. One patient had an ischemic stroke 4.7 months after implant; another patient developed a left atrial thrombus over the device 21.6 months after implant. Both patients had intra-procedural gap and discontinued warfarin therapy after the 45-day evaluation. The authors concluded that incomplete LAA occlusion with a gap between the Watchman device surface and the LAA wall is relatively common. Intra-procedural gaps are more likely to become bigger over time and persist, while new gaps also occur during follow-up. They stated that further studies are needed to verify if the presence and persistence of a peri-device gap is associated with increased risk of thrombo-embolic event in AF patients implanted with a Watchman device.

Alli et al (2013) evaluated quality-of-life (QOL) parameters in a subset of patients enrolled in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial. Quality-of-life using the Short-Form 12 Health Survey, version 2, measurement tool was obtained at baseline and 12 months in a subset of 547 patients in the PROTECT AF trial (361 device and 186 warfarin patients). The analysis cohort consisted of patients for whom either paired QOL data were available after 12 months of follow-up or for patients who died. With the device (the Watchman), the total physical score improved in 34.9 % and was unchanged in 29.9 % versus warfarin in whom 24.7 % were improved and 31.7 % were unchanged (p = 0.01). Mental health improvement occurred in 33.0 % of the device group versus 22.6 % in the warfarin group (p = 0.06). There was a significant improvement in QOL in patients randomized to device for total physical score, physical function, and in physical role limitation compared to control. There were significant differences in the change in total physical score among warfarin naive and not-warfarin naive subgroups in the device group compared to control, but larger gains were seen with the warfarin naive subgroup with a 12-month change of 1.3 ± 8.8 versus -3.6 ± 6.7 (p = 0.0004) device compared to warfarin. The authors concluded that patients with non-valvular AF at risk for stroke treated with LAA closure have favorable QOL changes at 12 months versus patients treated with warfarin. The major drawbacks of this study were small sample size and short follow-up period.
Cardiac Devices and Procedures for Occlusion of the Left Atrial Appendage

In an observational study, Reddy et al (2013) assessed the safety and effectiveness of LAA closure in non-valvular AF patients ineligible for warfarin therapy. A multi-center, prospective, non-randomized study was conducted of LAA closure with the Watchman device in 150 patients with non-valvular AF and CHADS₂ (congestive heart failure, hypertension, age greater than or equal to 75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score greater than or equal to 1, who were considered ineligible for warfarin. The primary efficacy end-point was the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death. The mean CHADS₂ score and CHA₂DS₂-VASc (CHADS₂ score plus 2 points for age greater than or equal to 75 years and 1 point for vascular disease, aged 65 to 74 years, or female sex) score were 2.8 ± 1.2 and 4.4 ± 1.7, respectively. History of hemorrhagic/bleeding tendencies (93 %) was the most common reason for warfarin ineligibility. Mean duration of follow-up was 14.4 ± 8.6 months. Serious procedure- or device-related safety events occurred in 8.7 % of patients (13 of 150 patients). All-cause stroke or systemic embolism occurred in 4 patients (2.3 % per year): ischemic stroke in 3 patients (1.7 % per year) and hemorrhagic stroke in 1 patient (0.6 % per year). This ischemic stroke rate was less than that expected (7.3 % per year) based on the CHADS₂ scores of the patient cohort. The authors concluded that LAA closure with the Watchman device can be safely performed without a warfarin transition, and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral anticoagulation. The main drawbacks of this study were its observational nature (prone to selection bias), non-randomization design, as well as the lack of a control or alternative treatment group.

In an observational study, Bartus and colleagues (2013) stated that embolic stroke is the most devastating consequence of AF. Exclusion of the LAA is believed to decrease the risk of embolic stroke. In an observational study, these researchers determined the safety and effectiveness of LAA closure via a percutaneous LAA ligation approach. A total of 89 patients with AF were enrolled to undergo percutaneous ligation of the LAA with the Lariat device. The catheter-based Lariat device consists of a snare with a pre-tied suture that is guided epicardially over the LAA. Closure of the LAA was confirmed with TEE and contrast fluoroscopy immediately, then with TEE at 1 day, 30 days, 90 days, and 1
year post-LAA ligation. Eighty-five (96%) of 89 patients underwent successful LAA ligation. Eighty-one of 85 patients had complete closure immediately. Three of 85 patients had a less than or equal to 2-mm residual LAA leak by TEE color Doppler evaluation. One of 85 patients had a less than or equal to 3-mm jet by TEE. There were no complications due to the device. There were 3 access-related complications (during peri-cardial access, n = 2; and trans-septal catheterization, n = 1). Adverse events included severe pericarditis post-operatively (n = 2), late peri-cardial effusion (n = 1), unexplained sudden death (n = 2), and late strokes thought to be non-embolic (n = 2). At 1 month (81 of 85) and 3 months (77 of 81) post-ligation, 95% of the patients had complete LAA closure by TEE. Of the patients undergoing 1-year TEE (n = 65), there was 98% complete LAA closure, including the patients with previous leaks. The authors concluded that LAA closure with the Lariat device can be performed effectively with acceptably low access complications and peri-procedural adverse events. They noted that this observational study provided evidence of the reliability of LAA exclusion with acceptable low access complications and adverse events; enabling this percutaneous LAA ligation procedure to be used in future randomized clinical trials to determine whether LAA exclusion prevents thrombo-embolic events in patients with AF. They also noted that future prospective studies will require a systematic protocol for discontinuing anti-coagulation by a pre-specified time point to accurately evaluate the long-term risk reduction for thrombo-embolic events following LAA ligation. The major drawbacks of this study included (i) this was a non-randomized, single-center trial. Much of the experience was concentrated with several operators, thus potentially skewing the efficiency of performing the procedures, (ii) the assessment of LAA closure by TEE might be over-estimated due to AF resulting in decreased inflow and outflow velocities in the LAA. This may result in the lack of detection of small communications between the LA and a sutured LAA by color flow or spectral Doppler flow assessment, and (iii) long-term results for thrombo-embolic event reduction were confounded by the high proportion (61%) of patients on warfarin at the time of last follow-up.
Massumi et al (2013) noted that AF increases by 5-fold a patient's risk for thrombo-embolic stroke. The main source of emboli in AF is the LAA. Thus, LAA closure could reduce the risk for thrombo-embolic events in AF. These investigators reported the first U.S. experience with a novel percutaneous LAA closure device, the Lariat snare device, and its outcomes in 21 patients with AF, CHADS(2) scores greater than or equal to 2, and contraindications to anti-coagulation. The LAA was closed with a snare containing suture from within the peri-cardial space. The intra-operative success of the procedure was confirmed by left atrial angiography and TEE color Doppler flow. The effectiveness of the procedure was evaluated by follow-up TEE. The incidence of peri-procedural and short-term complications was assessed by reviewing medical records. Twenty patients (100 %) had successful LAA exclusion that was preserved at 96 ± 77 days. No patient had a stroke during an average of 352 ± 143 days of follow-up. One patient had right ventricular perforation and tamponade that required surgical exploration and repair. Two patients required prolonged hospitalization: 1 because of peri-cardial effusion that required repeat peri-cardiocentesis and 1 because of non-cardiac co-morbidities. Three patients developed pericarditis less than 1 month after the procedure, of whom 1 had associated peri-cardial effusion that required drainage. The authors concluded that percutaneous LAA exclusion can be achieved successfully and with an acceptable incidence of peri-procedural and short-term complications. Moreover, they stated that further studies are needed to determine whether LAA exclusion lowers the long-term risk for thrombo-embolic events in patients with AF and contraindications to anti-coagulation. The authors also stated that “the present case series has the inherent limitations of all such retrospective series, including potential case selection bias, incomplete data, and the absence of a control group. No conclusions can be made about the clinical or stroke prevention efficacy of this procedure compared to long-term anticoagulation or other LAA exclusion techniques. Experience with many more patients and longer follow-up are necessary to demonstrate the efficacy of this novel technique and to refine its indications and contraindications to maximize patient safety”.

Urena et al (2013) evaluated the results associated with LAA closure (LAAC) with the AMPLATZER Cardiac Plug (ACP) (St. Jude Medical, Minneapolis, MN) in patients with non-valvular AF and absolute contraindications to anti-coagulation therapy. A total of 52 patients with
non-valvular AF underwent LAAC with the ACP device in 7 Canadian centers. Most patients received short-term (1 to 3 months) dual-antiplatelet therapy after the procedure and single-antiplatelet therapy thereafter. A TEE was performed in 74 % of patients at the 6-month follow-up. No patient was lost to follow-up (greater than or equal to 12 months in all patients). The mean age and median (interquartile range) CHADS2 score were 74 ± 8 years and 3 (2 to 4), respectively. The procedure was successful in 98.1 % of the patients, and the main complications were device embolization (1.9 %) and peri-cardial effusion (1.9 %), with no cases of peri-procedural stroke. At a mean follow-up of 20 ± 5 months, the rates of death, stroke, systemic embolism, peri-cardial effusion, and major bleeding were 5.8 %, 1.9 %, 0 %, 1.9 %, and 1.9 %, respectively. The presence of mild peri-device leak was observed in 16.2 % of patients at the 6-month follow-up as evaluated by TEE. There were no cases of device thrombosis. The authors concluded that in patients with non-valvular AF at high risk of cardio-embolic events and absolute contraindications to anti-coagulation, LAAC using the ACP device followed by dual-/single-antiplatelet therapy was associated with a low rate of embolic and bleeding events after a mean follow-up of 20 months. No cases of severe residual leak or device thrombosis were observed at the 6-month follow-up. Moreover, the authors stated that “these results do not provide sufficient evidence to state that LAAC without anti-coagulation provides sufficient safety to recommend this approach until adequate data from clinical trials can be obtained. Also, larger studies with a longer follow-up and a more complete echocardiographic follow-up will have to confirm these results”.

Nietlispach et al (2013) reported a 10-year single center experience with Amplatzer devices for LAA occlusion. Short- and intermediate-term outcomes of patients who underwent LAA occlusion were assessed. All procedures were performed under local anesthesia without TEE. Patients were discharged on acetylsalicylic acid and clopidogrel for 1 to 6 months. Occlusion of the LAA was attempted in 152 patients (105 males, age of 72 ± 10 years, CHA2 DS2 -Vasc-score 3.4 ± 1.7, HAS-BLED-score 2.4 ± 1.2). Non-dedicated devices were used in 32 patients (21 %, ND group) and dedicated Amplatzer Cardiac Plugs were used in 120 patients (79 %, ACP group). A patent foramen ovale or atrial septal defect was used for left atrial access and closed at the end of LAA occlusion in 40 patients. The short-term safety end-points (procedural complications, bleeds)
occurred in 15 (9.8 %) and the efficacy end-points (death, stroke, systemic embolization) in 0 patients. Device embolization occurred more frequently in the ND as compared to the ACP group (5 patients or 12 % versus 2 patients or 2 %). Mean intermediate-term follow up of the study population was 32 months (range of 1 to 120). Late deaths occurred in 15 patients (5 cardiovascular, 7 non-cardiac, and 3 unexplained). Neurologic events occurred in 2, peripheral embolism in 1, and major bleeding in 4 patients. The composite safety and effectiveness end-point occurred in 7 % and 12 % of patients. The authors concluded that LAA closure may be a good alternative to oral anti-coagulation. They stated that this hypothesis needs to be tested in a randomized clinical trial to ensure that all potential biases of this observational study are accounted for.

Ohtsuka et al (2013) evaluated thoracoscopic stand-alone left atrial appendectomy for thrombo-embolism prevention in non-valvular AF. A total of 30 patients (mean age of 74 ± 5.0 years) who had had thrombo-embolisms were selected. A subgroup of 21 patients (mean age of 75 years; mean CHA2DS2 VASc score of 4.5) urgently needed an alternative treatment to anti-coagulation: warfarin was contraindicated due to hemorrhagic side effects in 13, the international normalized ratio was uncontrollable in 7, and transient ischemic attacks had developed immediately after the warfarin dose was reduced for oncological treatment in 1. The LAA was thoracoscopically excised with an endoscopic cutter. Thoracoscopic appendectomy (mean operating time of 32 mins, switched to mini-thoracotomy in 2 cases) led to no mortality and no major complications. Three-month post-operative 3-dimensional enhanced computed tomography, performed with patients’ consent, confirmed the completeness of the appendectomy. Patients have been followed for 1 to 38 months (mean of 16 ± 9.7 months [18 ± 9.4 months for the subgroup]). One patient died of breast cancer 28 months after surgery. Despite discontinued anti-coagulation, no patients had experienced recurrence of thrombo-embolism. The authors concluded that thoracoscopic stand-alone appendectomy is potentially safe and may allow surgeons to achieve relatively simple, complete LAA closure. Moreover, they stated that further experience may demonstrate this technique to be a viable option for thrombo-embolism prevention in non-
valvular AF. Drawbacks of this study included small sample size, short follow-up, as well as lack of randomized, controlled comparisons with other therapeutic options.

In an editorial that accompanied the afore-mentioned study, Turi (2013) stated that “although this approach looks potentially useful, the single site, small number of patients, limited data, and limited follow-up do not allow for any claim of safety and efficacy .... It has the appeal of simplicity and ready availability of a generally inexpensive technology, but the safety in particular needs to be established .... Until then, although long-term anticoagulation is cumbersome and has its own significant (but well established) toxicities, for those who are appropriate candidates, it remains the best studied approach as well as standard of care”.

Don and colleagues (2013) stated that occlusion of the LAA may reduce the risk of stroke in patients with AF. Trials comparing LAA occlusion to warfarin anti-coagulation in patients with non-valvular AF showed a reduction in hemorrhagic stroke, although an increase in safety events due to procedural complications. While long-term follow-up suggested possible superiority of LAA occlusion due to fewer strokes and bleeding events, the superior dosing and safety profiles of the novel oral anti-coagulants raise the accepted threshold for safety and effectiveness of LAA occlusion procedures, and underscore the need for randomized studies comparing LAA occlusion with these newer anti-coagulants.

Emmert et al (2014) reported on the long-term safety and effectiveness data on LAA closure using a novel epicardial LAA clip device in patients undergoing cardiac surgery. A total of 40 patients with AF were enrolled in this prospective “first-in-man” trial. The inclusion criterion was elective cardiac surgery in adult patients with AF for which a concomitant ablation procedure was planned. Intra-operative TEE was used to exclude LAA thrombus at baseline and evaluated LAA perfusion after the procedure, while CT was used for serial imagery work-up at baseline, 3-, 12-, 24- and 36-month follow-up. Early mortality was 10 % due to non-device-related reasons, and thus 36 patients were included in the follow-up consisting of 1,285 patient-days and mean duration of 3.5 ± 0.5 years. On CT, clips were found to be stable, showing no secondary dislocation 36 months after surgery. No intra-cardial thrombi were seen, none of the LAA was re-perfused and with regard to LAA stump, none of the patients
demonstrated a residual neck of greater than 1 cm. Apart from 1 unrelated transient ischemic attack (TIA) that occurred 2 years after surgery in a patient with carotid plaque, no other strokes and/or neurological events demonstrated in any of the studied patients during follow-up. The authors concluded that this was the first 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. The authors concluded that minimal access epicardial LAA clip closure may become an interesting therapeutic option for patients in AF who are not amenable to anti-coagulation and/or catheter closure. Moreover, they stated that further data are needed to establish LAA occlusion as a true and viable therapy for stroke prevention.

Furthermore, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) practice guideline on “Management of patients with atrial fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations)” (Anderson et al, 2013) does not mention the use of epicardial clipping of the LAA, left atrial appendectomy, and cardiac devices for occlusion of the LAA as therapeutic options.

The European Society of Cardiology’s updated guidelines on “The management of atrial fibrillation” (Camm et al, 2012) and the Agency for Healthcare Research and Quality’s comparative effectiveness review on “Treatment of atrial fibrillation” (Al-Khatib et al, 2013) did not mention LAA occlusion (LAAO) as a therapeutic option.

Freixa et al (2014) noted that the Amplatzer™ Amulet™ (Amulet) is the evolution of the Amplatzer™ Cardiac Plug, a dedicated device for percutaneous LAAO. The new device has been designed to facilitate the implantation process, improve the sealing performance and further reduce the risk of complications. In a prospective, single-center study, these investigators described the initial experience with the Amplatzer Amulet for percutaneous LAAO. The indication for LAA closure was a formal contraindication for oral anti-coagulation or previous history of stroke due to international normalized ratio (INR) lability. All procedures were done under general anesthesia and TEE guidance. Transthoracic
Echocardiography was performed 24 hours after the procedure in order to rule out procedural complications before discharge. Further follow-up was done with a clinical visit and TEE at 1 to 3 months. Between July 2012 and June 2013, a total of 25 patients with a mean CHA2DS2-VASC of 4.3 ± 1.7 underwent LAAO with the Amplatzer Amulet. The device was successfully implanted in 24 patients (96%) without any procedural stroke, pericardial effusion or device embolization. None of the patients presented any clinical event at follow-up. Follow-up TEE showed complete LAA sealing in all patients with no residual leaks greater than 3 mm and no device embolization. One patient (4.1%) presented a device thrombosis at follow-up without clinical expression. The authors concluded that in this initial series of patients, the Amulet showed a remarkable acute and short-term performance in terms of feasibility and safety as depicted by the high successful implantation rate and the low incidence of complications. Moreover, they stated that further investigation is needed to ascertain the effectiveness of the Amulet.

Hussain et al (2014) stated that AF is the most commonly encountered clinical arrhythmia, and stroke prevention remains an integral part of management of AF. Long-term therapy with oral anti-coagulants, though effective, has many limitations, and these limitations have encouraged the search for device-based alternatives. In patients with non-valvular AF, approximately 90% of thrombi are thought to arise from the LAA. The LAA can be obliterated surgically or percutaneously, and this should reduce the incidence of systemic thrombo-embolic events in AF, ideally without the need for further anti-coagulation. These investigators examined the currently available LAAO devices and the evidence behind these devices. They concluded that although additional evidence from randomized controlled trials (RCTs) is needed to fully characterize the safety and effectiveness of all of these devices; LAAO has the potential to offer an attractive alternative for those at high stroke risk but are under-protected because of contraindications to anti-coagulant therapy.

In a meta-analysis, Tsai and colleagues (2015) evaluated current evidence on the safety and effectiveness between LAAO and LAA preservation cohorts for patients undergoing cardiac surgery. Electronic searches were performed using 6 electronic databases from their inception to November 2013, identifying all relevant comparative randomized and observational studies comparing LAAO with non-LAAO.
Lau and Lip (2014) discussed the anti-platelet agents, vitamin K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOACs), and their safety and effectiveness for stroke prevention in AF. Focus was placed on the NOACs, their limitations as well as special considerations. A short assessment of other non-pharmacological anti-thrombotic procedures was also made. An extensive PubMed search was used to identify suitable papers. The authors concluded that despite the advent of NOACs, the VKAs will remain as an important oral anti-coagulant due to its versatility. However, convenience and limited food or drug interactions will make NOACs attractive options. The choice between various NOACs will depend on several important factors. Over time, the role for anti-platelet agents will gradually diminish. Moreover, they stated that LAAO devices have shown promising results and may have the potential to change the way clinicians manage thromboembolism risks related to AF.

Horstmann et al (2014) evaluated the safety and feasibility of percutaneous LAAO in patients with AF and previous intra-cranial hemorrhage (ICH). In an explorative, prospective, single-center,
observational study, LAAO was performed in patients with previous ICH and AF using the Amplatzer Cardiac Plug device. Risks of ischemic strokes and hemorrhagic complications were estimated using the CHA2DS2Vasc score and the HAS-BLED score. Before and 1, 6, 12, and 24 months after the procedure, clinical status and complications were recorded. Major complications were predefined as peri-procedural stroke, death, peri-cardial effusion, and device embolism. Left atrial appendage occlusion was performed in 20 patients. Based on CHA2DS2Vasc score (mean 4.5 ± 1.4) and HAS-BLED score (mean 4.7 ± 1.0), annual risks of stroke and hemorrhagic complications were 4.0 % to 6.7 % and 8.7 % to 12.5 %, respectively. No patient had a procedure-related complication. Minor post-procedural complications were observed in 4/20 patients (2 inguinal hematoma, 1 self-limiting asystole, and 1 thrombus formation on device). No ischemic or hemorrhagic stroke occurred during a mean follow-up of 13.6 ± 8.2 months. The authors concluded that in this first study of LAAO in patients with previous ICH, LAAO appears feasible and safe. Moreover, they stated that a larger, controlled trial is needed to evaluate the safety and effectiveness of the procedure compared to other preventive measures.

Whitlock et al (2014) stated that occlusion of the LAA is a promising approach to stroke prevention in AF. However, evidence of its safety and effectiveness to-date is lacking. These researchers described the rationale and design of a definitive LAAO trial in cardiac surgical patients with AF. These investigators plan to randomize 4,700 patients with AF in whom on-pump cardiac surgical procedure is planned to undergo LAAO or no LAAO. The primary outcome is the first occurrence of stroke or systemic arterial embolism over a mean follow-up of 4 years. Other outcomes include total mortality, operative safety outcomes (chest tube output in the first post-operative 24 hours, rate of post-operative re-exploration for bleeding in the first 48 hours post-surgery and 30-day mortality), re-hospitalization for heart failure, major bleed, and myocardial infarction. Left Atrial Appendage Occlusion Study (LAAOS) III is funded in a vanguard phase by the Canadian Institutes for Health Research (CIHR), the Canadian Network and Centre for Trials Internationally, and the McMaster University Surgical Associates. As of September 9, 2013, a total of 162 patients have been recruited into the study. The authors concluded that LAAOS III will be the largest trial to explore the
effectiveness of LAAO for stroke prevention. Its results will lead to a better understanding of stroke in AF and the safety and effectiveness of surgical LAA occlusion.

An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBCA, 2014) concluded that percutaneous left atrial appendage closure for the prevention of stroke did not meet the TEC criteria. The assessment explained: "RCT data do not provide convincing evidence of a treatment benefit or noninferiority compared with anticoagulation for patients for whom anticoagulation is not contraindicated. Case series data are inadequate to support conclusions about efficacy in patients for whom anticoagulation is contraindicated. A preventive treatment should have definitive efficacy evidence, particularly when the treatment -- a complicated procedure -- has known acute risks and complications".

The Lariat Device/Procedure

Han et al (2014) examined if LAA ligation results in LAA electrical isolation. A total of 68 patients with contraindication or intolerance to OAC therapy underwent LAA ligation with the LARIAT suture delivery device. Patients had unipolar (n = 30) or bipolar (n = 38) LAA measurements pre- and post-LAA ligation. All 68 patients underwent successful LAA ligation. There was a statistically significant decrease in the mean LAA voltage from pre-ligation (unipolar pre-ligation voltage = 1.1 mV (SD ± 0.53); bipolar pre-ligation voltage = 4.7 mV (SD ± 2.83)) to post-ligation (unipolar post-ligation voltage = 0.3 mV (SD ± 0.38); bipolar post-ligation voltage = 0.6 (SD ± 0.27)); 94 % of patients had a reduction in the LAA voltage after closure of the snare with 33 % of patients having complete elimination of LAA voltage with the initial tightening of the suture. Pacing from the LAA after closure of the snare resulted in lack of capture of the left atrium in 28 of 31 patients. The authors concluded that the LARIAT snare closure of the LAA produced an acute reduction in the LAA voltage and inhibited capture of the left atrium during LAA pacing. Moreover, they stated that future studies are needed to determine whether LAA ligation affects AF burden.
Stone and colleagues (2015) evaluated early outcomes of LAAO via a percutaneous LAA ligation approach with the SentreHeart LARIAT snare device. A total of 27 patients with AF and contraindication or intolerance for OAC therapy underwent percutaneous ligation of the LAA with the LARIAT device. Initial LAAO was confirmed with TEE and contrast fluoroscopy. The acute procedural success was 92.6%; 1 patient sustained a perforation of the LAA and was treated conservatively. The patient underwent LAAO surgically the next day. In 1 patient the attempt to advance the LARIAT over the LAA was unsuccessful. Patients were followed for a mean of 4 months. Preserved LAAO was confirmed with a 45-day follow-up TEE in 22 of 25 patients completing the procedure. Peri-operative complications included 3 cases of pericarditis and 1 case of a peri-procedural cerebrovascular accident (CVA) due to thrombus formation on the trans-septal sheath. During follow-up, there was 1 stroke thought to be non-cardioembolic and 1 pleural effusion; there were no deaths. The authors concluded that these results showed that percutaneous LAAO can be achieved successfully with an acceptable rate of peri-procedural and short-term complications. Moreover, they stated that further studies and longer follow-up are needed to determine whether LAAO lowers the long-term risk of thrombo-embolic events in patients with AF and contraindications to anti-coagulation.

Chatterjee et al (2015) noted that the Lariat device has received FDA 510(k) clearance for soft-tissue approximation and is being widely used off-label for LAAO. A comprehensive analysis of safety and effectiveness has not been reported. These investigators performed a systematic review of published literature to assess safety and procedural success, defined as successful closure of the LAA during the index procedure, of the Lariat device. They performed a formal analytic review of the FDA MAUDE (Manufacturer and User Facility Device Experience) database to compile adverse event reports from real-world practice with the Lariat. For the systematic review, PubMed, EMBASE, CINAHL, and the Cochrane Library were searched from January 2007 through August 2014 to identify all studies reporting use of the Lariat device in 3 or more patients. The FDA MAUDE database was queried for adverse events reports related to Lariat use. Data were abstracted in duplicate by 2 physician reviewers. Events from published literature were pooled using a generic inverse variance weighting with a random effects model. Cumulative and individual adverse events were also reported using the FDA MAUDE data
Main outcome measures were procedural adverse events and procedural success. In the systematic review, 5 reports of Lariat device use in 309 participants were identified. Specific complications weighted for inverse of variance of individual studies were urgent need for cardiac surgery (2.3 %; 7 of 309 procedures) and death (0.3 %; 1 of 309 procedures). Procedural success was 90.3 % (279 of 309 procedures). In the FDA MAUDE database, there were 35 unique reports of adverse events with use of the Lariat device. Among these, these researchers identified 5 adverse event reports that noted pericardial effusion and death and an additional 23 reported urgent cardiac surgery without mention of death. The authors concluded that this review of published reports and case reports identified risks of adverse events with off-label use of the Lariat device for LAAO. They stated that formal, controlled investigations into the safety and effectiveness of the device for this indication are needed.

An UpToDate review on “Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation” (Cheng and Hijazi, 2015) states that “The LARIAT system (SentreHeart, Inc.) is a non-surgical (percutaneous) device approved by the United States Food and Drug Administration for soft tissue closure (“approximation”) only. It has been evaluated for efficacy and safety (but not specifically approved) in the United States for occlusion of the LAA in patients who cannot take oral anticoagulation and are at high risk for stroke due to AF. The LARIAT system places a lasso around the LAA and then “ties it off” from inside the pericardial space. Patients who have had prior cardiac surgery or unusual LAA anatomy are not candidates for this procedure. In a single-site study of 89 relatively low-risk patients with AF, the placement of the LARIAT device was successful in 96 % and there were no complications associated due to the device (there were 3 access-related complications). Complete closure was confirmed in 95 % at 1 and 3 months. No late strokes thought to be embolic were documented. In July of 2015, the United States Food and Drug Administration issued a safety communication stating that cases of death and complications such as laceration or perforation of the heart or complete LAA detachment from the heart associated with the use of the device had been reported. The Lariat system has not undergone clinical trials to evaluate its safety and effectiveness compared to medical therapy …. Surgical and percutaneous approaches (often referred to as LAA exclusion
Cardiac Devices and Procedures for Occlusion of the Left Atrial Appendage

procedures) that mechanically prevent embolization of LAA thrombi have been developed and tested. The LARIAT, Amplatzer, and WATCHMAN devices have not been approved by the United States Food and Drug Administration (FDA) for left atrial appendage occlusion or ligation. The LARIAT is approved for tissue approximation only and not specifically for LAA closure.

The Watchman Left Atrial Appendage Closure Device

On March 13, 2015, Boston Scientific Corporation received FDA’s approval for the Watchman Left Atrial Appendage Closure device, which offers a new stroke risk reduction option for high-risk patients with non-valvular AF (NVAF) who are seeking an alternative to long-term warfarin therapy (Boston Scientific, 2015). The Watchman device will be made available to U.S. centers involved in the clinical studies and additional, specialized centers as physicians are trained on the implant procedure.

Lee et al (2014) noted that percutaneous LAAO using the Watchman device (Atritech, Plymouth, MN) is suggested as an alternative modality to warfarin for stroke prevention in patients with NVAF. However, peri-device leakage resulting from incomplete LAAO remains one of the most frequent limitations. These investigators reported a case of progressive increase in peri-device leakage after Watchman device implantation on long-term TEE follow-up accompanied by stroke.

Bajaj et al (2014) stated that a recent RCT in patients with NVAF suggested non-inferiority of percutaneous LAAO versus medical management for stroke prevention. However, the use of percutaneous devices remains controversial because of limited literature on their safety and effectiveness. These researchers performed a systematic analytical review of existing observational studies to assess the rate of neurological events for patients treated with occlusion devices. A comprehensive search of the Medline, Scopus, and Web of Science databases from inception through August 1, 2013, was conducted using pre-defined criteria. These investigators included studies reporting implantation in at least 10 patients and a follow-up of 6 months or more. In 17 eligible studies, a total of 1,052 devices were implanted in 1,107 patients with 1,586.4 person-years (PY) of follow-up. The adjusted incidence rate of stroke was 0.7/100 PY (95 % CI: 0.3 to 1.1/100 PY), of TIA's was 0.5/100
PY (95 % CI: 0.1 to 1.8/100 PY), and of combined neurological events (strokes or TIA) was 1.1/100 PY (95 % CI: 0.6 to 1.6/100 PY). Access site vascular complications and pericardial effusion were the most commonly observed procedural complications at a rate of 8.6 % (95 % CI: 6.3 % to 11.7 %) and 4.3 % (95 % CI: 3.1 % to 5.9 %), respectively. The authors concluded that the findings of this systematic review suggested comparable effectiveness of LAAO devices compared with historical controls treated with adjusted-dose warfarin and other anti-coagulation strategies for prevention of stroke in patients with NVAF.

Couch and Sabir (2015) stated that AF is associated with a markedly increased risk of thrombo-embolic stroke. At present, lifelong antithrombotic therapy with warfarin or a novel OAC is indicated for prophylaxis in the majority of patients. Left atrial appendage occlusion devices have been developed as an alternative to these agents, aiming to avoid issues around consistency of anti-coagulation, bleeding risk, and drug-related side effects. The best evidence is available for Boston Scientific's Watchman device. The safety and effectiveness of Watchman and other similar devices have been questioned, although the increasing body of evidence supports a role in selected settings. A recently updated RCT of Watchman (Watchman Left Atrial Appendage System for Embolic PROTECTION in Patients with Atrial Fibrillation [PROTECT-AF]) demonstrated its non-inferiority to warfarin and suggested an advantage in terms of functional outcome for patients, with superior net clinical benefit 6 to 9 months after starting treatment. The authors concluded that the procedural risk associated with device implantation remains substantial, although improving device design and increasing operator experience means that this should decrease in the future. They stated that as the body of data and overall experience around Watchman grow, it may come to be recognized as the best option in selected patients.

Aminian et al (2015) provided a systematic review of reported cases of LAAO device embolization by focusing on the 2 most commonly implanted devices: the Watchman (WM) device and the Amplatzer Cardiac Plug (ACP). A comprehensive search of the PubMed database was conducted until October 1, 2014. Studies were included if they described at least 1 case of embolization of the WM and/or the ACP. A total of 20 studies reporting 31 cases of device embolization were identified, including 13 cases with WM and 18 cases with ACP with ACP.
The timing of embolization was described in 29 cases and was categorized as acute in 20 cases (65%) and late in 9 cases (30%). The anatomical location of embolized devices was reported in 21 cases: into the aorta in 9 cases, into the left ventricle (LV) in 9 cases and into the left atrial cavity in 3 cases. As compared to embolization into the aorta or the left atrial cavity, device embolization into the LV was associated with a higher rate of surgical retrieval (8/9 versus 2/12; 88% versus 17%, p = 0.0019). Major adverse events related to device embolization occurred in 3 patients (9.6%). The authors concluded that LAAO device embolization occurs mainly in the peri-procedural period but late embolizations are not uncommon. Although embolization into the aorta or the left atrium can be successfully managed by percutaneous techniques in most cases, device embolization into the LV is associated with a higher rate of surgical retrieval, increasing thereby procedure-related morbidity.

Bode and colleagues (2015) stated that when anti-coagulation for stroke prevention is contraindicated, LAAO may be performed. Studies of LAAO have been limited by their small size, disparate patient populations, and lack of control group. These researchers performed a meta-analysis of the safety and effectiveness of LAAO in comparison with standard therapy for stroke prevention in NVAF. Due to the lack of a control group in studies of LAAO, data on stroke prevention from multiple large outcomes studies were used to produce a hypothetical control group based on clinical variables in the individual studies. Results were stratified according to LAAO device type. These researchers identified 16 studies with a total of 1,759 patients receiving LAAO. Summary estimates demonstrated LAAO reduced risk of stroke in comparison with no therapy or aspirin therapy [RR, 0.34; 95% CI: 0.25 to 0.46] and in comparison with warfarin therapy (RR, 0.65; 95% CI: 0.46 to 0.91). Summary estimates differed based on the study used to derive the hypothetical control group. Device deployment was unsuccessful in 6.1% of patients, and overall complication rate was 7.1%. Efficacy and safety were similar across LAAO device type although a majority of patients in the meta-analysis received a Watchman device. The authors concluded that these findings suggested that LAAO is a reasonable option for stroke prophylaxis in AF when anti-coagulation is not an option, and the risk for stroke outweighs the risk of procedural complications. Moreover, they
stated that data were limited with the use of most available devices. To better establish the risk and benefit of LAAO in comparison with standard therapy, more RCTs are needed.

Furthermore, an UpToDate review on “Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation” (Cheng and Hijazi, 2015) states that “Three subsequent reports from PROTECT AF have increased our understanding of the potential benefits and limitations of the WATCHMAN device …. PROTECT AF included only patients who were eligible for long-term warfarin. The potential use of the WATCHMAN device in patients with contraindications to long-term anticoagulation was evaluated in the non-randomized ASAP study, which treated 150 such patients (CHADS2 score ≥1) with the device and 6 months of a thienopyridine (clopidogrel or ticlopidine) as well as lifelong aspirin. During a mean duration of follow-up of 14.4 months, the primary efficacy outcome of all-cause stroke or systemic embolism occurred at a rate of 2.3 % per year and ischemic stroke occurred at a rate of 1.7 % per year. This rate is lower than predicted rates for CHADS2 matched cohorts of individuals taking either aspirin (7.3 %) or clopidogrel (5.0 %). This device has received CE Mark approval in Europe and it is also approved in the United States to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation …. Occlusion of the LAA can be attempted using less-invasive percutaneous, catheter-based methods. The WATCHMAN device was as effective as warfarin in one randomized trial, but complications of the procedure (such as pericardial effusion) occurred more frequently with the device …. Surgical and percutaneous approaches (often referred to as LAA exclusion procedures) that mechanically prevent embolization of LAA thrombi have been developed and tested. The LARIAT, Amplatzer, and WATCHMAN devices have not been approved by the United States Food and Drug Administration (FDA) for left atrial appendage occlusion or ligation”. The Watchman device is undergoing further evaluation in clinical trials; its role in clinical practice remains to be established as investigation of its risks and benefits are ongoing.

The Heart Rhythm, Pacing Group, the Atheroma, Interventional Cardiology Group of the French Society of Cardiology’s expert consensus statement on “Percutaneous occlusion of the left atrial appendage” (Klug et al, 2015) stated that while proof of the effectiveness of OACs for this
Cardiac Devices and Procedures for Occlusion of the Left Atrial Appendage

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Indication is long-standing and convincing, they are associated with hemorrhagic complications. Consequently, their prescription is based on an estimate of the risk (hemorrhagic complications)/benefit (thromboembolic prevention) ratio. In a patient subset at high thromboembolic and hemorrhagic risk, whether to prescribe or abstain from prescribing an OAC is a challenging decision, and an alternative means of thromboembolic prevention is desirable. Percutaneous occlusion of the LAA is an alternative, interventional, non-pharmacological treatment that has been used widely in Europe and for a few years in France, with encouraging results. However, it remains an invasive procedure with a low level of proof in comparison with OACs. Moreover, the indications, the procedural environment and pre-peri-post procedural patient management are major questions about this technique, with consequences on its effectiveness and risk/benefit ratio.

Ramlawi and colleagues (2015) stated that patients with AF have a greater than 5% annual risk of major stroke, a 5-fold increase compared to the general population. While anti-coagulation remains the standard stroke prevention strategy, the nature of lifelong anti-coagulation inevitably carries an increased risk of bleeding, increased stroke during periods of interruption, increased cost, and significant lifestyle modification. Many patients with AF have had their LAA ligated or excised by surgeons during cardiac surgery, a decision based largely on intuition and with no clear evidence of effectiveness in stroke risk reduction. The observation that 90% of the thrombi found in NVAF patients and 57% found in valvular AF were in the LAA, triggered significant interest in the LAA as a potential therapeutic target. Until recently, the results were inconsistent, and high rates of incomplete occlusions precluded the medical community from confirming a definite relationship between LAA and stroke. As a result, anti-coagulation is still the recommended 1st-line stroke risk reduction in AF, and the ACC/AHA guidelines recommend LAA exclusion only with surgical ablation of AF or in the context of concomitant mitral valve surgery. A handful of devices have been developed for LAA exclusion. This includes percutaneous options such as WATCHMAN Left Atrial Appendage Closure Device, hybrid epicardial devices such as the LARIAT Suture Delivery Device, and epicardial surgical devices such as AtriClip LAA Occlusion System. Studies of the Watchman device have shown non-inferiority to warfarin in stroke prevention and this device has recently gained approval from the
FDA following lengthy delays due to safety concerns. The Lariat device, which received 510k clearance by the FDA for tissue approximation but not LAA exclusion, has been the target of significant criticism due to serious procedural safety concerns and high incomplete closure rates. The surgical AtriClip has been FDA-approved since 2009 and is currently the most widely used LAA exclusion device placed through an epicardial approach. Small studies have shown excellent reliability and success of complete LAA closure with the AtriClip device, which is implanted through an epicardial approach. The authors stated that currently, they are conducting a multi-center trial to demonstrate the stroke prevention potential of this epicardial device through a short (45 minute), stand-alone, minimally invasive procedure in lieu of lifelong anti-coagulation in patients at high risk of bleeding.

Uslar and Anabalon (2015) noted that for most AF patients OAC constitutes the standard treatment to prevent stroke. However, they carry a risk of bleeding, which is why alternative treatments have been put into practice, such as percutaneous closure of the LAA. However, it is unclear whether this is as effective as the conventional treatment with anti-coagulants. Searching in Epistemonikos database, which is maintained by screening 30 databases, these researchers identified 3 systematic reviews including only 1 pertinent RCT. These investigators combined the evidence and generated a summary of findings following the GRADE approach. They concluded that percutaneous LAAO may decrease stroke and mortality, but the certainty of the evidence is low. The effect on other outcomes is not clear because the certainty of the evidence is very low.

Tzikas and colleagues (2016) stated that the increasing interest in LAAO for ischemic stroke prevention in AF fuels the need for more clinical data on the safety and effectiveness of this therapy. Besides an assessment of the effectiveness of the therapy in specific patient groups, comparisons with pharmacological stroke prophylaxis, surgical approaches and other device-based therapies are needed. These researchers documented the consensus reached among clinical experts in relevant disciplines from Europe and North America, European cardiology professional societies and representatives from the medical device industry regarding definitions for parameters and end-points to be evaluated in clinical trials.

Adherence to these definitions is proposed in order to achieve a
consistent approach across clinical trials on LAAO among the involved stake-holders and various clinical disciplines and thus facilitate continued evaluation of therapeutic strategies available.

Holmes and Reddy (2016) noted that patients with NVAF have a 4- to 5-fold increase in strokes and that rhythm may be responsible for 15 % to 20 % of all strokes, especially in the elderly. In this setting, thrombus in the LAA has been found to be the source of stroke in 90 % of cases. Although OACs have been found effective in reducing stroke rates, for a variety of issues, they may only be used in 40 % to 50 % of patients at increased risk for stroke. Given pathophysiology of stroke, site-specific therapy directed at LAAO has been now studied for stroke prevention, and 1 device is FDA-approved (Watchman). A meta-analysis of 2 randomized clinical trials and 2 registries with this device documented the following: (i) patients receiving the device had significantly fewer hemorrhagic strokes (hazard ratio [HR] 0.22, p = 0.004); (ii) a significant reduction in cardiovascular or unexplained death (HR 0.48, p = 0.004); (iii) more ischemic strokes in the device group; however, when peri-procedural events were excluded, the difference was not significant; and (iv) a significant reduction in non-procedural bleeding with the device (HR 0.51, p = 0.006) versus control. At present, the only device approved in the United States is indicated in patients with NVAF with acceptable anatomy who are at increased risk for stroke and would be candidates for ant-coagulation in whom there is concern about the risk/benefit ratio for chronic anti-coagulation. Unresolved issues include optimal patient selection criteria, the role of devices in patients in whom anti-coagulation is contraindicated, and the relative role of novel OACs versus the device which has not been tested in randomized trials.

Furthermore, a recently published Medicare National Coverage Determination (February 8, 2016) considers LAA closure devices not reasonable and necessary and only allows coverage within certain clinical trials (CMS, 2016). The CMS Decision Memorandum states: "At this time, there is insufficient evidence to determine that percutaneous LAAC improves health outcomes compared to non-invasive guideline recommended first line standard medical therapies for Medicare beneficiaries with NVAF. We recognize the initial evidence is promising and rapidly evolving. Therefore, LAAC using an FDA PMA approved
device should only be considered in patients with NVAF with a high stroke risk and an inability to take long term anticoagulation in a clinical trial or comparative study under CED."

The European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTs) guidelines on “The management of atrial fibrillation” (Kirchhof et al, 2016) stated that “Adequately powered controlled trials are urgently needed to inform the best use of these devices, including LAA occluders in patients who are truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion”.

In a systematic review and meta-analysis, Hanif and colleagues (2018) evaluated the impact of LAA occlusion on mortality, major bleeding, and operative time. These investigators searched Medline, Embase, PubMed, and Cochrane Library for randomized trials comparing percutaneous or surgical LAA occlusion with standard of care in AF patients. Conventional meta-analysis found no difference between groups for stroke (5 trials, 1,285 patients; RR 0.78, 95 % CI: 0.47 to 1.29), and a significant reduction in mortality (5 trials, 1,285 patients; RR 0.71, 95 % CI: 0.51 to 0.99) favoring LAA occlusion. Network meta-analysis demonstrated a trend towards reduction in stroke (OR 0.84, 95 % credible interval [CrI]: 0.47 to 1.55) and mortality (OR 0.69, 95 % CrI: 0.44 to 1.10) for LAA occlusion versus warfarin, but no statistically significant effect. Statistical ranking curves placed LAA occlusion as the most effective treatment on the outcome of stroke and mortality when compared to warfarin, aspirin, or placebo. No significant differences between groups were seen in for major bleeding or operative time for surgical trials. The overall quality of the evidence was low as assessed by GRADE. The authors concluded that LAA occlusion appeared to preserve the benefits of OAC therapy for stroke prevention in patients with AF, however, the current evidence is of low quality.

Gorczyca-Michta and Wozakowska-Kaplon (2017) noted that ischemic stroke is a common complication of AF. Currently, OAC is the most commonly used method of stroke prevention. Left atrial appendage occlusion is thought to be the main source of thrombi in patients with AF. Percutaneous LAAO is a valuable therapeutic option for selected high-
risk patients with AF and contraindications for OAC therapy. While complete closure of the LAA is the goal of a device implantation the variable nature of the LAA anatomy makes this goal difficult to achieve. Currently, there are several types of devices available for LAAO. Since the 1st percutaneous LAAO in 2002 many studies have investigated both the safety and effectiveness of this therapy using different closure devices. Still unresolved issues include a lack of data on optimal patient selection, risk of complications, and anti-coagulant treatment after LAAO.

Nielsen-Kudsk and associates (2017) examined the prognosis in patients with AF and ICH having a LAAO versus patients receiving standard medical therapy. A total of 151 patients from the Nordic countries with AF and previous ICH who underwent LAAO using the Amplatzer Cardiac Plug or the Amplatzer Amulet were compared to a propensity score-matched group of 151 patients receiving standard medical therapy. The 2 groups were matched so that their risks for stroke and bleeding were similar (CHA2DS2-VASc and HAS-BLED scores). The standard care patients were identified from the Danish Stroke Registry among 787 patients with AF and ICH. The primary end-point was a composite of all-cause mortality, ischemic stroke and major bleeding. Patients with AF and a prior ICH treated with LAAO had a lower risk of the composite outcome as compared to patients treated with standard medical care (events/1,000 years [95 % CI: 53.3 [44.3 to 64.1] versus 366.7 [298.2 to 450.9]; HR 0.16 [0.07 to 0.37]). The authors concluded that LAAO is suggested to be of major clinical benefit in AF patients having sustained an ICH; however, these results have to be confirmed in a RCT.

Baman and associates (2018) noted that AF is commonly co-existent with heart failure (HF), and the management of patients with HF would be incomplete without an appreciation for AF management. There are many complications associated with oral anti-coagulation in the prevention of stroke related to AF. In recent years, the advent of several percutaneous LAA occlusion/closure strategies has sought to provide an alternative treatment modality. These investigators reviewed the published literature to examine the safety and efficacy of percutaneous LAA occlusion/closure devices. They searched PubMed, Embase, Cochrane database of systematic reviews, and the FDA Medical Devices database. Using pre-specified criteria, these researchers identified studies of the Amplatzer Cardiac Plug (St. Jude Medical), Amplatzer Amulet (St. Jude Medical),
Lariat suture delivery device (SentreHeart), and Watchman device (Boston Scientific). They analyzed 2 RCTs and 15 non-randomized registries that satisfied the study criteria. The 2 RCTs both studied the Watchman device versus standard warfarin therapy; the studies indicated that the Watchman may be non-inferior to warfarin. Long-term efficacy outcomes for the Watchman device are promising. Data regarding the Amplatzer Cardiac Plug, Amplatzer Amulet, and Lariat suture delivery device are limited by the paucity of RCT data. The authors concluded that high-quality prospective research is needed to directly compare LAA occlusion/closure strategies against one another as well as versus the direct oral anti-coagulation medications. Data regarding the role of LAAO in the HF population are lacking.

Reddy et al (2017) noted that the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) Trial demonstrated that LAAC with the Watchman device was equivalent to warfarin for preventing stroke in AF, but had a high rate of complications. In a 2nd randomized trial, the PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) Trial, the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy end-points inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time. The final results of the PREVAIL Trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF Trial, were reported with patients in both trials followed for 5 years. The PREVAIL and PROTECT AF Trials were prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 participants for 4,343 patient-years. Analyses are by intention-to-treat (ITT), and rates were events per 100 patient-years (PY). For the PREVAIL Trial, the 1st composite co-primary end-point of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve non-inferiority (posterior probability for non-inferiority = 88.4 %), whereas the 2nd co-primary end-point of post-procedure ischemic stroke/SE did achieve non-inferiority (posterior probability for non-inferiority = 97.5 %); the warfarin-arm maintained an unusually low ischemic stroke rate (0.73 %). In the meta-analysis, the composite end-point was similar between groups (HR: 0.820; p = 0.27), as were all-stroke/SE (HR: 0.961; p = 0.87). The ischemic stroke/SE rate was
numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively). The authors concluded that these 5-year outcomes of the PREVAIL Trial, combined with the 5-year outcomes of the PROTECT AF Trial, demonstrated that LAAC with Watchman provided stroke prevention in NVAF comparable to warfarin, with additional reductions in major bleeding, especially hemorrhagic stroke, and mortality.

The authors stated that this study had several drawbacks. Although the PREVAIL Trial was designed for a total of 5 years of follow-up, the primary efficacy end-points were pre-specified to only be evaluated at the time of the initial analysis: when the last patient enrolled reached 6 months of follow-up. Therefore, the current analysis should be considered post-hoc. In addition, the pre-specified informative prior for PREVAIL was at 1,500 PY of follow-up in PROTECT AF Trial only, and the additional 3 years of PROTECT AF follow-up were not incorporated into further analyses, including the current one. However, this was the more conservative approach, because use of the full 5-year PROTECT AF data for the informative prior would have further favored the LAAC group. Per the eligibility criteria, patients who enrolled in these trials had to be able to tolerate OAC. This was underscored by the fact that Watchman implantation was followed by a short-term anti-thrombotic regimen: warfarin for 6 weeks and dual anti-platelet therapy until 6 months. Therefore, these results did not necessarily apply to patients with true contraindications to OAC. However, an ongoing RCT of LAAC versus anti-platelet therapy (ASAP-TOO [Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation]; NCT02928497) has been designed to evaluate this strategy. After these LAAC RCTs were initiated, NOACs became clinically available and are now routinely used in clinical practice. It should be remembered that LAAC with the Watchman device has not been tested against these agents. RCTs of LAAC versus NOACs are likely to be conducted in forthcoming years; indeed, a small such study (PRAGUE-17 [Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation]; NCT02426944) is currently ongoing. Furthermore, the patient populations in real-world
clinical practice may differ from those enrolled during clinical trials.
Forthcoming results from the National Cardiovascular Data Registry
should provide further insight on this issue.

Mazzone et al (2018) analyzed the safety and efficacy profile of the LAAO
procedure at mid-term follow-up. The TRAPS Registry is an
observational, multi-center registry involving 4 Italian centers.
Consecutive patients who had undergone LAAO with Watchman device
were enrolled. Clinical, demographic, and procedural data were collected
at the time of implantation, and follow-up data were collected to assess
the clinical outcome. A total of 151 patients were included in the Registry
from May 2012 to October 2015. Implantation of the device was
successful in 150/151 patients, with no or minimal (less than 5 mm)
leakage as assessed by peri-procedural TEE. In the remaining patient,
early device embolization was reported, with no sequelae. Overall, intra-
procedural events were reported in 5 (3.3 %) patients. During a median
follow-up of 16 months (25th and 75th percentile, 10 to 25), 5 patients
died of any cause. The annual rate of all-cause stroke was 2.2 % (95 %
CI: 0.7 to 5.1), the rate of transient ischemic attack was 1.3 % (95 % CI:
0.3 to 3.8), and that of major bleeding 0.4 % (95 % CI: 0.01 to 2.4). The
authors concluded that LAAO for stroke prevention was safely and
effectively achieved by implantation of the WATCHMAN device in patients
with non-valvular AF. Moreover, regardless of the risk profile of the
population, these investigators observed low rates of death and thrombo-
embolic and bleeding events over a median follow-up of 16 months.
These findings were obtained in an unselected group of consecutive
patients who were variably eligible for chronic OAC therapy.

Schellinger et al (2018) reviewed the current status of percutaneous
LAAO therapy in patients with AF with the goal to prevent ischemic stroke
and systemic embolism and to reduce OAC-associated bleeding. While
these investigators covered the historical and also surgical background,
and all tested devices, the main focus rested on the single currently FDA-
approved LAA occluder, the Watchman device, and its approval process.
The authors concluded that there appeared to be merit and by now an
established reasonable safety profile for device based (preferably
Watchman) occlusion of the LAA in patients with AF is. While there is a
somewhat restricted label and approval in some countries, several
questions remain and ongoing trials have the chance to clarify these
outstanding issues. The results of randomized trials, especially comparisons against non-vitamin K antagonists (VKA) OACs are dearly awaited. Until then these researchers recommended either a restrictive indication of this procedure with FDA-approved devices following the wording in the FDA approval, or recruitment into ongoing clinical trials.

Boersma et al (2018) noted that the LAA is the main source of cardioembolic stroke in patients with AF without valvular disease; and OAC has proven effective for preventing strokes associated with AF but is complicated by inherent bleeding risk and therapeutic compliance. Mechanical closure of the LAA appeared an attractive alternative, especially in patients for whom long-term OAC is not a good option. In the past 10 years, several percutaneous techniques have become available for this, including the Watchman device. Randomized trials with the Watchman device suggested that closure of the LAA is not inferior to OAC in stroke prevention and that additionally there is reduced bleeding. Prospective registry studies of patients with contraindications for OAC confirmed that closure of the LAA is an attractive alternative to OAC. The authors concluded that ongoing investigations are focused on reducing complications of the closure procedure, the lowest form of anticoagulation, comparing existing techniques and comparing LAAO with direct OACs.

Aonuma et al (2018) conducted the SALUTE trial to confirm the safety and efficacy of the LAAO therapy for patients with NVAF in Japan. A total of 54 subjects (including 12 Roll-in) with NVAF who had a CHA2DS2-VASc score of greater than or equal to 2 were enrolled. All subjects were successfully implanted with the LAA closure device. No serious AEs related to the primary procedure-safety end-point occurred. The secondary co-primary end-point was a composite of all stroke, systemic embolism and cardiovascular/unexplained death. One ischemic stroke (1/42) occurred during the 6-month follow-up. The effective LAAO rate defined as the tertiary co-primary end-point was 100 % (42/42) at both 45-day and 6-month follow-up. The authors concluded that the procedural safety and 6-month results from the SALUTE trial demonstrated that the LAA closure device was safe and effective, similar to the results of large-scale randomized clinical trials, and provided a novel perspective of LAA closure for Japanese patients with NVAF in need of an alternative to long-term OAC.
The authors stated that this study had several drawbacks. As SALUTE was a single-arm study without a control group, this trial was not intended to compare the safety and efficacy of LAA closure with long-term warfarin therapy in Japanese patients with NVAF. Although the results in this trial were comparable to those from large-scale randomized clinical trials, results must still be interpreted with caution in the absence of a matched control arm. This 1st report of the SALUTE trial contained only up to 6-months of follow-up results of the intention-to-treat (ITT) cohort and longer follow-up is needed to further evaluate the efficacy of the device in this population. The numbers of each event related to the primary end-points or other end-points were very limited, and the sub-group and multi-variable analyses were not tested at this first analysis. In the trial, the device implanters were proctored by very experienced operators and this could have contributed to the low complication rate.

Sharma et al (2018) noted that stroke continues to be a major cause of morbidity and mortality in AF patients; OAC provides protection against stroke and peripheral embolization in AF but significant proportion of patients could not be started on anti-coagulation because of bleeding complications. Left atrial appendage harbors clot in about 90% of NVAF. The advent of LAAO techniques has provided these patients with alternative to OAC for stroke prophylaxis. Multiple LAAO devices are currently available with Watchman and Amulet being the most commonly used in clinical practice. Randomized studies are available for Watchman device only. Data on Amplatzer Cardiac Plug, Amulet and Lariat devices are limited by the paucity of randomized data. Long-term data on different LAAO techniques are showing promising results. Device related thrombosis continues to be a serious complication associated with LAAO. The authors concluded that future studies should look into comparative effectiveness between different LAAO techniques, optimal patient selection, risk of complications, and anti-coagulant treatment after LAAO.

These researchers stated that currently, there are a few important undergoing studies that can potentially change the practice and utilization of LAAO. The Interventional Left Atrial Appendage Closure versus Novel Anticoagulation Agents in High-risk Patients with Atrial Fibrillation (PRAGUE-17 Study, NCT02426944) is recruiting patients. This randomized, multi-center, open-label trial is recruiting a total of 400
patients into LAAO (Watchman or Amulet) and NOAC group. The primary end-point is the combination of stroke, other systemic cardiovascular event, clinically significant bleeding, cardiovascular death or procedure or device-related complications. The trial is expected to be completed by May 2020. A randomized clinical trial of patients with NVF at increased risk of stroke but who are not candidates for any anticoagulation (Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO; NCT02928497)) has been initiated, randomizing patients to either Watchman and aspirin/clopidogrel or conservative medical therapy alone with aspirin and/or clopidogrel. With estimated enrollment of 888 patients the study seeks to evaluate the primary safety end-point (7-day combined rate of death, ischemic stroke, systemic embolism and complications requiring major cardiovascular or endovascular intervention) and efficacy end-point (comparison of time to first event of ischemic stroke and systemic embolism). These investigators stated that as more data on LAAO becomes available expert consensus document from professional societies on both sides of the Atlantic is anticipated for best practice guidelines.

Kosturakis and Price (2018) AF is a major cause of stroke and systemic embolism, and is increasing in prevalence. Device closure of the LAA represents a non-pharmacologic approach to stroke prevention in AF patients. These researchers presented the rationale for LAAC, described current trans-catheter approaches to LAAC, and summarized the current evidence for LAAC for stroke prevention, highlighting the main randomized trials and the most recent data available. Meta-analysis of randomized clinical trials demonstrated similar rates of all-cause stroke with trans-catheter LAAC compared with vitamin K antagonist therapy and significantly less bleeding with LAAC after cessation of mandated post-procedure pharmacology. Recent prospective observational studies, including those evaluating outcomes after commercial approval in the U.S., showed significantly improved procedure safety compared with earlier experiences. LAAC appeared to be an attractive alternative strategy for stroke prevention in AF patients, particularly in those who can take short-term OAC, but are not optimal candidates for long-term OAC. Recent data suggested the procedure can be safely performed in patients with contraindications to OAC. The authors concluded that further, robust studies are needed to evaluate safety and efficacy in OAC-
contraindicated patients, to compare outcomes with non-vitamin K antagonist OACs, and to examine the relative safety and efficacy of different LAAC devices.

Atti et al (2018) evaluated the safety and efficacy of surgical LAAO (s-LAAO) during concomitant cardiac surgery. These researchers performed a comprehensive literature search through May 31, 2018 for all eligible studies comparing s-LAAO versus no occlusion in patients undergoing cardiac surgery. Clinical outcomes during follow-up included: embolic events, stroke, all-cause mortality, AF, re-operation for bleeding and post-operative complications. They further stratified the analysis based on propensity matched studies and AF predominance. A total of 12 studies (n = 40,107) met the inclusion criteria. s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95 % CI: 0.53 to 0.76; p < 0.001) and stroke (OR: 0.68, 95 % CI: 0.57 to 0.82; p < 0.0001). Stratified analysis demonstrated this association was more prominent in the AF predominant strata. There was no significant difference in the incidence risk of all-cause mortality, AF, and re-operation for bleeding and post-operative complications. The authors concluded that concomitant s-LAAO during cardiac surgery was associated with lower risk of follow-up thromboembolic events and stroke, especially in those with AF without significant increase in AEs. Moreover, these investigators stated that further RCTs are needed to evaluate long-term benefits of s-LAAO.

The authors stated that this study had several drawbacks. First, due to the small number of studies with small sample sizes, except the study by Friedman et al (2018), the results might be under-powered to detect the true clinical benefits of certain clinical outcomes. Second, there was a wide variation of surgical techniques of LAAO, so these researchers were unable to address the effect of individual techniques. Third, only Friedman et al (2018) reported long-term embolic events, whereas the other studies did not report long-term outcomes. The study by Friedman et al (2018) reported re-admissions for embolic events, so some of the events which did not require hospitalization were not included. The effect of anti-coagulation on post-operative outcomes remains unclear due to inadequate reporting in the included studies. Fourth, it was unclear if s-LAAO increased the duration of the surgical procedure as it was only
reported in 2 studies. Fifth, the burden of AF varied among the included studies, thus carrying risk of a selection bias. Finally, publication bias was an inherent limitation of any meta-analysis.

Cochet et al (2018) noted that TEE studies have reported frequent peri-device leaks and device-related thrombi (DRT) after percutaneous LAAO. These researchers examined the prevalence, characteristics and correlates of leaks and DRT on cardiac computed tomography (CT) after LAAO. Consecutive patients underwent cardiac CT before LAAO to assess left atrial (LA) volume, LAA shape, and landing zone diameter. Follow-up CT was performed after greater than 3 months to assess device implantation criteria, device leaks and DRT. CT findings were related to patient and device characteristics, as well as to outcome during follow-up. A total of 117 patients (age of 74 ± 9 years, 37 % women, CHA2DS2VASc 4.4 ± 1.3, and HASBLED 3.5 ± 1.0) were implanted with Amplatz cardiac plug (ACP)/Amulet (71 %) or Watchman (29 %). LAA patency was detected in 44 % on arterial phase CT images and 69 % on venous phase images. The most common leak location was posterior-inferior; LAA patency related to LA dilatation, left ventricular ejection fraction (LVEF) impairment, non-chicken wing LAA shape, large landing zone diameter, incomplete device lobe thrombosis, and disc/lobe misalignment in patients with ACP/Amulet. DRT were detected in 19 (16 %), most being laminated and of antero-superior location. DRT did not relate to clinical or imaging characteristics nor to implantation criteria, but to total thrombosis of device lobe. Over a mean 13 months follow-up, stroke/TIA occurred in 8 patients, unrelated to DRT or LAA patency. The authors concluded that LAA patency on CT was common after LAAO, particularly on venous phase images. Leaks relate to LA/LAA size at baseline, and device malposition and incomplete thrombosis at follow-up; DRT was also quite common but poorly predicted by patient and device-related factors.

Nishimura et al (2018) stated that although OAC with non-vitamin K antagonist and non-vitamin K antagonist oral anti-coagulants (NOACs) have been established to significantly reduce risk of stroke, real-world use of these agents are often suboptimal due to concerns for AEs including bleeding from both patients and clinicians. Particularly in patients with previous serious bleeding, OAC may be contraindicated. Left atrial appendage occlusion, mechanically targeting the source of most of the
thrombi in AF, holds an immense potential as an alternative to OAC in management of stroke prophylaxis. In this focused review, these investigators described the available evidence of various LAAO devices, detailing data regarding their use in patients with a contraindication for OAC. Although some questions of safety and appropriate use of these new devices in patients who cannot tolerate anti-coagulation remain, LAAO devices offer a significant step forward in the management of patients with AF, including those patients who may not be able to be prescribed OAC at all. These researchers stated that future studies involving patients fully contraindicated to OAC are needed in the era of LAAO devices for stroke risk reduction.

Ellis et al (2019) noted that incomplete s-LAAO with a narrow neck has been shown to predict an increased rate of embolic stroke. Patients with a previously attempted s-LAAO were systematically excluded from all clinical trials of LAA closure devices. In a prospective, single-arm study, these researchers evaluated the feasibility of Watchman LAA device closure for patients referred with chronically incomplete S-LAAO. This trial evaluated only subjects undergoing Watchman LAA closure following incomplete s-LAAO. Patients referred and implanted were followed in the Vanderbilt LAA Registry. Pre-procedure CT angiography (CTA) and TEE were performed to evaluate suitability for closure, with 45-day follow-up TEE post-implant. All attempted LAA closures after incomplete s-LAAO were successful (n = 6). Mean age was 76.3 ± 7 years. Mean CHADS2Vasc score was 3.8 ± 0.8, and HAS-BLED score was 3.5 ± 0.5. At 45-day follow-up, all subjects had complete device seal with no thrombus on device and had transitioned to clopidogrel plus aspirin; 3 subjects had narrow ostial necks with a maximum diameter less than or equal to 9 mm. In all cases, the 4.7-mm Watchman access sheath was able to cross the ostial stricture. Mean occluder size implanted was 28 ± 4 mm. Mean LAA dimension by TEE in the 45° and 135° views for depth was 31 mm and ostial diameter was 11 × 16 mm, below the minimum Watchman indication for use of 17 mm. No major intra-operative complications occurred. The authors concluded that the Watchman LAA closure appeared to be feasible in patients with chronically incomplete s-LAAO, including subjects with a narrow neck less than or equal to 9 mm in width. This was a small (n = 6) feasibility study with short-term follow-up (45 days); its findings need to be validated by well-designed studies.
Glassy et al (2019) compared patients with and without long-standing persistent AF (LSPAF) undergoing Watchman LAAO; TEE measures of LAA ostial diameter and depth, device compression, and residual leak were evaluated in 101 consecutive Watchman cases. Patients were categorized into LSPAF (n = 48) or non-LSPAF (n = 53) groups and compared. The average LAA ostial diameter for LSPAF versus non-LSPAF by TEE omniplane at 0° was 21.1 ± 4.1 mm versus 18.2 ± 3.6 mm (p = 0.0002); at 45° was 18.7 ± 3.4 mm versus 16.3 ± 3.1 mm (p = 0.0004); at 90° was 19.6 ± 3.8 mm versus 16.2 ± 3.4 mm (p = 0.00001); and at 135° was 21.0 ± 4.1 mm versus 18.0 ± 4.1 mm (p = 0.0005). The average LAA depth for LSPAF versus non-LSPAF by TEE at 0° was 28.1 ± 6.4 mm versus 25.2 ± 4.9 mm (p = 0.02); at 45° was 27.9 ± 5.8 mm versus 25.1 ± 4.3 mm (p = 0.007); at 90° was 27.2 ± 5.2 mm versus 22.8 ± 3.7 mm (p = 0.0001); and at 135° was 25.6 ± 5.4 mm versus 21.5 ± 3.8 mm (p = 0.0001). In successfully treated patients, 77 % of the LSPAF group received larger device (27, 30, or 33 mm) implants versus only 46 % in the non-LSPAF group (p = 0.003). While both groups had similar rates of moderate (3 to 5 mm) leaks at implant (2 % versus 0 %; p = 0.14), 27 % of the LSPAF versus 4 % of the non-LSPAF group had moderate leaks (p = 0.04) on 6-week follow-up TEE. The authors concluded that patients with LSPAF had significantly larger LAA sizes, required larger devices, and had more residual leak on follow-up TEE. They stated that LSPAF may represent a higher risk group that warrants more stringent long-term follow-up.

Lempereur et al (2019) noted that AF is the most common clinical arrhythmia and can be associated with severe thrombo-embolic complications. For different reasons, a large number of AF patients who would benefit from OAC are not treated. In case of contra-indications to long-term OAC, LAAO allows the exclusion of the LAA from the systemic circulation and significantly reduces the thrombo-embolism risk. Results from large randomized trials showed that this technique is non-inferior in terms of efficacy compared to OAC and that it can significantly reduce the rate of hemorrhagic complications. The authors stated that large-scale registries showed promising results in patients with contra-indications to long-term OAC; and clinical trials are under way to define the role and spectrum of LAAO and to optimize post-procedural treatment.
Cruz-Gonzalez et al (2019) noted that despite the efficacy of OAC therapy, some patients continue to have a high residual risk and develop a stroke on OAC therapy (resistant stroke [RS]), and there is a lack of evidence on the management of these patients. These investigators examined the safety and efficacy of LAAO as secondary prevention in patients with NVAF who have experienced a stroke/TIA despite OAC treatment. These researchers analyzed data from the Amplatzer Cardiac Plug multicenter registry on 1,047 consecutive patients with NVAF undergoing LAAO. Patients with previous stroke on OAC therapy as indication for LAAO were identified and compared with patients with other indications. A total of 115 patients (11 %) with RS were identified. The CHA2DS2-VASc and the HAS-BLED score were significantly higher in the RS group (respectively 5.5 ± 1.5 versus 4.3 ± 1.6; p < 0.001; 3.9 ± 1.3 versus 3.1 ± 1.2; p < 0.001). No significant differences were observed in peri-procedural major safety events (7.8 versus 4.5 %; p = 0.1). With a mean clinical follow-up of 16.2 ± 12.2 months, the observed annual stroke/TIA rate for the RS group was 2.6 % (65 % risk reduction) and the observed annual major bleeding rate was 0 % (100 % risk reduction).

The authors concluded that patients with RS undergoing LAAO showed similar safety outcomes to patients without RS, with a significant reduction in stroke/TIA and major bleeding events during follow-up. Moreover, these researchers stated that adequately powered controlled trials are needed to further examine the use of LAAO in RS patients.

Sivasambu et al (2019) stated that LAAC with the Watchman device is increasingly used in patients with NVAF for stroke prevention. Although clinical trials have shown similar combined risk of ischemic and hemorrhagic stroke, there is an increased risk of ischemic stroke in patients with a Watchman device compared to anti-coagulation. Some ischemic strokes are related to DRT, which may be attributable to delayed endothelialization of exposed fabric and metal. Patients undergoing Watchman LAA occlusion between January 2016 and June 2018 were enrolled in a prospective registry. From this cohort, 46 patients who had both TEE and CT at 45 days follow-up were selected for this study. The degree of LAAO and type of leak were assessed by CT and TEE. TEE identified no patients with a significant (greater than 5 mm) peri-device leak, 27 (58.6 %) with non-significant peri-device leak (less than 5 mm), and 19 (41.4 %) with complete occlusion. CT identified contrast in the LAA in 28 (60 %) patients. However in 10 (21.8 %) of these patients,
contrast entered the LAA through the fabric rather than around the device. No DRT were identified. The authors concluded that these findings revealed that the Watchman device remained porous 6 weeks after implantation in a substantial percentage of patients, suggesting delayed endothelialization of the device. Cardiac CT may help to differentiate between peri-device and trans-fabric leak. These investigators stated that additional studies are needed to examine if prolonged anti-coagulation in patients with trans-fabric leak may help to reduce the risk of DRT and ischemic stroke.

An assessment by the Ludwig Boltzmann Institute for Health Technology Assessment of left atrial appendage closure for the prevention of thromboembolic events in patients with atrial fibrillation. (2018) concluded: "The currently available evidence is not sufficient to prove that the percutaneous LAAC is as effective and as safe as OAC. Especially comparative studies on non-vitamin K oral anticoagulants (NOACs) are missing. For LAAC with the surgically implanted special clip, there is no evidence that allows an evaluation of efficacy and safety."

Combination of Amplatzer and MitraClip

Tichelbacker and colleagues (2016) stated that percutaneous mitral valve repair using MitraClip (MC) is a well-established method for a subset of patients with severe mitral regurgitation (MR) and high-risk for surgical intervention. Amplatzer Cardiac Plug occludes LAA and allows the discontinuation of OAC and prevention of thromboembolic stroke. Due to the need for femoral and trans-septal access in both procedures, a single approach could lead to minor risk of further complications and shorter cumulative intervention time. These researchers systematically analyzed 4 patients who underwent a combined procedure with MC and ACP in their heart-center. All procedures were performed under fluoroscopic as well as echocardiographic guidance, and follow-up controls in a mid-term period were carried out. In all patients (2 males/females; aged 73 to 88 years), MC (1 to 2 Clips) and ACP (size 18 to 28 mm) were successfully implanted in 1 procedure (mean total time of 114 ± 17 mins). At least moderate MR was achieved and 2 patients had no complications and therefore were discharged early. In a 3rd patient, a dislocation of ACP occurred 2 hours after the implantation. The oldest patient developed a respiratory insufficiency due to cardiac decompensation and
further complications. The authors concluded that a combination of MC and ACP in a single procedure was feasible in this first case series of patients without a significant extension of procedure time. However, they stated that it might be important to select patients carefully. The location of optimal trans-septal puncture may be challenging in regard to ACP placement, even in experienced hands and subsequent complications can occur. These preliminary findings need to be validated by well-designed studies.

Francisco and colleagues (2017) evaluated the feasibility of a combined approach with MitraClip implantation and LAAO in a single procedure. These investigators reported the first case series regarding this issue, and discussed the specific advantages, pitfalls and technical aspects of combining these 2 procedures. A total of 5 patients underwent LAAO with the Watchman device followed by MitraClip implantation in the same procedure. All patients experienced significant reduction in mitral valve regurgitation of at least 2 grades, optimal occluder position, no associated complications and significant clinical improvement assessed by NYHA functional class (reduction of at least 1 functional class, with 4 patients in class I at 1-month follow-up). The authors concluded that in selected patients rejected for surgical mitral valve repair, with AF and increased risk of bleeding and embolic events, a combined approach with MitraClip implantation and LAAO in a single procedure is feasible, safe and effective. This was a small study (n = 5) with short-term follow-up (1 month); its findings need to be validated by well-designed studies.

Cryoballoon Ablation and Percutaneous Closure of Left Atrial Appendage

Fassini and associates (2016) evaluated the feasibility of combining cryoballoon (CB) ablation and LAA occlusion in patients with AF and a high thromboembolic risk or contraindication to anti-thrombotic therapy. A total of 35 patients (28 males, 74 ± 2 years) underwent CB ablation. Left atrial appendage occlusion was carried out by using 2 occluders (Amplatz Cardiac Plug [ACP] in 25 patients; Watchman in 10 patients); 30 patients (86 %) had previous stroke/TIA episodes, 6 patients (17 %) had major bleeding while on VKA therapy, and 7 patients (20 %) had inherited bleeding disorders. Over the follow-up (24 ± 12 months), atrial arrhythmias recurred in 10 (28 %) patients; 30 patients (86 %) had
complete sealing; 5 patients (14 %) showed a residual flow (less than 5 mm) at first TEE check, while at 1-year TEE residual flow was detected in 3 patients. In 13 patients (37 %), VKA therapy was immediately discontinued; 6 patients (17 %) received novel OAC treatment and then discontinued 3 months thereafter. No device-related complications or clinical thromboembolic events occurred. The authors concluded that combined CB ablation and LAA closure using different devices appeared to be feasible in patients with non-valvular AF associated with high risk of stroke or contraindication to anti-thrombotic treatment. These preliminary findings need to be validated by well-designed studies.

Electrical Isolation of the Left Atrial Appendage

In a first-in-human safety, feasibility, and efficacy study, Panikker and colleagues (2016) evaluated the feasibility, safety, and efficacy of LAA electrical isolation and occlusion in patients undergoing long-standing persistent AF ablation. Patients with long-standing persistent AF (age of 68 ± 7 years; left atrium diameter, 46 ± 3 mm; and AF duration, 25 ± 15 months) underwent AF ablation, LAA electrical isolation, and occlusion. Outcomes were compared with a balanced (1:2 ratio) control group who had AF ablation alone. Among 22 patients who underwent ablation, LAA electrical isolation was possible in 20. Intra-procedural LAA reconnection occurred in 17 of 20 (85 %) patients, predominantly at anterior and superior locations; all were re-isolated. Occlusion of the LAA was successful in all 20 patients. There were no major peri-procedural complications. Imaging at 45 days and 9 months confirmed satisfactory device position and excluded peri-cardial effusion; 1 of 20 (5 %) patients had a gap of greater than or equal to 5 mm requiring anti-coagulation; 19 of 20 (95 %) patients stopped warfarin at 3 months. Without anti-arrhythmic drugs, freedom from AF at 12 months after a single procedure was significantly higher in the study group (19/20, 95 %) than in the control group (25/40, 63 %); p = 0.036. Freedom from atrial arrhythmias was demonstrated in 12 of 20 (60 %) and 18 of 20 (90 %) patients after 1 and less than or equal to 2 procedures (mean of 1.3), respectively. The authors concluded that persistent AF ablation, LAA electrical isolation, and mechanical occlusion can be performed concomitantly. They stated that this technique may improve the success of persistent AF ablation while obviating the need for chronic anti-coagulation. These preliminary findings need to be validated by well-designed studies.
Amplatzer Amulet for Left Atrial Appendage Occlusion

Chanda and Reilly (2017) stated that more than 2.3 million adults in the U.S. have AF, which exposes them to a 5-fold increased risk of stroke. The LAA appears to be the source of thrombus formation in the vast majority of these patients. Anti-coagulation significantly reduces the risk of stroke, but often physicians/clinicians encounter patients who have absolute or relative contraindication to anti-coagulation. Percutaneous LAAO offers an alternative to anti-coagulation to decrease the risk of stroke; and 3 device systems are currently available in the U.S. The Watchman device is the most studied and FDA-approved for use in patients with AF unsuitable for anti-coagulation who are at a high risk of stroke. The Amulet device is currently being used as part of the Amplatzer Amulet LAA Occluder Trial, which is a non-inferiority randomized trial comparing the Amulet to the Watchman device. The 3rd device in use is the LARIAT, which is an FDA-approved snare and pre-tied stitch system. It is used to approximate soft tissue which in this case is the LAA. It is a hybrid system and requires both epicardial and endocardial access. The authors concluded that the main obstacle to percutaneous LAA closure is procedural related complications, which can be minimized with optimum operator experience.

Landmesser and associates (2017) noted that the global, prospective Amplatzer Amulet observational study documents real-world peri-procedural, TEE and clinical outcomes from LAAO using the Amplatzer Amulet device. In a multi-center, prospective, real-world registry, these investigators described the peri-procedural and early clinical/TEE results from this study. This registry included 1,088 patients (75 ± 8.5 years, 64.5 % men, CHA2DS2-VASc: 4.2 ± 1.6, HAS-BLED: 3.3 ± 1.1) with NVAF; 82.8 % of patients were considered to have an absolute or relative contraindication to long-term OAC and 72.4 % had had a previous major bleeding. Peri-procedural results, clinical outcomes up to the first 3 months and the available TEE results from the first scheduled follow-up (1 to 3 months post-implantation) were reported. Successful device implantation was achieved in 99.0 % of patients. During the procedure and index hospitalization, MAEs occurred in 3.2 % of patients. Patients were discharged on a single anti-platelet agent (23.0 %), dual anti-platelets (54.3 %) or an OAC (18.9 %); TEE follow-up 67 ± 23 days post procedure in 673 patients showed adequate (less than 3 mm jet)
occlusion of the appendage in 98.2% of patients and device thrombus in 10 patients (1.5%), as evaluated by core laboratory analysis. The authors concluded that this large real-world prospective registry of catheter-based LAAO using the Amplatzer Amulet device reported a high implant success rate and a low peri-procedural complication rate in a population with a high risk of stroke and bleeding; and TEE data confirmed good closure rates during follow-up and low rates of device-associated thrombus. This registry provided only short-term follow-up data (3 months).

Kleinecke and colleagues (2017) noted that the Amplatzer Amulet (St. Jude Medical, Minneapolis, MN) is a second generation Amplatzer device for LAAO for stroke prevention in patients with AF. In a single-center registry, these researchers evaluated the clinical performance of the Amplatzer Amulet device and in follow-up for 12 months. Patients with AF and contraindication to oral anti-coagulation underwent LAAO with the Amplatzer Amulet device. Follow-up was performed before discharge, by TEE after 6 weeks and telephone interview after 3, 6 and 12 months.

Between October 2014 and August 2015, a total of 50 patients (76.1 ± 8.3 years; 30 men) were enrolled. Procedural success was achieved in 49 (98%) patients. Major peri-procedural AEs were observed in 4 (8%) of patients: 1 device embolization, 2 pericardial effusions requiring pericardiocentesis and 1 prolonged hospital stay due to retropharyngeal hematoma from the TEE probe. Follow-up TEE was available in 38 of 50 patients showing complete LAA sealing in all; 2 device-related thrombi were also documented. At 12-month follow-up, 7 patients had died unrelated to the device; ischemic stroke occurred in 3 patients. According to neurological examination, 2 were classified as microangiopathic and not cardio-embolic; the other one could not be classified. Bleeding complications (5 minor, 3 major) were documented in 8 patients. The authors concluded that although minimizing procedure-related complications remains challenging, LAAO with the Amplatzer Amulet device showed high procedural success and excellent LAA sealing.

The main drawbacks of this study were: (i) its retrospective design and observational character did not exclude selection bias, (ii) a single-center experience may not reflect clinical practice in other catheterization laboratories, (iii) since this was a non-randomized
The Amplatz cardiac plug is FDA-approved for closure of atrial septal defects; but not for left atrial appendage closure. A 2nd-generation device, the Amplatz Amulet, has been developed. According to the National Institutes of Health (NIH), there is 1 clinical trial on the Amplatz Amulet that is currently recruiting subjects (last verified May 2017).

In a meta-analysis, Sahay and colleagues (2017) evaluated the safety and efficacy of percutaneous LAA closure (LAAC) compared with other strategies for stroke prevention in patients with AF. These investigators pooled together all RCTs comparing warfarin with placebo, anti-platelet therapy (APT) or non-vitamin K antagonist oral anti-coagulants (NOAC) in patients with AF using meta-analysis guidelines. Two major trials of LAAC were also included and a network meta-analysis was performed to compare the impact of LAAC on mortality, stroke/systemic embolism (SE) and major bleeding in relation to medical treatment. The network meta-analysis included 19 RCTs with a total of 87,831 patients with AF receiving anti-coagulants, APT, placebo or LAAC. Indirect comparison with network meta-analysis using warfarin as the common comparator revealed efficacy benefit favoring LAAC as compared with placebo (mortality: HR 0.38, 95 % CI: 0.22 to 0.67, p < 0.001; stroke/SE: HR 0.24, 95 % CI: 0.11 to 0.52, p < 0.001) and APT (mortality: HR 0.58, 95 % CI: 0.37 to 0.91, p = 0.0018; stroke/SE: HR 0.44, 95 % CI: 0.23 to 0.86, p = 0.017) and similar to NOAC (mortality: HR 0.76, 95 % CI: 0.50 to 1.16, p = 0.211; stroke/SE: HR 1.01, 95 % CI: 0.53 to 1.92, p = 0.969); LAAC showed comparable rates of major bleeding when compared with placebo (HR 2.33, 95 % CI: 0.67 to 8.09, p = 0.183), APT (HR 0.75, 95 % CI: 0.30 to 1.88, p = 0.542) and NOAC (HR 0.80, 95 % CI: 0.33 to 1.94, p = 0.615). The authors concluded that the findings of this meta-analysis suggested that LAAC was superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with NVAF. However, they stated that these findings

design, comparisons could not be made to other devices or treatment with OAC, and (iv) the 12-month follow-up was of insufficient length and the sample size (n = 50) was not large enough to draw definitive conclusions regarding the risk of thromboembolism and bleeding after LAAO with the Amplatzer Amulet.
should be interpreted with caution and more studies are needed to further substantiate this advantage, in view of the wide CIs with some variables in the current meta-analysis.

The Munich consensus document on “Definitions, endpoints, and data collection requirements for clinical studies of percutaneous left atrial appendage occlusion” (Tzikas et al, 2017) noted that several studies have shown the safety and efficacy of LAAO for stroke prevention in AF patients who are contraindicated or less suited for long-term OAC. These investigators stated that in order to further explore and demonstrate the potential of this therapy, additional clinical evidence is needed. This document proposed a consistent approach in the assessment and reporting of clinical results by providing definitions for parameters relevant to studies on LAAO, including comparisons with other devices and with surgical or pharmacological therapies.

Health Quality Ontario (2017) noted that AF is a common cardiac arrhythmia, and 15 % to 20 % of those who have experienced stroke have AF. Therapeutic options to prevent stroke in people with AF include pharmacological agents such as novel oral anti-coagulants or non-pharmacological devices such as the left atrial appendage closure device with delivery system (LAAC device). The objectives of this health technology assessment were to evaluate the clinical effectiveness and cost-effectiveness of the LAAC device versus novel oral anti-coagulants in patients without contraindications to oral anti-coagulants and versus anti-platelet agents in patients with contraindications to oral anti-coagulants. These researchers performed a systematic review and network meta-analysis. They also conducted an economic literature review, economic evaluation, and budget impact analysis to assess the cost-effectiveness and budget impact of the LAAC device compared with novel oral anti-coagulants and oral anti-platelet agents (e.g., aspirin). These investigators also spoke with patients to better understand their preferences, perspectives, and values. A total of 7 RCTs met the inclusion criteria for indirect comparison; 5 studies assessed the effectiveness of novel oral anti-coagulants versus warfarin, and 2 studies compared the LAAC device with warfarin. No studies were identified that compared the LAAC device with aspirin in patients in whom oral anti-coagulants were contraindicated. Using the random effects model, these researchers found that the LAAC device was comparable to novel oral
anti-coagulants in reducing stroke (OR 0.85; CI: 0.63 to 1.05). Similarly, the reduction in the risk of all-cause mortality was comparable between the LAAC device and novel oral anti-coagulants (OR 0.71; CI: 0.49 to 1.22). The LAAC device was found to be superior to novel oral anti-coagulants in preventing hemorrhagic stroke (OR 0.45; CI: 0.29 to 0.79), whereas novel oral anti-coagulants were found to be superior to the LAAC device in preventing ischemic stroke (OR 0.67; CI: 0.24 to 1.64).

The body of clinical evidence was found to be of moderate quality as assessed by the GRADE Working Group criteria. Results from the economic evaluation indicated that the LAAC device was cost-effective compared with aspirin in patients with contraindications to oral anti-coagulants. In patients without contraindications to oral anti-coagulants, these researchers found that the LAAC device was not cost-effective compared with novel oral anti-coagulants. Publicly funding the LAAC device in patients with NVAF with contraindications to oral anti-coagulants could result in additional funding of $1.1 million to $7.7 million over the first 5 years. Patients interviewed reported on the impact of living with NVAF and were supportive of the LAAC device as a therapeutic option. The authors concluded that moderate-quality evidence suggested that the LAAC device was as effective as novel oral anti-coagulants in preventing stroke in people with NVAF. However, these findings indicated that the LAAC device was cost-effective only in patients with contraindications to oral anti-coagulants. Moreover, they noted that people with NVAF with whom the authors spoke reported positive support for the LAAC device.

Yerasi and co-workers (2018) stated that LAAO is a promising intervention for stroke prevention in patients with NVAF. Early outcomes following LAAO have been published in many studies with variable results. This updated meta-analysis aimed to provide a summary of the early outcomes of LAAO. Medline/PubMed, Ovid Journals, Clinical trials, meetings abstracts, Cochrane databases were searched from January 1st, 1999 to November 30th, 2016. This meta-analysis included 49 studies involving 12,415 patients. The median age was 73.5 years (IQR 72 to 75 years) and 43 % were men. Hypertension and diabetes were present in 36 % and 15 % of the population, respectively. There was a prior history of stroke and congestive heart failure (CHF) in 14 % and 18 % of the population, respectively. The median CHADS2 score was 2.9 (IQR 2.6 to 3.3) and the median HAS-BLED score (hypertension, abnormal renal function, strike, bleeding, labile INR, age greater than 65
years, prior alcohol or drug usage history [greater than or equal to 8 drinks/week], medication usage predisposing to bleeding [anti-platelet agents, NSAIDs]) was 3.3 (IQR 3 to 4). LAAO implantation was successful in 96.3% of patients (95.40 to 97.08, I2 = 76.1%). The pooled proportion of all-cause mortality was 0.28% (0.19 to 0.38, I2 = 0%). The pooled proportion of all-cause stroke was 0.31% (0.22 to 0.42, I2 = 9.4%), major bleeding requiring transfusion was 1.71% (1.13 to 2.41, I2 = 73.2%), and peri-cardial effusion was 3.25% (2.46 to 4.14, I2 = 79%). Sub analysis of randomized clinical trials comparing LAAO devices to warfarin showed lower mortality (p = 0.03) with similar bleeding risk (p = 0.20) with LAAO. The authors concluded that this meta-analysis reported that LAAO occlusion is a safe and effective stroke prevention strategy in patients with NVAF.

Fauchier and co-workers (2018) determined the incidence, predictors, and prognosis of thrombus formation on devices in patients with AF who were treated with LAAO. The study retrospectively analyzed data from patients treated with 2 LAA closure devices seen in 8 centers in France from February 2012 to January 2017. A total of 469 consecutive patients with AF underwent LAAO (272 Watchman devices and 197 Amplatzer devices). Mean follow-up was 13 ± 13 months, during which 339 (72.3%) patients underwent LAA imaging at least once. There were 98 MAEs (26 thrombi on devices, 19 ischemic strokes, 2 TIA, 18 major hemorrhages, 33 deaths) recorded in 89 patients. The incidence of device-related thrombus in patients with LAA imaging was 7.2% per year. Older age (HR: 1.07 per 1-year increase; 95% CI: 1.01 to 1.14; p = 0.02) and history of stroke (HR: 3.68; 95% CI: 1.17 to 11.62; p = 0.03) were predictors of thrombus formation on the devices, whereas dual APT (HR: 0.10; 95% CI: 0.01 to 0.76; p = 0.03) and OAC at discharge (HR: 0.26; 95% CI: 0.09 to 0.77; p = 0.02) were protective factors. Thrombus on the device (HR: 4.39; 95% CI: 1.05 to 18.43; p = 0.04) and vascular disease (HR: 5.03; 95% CI: 1.39 to 18.23; p = 0.01) were independent predictors of ischemic strokes and TIA during follow-up. The authors concluded that thrombus formation on the device is not uncommon in patients with AF who are treated by LAAO; such events are strongly associated with a higher risk of ischemic stroke during follow-up.
Ando and colleagues (2018) stated that although percutaneous LAAO is supported as a potential alternative to lifelong anti-coagulation in patients with AF, comprehensive evidence on surgical LAA closure in heart surgery is limited. These investigators conducted a meta-analysis of studies comparing patients who underwent open cardiac surgery with or without LAA closure. A literature search was performed on PubMed, Embase, and Cochrane Trials databases. Outcomes of interest were 30-day/in-hospital mortality and CVA; I² statistics were used to evaluate heterogeneity, and publication bias was evaluated by Begg's and Egger's tests. These investigators reviewed 1,284 articles and selected for main analysis 7 articles including 3,897 patients (1,963 in the LAA closure group and 1,934 in the non-LAA closure group). Among the 7 studies, 3 were RCTs, 3 were propensity-matched studies, and 1 was a case-matching study. At 30-day/in-hospital follow-up, LAA closure was significantly associated with decreased risk of mortality and CVA (OR, 0.384, 95 % CI: 0.233 to 0.631 for mortality, and OR, 0.622, 95 % CI: 0.388 to 0.998 for CVA). Stratified analysis demonstrated that this association was more prominent in pre-operative AF strata. The authors concluded that concomitant surgical LAA closure should be considered at the time of open cardiac surgery, particularly among those in AF pre-operatively. The benefit of LAAO for patients not in AF and for those undergoing non-valvular surgery is still unclear. They stated that further prospective investigations are indicated.

Fink and associates (2018) noted that epicardial LAA ligation may be an alternative to OAC management and to endocardial LAA closure devices. These investigators reported long-term results after LAA ligation with the 2nd-generation LARIAT device. They carried out a retrospective study on patients who underwent LAA ligation at the authors’ center; follow-up included patient visits and TEE to assess LAA-to-LA leakages. A total of 76 patients with an indication for LAA closure underwent cardiac CT-based screening with 16 patients (21 %) excluded from LAA ligation due to anatomical reasons. Finally, 48 patients (70 ± 9 years, 23 women) underwent LAA ligation with successful LAA closure in 44 patients (92 %). Major peri-procedural complications occurred in 3 patients (6 %; 1 major femoral bleeding, 1 pneumothorax with surgical drainage, 1 right ventricular perforation with concomitant stroke). Additionally, minor complications occurred in 27 % of the patients with mild pericarditis in 8 of these patients being the most common AE. Clinical follow-up (median of
443 days, IQR 158 to 773) was obtained from 38 patients; 1 thromboembolic event (TIA) occurred. Complete LAA closure was demonstrated in 23/35 patients (66 %) with TEE follow-up. Major leakages of greater than 5 mm without documentation of intra-cardiac thrombi were documented in 4 patients (11 %). The authors concluded that epicardial LAA ligation with the 2nd-generation LARIAT device was associated with a high acute success rate comparable to endocardial LAA closure devices; LAA ligation was accompanied by a relevant incidence of peri-procedural complications with mild pericarditis being the most common AE. Follow-up demonstrated a moderate incidence of leakages after LAA exclusion, no intra-cardiac thrombus formation and only a single thromboembolic event. These researchers stated that the effectiveness of epicardial LAA ligation in preventing thromboembolic events needs further investigation in larger patient cohorts.

**AtriClip**

Toale and colleagues (2019) the LAA is thought to be the source of embolic strokes in up to 90 % of cases, and LAAO may be safer than the alternative of OAC. These investigators carried out a systematic review in May 2018, based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, using the keyword “AtriClip”. A total of 68 papers were identified and reviewed; 11 studies were included. Data including demographics, medical history intervention(s) performed, peri-procedural outcomes and follow-up were assessed and analyzed. A total of 922 patients were identified; LAAO was achieved in 902 out of 922 patients (97.8 %). No device-related AEs were reported across the studies. The reported incidence of stroke or TIA post-clip placement ranged from 0.2 to 1.5/100 patient-years; 477 of 798 patients (59.7 %) had ceased anti-coagulation on follow-up. The authors concluded that this review highlighted the safety, efficacy and durability of the AtriClip device in the management of patients with AF. Rates of total LAAO compared favorably to conventional surgical closure methods and percutaneous closure techniques. Success with thoracoscopic placement may lead to the increased utility of the AtriClip devices in patients undergoing non-cardiac thoracic surgery or as a stand-alone therapy. These researchers stated that future trials should aim to compare the safety and efficacy of epicardial clipping with established surgical and percutaneous methods of LAC. They stated that clear guidelines are
needed regarding the need for post-operative anti-coagulation in patients post-epicardial clipping. Whether the elimination of the LAA by this method has long-term implications for patients, in light of its role in fluid dynamics, it should be assessed by long-term follow-up of the cohorts included in the above studies.

The authors stated that this study had several drawbacks. This review examined data from a number of heterogeneous studies of differing design and methodology. Epicardial clipping was performed via a number of different approaches including open placement via sternotomy/mini-thoracotomy and thoracoscopic techniques. Furthermore, the approach to combined ablative procedures varied both within and across studies. Although some patients underwent epicardial clipping as part of a stand-alone procedure, others underwent ablation, epicardial maze or other operations for the management of AF. Post-operatively, the approach to anti-coagulation was inconsistent across studies. Data regarding post-procedural stroke rates should be interpreted with caution, especially as other potential embolic factors such as carotid stenosis were not recorded or adjusted for many included patients; and publication bias was not formally evaluated.

Appendix

- CHADS2 score calculator (https://www.mdcalc.com/chads2-score-atrial-fibrillation-stroke-risk)
- CHA2DS2-VASc score calculator (https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk)
- HAS-BLED score calculator (https://www.mdcalc.com/has-bled-score-major-bleeding-risk)

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "*":*
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33340</td>
<td>Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supe</td>
</tr>
<tr>
<td>93318</td>
<td>Echocardiography, transesophageal (TEE) for monitoring purposes, including probe placement, real time 2-dimensional image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate time basis</td>
</tr>
<tr>
<td>C1760</td>
<td>Closure device, vascular (implantable/insertable)</td>
</tr>
<tr>
<td>C1817</td>
<td>Septal defect implant system, intracardiac</td>
</tr>
<tr>
<td>C2628</td>
<td>Catheter, occlusion</td>
</tr>
<tr>
<td>I63.30 - I63.9</td>
<td>Cerebral infarction [stroke]</td>
</tr>
<tr>
<td>I66.01 - I66.9</td>
<td>Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction [stroke]</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


27. Health Technology Inquiry Service (HTIS). Left atrial appendage occlusion: Economic impact and existing HTA recommendations. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); September 29, 2010.


64. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Percutaneous left atrial appendage closure therapy for the prevention of stroke. TEC Assessments. Chicago, IL: BCBSA; October 2014;29(5).


100. Reddy VY, Doshi SK, Kar S, et al; PREVAIL and PROTECT AF Investigators. 5-year outcomes after left atrial appendage occlusion.
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110. Nishimura M, Sab S, Reeves RR, Hsu JC. Percutaneous left atrial appendage occlusion in atrial fibrillation patients with a


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Amendment to
Aetna Clinical Policy Bulletin Number: 0791
Cardiac Devices and Procedures for Occlusion of the Left Atrial Appendage

Aetna Better Health of Pennsylvania reviews every prior authorization request on an individual case by case basis.