CONTEMPORARY REVIEW

Left atrial appendage closure: A new technique for clinical practice

A John Camm, MD, FHRS,[*] Antonio Colombo, MD,[†] Giorgio Corbucci, PhD,[‡] Luigi Padeletti, MD[§]

From [*]Clinical Sciences, St. George's University of London, London, United Kingdom, [†]Catheterization Laboratory, EMO Centro Cuore Columbus and San Raffaele Hospital, Milan, Italy, [‡]Boston Scientific Italy, Milan, Italy, and [§]Department of Cardiology, University of Florence, Florence, Italy.

BACKGROUND/OBJECTIVE Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is associated with increased risk for stroke mainly due to cardiac embolism from the left atrial appendage (LAA). Occlusion of the LAA by means of a device represents a valid alternative to oral anticoagulation, mainly in patients who cannot tolerate this therapy because of a high bleeding risk. Recent data on the endocardial device WATCHMAN show encouraging results for this patient population in terms of stroke risk reduction compared to the expected rate as well as in terms of implant success. This article reviews all relevant publications related to the main surgical and transcatheter devices used for LAA closure (LAAC).

METHODS/RESULTS PROTECT-AF, the first prospective randomized trial conducted on this technique, showed that LAA occlusion using the WATCHMAN was noninferior to warfarin for a combined endpoint in patients with nonvalvular AF. There is a lack of large-scale randomized trials on long-term stroke risk in patients submitted to LAAC. Most studies are relatively small and focus on the comparison of different surgical techniques with regard to complete/incomplete closure success. More recently, PROTECT-AF long-term results (4-year follow-up) demonstrated that LAAC was statistically superior to warfarin in terms of efficacy.

CONCLUSION This review concludes that it is now appropriate to consider these techniques for patients with AF who are at high risk for stroke for whom effective conventional or novel anticoagulant therapy is not available or who present problems in managing drug treatment.

KEYWORDS Left atrial appendage; Left atrial appendage closure; Atrial fibrillation; Stroke risk; Thromboembolism

ABBREVIATIONS **ACP** = Amplatzer cardiac plug; **AF** = atrial fibrillation; **ESC** = European Society of Cardiology; **INR** = international normalized ratio; **LA** = left atrium; **LAA** = left atrial appendage; **LAAC** = left atrial appendage closure; **OAC** = oral anticoagulation; **TEE** = transesophageal echocardiography; **VKA** = vitamin K antagonism

Introduction

Most strokes in patients with atrial fibrillation (AF) result from thrombus formation in the left atrial appendage (LAA). Beinart et al[1] and Thambidorai et al[2] found up to 90% of thrombi in the LAA in patients undergoing cardioversion.

The LAA lies anteriorly in the atrioventricular sulcus in close proximity to the left circumflex artery, the left phrenic nerve, and the left pulmonary veins. The shape of the LAA is variable; four main morphologies can be identified: "cactus," "chicken wing," "windsock," and "cauliflower." LAA morphology appears to be associated with different degrees of thromboembolic risk.[3] Patients with non–chicken wing LAA morphology are significantly more likely to have an embolic event, even after controlling for comorbidities and $CHADS_2$ score.[3,4]

In addition to LAA structure and function, the size of the left atrium (LA), left ventricular function, disorders of coagulation,[5,6] endothelial dysfunction, platelet activation,[7–10] and many comorbid conditions play a relevant role in stroke risk. Several scores have been developed and recommended in clinical practice to determine whether anticoagulation therapy should be prescribed for prevention of ischemic AF-related stroke.[11] $CHADS_2$ and CHA_2DS_2-VASc, the two most popular scores for assessing the risk of ischemic stroke, are recommended by guidelines; they take into consideration the comorbid conditions of the patient with AF.[12–14]

A large proportion of patients with indications for oral anticoagulation (OAC) either are never prescribed the therapy[15] or stop the treatment because of side effects, advice from their physicians, or their own decisions related to quality of life or bleeding concerns. In the RE-LY

Dr. Camm is a consultant for and an advisor to Medtronic, St. Jude Medical, and Boston Scientific Corporation and is a member of the data safety monitoring board for a study by Biotronik GmbH, Berlin, Germany. Dr. Corbucci is an employee of Boston Scientific. Dr. Padeletti is a consultant for Medtronic, Boston Scientific Corporation, St. Jude Medical, and Sorin. **Address reprint requests and correspondence:** Dr. A. John Camm, Clinical Sciences, St. George's University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom. E-mail address: jcamm@sgul.ac.uk.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2013.11.030

(Randomized Evaluation of Long-term anticoagulant therapy) trial, 10% and 17% of patients treated with warfarin stopped the treatment at 1 and 2 years, respectively.[16] Similarly, 15% and 16% of patients treated with dabigatran 110 mg stopped the treatment at 1 and 2 years, respectively (21% if considering dabigatran 150 mg).[16] In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, 25% and 28% of patients discontinued apixaban and warfarin, respectively, during the trial.[17] Similarly, in the ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism [VKA] for prevention of stroke and Embolism Trial in AF) trial, 24% and 22% of patients stopped the treatment with rivaroxaban and warfarin, respectively, during the trial.[18] All patients who discontinue OAC are then treated with nothing or with antiplatelet therapy, unless the side effect is specific to a particular anticoagulant and therefore the patient becomes exposed to a high thromboembolic risk.

Warfarin and even more so the new OACs play a relevant role in reducing the thromboembolic risk associated with AF. On the other hand, inconsistent and inappropriate use, food–drug (VKA only) and drug–drug (VKA and novel OACs) interactions, and other side effects, particularly bleeding, must be considered when treatment based on anticoagulants is prescribed. Furthermore, as discussed earlier, some patients cannot be treated with anticoagulants because they have contraindications or are intolerant. Therefore, additional approaches to preventing AF-related stroke are needed.

Bleeding is also a clinically relevant adverse event in patients treated with antithrombotic therapy, and the physician must balance this risk with the risk of thromboembolism when deciding about OAC in patients with AF. The risk of bleeding can be determined using, for example, the HAS-BLED[19] or ATRIA[20] score. The 2012 update of the European Society of Cardiology (ESC) guidelines recommends using the HAS-BLED score to assess bleeding risk in AF patients, with a score ≥ 3 indicating high risk.

For all these reasons, surgical and transcatheter techniques have been explored to reduce the risk of stroke in persons with AF by excluding or occluding the LAA. Several methods can be used to close the appendage: direct suture during concomitant cardiac surgery, epicardial exclusion by stapling or clips, or endovascular occlusion by percutaneous application.

Nonpharmacologic treatments

The surgical approach

Amputation or obliteration of the LAA is considered in two possible situations: (1) as an additional procedure to either unrelated surgery or surgical MAZE procedures done specifically for management of AF, and (2) as an isolated closed chest (e.g., thoracoscopic) procedure.[21]

However, there is a lack of large-scale randomized trials on long-term stroke risk in patients submitted to surgical closure of the LAA. Most studies are relatively small and focus on the comparison of different surgical techniques with regard to complete/incomplete closure success. A larger randomized trial (Left Atrial Appendage Occlusion Study III [LAAOS III]) has been designed and is currently recruiting participants to evaluate the safety and efficacy of LAA removal in patients with AF undergoing heart surgery (Table 2).

Conclusions about stroke prevention by LAA exclusion or excision through surgery are still controversial.

The transcatheter approach

A technique that is intermediate between the surgical approach and the transcatheter approach is the endocardial/epicardial technique based on the LARIAT (SentreHEART Inc, Redwood City, CA) device.[22,23] The device is used for LAA ligation through a catheter (Figure 1D). Initial data on humans reported 96% implant success, and of the patients undergoing transesophageal echocardiography (TEE) at 1 year, there was 98% complete LAA closure (LAAC), including the patients with previous leaks.[22] Initial experience in the United States reported encouraging results in 25 patients, with 100% implant success and no strokes.[23]

To date, four devices with a purely endocardial approach have been investigated for LAA occlusion: the percutaneous LAA transcatheter occlusion (PLAATO) system (eV3, Plymouth, MN; Figure 1A), the Amplatzer cardiac plug (ACP) (St. Jude Medical, Minneapolis, MN; Figure 1B), the WATCHMAN device (Boston Scientific, Maple Grove, MN; (Figure 1C), and the Wavecrest System (Coherex Medical, Salt Lake City, UT; very little information available).[24]

All systems are delivered percutaneously through transseptal access to the LA.[24] Preprocedural evaluation of the LA and LAA, exclusion of thrombus, verification of placement, and evaluation of postprocedural pericardial effusion require skilled fluoroscopic and TEE coordination.[25] Cardiac magnetic resonance may offer some imaging advantages and help to select the type and size of device.[26,27] Computed tomography may also be a valid option to assist preoperative planning of LAA closure device placement.[28]

The PLAATO experience showed that, in a nonrandomized cohort, device implantation was feasible and safe, and, when compared with the historical stroke risk estimated using the $CHADS_2$ score, apparently cut the stroke rate by 40% to 65% in higher-risk AF patients. The PLAATO device has been discontinued for commercial reasons.

The ACP is a self-expanding device constructed from a nitinol mesh and polyester patch developed on the basis of Amplatzer double-disk septal occluders.[29] Patients implanted with this device are maintained on dual antiplatelet therapy with 1 to 3 months of clopidogrel followed by at least 5 months of aspirin. Limited data are available for the ACP, and the only randomized clinical trial that evaluated the device against optimal anticoagulation medical therapy (warfarin and dabigatran) is now underway.[30]

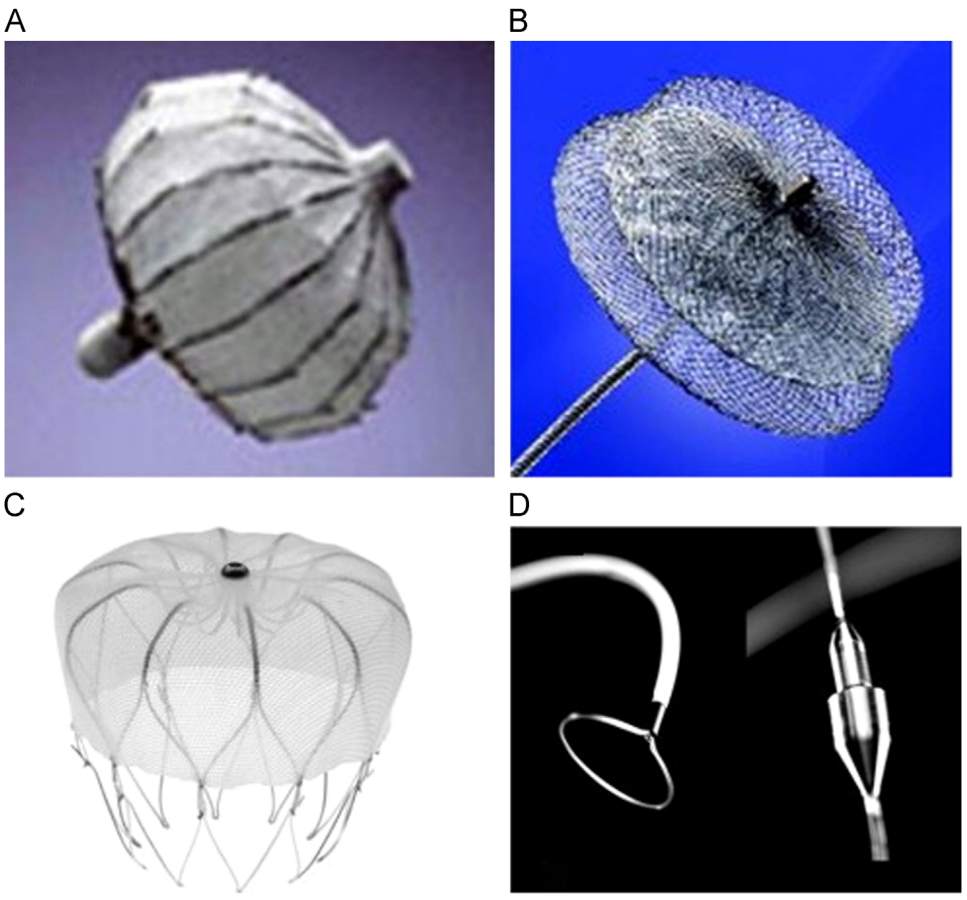

Figure 1 **A:** PLAATO. **B:** Amplatzer cardiac plug. **C:** WATCHMAN device, **D:** LARIAT. (From Chatterjee S, Alexander JC, Pearson PJ, Feldman T. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. Reproduced from Ann Thorac Surg 2011;92:2283–2292.)

In the initial European experience, the ACP device was successfully implanted in 96% (137/143) of patients in whom LAA closure was attempted. Serious complications were reported in 10 (7.0%) patients (ischemic stroke, device embolization, significant pericardial effusions). Minor complications were insignificant pericardial effusions, transient myocardial ischemia, and loss of the implant in the venous system. Interim data from the ACP European postmarket registry showed similar procedural success (96.5%) with no device embolization during the implant procedure.[31] Procedure-related adverse events were not significantly changed compared to the previous data (3 significant pericardial effusion, 3 device embolization, 1 cardiac perforation, 1 arteriovenous fistula). Three cases of thrombus on the device and one case of late device embolization were detected during the post 7-day follow-up.

The WATCHMAN device has a porous polyethylene terephthalate membrane on the proximal face of a self-expanding nitinol cage with fixation barbs for secure implantation within the LAA. The efficacy of this device has been evaluated in a large-scale trial, the only randomized study available at the present time for analyzing LAA closure by means of devices—WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF). The study randomized 707 patients with nonvalvular AF from 59 sites worldwide 2:1 to the WATCHMAN device. The study was designed to assess the noninferiority of the device against chronic warfarin therapy.[32] Patients $\geq$18 years with paroxysmal, persistent, or permanent nonvalvular AF were eligible for enrollment if they had a $CHADS_2$ risk score $\geq$1. Exclusion criteria included contraindications to warfarin, comorbidities other than AF that required chronic warfarin use, LAA thrombus, patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. Patients allocated to the intervention group were treated postimplant with warfarin for 45 days to facilitate device endothelialization, with the warfarin discontinued if 45-day TEE showed either complete LAAC or acceptable residual peri-device flow (jet $<$5 mm in width) (Figure 2). After warfarin treatment was stopped, once-daily clopidogrel (75 mg) and aspirin (81–325 mg) were prescribed until completion of 6-month follow-up visit, then aspirin alone was continued indefinitely. Patients in the control group received warfarin for the duration of the study, with monitoring of the target international normalized ratio (INR) between 2.0 and 3.0 at least every 2 weeks for 6 months and at least once per month thereafter. At 1.065 patient-years of follow-up, the trial showed that the efficacy of a strategy for percutaneous closure of the LAA was noninferior to that of chronic warfarin therapy (Figure 3), providing evidence for the role of the LAA in stroke

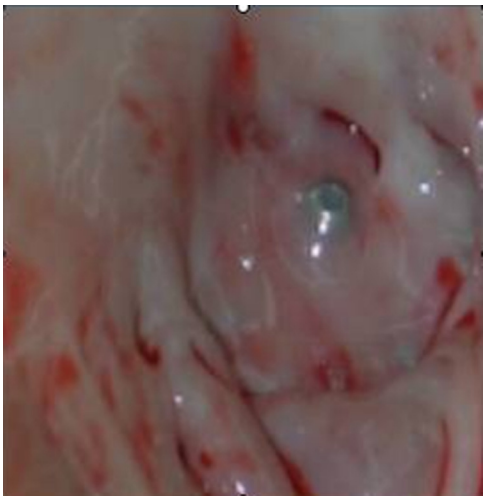

Figure 2 Endothelialization of the WATCHMAN device 9 months after the procedure. (From Sick PB, Schuler G, Holmes D, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. Reproduced from J Am Coll Cardiol 2007;49:1490–1495.)

pathogenesis and for a new treatment strategy. In the control group, the therapeutic INR range was achieved 66% of the time despite close INR follow-up. Although the advent of new OACs may improve the quality of medical treatment, the safety and efficacy of the device for LAA closure were well assessed in comparison with warfarin by this trial.

The influence of the operator's experience on the safety of percutaneous LAAC was assessed in an analysis of patients from the PROTECT-AF trial who underwent attempted device LAAC (n = 542 patients) and from a subsequent nonrandomized registry of patients undergoing WATCHMAN implantation (Continued Access Protocol [CAP] Registry; n = 460 patients).[33] The safety end-point included bleeding and procedure-related events (pericardial effusion, stroke, device embolization). There was a significant decline in the rate of procedure or device-related safety events within 7 days of the procedure across the two studies, with 7.7% and 3.7% of patients, respectively, experiencing events (with reduction of 52%, $P = .007$), and, between the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events ($P = .006$). These data have shown that complications associated with WATCHMAN implantation are typically clustered early in the periprocedural period and significantly decrease in frequency with operator experience.

Preliminary results of the Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) showed other encouraging data in terms of safety for the procedure performed with the WATCHMAN device. Implant success was 95%, and safety events (defined as acute [i.e., within 7 days] occurrence of death, ischemic stroke, systemic embolism, and procedure- or device-related complications requiring major cardiovascular or endovascular intervention) occurred in only 2.2% of patients. Of interest, a minimum of 20% of subjects were enrolled at new centers, and 25% of subjects were enrolled by new operators.[34]

Recently presented long-term follow-up data of the PROTECT-AF trial (4-year follow-up) have demonstrated a 40% relative risk reduction (combined end-point of all strokes, cardiovascular, or unexplained death and systemic embolism) in the WATCHMAN group compared to the control group (observed primary efficacy event rate 2.3% and 3.8%, respectively), with 96% posterior probability of superiority. Secondary analysis also showed a statistical superiority in all-cause mortality (34% relative risk reduction) and cardiovascular mortality (60% relative risk reduction).[35] Long-term efficacy from PROTECT-AF coupled with safety results of PREVAIL and CAP provide strong evidence that WATCHMAN, the most studied device for LAAC and the only one with randomized and long-term clinical data, may be a viable alternative to chronic warfarin therapy for stroke reduction in nonvalvular AF patients.

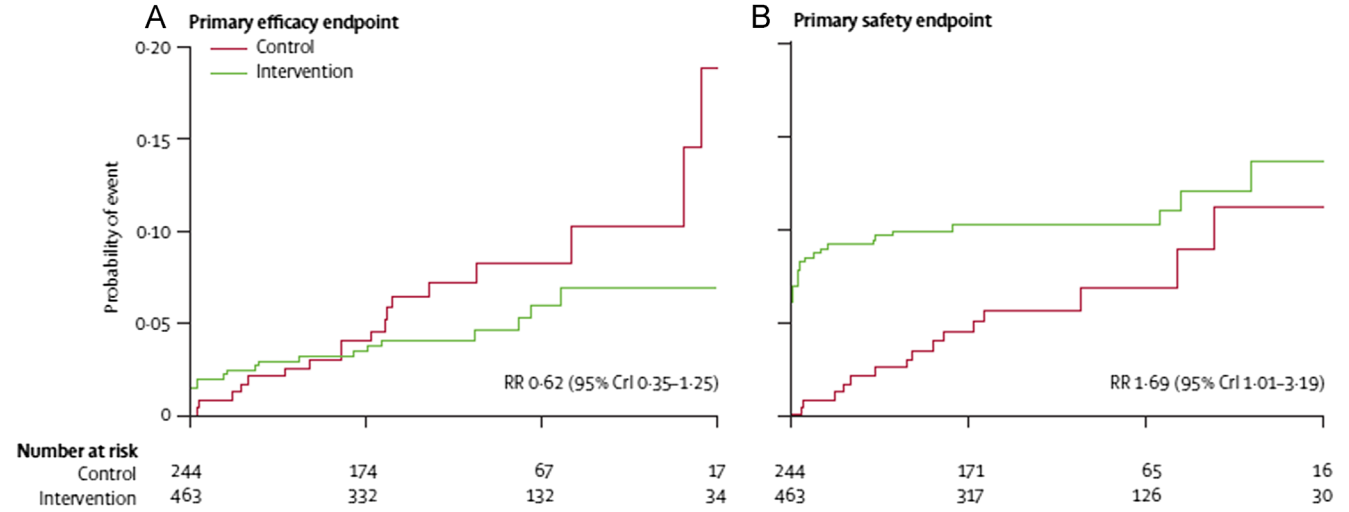

Figure 3 Kaplan-Meier curves of incidence of study end-points in intervention and control groups for the PROTECT-AF trial. (From Holmes DR, Reddy VY, Sick P, et al; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Reproduced from Lancet 2009;374:534–542.[32])

Table 1 $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores for ischemic stroke and bleeding risk stratification

$CHADS_2$			CHA_2DS_2-VASc			HAS-BLED		
	Risk Factor	Points		Risk Factor	Points		Risk Factor	Points
C	Congestive heart failure	1	C	Congestive heart failure	1	**H**	**Hypertension**	**1**
H	**Hypertension**	**1**	**H**	**Hypertension**	**1**	A	Abnormal liver and renal function (1 point each)	1 or 2
A	**Age ≥ 75 years**	**1**	**A_2**	**Age ≥ 75 years**	**2**	**S**	**Stroke**	**1**
D	Diabetes mellitus	1	D	Diabetes mellitus	1	B	Bleeding	1
S_2	**Previous stroke or TIA**	**2**	**S_2**	**Previous stroke or TIA**	**2**	L	Labile INR	1
			V	Vascular disease	1	**E**	**Elderly (age > 65)**	**1**
			A	**AGE 65-74 years**	**1**	D	Drugs or alcohol (1 point each)	1 or 2
			Sc	Sex (female gender)	1			

Hypertension is a common factor only if it relates to an ongoing disease and not to a history of the same.
Common factors are shown in bold.
INR = international normalized ratio; TIA = transient ischemic attack.

On the other hand, many AF patients at highest risk for embolic stroke may also have the greatest risk for hemorrhagic complications of anticoagulation (Table 1). Thus, patients with contraindications to OAC might benefit from LAAC; this was the objective of the ASA Plavix Registry (ASAP) study, which enrolled patients with contraindications to chronic warfarin treatment.[36] This prospective registry enrolled 150 patients with nonvalvular AF, $CHADS_2$ score ≥ 1 (mean 2.8 ± 1.2), and a contraindication to warfarin use. Postimplant, patients were discharged taking clopidogrel for 6 months and aspirin lifelong. At mean follow-up of 14.4 ± 8.6 months and 98% 1-year follow-up compliance, there were four strokes; five pericardial effusions, of which only two with tamponade required percutaneous drainage; and six instances of device-related thrombus by TEE, only one of which resulted in a clinical sequela [ischemic stroke]). The observed rate of ischemic stroke was 1.7% (Figure 4), corresponding to a 77% reduction from the expected event rate in patients with a similar $CHADS_2$ score treated with aspirin alone (7.3%) and a 64% reduction vs aspirin and lifelong clopidogrel (5.0%). The success rate of WATCHMAN implantation was 142 of 150 patients (94.7%). The authors concluded that WATCHMAN implantation without a warfarin transition might be safe and effective in AF patients with contraindications to even short-term OAC.

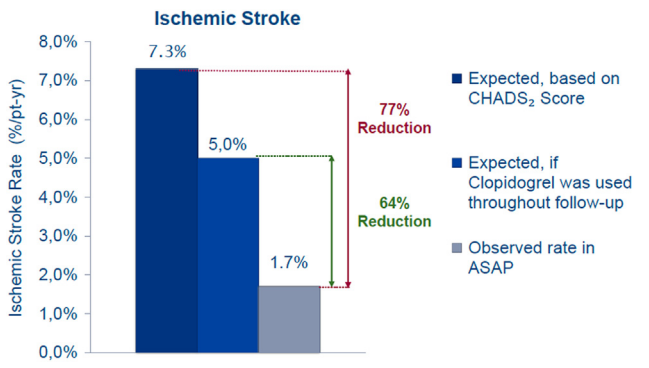

Figure 4 Observed rate of ischemic stroke in the ASAP registry (1.7%) compared to the expected event rate in patients with a similar $CHADS_2$ score treated with aspirin (7.3%) and if clopidogrel also was used (5.0%). (From Reddy VY, Möbius-Winkler S, Sievert H, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP Study). Reproduced from J Am Coll Cardiol 2013;61:2551–2556.[36]).

Conclusion

The endocardial approach may be considered a safe and effective alternative to OAC, especially when this treatment is contraindicated or when OAC may place patients at high risk for major bleeding. Noninferiority to standard anticoagulant treatment of LAAC with the WATCHMAN device has been proven by the PROTECT-AF trial.[32] Further clinical data will help to reinforce this result by enlarging the population of patients evaluated as well as by having longer follow-up data on patients treated with percutaneous devices in general. Further information is needed with regard to the efficacy and safety of LAAC in comparison to novel OAC drugs.

Current European guidelines recommend treating patients at risk for stroke with the appropriate antithrombotic therapy depending on the risk factors for stroke as evaluated by the CHA_2DS_2-VASc score and the risk of bleeding as assessed by the HAS-BLED score.[12] Physicians should pay attention to managing those patients with contraindications to OAC or

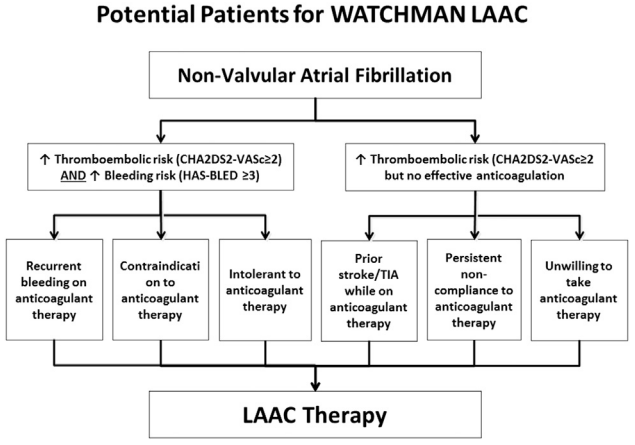

Figure 5 Main conditions when left atrial appendage closure (LAAC) alternative can be evaluated. TIA = transient ischemic attack.

Table 2 Ongoing trials on LAA occlusion/excision

Trial	Expected no. of patients	Intervention	Condition	Study design	Primary end-point	Status	Start date	Estimated completion date
LAAOSIII	4700	LAA occlusion (suture and/or surgical stapler)	AF and cardiac surgery with cardiopulmonary bypass	Randomized	Stroke or systemic arterial embolism	Recruiting	July 2012	May 2019
Safety and Efficacy of Left Atrial Appendage Occlusion Devices	150	Device: LARIAT Device: WATCHMAN	AF	Observational model: Case control	Effect of LAA occlusion by LARIAT device Effect of LAA occlusion by WATCHMAN device	Recruiting	May 2012	May 2018
ELIGIBLE	120	LAA occlusion with Amplatzer device	AF	Randomized	Combined overall mortality, major bleeding, stroke, or procedure-related complications	Recruiting	February 2012	July 2014
ISAR-AF	120	Percutaneous closure of LAA by a closure device (not specified) Catheter ablation of AF	AF	Randomized	Composite endpoint of all-cause death, thromboembolic events, major bleeding BARC type III, rehospitalization, severe symptoms due to arrhythmias	Recruiting	November 2010	November 2013
PLACE III	100	LARIAT suture delivery device and accessories	AF	Single group assignment	Rate of complete exclusion	Not yet recruiting	September 2012	March 2014
Exclusion of the Left Atrial Appendage (LAA) with the TigerPaw System (LAAx Inc)	60	Device: LAAx TigerPaw System	Stroke	Safety/efficacy study	Dual primary safety and effectiveness outcomes including rate of device-related adverse and serious adverse events and extent of complete exclusion of LAA with minimal residual cavity	Recruiting	August 2009	October 2010
LAAOSII	50	Surgical occlusion of LAA Best medical practice for AF/stroke prevention per guidelines	AF and stroke	Randomized	Demonstration of efficacy of cut-and-sew and stapler technique of appendage occlusion by intraoperative transesophageal echocardiography, central adjudication	Recruiting	August 2009	October 2013
Atrial and Brain Natriuretic Peptide Secretion After Percutaneous Closure of the Left Atrial Appendage	50	WATCHMAN LAA closure technology	AF and stroke	Efficacy study	Change from baseline plasma ANP and BNP levels after transcatheter closure of LAA	Not yet recruiting	May 2010	January 2012
AMPLATZER Cardiac Plug Clinical Trial	3000	Device: AMPLATZER cardiac plug Active comparator: Optimal medical therapy (control)	AF	Randomized	Acute safety Long-term safety Effectiveness end-point: Occurrence of ischemic stroke and peripheral thromboembolism	Recruiting	May 2010	June 2017
Left Atrial Appendage (LAA) Occluders After Catheter Ablation of Atrial Fibrillation	40	Device: LAA occlusion Procedure: Radiofrequency ablation	AF	Randomized	All stroke, systemic embolism, cardiovascular death	Recruiting	December 2011	December 2013
Safety and Effectiveness of Left Atrial Appendage Occlusion	37	AtriCure LAA exclusion system	AF	Safety/efficacy study	Safety: Device-related complications Efficacy: LAA occlusion	Not yet recruiting	September 2007	September 2012

AF = atrial fibrillation; ANP = atrial natriuretic peptide; BARC = Bleeding Academic Research Consortium; BNP = brain natriuretic peptide; LAA = left atrial appendage.

patients who must discontinue OAC treatment because of major bleeding. Patients who already have a documented history of major gastrointestinal bleeding or hemorrhagic stroke but have a high thromboembolic risk and ischemic patients with AF treated with drug-eluting stent who require triple antithrombotic therapy can be considered for this alternative option. The schematic chart shown in Figure 5 summarizes the main cases when LAAC alternative can be evaluated.

What next?

Any intervention that successfully prevents stroke will have a large impact on clinical practice and the health care system. Device therapy must be carefully considered, but there is still much to be done in order to understand the full value of this approach. It is crucial to know how many strokes can be prevented by excluding the LAA and which patients might benefit most from this procedure.

Table 2 lists the 11 LAA occlusion/excision trials that are ongoing. It demonstrates the high interest in this topic and the large volume of additional data needed to fully understand the phenomenon of clot formation and the best solutions for stroke prevention.

Studies comparing LAAC against the new direct OACs and against placebo in patients who cannot tolerate any form of anticoagulation must also be considered in order to complete the development of this therapy. Other studies will involve new designs of such devices and the systems developed to deliver them safely to the left atrial appendage.

At the present time, the evidence base on LAAC supports the use of LA occlusion in those patients who cannot be treated long term with OAC. The current ESC guidelines on AF management recommend that percutaneous LAAC "may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation." The cited level of evidence is "B." Although there is ample evidence of the value of device implantation in patients who can tolerate warfarin in order for the comparison to be made, there is only limited information relevant to patients refractory to or incapable of taking oral anticoagulants, and it is this latter group in which the unmet clinical need is dire and toward which the guideline recommendation was directed.

Acknowledgments

We thank Alberto Totaro, Matteo D'Acri, Marcella Peluso, and Laura Gillio Meina for sharing technical information.

References

1. Beinart R, Heist EK, Mansour M, et al. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2010;22:10–15.
2. Thambidorai SK, Murray RD, Klein AL, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). Am J Cardiol 2005;96:935–941.
3. Di Biase L, Santangeli P, Gaita F, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol 2012;60:531–538.
4. Kimura T, Takatsuki S, Inagawa K, et al. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low $CHADS_2$ scores. Heart Rhythm 2013;10:921–925.
5. SPAF Investigators. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. Ann Intern Med 1998;128:639–647.
6. AF Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. Arch Intern Med 1998;158:1316–1320.
7. Uemura T, Kaikita K, Ogawa H, et al. Changes in plasma von Willebrand factor and ADAMTS13 levels associated with left atrial remodeling in atrial fibrillation. Thromb Res 2009;124:28–32.
8. Duygu H, Barisik V, Kose S, et al. Prognostic value of plasma soluble CD40 ligand in patients with chronic non-valvular atrial fibrillation. Europace 2008;10:210–214.
9. Alberti S, Angeloni G, Cerletti C, et al. Platelet-leukocyte mixed conjugates in patients with atrial fibrillation. Platelets 2009;20:235–241.
10. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999;82:547–555.
11. Fang MC, Go AS, Singer DE, et al. for the ATRIA Study Group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol 2008;51:810–815.
12. Camm AJ, Lip GY, Kirchhof P, et al. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719–2747.
13. Fuster V, Rydén LE, Wann LS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:e101–e198.
14. Puwanant S, Varr BC, Klein AL, et al. Role of the $CHADS_2$ score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. J Am Coll Cardiol 2009;54:2032–2039.
15. Nieuwlaat R, Capucci A, Crijns HJ, et al. on behalf of the European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries. The Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26:2422–2434.
16. Connolly SJ, Ezekowitz MD, Wallentin L, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–1151.
17. Granger CB, Alexander JH, Wallentin L, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992.
18. Patel MR, Mahaffey KW, Califf RM, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–889.
19. Pisters R, Lane DA, Lip GY, et al. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest 2010;138:1093–11100.
20. S Go A, Hylek EM, Singer DE, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study FREE. JAMA 2001;285:2370–2375.
21. Odell JA, Blackshear JL, Orszulak TA, et al. Thoracoscopic obliteration of the left atrial appendage: potential for stroke reduction? Ann Thorac Surg 1996;61:565–569.
22. Bartus K, Han FT, RJ, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108–118.
23. Massumi A, Chelu MG, Masekh A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. Am J Cardiol 2013;111:869–873.
24. Cruz-Gonzalez I, Yan BP, Lam YY. Left atrial appendage exclusion: state of the art. Cathet Cardiovasc Interv 2010;75:806–813.
25. Budge LP, Shaffer KM, Mangrum JM, et al. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: a direct comparison of transesophageal echocardiography, planar cardiac CT, and segmental three dimensional cardiac CT. J Interven Card Electrophysiol 2008;23:87–93.
26. Mohrs OK, Wunderlich N, Kauczor HU, et al. Contrast-enhanced CMR in patients after percutaneous closure of the left atrial appendage: a pilot study. J Cardiovasc Magn Reson 2011;13:33.

27. Hong SN, Rahimi A, O'Halloran TD, et al. Cardiac magnetic resonance imaging and the WATCHMAN device. J Am Coll Cardiol 2010;55:2785.
28. Wang Y, Di Biase L, Natale A, et al. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. J Cardiovasc Electrophysiol 2010;21:973–982.
29. Park JW, Bethencour A, Leithäuser B, et al. Left atrial appendage closure with Amplatzer cardiac plug in AF: initial European experience. Catheter Cardiovasc Interv 2011;77:700–706.
30. AMPLATZER cardiac plug clinical trial. Available at: http://clinicaltrials.gov/ct2/show/record/NCT01118299?term = LAA+ACP&rank = 3.
31. Park J, Sievert H, Omran H, et al. TCT-112 interim data from Amplatzer Cardiac Plug Registry. J Am Coll Cardiol 2011;58(20 s1):B33-B33.
32. Holmes DR, Reddy VY, Sick P, et al. PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet 2009;374:534–542.
33. Reddy VY, Holmes D, Kar S, et al. Safety of percutaneous left atrial appendage closure: results from the WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123:417–424.
34. Holmes, DR. Randomized Trial of LAA Closure vs Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL). CIT. CNCC, Beijing, China. 20 March 2013. Interventional Innovation Summit Lecture.
35. Reddy V, Doshi S, Sievert H, et al. Long term results of PROTECT-AF: the mortality effects of left atrial appendage closure versus warfarin for stroke prophylaxis in AF. Heart Rhythm Society 2013 LBCT Scientific Sessions, May 9, 2013, Denver, Colorado.
36. Reddy VY, Möbius-Winkler S, Sievert H, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP Study). J Am Coll Cardiol 2013;61:2551–2556.