

The Next Wave of LAA Occlusion Technologies

Interventional stroke prevention in patients with atrial fibrillation.

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Patients with atrial fibrillation (AF), whether paroxysmal, persistent, or permanent, are at a several-fold increased risk of thromboembolic events compared to patients with sinus rhythm.¹ Strokes in patients with AF come with an increased risk of permanent mental and physical disability; risk of stroke and the clinical effects become more dramatic with increasing age. The risk for individual patients can be calculated by employing the CHA₂DS₂-VASc score; several online calculators and mobile apps are available to incorporate this score into everyday practice.

Current guidelines recommend lifelong oral anticoagulation for patients with an annual stroke risk in excess of 2%. Newly available direct, oral anticoagulants (eg, non-vitamin K oral anticoagulants [NOAC]) do not need continuous INR monitoring. Both randomized trials, as well as large registries, have shown NOAC to exhibit an improved safety profile regarding intracerebral bleeding compared to warfarin, yet gastrointestinal and other major bleedings occur at a similar rate if NOAC are used in appropriate doses.²⁻⁴ Single- or dual-antiplatelet therapy does not provide effective stroke prevention and is therefore not an alternative.⁵ Individual bleeding risk can be calculated by several scores, including the HAS-BLED and the recently published ORBIT score⁶; the latter takes the need for prolonged antiplatelet therapy after intervention for acute coronary syndrome into account.

INDICATION AND DATA

Specifically, patients with a history of gastrointestinal, brain, bladder, or skin bleeding; other conditions predisposing to bleeding, such as liver cirrhosis or severe renal failure (glomerular filtration rate < 30 mL/min); or a need for continuous antiplatelet therapy due to significant coronary heart disease, are candidates for alternative treatment strategies to anticoagulant drug therapy. Data from the transesophageal echo series prior to cardioversion found that 90% of thrombi originate from the left atrial append-

age (LAA; “nonvalvular AF”). It is only in the presence of mitral stenosis (“valvular AF”) that 50% of thrombi originate from the free left atrial cavity.⁷ This observation has led to the development of interventional LAA occlusion, which began in 2002 with publication on the first 15 patients who received the PLAATO device. Prospectively collected data, including randomized trials and registries, are now available for the single-disc Watchman device (Boston Scientific Corporation). The PROTECT AF trial has the longest follow-up, with 463 patients receiving the Watchman device between 2004 and 2008. These patients benefited at the 4-year follow-up data analysis compared to 244 patients treated with warfarin. Both cardiovascular mortality, as well as all-cause mortality, was not only noninferior, but also superior, in the device group compared to the warfarin treatment arm.⁸ Continuous access registries performed in the United States, as well as several prospective registries, including the ASAP trial in Europe, demonstrated an increase in safety and reduction of periprocedural complications with growing expertise, even when dual-antiplatelet therapy was used during the follow-up period.⁹ The latest randomized trial on LAA occlusion, PREVAIL, was designed to test current training standards and implantation techniques to reduce periprocedural risk, even in new centers, compared to the initial phase of the PROTECT AF trial. Periprocedural risk, including pericardial effusion, peri-interventional stroke, vascular complications, and major bleeding, decreased from 8.7% in the PROTECT AF trial to 4.2% in the PREVAIL trial.¹⁰ The Watchman LAA occluder was approved by the FDA in March 2015, “For patients that are indicated for oral anticoagulation, but have an appropriate reason to seek a non-drug alternative to warfarin.”

European guidelines published in 2012 recommend LAA occlusion for patients with an absolute or relative contraindication for oral anticoagulation; effectively, this is a very similar patient population as noted in the recent FDA approval. The largest prospective patient cohort was collected by 50 centers in Europe between October 2013

TABLE 1. CURRENTLY AVAILABLE LAA OCCLUDER DEVICES

Device	No. of Discs	Approval Status (United States)	Approval Status (European Union)
Watchman	Single	FDA approval, March 2015	Initial CE Mark, 2005; extended CE Mark, August 2012
Watchman Flx (Boston Scientific Corporation)	Single	No	CE Mark, November 2015
Amplatzer Cardiac Plug (St. Jude Medical)	Dual	No	CE Mark, December 2008
Amplatzer Amulet (St. Jude Medical)	Dual	No	CE Mark, January 2013
CohereX Wavecrest (Biosense Webster)	Single	No	CE Mark, September 2013 device modification; new CE Mark, September 2015
LAMBRE (Lifetech Scientific Corporation)	Dual	No	Expected 2016
Occlutech	Single	No	Expected 2016
Lariat device (SentreHeart, Inc)	Epicardial	FDA safety alarm communication, July 2015	CE Mark, October 2015

and May 2015: 1,019 patients who were scheduled for LAA occlusion with the Watchman device were included in the EWOLUTION registry.¹¹ Initial results are now published as an American Heart Association fast track manuscript in the *European Heart Journal*.¹² Implantation success was 98.5%, with a 7-day procedure- and device-related serious adverse event rate of 2.8%. Interestingly, 62% of patients were deemed to be ineligible for oral anticoagulation; this patient group had not been included in the previous trials. Patients who were ineligible for oral anticoagulation had even lower 7-day serious adverse event rates compared to the group eligible for oral anticoagulation. Sixty percent of patients in the EWOLUTION registry were treated with dual-antiplatelet therapy during follow-up, with further results to be presented at the upcoming international meetings.

The Amplatzer Cardiac Plug LAA dual-disk occluder has been available in Europe since 2008. A large, investigator-driven retrospective registry analysis on 1,047 patients published in 2015 found that LAA occlusion in this patient cohort reduced thromboembolic events to 2.2%. At 1-year follow-up, the observed stroke risk of 2.7% was lower than expected from the mean CHA₂DS₂-VASc score (5.6%).¹³ In summary, these retrospective data also support LAA occlusion to be feasible, safe, and effective.

CURRENTLY AVAILABLE DEVICES AND TECHNIQUES

The current status of the most advanced device developments is summarized in Table 1, while recent reviews describe the range of available devices.^{14,15} The Amplatzer

Amulet dual-disk device has been used since 2013 and has replaced the Amplatzer Cardiac Plug in Europe. Investigator-initiated registries found the device to be deliverable with a high success rate, device and implantation technique modifications have reduced embolization rates and residual leaks, and thrombus formation is infrequently observed with the Amplatzer Amulet dual-disk device.

The Watchman Flx device became available in November 2015 in Europe and has undergone major modifications (summarized and shown in Figure 1). Increased radial strength and two rows of J-shaped, atraumatic anchors, in combination with a closed-loop design at the distal part of the device, are aimed to increase safety and allow for full recapture and repositioning. In addition, the device can now be employed in two versions: with an oversizing of 30%, the device has similar depth to the previous generation Watchman, anchoring in a distal, mostly anterior/superior LAA lobe. At 10% compression, the device has a depth of only half the diameter, which allows for proximal positioning, but still safe anchoring. With the previous generation of Watchman devices, oversizing of up to 30% successfully decreased residual leaks and the need for device size changes.¹⁶ The Watchman Flx may need much less compression during implantation (Figure 1); in fact, the increased radial force of the device appears to lead to a proximal movement of the device during release from the delivery sheath if the distal lobe used as a landing zone has a small diameter; this can be regarded as a new safety feature. Therefore, the default sizing strategy for the Watchman Flx may be to aim for 10% compression with most LAA anatomies.

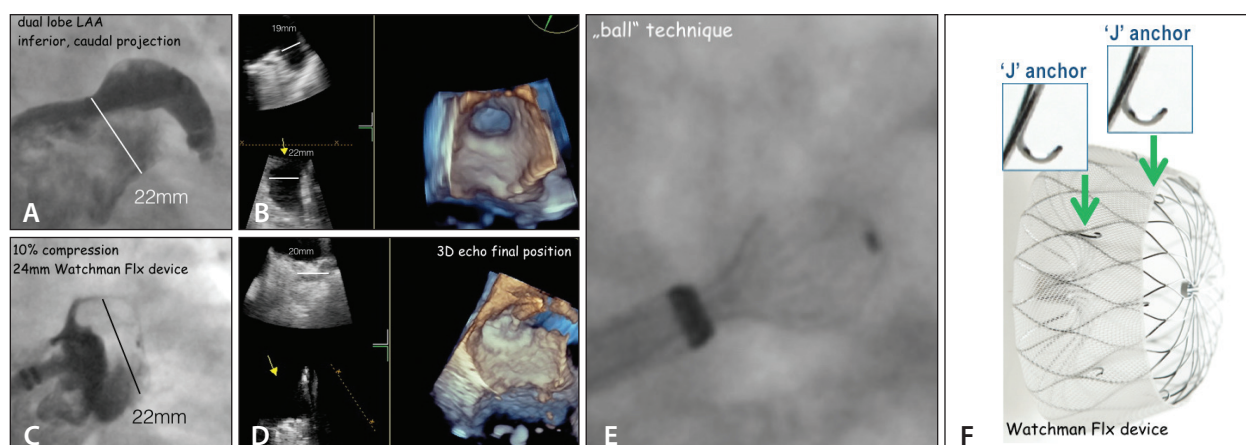


Figure 1. Exemplary implantation of the Watchman FLX device is shown. Typical LAA anatomy with two lobes and a difficult-to-interpret, proximal tissue ridge between the two lobes (A). Three-dimensional echo imaging of the oval-shaped LAA ostium (B). Successful closure, as judged by angiography and echocardiography of the LAA employing the new device features of increased radial force, dual rows of anchors, and reduced depth if implanted with only 10% compression (C and D). The device forms a bulb or “ball” when partially released due to the distal closed-loop design, allowing for safe antegrade negotiation of the LAA depth (E). Design specifics of the new Watchman FLX with the polyethylene terephthalate fabric covering 90% of the device, two rows of J-shaped anchors, an 18-strut frame, and a recessed metal screw on the proximal face (F).

The third CE Marked device available in Europe is the Coherex Wavecrest device, which was recently acquired by Biosense Webster. The single-disc device is positioned in the LAA neck; anchors are rolled out in a second step after confirmation of sealing. LAA sealing is checked by contrast injection through an extra channel distal to the device. As with the other devices, a larger number of implantations and prospective registries are required to judge the device on procedural success, periprocedural complication rates, and long-term results.

The CE Marked Lariat device was used for LAA closure in the United States in past years; it was not specifically approved for this purpose, but it was cleared as a surgical tool to deliver a pretied stitch (ie, suture) to aid in soft tissue closure during surgery. A screening CT is required to assess suitability of the LAA anatomy, and around 60% to 80% of patients are positively screened. The device requires epicardial, as well as intracardial LAA access, to deliver a suture ring over a magnetic rail to the neck of the LAA. On July 13th, 2015 the FDA alerted patients and health care providers of patient deaths and other serious adverse events related to the use of the Lariat device for LAA closure.

Two devices are currently in CE Mark trials, namely the LAmbré two-disk device and the Occlutech LAA occluder single-disk device. These devices have specific design features to overcome certain challenges in successful LAA occlusion due to the highly variable LAA anatomy. It would be beneficial to gain experience regarding device delivery, release, and sealing, as well as thrombus formation on the surface of the device, which currently occurs in approxi-

mately 5% of patients during follow-up. Thrombus formation appears to be independent from a postimplantation anticoagulation regimen, but rather related to general thrombus risk of the patient. So far, most thrombi detected during follow-up transesophageal echocardiography resolve with a 4-week course of low-molecular-weight heparin and are not associated with an increased stroke risk.

OUTLOOK FOR LAA OCCLUSION

Because AF is still increasing in prevalence, LAA occlusion is increasingly part of the treatment algorithm in these patients. Due to the unresolved issue of major bleeding with all available oral anticoagulants and the increasingly clear benefits of more aggressive, long-term antiplatelet therapy to be required in patients with coronary heart disease, LAA occlusion is likely to be used more frequently in the near future. Devices need to show low periprocedural complication rates, short procedure times, and successful, long-term LAA closure. Currently, these aims are best achieved with the procedure being performed in experienced centers with the operator being familiar with at least one of the available devices, with each achieving > 95% implantation success rates. Imaging with correct visualization and measurement of the LAA ostium, possibly employing three-dimensional echo imaging techniques, may further improve procedural success. Similar to the transcatheter heart valve field, some centers have started to routinely use CT for screening and LAA imaging. Specific software tools have been developed to use these data sets in procedure planning. Furthermore,

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the cost effectiveness of LAA occlusion for stroke prevention, in comparison to warfarin at 10 years and NOAC at 5 years, has recently been established based on the available data from randomized LAA occluder trials and current cost calculations.¹⁷ Patient comfort, independence from drug compliance issues, and no need for special perioperative considerations, added positively to the equation regarding procedural risk versus benefit.

CONCLUSION

Interventional LAA occlusion for stroke prevention is a rapidly growing field with an interest among electrophysiologists, interventionalists, and structural heart specialists. The newly available, fourth-generation devices will allow for further improvement in safety and ease of the procedure from start to finish. Preprocedural imaging for procedure planning may shorten procedure duration and improve sealing. LAA occlusion is a viable alternative to long-term oral anticoagulation in patients with AF requiring stroke protection in the absence of mitral valve stenosis. ■

1. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of AF: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369-2429.
2. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular AF. *Circulation*. 2015;131:157-164.
3. Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with AF treated with rivaroxaban or warfarin: ROCKET AF trial. *J Am Coll Cardiol*. 2015;66:2271-2281.
4. Maura G, Biotiere PO, Bouillon K, et al. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular AF patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study. *Circulation*. 2015;132:1252-1260.
5. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with AF. *N Engl J Med*. 2011;364:806-817.
6. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in AF. *Eur Heart J*. 2015;36:3258-3264.
7. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with AF. *Ann Thorac Surg*. 1996;61:755-759.
8. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for AF: a randomized clinical trial. *JAMA*. 2014;312:1988-1998.
9. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA plavix feasibility study with Watchman left atrial appendage closure technology). *J Am Coll Cardiol*. 2013;61:2551-2556.
10. Holmes DR, Jr, Doshi SK, Kar S, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in AF: a patient-level meta-analysis. *J Am Coll Cardiol*. 2015;65:2614-2623.
11. Boersma LV, Schmidt B, Betts TR, et al. EWOLUTION: design of a registry to evaluate real-world clinical outcomes in patients with AF and high stroke risk treated with the Watchman left atrial appendage closure technology. *Catheter Cardiovasc Interv*. 2015;Epub ahead of print. doi: 10.1002/ccd.26358.
12. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry [published online ahead of print (January 27, 2016)]. *Eur Heart J*. doi:10.1093/eurheartj/ehv730.
13. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in AF: multicentre experience with the AMPLATZER cardiac plug. *EuroIntervention*. 2015;10.
14. Feldmann KJ, Arshi A, Yakubov SJ. An overview of left atrial appendage occlusion devices. *Curr Cardiol Rep*. 2015;17:22.
15. Bergmann MW, Landmesser U. Left atrial appendage closure for stroke prevention in non-valvular AF: rationale, devices in clinical development and insights into implantation techniques. *EuroIntervention*. 2014;10:497-504.
16. Meincke F, Schmidt-Salzmann M, Kreidel F, et al. New technical and anticoagulation aspects for left atrial appendage closure using the Watchman device in patients not taking warfarin. *EuroIntervention*. 2013;9:463-468.
17. Reddy VY, Akehurst RL, Armstrong SO, et al. Time to cost-effectiveness following stroke reduction strategies in AF: warfarin versus NOACs versus LAA closure. *J Am Coll Cardiol*. 2015;66:2728-2739.

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