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REVIEW

Clinical update

The left atrial appendage: from embryology to prevention of thromboembolism

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The left atrial appendage (LAA) is the main source of thromboembolism in patients with non-valvular atrial fibrillation (AF). As such, the LAA can be the target of specific occluding device therapies. Optimal management of patients with AF includes a comprehensive knowledge of the many aspects related to LAA structure and thrombosis. Here we provide baseline notions on the anatomy and function of the LAA, and then focus on current imaging tools for the identification of anatomical varieties. We also describe pathogenetic mechanisms of LAA thrombosis in AF patients, and examine the available evidence on treatment strategies for LAA thrombosis, including the use of non-vitamin K antagonist oral anticoagulants and interventional approaches.

Keywords Left atrial appendage • Thromboembolism • Atrial fibrillation • Stroke • Systemic embolism • Anticoagulants • Non-vitamin K antagonist oral anticoagulants • NOACs • Occlusion devices

The left atrial appendage (LAA) is the focus of growing interest, as it is the main source of thromboembolism in patients with non-valvular atrial fibrillation (AF). Since an optimal management of patients with AF includes a comprehensive knowledge of the various aspects related to LAA structure and thrombosis, a practically oriented review paper on the topic is important for cardiologists. To this aim, we accessed MEDLINE/PubMed and Cochrane databases up to May 31, 2015, and reviewed cited references to identify relevant studies. Search keywords were 'left atrial appendage', 'imaging', 'thrombosis', 'atrial fibrillation', 'stroke', 'embolism', 'anticoagulants', 'occlusion device'.

Embryology, anatomy and physiology of the left atrial appendage

The LAA begins to develop during the 3rd week of gestational life. It derives from the embryonic left atrium, whereas the remaining portion of the left atrium is formed from the branches of the primordial pulmonary veins.[1,2] The LAA is a finger-like structure with a cramped, lobulated end, in contrast to the wide triangular shape of the right atrial appendage; unlike the right atrium, pectinate muscles are located within the LAA and do not stretch into the remaining

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parts of the left atrium. Several LAA shapes and variants have been described, with 1–4 lobes and 4 prevalent morphologies, named 'windsock', 'chickenwing', 'cauliflower', and 'cactus-like' (*Figure 1*).[3,4] The ostium is usually oval; less frequently round, triangular or drop shaped.

Flow in the LAA during sinus rhythm, measured by Doppler ultrasound, is typically quadriphasic (*Figure 2*).[5] In sinus rhythm, a washout from the LAA prevents blood from pooling and stagnating. The normal flow cycle begins just after the mitral valve opening, with an early diastolic forward flow (LAA emptying) determined by the intracavitary suction by ventricular filling.[6] The left ventricular dilation occurring during diastolic filling may further contribute to LAA emptying by compressing the infero-medial wall of the LAA between the ventricular free wall and the fixed pericardium[7]. This

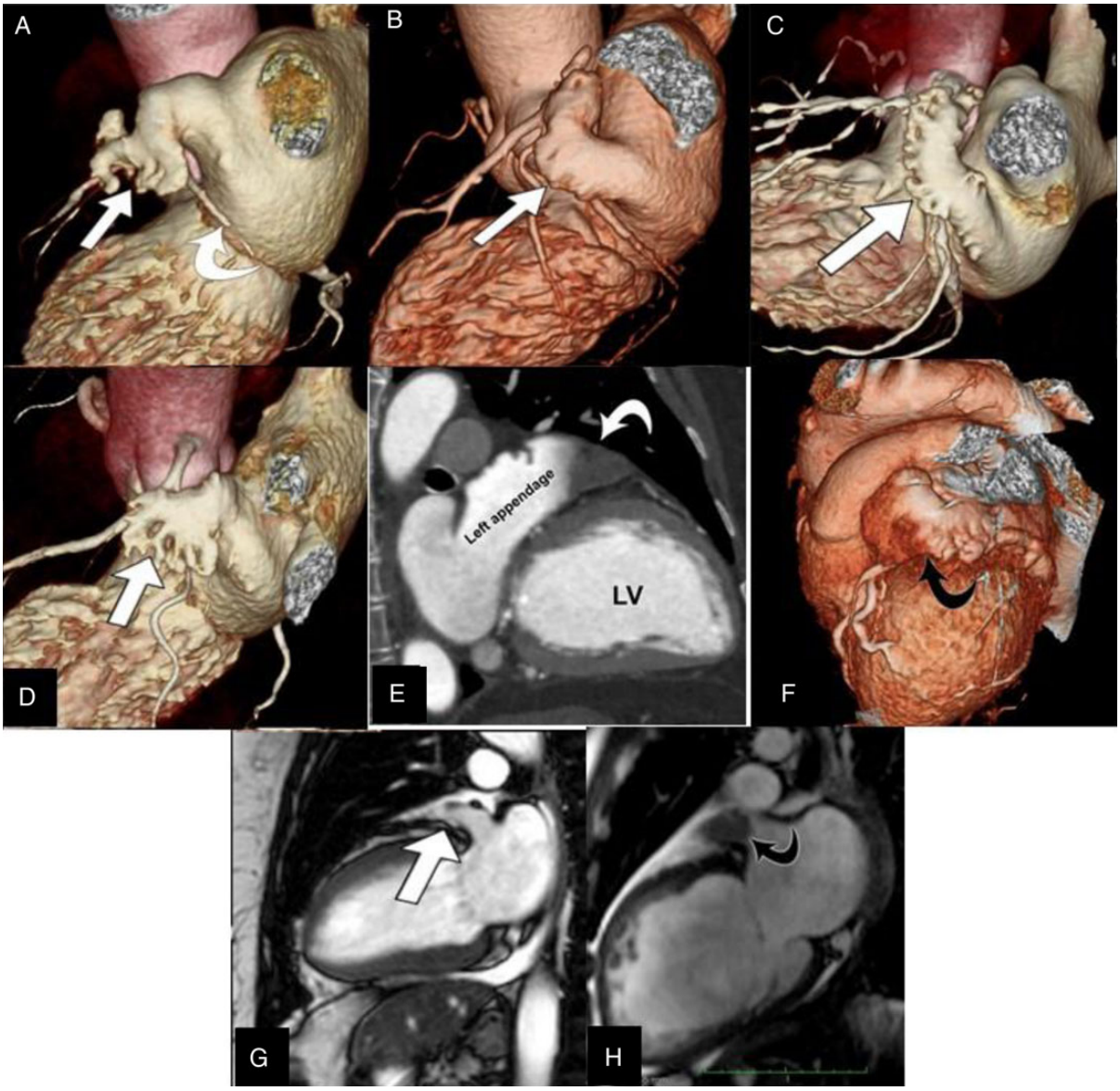

Figure 1 Computed tomography/magnetic resonance imaging of the left atrial appendage. (*A*–*D*) Computed tomography three-dimensional volume rendering reconstructions illustrating different left atrial appendage shapes. In (*A*), a windsock morphology (arrow) with a dominant lobe and an accessory secondary lobe; note the left circumflex coronary artery below the left atrial appendage (curved arrow). In (*B*), a chickenwing shape, with an evident bend in the proximal part of the dominant lobe (arrow). In (*C*), a cauliflower morphology (arrow). In (*D*), a cactus-like shape, with a dominant central lobe and secondary lobes extending from the central lobe in both superior and inferior directions (arrow). (*E*) Computed tomography image delineating the entire extension of the LAA with a filling defect in the apex consistent with intracavitary thrombus (curved arrow). Left ventricle is indicated. (*F*) Computed tomography three-dimensional volume rendering reconstruction showing a reduced colour brightness in the apex of the left atrial appendage (curved arrow) due to lack of intracavitary contrast enhancement caused by *in situ* thrombosis. (*G*) Left atrial appendage (arrow) on a two-chamber magnetic resonance imaging (magnetic resonance imaging-SSFP sequence). (*H*) Left atrial appendage with *in situ* thrombosis (curved arrow) on magnetic resonance imaging.

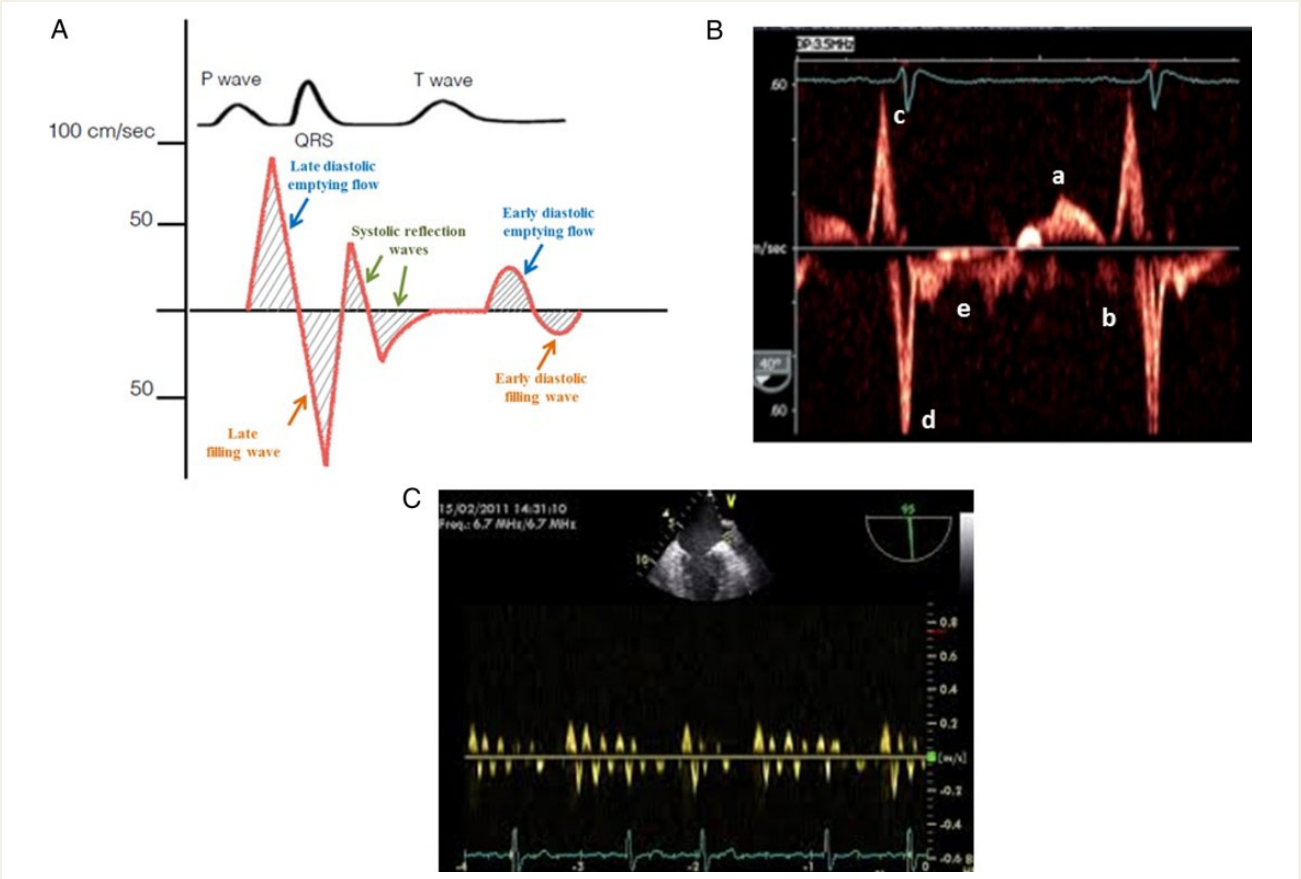

Figure 2 Left atrial appendage flow. (*A*) Schemedepicting the quadriphasic left atrial appendage flow pattern during sinus rhythm with two diastolic emptying phases and two filling waves. (*B*) Transoesophageal echocardiography image of left atrial appendage flow velocities by pulsed-wave Doppler from a patient in sinus rhythm: (a) early diastolic emptying; (b) early diastolic filling wave; (c) late diastolic emptying, following the P wave on electrocardiogram; (d) late filling wave; (e) systolic reflection waves. (*C*) Left atrial appendage flow pattern by transoesophageal echocardiography pulsed-wave Doppler in a patient with atrial fibrillation, characterized by decreased, irregular, and variable flow velocities. LAA, left atrial appendage; TOE, trans-oesophageal echocardiography.

phase is followed by a short, low-velocity backward flow (LAA filling), reflecting continuous left atrial (LA) filling from the pulmonary veins during mid-diastole. In end-diastole, there is a second forward flow due to LAA contraction, just after the P-wave on the electrocardiogram, with velocities up to 100 cm/s, correlating with LAA function, size, and pressure.[6] This late diastolic emptying is followed by a late diastolic backward negative wave, possibly caused by the elastic recoil of the appendage.[6,7] Systolic reflection waves are low, multiple, with an alternate inflow and outflow pattern, and are usually observable at slow heart rates.[7]

The LAA is more compliant than the LA main chamber; thus, in conditions of physiologic (e.g. during exercise) or pathologic increase of LA pressure and/or volume, the LAA enlarges and acts as a blood reservoir, contributing to modulate LA pressure and eliciting adaptive responses (increase of heart rate, diuresis, natriuresis) homeostatically 'aimed' at improving cardiac output and controlling circulating blood volume;[3,8] of note, clamping of the LAA during cardiac surgery has been associated with augmentation of LA pressure and trans-mitral flow velocities.[9] Finally, the right and LAAs are the main sources of atrial natriuretic peptide in humans, with concentrations in the LAA walls being 40-fold higher than in the LA-free wall and ventricles.[10]

Imaging of the left atrial appendage

Defining LAA anatomy and function and detecting or excluding of *in situ* thrombosis are crucial before cardioversion of supraventricular arrhythmias, LA ablations and in guiding catheter-based therapies, particularly LAA closure.

Echocardiography

Trans-thoracic echocardiography has a limited ability to investigate the LAA, whereas transoesophageal echocardiography (TOE) is the accepted gold standard (*Figure 3*). Ultrasound contrast agents improve TOE visualization by eliminating artefacts, opacifying the appendage, and identifying filling defects.[11] Compared with 2D-TOE, 3D-TOE may help differentiating between adjacent structures and provide a more complete evaluation of complex morphologies (*Figure 4*).[12] Transoesophageal echocardiography also allows functional assessment of LAA flow by Doppler techniques and

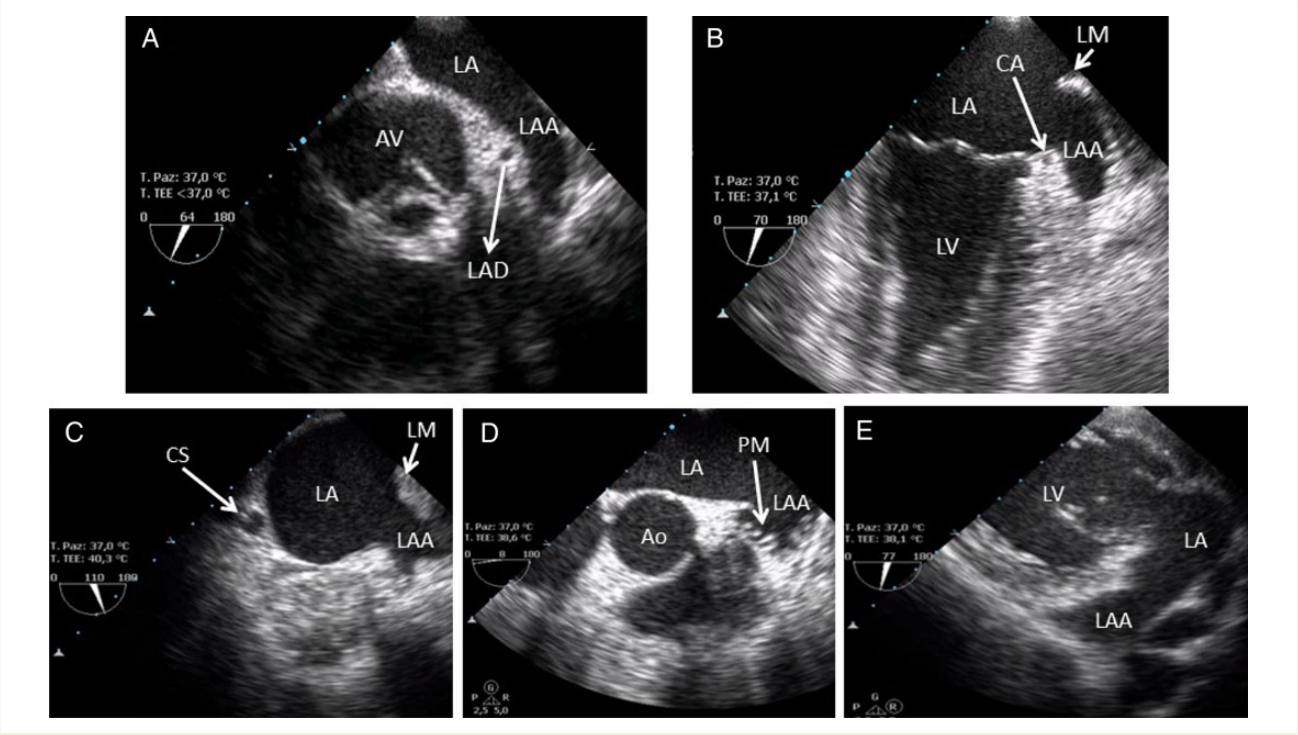

Figure 3 Left atrial appendage evaluation by transoesophageal echocardiography. Main views (*A* and *B*). (*A*) Mid-upper oesophageal view at 40–65° (aortic valve short-axis view). (*B*) Mid-oesophageal view at 70–90° (two-chamber view) achieved with slight withdrawal and anteflexion of the probe from the mid-oesophageal four-chamber image. The ligament of Marshall separates the left atrial appendage from the left upper pulmonary vein. The circumflex artery can be seen. Additional views (*C*–*E*). (*C*) Mid-oesophageal view at 110–130°. The ridge on top of the appendage is the ligament of Marshall. (*D*) Mid-upper oesophageal view at 0–10°. The left atrial appendage is generally visualized using a moderate anteflexion of the probe. Prominent pectinate muscles can be seen and are sometimes confused with a thrombus. Unlike thrombus, pectinate muscles are generally repetitive, hyperrefractile, and organized in a regular pattern. (*E*) 'Modified' trans-gastric long axis view (at ~75–90°). Ao, ascending aorta; AV, aortic valve; CS, coronary sinus; LA, left atrium; LAD, left anterior descending artery; LV, left ventricle; TOE, transoesophageal echocardiography.

tissue-Doppler imaging may complement standard TOE.[13] In particular, recent investigations have suggested that data from the speckle tracking technique, providing quantitative and qualitative information on tissue deformation and motion, may correlate with the risk of LAA thrombosis.[2] Compared with intraoperative findings, the sensitivity, and specificity of TOE for the diagnosis of LAA thrombosis in AF patients are reported to be 92 and 98%, respectively, with negative and positive predictive values of 100 and 86% (*Figure 4*).[14,15]

The relevance of TOE in AF patients is also related to the identification of other predictors of thromboembolism, e.g. complex aortic plaques, spontaneous echo-contrast (indicating blood stasis) (*Figure 4*), and low LAA flow velocities. Transoesophageal echocardiography to exclude intra-atrial thrombosis before cardioversion is recommended in AF patients (a) as an alternative to 3-week pre-cardioversion anticoagulation; (b) when early cardioversion is needed; (c) when pre-cardioversion anticoagulation is not indicated; (d) when there is a high risk of LAA thrombosis.[16] In particular, TOE for intra-atrial thrombus detection is warranted before electrical cardioversion in patients with AF or atrial flutter not on anticoagulant therapy. Moreover, excluding LAA thrombosis by TOE is needed prior to any (catheter-based or surgical) type of procedures involving the deliberate or accidental LAA manipulation that might result in embolization of the LAA content.[16] Transoesophageal echocardiography also has a crucial role for the pre-, intra-, and post-procedural evaluation of patients undergoing percutaneous LAA closure, in whom intra-cardiac echocardiography may be an alternative to TOE, as it avoids the need of sedation.

Computed tomography and magnetic resonance imaging

Cardiac multidetector computed tomography (CT) with electrocardiographic gating has high spatial and temporal resolution and can accurately reproduce LA and LAA anatomy, volumes, and wall thicknesses. The intravenous (i.v.) injection of iodinated contrast is here mandatory to define anatomy and exclude intracavitary thrombosis. Multi-detector CT has a negative predictive value and a sensitivity of 100% for excluding LAA thrombosis compared with TOE (*Figure 1*).[17] In some centres, CT is routinely performed prior to pulmonary vein isolation (PVI) to define pulmonary vein anatomy and exclude LAA thrombosis. However, CT scan is not highly specific for thrombus detection, accounting for false-positive test results and the subsequent need of confirmatory TOE imaging;[18] thus,

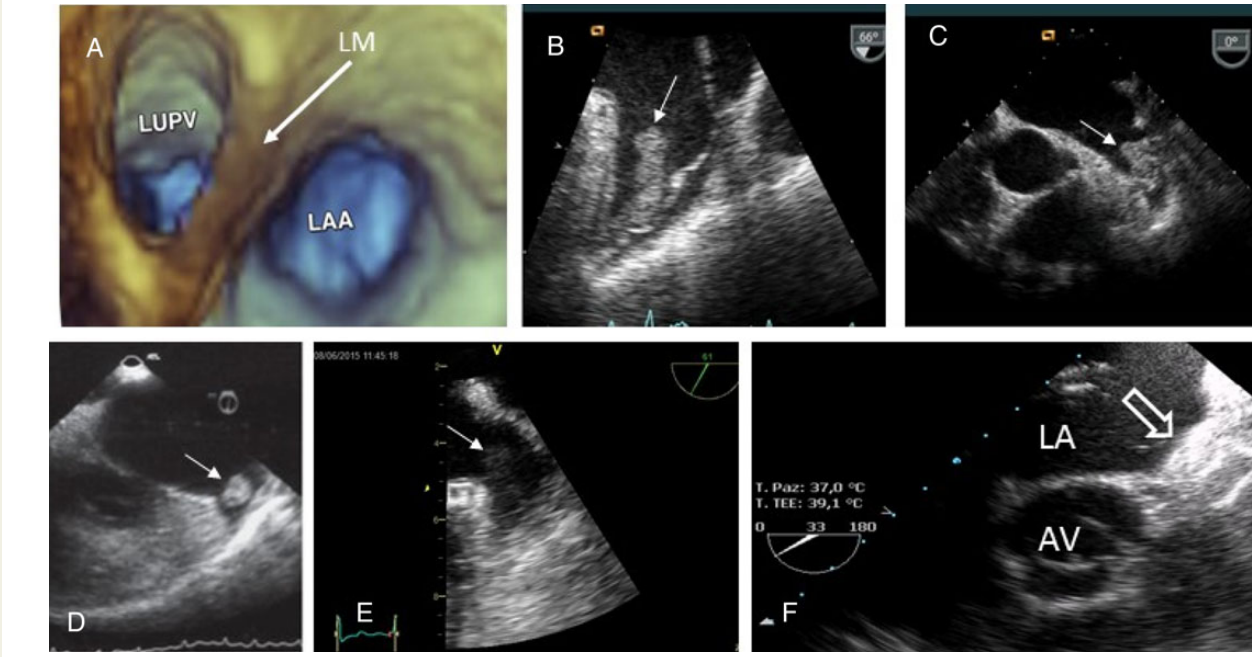

Figure 4 (*A*) Three-dimensional echocardiographic imaging of the left atrial appendage, left upper pulmonary vein, and ligament of Marshall. (*B*–*E*) Transoesophageal echocardiography imaging of left atrial appendage thrombosis/echo-contrast in patients with atrial fibrillation. (*B*) Soft elongated thrombus. (*C*) Soft ovaloid thrombus. (*D*) Calcified thrombus. (*E*) Spontaneous echo-contrast (smoke effect). (*F*) Percutaneous left atrial appendage closure procedure (arrow indicates the implanted device). AV, aortic valve; LA, left atrium; LAA, left atrial appendage.

the use of CT alone in this setting has been proposed especially in patients with low thromboembolic risk.[19] Cardiac magnetic resonance imaging (MRI) is an accurate non-invasive technique to assess atrial structures and volumes, given its high temporal/contrast resolution and excellent myocardial border detection (*Figure 1*). Magnetic resonance imaging can also identify LAA thrombosis, with sensitivity and specificity comparable with multidetector CT, and measure LAA blood flow by velocity-encoded techniques.[20] Moreover, high atrial fibrosis (>20%) detected by MRI T1 mapping with late gadolinium enhancement has been associated with LAA thrombosis (odds ratio 4.6) and might represent an additional risk stratification parameter beyond conventional clinical risk factors.[21] Finally, in the setting of PVI, the degree of LA fibrosis assessed by MRI before the procedure is able to predict the success of the AF ablation, thus selecting the appropriate patient.[22]

Pathogenesis of left atrial appendage thrombosis in patients with atrial fibrillation

The risk of thromboembolism in AF accompanying 'valvular' AF (in the presence of moderate-to-severe rheumatic mitral stenosis or mechanical prosthetic valve) is higher than that observed for 'non-valvular' AF.[23] Multiple mechanisms of thrombosis, in addition to the possible occurrence of AF, come into play for a mechanical prosthetic valve, including the contact between the blood and the artificial surface of the prosthesis, as well as abnormal flow conditions, such as relative stagnation and high-velocity disturbed flow.[24] Moreover, it is not clear whether the pathogenesis of thrombosis in AF accompanying mitral stenosis is qualitatively different from those of most common forms of 'non-valvular' AF; however, thrombi in mitral stenosis, even in the absence of AF, appear to have a more frequent location out of the LAA, and are much more often 'giant'.[25] Atrial fibrillation predisposes to LA thrombosis, and in patients with non-valvular AF this is localized within the appendage in 90% of cases.[26] Left atrial appendage thrombus formation in AF patients is explained by a combination of factors, with a prevailing role of blood stasis. Other elements of Virchow's triad, such as endothelial dysfunction and hypercoagulable state, may also play a role.[27]

Blood flow

In AF patients, flow in the LAA is characterized by rapid alternation of emptying and filling at low velocities, reflecting lack of valid atrial contraction, blood stasis, and a pro-thrombotic milieu (*Figure 2*). Handkle *et al.* reported an increased risk of LAA thrombosis at velocities ≤55 cm/s, independent of the underlying cardiac rhythm; velocities <37 cm/s showed the highest accuracy (assessed as the sum of sensitivity and specificity) in predicting stroke occurrence.[28] The relation between specific LAA shapes and *in situ* thrombosis is controversial. Patients with non-chickenwing morphology may be more likely to develop thromboembolic events than those with a chickenwing shape, independent of the CHA_2DS_2-VASc score;[4] the higher presence of trabeculations and lower flow velocities in patients with non-chickenwing morphology might, at least in part,

explain this correlation in some investigations,[29] but not in others.[30,31]

Endothelial dysfunction

Endothelial damage predisposing to *in situ* thrombosis has been documented by electron microscopy in the LAA of AF patients. In particular, a 'rough endocardium', with oedema, large amounts of fibrin, and zones of denudation, has been identified.[32] Higher levels of von Willebrand factor, an established marker of endothelial dysfunction, are present in the atrial endocardium of patients with AF and LA enlargement, and this correlates with LAA thrombosis.[33]

Hypercoagulable state

Ex vivo models with human blood show a close relation between spontaneous echo-contrast and fibrinogen/red blood cell interactions, partly dependent on the haematocrit;[34] thus, transient haemoconcentration (e.g. induced by diuretic therapy) may contribute to thrombus formation.[35] Increased plasma levels of fibrinogen and D-dimer (a marker of both coagulation and fibrinolysis activation) have been demonstrated in patients with AF vs. those without;[35] levels of D-dimer can predict the risk of thrombotic events in AF patients, and the persistence of high levels despite warfarin therapy further predicted subsequent cardiovascular events.[36] Finally, platelet activation has been observed within 12 h of AF onset,[37] declining 24 h after cardioversion.[38]

Timing of thrombus formation

In case of AF duration $<$48 h, the common practice to perform cardioversion without TOE or prolonged pre-cardioversion anticoagulation derives from previous data indicating that this approach is associated with rates of thromboembolism $<$1%, similar to what was observed in patients undergoing cardioversion while on anticoagulation.[39] Accordingly, it may be concluded that thrombus generation in the LAA requires an AF duration $>$48 h; however, this assumption may not hold true in high-risk patients with more pronounced components of the Virchow's triad, i.e. with severe stasis as shown by spontaneous echo-contrast, abnormal wall changes related to marked LAA enlargement, and a hypercoagulable state.[27] Thus, the propensity and the timing of *in situ* thrombus formation in AF patients should be estimated on an individual basis.

Treatment of left atrial appendage thrombosis

The observed prevalence of LAA thrombosis by TOE in AF patients is relatively low (9.6% in a large contemporary cohort),[40] and depends on the risk profile of the population examined and on concomitant antithrombotic therapies. Left atrial appendage thrombosis is more common in patients at high risk of ischaemic stroke without, or on sub-therapeutic, oral anticoagulant therapy, but has been described also with adequate anticoagulation.[41] Of note, the presence of *in situ* thrombosis has been associated with an ~5-fold higher risk of transient ischaemic attack.[42]

Investigations specifically exploring antithrombotic strategies for LAA thrombus resolution are scarce, often retrospective, and based on small patient numbers. Nonetheless, according to current guidelines, when an intra-atrial thrombus is detected by TOE, a vitamin K antagonist (VKA) oral anticoagulant, with INR values ranging from 2 to 3, is recommended for 3 weeks; follow-up TOE after this period to ensure thrombus resolution appears warranted.[16,43] A variety of antithrombotic approaches for LAA thrombus resolution have been described and are listed below.

Thrombolytic therapy

Thrombolysis may be effective in patients with thrombosis of a mitral prosthesis,[44] but only few cases have been reported,[45] with limited data on the associated bleeding risk. Fresh and poorly organized thrombi are more prone to effectively dissolve with this therapy, whereas the efficacy of thrombolysis in the presence of an organized or partially organized thrombus (usually of older age) is unknown.

Low-molecular-weight heparins

Studies have suggested that low-molecular-weight heparins may be as effective as VKAs in patients with non-valvular AF waiting for cardioversion,[46] but no study has so far explored their efficacy on intra-atrial thrombus resolution, and there are no outcome data supporting this use.

Vitamin K antagonists

Vitamin K antagonists are the main therapy for intra-atrial thrombus resolution, although data documenting their efficacy are limited (*Table A1*). Reported resolution rates range from 16 to 90%, with different treatment durations.[47–55] In one investigation, LAA thrombosis was still present by TOE in 8% of patients despite optimal INR control during the previous 3 weeks.[49] Prolongation of VKA treatment beyond 7 weeks resulted in limited additional benefit in terms of thrombus resolution compared with 7-week anticoagulation.[52] In case of detection of LAA thrombosis while on adequate anticoagulation, it has been reported that the increase in the therapeutic range to 2.5–3.5 may be appropriate (resolution rates of 55% after 4 weeks);[49] however, this strategy exposes patients to a higher risk of bleeding complications.[56] Alternative approaches, such as heparins or non-vitamin K antagonist oral anticoagulants (NOACs), have not been evaluated extensively.

Non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants are an appealing alternative to VKAs for achieving LAA thrombus resolution, because of their overall superior safety profile, fast onset of action, and no need of routine coagulation monitoring. Data with the direct thrombin inhibitor dabigatran consist of case reports or small case series. Complete thrombus resolution after 7 weeks of dabigatran therapy has been described in one patient with inadequate INR control.[57] However, isolated cases of dabigatran failure to achieve thrombus resolution have also been published.[58]

Factor Xa (FXa) is considered an appropriate target for thrombus inhibition, given its role at the convergence of the intrinsic and extrinsic coagulation pathways, and because blockage of one FXa molecule has been reported to prevent the formation of ~1.000

thrombin molecules.[59] Clinical results with FXa inhibitors on this issue are limited to small series, which indicate thrombus resolution with apixaban and rivaroxaban at various dosages (rivaroxaban 15 and 10 mg OD; apixaban 2.5 and 5 mg BID) and after a wide range of treatment durations (from 8 days to 11 weeks).[60–63] More recent data, however, have questioned the ability of apixaban to dissolve LAA thrombi, especially if mobile and with a fragile appearance.[64]

Surgical left atrial appendage closure for preventing cardio-embolic stroke

Open-chest techniques

Performed primarily in the context of mitral valve surgery, surgical LAA closure consists of either LAA excision with scissors or amputating staples, or LAA exclusion with sutures (running suture, purse string, or external ligation) or staples. A TOE study of 137 patients, at 8 ± 12 months after surgery found incomplete LAA closure in 60% of patients,[65] with excision techniques being more effective (73% success rate). The LAA is more compliant than the LA main chamber; thus, in conditions of physiologic (e.g. during exercise) or pathologic increase of LA pressure and/or volume, the LAA enlarges and acts as a blood reservoir, contributing to modulate LA pressure and eliciting adaptive responses (increase of heart rate, diuresis, and natriuresis) homeostatically 'aimed' at improving cardiac output and controlling circulating blood volume;[3,8] of note, clamping of the LAA during cardiac surgery has been associated with augmentation of LA pressure and trans-mitral flow velocities.[66] Of note, an ~2-fold higher thromboembolic risk related to incomplete closure than to no closure has been observed.[67]

Thoracoscopic techniques

Blackshear *et al.*[68] have described a less invasive thoracoscopic technique for LAA obliteration, using stapling or snaring. The procedure was completed in 14 of 15 patients, but, given the risk of procedure-related bleeding, there is concern that surgeons may accept a larger residual LAA remnant, which might compromise the efficacy of the intervention.

Surgical closure with device

The AtriClip system™ (*Figure 5*) is a self-closing, implantable clip applied from the epicardium by open-chest or a minimally invasive technique. In a non-randomized investigation, successful closure was obtained in 60 of 61 patients at 90 days, with no device-related adverse event.[69] The TigerPaw system™ (*Figure 5*) is a fastener delivered surgically around the LAA ostium; non-randomized data in 60 patients reported its efficacy, without residual leaks at a 3-month follow-up.[70]

At the moment, peri-operative morbidity, high rates of incomplete closure, and dearth of randomized trial data do not support an extensive use of surgical LAA closure. Current guidelines suggest that surgical LAA excision *may* be considered in AF patients undergoing open heart surgery (class IIb, level of evidence C).[71]

Percutaneous interventions on the left atrial appendage to prevent cardio-embolic stroke

Left atrial appendage closure

The rationale for percutaneous LAA closure is to provide permanent protection from thromboembolism, avoiding lifelong antithrombotic therapy, and minimizing the risk of anticoagulation-related bleeding. The 2012 ESC guidelines on AF give non-surgical LAA closure a class of recommendation IIb, with level of evidence B, in patients in whom anticoagulant therapy is contraindicated or impractical.[43] Currently approved closure devices are illustrated in *Figure 5*. *PLAATO* was the first system tested and, despite promising results in pivotal randomized studies,[72] was withdrawn from the market for unspecified commercial reasons. The *WATCHMAN* device has been approved by the U.S. Food and Drug Administration as an alternative to warfarin therapy. It was randomly tested vs. warfarin on 707 patients with non-valvular AF in the *Embolic Protection in Patients with Atrial Fibrillation* (PROTECT AF) trial;[73] this interventional approach was non-inferior to warfarin for the primary efficacy outcome, including a composite of stroke, cardiovascular death, and systemic embolism; at the long-term follow-up (3.8 years), the use of *WATCHMAN* was associated with lower cardiovascular and all-cause mortality.[74] Because of peri-procedural safety concerns raised by the PROTECT-AF trial, a further randomized study was performed with the *WATCHMAN* device, the *Patients with Atrial Fibrillation* vs. *Long-Term Warfarin Therapy* – PREVAIL study;[75] in this investigation, the rate of procedure-related adverse events in the intervention group was 2.2% (i.e. significantly lower than in PROTECT AF), satisfying the pre-specified safety goal. The *Amplatzer Cardiac Plug (ACP)*, and its very recent evolution *(Amulet)* have not been evaluated in randomized studies. However, over 8000 of these devices have been implanted worldwide, and efficacy and safety data derive from observational registries. The largest to date is a pooled analysis of 1047 patients from 22 centers,[76] in whom the occurrence of a peri-device leak by TOE was found to be 11.6% at 7 months: However, in the large majority of cases, this was <3 mm; peri-device leaks after percutaneous LAA closure apparently did not correlate with any adverse event during the follow-up.[76] Characteristics and main results of safety and efficacy with *WATCHMAN* and *ACP/Amulet devices* are summarized in *Table A2*. Initial experiences are now available with the latest marketed device, the WaveCrest LAA System (*Figure 5*).

The combination of LAA closure with AF catheter ablation using PVI might be a comprehensive approach to ameliorate the arrhythmia-related symptoms and at the same time reduce the risk of stroke and the need for anticoagulant therapy. A randomized study showed that, compared with PVI only, the combined procedure was safe and did not increase the occurrence of post-operative complications, despite incremented procedural time.[77] Of note, a higher AF burden was observed in the 'blanking period' after the combined procedure, and an elevated inflammatory status or a device-related mechanical irritation of the LAA might contribute to this arrhythmic propensity. Recent data have reported 3-year follow-up after combined procedure of catheter AF ablation and

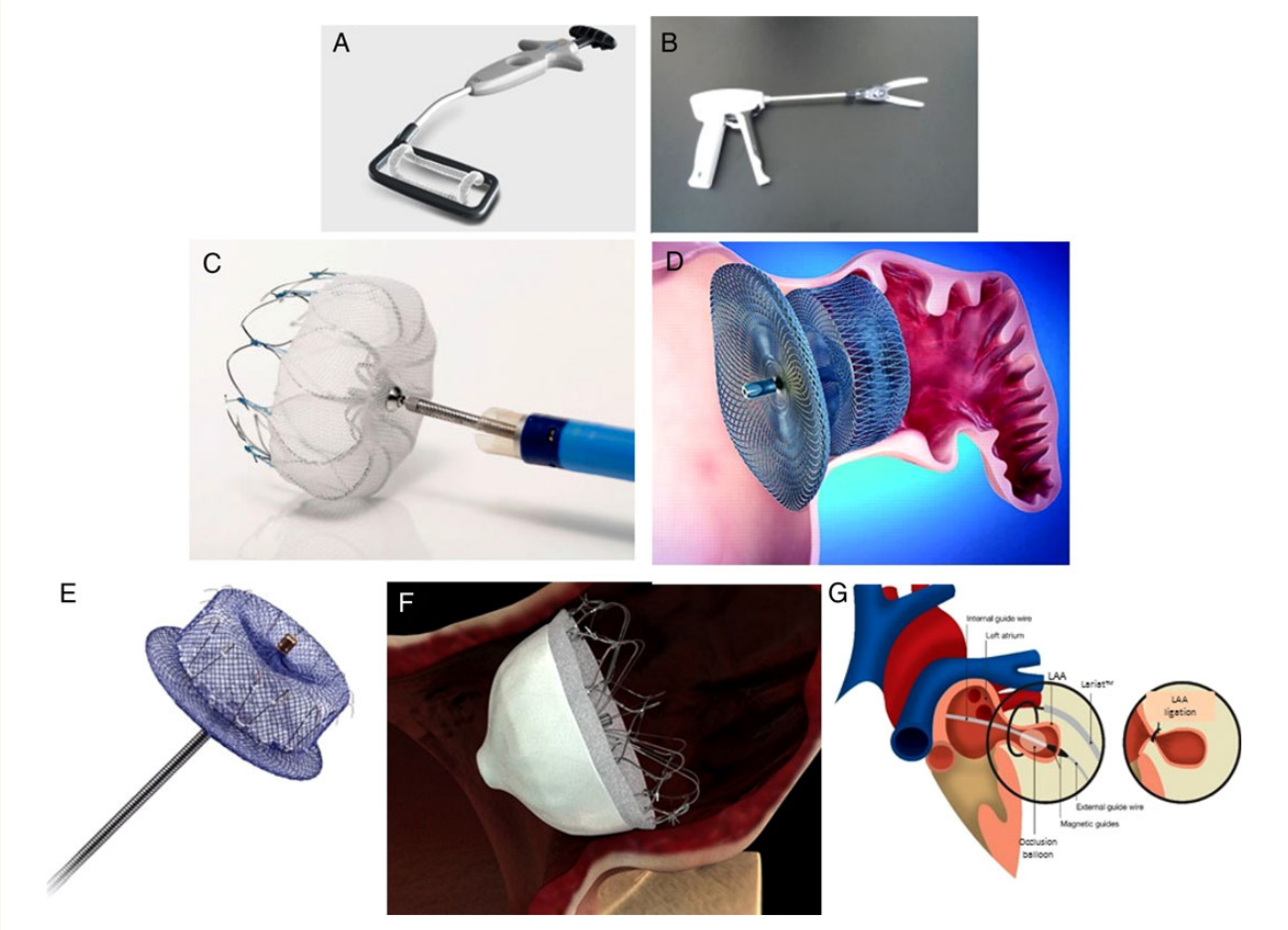

Figure 5 Devices for surgical left atrial appendage closure. (*A*) AtriClip system™ (AtriCure Inc., West Chester, OH, USA); (*B*) TigerPaw system™ (Terumo Cardiovascular Systems, Ann Arbor, MI, USA). Currently approved devices for percutaneous left atrial appendage closure/ligation. (*C*) WATCHMAN™ (Boston Scientific Corp., Maple Grove, MN, USA); (*D*) AMPLATZER Cardiac Plug—ACP™ (St Jude Medical, Minneapolis, MN, USA); (*E*) Amulet™ (St Jude Medical, Minneapolis, MN, USA); (*F*) WaveCrest LAA System™ (Biosense Webster Inc., South Diamond Bar, CA, USA); (*G*) Schematic representation of the Lariat™ system (SentreHeart, Redwood City, CA, USA).

LAA closure, indicating that 95% of the patients had successful LAA sealing, 72% could discontinue oral anticoagulation, 42% had recurrence of the arrhythmia, and that the yearly incidence of stroke was 1.7%, i.e. lower than the expected 6.5%.[78] However, after LAA closure any further LA ablation has to deal with the obstacle of the LAA occluder which is additionally placed in closest proximity to the os of the left superior pulmonary vein, and in worst case scenario, this can render a repeat PVI impossible.

Percutaneous left atrial appendage ligation

To avoid the permanent implant of an LAA occlusion device and the consequent risk of device embolism, erosion, thrombosis, and infections, the percutaneous LAA ligation with the Lariat system was recently developed. It consists of a magnet-tipped guidewire advanced through a trans-septal puncture into the anterior part of the LAA; using the sub-xiphoid approach, another magnet-tipped wire is placed into the pericardium to connect with the magnet-tipped wire in the LAA and to allow the delivery of a surgical suture from the pericardial space (*Figure 5*). In a multicentre U.S. registry of 154 patients, the use of Lariat was associated with 94% procedural success, but high rates of major bleeding (9.1%) and of significant pericardial effusion (10.4%).[79] At the 112 days follow-up, the incidence of cardiac and cerebro-vascular adverse events was 2.9%, with residual leak by TOE observed in 20% of patients. Thus, further investigations are needed to definitely establish the clinical utility and safety of this technique.

Antithrombotic therapy in patients undergoing percutaneous left atrial appendage closure/ligation

Antithrombotic therapy during and after percutaneous LAA closure has the goal of minimizing the thrombogenicity of a foreign body in contact with blood. Peri-procedural antithrombotic therapy for all LAA occlusion procedures typically involves i.v. unfractionated

heparin at doses of 70–85 IU/kg, aiming at an activated clotting time >250 s. The optimal antithrombotic regimen in the first weeks/months after LAA closure, which is the time considered necessary for complete device endothelialization, is still undefined and guidelines on the topic are lacking. The minimal duration of dual antiplatelet therapy (DAPT) is extrapolated from clinical experience with coronary artery bare metal stents[80] and, with limitations, peripheral artery stents,[81] for which 4 weeks of DAPT with subsequent lifelong single antiplatelet therapy are usually considered sufficient. In patients without absolute contraindications for warfarin treatment and undergoing LAA closure, an approach similar to that performed in the intervention arm of both PROTECT-AF[73] and PREVAIL[75] trials appears indicated: warfarin plus low-dose aspirin given for at least 45 days after the intervention, when a TOE—performed to verify device stability and rule-out residual leaks or thrombus formation—provides a green light for replacing anticoagulation with clopidogrel up to 6 months. However, most AF patients currently requiring LAA closure do have a contraindication to oral anticoagulation; this type of patients was recently enrolled in the non-randomized *ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology* (ASAP) study,[82] in which 150 patients were safely managed by protocol with aspirin plus a thienopyridine (clopidogrel or ticlopidine) for 6 months after the procedure. A strategy with DAPT has been also used in most studies on the ACP device, in which aspirin plus clopidogrel were given for 1–6 months, depending on the patients' risk profile, indication for LAA closure, and physicians' preferences. A recent investigation evaluated an approach with shortened (6 weeks) antithrombotic therapy

Table 1 Antithrombotic strategies in patients undergoing percutaneous left atrial appendage closure/ligation

Patients without contraindication to anticoagulant therapy
– INR-titrated VKA treatment (range 2–3, target 2.5) plus low-dose aspirin (75–100 mg/day) until 45 days, verifying the absence of significant LAA flow by TOE, then clopidogrel 75 mg/day plus aspirin 75–100 mg/day until 6 months, and then aspirin (75–100 mg/day) alone lifelong[a]
– No data reported with NOACs; given the safety and efficacy signals from NOAC trials in non-valvular AF, their use instead of VKAs may be considered, with caution as to their ability to prevent activation of coagulation on the device surface
Patients with contraindication to anticoagulant therapy
– DAPT with aspirin plus clopidogrel (as above) maintained for a variable period of 1 to 6 months, with preference for shorter durations in patients at high bleeding risk; then single antiplatelet therapy (aspirin 75–100 mg/day) alone lifelong[a]
– No experience with the newer P2Y12 inhibitors, such as prasugrel or ticagrelor, that carry higher bleeding risk than clopidogrel
Patients treated with the epicardial LAA exclusion system (Lariat)
– Low-dose aspirin (or clopidogrel) monotherapy already at discharge. Dual antiplatelet therapy after the procedure not required[b]

AF, atrial fibrillation; DAPT, dual antiplatelet therapy; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist.

[a]Lifelong aspirin is suggested if indication for long-term antiplatelet therapy co-exists, mainly because of concomitant atherosclerotic cardiovascular disease. The AVERROES trial[84] showed that in patients for whom VKA therapy was considered unsuitable, apixaban, when compared with aspirin, reduced the risk of stroke or systemic embolism by 55% without significant increase in the rates of major bleeding. Thus, in patients without pre-existing indication for long-term antiplatelet therapy, treatment with apixaban instead of LAA closure may be considered for the prevention of AF-related thromboembolic events or LAA closure may be an alternative option with aspirin given for a maximum of 6 months after the procedure.

[b]This is a reasonable suggestion based on currently available data, although there is limited evidence on the safety of avoiding anticoagulation after percutaneous LAA ligation and no specific investigation was focused on the evaluation of device thrombosis with Lariat system.

Table 2 Gaps in our knowledge and priority areas for research

Gaps in knowledge
Efficacy of NOACs for LAA thrombus resolution?
Which patients benefit most from LAA closure?
Precisely how many and what kind of strokes are prevented by LAA closure?
What is the optimal type and duration of antithrombotic therapy after LAA closure?
Research priorities
Randomized studies on VKA vs. NOACs for LAA thrombus resolution
Large prolonged randomized trial on transcatheter LAA closure—results of ACP RCT on ~3000 patients expected in 2017
Large prolonged randomized trial on surgical LAA closure—results of LAAOS III on ~4700 patients expected in 2019
Randomized trials/registries on LAA closure vs. NOACs in VKA ineligible patients
Randomised trials/registries on LAA closure vs. medical therapy in AF patients with ACS and/or coronary stenting
Improved LAA closure techniques assessed by closure success and clinical event rates

ACP, Amplatzer Cardiac Plug; ACS, acute coronary syndrome; AF, atrial fibrillation; LAA, left atrial appendage; LAAOS, Left Atrial Appendage Occlusion Study; NOACs, non-vitamin K antagonist oral anticoagulants; RCT, randomized controlled trial; VKA, vitamin K antagonist.

after percutaneous LAA closure. Here device-related thrombosis occurred in 4/80 patients: thus, the effectiveness of such a strategy needs to be evaluated in larger series.[83]

With the Lariat system, only a minority of patients was maintained on VKAs beyond the procedure, whereas most were discharged with aspirin alone. Of note, Price *et al.*[79] reported no significant differences in outcome among patients with no antithrombotic therapy after the procedure and those treated with VKAs, DAPT, or aspirin alone.

Accepting the limited overall experience and the lack of randomized data, in *Table 1* we indicate the current safest post-procedural options for antithrombotic strategies in patients undergoing percutaneous LAA closure/ligation.

Conclusion and perspectives

Optimal management of AF patients includes a thorough knowledge of the LAA, from anatomy and function to occluding devices and drugs for stroke prophylaxis. The LAA has an undisputed role in AF-related thrombosis and cardio-embolic stroke. Transoesophageal echocardiography-Doppler and other techniques provide high-resolution images of variants and of the occurrence of *in situ* thrombosis, both of which are an indispensable guide for catheter-based procedures. While NOACs are now recommended as alternative to VKAs for non-valvular AF patients, percutaneous LAA closure devices are promising non-pharmacological options when long-term anticoagulation is contraindicated. Gaps in evidence (*Table 2*) on optimal antithrombotic strategies for LAA thrombus resolution and after device implantation are being addressed in randomized controlled trials.

Authors' contributions

G.P., F.A., R.D.C. handled funding and supervision; G.P., F.A., R.D.C., V.P., R.M., P.C., G.R., F.S., P.C., E.G., I.C., E.R., A.R.D.C., G.Z., G.D.G. acquired the data; G.P., V.M.P. conceived and designed the research; G.P., F.A., R.D.C., V.P., R.M., P.C., G.R., F.S., P.C., E.G., I.C., E.R., A.R.D.C., G.Z., P.S. drafted the manuscript; all the authors made critical revision of the manuscript for key intellectual content.

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Appendix

Table A1 Studies on the efficacy of vitamin K antagonist therapy for left atrial appendage thrombus resolution

Study	No. of patients included	Type of anticoagulation	Mean duration of anticoagulation	Resolution rates (no. of patients)
Akdeniz[47]	11	Warfarin (INR 2.0–3.0)	4–6 weeks	64% (7)
Collins[48]	14 (50% males)	Warfarin (INR 2.0–2.8)	5.8 ± 3.9 weeks	86% (12)
Scardi[51]	45 (60% males)	Warfarin (INR 2.0–3.0)	16 months	58% (26)
Jaber[52]	161 (47% males)	Warfarin (mean INR 2.2) or UFH (3 patients)	7 ± 2 weeks	80% (129)
Bernhardt[54]	43 (42% males)	Phenprocoumon (target INR >2)	Variable (see resolution rates)	16% (7) at 1 month 42% (18) at 3 months 49% (21) at 6 months 56% (24) at 12 months
Corrado[50]	11 (55% males)	Warfarin (INR ≥2)	4.8 weeks	82% (9)
Saeed[53]	20 (70% males)	Warfarin (INR 2.0–3.0)	Median 4 weeks	90% (18)
Weigner[55]	28 (46% males)	Warfarin (INR 2.0–3.0)	3–4 weeks	79% (22)
Seidl[49]	55 already on warfarin (INR 2–3)	Warfarin (INR 3.0–3.5)	4 weeks	55% (30)

LAA, left atrial appendage; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Table A2 Characteristics and main results of safety/efficacy with WATCHMAN and Amplatzer Cardiac Plug/Amulet devices

	WATCHMAN	ACP/Amulet
Device materials	Nitinol basket frame	Braided nitinol frame
Device anchoring system	Nitinol stabilizing wires and barbes	Nitinol stabilizing wires and barbes
Occlusion technology	Polyester cover	Polyester patches
Device sizes	21–33 mm	16–30 mm/16–34 mm
Minimum LAA length	21 mm	10 mm/10–12 mm
Minimum LAA width	17 mm	12.6 mm/11 mm
Maximum LAA width	31 mm	28.5 mm/31 mm
Procedural success	93%[a]	97%[b]
Stroke/systemic embolism/CV death	2.7 per 100 PY with device vs. 3.5 per 100 PY with warfarin[a]	3.2 per 100 PY[b]
Major bleeding	2.3 per 100 PY with device vs. 2.7 per 100 PY with warfarin[a]	2.1 per 100 PY[b]

1047 patients from 22 centres receiving ACP implantation;[76] to date, no specific clinical data are available for the Amulet device.
ACP, Amplatzer Cardiac Plug; CV, cardiovascular; LAA, left atrial appendage; PY, per year.
[a]Pooled data from the randomized PROTECT-AF[73] and PREVAIL[75] studies; [b]Results of the largest observational study on.

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