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Remaining Challenges With Transcatheter Left Atrial Appendage Closure

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Learning Objectives: On complication of this article, the reader should be able to: 1) describe the current indications for percutaneous left atrial appendage closure; 2) discuss the key remaining challenges with left atrial appendage closure; and 3) recognize the current strategies in place to mitigate the unresolved issues with left atrial appendage closure.

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Abstract

Left atrial appendage closure has emerged as a feasible stroke prevention strategy in selected patients with nonvalvular atrial fibrillation. Since its commercial approval in the United States in 2015, the use of percutaneous left atrial appendage closure has witnessed a substantial growth. However, certain issues remain unresolved with the technology. Knowledge of these issues, their significance, and the current and future efforts to resolve them is key for proper informed decision making by physicians and patients.

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Stroke prevention has been a cornerstone in the management of patients with nonvalvular atrial fibrillation (NVAF).[1] Oral anticoagulation (OAC) is the dominant stroke prevention strategy in these patients, but its use has been hindered by the high prevalence of contraindications and patient noncompliance.[2] Percutaneous left atrial appendage closure (LAAC) has recently emerged as a feasible alternative to anticoagulation in selected patients with NVAF.[3] To date, more than 100,000 patients have received LAAC with the Watchman device alone (Boston Scientific, Marlborough,

MA).[4] However, concerns have been raised about the limited data supporting routine use of LAAC, and certain remaining issues with the procedure itself.[5] Hence, LAAC was only assigned a class-IIb recommendation in the recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for the management of NVAF.[6] In this perspective, we discuss the current state and future directions of LAAC focusing on the remaining challenges and unresolved issues with this technology.

EFFICACY DATA

The safety of LAAC has now been established through a large body of literature.[3] However, comparative effectiveness data between LAAC and OAC are limited to two randomized clinical trials (RCTs) totaling 1114 patients, which likely contributed to the modest level of recommendation (IIb) assigned to LAAC in the most recent guidelines. In a patient-level meta-analysis of these 2 trials, there was no difference in all-cause stroke or systemic embolization between LAAC and OAC with warfarin (1.75 vs 1.87 events/100 patient/year; hazard ratio, 1.02; 95% CI, 0.62 to 1.7; P=.94). However, there were more ischemic strokes in the device group (1.6 vs 0.9 events/100 patient/year; hazard ratio, 1.95; P=.05).[7] Hence, questions arose on whether LAAC is effective in preventing ischemic stroke or whether its efficacy is limited to mitigating hemorrhagic strokes. This is particularly important considering that the warfarin group had higher bleeding rates compared with similar contemporary cohorts. Although a large number of studies was recently published suggesting efficacy of LAAC in real-world, those observational studies compared the efficacy of LAAC to a theoretical risk predicted by the CHA_2DS_2-VASc score.[8] Albeit commonly used, the CHA_2DS_2-VASc score does not account for key risk factors for stroke in NVAF (duration of atrial fibrillation, left atrial size, left atrial appendage [LAA] shape and function, etc), and has been found to have a modest predictive value overall.[9] In addition, there are, to date, no comparative data between LAAC and direct oral anticoagulants which are known to be associated with lower odds of hemorrhagic strokes than Warfarin.[1] To address these concerns, two large RCTs (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] and Amplatzer Amulet LAAO vs NOAC [CATALYST]) will randomize more than 5000 patients to receive LAAC with contemporary LAAC devices or a direct oral anticoagulant. The results of those trials will have a major impact on the future of the LAAC therapy.

PATIENT SELECTION

Observational registries have documented short- and mid-term mortality rates that were two- to three-fold higher than what was observed in RCTs.[10,11] A cohort study using the Medicare database showed a 7.5% mortality rate at 1 year in 13,627 patients who underwent LAAC.[10] In another multicenter French registry, 1-year mortality was 7.4%, of which 82% was due to noncardiac mortality.[11] These data suggested that LAAC is being used in older and sicker patients in practice compared with patients enrolled in clinical trials, which highlights the need to optimize patient selection in clinical practice considering the preventive nature of the procedure. Although elderly patients with a host of comorbidities might be a higher-risk group that might derive a significant benefit from LAAC, the utility versus futility of the procedure must be considered among those with limited expected longevity. On the other hand, it is plausible that the younger population might derive a substantial benefit of LAAC given their expected longevity and cumulative risk of stroke. Long-term data assessing the feasibility of an LAAC device versus tablets for life in this population are warranted. In addition, in light of the typical "indication creep" that is observed after the commercial approval of most interventional devices, caution should be exercised in extending LAAC to patient cohorts that have not been studied in clinical trials (eg, patients

with atrial flutter; 13.6% of all patients who underwent LAAC in the United States between 2015 and 2018).[12]

ANATOMICAL LIMITATIONS

The LAA anatomy is highly variable in size, shape, orientation, and number of lobes, which may hinder its effective sealing with endovascular devices. This was evident by the high incidence (20% to 40%) of incomplete LAAC in RCTs and observational registries.[13,14] Limited data exist with regards to the prognostic impact of incomplete LAAC. In the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial, no association was observed between incomplete LAAC and subsequent ischemic events.[14] However, the low number of events (16 ischemic events only in the overall cohort), and the short-term follow-up (~1 year) precluded firm conclusions. A large observational study using the National Cardiovascular Data Registry (NCDR) − Left Anterior Appendage Occlusion (LAAO) registry is currently examining the association between peridevice leaks and thromboembolic events in a large cohort of patients (Freeman J, personal communication, May 6, 2020). In addition, although several studies have documented the safety of transcatheter leak closure using coils or vascular plugs, long-term efficacy data of these approaches are lacking.[15] These limitations are hoped to be at least partially addressed with novel newer generation devices that aim to address specific LAA anatomy.[16,17] For example, the LAmbre LAAC device (Lifetech, Shenzhen, China) is available with two different designs to allow closure of single and multilobulated LAAs. In addition, the second-generation Watchman Flx device, with its enhanced seal and compact and closed distal cell design, achieved complete seal in 92.6% of patients in the Investigational Device Evaluation of the WATCHMAN FLX LAA Closure Technology (PINNACLE FLX) study.[17] However, the availability of multiple devices with different sheath shapes may also introduce additional complexity and potential hazard to the LAAC procedure. Eventually, the optimal LAAC device must be less operator-dependent, easy to use, and compatible with most LAA anatomies to maintain the safety of the LAAC procedure.

PROCEDURE INVASIVENESS/WORKFLOW

The LAAC procedure is traditionally performed under transesophageal echocardiography (TEE) guidance. In the current workflow for the procedure in most institutions, it is recommended that patients undergo a preprocedural TEE to assess anatomical suitability and at least two postprocedural TEEs (at 45 and 365 days) to examine device seal and thrombus. This resource-intensive and relatively invasive process is not well tolerated by elderly or frail patients. Hence, several attempts have been made to identify a more efficient and less invasive strategy for LAAC. Computed axial tomography has been found to provide a more accurate assessment of the LAA size and anatomy compared with TEE, and is hence being increasingly used for pre- and post-procedural imaging.[18] There is also a growing interest in intracardiac echocardiography (ICE) to guide LAAC without the need for general anesthesia.[19] In addition, ICE mitigates the need for aerosolized procedures (ie, TEE); this strategy may become routine in guiding future LAAC in the post−coronavirus disease 2019 era. The anticipated future improvement in ICE catheter designs (eg, adding three-dimensional and x-plane capabilities) will further facilitate the growth of these trends.[1] Considering that a large proportion of patients undergoing transcatheter aortic valve implantation, mitral valve repair, or pulmonary vein isolation have NVAF and at least a relative contraindication to OAC,[2] combining these procedures with LAAC, when appropriate, might further decrease the burden and risk of repeated procedures and imaging studies in these patients. Several studies are currently underway to assess the safety and efficacy of combined procedures (eg, Watchman for Patients With Atrial Fibrillation Undergoing Transcatheter Mitral Valve Repair; WATCH-TMVR).[20]

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ADJUNCTIVE ANTITHROMBOTIC THERAPY

The Watchman device is currently the only approved LAAC device in the United States. The adjunctive use of warfarin is required for at least 45 days after device implantation per the manufacturer instructions for use. Warfarin can then be discontinued if follow-up imaging revealed no major leak (>5 mm) around the device and no device related thrombus (DRT). However, this is counterintuitive as the majority of patients are referred for LAAC due to a contraindication to OAC. Therefore, continuing or restarting OAC in these patients may pose a considerable risk of bleeding. This leads to a management conundrum, which is reflected by the inconsistent antiplatelet and anticoagulant regimen after LAAC in clinical practice.[12] The uncertainty about the best adjunctive therapy is further heightened with the emergence of European data suggesting that use of antiplatelets alone after LAAC may not be associated with adverse events as compared with OAC.[5] Further data are direly needed to guide the decisions on adjunctive therapy in the increasing number of patients undergoing LAAC.

DEVICE-RELATED THROMBUS

This complication is currently considered the Achilles heel of LAAC due to its unpredictable timing, poorly understood risk factors, and its strong association with ischemic events. In a meta-analysis of more than 10,000 patients who underwent LAAC, DRT occurred in 3.8%, and those had a five-fold increase in stroke or systemic embolization.[21] Timing of DRT was unpredictable, with the diagnosis being made at less than 90, 90 to 365, and more than 365 days in 42%, 57%, and 1% of patients, respectively. Although thrombus resolution was achieved in most patients with short-term OAC, approximately 50% of patients who stopped OAC had a recurrent DRT.[22] Furthermore, data on the predictors of DRT are heterogenous and are hindered by the small number of events.[23,24] At present, it remains unknown whether DRT is mostly related to patient factors (eg, ventricular function, duration of NVAF, etc), procedural factors (eg, peridevice leak or deep implantation), or to the type and duration of adjunctive antithrombotic therapy, or to a combination of these factors. Additional studies are needed to model a DRT score that allows the identification of patients at highest risk for DRT, and to discern its modifiable predictors. Optimization of the LAAC devices is also expected to further reduce the risk of DRT. The Watchman Flx device is engineered to have minimal exposed metal material to minimize the risk of DRT. Early experience with this device showed a DRT rate of 1.8% (7 of 395 patients) at 1 year, which is lower than what has been observed in prior studies. Additionally, preliminary animal work with future-generation LAAC devices suggests a promising role of novel antithrombotic coatings to further decrease the odds of DRT after LAAC.

CONCLUSION

Left atrial appendage closure has emerged to address the large unmet need of stroke prevention in NVAF. However, the field of LAAC is in its infancy, and several unresolved issues remain to be addressed. The next 5 years will bring forth a wealth of data from a large portfolio of planned and ongoing clinical and preclinical investigations that will inform the future of LAAC therapy.

Abbreviations and Acronyms: **DRT** = device-related thrombus; **ICE** = intracardiac echocardiography; **LAAC** = left atrial appendage closure; **NVAF** = non-valvular atrial fibrillation; **OAC** = oral anticoagulation; **RCT** = randomized clinical trials; **TEE** = transesophageal echocardiography

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