Interventional and surgical occlusion of the left atrial appendage

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Abstract | With a steadily increasing prevalence, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and an independent risk factor for stroke caused by thromboembolic events. The left atrial appendage (LAA) is the primary source of thromboemboli in patients with nonvalvular AF who have a stroke. Novel strategies (such as mechanical and nonpharmacological intervention) targeting the LAA in patients with AF for stroke prevention have become a major focus during the past decade. Some devices for percutaneous LAA occlusion are supported by robust clinical data obtained from randomized trials or large registries, and are a valid alternative to pharmacological stroke prevention. However, the incidence of periprocedural complications and the presence of device-related thrombi or residual LAA leaks, whose long-term clinical implications are still unknown, are limiting factors in wider acceptability of these techniques. In this Review, we discuss the available techniques for LAA occlusion in patients with nonvalvular AF at high risk of stroke. We describe the pharmacological and mechanical approaches to LAA occlusion, and provide the current clinical evidence for various strategies. We particularly focus on the current management of the LAA, and discuss the challenges and future implications of the available approaches to LAA occlusion.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and an independent risk factor for stroke and systemic thromboembolism caused by thromboembolic events[1]. With a steadily increasing prevalence of 1–2% in the population, AF is not only a growing epidemic, but also a major public health burden owing to its associated morbidity and mortality[2–7]. Being an age-dependent disease, the prevalence of AF is expected to increase further owing to the ageing population worldwide and enhanced awareness of, and surveillance for, undetected AF in a considerable number of patients[8].

The most detrimental complication of AF is stroke caused by thromboembolism. The risk of stroke in AF is age-dependent and increases from 1.5% for patients with AF aged 50–59 years to 23.5% for those aged 80–89 years[1]. Nonvalvular AF (NVAF, which includes absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair) accounts for an estimated overall stroke risk of 5% per year in affected patients (fivefold higher than that in individuals without AF), and 15–20% of all ischaemic strokes in these patients are attributable to AF, especially in the elderly[1]. However, the risk of stroke is 17-fold higher in patients with valvular AF (mainly rheumatic mitral stenosis) than in individuals without AF[1].

Although stroke mortality has substantially declined since the early 20th century, stroke is still the fifth most common cause of death in the USA[9,10]. AF-related stroke is often more severe than non-AF-related strokes, and is more likely to be associated with a fatal outcome or severe disability and a higher rate of recurrence[7,11,12]. AF-related strokes can have a considerable psychological and socioeconomic effect on patients with AF, with a steep increase in health-care costs[13,14].

During the past decade, mechanical occlusion of the LAA has been adopted by clinicians as a potential approach for stroke prevention in selected patients with NVAF. However, data from randomized, controlled trials (RCTs) of the effect of LAA occlusion on the incidence of AF-associated stroke are limited. In addition, RCT data are available only for the Watchman device (Boston Scientific, USA) in patients who are eligible for oral anticoagulation (OAC), although a number of additional approaches are available worldwide, and the typical patient undergoing these procedures is not a good candidate for OAC.

In this Review, we describe the available techniques for LAA occlusion in patients with NVAF at high risk of stroke. Furthermore, we describe the pharmacological and mechanical approaches to LAA occlusion,

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Key points

- The left atrial appendage (LAA), a site of predilection for thrombus formation, is the primary source of thromboemboli in patients with nonvalvular atrial fibrillation (NVAF) who have a stroke
- Anticoagulation with vitamin K antagonists or non-vitamin K-dependent (direct-acting) oral anticoagulants is the gold standard for stroke prevention, but are contraindicated in some patients with NVAF, necessitating novel (nonpharmacological) strategies targeting the LAA
- Interventional LAA occlusion devices are a valid alternative to pharmacological stroke-prevention therapies; however, use is limited by an unsatisfactory rate of periprocedural complications and the unknown long-term clinical implications of residual peri-device flow
- The majority of studies reporting on outcomes of surgical LAA occlusion are inconclusive and had heterogeneous outcomes owing to failure to achieve occlusion
- Whereas robust clinical data from randomized, controlled trials are still lacking for surgical techniques to exclude the LAA, epicardial, device-enabled LAA occlusion might offer a safe, durable, and efficacious surgical approach
- An outcome-oriented collaboration between cardiologists and surgeons — the Heart Team approach — as successfully applied in the transcatheter aortic valve replacement or MitraClip experience, is imperative

and provide the latest clinical evidence for the different strategies. We particularly focus on current management of the LAA, and discuss the ongoing challenges and future implications of the various approaches.

Rationale for stroke-prevention therapy

AF is a common heart rhythm disorder characterized by an abnormal, rapid, and irregular heartbeat. AF is classified clinically as paroxysmal, persistent, long-standing persistent, or permanent (TABLE 1). The LAA has a complex and variable anatomy[15] (FIG. 1), and is typically divided into three anatomical regions: the ostium (or orifice), the neck, and the lobar region. According to the CT-based classification, the LAA morphology can be divided into 'chicken wing' (48%), 'cactus' (30%), 'windsock' (19%), and 'cauliflower' (3%), although this anatomical classification has been called into question[16–19]. Despite being an embryonic remnant, several important functions are attributed to the LAA. As a highly contractile chamber, the LAA is more compliant than the left atrium itself, suggesting that the LAA has a reservoir function during left ventricular systole[20]. In addition, several studies indicate that the LAA has neurohormonal properties, such as the regulation of thirst through stretch-sensitive receptors, modulation of intravascular volume, and regulation of haemodynamics by endocrine release of atrial and B-type natriuretic peptides[21–26]. However, little is known about the clinical effects of these properties, especially in the setting of an altered LAA function related to AF.

AF influences the transport function of the left atrium by decreasing not only its contractility, but also that of the LAA, resulting in blood stasis with diminished LAA peak flow velocities. AF is also associated with endothelial damage with endocardial fibroelastosis and a prothrombotic and hypercoagulable state[27–31]. This association is consistent with the historical 'Virchow's triad' for thrombogenesis and perception of the LAA as the "most lethal human attachment" (REFS 32–34). Indeed, 57% of thrombi in valvular AF and 91% in NVAF originate in the LAA, making this structure the main source of thromboembolism[35].

The assessment of stroke risk in patients with NVAF depends on various risk factors. Several different stroke risk scoring systems have been validated in the past decade, including the $CHADS_2$, CHA_2DS_2-VASc, and ATRIA scores[36–38]. The CHA_2DS_2-VASc scoring system is recommended in the current guidelines[39,40].

Stroke risk reduction

The first option in the prevention of AF-related stroke or the reduction of the risk should be the elimination of the underlying cause, which is achieved by permanently converting the abnormal rhythm disorder into a sinus rhythm. Unfortunately, antiarrhythmic drugs, surgical interventions, and catheter ablations are only partially successful in restoring a stable sinus rhythm in patients with AF and eliminating the need for further stroke-prevention therapies. AF ablation aims at alleviating AF symptoms, and whereas successful AF therapies relieve both the symptoms of AF and its attendant risk of stroke, unsuccessful AF therapies do neither. Interestingly, current guidelines typically indicate continued anticoagulation in patients with a high CHA_2DS_2-VASc score (≥3) receiving AF ablation, even if the procedure was successful[40]. Thus, additional stroke-prevention strategies are often required for patients with AF.

Pharmacological approaches

Several randomized trials and observational studies support the role of the antiplatelet agent acetylsalicylic acid (aspirin) in primary and secondary prophylaxis in cardiovascular disease to decrease the risk of cardiovascular events[41–44]. However, data supporting the efficacy of acetylsalicylic acid in stroke prevention in patients with AF are limited[45,46]. Large randomized trials showed that the use of dose-adjusted vitamin K antagonists (VKAs;

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Table 1 | **Classification of atrial fibrillation**

Clinical type/ pattern of AF	Definition
First diagnosed	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms
Paroxysmal	AF that terminates spontaneously or with intervention (cardioversion by antiarrhythmic drugs or direct-current shock) within 7 days
Persistent	AF episodes that last >7 days
Long-standing persistent	AF episodes that last >1 year with ongoing rhythm-control strategy
Permanent	AF that involves an agreement between the patient and clinician not to attempt further restoration and/or maintenance of sinus rhythm
Nonvalvular (AHA/ACC/ HRS)	AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

According to the 2014 AHA/ACC/HRS[39] and 2016 ESC[40] guidelines. AF, atrial fibrillation; HRS, Heart Rhythm Society.

such as acenocoumarol, phenprocoumon, or warfarin with an international normalized ratio of 2.0–3.0) for oral anticoagulation significantly reduced stroke risk in patients with AF[46–51]. Furthermore, a meta-analysis of large randomized trials showed that warfarin reduced the risk of stroke in patients with AF by 64%, and all-cause mortality by 26% compared with placebo, whereas the difference in the relative risk reduction of stroke between acetylsalicylic acid and placebo was only 22%[52]. In trials involving patients with AF treated only with acetylsalicylic acid, the reduction in stroke risk was even lower, with a stroke event rate of 19%[45,53].

OAC with VKAs has major limitations, such as inter-patient and intra-patient variability of anticoagulant effects owing to multiple drug–drug and drug–diet interactions, a narrow therapeutic window necessitating regular monitoring, and the frequent need for discontinuation owing to therapeutic or diagnostic interventions. In addition, antithrombotic therapies are characterized by major and minor bleeding complications. These disadvantages lead to poor patient compliance, patient refusal of anticoagulation therapy, reluctance of physicians to prescribe VKAs owing to concerns about the adverse risk–benefit ratio, and absolute contraindications to anticoagulation (such as a history of major cerebral bleeding events)[54]. Consequently, VKAs remain underutilized in clinical practice, especially in elderly patients who have the highest risk of stroke[55–58].

The concerns about the use of VKAs led to decades of efforts to identify safer and more effective anticoagulant therapies, which culminated in the development of non-vitamin-K-dependent oral anticoagulants (NOACs; also known as direct-acting oral anticoagulants or DOACs), which directly inhibit thrombin or factor Xa. NOACs have demonstrated improved safety and similar or superior efficacy profiles compared with other anticoagulants, and have now become the standard-of-care for many patients[59–62]. Meta-analyses of the main NOAC trials showed that these anticoagulants significantly reduce stroke, intracranial haemorrhage, and mortality in patients with AF compared with the use of VKAs, with rates of major bleeding events similar to those with warfarin, but increased rates of gastrointestinal bleeding[63,64]. Given these favourable risk–benefit profiles, the latest guidelines for the management of AF now recommend NOACs as the first-line treatment option for anticoagulation[40,65]. Nevertheless, this new class of anticoagulants has several shortcomings, such as high costs, bleeding risk (especially increased gastrointestinal bleeding), drug interactions, and the requirement for dose adjustment in elderly patients or those with low weight and reduced renal or liver function[65]. The lack of a need for regular monitoring, unlike with VKA therapy, might increase the problem of patient noncompliance and impair the recognition of necessary dose adjustments. Previous concerns about the lack of antidotes have been successfully addressed for NOACs, but these antidotes might not be widely available except in major tertiary medical centres.

Mechanical approaches

Despite the favourable risk–benefit profile of NOACs as compared with warfarin, an inherent risk of bleeding characterizes all antithrombotic agents. This shortcoming prompts the consideration of other methods for the prevention and risk reduction of AF-related stroke. In 1947, Hellerstein *et al.* first reported the feasibility of resecting LAAs in a canine model and also suggested LAA occlusion as a possible approach[66]. Approximately 2 years later, Madden described two cases of LAA resection in humans as an ideal prophylaxis for recurrent arterial emboli by physical elimination of the site of predilection for thrombus formation[67]. Subsequently, concomitant surgical LAA occlusion was performed sporadically in high-risk mitral valve procedures, until Coulshed and colleagues questioned its efficacy in reducing embolic events in a review article published in 1970 (REF. 68).

LAA occlusion had a revival in the mid-1980s when James Cox described resection of both the right atrial and left atrial appendages as a part of the original Cox-maze procedure[69,70]. Right atrial appendage resection was soon removed from this procedure because of concerns about the endocrine function of the atrial appendages, but LAA resection remained an important part of any maze procedure for the subsequent 30 years[71,72]. BOX 1 provides an overview of surgical and percutaneous LAA occlusion or exclusion devices and techniques.

Surgical LAA exclusion/occlusion

The LAA can be excluded from the systemic circulation by occluding its orifice with or without excising the body of the appendage[73,74]. Surgical LAA occlusion has been attempted both epicardially and endocardially with or without enabling devices. The LAA can be excluded without using enabling devices in three ways: epicardial suture ligation, endocardial suture occlusion, and excision and epicardial suturing[75–78] (FIG. 2). Excision is the most effective and definitive surgical technique because both epicardial and endocardial suture occlusions are fraught with a high rate of persistent, residual, or recurrent connections between the LAA and left atrium.

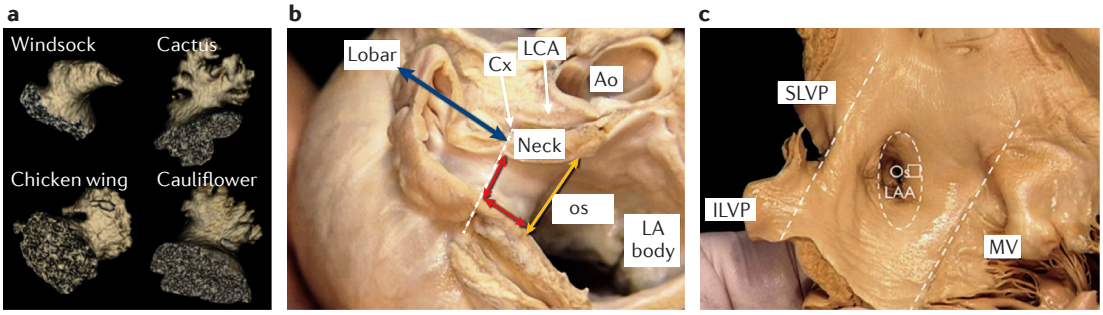


Figure 1 | **Anatomy and morphology of the left atrial appendage. a** | The cardiac CT-based classification of the left atrial appendage (LAA) morphology includes the windsock (19%), chicken wing (48%), cactus (30%), and cauliflower (3%) morphologies[19]. **b,c** | The LAA is located near to the atrioventricular groove between the left ventricle and the pulmonary artery trunk, with its base being close to the proximal left circumflex coronary artery (Cx). The LAA is typically divided into three anatomical regions: the opening/orifice (os), the neck, and the lobar region. The os can be teardrop shaped, round, elliptical (or oval), foot-like or triangular, and its diameter can range from 10 mm to 40 mm and be located at the junction of the appendage with the body of the left atrium (LA). The neck region is a short tubular segment between the os and the lobar region[172,173]. The lobar region of the LAA usually consists of two lobes and is the most complex region of the LAA with heavy trabeculations and pectinate muscles; by contrast, the surface of the os and neck regions are mostly smooth[174]. The length and width of the neck as well as the number of lobes vary considerably. Ao, aorta; ILPV, inferior left pulmonary vein; LCA, left coronary artery; MV, mitral valve; SLPV, superior left pulmonary vein. Panel **a** reproduced from Saw, J. *et al.* Cardiac computed tomography angiography for left atrial appendage closure. *Can. J. Cardiol.* **32**, 1–9 © 2016, with permission from Elsevier. Panels **b** and **c** adapted from Don, C. W. *et al.* in *Left atrial appendage closure: mechanical approaches to stroke prevention in atrial fibrillation*. Ch. 4 (eds Saw, J., Kar, S. & Price, M. J.) 45–57 (Humana Press, 2016), with permission from Springer.

The surgical exclusion of the LAA using devices that are applied epicardially can be performed in several ways. Surgical staplers might include cutting or non-cutting components (such as Endo GIA II, Medtronic, USA, or EZ45, Ethicon, USA) and might employ a bovine pericardial strip to buttress the staple line[79,80]. Endoloop (Ethicon, USA) snaring excludes the LAA with a detachable snare loop, positioned at the base of the LAA[81]. Furthermore, the LigaSure Vessel Sealing System (Medtronic, USA) uses radiofrequency energy to weld tissue at the base of the LAA[82], whereas the AtriClip LAA Exclusion System (AtriCure, USA) enables epicardial LAA occlusion with concomitant open cardiac surgery or as a stand-alone thoracoscopic surgical procedure[83]. When deployed, the AtriClip applies uniform, dynamic pressure over the length of two parallel tubes ensuring consistent and secure occlusion of the LAA (FIG. 2). The TigerPaw system (Getinge, Sweden), an implantable soft silicone occlusion fastener delivered epicardially around the base of the LAA, was removed from the market in 2015 because of safety concerns. This device is expected to be re-launched as a next-generation version in 2017 (REF. 84).

Stand-alone or concomitant surgical LAA occlusion during cardiac surgery has been performed for decades. However, the majority of studies reporting on outcomes of surgical LAA occlusion are nonrandomized case series, observational cohort studies, or registries and smaller pilot trials, and, therefore, mostly inconclusive in their results[35,74,85,86]. Robust data from randomized clinical trials supporting the true efficacy for stroke risk reduction are scarce. The only randomized trial (which, notably, involved patients who had risk factors for stroke, but not all patients had a history of AF) was prematurely abandoned in the pilot phase when issues about completeness of LAA occlusion and residual leaks became apparent[87]. Meta-analysis showed that the rate of successful occlusion in attempted LAA occlusion performed by a variety of surgical methods was only 55–66%[88].

A study involving transoesophageal echocardiography (TEE) reported incomplete ligation in 36% of 50 patients with AF undergoing mitral valve surgery[85]. In another TEE study, the investigators reported up to a 12-fold increased risk of thromboembolism in the presence of incompletely ligated LAAs, together with the absence of LAA ligation[86]. Furthermore, in 92 patients undergoing mitral valve replacement with or without CABG surgery and concomitant LAA ligation, those with a ligated LAA had a higher risk of late stroke[89]. In line with these findings, a propensity score-matched analysis showed that LAA occlusion (performed by ligation in 98% of patients) did not significantly change the risk of stroke or death[90]. Furthermore, incompletely surgically ligated LAAs were found to be predictors of ischaemic stroke or systemic embolization[91].

In a landmark study published in 2008, different surgical techniques were evaluated through TEE in 137 patients who underwent surgical LAA occlusion from 1993 to 2004 (REF. 74). The LAA was amputated in 52 patients (38%) using either the cut-and-sew technique or surgical staplers, and excluded in 85 patients (62%) using sutures or noncutting surgical staplers. Interestingly, 73% of patients with excision had successful LAA occlusion, whereas a remnant LAA pouch >1 cm was present in 14 patients. The success rate with suture exclusion was only 23%, and LAA exclusion with noncutting staplers was unsuccessful in all 12 patients.

The studies discussed above demonstrated a low success rate of various surgical LAA occlusion techniques, and, therefore, limited conclusions regarding their potential capacity to reduce stroke risk can be

drawn. In the past decade, there has been a tendency towards higher success rates of surgical LAA occlusion, with encouraging data suggesting a positive effect on stroke risk reduction owing to improved surgical techniques and the development of new devices[92]. As a result, the TigerPaw System (not currently available in clinical practice) and the AtriClip device were approved by the FDA for LAA occlusion under direct visualization and in conjunction with other open-heart procedures.

The AtriClip was first introduced to the clinic in 2007 and, to date, almost 100,000 devices have been sold and are being used for LAA occlusion. Early clinical results from the first-in-human pilot trial showed safe and durable clip deployment with 100% successful LAA occlusion in 40 patients undergoing elective cardiac surgery[93]. These results were confirmed in the multicentre EXCLUDE trial[94], which involved 70 patients. Outcome data at 3 years of follow-up showed an excellent safety and durability profile, without the occurrence of any strokes in patients with discontinued OAC. A long-term, follow-up study with the initial 40 patients and an institutional registry with 251 consecutive patients undergoing open-heart surgery showed that, in patients with discontinued OAC during follow-up, the relative stroke risk was reduced by 87.5%, with an observed rate of ischaemic stroke of 0.5 per 100 patient-years, compared with the rate expected in a group of patients with similar CHA_2DS_2-VASc scores (4.0 per 100 patient-years)[95]. In all patients, the LAA was successfully excluded, and no device-related complications were detected throughout the follow-up period. These data are encouraging for the potential efficacy of device-enabled concomitant LAA occlusion with the AtriClip device in reducing the incidence of stroke. Furthermore, CT imaging in selected patients (performed 5.1–8.1 years after device implantation) showed long-term durability, with complete LAA occlusion and no signs of residual reperfusion or substantial LAA stumps[95].

In addition, a prospective, multicentre, feasibility study investigating the safety and efficacy of stand-alone minimally-invasive AtriClip LAA occlusion for patients with NVAF and contraindications to OAC treatment was completed in August 2015 (REF. 96). Although more data on surgical LAA occlusion is emerging, evidence from RCTs that indicate risk reduction with LAA occlusion is still limited. The LAAOS III study[97], a randomized trial involving 4,700 patients which started in 2012, is designed to evaluate concomitant surgical LAA occlusion in patients with AF who are undergoing routine cardiac surgery. Although the LAAOS III study is the first randomized trial on stroke prevention by LAA occlusion versus OAC, several methodological issues remain. Surgical LAA occlusion during cardiac surgery is a weakness of this study because it limits the direct comparison to routine stand-alone percutaneous interventional approaches. Also, the choice of LAA occlusion method is left to the discretion of the surgeon, and, therefore, might considerably bias the results. Without standardization of the LAA occlusion techniques, these results might not be much different from those described in previous studies. Recommendation of OAC in both study groups of the LAAOS III trial is another limiting factor for determining the specific effect of LAA occlusion on stroke risk reduction. In addition, the OAC regimens vary between the different participating centres.

Box 1 | **LAA occlusion/exclusion devices and techniques**

Surgical

Suture-enabled

- Epicardial suture occlusion (ligation)
- Endocardial suture occlusion
- Surgical excision and suturing

Device-enabled

- AtriClip LAA Exclusion System
- Surgical stapler (such as Endo GIA II, EZ45)
- Endoloop
- LigaSure
- TigerPaw (currently not available for clinical use)

Interventional/percutaneous

Endocardial

- Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) system (no longer commercially available)
- Amplatzer atrial septal defect occluder (nondedicated device)
- Amplatzer Cardiac Plug (ACP) (first-generation dedicated device)
- Amplatzer Amulet (second-generation dedicated device)
- Watchman LAA closure device (first generation)
- Watchman FLX LAA closure device (second generation)
- Coherex WaveCrest occlusion system
- Transcatheter Patch
- LAmbre LAA closure system
- Occlutech LAA Occluder
- pfm LAA Occluder
- Ultraseal LAA closure device

Hybrid endocardial and epicardial

- Lariat suture delivery system

Epicardial

- Aegis Sentinel Ligation System (SENTINEL)

Percutaneous LAA occlusion

Physician and patient desire for less invasive alternative approaches (also not requiring anticoagulants) triggered the development of percutaneous LAA occlusion devices for stroke risk reduction, which are summarized in TABLE 2. An overview of the trials on both interventional and surgical LAA occlusion devices is provided in TABLE 3.

PLAATO. The PLAATO device (ev3 Endovascular, USA) was the first percutaneous LAA occlusion device, and was implanted in humans in 2001. After successful testing in a canine model[98], international, multicentre, prospective, nonrandomized feasibility trials in Europe and the USA were conducted to evaluate the safety, feasibility, and efficacy of the PLAATO system in high-risk patients with nonrheumatic AF and contraindications for OAC[99]. The device was successfully implanted in 108 of 111 patients. Seven major adverse events (two strokes, one procedure-related need for cardiovascular surgery,

and four cardiac or neurological deaths) in five patients occurred during an average follow-up of 9.8 months. TEE performed at 1 month and 6 months after device implantation showed no device migration or mobile thrombus. The observed stroke rate of 2.2 events per 100 implant-years as compared with the expected stroke rate of 6.3% based on the $CHADS_2$ score indicated a relative risk reduction of 65%. A European PLAATO study[100] involving 180 patients showed successful implantation of the device in 90% of patients. A total of 16 major adverse events occurred in 12 patients during 129 patient-years (12.4%), including three strokes, six cardiac tamponades (with two patients requiring surgery), and five non-procedure-related and two procedure-related cardiac deaths. The relative stroke risk reduction achieved in this study was 65%. For financial reasons, the European PLAATO study was discontinued and, in 2006, the PLAATO device was withdrawn from the market[100].

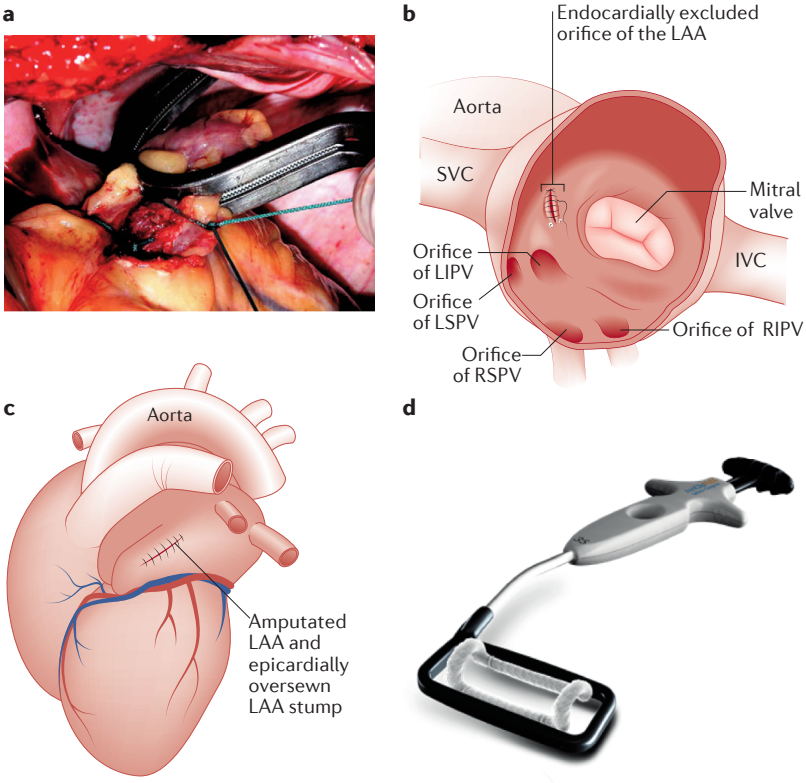


Figure 2 | **Surgical occlusion of the left atrial appendage. a** | Exclusion of the left atrial appendage (LAA) by epicardial suture ligation. A suture is placed epicardially around the neck, at the base of the LAA and tied down excluding the LAA. **b** | Endocardial suture occlusion. Running or mattressed sutures are placed from the open left atrium at the orifice of the LAA in a single-layer or double-layer fashion. **c** | The surgical excision technique (cut-and-sew method) incorporates first the amputation of the LAA at the neck by excision, and then oversewing of the opening by various methods (running or mattressed sutures, single or double layer, with or without felt pledget reinforcement). **d** | The AtriClip LAA Exclusion System (AtriCure, USA) consists of a single-use, sterile, repositionable, self-closing, implantable clip preloaded on a single-use clip applier made from two parallel titanium tubes. The elastic nitinol springs are covered by knit braided polyester and deployed after optimal placement at the base of the LAA. ILPV, inferior left pulmonary vein; IRPV, inferior right pulmonary vein; IVC, inferior vena cava; SLPV, superior left pulmonary vein; SRPV, superior right pulmonary vein; SVC superior vena cava. Panel **a** adapted from Bakhtiary, F. *et al.* Simplified technique for surgical ligation of the left atrial appendage in high-risk patients. *J. Thorac. Cardiovasc. Surg.* **135**, 430–431 (2008), with permission from Elsevier. Panel **b** adapted from Hanif, H. & Whitlock, R. in *Left atrial appendage closure: mechanical approaches to stroke prevention in atrial fibrillation*. Ch. 5 (eds Saw, J., Kar, S. & Price, M. J.) 61–80 (Humana Press, 2016), with permission from Springer. Panel **d** reproduced with permission from AtriCure.

Amplatzer devices. The non-dedicated Amplatzer atrial septal defect occluder (Abbott, USA) for LAA occlusion was first used in 2002 (REF. 101). Subsequently, the first dedicated Amplatzer device for LAA occlusion, the Amplatzer Cardiac Plug (ACP), was introduced and received CE mark approval in 2008. The Amplatzer Amulet device superseded the ACP as the second-generation modification of Amplatzer LAA occlusion devices and received CE mark approval in 2013.

Data on Amplatzer devices are mostly available from retrospective, nonrandomized case series, single or multicentre registries, and small prospective safety and feasibility trials. To date, data from RCTs are not available for any of the Amplatzer LAA occlusion devices. The first report on the use of the Amplatzer atrial septal defect occluder for LAA occlusion in 16 patients was published in 2003 (REF. 101). Successful LAA occlusion was achieved in all but one patient, and device embolization occurred in one patient who had to undergo cardiac surgery to remove the device.

The development of the dedicated ACP LAA occlusion device and its first implantation in 2008 led to broader use worldwide. The initial European study evaluated procedural feasibility and safety up to 24 h after implantation of the ACP in 143 patients; the LAA occlusion was successful in 96% of patients[102]. The initial Asia-Pacific study showed that implantation success rates were similar to those in the European study, and that procedural safety was improved, with one catheter-related thrombus formation and no acute device embolization[103]. Consistent with these data, reports from subsequent registries involving the ACP showed high implantation success and improved safety event rates[104–107]. Multicentre registry data derived from a subsequent study performed in 22 European and Canadian large-volume centres support the short-term and long-term safety and efficacy of the ACP device[108]. A total of 1,047 patients were followed up for an average of 13 months (1,349 patient-years in total). Procedural success was achieved in 97.3% of patients, and 52 major adverse events (5%) occurred periprocedurally. The annual rate of thromboembolism (including nine strokes and nine transient ischaemic attacks) during follow-up was 2.3%, corresponding to a relative stroke risk reduction of 59%.

Data on the second-generation Amplatzer LAA occlusion device, the Amulet, were limited to small registries showing high successful implantation and low periprocedural complication rates[109–111]. However, short-term data from a large Amulet observational study (a multicentre, prospective registry involving 1,073 patients) confirmed the initial promising results. Implantation of the device was successful in 98.8% of patients, with TEE-verified occlusion rate of 99% (no residual flow or <3 mm), whereas device-related or procedure-related rates of major adverse events were 2.7%.

The ACP trial, a prospective, randomized, multicentre, clinical study, was commenced under an investigational device exemption from the FDA in 2013, but was terminated by the manufacturer in order to modify the initial protocol in response to the changing landscape of stroke management (such as the use of NOACs and novel devices). Since 2016, this trial has started again to evaluate the latest generation of the device as a noninferiority trial versus the commercially available Watchman device[112]. A post-approval study in China is expected to enrol patients soon[113], and another post-approval study in Canada is currently recruiting patients[114].

Watchman. The Watchman LAA occlusion device is the only device approved by the FDA indicated to reduce the risk of thromboembolism from the LAA in patients with NVAF, and has undergone refinements since the first implantation in 2002. The next-generation Watchman FLX LAA occlusion device received CE mark approval in late 2015. However, the manufacturer withdrew the device from the market after unusually high rates of device embolization were reported during the limited market release in Europe.

The Watchman device is the only LAA occlusion device that has been tested in randomized clinical trials. After an initial pilot feasibility study, the PROTECT AF trial[115,116], a randomized, noninferiority trial, assessed the safety and efficacy of percutaneous LAA occlusion for stroke prevention with the Watchman device as compared with warfarin treatment in anticoagulation-eligible patients with NVAF. A total of 707 patients were enrolled at 59 sites in the USA and Europe and assigned to either intervention (device) or control (warfarin) groups in a 2:1 ratio[115]. Device implantation was successful (defined as complete occlusion or width of residual peri-device flow-jet <5 mm) in 91% of patients. At 1,065 patient-years of follow-up (18 months mean follow-up per patient), the criterion of noninferiority of the intervention with a probability >99.9% was met for the primary composite efficacy end point. The primary composite efficacy end point (occurrence of ischaemic or haemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism) was 3.0 events per 100 patient-years in the intervention group compared with 4.9 events per 100 patient-years in the control group. The higher rate (7.4 events per 100 patient-years) of primary safety events in the intervention group, which included serious pericardial effusion, major bleeding, and procedural ischaemic stroke, compared with that in the control group (4.4 events per 100 patient-years), were mainly due to periprocedural complications. Following this trial, the FDA did not approve the Watchman device owing to concerns related to patient selection criteria (inclusion of low-risk patients with a $CHADS_2$ score of 1), selection of low noninferiority margins, and periprocedural safety events. The FDA requested a second trial addressing these issues, and 460 additional patients were included in the CAP study[117], an ongoing, nonrandomized, investigational, device exemption registry. Initial data from the CAP registry showed that the success rate for the implantation of the Watchman device significantly increased to 95%, and the rate of procedure-related or device-related adverse events within 7 days of the procedure (3.7%) significantly declined. Furthermore, the safety of the Watchman device implantation was considerably improved by the increased experience of the operator, suggesting a learning curve associated with implantation of this device[117,118]. As required by the FDA, a second multicentre RCT, the PREVAIL trial[119], was conducted to further evaluate the safety and efficacy of the Watchman device in patients with AF eligible for OAC. Three co-primary end points were defined to address the concerns raised by the FDA following the PROTECT AF trial and CAP registry, including primary efficacy (composite of ischaemic or haemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism), late-ischaemic efficacy (composite of ischaemic stroke or systemic embolism >7 days after randomization), and early safety (composite of all-cause death, ischaemic stroke, systemic embolism, or device-related events requiring open-heart surgery or major endovascular intervention between randomization and 7 days from the procedure or during index hospitalization)[119]. The implantation success rate in the PREVAIL trial was improved compared with that in the PROTECT AF trial (95% versus 91%, respectively), and was similar to that in the CAP registry despite 20% of the institutions and 25% of the operators involved in the study being new. At 18 months after the implantation, LAA occlusion with the Watchman device did not achieve statistical noninferiority for the primary efficacy end point compared with long-term warfarin therapy. Although late-ischaemic efficacy and early safety end points (event rates of 2.5% and 2.2%, respectively) met the criteria for statistical noninferiority, the overall noninferiority was not achieved in this trial because noninferiority was not achieved in the first coprimary end point, as required by the trial design. An overperforming control group (warfarin treatment) characterized by an unexpectedly low rate of ischaemic stroke (compared with that in other NOAC trials) might have contributed to these results. Notwithstanding, in 2015, the FDA approved the commercialization of the Watchman device in the USA on the condition that two post-approval cohort studies be performed[120].

A meta-analysis of the PROTECT AF and PREVAIL trials as well as their respective registries (CAP and CAP2), which included a total of 2,406 patients and 5,931 patient-years of follow-up[121], demonstrated that LAA occlusion with the Watchman device resulted in reduced rates of haemorrhagic stroke, death, and major nonprocedural bleeding compared with those with warfarin treatment.

Data from the multicentre, prospective EWOLUTION registry, which evaluated the application of the Watchman device in a real-world setting, showed further improved implantation success and a favourable safety profile compared with those in previous studies[122]. In contrast to these findings, a survey of the European Heart Rhythm Association (EHRA)

Table 2 | **Devices for percutaneous or interventional LAA occlusion**

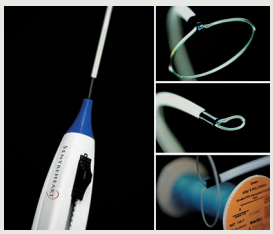
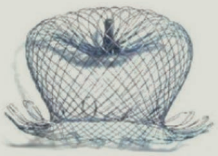
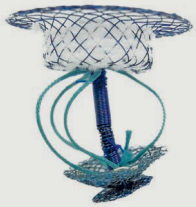
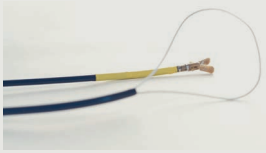
Device	Description	CE mark	Size (mm)
Watchman LAA closure device (Boston Scientific, USA)  Reproduced with permission from Boston Scientific	Nitinol frame with 10 active fixation anchors. The parachute-shaped core cage is covered by a permeable polyethylene terephthalate cap designed to block emboli and promote device endothelialization[116,175]	Yes, FDA approved	21–33
Amplatzer Amulet LAA occluder (Abbott, USA)  Reproduced with permission from St. Jude Medical © 2017	Self-expandable device made from braided nitinol with a polyester fabric patch consisting of a proximal disc and distal lobe sealing the ostium and body of the LAA (pacifier principle). The lobe and disc are connected with a short flexible central waist, and fixation hooks at the lobe anchor the device inside the body of the LAA. The Amplatzer devices are all repositionable and retrievable until final release. New features of the Amulet device to minimize complications and facilitate device deployment include: a preloaded system, larger disc diameters, overall availability of larger sizes, longer lobes and waist lengths, more stabilizing wires, and inversion of the attaching screw on the proximal disc[176]	Yes	16–34
Lariat (+/XT) suture delivery device (SentreHEART, USA)  Reproduced with permission from SentreHEART	The Lariat suture delivery system comprises three components: a 15 mm compliant balloon catheter (EndoCATH); magnet-tipped guidewires (FindrWIRZ) of 0.635 mm and 0.889 mm; and a 12-French suture-delivery device (Lariat) with a preloaded USP 0 Teflon-coated braided polyester suture with a suture-tensioning and cutting device (TenSURE)[128]. The latest evolution of the Lariat device, the Lariat$^+$, includes a larger snare size (45 mm), a platinum–iridium 'L' Marker for correct identification of snare loop orientation in fluoroscopy, and improved 'torque-ability' of the delivery catheter[134]	Yes	≤45
Coherex WaveCrest occlusion system (Coherex Medical, Biosense Webster, Johnson&Johnson, USA) 	An umbrella-shaped device covered with an occlusive and nonthrombogenic expanded polytetrafluoroethylene membrane and retractable role-out anchors allowing controlled release[136]	Yes	22, 27, 32
Transcatheter Patch (Custom Medical Devices, Greece) 	A frameless, balloon-deliverable, bioabsorbable device made from polyurethane foam. The supporting balloon is made of latex and a two-stage pH-activated polyethylene glycol-based surgical adhesive is necessary to fix the device within the LAA. Delivery is achieved by balloon inflation with diluted contrast stretching the device to the LAA and then activation of the surgical adhesive after proper position is confirmed by fluoroscopy and transoesophageal echocardiography. The supportive balloon catheter is deflated 45 min after activation and then retracted[137]	Yes	15–25

Table 2 (cont.) | **Devices for percutaneous or interventional LAA occlusion**

Device	Description	CE mark	Size (mm)
LAmbre LAA closure system (Lifetech Scientific, China) 	A nitinol-based, self-expanding device comprising a hook-embedded umbrella and a polyethylene terephthalate fabric-enriched cover connected with a short central waist. The articulating waist allows self-orientation of the device. Whereas the larger proximal part covers the LAA orifice, the distal umbrella facilitates anchoring to the LAA wall by stabilizing hooks attached to claws. An additional membrane was added to the umbrella in the next-generation LAmbre device. The occluder is available in special sizes with various diameters for the umbrella and cover to adapt to the highly variable anatomy of the LAA[177]	Yes	Umbrella 16–22 Proximal cover 36–40
Occlutech LAA Occluder (Occlutech International, Sweden) 	A self-expanding, flexible, nitinol mesh structure with a cylindrical shape. The outer surface is covered with a nonwoven, biostable polycarbonate urethane layer. Anchoring is achieved by expandable, rounded loops at the distal end that fix the device at the landing zone. Owing to the flexible nature of the cage, the Occlutech LAA Occluder adapts to most differences in LAA anatomy. The Occlutech steerable sheath facilitates flexible rotation up to 180° for optimal implantation of the device[138]	Yes	15–39
pfm LAA Occluder (pfm Medical, Germany) 	A nitinol construction with an anchor, a middle variable length connector, and an occluder disc with a self-centring design	Yes	NA
Ultraseal LAA closure device (Cardia, USA) 	The fully retrievable and repositionable Ultraseal LAA closure device consists of a proximal sail section and a distal bulb. The proximal sail section covered with a dual layer polyvinylacetate foam occludes the LAA orifice, whereas the distal bulb with hooks facilitates anchoring of the device. The two parts are connected with a dual articulating joint ensuring proper positioning and deployment	No	Distal bulb 16–22 Proximal sail 22–38
Sierra Ligation System (Aegis Medical Innovations, Canada)  Reproduced with permission from Aegis Medical Innovations	An electrocardiogram-based LAA capture and ligation system comprising two elements, a LAA Stabilizer (appendage grasper with an articulating jaw and electrodes on the distal shaft) and a Ligating device (hollow suture preloaded with a 0.3 mm support wire). After puncture, an introducer sheath is placed in the pericardial space. The stabilizer is introduced and placed near the LAA and the recorded electrocardiogram is used to identify proper grasping of LAA tissue. After injection of contrast to outline the LAA, the hollow suture is advanced over the grasper at the LAA base, cinched down to occlude the LAA, and the preformed knot is then tightened and cut[143]	No	NA

LAA, left atrial appendage; NA, not available; USP, United States Pharmacopeia.

conducted in 33 European centres revealed worrisome complication rates associated with the implantation of the Watchman device[123]. However, a report on real-world experience with the Watchman device after the FDA approval revealed promising high procedural success and low complication rates[124]. A network meta-analysis on comparative effectiveness of interventions for stroke prevention in AF ranked the Watchman device first with regard to reduction of all-cause mortality and stroke risk as compared with the leading NOACs and warfarin[125].

Lariat. The Lariat suture delivery system (SentreHEART, USA) for exclusion of the LAA is based on a hybrid approach; the suture ligates the LAA epicardially whereas the endocardial access facilitates optimal navigation and positioning. After promising results in a canine model, the first-in-human clinical study demonstrated feasibility of the Lariat suture delivery system[126,127]. In 2013, a single-centre, nonrandomized trial showed that successful deployment of the Lariat suture was achieved in 95.5% of 89 patients, with complete occlusion in 82 patients (92%)[128]. Access-related

Table 3 | **Main interventional and surgical LAA occlusion/exclusion devices and corresponding trials**

Device/ technique	Number of patients	Study design	Mean $CHADS_2$ score (±SD)	Mean CHA_2DS_2-VASc score (±SD)	Patient-years	Mean follow-up	Rate of successful LAA occlusion	Results, complications, or comments
PLAATO								
PLAATO[99]	111	Prospective, multicentre registry	2.5 (1.3)	NA	90.7	9.8 months	97.3	Three pericardiocenteses, one cardiovascular surgery, and one neurological death; 2.2 stroke events per 100 patient years, RRR 65%
PLAATO[178]	64	Prospective, multicentre registry	2.6 (NA)	NA	239.9	3.75 years	98.2	Five major strokes, three minor strokes, one cardiovascular surgery, one neurological death; rate of annual stroke 3.8%, RRR 42%
PLAATO[100]	180	Prospective, multicentre registry	3.1 (0.8)	NA	129	9.6 months (±6.9)	90	Cardiovascular surgery (one LAA perforation, two cardiac tamponades), four pericardiocenteses, two periprocedural deaths; 2.3 stroke events per 100 patient-years, RRR 65%; the trial was halted prematurely during follow-up
Watchman								
Watchman[115,179]	707 (463 implanted with the device)	Prospective RCT	2.2 (1.2)	NA	2,621	3.8 years (±1.7)	90.9	Primary efficacy rate of 2.3 events per 100 patient-years (device), primary safety rate of 3.6 events per 100 patient-years; LAA occlusion met the criteria for both noninferiority and superiority as compared with warfarin therapy
Watchman[117]	460	Prospective, multicentre registry	2.4 (1.2)	NA	NA	25 months (±10)	95	Substantial decline in the rate of procedure-related or device-related safety events within 7 days from the procedure across PROTECT AF trial and CAP registry, with 7.7% and 3.7% of patients, respectively. Complications substantially decreased in frequency with operator experience
Watchman[119]	407 (269 implanted with the device)	Prospective RCT	2.6 (1.0)	3.8 (1.2)	NA	11.8 months (±5.8)	95.1	Serious procedure-related or device-related events within 7 days in 4.2% of patients; early safety events occurred in 2.2% of patients receiving the device (the number of safety events was significantly lower than that in the PROTECT-AF trial); LAA occlusion was noninferior to warfarin for ischaemic stroke prevention, and noninferiority was not achieved for overall efficacy; procedural safety substantially improved as compared with the initial experience in the PROTECT-AF trial
Watchman[122]	1,021	Prospective, multicentre registry	2.8 (1.3)	4.5 (1.6)	NA	NA	98.5	Serious procedure-related or device-related events within 7 days in 2.7% of patients; reduction in periprocedural complications compared with the previous experience in the PROTECT-AF trial
Amplatzer								
Amplatzer[102]	137	Retrospective, multicentre registry	NA	NA	NA	24 h	96	Serious complications in 7% of patients (thromboembolism, loss of implant in venous system, device embolism, air embolism, procedural stroke, cardiac tamponade)
Amplatzer[104]	152	Retrospective, single-centre registry	2.7 (1.3)	3.4 (1.7)	NA	32 months	98	Composite efficacy (stroke, cardiac and unexplained deaths) and safety (cardiac tamponade, device embolization, stroke, major bleeding) end points occurred in 7% and 12% of patients, respectively

Table 3 (cont.) | **Main interventional and surgical LAA occlusion/exclusion devices and corresponding trials**

Device/ technique	Number of patients	Study design	Mean $CHADS_2$ score (±SD)	Mean CHA_2DS_2-VASc score (±SD)	Patient-years	Mean follow-up	Rate of successful LAA occlusion	Results, complications, or comments
Amplatzer (cont.)								
Amplatzer[108]	1,047	Prospective, multicentre registry	2.8 (1.3)	4.5 (1.6)	1,349	13 months (IQ range 25 months)	97.1	Major periprocedural adverse events in 4.97% of patients; eight procedure-related deaths, nine strokes, and 13 cardiac tamponades; annual stroke rate of 2.3%; RRR 59%
Amplatzer[180]	1,073	Prospective, multicentre registry	NA	4.2 (1.6)	NA	1–3 months	98.8	Major periprocedural adverse events in 2.7% of patients, three procedure-related deaths, three strokes, and five cardiac tamponades
Lariat								
Lariat[128]	89	Prospective, single-centre registry	1.9 (1.0)	2.8 (1.6)	NA	12 months	92	Two cases of haemopericardium with subsequent pericardial drainage and one epigastric vessel laceration
Lariat[129]	154	Retrospective, multicentre registry	2.8 (1.4)	4.1 (1.6)	NA	112 days (median)	92 (procedural success 86)	Substantial pericardial effusion in 16 patients (10%), emergency surgery required in three patients (2%), two for right ventricular perforation during pericardial access with subsequent cardiac tamponade, and one for repair of LAA perforation
Lariat[133]	712	Prospective, multicentre registry	2.7 (1.3)	3.9 (1.8)	NA	NA	98	One procedure-related death, 24 cardiac perforations with 10 patients necessitating cardiac surgery (substantial decrease with Pajunk needle), leak of 2–5 mm in 6.5% of patients and thrombus in 2.5% of patients as measured by TEE at follow-up
AtriClip								
AtriClip[92,93]	40	Prospective, single-centre registry	2.0 (1.4)	3.7 (1.7)	NA	3.5 years (±0.5)	100	One case of TIA during follow-up, 10% early mortality (non-device-related), no secondary dislocation of clip, no LAA reperfusion/stump
AtriClip[94]	71	Prospective, multicentre registry	NA	NA	NA	3 months	95.7	Adverse events occurred in 48.6% of patients (all non-device-related); two strokes (3.1%) at 12-month follow-up
AtriClip[95]	291	Prospective, single-centre registry	1.8 (1.2)	3.1 (1.5)	826.8	36 months (±23)	100	Early and late mortality (non-device-related) of 5.5% and 17.9%, respectively; no device-related complications, no secondary dislocation of clip, no LAA reperfusion/stump; observed rate of ischaemic stroke of 0.5 per 100 patient-years, RRR 87.5%

LAA, left atrial appendage; NA, not available; RRR, relative risk ratio; TEE, transoesophageal echocardiography; TIA, transient ischaemic attack.

complications were reported in three patients (3.3%); however, at 1 year, 45% of patients from the study cohort were receiving anticoagulant therapy.

A retrospective, multicentre study of 154 consecutive patients at eight sites in the USA showed that device success (defined as suture deployment and a residual shunt <5 mm by postprocedural TEE) was achieved in 94% of patients, whereas procedural success (defined as device success, and no major complication at hospital discharge, including death, myocardial infarction, stroke, major bleeding, or emergency surgery) was 86% and mainly limited by bleeding[129]. Major bleeding events necessitating transfusion occurred in 14 patients (9%), whereas 16 patients (10%) experienced clinically significant pericardial effusion, with emergent cardiac surgery required in three patients.

A systematic review published in 2015, which included data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database and published literature, raised concerns about adverse events associated with the off-label use of the Lariat for LAA exclusion[130]. A total of 45 serious adverse events (including six deaths) associated with the Lariat procedure were reported to the FDA between 2009 and 2015, 75% of which required urgent

surgery. Despite the lack of information regarding the total number of procedures performed in the MAUDE database — a major criticism of the dataset — an FDA Safety Communication Alert was issued in July 2015 to health-care providers and patients[131,132].

Technological improvement and improved safety profile of the Lariat procedure was demonstrated in a large multicentre registry comprising 18 centres and 712 patients with AF[133]. Successful deployment of the Lariat suture was achieved in 682 of 712 patients, with acute complete occlusion of the LAA in 669 patients (98%). Trace leak (<2 mm) at the end of the procedure was observed in 13 patients. A total of ten patients with periprocedural cardiac perforation required open-heart surgery, whereas 14 patients were conservatively managed with pericardial tap and drain. One early procedure-related death occurred owing to multisystem failure after cardiac perforation and surgical repair. After initial cases of access-site bleeding associated with the use of a large-bore Pajunk needle for pericardial access, centres shifted to the use of a micropuncture needle, which was eventually used in 60% of patients. This change substantially decreased the overall incidence of acute complications. Severe pericarditis, late pericardial effusion, and late pleural effusion were reported in earlier studies as important periprocedural complications owing to post-inflammatory response associated with LAA ligation and pericardial access. The use of colchicine seemed mainly to prevent these periprocedural complications. Evidence of late leak of 2–5 mm was found in 6.5% of 480 patients. The decreasing complication rates of this study[134], as well as the preliminary results from a study involving the next-generation Lariat$^+$ suture delivery device[134], strongly suggests a learning curve associated with this new technology with regard to periprocedural complications, as observed with other LAA occlusion devices. Of note, the Lariat device is indicated for tissue approximation, and has not received approval for stroke prevention in patients with NVAF.

New devices. The results of the Coherex WaveCrest I LAAO study[135,136], which assessed the safety and efficacy of the Coherex WaveCrest device (Johnson&Johnson, USA) were presented at the Heart Rhythm Society's 35th Annual Scientific Sessions in 2014. Device deployment was achieved in 96% of 73 patients, whereas acute procedural success was achieved in 93% of patients. Major adverse events (such as pericardial effusion) occurred in 2.7% of patients and were treated with percutaneous pericardial drainage. Successful LAA occlusion was reported in 92% of patients at 45 days after the procedure. A pivotal WaveCrest II trial has been planned to obtain regulatory approval in the USA.

The first experiences with the Transcatheter Patch (Custom Medical Devices, Greece) showed successful occlusion of the LAA in 17 out of 20 patients[137]. However, subsequent data on this device have not been published.

After initial feasibility studies of the Occlutech LAA occluder (Occlutech International, Sweden) in canine and pig models, results of a first-in-human, prospective, nonrandomized safety and efficacy study showed high acute procedural success (93%) and confirmed the correct position of the device at 3-month follow-up in 27 out of 28 patients[138–140].

The first evaluation of the Ultraseal LAA occluder (Cardia, USA) *in vivo* showed feasibility and safety in a canine model[141]. A study involving 12 patients with NVAF published in 2016 showed safety and feasibility of the Ultraseal device[142]; however, larger studies with long-term follow-up data are necessary to test the efficacy of this device.

Although animal studies have demonstrated the feasibility of implanting the LAmbre (Lifetech Scientific, China) and AEGIS devices (Aegis Medical Innovations, Canada), human data have not been published[143,144]. In addition, investigators in the LASSO-AF trial[145], a feasibility study of the Sierra Ligation System (Aegis Medical Innovations, Canada) performed under an investigational device exemption from the FDA, are currently recruiting patients.

Current guidelines and recommendations

Limited recommendations on surgical or percutaneous LAA occlusion for stroke prevention exist in the latest guidelines. Although the 2014 AHA/ACC/HRS guidelines for the management of patients with AF[39] and the 2016 ESC guidelines for the management of AF[40] suggest that surgical LAA excision might be considered in patients undergoing open-heart surgery (class IIb; level of evidence B), the European guidelines suggest that interventional LAA occlusion might be considered only in patients with high risk of stroke and contraindications for long-term oral anticoagulation (class IIb; level of evidence B). Paradoxically, these criteria for interventional LAA occlusion were not met in the PROTECT-AF trial[115,117].

Despite the robust evidence from RCTs on the efficacy of the Watchman device in patients eligible for OAC, a substantial lack of clinical evidence exists regarding the use of the Watchman device as well as other interventional devices and surgical approaches in patients ineligible for OAC. An expert consensus statement of the EHRA and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) proposed an algorithm to select patients for catheter-based LAA occlusion[146]. However, the type of procedure (either surgical or interventional) remains to be identified to ensure a safe, complete, and durable LAA occlusion in patients with NVAF. Patient-specific anatomical and morphological considerations are mandatory to define a patient-tailored treatment strategy. In addition to the need for further data on different devices and techniques, the need to establish an outcome-oriented collaboration between cardiologists and surgeons is becoming increasingly important. A joint collaboration between cardiologists and surgeons — the 'Heart Team' approach, as successfully proven in the development of the MitraClip (Abbott Vascular, USA) — seems a judicious strategy[147–151].

Complications: effects and management

Surgical and percutaneous interventions have inherent risks of a variety of complications. In the case of LAA occlusion, these risks are aggravated by the fragile nature

of the LAA. Whereas surgical approaches involve direct visualization of the target tissue, interventional strategies rely on indirect visualization (imaging) by TEE and fluoroscopy. Intraoperative surgical complications might include injury to adjacent structures such as the circumflex artery, myocardial tears, and bleeding from stapler, suture lines, or simple manipulation of a fragile LAA. However, data on the complication rates with surgical occlusion of the LAA are scarce. Although investigators of the AtriClip device study reported no device-related complications, the TigerPaw system was recalled from the market by the FDA owing to worrisome reports of complications. Nevertheless, intraprocedural injuries to the LAA or adjacent structures during surgical LAA occlusion can be managed intraoperatively in most cases without increasing the morbidity or mortality. Thoracoscopic approaches might necessitate conversion to conventional open surgical access such as sternotomy or thoracotomy if an uncontrolled complication occurs, although this scenario is very rare. As mentioned above, the inadvertent creation of residual thrombogenic pouches at the LAA base, and residual perfusion or late reperfusion of the LAA might cause an increased risk of recurrent stroke and systemic thromboembolism, although increased thromboembolism in patients with LAA reperfusion receiving the Watchman device has not been observed[87,88,152]. Although the definition of what constitutes a clinically significant residual pouch has not been supported by scientific data, a residual pouch >1 cm is considered clinically significant in the surgical community[87].

Major procedure-related or device-related complications can occur during interventional LAA occlusion, including stroke, pericardial effusion or perforation, device embolization, and access-related vascular complications. The progressive reduction in complication rates observed with the Watchman device, as well as with other devices, strongly suggests that the implantation of percutaneous LAA occlusion devices is associated with an important learning curve. Considering interventional LAA occlusion as a stand-alone procedure, its rate of periprocedural events affecting morbidity and mortality seems still to be high when compared with newer-generation devices for surgical LAA occlusion, such as the AtriClip. Nonetheless, patients receiving LAA occlusion with the Watchman device experienced reduced cardiovascular and all-cause mortality compared with patients who received warfarin[121].

Interestingly, analyses of pooled 3-year and 5-year patient-level data from PROTECT-AF, as well a study on the ACP, indicate that the number of nondisabling strokes is higher in patients with NVAF receiving LAA occlusion than in those receiving warfarin or NOACs[153,154]. Mostly, periprocedural strokes are thought to be caused by air emboli resulting from the transseptal access to the systemic circulation. Pericardial effusion might require haemodynamic resuscitation and pericardiocentesis, and might sometimes even require surgical intervention. Device embolization is associated with high morbidity and sometimes requires surgical retrieval of the device.

The implantation of foreign materials in the heart poses an inherent risk of thrombus formation until the device is fully endothelialized. Furthermore, most interventional devices have a circular shape, whereas the ostium of the LAA is rather oval. A residual leak (or niche) formed around the device (with or without residual connection to the LAA cavity) can be a predilection site for thrombus formation and can be identified by TEE or CT imaging. Device design (central portion of the device with the connection tip), positioning and sizing, patient-specific factors as well as the procoagulatory state of the AF itself might enhance thrombus formation. As a consequence, patients from the PROTECT-AF trials[115] received warfarin treatment for 45 days after device implantation, followed by a dual antiplatelet regimen of clopidogrel and aspirin until the 6-month follow-up visit if no device-related thrombi or residual peri-device flow were present, and then aspirin alone indefinitely. However, the nonrandomized, prospective, multicentre ASAP study[155], in which the safety and efficacy of LAA occlusion were evaluated in patients with NVAF who were ineligible for warfarin therapy, showed that in patients treated with clopidogrel and aspirin for 6 months after implantation, and aspirin alone thereafter, the safety and efficacy outcomes were similar to those observed in the PROTECT-AF trial. The epicardial implantation of the AtriClip device, as well as the epicardially performed Lariat procedure, offers a clear advantage given that no postprocedural anticoagulation therapy is necessary.

The issues of peri-device flow and device-related thrombi associated with interventional endocardial devices are of paramount interest because their incidence is fairly high, but their clinical implications are still uncertain. A PROTECT-AF substudy showed that residual peri-device flow after LAA occlusion is common (up to 32% at 12 months), but as mentioned above, is not associated with an increased risk of thromboembolism[152]. Accordingly, peri-device flow was reported in 11.6% and device-related thrombi in 4.6% of patients receiving the ACP, but no correlation with stroke or transient ischaemic attacks was found[108]. Further studies are needed to confirm these findings.

Additional temporary or indefinite OAC therapy with VKAs or NOACs might be indicated in some cases of device-related thrombi[156]. Anecdotal reports or case series demonstrated additional surgical or interventional attempts to treat substantial residual leaks after LAA occlusion[157–160]. Again, additional temporary or indefinite OAC treatment with VKAs or NOACs might be indicated in selected patients as a combination therapy.

Conclusions

Although RCTs are considered to be a prerequisite to establish the risk–benefit ratio for medical therapy, these trials have several inherent limitations[161]. For example, in the PROTECT-AF and PREVAIL trials, strict inclusion criteria were applied and patients with contraindications for OAC therapy were excluded. This protocol prevented the applicability of the trial results in a vast number of patients, especially those with a high risk of stroke

and bleeding who urgently need an alternative stroke-prevention therapy. Owing to the complex nature of interventional LAA occlusion and its associated learning curve, extrapolation of procedural outcomes observed in such RCTs to other centres with different experiences might be difficult[162].

To overcome these limitations and reflect a real-world setting, large-scale, well-designed observational registries with long-term follow-up are crucial as a complement to RCTs[163]. As mentioned above, the FDA approved the Watchman device provided that two observational, post-market studies were conducted. The ACC National Cardiovascular Data Registry (NCDR) will provide support for these post-market studies with the NCDR LAAO registry[164]. Moreover, the NCDR LAAO registry includes not only the Watchman device, but also all other percutaneous LAA therapies.

The socioeconomic burden of AF and AF-related morbidity is of great interest, and percutaneous LAA occlusion should be cost-effective in the long term. Two analyses showed a superior cost-effectiveness of LAA occlusion with the Watchman device compared with warfarin or NOACs[165,166]. Cost-effectiveness analyses of surgical LAA occlusion are not yet available; however, given that surgical LAA occlusion is most often performed concomitantly to open-heart surgery, its costs arise only from the device or suture used for occlusion (<1,000–1,500 euros or US dollars). Therefore, cost-effectiveness of surgical LAA occlusion could be much higher than that of other stroke-prevention strategies, including percutaneous LAA occlusion.

The nonstroke aspects of LAA exclusion remain to be clarified. Previous reports suggest substantial alterations to the levels of atrial natriuretic peptide and B-type natriuretic peptide[167,168]. Although associated with obesity, glucose intolerance, type 2 diabetes mellitus, and essential hypertension, the clinical effect of a dysregulated natriuretic peptide system in the setting of LAA exclusion remains unclear[169]. Further studies are required to assess the effect of LAA exclusion on AF burden, atrial compliance, reservoir function, as well as changes in the neuroendocrine modulation of the renin–angiotensin system.

Agreement on uniform reporting and the definitions of parameters, end points, and data collection requirements for both RCTs and observational studies are needed for research on LAA occlusion in patients with NVAF. The Munich consensus document for percutaneous LAA occlusion was agreed by experts across Europe and the USA[170]. The surgical community also lacks common reporting standards and needs a similar consensus statement that is similar to the robust data reporting of the cardiology community. Undoubtedly, future research is warranted to clarify controversies and remaining issues surrounding the effectiveness of LAA occlusion in the prevention of stroke. Additional RCTs should be designed to assess superiority and include more patients at high risk of stroke or major bleeding.

An urgent need exists for reliable clinical data to determine the efficacy and safety of surgical LAA occlusion, from either RCTs or registries of LAA exclusion or occlusion. We are concerned that, owing to conceptual issues, the aforementioned LAAOS III trial will not provide these data on surgical LAA occlusion. The increasing use of NOACs and the development of new devices will necessitate head-to-head comparisons against approved devices and/or NOACs[54,171]. Further data from ongoing registries will help to identify the ideal patient population to benefit from LAA occlusion. Finally, with the development of newer LAA occlusion devices (surgical or nonsurgical), collaboration between surgeons and cardiologists in the form of a Heart Team is imperative.

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J.L.C. is a consultant for and holds shares in Atricure, Inc. and SentreHEART, Inc. B.M. has received speaker fees from Abbott. D.R.L. is the steering committee chair for the AMULET IDE and AMAZE IDE trials. S.P.S. and M.Y.E. have received speaker fees from Atricure and Maquet. E.C., D.R.H., and V.F. declare no competing interests.

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Review criteria
Articles included in this Review were identified from a literature search in the PubMed database (completed in December 2016) using the term "left atrial appendage". Only reports in English presenting original data and abstracts from scientific meetings were included. The reference lists of identified clinical and research publications as well as relevant review articles were also screened to identify further relevant information.