

# Non-pharmacologic approach to prevent embolization in patients with atrial fibrillation in whom anticoagulation is contraindicated

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## Abstract

Ischemic stroke is the most common complication of atrial fibrillation (AF). Anticoagulation therapy reduces the risk of systemic embolization in almost all patients with AF irrespective of the type of AF (paroxysmal, persistent or permanent). But, all patients are not suitable candidates for systemic anticoagulation mainly due to the risk of bleeding. Left atrial appendage closure (LAAC) devices have been found to be very effective non-pharmacologic alternative therapy for such patients. There are various types of LAAC devices but United States Food and Drug Administration (USFDA) have approved only Watchman device. Initially, bigger medical centers in the US had started the insertion of Watchman device but with improving procedural techniques and exciting outcomes, even the community-based hospitals have started to embrace this therapy. We have presented the first three cases of Watchman device placement performed in our hospital and discussed about the indications for placement of LAAC devices. We have also reviewed their efficacy individually.

## Introduction

Arterial thromboembolism is the most common complication of AF. It consists of both peripheral embolization and stroke. Ischemic stroke is the most common embolic complication of AF while peripheral embolization constitute of less than 10 percent of such cases. Fifteen percent of all strokes originate from cardio embolic source and up to 30 % of all strokes in patients older than 80 years are due to AF.<sup>1</sup> Anticoagulation therapy reduces the risk of systemic embolization in almost all patients with AF irrespective of the

type of AF (paroxysmal, persistent or permanent). But, not all individuals are ideal candidates for anticoagulation due to varying degrees of associated bleeding risk. There are no clear strategies to reduce the risk of embolization in patients with AF for whom long-term anticoagulation is contraindicated. Novel non-pharmacologic strategies like radiofrequency catheter ablation have not been proven to reduce the risk of embolic stroke.<sup>2</sup> In this context, we present three cases of percutaneous LAAC device placement done for an alternative embolization risk reduction strategy for non-valvular atrial fibrillation (NVAF) patients who were eligible for warfarin or novel oral anticoagulants (NOACs), but had reasons to seek another long-term therapeutic option. We will also review the indications for the use of the LAAC device, types of such devices and will analyze their efficacy.

## Case Reports

### Case #1

A 74-year-old woman with history of recurrent symptomatic permanent NVAF due to hypertension presented with worsening shortness of breath, melena and a drop in hemoglobin requiring hospitalization. Patient had been on anticoagulation with warfarin, however due to severe symptomatic anemia manifested as shortness of breath and dizziness secondary to bleeding duodenal ulcer it was stopped. She also had risk of fall due to severe degenerative joint disease (DJD). Patient had a CHA2DS2-VASc score of 4 (age more than 65, female gender, coronary artery disease status post angioplasty and hypertension). She had HAS BLED score of 3 (age more than 65, bleeding from duodenal ulcer, hypertension). In the view of recurrent symptomatic AF and high CHA2DS2-VASc score, secondary prevention of arterial embolization was deemed necessary. After the discussion with patient and her family members a non-pharmacologic approach with implantation of LAAC device was considered. A pre-operative transesophageal echocardiogram (TEE) and Transthoracic echocardiogram (TTE) were done. Left atrial appendage (LAA) was well visualized with no evidence of thrombus (Figure 1). LAA measurements were done at the standard views. Right atrium was normal in size. Right ventricle was normal in size. Left ventricle was normal in size with well-preserved systolic function (60-65 percent). No regional wall motion abnormalities were noted in both TTE and TEE pre-operatively. There was no evidence of left ventricular thrombus. We

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Key words: Non-valvular atrial fibrillation; warfarin; Watchman device; ischemic stroke; novel oral anticoagulants.

Received for publication: 19 September 2016.

Revision received: 9 December 2016.

Accepted for publication: 28 December 2016.

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*Clinics and Practice* 2017; 7:898  
doi:10.4081/cp.2017.898

used M mode 2D and 3D TEE.

Patient underwent successful insertion of a 27 mm Watchman LAAC device under fluoroscopy and TEE guidance. Patient was discharged on aspirin 81 mg daily and warfarin for 45 days. A follow up TEE done postoperatively on 45<sup>th</sup> day showed no new changes and was consistent with the immediate postoperative TEE findings (Figure 2). Patient has shown no features of embolization on 1 year follow up so far. No flow was seen in LAA after device placement.

### Case #2

An 89-year-old woman with history of persistent NVAF due to long standing hypertensive cardiovascular disease presented with shortness of breath and weakness associated with severe anemia due to gastrointestinal (GI) bleeding secondary to arteriovenous malformation (AVM). Her hemoglobin level dropped from 11.5 to 6.0 mg/dl. Her CHA2DS2-VASc score was 5 (age more than 75, female gender, hypertension and Diabetes mellitus). Her HAS BLED score was 3 (hypertension, age more than 65 and previous bleeding episode). Due to high risk for recurrent GI bleeding, she was evaluated for a LAAC device placement. Her pre-operative TEE showed moderately dilated Left Atrium (LA) with at least 5 cm diameter. LAA was free of any intra-cavitary thrombi. There was a small remnant of patent foramen ovale with minimal degree of right-to-left shunting with Valsalva maneuvers. There was no significant pericardial effusion.

Thus, she underwent successful implantation of 21 mm Watchman device. Post-operative TEE showed a well-seated LAAC

device (Figure 3). There was no evidence of thrombus in the LAA or on the closure device. There was a very small hemodynamically insignificant central leak in the middle of the device (0.1 centimeter in diameter with a jet of less than 0.1 centimeter in diameter)

Patient was started on aspirin 81 mg daily and warfarin after the procedure and INR was maintained around 2 to 2.5. However within 45 days of the procedure, she was readmitted with severe GI bleeding, requiring immediate blood transfusion and re-endoscopy and subsequent cauterization of a new duodenal AVM. A repeat TEE did not show any new changes. Her warfarin was discontinued, and she was discharged on aspirin 81 mg daily and clopidogrel 75 mg daily. She presented again within 3 months due to another episode of GI bleed. Thus, clopidogrel was also stopped and only aspirin 81 mg daily was continued. Patient has shown no features of embolization on 6 months follow up so far.

### Case #3

This was an 87-year-old man with history of hypertensive cardiovascular disease, COPD, permanent AF and tachycardia bradycardia syndrome requiring permanent pacemaker in past. He also had history of advanced DJD, ambulatory dysfunction, chronic back pain and acute traumatic multiple rib fractures due to fall incident prior to Watchman procedure. He had a high CHA2DS2-VASc score of 5 (advanced age, history of diastolic heart failure, TIA, hypertensive cardiovascular disease), and HAS-BLED risk score of 4 (Elderly, bleeding tendency, hypertension, labile INR) and thus he was considered for LAAC device procedure for secondary stroke prevention.

His perioperative TEE showed no evidence for LAA thrombi or mass. His LA was moderately dilated measuring 5.0 cm in diameter. His right atrium and ventricle were in the upper limits of normal in size and function. His left ventricle was normal in size with a well-preserved systolic function (60-65%), with no regional wall motion abnormalities, moderate concentric left ventricular hypertrophy and no evidence of left ventricular thrombus.

He underwent a successful implantation of a 24 mm Watchman device under fluoroscopy and TEE guidance. He was discharged on low dose aspirin (81 mg daily) and warfarin to maintain an INR of about 2 for 45 days, and then a follow-up TEE showed no evidence for LA thrombus. The LAAC device was well seated with no echocardiographic evidence for device thrombus with leak or shunts on the Watchman device (Figure 4). Therefore, as

per US-FDA protocol, warfarin therapy was discontinued and he is currently on dual antiplatelet therapy with aspirin 81 mg daily and clopidogrel 75 mg daily for six months post-operative period, after which only a low dose aspirin will be continued. He has remained asymptomatic for 5 months post-operatively so far.

### Discussion

AF is the most commonly encountered cardiac dysrhythmia. According to Framingham heart study, lifetime risk of developing AF from age 40 to 95 was 26 percent for men and 23 percent for women.<sup>3</sup> North America has highest age adjusted

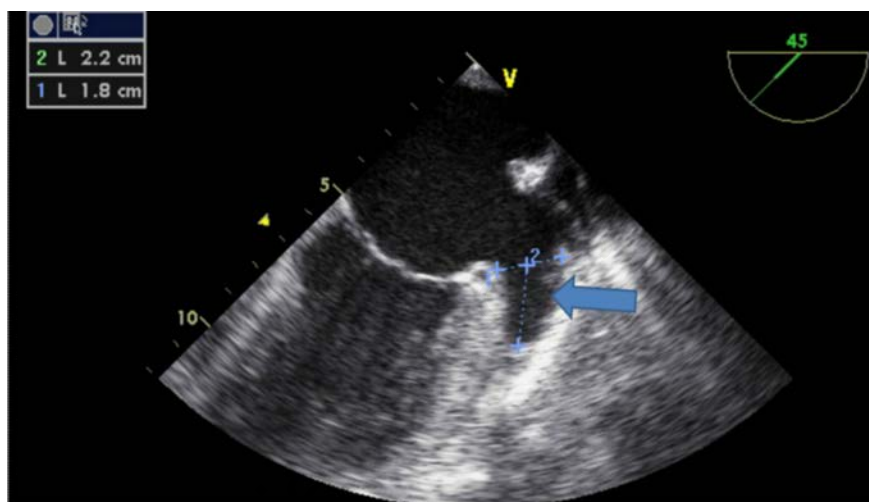


Figure 1. Pre-operative left atrial appendage dimension at 45 degrees.



Figure 2. Watchman device (arrow) in left atrial appendage at 54 degrees on follow up transesophageal echocardiogram.



prevalence rate of 700-775 per 100,000 population compared to relatively lower rate in countries like China, Japan and South Korea.<sup>4</sup> In ATRIA study, around 2.3 million adults in United States had AF in 1996 and 1997. This number was expected to increase to 5.6 million by the year 2050.<sup>5,6</sup> AF was associated with a 1.5 to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions with which AF was related.<sup>3</sup> Several studies have indicated that most common cardiovascular event associated with mortality in AF is heart failure followed by stroke/ systemic embolization (3 and 6). If we analyze embolic events in AF, which is by far the most common complication, data reveal that there is 4-5 fold increase in risk of stroke in patients with NVAf. CHA2DS2-VASc score of 1 represents annual risk of stroke of around 1 percent. While the score of 2 or greater represents an annual stroke risk of 2-15 percent. Thus, AF poses a significant mortality and morbidity burden and effective therapeutic and preventative strategies are imperative to minimize the effect of this health catastrophe.

### Left atrial appendage as a source of emboli in atrial fibrillation

Normally, left atrial appendage (LAA) plays a role in atrial contractility and contributes to the *atrial kick* contributing to up to 25% of Ejection fraction. However, fibrosis and inflammation leading to remodeling of the LAA in patients with long standing AF predisposes to thrombus formation and loss of contribution to filling of ventricle.<sup>7</sup> LAA acts as the source of emboli in around 90 % of cases.<sup>8</sup> Generally, patients with CHA2DS2-VASc score of 1 can be managed with aspirin or warfarin for prevention of embolization while score of 2 or more requires anticoagulation with warfarin or NOACS in NVAf. For patients who cannot be placed on anticoagulants due to unacceptable risk of bleeding or other reasons cited below ligation, amputation or occlusion of the LAA definitely provide a feasible option.

### Indications for left atrial appendage closure device placement

For patients undergoing cardiac surgery for other indications like Mitral valve or Maze surgery, surgical amputation or ligation of the LAA can be performed. The ligation or amputation may be incomplete posing the patient to continuous risk of LAA thrombus. This incidence was as high as 22 % in two series.<sup>9,10</sup>

For patients who are not undergoing cardiac surgery following may be the indi-



Figure 3. Watchman device, shown by the bracket, is well seated at the ostium of the left atrial appendage.

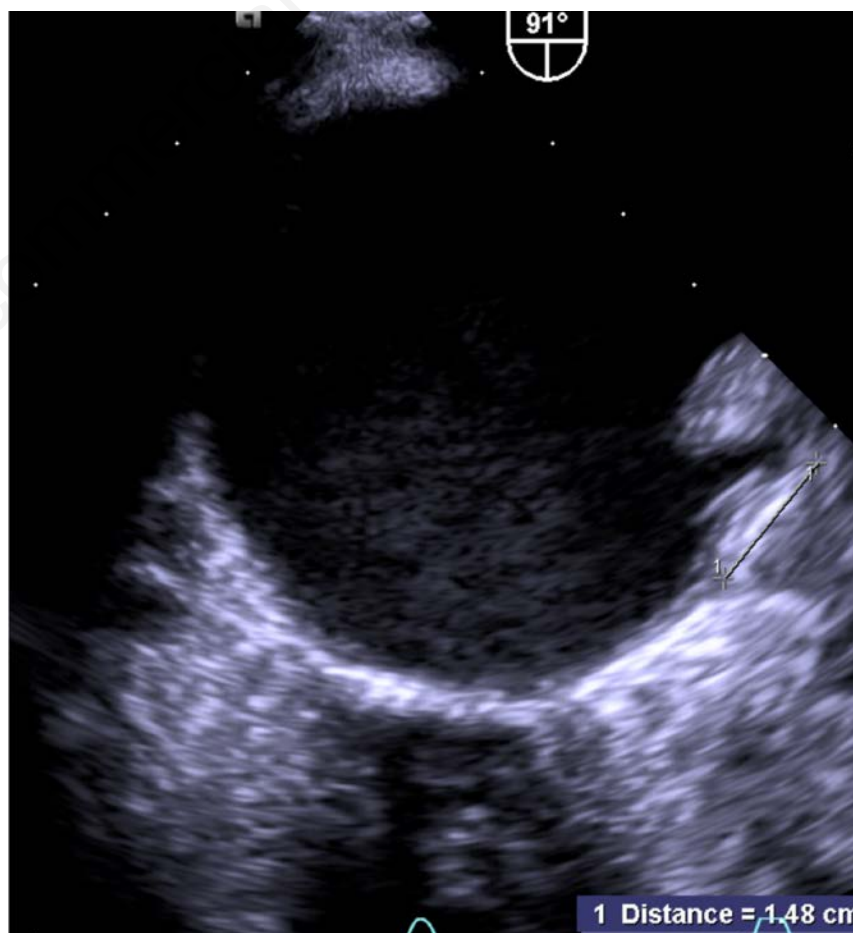


Figure 4. Post-insertion of Watchman device seen at 91 degrees.

cations for LAAO: i) history of recurrent falls especially prior fall episodes resulting in injury; ii) recurrent GI bleeding; iii) thrombocytopenia or bleeding diathesis; iv) dual antiplatelet and anticoagulation therapy like in cases of Coronary artery disease with stent placement with concomitant AF; v) poor compliance with anticoagulation.

### Types of devices

The only one device which is US-FDA approved is Watchman device.<sup>11</sup> It has shown to have comparable efficacy and safety to long-term oral anticoagulation. There are other devices also which have European CE Mark approval but they lack randomized control trial to justify their benefit. Historical data suggest that catheter based LAA occlusion was performed in 2001<sup>12</sup> but this device was not used further.<sup>13</sup>

Watchman device is a self-expanding nitinol device with fixation barbs and covered by permeable polyethylene terephthalate (PTFE) membrane. It comes in 5 different sizes and is placed through 14-French sheaths. There are 3 access sheaths namely double curve, single curve and anterior curve. Mostly, double curve sheath is preferred as it allows easier access.

*Amplatzer cardiac plug* (St Jude Medical) is another device for LAA closure. Globally it is the second most commonly used LAA closure endovascular device after Watchman but it has not yet received US FDA approval. But, it received its CE Mark approval in Europe in 2008. There is a second generation of this device available named as Amplatzer Cardiac plug (Amulet) which received CE Mark approval in 2013. Basically, these devices consist of nitinol mesh and a proximal left atrial disk and a distal LAA lobe. Interestingly, both the lobe and the disk consist of Dacron mesh sewn by hand. Second generation device (Amulet) is more stable due to larger lobe and is also more useful in patients with larger left atrial appendage.

*Trans catheter patch* (Custom medical devices, Greece) consists of a bio absorbable balloon that is originally used for the occlusion of the heart defects. Adjustment in shape and size allows it to be used as LAA closure device.

*LARIAT system* is a percutaneous device placed non-surgically. It is not approved for LAA occlusion to prevent thromboembolism but soft tissue approximation is approved by US-FDA. It has 3 components consisting of occlusion balloon catheter, magnet tipped guide wires and suture delivery device.

*Wavecrest device* is an alternative to the Watchman if LAA is very small to accom-

modate other devices. Its advantage is due to the fact that a foam layer covers it on the LAA side and PTFE on the side facing left atrium. Again, it has not received US-FDA approval but did receive CE approval in 2013.

### Management after device placement

Generally patients receive warfarin and aspirin for 45 days after Watchman device implantation. This is followed by replacing warfarin with clopidogrel and aspirin for up to 6 months after which clopidogrel is discontinued and patient is continued indefinitely on Aspirin.

In patients who cannot tolerate oral anticoagulation, aspirin and clopidogrel is used for 6 months post procedure.

However, it is imperative to detect any evidence of leak around the LAA occlusion device or thrombus associated with device. Thus, a TEE must be ordered between one and six months of the procedure. Generally there is a trend to order TEE at 45 days after the procedure.

### Outcomes of left atrial appendage closure device: Watchman device

There are two major left atrial appendage closure (LAAC) randomized clinical trials that have been performed: PROTECT AF and PREVAIL trials. Both these trials were performed in patients with NVAF eligible for oral anticoagulation.<sup>14</sup> PROTECT AF included 707 patients who were randomly assigned to either the device or to long-term anticoagulation in an almost 2:1 ratio. Patients with paroxysmal, persistent or permanent AF and CHADS2 score > 1 were included. 91 patients underwent device implantation. Patients were continued on warfarin and aspirin for 45 days followed by clopidogrel and aspirin for up to six months and finally aspirin alone for indefinite period. After a mean follow-up of 18 months, the primary efficacy event rate was similar in the intervention control groups (3.0 versus 4.9 events per 100 patient years, respectively; rate ratio 0.62, 95% Bayesian credible interval 0.35-1.25). After a mean follow-up of 2.3 years, the primary efficacy event rates were 3.0 and 4.3 percent, respectively. These results allowed for a finding of non-inferiority of the device with its specific antithrombotic protocol compared to warfarin.<sup>15</sup> There was also a 60 % relative risk reduction of cardiovascular death in patients receiving Watchman device.

Meta-analysis of 2 randomized clinical trials and 2 registries with Watchman device also revealed that patients had significantly fewer hemorrhagic strokes (hazard ratio

0.22, P=0.004). Patients also had a significant reduction in cardiovascular or unexplained death (hazard ratio 0.48, P=0.004). There was also significant reduction in non-procedural bleeding with the device (hazard ratio 0.51, P=0.006).

In another study,<sup>16</sup> where registry data of LAAC from two centers were prospectively collected from 110 patients with NVAF at risk of stroke, suitable and unsuitable for long-term anticoagulation showed significantly lower bleeding rates than PROTECT AF trials. There was mean absolute difference of stroke, 0.89 % (P=0.02) and major bleeding, 5.48 % (P<0.001). There was also significant cost effectiveness with LAAC device in a short period of time (cost saving against all therapies being 1162-7194 pounds).

### Outcome of other left atrial appendage closure devices

Amplatzer cardiac plug has so far been evaluated in observational studies only. Globally this is the second most commonly used LAAC device but it has not received US-FDA approval. This device showed 59 percent risk reduction compared with the expected rate based upon the CHA2DS2-VASc score in a large pooled study from 22 European and Canadian centers. This study included 1047 patients.<sup>17</sup> Asymptomatic migration and dislocation have been reported with this device though which is concerning.<sup>18,19</sup>

LARIAT system evaluated in a retrospective series of 154 patients reported by the United States Trans catheter LAA Ligation Consortium showed 9.1 percent major bleeds while death, stroke or myocardial infarction occurred in 2.9 percent.<sup>20,21</sup> But, complications such as laceration or perforation of the heart or complete LAA detachment from the heart have been reported.<sup>22</sup> For Coherex WaveCrest device there currently are no peer-reviewed data published. They have encouraging results in animal studies though.

Currently, the main challenges for placement of Watchman device are cost of the device, easy availability of well-trained and experienced operators and ancillary staff and well equipped electrophysiology (EP) or interventional lab. These drawbacks are more prominent at a level of a community hospital than tertiary centers in the USA. With availability of advanced newer fluoroscopic devices and 3D image guidance in a new hybrid EP, we were able to initiate the Watchman procedure at our institution. Due to serious potential intraoperative complications such as cardiac tamponade and perforation, immediate availability of cardiothoracic surgeon in the EP lab is manda-

tory in our institution. Hybrid EP lab provides the option to convert it into a fully equipped operating room for surgeons in case of complications.

## Conclusions

In patients with NVAf, LAA acts as the major site for thrombi formation and this forms the rationale for occlusion, ligation or amputation of the LAA. Patients who have NVAf and are not eligible for cardiac surgeries but have reasons to avoid long-term oral anticoagulation can definitely benefit from LAAC devices. According to the initial outcomes, Watchman device carries a great potential in prevention of stroke in NVAf but some of its benefits are obscured by procedure related complications. Thus, improvement in implantation techniques and devices will probably result in better procedural safety in the future and enhance the popularity and effectiveness of this device even in the community hospital settings. There is a glaring need to obtain results of well-structured comparative studies between LAAC and NOACS as they are more frequently used now (19). Currently, Watchman device is the only US-FDA approved device for the LAAC procedure but other devices like Amplatzer cardiac plug, Amulet, LARIAT system, Wavecrest device have also proven to be beneficial. Results of randomized control trials are needed in the USA to justify their benefit.

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