



## Atrial Fibrillation and Prophylactic Obliteration of the Left Atrial Appendage: Which is the Best Option?

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### Short Communication

Atrial fibrillation (AF) affects 2.3 million Americans and it is estimated that it causes approximately 15% to 20% of ischemic strokes [1]. The risk of stroke is low in those younger than 60 years but approaches 24% in those older than 80 years. The risk of stroke also correlates with increasing CHADS<sub>2</sub> (Congestive heart failure, hypertension history, Age >75yrs, diabetes and history of previous stroke or TIA) and CHA<sub>2</sub>DS<sub>2</sub>-VASc (as with CHADS<sub>2</sub> but age and previous stroke with doubled scores, inclusion of vascular disease and age 65-74 years and female sex category) [2]. Anticoagulation with Vitamin K inhibitors (warfarin) is effective in decreasing stroke risk, but is associated with an increased risk of bleeding; is relatively or absolutely contraindicated in approximately 40% of patients and there are issues with compliance and difficulty in maintaining a satisfactory therapeutic range. Newer oral anticoagulants (NOAC's) have additional issues associated with cost and lack of an antidote.

Relevant to the patient with AF who is unable to take anticoagulants (the 40% described above), the European Atrial Fibrillation Trial (EAFT) was an important study looking at secondary prevention of stroke in patients with non-rheumatic AF after transient ischemic stroke or minor stroke [3]. Of just over a thousand patients studied, two thirds were eligible for anticoagulation and of this group a third were randomized to anti-coagulation, aspirin alone or placebo. In the other randomized group -- those unable to take anticoagulation, half received aspirin and the other half placebo. In those patients receiving anticoagulants the stroke risk was 4%/y, In those receiving aspirin (both randomized groups) the risk was 10%/y and those on placebo only (both randomized groups) the risk was 12%/y. Described in another way, the patient who has had a previous stroke associated with AF and cannot take anticoagulants will have a 70% chance of having a stroke within 10 years [4].

The fore mentioned study prompted us to look at an option for treatment in this high risk group - the patient who could not take anticoagulation therapy. We hypothesized that those patients who were at high risk of stroke and could not take anticoagulants may benefit from obliteration of the left atrial appendage. Data from surgical, autopsy and transesophageal echocardiography (TEE) series of patients with AF relating to the location of thrombi within the left atrial appendage were reviewed. In patients with non-rheumatic AF 90% of thrombi were located within the left atrial appendage whereas in those patients with AF associated with rheumatic fever (RF), the thrombus was located solely in the atrial appendage in 57% [5]. In the same journal edition an experimental study of thoracoscopic obliteration of the left atrial appendage was described, and shown to be safe and feasible [6]. The hypothesis of left atrial appendage obliteration was in fact not original. In 1949 and 1950 two separate small series were described, but the procedure was not pursued further because of a high incidence of perioperative stroke, presumable due to manipulation of pre-existent thrombus, and post operative stroke (RF patients and echocardiography not yet available) [7,8].

Intuitively, the concept of atrial appendage obliteration to reduce thromboembolic events seems correct, but it would need to be proven. The procedure advocated would be a prophylactic one in which success is measured by an event that does not happen. We are already doing prophylactic procedures to reduce stroke - carotid endarterectomy, closure of a patent foramen ovale and coil embolization of intracerebral aneurysms. In medicine a randomized trial is regarded as the means to prove the hypothesis. Two options exist, to obliterate the atrial appendage in patients who are having cardiac or left-sided thoracic surgical procedures, or to obliterate the atrial appendage in warfarin ineligible patients who have had a previous thromboembolism. Using the 4% and 12% risk of stroke in the EAFT trial and using endpoints of stroke, embolism or major hemorrhage the option of obliteration of the appendage at the time of surgery would require a sample size in excess

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of a thousand patients. For the group of patients warfarin ineligible and assuming appendage obliteration would reduce events by 10% the sample size would be much smaller -- a group of 164 patients followed for two years [5].

The concept of left atrial appendage occlusion has been embraced by both the cardiologic and the surgical communities. The former have endeavored to develop intravascular and percutaneous approaches; the surgeons have developed, in addition to standard surgical approaches, devices to specifically close the atrial appendage. Prior to our report in 1996 there were 12 papers listed in PubMed using the search term "atrial appendage closure." Since then 612 papers are listed. If we use the term "left atrial appendage" the corresponding numbers are 659 and 3,338. Most papers deal with devices developed to obliterate the appendage, the assessment, technique of placement of these devices and complications. Lacking is definitive proof of efficacy.

## Transcatheter Approaches to Left Atrial Appendage Closure

These devices are introduced transvenously across the atrial septum and deployed within, or at the left atrial appendage ostium. The device is usually held in place by small hooks. Transesophageal echocardiography and installation of contrast is used to exclude thrombus within the appendage and to size the neck of the appendage.

The first device used was the PLAATO system (Percutaneous Left Atrial Appendage Transcatheter Occlusion) [9]. It comprised a self-expanding nitinol cage with an occlusive polytetrafluorethylene membrane laminated onto the frame. This product has been removed from the market.

The WATCHMAN device is currently the only percutaneously occlusion device approved in the United States, yet the approval process was not a smooth one. The initial study was the PROTECT-AF trial (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in patients with atrial fibrillation vs. long-term warfarin therapy) [10]. The trial randomized 707 patients with non-valvular AF in a 2:1 ration to either the device or long-term warfarin therapy. The primary combined endpoint included all causes of stroke, systemic thromboembolism and cardiovascular death. In 9.3% of those randomized to the device, the device was not implanted either because a device release criterion was not met or there was a procedural event. In 16.9%, warfarin was not discontinued after 45 days because of either thrombus on the device, incomplete closure or a peri-device jet greater than 5 mm. The trial was plagued by adverse events. Twenty-two patients had a serious pericardial effusion, there were 5 procedure related ischemic strokes and 3 device embolizations. The conclusion of the study was that the device was non inferior to warfarin on the basis of a significant reduction in hemorrhagic stroke (0.2% vs. 1%). Because of procedural complications, the risk profile of patients and confounding use of clopidogrel the FDA issued in 2009 a non-approval letter.

The device continued to be implanted by experienced operators who had participated in the PROTECT trial and these patients were studied in the CAP registry (Continuous Access Protocol) with a significant decline in the rate of safety events. This suggested that results could be improved with more experience [11].

The PREVAIL trial was very similar to the PROTECT trial, but included patients with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and excluded

pre-procedure clopidogrel. Approximately 40% of operators were new, but despite this the complication rate was lower indicating improvement in physician education. In 2013 the FDA gave a positive vote for safety (7 to 5), efficacy and benefit/risk, but a later panel raised efficacy concerns.

The data from the PROTECT, PREVAIL and CAP registries were combined in a Meta analysis [12]. Rates of hemorrhagic stroke, non-procedural bleeding and cardiovascular death were reduced in the device group. However, if peri-procedural complications are included, all-cause stroke and systemic embolism were similar. Additionally there was no significant difference in all-cause mortality or in major bleeding complications. Based on the data from the PROTECT and PREVAIL trials the WATCHMAN device was approved by the FDA in March 2015. The current FDA approval indication is as follows: patients with non-valvular AF who are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores, deemed by their physicians to be suitable for warfarin, but who "have an appropriate rationale to seek a non-pharmacologic alternative to warfarin."

Reports from a registry experience in patients ineligible for oral anticoagulation -- the ASAP study (Aspirin Plavix Feasibility study with WATCHMAN Left Atrial Appendage Technology) documented, at a median follow-up of 55.4 months, an annualized ischemic stroke or systemic embolism rate of 1.8%. This rate was lower than the expected 7.3% rate if they were receiving aspirin alone, suggesting that the device may be safely used without anticoagulation.

There are a number of other similar transcatheter devices that have CE mark approval in Europe, the Amplatzer and Amulet Cardiac Plug, the Wavecrest device, Occultech occluder, and Lambre device. Others are in the process of development. None of these devices have been studied in a randomized fashion [13].

## Epicardial Left Atrial Appendage Closure

The LARIAT device is an ingenious system that utilizes both an endovascular and epicardial approach. A transvenous magnet-tipped, balloon containing catheter is introduced transeptally into the tip of the left atrial appendage. An epicardial magnet tipped wire is introduced into the pericardium and latches on to the magnet catheter lying in the left atrial appendage. Over the pericardially introduced wire a suture loop is passed over the wire. The balloon at the tip of the endovascular catheter is inflated and the suture loop passed over the balloon and tightened. The catheter and wire are removed and the suture lasso tightened further. The LARIAT system is approved by the FDA for soft tissue approximation, but not specifically for left atrial appendage occlusion.

As a surgeon many of the problems encountered with this device were predictable. The left atrial appendage is much more friable and likely to tear that the right atrial appendage with its numerous trabeculae: the positioning of an atrial pacing lead is far safer on the right side than a catheter placed in the left atrial appendage. Additionally, the placement of a pericardial catheter into a "dry" pericardial space is not as easy as placement into a pericardial effusion. In a large series of 712 patients from numerous institutions 10 patients had cardiac perforations requiring surgery, 14 had cardiac perforations not requiring surgery and nine patients required blood transfusions. Some patients had injury to the internal thoracic artery, the inferior epigastric artery and coronary arteries. Pericarditis, pericardial and pleural effusions involved close to 5% of patients.

These complications were reduced by using a smaller needle and colchicines [14].

In July 2015 the FDA issued a safety communication regarding the LARIAT device. They had reviewed data submitted to the Manufacturer and User Facility Device Experience (MAUDE) database which identified 45 adverse events including 6 patient deaths. The FDA has allowed the aMAZE trial using the LARIAT device to proceed [15]. This is a prospective, multicenter randomized study of 600 patients with persistent AF to either LAA ligation plus pulmonary vein isolation or to PVI alone in a 2:1 randomization. If this study is able to be completed it offers the potential of proving that left atrial appendage obliteration reduces embolic thromboembolism.

### **Surgical Closure of the Left Atrial Appendage**

Low tech approaches to closure of the left atrial appendage include sutures, a stapler or an endoloop [16]. Most surgeons use one of these approaches.

One of the first papers describing surgical closure of the left atrial appendage in association with mitral valve replacement was by García-Fernández in 2003. Of 205 patients 58 had the atrial appendage closed (incomplete in 6 at follow up TEE). During follow up, in the group not having ligation of the left atrial appendage, embolism occurred in 25 patients (17%) and only in 2 (3.4%) of the occluded appendage group. On multivariate analysis the absence of left atrial appendage ligation and the presence of left atrial thrombus were the only independent predictors of an embolic event (Odds ratio 6.7) [17].

The reader will note that the atrial appendage was not completely closed in all patients. Incomplete closure has been noticed by others (18-20) and it is stressed that the effectiveness of closure must be assessed intraoperatively by TEE. If flow is demonstrated the surgeon must go back and close the appendage. The best surgical option may be amputation. Some of the high rates of incomplete closure may be because of the definition used; Doppler flow into or from the left atrial appendage is unquestionable, but the nature of a residual remnant, which must be close to the orifice, if there is no flow, greater than one cm is less certain. Is a broad remnant of 1.2 cm a risk for thrombus formation? This issue has not been studied.

A current trial, the Left Atrial Appendage Occlusion Study (LAAOS) III is currently recruiting patients [21]. Two previous versions of this trial have been published; the first dealt with the rationale [18], the second was a pilot study [22]. The current trial plans to randomize 4,700 patients having cardiac surgery to groups having or not having atrial appendage occlusion and hopefully will prove definitively whether left atrial appendage occlusion is effective in reducing thromboembolism in patients with AF.

Two devices have been developed to close the left atrial appendage surgically either at thoracoscopic or open cardiac surgery, the Tigerpaw device which was withdrawn from the market in 2015 following a FDA Class 1 recall and the Atriclip device which was approved by the FDA in 2010. Results of a multicenter trial were published in 2011[23]. Intraprocedural success occurred in 67/70 patients (95.7%). In the 3 not successful the stump was >1 cm. Of those imaged at 3 months. 58/61 (95.1%) had exclusion. Two of the 3 the stumps previously present were now excluded. At 6mths no thromboembolism was noted but at 12 months, 2 (3.1%) had a neurologic event.

A meta-analysis published in 2015 [24] identified seven relevant

studies for qualitative and quantitative analyses, including 3653 patients undergoing LAAO (n=1716) versus non-LAAO (n=1937). Stroke incidence was significantly reduced in the LAAO occlusion group at the 30-day follow-up [0.95 vs. 1.9%; odds ratio (OR) 0.46; P=0.005] and the latest follow-up (1.4 vs. 4.1%; OR 0.48; P=0.01), compared with the non-LAAO group. Incidence of all-cause mortality was significantly decreased with LAAO (1.9 vs. 5%; OR 0.38; P=0.0003), while postoperative AF and reoperation for bleeding was comparable.

Our group published in 2003 a small series of 15 patients who had contraindications to warfarin and had had previous thromboembolic events in which the appendage was obliterated thoracoscopically. One patient required urgent thoracotomy for a torn appendage [25]. A similar larger study of 30 patients all with previous TE (7 multiple) and mean CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 3.5 and 4.5 had thoracoscopic appendectomy using a standard endoscopic stapler (two patients required a mini-thoracotomy for an adherent pleura) has been reported [26]. The mean operating time was 32 min, the mean hospital stay 3.1 days. There was no mortality or complications. No patient received anticoagulation. The mean follow-up was 17 months. No thromboembolic event occurred. There was one death from breast carcinoma [26].

### **Conclusion**

Despite the many studies published on the subject and a belief intuitively that atrial appendage occlusion may, because of the finding that 90% of thrombi are located within the left atrial appendage in patients with non-rheumatic atrial fibrillation [5] reduce stroke, definitive conclusions regarding whether atrial appendage obliteration reduces stroke do not exist. Skepticism remains amongst many. One of the largest health insurance companies in the United States issued a 40 page document in December 2015 stating that left atrial appendage occlusion and devices used to achieve this aim were experimental and investigational.

The WATCHMAN device has been studied extensively in respect to the role of atrial appendage obliteration. The authors state that the device is non-inferior to warfarin because it reduces hemorrhagic stroke, unexplained or cardiovascular death and major bleeding and that this is "possibly due to lack of exposure to anticoagulants" (their words). On the contrary side ischemic strokes were higher in those with the device - "possibly due to failures of the device, leaks or thrombus on the device" (again their words) [11]. The approved indication by the FDA is not a strong endorsement - Patients with non-valvular AF who are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores, deemed by their physicians to be suitable for warfarin, but who "have an appropriate rationale to seek a non-pharmacologic alternative to warfarin".

If one reviews the endovascular approaches there exist a number of steps where complications, in many instances very low and reduced over time and with experience, can occur. Vascular access issues may result in deep vein thrombosis and arteriovenous fistulae, the septal puncture may result in air embolism [27]. The watchman device is introduced with a 14 Fr catheter and 23% of patients will have an iatrogenic atrial septal defect after use of a 14-20 Fr catheter [28]. Deployment of the device may result in embolization [27], left atrial tear or perforation, tamponade and pulmonary artery laceration from the barbs holding the device within the appendage [29,30]. Thrombus



can form on the device which may result in embolization [31]. In the PROTECT trial at least one TEE was positive for device related thrombus in 5.7% of PROTECT-AF patients. In these patients stroke, peripheral embolism or unexplained death occurred at a rate of 3.4 per 100 patient's years. Leaks are not unique to surgical series [32,33]. In a single center experience using the WATCHMAN device gaps were present during the procedure, at 45 days and at 12 months in 27.6%, 29.3% and 34.5% of patients respectively. In this same experience they noted that gaps became bigger with time. On follow up they had one stroke and one thrombus noted - both patients had gaps [32], with the LARIAT device leaks were present intra-procedurally, at 6 months and at 12 months in 5%, 15% and 20% of patients respectively [33]. Anticoagulation is necessary until endothelialization of the device occurs. During this period complications associated with anticoagulation can occur. The device, a foreign body, is located within the vascular system and potential endocarditis can occur.

Contrast the surgical approach with the endovascular approach. The patient is anesthetized with blood cross-matched and instruments available to deal with any intraoperative complication. Surgical access in most instances is by thoracoscopy or limited thoracotomy if pleural adhesions are found. During pericardial access the phrenic nerve could be damaged, but this structure is easily seen and no reports of this complication have been described. Obliteration of the appendage may result in bleeding or tearing [25] but should be able to be controlled. Leaks may occur if the appendage is not stapled [16-20]. There is no need for postoperative anticoagulation and the risk of bacterial endocarditis is nil as there is no intravascular device. The device used for obliteration can be one that is available in every operating room and is familiar to the surgeon. The two small series previously described [25,26] embody what we consider necessary, for what left atrial appendage obliteration, as a prophylactic operation to reduce stroke should be. It should have low morbidity, low mortality, be simple and reproducible and also inexpensive.

## References

- Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837-47.
- 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. *Eur Heart J*. 2012;33(21):2719-47.
- [No authors listed] Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342(8882):1255-62.
- Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. *J Thorac Cardiovasc Surg*. 1999;118(5):833-40.
- Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61(2):755-9.
- Odell JA, Blackshear JL, Davies E, Byrne WJ, Kollmorgen CF, Edwards WD. Thoracoscopic obliteration of the left atrial appendage: potential for stroke reduction? *Ann Thorac Surg*. 1996;61(2):565-9.
- MADDEN JL. Resection of the left auricular appendix; a prophylaxis for recurrent arterial emboli. *J Am Med Assoc*. 1949;140(9):769-72.
- Barnofsky ID, Skinner A. Ligation of left auricular appendage for recurrent embolization. *Surgery* 1950; 27:848-52. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation*. 2002;23;105(16):1887-9.
- Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation*. 2013 Feb 12;127(6):720-9.
- Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol*. 2015 Jun 23;65(24):2614-23.
- Sharma D, Reddy VY, Sandri M, Schulz P, Majunke N, Hala P, et al. Left Atrial Appendage Closure in Patients With Contraindications to Oral Anticoagulation. *J Am Coll Cardiol*. 2016;67(18):2190-2.
- Suradi HS, Hijazi ZM. Left atrial appendage closure: outcomes and challenges. *Neth Heart J*. 2017;25(2):143-151.
- Lakkireddy D, Afzal MR, Lee RJ, Nagaraj H, Tschopp D, Gidney B. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: Results from a US multicenter evaluation. *Heart Rhythm*. 2016;13(5):1030-6.
- Lee RJ, Lakkireddy D, Mittal S, Ellis C, Connor JT, Saville BR, et al. Percutaneous alternative to the Maze procedure for the treatment of persistent or long-standing persistent atrial fibrillation (aMAZE trial): Rationale and design. *Am Heart J*. 2015;170(6):1184-94.
- Chatterjee S, Alexander JC, Pearson PJ, Feldman T. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. *Ann Thorac Surg*. 2011;92(6):2283-92.
- García-Fernández MA, Pérez-David E, Quiles J, Peralta J, García-Rojas I, Bermejo J, et al.
- Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 2003 Oct 1;42(7):1253-8.
- Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J*. 2005;150(2):288-93.
- Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol*. 2008;52(11):924-9.
- Cullen MW, Stulak JM, Li Z, Powell BD, White RD, Ammass NM, et al. Left Atrial Appendage Patency at Cardioversion After Surgical Left Atrial Appendage Intervention. *Ann Thorac Surg*. 2016;101(2):675-81.
- Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A., Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg*. 2014;3(1):45-54.
- Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, et al. Left Atrial Appendage Occlusion Study II (LAAOS II). *Can J Cardiol*. 2013;29(11):1443-7.
- Ailawadi G, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ Jr, Salamon T, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg*. 2011;142(5):1002-9.
- Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg*. 2015;47(5):847-54.

25. Blackshear JL, Johnson WD, Odell JA, Baker VS, Howard M, Pearce L, Stone, et al. Thoroscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. *J Am Coll Cardiol.* 2003 Oct 1;42(7):1249-52.
26. Ohtsuka T, Ninomiya M, Nonaka T, Hisagi M, Ota T, Mizutani T. Thoroscopic stand-alone left atrial appendectomy for thromboembolism prevention in nonvalvular atrial fibrillation. *J Am Coll Cardiol.* 2013;62(2):103-7.
27. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol.* 2007;49(13):1490-5.
28. Alkhouli M, Sarraf M, Holmes DR. Iatrogenic Atrial Septal Defect. *Circ Cardiovasc Interv.* 2016;9(4):e003545.
29. Sepahpour A, Ng MK, Storey P, McGuire MA. Death from pulmonary artery erosion complicating implantation of percutaneous left atrial appendage occlusion device. *Heart Rhythm.* 2013 ;10(12):1810-1.
30. Bianchi G, Solinas M, Gasbarri T, Bevilacqua S, Tiwari KK, Berti S, et al. Pulmonary artery perforation by plug anchoring system after percutaneous closure of left appendage. *Ann Thorac Surg.* 2013;96(1):e3-5.
31. Main ML, Fan D, Reddy VY, Holmes DR, Gordon NT, Coggins TR, et al. Assessment of Device-Related Thrombus and Associated Clinical Outcomes With the WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients With Atrial Fibrillation (from the PROTECT-AF Trial). *Am J Cardiol.* 2016;117(7):1127-34.
32. Bai R, Horton RP, Di Biase L, Mohanty P, Pump A, Cardinal D, et al. Intraprocedural and long-term incomplete occlusion of the left atrial appendage following placement of the WATCHMAN device: a single center experience. *J Cardiovasc Electrophysiol.* 2012;23(5):455-61.
33. Gianni C, Di Biase L, Trivedi C, Mohanty S, Gökoğlan Y, Güneş MF, et al. Clinical Implications of Leaks Following Left Atrial Appendage Ligation With the LARIAT Device. *JACC Cardiovasc Interv.* 2016 ;9(10):1051-7.