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Left Atrial Appendage Occlusion: Where are We Going?

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Abbreviations: AF: Atrial Fibrillation; OAC: Oral Anticoagulant; LAA: Left Atrial Appendage; LAAO: Left Atrial Appendage Occlusion; NVAF: Non-Valvular Atrial Fibrillation; VKA: Vitamin-K Antagonist; NCB: Net Clinical Benefit; NOAC: Non-VKA OAC; SR: Sinus Rhythm; EF: Ejection Fraction; MRI: Magnetic Resonance Imaging; ICE: Intra-Cardiac Echocardiography; TEE: Trans-oesophageal Echocardiography.

Prevention of ischemic stroke is one of the most important issues in patients with atrial fibrillation (AF). Currently, most patients are managed satisfactorily with oral anticoagulant (OAC) therapy. The remaining patients, who cannot tolerate long-term systemic OAC or who have an excess thrombotic burden that cannot be adequately controlled by OAC alone, require local anti-thrombotic therapy such as left atrial appendage (LAA) mechanical exclusion, either by surgical excision or percutaneous closure device implantation. Since the first percutaneous left atrial appendage occlusion (LAAO) device implantation was performed in 2001, there have been numerous unanswered questions, which might be clarified only after additional experience in this field. Although an enormous number of non-valvular atrial fibrillation (NVAF) patients require thrombo-prophylactic management, which can be either systemic or local management, LAAO has not yet been widely adopted as an alternative to anticoagulant therapy because of the extraordinarily diverse anatomical variation within the LAA as well as the complexity of clinical situations (i.e. relative / absolute contraindication to anticoagulant, high bleeding risk with or without prior major bleeding events, recurrent stroke during proper secondary prevention, comorbidities that increase the bleeding risk or thrombotic risk, and are accompanied by a compromised life expectancy, such as malignancy). The preliminary answer to the question regarding the meaningful destination of LAAO has been carefully discussed in this article.

Can LAAO replace OAC?

Based on the results of two randomized controlled trials (PROTECT-AF and PREVAIL) that compared systemic anticoagulation (vitamin-K antagonist [VKA]) and local exclusion of the potential thrombotic source (LAAO), it was concluded that LAAO was non-inferior to systemic anticoagulation in terms of the composite efficacy for preventing stroke, systemic embolism, and cardiovascular death in patients with AF (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.53–1.2, P=0.22) [1]. On performing post hoc analysis of the net clinical benefit (NCB) reflecting the clinical weight of events including haemorrhagic events, thrombotic events, and mortality, long-term NCB of LAAO was demonstrated over time by the reduction in bleeding events and mortality [2]. When the comparison target was switched to Non-VKA OAC (NOAC) in the PRAGUE-17 trial, LAAO was found to be non-inferior to NOAC in terms of the composite end points (all strokes or transient ischemic attacks, clinically significant bleeding, cardiovascular death; 10.99 % in LAAO and 13.42 % in NOAC, HR 0.84, 9 5%CI 0.53–1.31, P=0.44; P=0.004 for non-inferiority) [3]. In patients who can tolerate anticoagulation, LAAO can be the non-inferior option, although we have to be careful to apply these outcomes to our AF patients because the patients in the clinic are different from those included in randomized clinical trials, in whom both treatment options are considered feasible. On the other hand, most of the LAAO target patients are intolerant to long-term anticoagulation. Therefore, the question of *"Can LAAO replace OAC?"* is a clinically important issue.

In order to discontinue OAC after successful LAAO, appropriate correction and removal of the factors contributing to local thrombus formation are required. First of all, complete mechanical exclusion of LAA may reduce the size and shape

of the available physical space. In order to minimize the risk of thrombus formation, the ideal procedural outcome is a reduction in the size of the space as much as possible while making the LA shape as close as possible to a spherical shape.

However, all three factors of Virchow's triad (increased coagulability, blood stasis, endothelial injury) cannot be corrected by LAAO alone. By reducing the chamber size and modifying the chamber shape along with decreased blood stasis, LAAO can substantially reduce the risk of local thrombus formation. According to an individual patient's integrated thrombotic burden after LAAO, appropriate antithrombotic management (i.e., follow-up without antithrombotic medication, antiplatelet therapy, anticoagulant therapy, or combinations) should be chosen and maintained. Recently, complete LAA surgical exclusion was found to significantly reduce ischemic stroke or systemic embolism in the LAAOS III trial (4.8 % in the occlusion group vs. 7.0% in the non-occlusion group, HR 0.67; 95% CI 0.53–0.85, P = 0.001) [4]. Although it had the limitation that it examined heterogenous patients who underwent various cardiac surgeries, it clearly showed LAAO's preventive efficacy in reducing ischemic stroke or systemic embolism regardless of the accompanying cardiac disease requiring surgery. In one-third of the participants (31.5% in the occlusion group vs. 34.0% in the non-occlusion group), surgical ablation was performed during surgery, and anticoagulation was discontinued in 16.6% (occlusion group) and 19.0% (non-occlusion group) patients at hospital discharge. OAC discontinuation rate temporarily increased to 20.4% (occlusion group) and 21.1% (non-occlusion group) at the 1-year visit, while it decreased to 14.7% (occlusion group) and 11.8% (non-occlusion group) at the 3-year visit. On subgroup analysis, ablation of AF did not show a difference between the groups, although the amplitude of reduction was larger in the ablation group (0.71 [0.54–0.95] in the non-ablation group vs. 0.60 [0.39–0.92] in the ablation group). On the other hand, AF or flutter rhythm state was associated with a larger reduction than sinus rhythm (SR), and the incidence of thrombotic events was the highest in the AF rhythm state without LAAO (7.8%) than in the other groups (Non-LAAO in SR [5.7%], LAAO in AF or flutter [4.4%], and LAAO in SR [4.4%]). In addition, the thrombotic event reducing efficacy of LAAO was more pronounced in patients with baseline left ventricular ejection fraction (EF) ≥ 50% (0.68 [0.51–0.92] in patients with EF ≥ 50% vs. 0.72 [0.46–1.13] in patients with EF<50%). These observations can be interpreted as follows: the overall risk of thrombus formation is determined not only by LAAO, but also by factors such as the rhythm status and EF. Thus, anticoagulation usage can be switched according to the rhythm status (AF or SR) or heart failure status (compensated or decompensated). Although it is impossible to draw a final conclusion from the small size of the subgroup analysis, ongoing studies comparing LAAO vs. NOAC with or without AF ablation may provide an answer to this question (OPTION [Comparison of Anticoagulation with Left Atrial Appendage Closure After AF Ablation] trial, NCT 03795298; AF ablation + LAAO vs. AF ablation + OAC, 1:1 randomised controlled trial [RCT]). In addition, on-going large scale RCTs (CHAMPION-AF [WATCHMAN FLX vs. NOAC for Embolic ProtectION in the Management of Patients With Non-Valvular Atrial Fibrillation] trial; WATCHMAN FLX vs. NOAC, 1:1 RCT, NCT 04394546; CATALYST trial [Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonists], AmuletTM vs. NOAC, 1:1 RCT, NCT 04226547) may provide us more insight into post-procedural anti-thrombotic management according to the integrated thrombotic risk. Furthermore, a RCT to compare the effect of LAAO + NOAC vs. NOAC alone as the best anti-thrombotic management in a selected patient group is expected in the future.

Before deciding whether to use OAC, a completely closed LAA with minimal blood stasis must be achieved. Although newer device designs are continuously being developed, a closure device with a suitable design and size in a given patient cannot be appropriately implanted due to the anatomical complexity and potential complication risk of repeated implantation attempts. Due to the rapid improvement in imaging technology, accurate and 3D evaluation of LAA is possible, which enables realistic simulation similar to real implantation in patients [5]. Despite availability of only small-scale studies, it may improve the accuracy and safety of the procedure.

Complete LAAO accompanied by integrated thrombotic risk assessment that reflects all three contributing factors of Virchow's triad may guide OAC re-usage even after OAC discontinuation post LAAO in selected patients. However, the integrated thrombotic risk and bleeding risk for a given patient are not static, but constantly changing according to the rhythm status and comorbidities such as worsening of heart failure, valve disease, chronic kidney disease, and malignancy. Therefore, OAC usage after LAAO should be guided by integrated thrombotic risk assessment, which can be variable and needs to be re-assessed regularly. This approach follows the principles of a personalized medicine.

Who Can Benefit the Most from LAAO?

Even complete occlusion cannot completely replace OAC. Which patients can benefit from LAAO the most? The current guidelines recommend that LAAO should be considered in patients who have contraindications for OACs or excess thrombotic burden despite receiving proper OAC. First, when planning LAAO in patients who have an OAC contraindication, if complete occlusion is possible, it can be actively pursued. Once complete occlusion is achieved, the need for anticoagulation can be periodically re-assessed according to the integrated thrombotic burden in a given patient. Even with the best treatment other than OAC, if a given

patient with complete LAAO requires OAC due to increased thrombotic burden associated with worsening of blood stasis, increased coagulability, or endothelial dysfunction, OAC re-initiation should be carefully considered. Accordingly, various biomarkers, physiological or functional imaging analysis must be comprehensively utilized.

Unless complete occlusion can be achieved, is there no benefit of LAAO? Shape and size modification caused by LAAO changes the thrombotic risk. The greater the distance from the LAA ostium to the first bend of LAA or the closure plane, the higher the thrombotic risk [6]. Thus, an operator should try to acquire the occlusion plane closest to the ostial plane. In other words, the benefit of reduced thrombotic risk will be in proportion to the reduced distance from the ostial plane to the closure plane. This situation can be reconfirmed by the stroke occurrence pattern after LAAO. Although it is important to reduce the incidence of stroke, there is also a difference in the neurological outcomes [7]. Even in patients in whom it is difficult to control the thrombotic burden by anticoagulation therapy alone, the role of LAAO is controversial. In a recent retrospective analysis, intensified anticoagulation therapy was the preferred strategy in more than half of the patients with LAA thrombus [8]. However, the thrombus did not completely resolve despite prolonged intensified anticoagulation therapy in approximately one quarter of the patients, and more frequent bleeding events and stroke were observed during the intensified anticoagulation therapy. On the contrary, less bleeding events and no stroke events were reported in patients with direct LAA closure with or without an embolic protection device. Thrombi or embolic materials were found in about 20% of the embolic protection devices. Considering that the rate of acute brain lesions confirmed by brain magnetic resonance imaging (MRI) after LAAO reaches about 48% [9], it can be interpreted that embolic events that demonstrate neurologically significant changes are relatively uncommon, and can be avoided by using embolic protection devices.

Besides, it is desirable to use a minimalistic approach in order to minimize the risk of embolic events. Since embolization that can be identified in brain imaging is observed in about half of the patients whose thrombus was not confirmed in the pre-procedural image, intra-procedural manipulation should be minimized regardless of the definite presence or absence of a LAA thrombus. Currently, the detailed techniques of the minimalistic approach are as follows: (1) pre-procedural device size determination through 3D simulation, (2) intra-procedural imaging guidance by intra-cardiac echocardiography (ICE) under conscious sedation, (3) device implantation with a 'no-touch technique'. Intra-procedural measurement of the landing zone diameter, ostium diameter, and depth by intra-procedural trans-oesophageal echocardiography (TEE) or multi-view angiography showed wide variations and device size mismatch that frequently result in repeated implantation attempts or device size change, which may increase the risk of incomplete closure, thromboembolism, and cardiac perforation. Pre-procedural simulation is not only an excellent preparation and training for the implanter but also an opportunity to anticipate the appropriate device size, and minimizes the number of manipulations, particularly minimizing the number of implantation attempts as well as the number of device size changes. Although various simulations have been tried, 3D printed model based simulation is one of the most useful methods for the intuitive understanding of the procedure in the individual patient and for detailed procedure planning [5]. Intra-procedural TEE related oesophageal injury is not uncommon and can be critical in patients with several risk factors such as low body weight, history of gastro-intestinal bleeding, and longer procedure time [10]. Recently, ICE has been proven to be a feasible alternative for guiding device implantation and checking peri-device leakage with reduced invasiveness [11]. In combination with 3D simulation, the flaws of an ICE guided approach were further eliminated, which was associated with the limitation of accurate size determination based on ICE-based size measurements. Routine use of ICE is becoming a widely accepted approach because of the outcomes and cost [12]. To minimize the risk of thrombo-embolism, operators can actively try the no-touch implantation method. When the implantation step is initiated inside the LAA, there is a potential risk of mobilizing small thrombi harboured within the trabeculations.

This no-touch technique, also known as the ball-advancing technique, requires:

1. The avoidance of contrast injection or gentle injection of the contrast from the tip of the delivery sheath outside the LAA.

2. Pre-loading of the device into the delivery sheath in the left superior pulmonary vein.

3. Careful and atraumatic jumping down to the orifice of the LAA while the device is partially unsheathed to a small ball to avoid damage to the heart structure, feasible with ACP, AMULET, LAmbre, Cardia Ultraseal, and WATCHMAN Flex, but not with WATCHMAN.

Especially in patients with obvious or suspected LAA thrombi, the combination of no-touch technique and embolic protection device may maximize the patient benefit by reducing the potential risk of stroke. In summary, complete implantation of a LAAO device by a minimalistic approach as well as usage of an embolic protection device in AF patients with suspected or obvious LAA thrombi and OAC usage or re-usage after LAAO, when guided by recurrent and regular integrated thrombotic risk assessment in accordance with the principles of real personalized medicine, may maximize the benefit of LAAO. Two Three milestone trials (PROTECT-AF, and LAAOS-III, and a randomized trial of LAAO + OAC versus LAAO without OAC) may provide definite proof regarding the benefit of LAAO.

Conclusion

Currently, our experience of LAAO is not sufficient to draw a final conclusion, but comprehensive decision making is recommended by considering the integrated thrombotic risk and bleeding risk even after complete LAAO in AF patients with a high risk of stroke and bleeding. In order to ensure the most benefits for a given patient, LAAO should be carefully planned and performed as meticulously as possible.

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