

Left atrial appendage occlusion for stroke prevention in atrial fibrillation in Europe: results of the European Heart Rhythm Association survey

Gregory Y.H. Lip^{1*†}, Nikolaos Dagres^{2†}, Alessandro Proclemer³, Jesper Hastrup Svendsen⁴, Laurent Pison⁵, and Carina Blomstrom-Lundqvist⁶, conducted by the Scientific Initiative Committee, European Heart Rhythm Association

¹University of Birmingham Centre for Cardiovascular Sciences, City Hospital Birmingham, England, UK; ²Second Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; ³Department of Cardiothoracic Science, University Hospital S. Maria della Misericordia, Udine, Italy; ⁴Department of Cardiology, The Heart Centre, Rigshospitalet, University of Copenhagen and The Danish National Research Foundation Centre for Cardiac Arrhythmia, Denmark; ⁵Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands; and ⁶Department of Cardiology, Institution of Medical Science, Uppsala University, Sweden

Received 25 November 2012; accepted after revision 26 November 2012

The purpose of this EP wire survey was to assess clinical practice in relation to the use of left atrial appendage occlusion (LAAO) devices for stroke prevention in atrial fibrillation (AF) among members of the European Heart Rhythm Association research network. The average number of performed LAAO was 10.6 per year and most (73%) centres performed ≤ 10 procedures per year. We found that LAAO was being performed for stroke prevention in AF, for the most common indication being 'the patient has absolute contraindication to long term oral anticoagulants'. Among survey respondents, LAAO procedures are most often performed by interventional cardiologists. Experience varied widely, and this was reflected in the wide range of thromboembolic and procedural (tamponade, bleeding) complications reported by the respondents to this EP wire survey.

Keywords

Anticoagulation • Atrial fibrillation • Left atrial appendage occlusion • Stroke

Introduction

Stroke prevention is central to the management of atrial fibrillation (AF), and all contemporary guidelines have increased focus on the use of effective stroke prevention, which is oral anticoagulation therapy—whether given as vitamin K antagonist (e.g. warfarin) or one of the novel oral anticoagulants (NOACs).¹ Antiplatelet therapy has a minimal role, given its limited efficacy for stroke prevention, since the risk of bleeding is not different between aspirin and warfarin.^{2–4}

However, some patients have absolute contraindications of any antithrombotic therapy use, and left atrial appendage occlusion (LAAO) has been proposed as a means to reduce the risk of stroke in these patients.^{1,5} Indeed, it is presumed that most thrombus forms in the left atrial appendage (LAA) and that occlusion of

the LAA would result in a reduced risk of stroke and thromboembolism in AF.

The 2012 focused update of the European Society of Cardiology guidelines on AF¹ recommends that LAA closure may be considered in patients with high stroke risk contraindications for long term oral anticoagulation (Class IIb recommendation). Also, surgical excision of the LAA may be considered in patients undergoing open heart surgery (Class IIb recommendation).

The purpose of this EP wire survey was to assess European clinical practice in relation to the use of LAAO devices for stroke prevention in AF. We were interested in LAAO as a management strategy, and thus did not focus on the type of device *per se*—as we recognized that there were a number of LAAO devices available for use.⁵

* Corresponding author. Tel: +44 121 5075080; fax: +44 121 5544083. Email: gy.h.lip@bham.ac.uk

† These authors contributed equally to the study.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com.

Results

Thirty-six centres participated in this survey and of these, 24 (67%) performed LAAO. The average number of LAA occlusion performed on average each year in the 24 centres performing LAAO (22 valid answers) was 10.6 ± 11.7 , ranging from 1 to 50. Most centres (73%) reported performing ≤ 10 procedures.

The primary operator in the 24 centres performing LAAO were the electrophysiologist [seven of 24 responses (29%)], with the interventional cardiologist (i.e. angioplasty/stent specialist) in 37.5% (in 9 of 24). Dual cardiologist operators (i.e. interventionist and electrophysiologist) performed the procedure in 6 of 24 (25%), while 'other operators' (i.e. non-intervention/non-electrophysiologist) were reported in 2 of 24 (8%).

Of the usual indication(s) for LAAO (all 36 replying centres considered), the most common answer was 'patient has absolute contraindication to long term oral anticoagulants' (31 of 36, i.e. 86%). Other answers included the procedure being performed as concomitant procedure in patients undergoing AF ablation procedure, $n = 3$ (8%), and 'the patient asks for it' in 2 (6%).

Peri-procedural practice

In the 24 centres performing LAAO, routine use of oral anticoagulants pre-procedure for >4 weeks was the norm in 9 (38%), while use of oral anticoagulants pre-procedure for 1–4 weeks was performed in 3 (13%). There were no oral anticoagulants before the procedure, but heparin on day of LAAO procedure was performed in seven centres (29%), with low molecular weight heparin being used in five centres (21%).

The LAAO procedure itself was performed in the 24 centres under sedation only in 12 (50%), and under general anaesthetic in the remaining 12 (50%). Transoesophageal echo pre- and post-procedure was performed for LAAO procedures in 23 (96%), but only pre-procedure in 1 (4%) centre.

Anticoagulation post-procedure

If an anticoagulant is used post-procedure, a vitamin K antagonist (e.g. warfarin) was used in nine (38%), subcutaneous heparin (e.g. low molecular weight) in three (13%), and a novel oral anticoagulant (e.g. dabigatran or rivaroxaban) was used in one (4%). This question was considered 'not relevant, as these patients are not suitable for oral anticoagulants' by 11 respondents (46%).

If oral anticoagulants were used post-procedure, this was administered for 4 weeks to 3 months, in nine (38%); for <4 weeks in two (8%), and for >3 months in two (8%). This question was considered 'not relevant, as these patients are not suitable for oral anticoagulants' by 11 respondents (46%).

Complications

Approximate rate (%) of thromboembolic cerebrovascular events (including peri-procedure ones) related to LAAO procedure over the last year (22 valid answers) was 0% in 16 centres, 0.5% in one centre, 5% in one centre, 7% in one centre, and 10% in two centres. In one centre, the response was 'one case so far'.

Approximate rate (%) of pericardial tamponade related to LAAO procedure over the last year (only the 24 centres performing LAAO were considered, with 22 valid answers) was 0% in 15

centres, $\leq 1\%$ in 2 centres, 5% in 2 centres, and 10% in 3 centres. Approximate rate (%) of major bleeding (including peri-procedure ones) related to LAAO procedure over the last year (22 valid answers) was 0% in 16 centres, 1% in 3 centres, $\leq 5\%$ in 2 centres, and 8% in 1 centre. Approximate rate (%) of device dislodgement related to LAAO procedure over the last year (22 valid answers) was 0% in 15 centres, 2–5% in 4 centres, 10% in 1 centre, and 20% in 2 centres.

Obstacles to widespread left atrial appendage occlusion use

These were scored, ranging from 1 = 'least important' to 5 = 'most important' (all 36 replying centres considered, 6 did not answer, so 30 valid answers), with the average scores as follows:

- Price is too high, that is, reimbursement issues: average 3.1 ± 1.5
- Limited efficacy data to show comparability for stroke against warfarin or new oral anticoagulants: average 2.8 ± 1.5
- Risk of complications e.g. tamponade and major bleeding: average 2.4 ± 1.3
- Too technically difficult procedure: average 2.3 ± 1.2

Discussion

In this EP wire survey, we have provided some insights into current practice in Europe for the use of LAAO procedures for stroke prevention in AF, although the low response rate is a limitation.

Of the responding centres, 67% performed LAAO with an average of 10.6 procedures, with most (73%) performing ≤ 10 procedures per year, either under sedation or under general anaesthetic. The procedure was largely performed by an interventional cardiologist for the most common indication being 'patient has absolute contraindication to long-term oral anticoagulants'. Despite the latter, oral anticoagulants were used pre-procedure for >4 weeks in 38%, and post-procedure in 54%. In a minority of centres (8%), LAAO was performed as a concomitant procedure in patients undergoing AF ablation.

Complications reported in the previous year varied widely, with pericardial tamponade in 1–10%, major bleeding in 0–8%, thromboembolism in 0–10%, and device dislodgement in 0–20%. In the PROTECT-AF randomized clinical trial,⁶ the use of an LAA occlusion device (WATCHMAN) was non-inferior to warfarin for the primary composite endpoint of stroke, cardiovascular death, and systemic embolism. However, there was an increased risk of adverse events particularly in the initial period, when performed in centres with low operator experience. In the Continued Access Protocol Registry,⁷ procedure time decreased, and the rate of serious complications was reduced with increasing operator experience. Indeed, some centres in this EP wire survey reported high complication rates, and could be related to operator and centre experience.

Post-LAAO device implantation, it is recommended that patients should be maintained on a short period of OAC and/or long-term antiplatelet therapy—and this practice was seen in our EP wire survey. Given that the risk of bleeding with antiplatelet therapy was similar to OACs,⁴ it remains uncertain how the LAA occlusion devices would perform when compared with NOACs.

One indirect comparison analysis suggests that use of the WATCHMAN device would fail to meet non-inferiority criteria compared with dabigatran.⁸ Also, the identified obstacles to widespread LAAO use were important, with reimbursement issues and limited efficacy data being listed as the most common issues.

The appraisal by the United Kingdom National Institute for Health and Clinical Excellent (NICE) concluded that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with non-valvular AF, although there is a risk of life-threatening complications (although low) from the procedure.⁹ The NICE appraisal recommended that the procedure may be used provided that patient selection should be carried out by a multidisciplinary team including a cardiologist and other appropriate clinicians experienced in the management of patients with AF at risk of stroke. It was also recommended that the procedure should only be carried out by clinicians with specific training and appropriate experience in the procedure, in units with on-site cardiac surgery.

In March 2009 the United States Food and Drug and Administration advisory committee meeting voted against approval of the WATCHMAN device for LAAO, requiring further study of the device.¹⁰ Other devices are available, the most common being the Amplatzer device or cardiac plug LAAO device.

Some arguments against LAAO for stroke prevention in AF have been made.¹¹ For example, the pathophysiology of stroke in AF may be related to a hypercoagulable state and systemic risk factors commonly in association with AF (e.g. diabetes and hypertension) contribute to stroke. Thrombus also forms in other sites apart from the LAA. Technical issues and safety remain of concern, although operator experience may overcome some of the high procedural complications during the 'learning curve'. The clinical results from non-randomized trials also do not prove that conclusive evidence exists to demonstrate that LAA exclusion reduces stroke in AF patients. Finally, there are no major surgical randomized trials of LAA closure published that examine stroke as the primary outcome in the surgical literature. The only randomized trial, PROTECT-AF⁶ was too small to conclusively claim non-inferiority to warfarin, reflected by the wide 95% confidence interval (0.36–1.76) for the efficacy outcome of greatest interest, stroke.

The availability of NOACs have changed the landscape of stroke prevention in AF, given that they offer efficacy, safety, and convenience compared with the VKAs.^{12,13} It remains uncertain how the LAAO devices would perform when compared with NOACs especially when used in patients where there is a contraindication to VKA therapy, although one NOAC (apixaban) has been investigated in a randomized trial that included patients with contraindications to VKAs.¹²

In conclusion, LAAO is being performed in some European centres for stroke prevention in AF, for the most common indication being 'the patient has absolute contraindication to long-term oral anticoagulants'. Experience varied widely, and this was

reflected in the wide range of thromboembolic and procedural (tamponade, bleeding) complications reported.

Acknowledgements

The production of this EP wire document is under the responsibility of the Scientific Initiative Committee of the European Heart Rhythm Association: Carina Blomström-Lundqvist (chairman), Philippe Mabo (co-chair), Maria Grazia Bongiorni, Nikolaos Dagres, Dan Dobreanu, Isabel van Gelder, Thorsten Lewalter, Gregory YH Lip, Germanas Marinkis, Laurent Pison, Alessandro Proclemer, and Jesper Hastrup Svendsen.

The authors acknowledge the EHRA Research Network centres participating in this EP wire. A list of the Research Network can be found on the EHRA website.

Conflict of interest: none declared.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the esc guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation * developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012; **14**:1385–413.
2. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011; **106**:739–49.
3. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011; **8**:602–6.
4. Friberg L, Rosengqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the swedish atrial fibrillation cohort study. *Eur Heart J* 2012; **33**:698–704.
5. Landmesser U, Holmes DR Jr. Left atrial appendage closure: a percutaneous transcatheter approach for stroke prevention in atrial fibrillation. *Eur Heart J* 2011.
6. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**:534–42.
7. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. 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**:417–24.
8. Kaul S, Cigolani E, Shehata M, Diamond GA. How does left atrial appendage occlusion using the watchman device compare to dabigatran for reducing thromboembolic events in patients with nonvalvular atrial fibrillation? *J Am Coll Cardiol* 2010; **55**:A4.E39 (abstract).
9. National-Institute-for-Health-and-Clinical-Excellence. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. *Interventional procedure guidance 349*. 2010: June 2010. <http://www.nice.org.uk/IP2310aoverview> (24 November 2012, date last accessed).
10. O'Riordan M. Watchman delayed: FDA wants more data on the LAA-closure device before approving. *The heart. Org. [clinical conditions > arrhythmia/ep > arrhythmia/ep]*; 19 March 2010. <http://www.Theheart.Org/article/1060779.Do> (24 November 2012, date last accessed).
11. Whitlock RP, Healey JS, Connolly SJ. Left atrial appendage occlusion does not eliminate the need for warfarin. *Circulation* 2009; **120**:1927–32; discussion 1932.
12. Ahrens I, Lip GY, Peter K. What do the re-ly, averroes and rocket-af trials tell us for stroke prevention in atrial fibrillation? *Thromb Haemost* 2011; **105**:574–8.
13. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clements A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012; **107**:838–47.