

## Left atrial appendage closure for prevention of cardioembolic events

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### Summary

Atrial fibrillation (AF) is the most common atrial arrhythmia, with a prevalence of 1–2% in the general population. It increases with age, affecting approximately 7% of individuals age >65 years and 15–20% of octogenarians. The human left atrium has a blind sac-like remnant, called left atrial appendage (LAA). It originates from a primordial pulmonary vein. Due to its complicated structure, blind end and inner surface trabeculated by pectinate muscles, thrombi in nonvalvular AF form almost exclusively in the LAA and not in the smooth-walled left atrium. For the last 50 years, oral anticoagulation (OAC) with vitamin K antagonists (VKAs) has been the only treatment option to prevent stroke and systemic embolism from thrombi in AF. More recently, non-vitamin K-dependant oral anticoagulants (NOACs) have been shown to be noninferior or even superior to VKA with respect to efficacy and safety. In light of the limitations of indefinite OAC, particularly among patients at increased risk for bleeding and because thrombi arise predominantly from the LAA among AF patients, exclusion of the LAA with closure devices (LAAC) provides a novel treatment strategy for prevention of stroke and bleeding. Recently, LAAC has been compared with VKA therapy in prospective randomised trials with promising results. Today, the decision to provide the most appropriate treatment for a patient with AF (OAC, NOAC or LAAC) is complex and needs to be individualised. This review provides an update on the current state of LAAC in the field of stroke prevention in patients suffering from non-

valvular AF. We describe the pathophysiology of the LAA with regard to stroke. Aside from the evidence and limitations of anticoagulation as the classical treatment paradigm for stroke prevention, devices and techniques for LAAC are outlined and the current clinical evidence with regard to efficacy and safety is reviewed. Finally, contemporary recommendations for patient selection are provided.

**Key words:** anticoagulation; atrial fibrillation; left atrial appendage closure; stroke; bleeding

### Introduction

Atrial fibrillation (AF) is the most common atrial arrhythmia, with a prevalence of 1–2% in the general population that increases with age to affect approximately 7% of individuals aged >65 years and 15–20% of octogenarians [1–3]. Patients with AF are at increased risk of thromboembolism, in particular ischaemic stroke. It is estimated that every fifth stroke is related to AF [3]. Strokes related to AF tend to be especially severe and disabling, and half of the patients die within 1 year of the event. Patients with AF are also at increased risk of death (two-fold) and heart failure (three-fold), and AF is responsible for 3–6% of acute medical admissions for management of arrhythmia [4]. Of note, AF frequently goes undetected and therefore not all affected patients receive appropriate treatment [5].

For estimation of individual stroke risk, the comorbidities of any patient suffering from AF have to be taken into consideration. Current guidelines recommend the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which provides an estimate of the annual stroke risk with the advice to implement oral anticoagulation (OAC) for prevention of thromboembolism in the case of CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ≥1 [4, 6].

### Structure and function of the left atrial appendage

The left atrial appendage (LAA) is a remnant of a primordial pulmonary vein and is located anteriorly in the atrioventricular groove in close proximity to the left circumflex coronary artery, the annulus of the mitral valve, the left upper pulmonary vein and the left phrenic nerve. Owing to the small volume and in spite of the contractility

#### Abbreviations

AF	atrial fibrillation
CT	computed tomography
FDA	Food and Drug Administration of the United States of America
INR	international normalised ratio
LAA	left atrial appendage
LAAC	left atrial appendage closure
NOAC	non-vitamin K-dependent oral anticoagulant
OAC	oral anticoagulation
PFO	patent foramen ovale
RRR	relative risk reduction
TIA	transient ischaemic attack
TOE	transoesophageal echocardiography
VKA	vitamin K antagonist

of the LAA during normal sinus rhythm, it plays only a minor role in the regulation of pressure, volume and left ventricular filling [7]. With volumes of 5–15 ml, the LAA is markedly smaller than the right atrial appendage and its inner surface is trabeculated by pectinate muscles [8, 9]. Although the shape of the LAA is highly variable, it usually resembles a rather narrow tube with numerous bends. Four principal morphologies have been described: cactus, chicken wing, windsock and cauliflower appearances. It has also been suggested that LAA morphology is directly linked to the risk of stroke [10, 11], where patients with LAA morphology other than chicken wing appear at higher risk for thromboembolic events after controlling for comorbidities and CHADS<sub>2</sub> score [12].

### Remodelling of the left atrial appendage and pathophysiology in atrial fibrillation

AF results in loss of physiological atrial systole and irregular ventricular activation, which in turn affects left ventricular filling and contractility, and cardiac output. As a result, left atrial pressures and volumes are typically increased due to stasis. Depending on the frequency and duration of AF, as well as left ventricular systolic and diastolic function and afterload, both the left atrium and the LAA undergo a progressive process of remodelling with subsequent enlargement and reduced blood flow velocities including turbulent flow and stasis [9, 13–15].

The LAA has been known as a potential nidus of thrombus formation and location for more than 60 years and the first surgical resection of the LAA was published in 1949 [16]. A recent meta-analysis of >20000 AF patients with non-valvular AF reported a mean prevalence for any left atrial thrombi of 10%, which was linked to a 3.5-fold increase in stroke risk [17]. Evidence from echocardiographic, surgical and postmortem studies revealed that the vast majority of intracardiac thrombi in patients with nonvalvular AF are located in the LAA. In a large study using transoesophageal echocardiography (TOE), 91% of thrombi were located in the LAA [18]. Of note, thrombi can be detected within a relatively short period of time in the LAA in up to 14% of patients with acute or new onset (<3 days) AF [19]. In valvular AF, which comprises patients with rheumatic mitral stenosis or metallic valve prostheses, left atrial flow is even more reduced and therefore the prevalence of left atrial thrombi is as high as 45% [20]. At variance with nonvalvular AF and owing to the even more thrombogenic milieu in the presence of mitral stenosis or a mechanical prosthesis, thrombi originate more frequently from the left atrium: in a clinicopathological study, about half of the left-sided thrombi were observed in the LAA, whereas the remainder were located at the free walls of the left atrium [21].

### Oral anticoagulation for stroke prevention

Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or, more recently, non-vitamin K-dependent oral anticoagulants (NOACs) is the mainstay of the prevention

of thromboembolism among patients with AF. OAC with a VKA as compared with placebo is associated with an absolute stroke risk reduction of 2.7% per year, which corresponds to a relative risk reduction of 64% and a number needed to treat of 37 per year [22]. Although antiplatelet therapy with acetylsalicylic acid alone or dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel lowers the risk of stroke as compared with placebo by approximately 20%, OAC with a VKA is substantially more effective than antiplatelet therapy by approximately 40%. More recently, NOACs have been introduced into clinical practice. They have several advantages over VKAs including rapid onset (2–4 hours), rapid offset (24 hours) and predictable pharmacokinetic effects, combined with a favourable safety and efficacy profile. A prespecified, pooled analysis of four randomised clinical trials (RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI) included 71 683 patients with AF and compared clinical outcomes of different NOACs with VKAs. The results showed a 19% lower risk of stroke and systemic embolism (relative risk [RR] 0.81, 95% confidence interval [CI] 0.73–0.91), a 50% lower risk of haemorrhagic stroke (RR 0.49, 95% CI 0.49–0.61,  $p < 0.0001$ ), and a 10% lower risk of mortality (RR 0.90, 95% CI 0.85–0.95,  $p = 0.0003$ ) in favour of NOACs [23]. Of note, major bleeding tended to be lower with NOACs than VKAs (RR 0.86, 95% CI 0.73–1.00,  $p = 0.06$ ). AVERROES compared the NOAC apixaban with acetylsalicylic acid in patients with AF who had an absolute or relative contraindication for a VKA. In this study, the treatment with apixaban as compared with acetylsalicylic acid improved efficacy in terms of reducing the risk of stroke and systemic embolism (hazard ratio [HR] 0.45, 95% CI 0.32–0.62,  $p < 0.01$ ) while providing a similar safety profile (HR = 1.13, 95% CI 0.74–1.75,  $p = 0.57$ ) [24]. In view of the robust evidence in favour of OAC in patients with AF, current guidelines recommend the initiation of an (N)OAC in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1 (class IIa A) and CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 2$  (class I A) after weighing the bleeding risk using the HASBLED score. These guidelines also give preference to NOACs over VKAs (Class IIa A) for most AF patients based on the net clinical benefit outlined above, with the exception of patients with valvular AF, for whom OAC with a VKA is still recommended as the preferred treatment [4].

### Shortcomings of oral anticoagulation

OAC is highly effective but is not free of limitations. As it relates to VKAs, a large US study has recently shown that only about half (54%) of patients are adequately protected as maintenance of a therapeutic prothrombin time international normalised ratio (INR) remains infrequent [25]. Moreover, approximately one third of patients with AF do not receive OAC or discontinue therapy once started for a variety of reasons, and therefore have no protection against thromboembolism [26, 27]. Thus, the rate of premature and permanent discontinuation amounted to 55% in patients treated with warfarin [28] and 34% in patients who had received edoxaban [29] within 2–3 years after initiation of treatment in well supervised, controlled clinical trials. Ac-

cordingly, a substantial proportion of patients who have an indication for OAC remain untreated and have no sufficient stroke prophylaxis.

Bleeding complications are more common with therapeutic OAC. The assessment of individual bleeding risk according to scores such as the HAS-BLED (hypertension, abnormal liver function, abnormal renal function, stroke, bleeding, labile INR, elderly, drugs, or alcohol) score [30] or ATRIA score [31] should be part of any risk/benefit evaluation for optimal treatment of patients with AF. HAS-BLED scores in excess of 3 are associated with a high bleeding risk, i.e., an incidence of major bleedings of 5.8% per 100 patient-years [4]. Recent data from randomised trials comparing a NOAC with warfarin indicate major bleeding event rates in the range of 1.9% to 3.6% per year for NOACs and 3.1% to 4.2% per year for warfarin [29, 32–34]. Although NOACs have substantially reduced the risk of intracranial haemorrhage as compared with VKAs, the risk of gastrointestinal bleeding is similar or higher. It also has to be taken into consideration that patients with the highest CHA<sub>2</sub>DS<sub>2</sub>-VASC score frequently have the highest HAS-BLED score. Particularly, the growing population of very elderly patients is at increased bleeding risk or has already experienced either spontaneous bleeding or bleeding under OAC. Finally, specific patient populations such as those with severe, chronic renal failure are at increased risk of bleeding, have not been studied in randomised trials and represent a relative contraindication for NOAC therapy.

### Rationale for left atrial appendage closure

Owing to the intrinsic limitations of oral anticoagulation and the anatomical and pathophysiological features of the LAA in patients with AF, an alternative concept for thromboembolic protection has been developed: the surgical exclusion or percutaneous closure of the LAA (LAAC). It was first performed surgically in the late 1940s. In this millennium, effective LAAC has been introduced by means of a nonsurgical, minimally invasive catheter-based intervention [35, 36].

### Surgical exclusion of the left atrial appendage

The initial version of the cut and sew Cox-Maze procedure for treatment of AF included the excision or closure of the LAA [37] (fig. 1, panel A). In a large study (>400 patients) by Johnson and colleagues, prophylactic LAA removal was reported to be feasible and safe. It was advocated that it should be considered as an additional therapy to any heart surgery [38]. A retrospective study, investigating the addition of surgical LAA removal among patients undergoing mitral valve replacement in a high-risk population, reported a reduction of the risk of stroke and systemic embolism [39]. A recent large, observational study in 1831 patients has shown that additional surgical LAA removal during cardiac surgery in patients at low stroke risk reduced the incidence of postoperative cerebrovascular accidents [40]. Currently, the large-scale (4700 patients) Left Atrial Appendage Occlusion Study (LAAOS) III is comparing con-

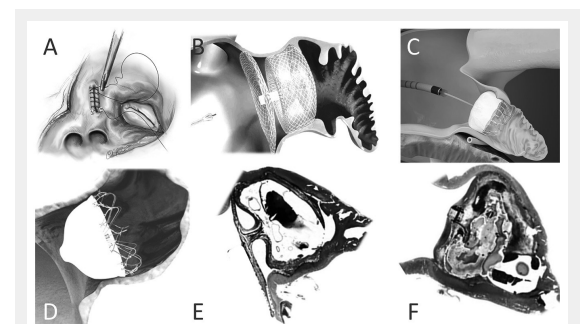
comitant surgical LAAC with no LAA closure in patients with AF or atrial flutter who are undergoing routine cardiac surgery. Of note, OAC is continued in both groups [41], with follow-up through 4 years.

The 2014 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularisation provide guidance as to the addition of LAAC to surgical coronary revascularisation or valvular surgery in patients with AF with a class IIb B recommendation [42].

Apart from suture-based endocardial surgical techniques, placement of an epicardial clip with a dedicated device (AtriClip, Atricure Inc., Ohio, USA) has shown a high procedural success in >95% with favourable safety and persistent closure (98%) at follow-up. Long-term studies to determine the clinical efficacy are not yet available [43].

### Percutaneous closure of the left atrial appendage

The first dedicated LAAC device was implanted in humans in 2001 (PLAATO, percutaneous left atrial appendage transcatheter occlusion device, Appriva Medical Inc., California, USA), but is no longer commercially available [35]. Only shortly thereafter in 2002, the first LAAC was performed with implantation of a nondedicated Amplatzer atrial septal occluder device (St. Jude Medical, Minnesota, USA) [36]. Subsequently, the specifically designed and dedicated Amplatzer cardiac plug (ACP) was launched and CE-mark approved in 2008. The device, which is currently



**Figure 1**

Different techniques, devices, and results for left atrial appendage closure (LAAC).

In panel A, surgical endocardial closure by exclusion with a double layer suture is depicted. Note the proximity of the left atrial appendage (LAA) to the left pulmonary veins (LPVs) and the mitral valve (MV). Derived and modified from Robertson et al. [71] (© 2016 Beth Croce).

In panels B and C, the two most common devices for percutaneous LAAC are shown (B: derived and modified from St. Jude Medical, Minnesota, USA; C: Image provided courtesy of Boston Scientific. © 2016 Boston Scientific Corporation or its affiliates. All rights reserved).

In contrast to the Watchman, a membrane-cap device (C), the Amplatzer systems are plug-and-disc (pacifier) devices. Panel D depicts another membrane-cap device, the Coherex Wavecrest (derived and modified from Coherex Medical, Utah, USA). In panels E and F, the Amplatzer and Watchman devices are shown after endocardialisation in anatomical preparations of canine models (derived and modified from Kar et al. [72] Impact of Watchman and Amplatzer devices on left atrial appendage adjacent structures and healing response in a canine model. *JACC Cardiovasc Interv.* 2014;7(7):801–9, with permission from Elsevier).

in its second generation (Amulet) consists of a distal body with small stabilisation wires that results in obliteration of the LAA cavity and anchors the device, as well as a proximal disc to enable coverage, i.e., exclusion of the LAA ostium according to the pacifier principle. The device is manufactured from a self-expanding nitinol mesh (fig. 1, panels B and E).

The Watchman LAAC device (Boston Scientific, Massachusetts, USA, CE approved in 2005 and approved by the US Food and Drug Administration [FDA] in 2015) was implanted for the first time in the year 2002, a few months after the Amplatzer device, and since then has undergone further refinement [44]. Unlike the plug-and-disc (pacifier) concept of the Amplatzer systems, the Watchman is a membrane-cap plug system (fig. 1, panel C and F). It is made of a self-expanding nitinol frame with ten fixation anchors and a cover of permeable polyethylene terephthalate.

The Coherex Wavecrest occluder (Coherex Medical, Utah, USA) is the third catheter-based device, which also comes with a membrane-cap plug design. It received CE approval in 2013 (fig. 1, panel D). As yet, no clinical data with meaningful follow-up have been published.

Several additional interventional devices are in the stage of clinical or preclinical evaluation. The catheter-based LARIAT (SentreHEART Inc., California, USA) device uses a hybrid endocardial and epicardial approach, is approved by FDA and has obtained the CE mark. The Amplatzer ACP/Amulet and the Watchman are the devices with which there is most clinical experience reported to date.

The wide variability of LAA morphology requires careful preprocedural planning in order to determine the most adequate device [45]. Prior to the procedure, most patients undergo TOE to rule out any thrombi in the LAA and to determine anatomical specifications and size. Computed tomography (CT) of the heart with three-dimensional reconstruction of the LAA also provides high spatial and temporal resolution allowing for detailed description of the anatomy. It plays an increasing role in device selection and intervention planning [45–47]. On the other hand, *ad hoc* LAAC with invasive angiography and fluoroscopic guidance only, with no prior imaging of any kind, has been successfully performed [48]. Following percutaneous puncture of the femoral vein, left atrial access is usually gained via transseptal puncture or, less frequently, by passage through a patent foramen ovale (PFO) or an atrial septal defect [49]. Thereafter, a device-specific sheath is advanced over a guidewire into the left atrium and directed into the LAA in order to enable device delivery (fig. 1, panels B and C), with great care to avoid injury to the thin-walled left atrial structures [50].

After the procedure, which either requires only a short hospital stay or can be an outpatient procedure, patients can resume routine daily activities immediately. There are different regimens of antithrombotic treatment after transcatheter LAAC. While some maintain OAC for a period of several weeks to months (recommended after implantation of the Watchman device), others prescribe dual antiplatelet therapy (recommended after the Amplatzer devices) consisting of low dose acetylsalicylic acid (100 mg per day) and

clopidogrel (75 mg per day) to prevent early device-related thrombosis until endocardialisation has covered the device (fig. 1, panels E and F). Whereas the procedure is usually performed using TOE guidance, it can also be done without TOE, with fluoroscopic guidance only [50–52].

To ensure effective LAA closure and absence of device-related thrombi, TOE is usually repeated at least once 3–6 months after the procedure.

## Clinical evidence for left atrial appendage closure

A large study (LAAOS III) assessing surgical LAA closure is currently recruiting patients [41]. Of note, in this trial, OAC is continued after surgical LAAC in all patients, precluding any data on the efficacy of surgical LAAC without concomitant use of OAC.

With regard to percutaneous LAAC, two randomised clinical trials, one meta-analysis, and several registry studies have been reported so far [53–58]. Table 1 summarises current clinical trial and registry data.

Using the Watchman device, the Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT AF) trial was the first randomised, noninferiority clinical trial comparing LAAC with warfarin in 707 patients with a mean CHADS<sub>2</sub> score of  $2.2 \pm 1.2$ , who were eligible for OAC. Warfarin was continued in addition to acetylsalicylic acid for the first 6 weeks after implantation, at which time a follow-up TOE was performed. The device was successfully implanted in 88% of randomly assigned patients and most discontinued warfarin after 6 weeks. At 1065 patient-years of follow-up, LAAC with the Watchman device was found noninferior to OAC for the composite primary efficacy endpoint: an endpoint event (stroke, cardiovascular death, or systemic embolism) occurred in 3.0% per 100 patient-years in the LAAC group versus 4.9% in the OAC group with a probability of noninferiority of the intervention of >99.9%. Patients treated with the device had fewer haemorrhagic strokes (0.1 vs 1.6%, probability of superiority of the LAAC group 99.8%). The primary safety endpoint – a composite of major bleeding and periprocedural complications – was more common in the device closure group (7.7 vs 4.4% per 100 patient-years), mainly driven by serious pericardial effusions in 4.8% of patients [53]. Of note, during long-term follow-up (2621 patient-years) the Watchman device fulfilled criteria for superiority to OAC for the primary efficacy endpoint, and mortality was significantly reduced [54] (fig. 2). Subsequently, a second randomised trial, the Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) was performed and showed improvements in procedural success and safety [55]. Whereas the successful closure rate increased from 88 to 95%, the rates of the coprimary endpoint of cardiovascular death, stroke or systemic embolism were comparable in both treatment arms at 18 months of follow-up, although the device arm did not formally reach noninferiority as the upper bound of the 95% credibility interval was not within the prespecified margin. In

Table 1: Procedural success and adverse event rates of the principal left atrial appendage closure trials and registries.																
Trial / registry studies >100 patients	n	Design	CHADS2 score Mean $\pm$ SD	Procedural/technical success %	Peri-procedural death %	Severe pericardial effusion %	Major device embolisation %	Disabling stroke %	Safety events (periprocedural complications)	Total rate of relevant/severe safety events %	Adjudication of events	Follow-up: Total number of patient years observed	Efficacy events	Efficacy event rate (per 100 patient-years)	Duration of follow-up in months Mean $\pm$ SD	Remarks
PLAATO																
PLAATO [73]	111	Registry	2.4 $\pm$ 1.3	97.0	0.0	0.9	0.0	Na	Surgery due to cardiac tamponade, death	0.9	No	91.0	Stroke	2.2	9.8	Early study; safety events likely underreported
PLAATO European Study [74]	180	Registry	3.1 $\pm$ 1.6	90.0	1.1	3.3	Na	Na	Stroke, tamponade, death, embolisation, others	8.9	No	129.0	Stroke	2.3	9.6 $\pm$ 6.9	
AMPLATZER CARDIAC PLUG and AMULET																
Initial European registry [75]	143	Registry	Na	96.0	0.0	3.5	1.4	2.1	Thromboembolism, loss of implant in venous system, device embolism, air embolism, procedural stroke, pericardial tamponade	7.0	No	Na	Na	Na	Na	Feasibility study, only procedural safety events reported
Iberian Amplatzer registry [76]	167	Registry	3.0 $\pm$ 1.0	95.0	0.0	1.2	0.6	Na	Major vascular complications, device embolisations, pericardial tamponade, TIA	5.4	No	290.0	Stroke, TIA	2.4	22.0 $\pm$ 8.3	
Bern LAAC registry [51]	152	Registry	2.7 $\pm$ 1.3	98.0	0.0	2.6	4.6	0.0	Pericardial tamponade, device embolisation, stroke, major bleeding	7.2	No	Na	Stroke, systemic embolism, unexplained death	2.6	32.0	Early data of the Bern registry including early results with non-dedicated devices
Early safety Israel experience [77]	100	Registry	3.2 $\pm$ 1.2	100.0	0.0	1.0	0.0	0.0	pericardial tamponade, pulmonary oedema	1.0	No	Na	Na	Na	Na	Cumulative experience of a single operator
Multicentre Amplatzer experience [58]	1047	Registry	2.8 $\pm$ 1.3	97.0	0.8	1.2	0.8	0.9	Death, myocardial infarction, stroke, TIA), systemic embolisation, air embolisation, device embolisation, cardiac tamponade, major bleeding	5.0	No	1349.0	Stroke, TIA, systemic embolism	2.3	13.0	
Bern-Zurich LAAC registry (unpublished data)	500	Registry	2.6 $\pm$ 1.3	98.0	0.4	3.0	0.6	0.2	Death, stroke, tamponade, major bleeding, major access vessel complication, surgery, severe kidney injury, need for resuscitation	4.8	Yes	Na	Na	Na	Na	
WATCHMAN																
PROTECT-AF trial. [53, 54, 56]	707	RCT vs warfarin	2.2 $\pm$ 1.2	88.0	0.0	4.8	0.6	1.1	Severe pericardial effusion, major bleeding, procedure-related stroke, device embolisation, haemorrhagic stroke	8.7	Yes	2621.0	Stroke, systemic embolism, cardiovascular or unexplained death	2.3	46.0 $\pm$ 20.0	First randomised trial; proof of concept for LAAC with Watchman

PREVAIL trial [55]	407	RCT vs warfarin	2.6 ± 1.0	95.0	0.0	0.8	0.7	0.0	Device embolisation, arteriovenous fistula, cardiac perforation, cardiac tamponade, major bleeding	4.5	Yes	Na	Stroke, systemic embolism, unexplained death	0.7	28.0 ± 13.0	Second randomised trial with Watchman vs warfarin
CAP [61]	460	Registry	2.4 ± 1.2	94.4	0.0	2.2	Na	0.0	Severe pericardial effusion, major bleeding, stroke, device embolisation, haemorrhagic stroke	4.2	Yes	Na	Stroke, systemic embolism or cardiovascular death	2.0	25.0 ± 10.0	
ASAP [56]	150	Registry	2.8 ± 1.2	95.0	0.0	1.3	1.3	0.7	Device embolisation, cardiac tamponade, stroke, pseudoaneurysm, bleeding	8.7	Yes	129.0	Stroke	2.3	14.0 ± 9.0	Study for safety and efficacy in patients who are not eligible for warfarin
EWOLUTION [62]	1019	Registry	2.8 ± 1.3	98.5	0.0	0.2	0.2	0.1	Severe pericardial effusion, major bleeding, stroke, device embolisation, haemorrhagic stroke	2.8	Yes	Na	Na	Na	Na	
LARIAT																
Multicentre registry [65]	154	Registry	2.8 ± 1.4	86.0	1.9	10.4	0.0	1.3	Death, myocardial infarction, stroke, bleeding, cardiac surgery	10.4	No	Na	Stroke, systemic embolism, cardiovascular or unexplained death	2.9	4.0	
COHEREX WAVECREST																
Wavecrest 1 trial. (Reddy et al., oral presentation ICI 2013)	73	Registry	Na	96.0	0.0	2.0	0.0	0.0	Severe pericardial effusion, procedure-related stroke, device embolisation	0.0	No	Yes	Na	Na	1.5	
ASAP = acetylsalicylic acid plavix feasibility study with Watchman left atrial appendage closure technology; CAP = continued access protocol; CHADS2 = congestive heart failure history, hypertension history, age >75 years, diabetes mellitus history, stroke or transient ischaemic attack symptoms previously; CV = cardiovascular; LAAC = left atrial appendage closure; Na = not available; PREVAIL = prospective randomised evaluation of the Watchman LAA closure device in patients with atrial fibrillation vs long-term warfarin therapy; PROTECT-AF = Watchman left atrial appendage closure system for embolic protection in patients with atrial fibrillation; pt-yrs = patient-years; RCT = randomised controlled trial; RR = risk ratio; WM = Watchman; TIA = transient ischaemic attack																

a patient-level meta-analysis of PROTECT AF, PREVAIL and registry data, LAAC with the Watchman device as compared with OAC was found to result in similar rates of all-cause stroke and systemic embolism (HR 1.02, 95% CI 0.62–1.17,  $p = 0.94$ ), although the lower rate of haemorrhagic stroke (HR 0.22,  $p = 0.004$ ) was offset by the higher rate of ischaemic stroke (HR 1.95,  $p = 0.05$ ). In addition, LAAC was associated with lower rates of cardiovascular and unexplained death (HR 0.48,  $p = 0.006$ ) and fewer non-procedural bleeding events (HR = 0.51,  $p = 0.006$ ) [57]. Quality of life has also been shown to improve in patients who underwent LAAC compared with OAC, as well as cost-effectiveness [59, 60].

In patients ineligible for OAC, the ASAP Study (Aspirin Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) reported that LAAC with the Watchman device can be safely performed with favourable results in terms of stroke prevention in the absence of treatment with warfarin during the first 6 weeks after implantation [56]. Patients were treated with dual antiplatelet therapy for 6 months followed by acetylsalicylic acid indefinitely and the observed rate of systemic embolism or

stroke was 2.3% per year after 14 months of follow-up (expected rate 7.3% per year).

In addition to the controlled trials, the Watchman Continued Access Protocol Registry (CAP) showed improvements in device safety overcoming the initial learning curve [61]. Furthermore, the recently published results of the EWOLUTION registry, which included 1021 patients with a relatively high risk for stroke and bleeding, showed an additional reduction of major safety events to 2.8% after 7 days and to 3.6% after 30 days after LAAC with the Watchman device [62].

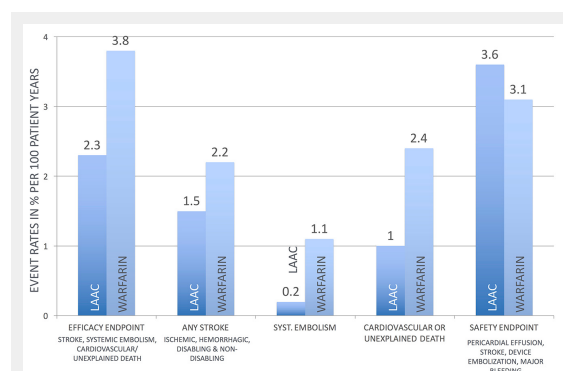
Along with further improvement of implantation techniques and operator skills, the net clinical benefit of LAAC can be further increased.

As a consequence, the second generation of the Watchman device has gained approval of the FDA in early 2015 for stroke prevention in patients with AF as an alternative to OAC, currently being the only FDA-approved system for percutaneous LAAC.

Beside the Watchman device, the Amplatzer cardiac plug and Amulet devices have been investigated in several studies, some of which were limited by retrospective design or performance by a single operator. Most studies using the

Amplatzer cardiac plug were performed in patients with (relative) contraindications for OAC and hence represent a population at higher risk for stroke and bleeding. Patients were usually treated with acetylsalicylic acid and clopidogrel after the procedure. Data regarding safety and efficacy from various studies are summarised in table 1. So far, the largest data set regarding procedural safety and clinical efficacy is derived from a multicentre registry including 1047 patients at 20 international centres [58]. The mean age was 75 years, the mean CHADS<sub>2</sub> score  $2.8 \pm 1.3$ , the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $4.5 \pm 1.6$ , and the HAS-BLED score  $3.1 \pm 1.2$ . A considerable proportion of patients underwent concomitant structural or coronary interventions. Procedural success was high (>97%). The rate of periprocedural major adverse events (7-day rates of death, ischaemic stroke, systemic embolism, and procedure-related or device-related complications requiring major cardiovascular or endovascular intervention) amounted to 5% (mortality 0.8%, cardiac tamponade 1.2%, device embolisation 0.1%, stroke 0.9%).

During 1349 patient-years of follow-up the rate of stroke and systemic embolism was 2.3% in the overall population and 1.3% in the subgroup of more than 600 patients without concomitant coronary or structural interventions. Compared with the expected stroke rate according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, a 59–77% relative risk reduction for the efficacy endpoints of stroke and systemic embolism, respectively, was shown. Major bleeding was reported at a rate of 1.3% per 100 patient-years in patients with a follow-up time longer than 1 year, and 2.1% per 100 patient-years for the entire population. TOE investigations 3–6 months after device implantation found a closure rate of 98% with absence of a significant residual shunt. To date, data from randomised trials comparing the Amplatzer Cardiac Plug with oral anticoagulation in patients with AF are missing.



**Figure 2**

Primary outcomes of the Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT AF) study [54]. In comparison with warfarin, left atrial appendage closure (LAAC) with the Watchman was superior in preventing death, stroke, and systemic embolism. Due to periprocedural safety events, e.g., severe bleeding as a result of major pericardial effusion, device embolisation and stroke, LAAC with the Watchman device was not superior (yet not inferior either) to warfarin during a mean follow-up time of 3.8 years with regard to safety. For the first time, LAAC has not only shown superior results with regard to stroke prevention, but remarkably also with regard to all cause and cardiovascular mortality, indirectly pointing towards the hazards of oral anticoagulation. Data reproduced from Reddy et al. [54].

A multicentre pivotal trial, comparing LAAC with Amplatzer devices to NOAC was stopped owing to slow patient recruitment [63].

The LARIAT device has been investigated in nonrandomised, small-scale observational studies. Bartus and colleagues reported the results of a study in 89 patients with a success rate of 96%. The rate of serious adverse events (pericarditis, cardiac tamponade, late strokes, unexplained sudden cardiac death) was relatively high (10 events, 11.2%) [64]. A more recent, retrospective study of 154 patients reported a device success rate of 94%, while 10.4% of patients experienced a relevant pericardial effusion and 9.1% of patients had major bleedings. Clinical efficacy endpoints including death, myocardial infarction or stroke occurred in 2.9% of patients after a median follow-up period of 4 months. TOE revealed a relatively high rate of residual leaks and device-related thrombi (20% and 4.8%, respectively) [65].

Due to the wide variability and partly inconsistent definitions of reported complications (table 1) in the various registries and trials, direct and indirect comparisons are problematic. Therefore, standardised criteria and predefined composite endpoints, in analogy to the Bleeding Academic Research Consortium (BARC) and Valve Academic Research Consortium (VARC) criteria, are desirable. Similarly, clinical outcome data have to be monitored and adverse events need to be recorded and adjudicated according to the upcoming left atrial appendage closure criteria.

Current guidelines provide a class IIb, level of evidence B, recommendation for percutaneous LAAC [4] in patients who are not candidates for OAC. Presumably, the role of LAAC as a second concept in the management of AF will grow along with development of new devices, progressive skills and routine of interventional cardiologists, and of course, with further evidence from new studies.

## Safety aspects when considering left atrial appendage closure

LAAC is a preventive treatment without immediate effect on symptoms. Therefore, the rate of procedure-related adverse events must be as low as possible. Due to the complex anatomy and topography of the LAA, closure techniques are more complex, technically more demanding, and more risky than other preventive treatment strategies such as PFO closure. PFO closure can be performed with very low risk as attested by the absence of relevant periprocedural outcome differences in three randomised trials comparing PFO closure with medical therapy [66–69]. The event rate among AF patients undergoing LAAC is considerably higher during the early period after the intervention, and beneficial effects regarding prevention of haemorrhagic stroke and nonprocedural bleeding emerge only during longer term follow-up [54, 57]. Regarding overall bleeding rates, also including all procedure-related bleedings, a recent analysis in 1114 patients with a median follow-up of 3.1 years revealed noninferiority [70].

Delayed procedure-related adverse findings such as device-related thrombi and incomplete closure with residual shunts in the LAA are detected infrequently (fig. 4). In the largest series of 632 patients after a median follow-up of

7 months, thrombi were found in 4.4% and mostly treated by reinitiation of (non-vitamin K-dependent) oral anticoagulants. Peridevice leaks or relevant shunts were found in 1.9%, yielding a rate of complete LAA closure of 98.1%. Of note, these findings were not linked to adverse events in that multicentre study [58]. Also, late pericardial effusions

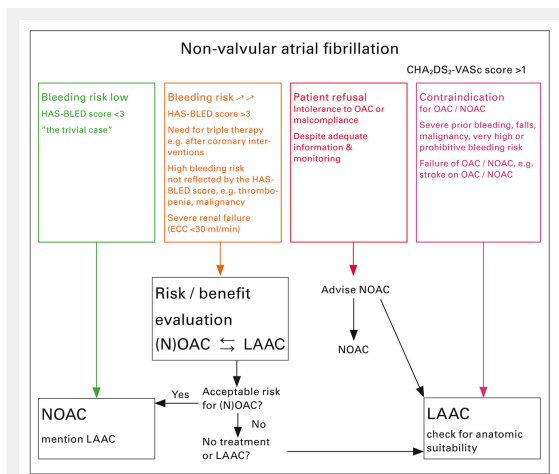
with or without need for drainage and late device embolisations occurred infrequently.

LAAC is a challenging intervention and both procedural success and adverse events depend on the individual experience of the operator. The learning curve of the procedure is shallow, which means that LAAC should be preferentially performed at high-volume centres by experienced operators.

## Patient selection and indications for left atrial appendage closure

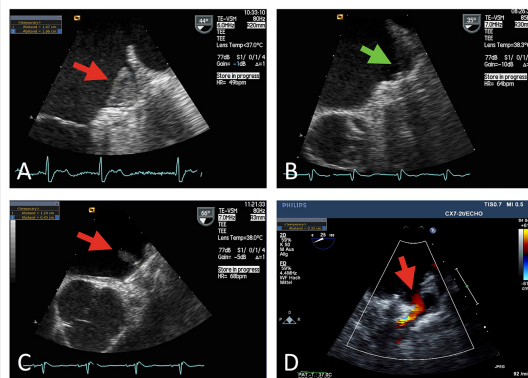
Prevention of stroke and systemic embolism is of paramount importance in patients with AF and risk factors for stroke. OAC with a VKA or NOAC is the current standard of care and provides excellent efficacy in terms of stroke prevention. LAAC emerges as an additional, nonpharmacological treatment. The available therapeutic strategies need to take into consideration the long-term risk of thromboembolism as determined with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score as well as long-term bleeding risk as determined with the HAS-BLED score. When considering LAAC, the periprocedural risks need to be carefully weighed, particularly as the intervention is performed frequently in asymptomatic patients with primary preventive intentions, thus highlighting low adverse event rates as an important prerequisite. Other considerations include patient compliance and tolerance of long-term pharmacological treatment, as well as patient preference.

Randomised clinical trials have been performed among patients who were eligible for OAC and therefore LAAC may be considered as an alternative to OAC for patients similar to those included in these studies. LAAC is certainly very useful in those patients who have suffered from life-threatening bleeding or are at high risk for bleeding and are therefore not candidates for long-term OAC. Also, the small group of patients who suffered from stroke despite OAC should be considered, perhaps even for a combined strategy. From a conceptual point of view, patients with moderate to high risk of both stroke and bleeding may likely benefit most from LAAC, but evidence from clinical trials regarding this patient population is not available. All patients with AF who do not receive any anticoagulation for various reasons should be considered for LAAC. Patients who undergo structural, electrophysiological or coronary interventions could also benefit. Figure 3 provides a modified algorithm of the European Heart Rhythm Society and the European Association of Percutaneous Cardiovascular Interventions 2014 [50].



**Figure 3**

Recommended algorithm for stroke prevention in patients with atrial fibrillation (reproduced modified from the 2014 expert consensus statement of the European Heart Rhythm Society and the European Association of Percutaneous Cardiovascular Interventions [50]). The additional strategy of LAAC centres on a risk/benefit evaluation of the optimal treatment for each patient. Hereby, it is supposed to contribute both to improved safety and efficacy outcomes as well as to offer protection from stroke and death to patients who have been left without any treatment so far. LAAC = left atrial appendage closure; NOAC = non-vitamin K-dependent oral anticoagulant; OAC = oral anticoagulation



**Figure 4**

Examples of procedure-related adverse findings in the TOE follow-up 4 months after LAAC.

The red arrow in panel A shows a device-adherent thrombus of 15 x 17 mm. After resumption of OAC, the thrombus had dissolved without clinical sequelae after 3 months (panel B, green arrow pointing on device surface). In panel C, the red arrow points towards a mobile thrombus of 12 x 5 mm which adheres to the central screw of the Amplatzer device. Also in this case, the thrombus could be dissolved by OAC without clinical consequences. The red arrow in panel D points at a residual shunt of 3 mm into the LAA due to suboptimal closure.

LAA = left atrial appendage; LAAC = left atrial appendage closure; OAC = oral anticoagulation; TOE = transoesophageal echocardiography

**Disclosure statement:** Bernhard Meier is a consultant to St. Jude Medical and has also received grants to the institution from St. Jude Medical. Steffen Gloekler has received grants to the institution from the Swiss Heart Foundation. Stephan Windecker has received grants to the institution from Abbott, Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences, and St Jude Medical.

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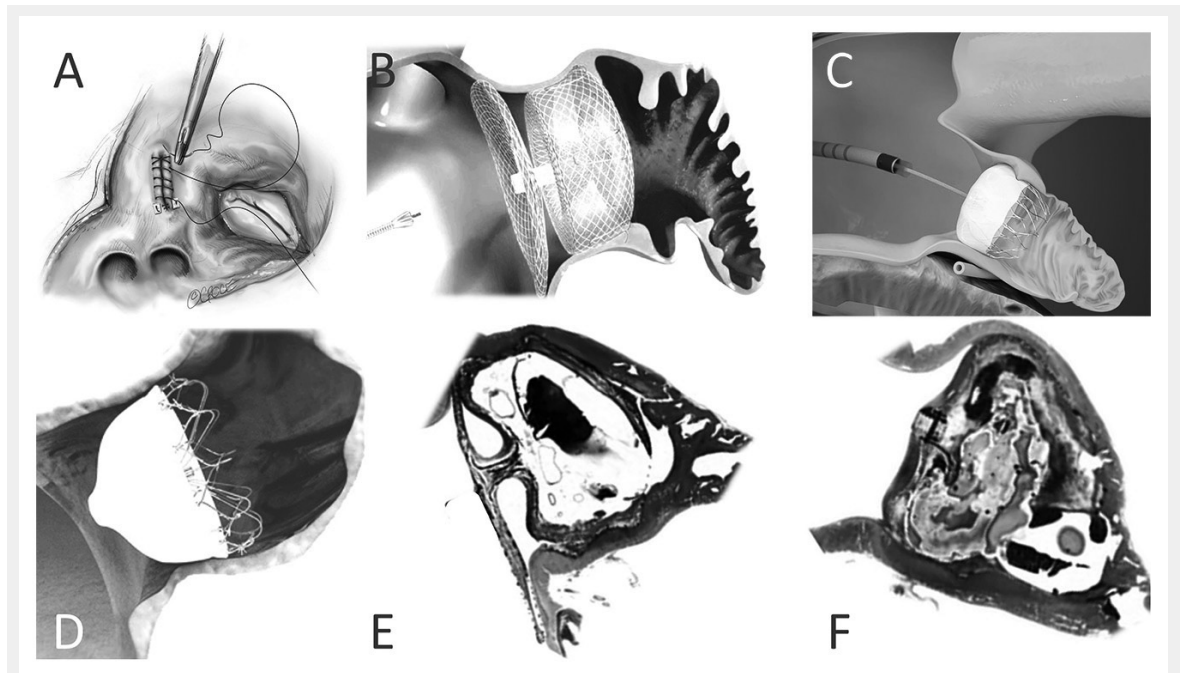
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## Figures (large format)



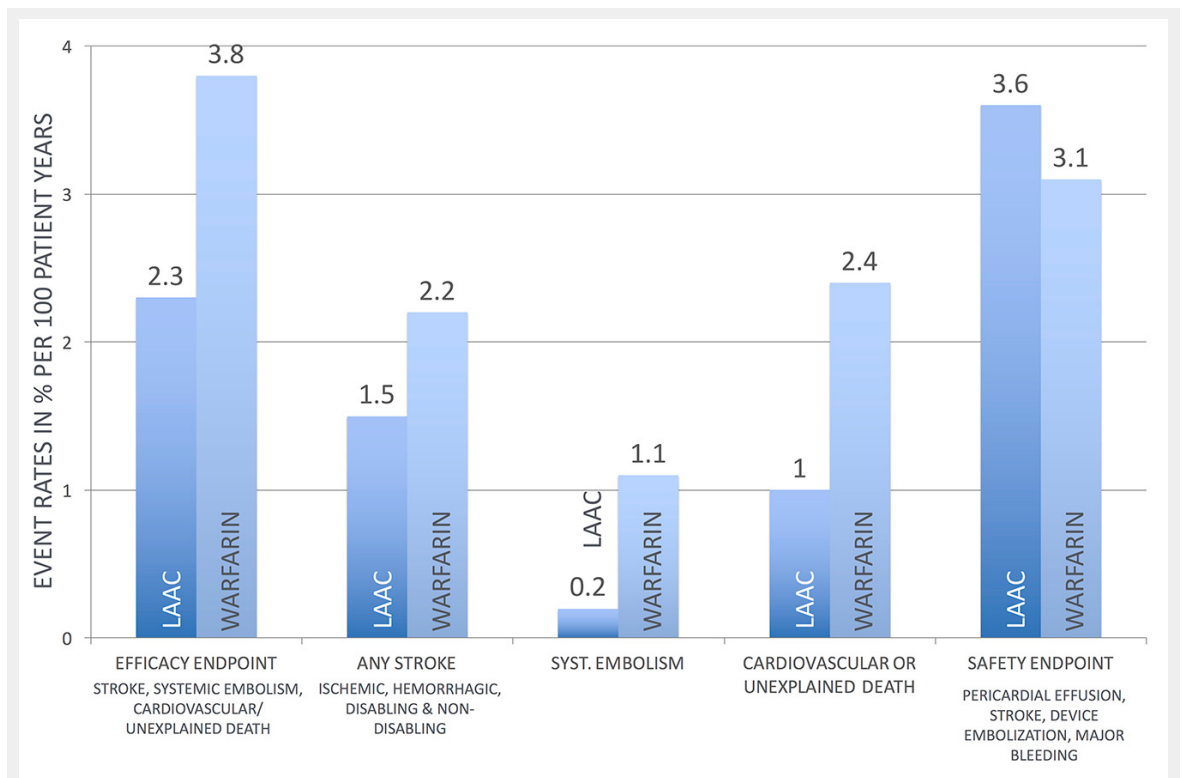
**Figure 1**

Different techniques, devices, and results for left atrial appendage closure (LAAC).

In panel A, surgical endocardial closure by exclusion with a double layer suture is depicted. Note the proximity of the left atrial appendage (LAA) to the left pulmonary veins (LPVs) and the mitral valve (MV). Derived and modified from Robertson et al. [71] © 2016 Beth Croce).

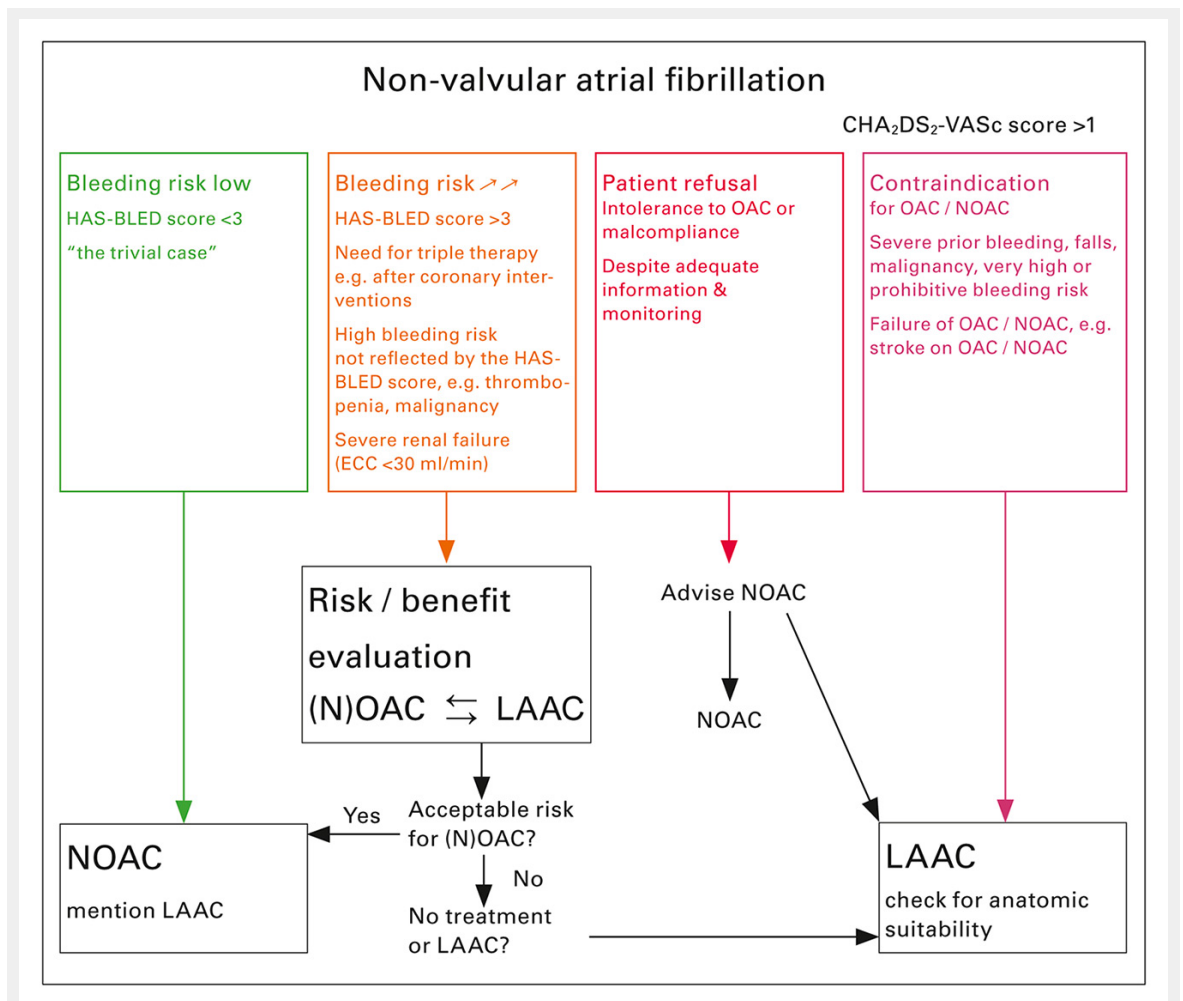
In panels B and C, the two most common devices for percutaneous LAAC are shown (B: derived and modified from St. Jude Medical, Minnesota, USA; C: Image provided courtesy of Boston Scientific. © 2016 Boston Scientific Corporation or its affiliates. All rights reserved).

In contrast to the Watchman, a membrane-cap device (C), the Amplatzer systems are plug-and-disc (pacifier) devices Panel D depicts another membrane-cap device, the Coherex Wavecrest (derived and modified from Coherex Medical, Utah, USA). In panels E and F, the Amplatzer and Watchman devices are shown after endocardialisation in anatomical preparations of canine models (derived and modified from Kar et al. [72] Impact of Watchman and Amplatzer devices on left atrial appendage adjacent structures and healing response in a canine model. *JACC Cardiovasc Interv.* 2014;7(7):801–9, with permission from Elsevier).



**Figure 2**

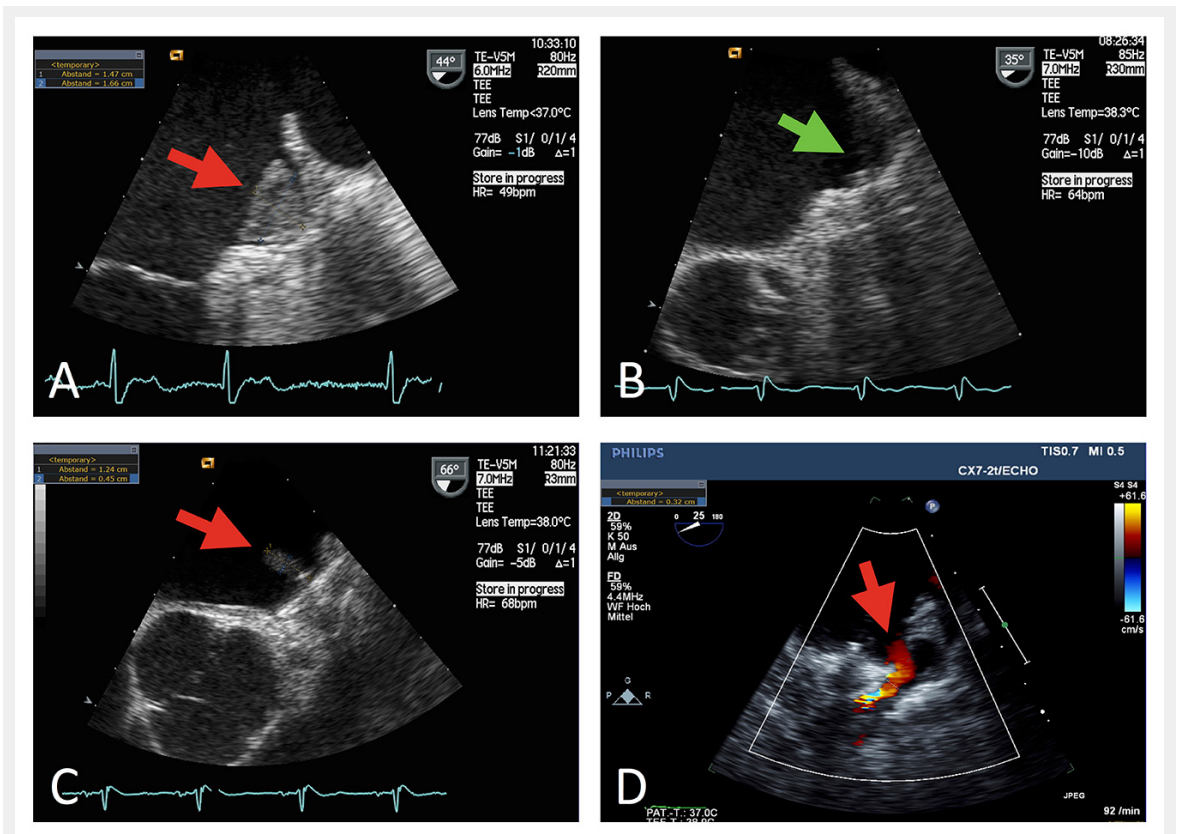
Primary outcomes of the Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT AF) study [54]. In comparison with warfarin, left atrial appendage closure (LAAC) with the Watchman was superior in preventing death, stroke, and systemic embolism. Due to periprocedural safety events, e.g., severe bleeding as a result of major pericardial effusion, device embolisation and stroke, LAAC with the Watchman device was not superior (yet not inferior either) to warfarin during a mean follow-up time of 3.8 years with regard to safety. For the first time, LAAC has not only shown superior results with regard to stroke prevention, but remarkably also with regard to all cause and cardiovascular mortality, indirectly pointing towards the hazards of oral anticoagulation. Data reproduced from Reddy et al. [54].



**Figure 3**

Recommended algorithm for stroke prevention in patients with atrial fibrillation (reproduced modified from the 2014 expert consensus statement of the European Heart Rhythm Society and the European Association of Percutaneous Cardiovascular Interventions [50]). The additional strategy of LAAC centres on a risk/benefit evaluation of the optimal treatment for each patient. Hereby, it is supposed to contribute both to improved safety and efficacy outcomes as well as to offer protection from stroke and death to patients who have been left without any treatment so far.

LAAC = left atrial appendage closure; NOAC = non-vitamin K-dependent oral anticoagulant; OAC = oral anticoagulation



**Figure 4**

Examples of procedure-related adverse findings in the TOE follow-up 4 months after LAAC.

The red arrow in panel A shows a device-adherent thrombus of 15 x 17 mm. After resumption of OAC, the thrombus had dissolved without clinical sequelae after 3 months (panel B, green arrow pointing on device surface). In panel C, the red arrow points towards a mobile thrombus of 12 x 5 mm which adheres to the central screw of the Amplatzer device. Also in this case, the thrombus could be dissolved by OAC without clinical consequences. The red arrow in panel D points at a residual shunt of 3 mm into the LAA due to suboptimal closure. LAA = left atrial appendage; LAAC = left atrial appendage closure; OAC = oral anticoagulation; TOE = transoesophageal echocardiography