

REVIEW TOPIC OF THE WEEK

Strategies to Incorporate Left Atrial Appendage Occlusion Into Clinical Practice



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ABSTRACT

The left atrial appendage (LAA) has been identified as a predominant source of thrombus formation leading to significant thromboembolic events in patients with nonvalvular atrial fibrillation. Medical therapy to eliminate thrombus formation in the LAA has been the standard of care for several decades, but mechanical approaches designed to exclude the LAA from the circulation have recently been developed. The largest body of randomized and nonrandomized data to date has been for the Watchman device (Boston Scientific, Natick, Massachusetts), which was recently approved by the Food and Drug Administration for selected patients in the United States. There are no current guidelines or guidance for institutions and operators looking to become involved in this therapy. This perspective is aimed at exploring these issues and providing necessary information and guidance to these programs and operators to help ensure a successful launch of a LAA occlusion program and optimize patient selection, procedural performance, and outcome. (J Am Coll Cardiol 2015;65:2337-44) © 2015 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is a common arrhythmia encountered in clinical practice, with a prevalence of 2 million in the United States; this number is expected to increase to 16 million individuals by 2050 (1). A major consequence of AF is thromboembolism, particularly ischemic stroke; the risk of stroke in patients with AF is approximately 5% per year (2). Oral anticoagulation with warfarin and novel oral anticoagulant agents (NOACs) remain the cornerstone of stroke prevention in AF; warfarin has been shown to decrease the risk of stroke by as much as 65% (3), and the NOACs have similar efficacy with reduced risk of intracerebral hemorrhage.

Left atrial appendage (LAA) occlusion has emerged as a safe and effective alternative to the use of oral anticoagulation for stroke prevention in selected patients with nonvalvular AF (4-8). There are several

devices currently in use for LAA occlusion, but the Watchman device (Boston Scientific, Natick, Massachusetts) has the most clinical trial data and is currently CE-marked and approved for use in Europe, with experience in approximately 50 countries. The U.S. Food and Drug Administration (FDA) recently approved the use of the Watchman device for reducing the risk of thromboembolism in patients with nonvalvular AF and increased risk of stroke where there is concern about the risks of long-term anticoagulant agents because of the risk of bleeding. At this time, institutions are beginning the process of designing and implementing clinical practice approaches for the introduction and use of these devices. This article aims to provide potential guidance for operators and institutions aiming to implement a LAA occlusion program.

From the *Division of Cardiovascular Diseases and Department of Internal Medicine, University of Alabama, Birmingham, Alabama; and the †Division of Cardiovascular Diseases and Department of Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Dr. Alli has been a speaker for Edwards Lifesciences; and has received proctorship fees from Edwards Lifesciences. Dr. Asirvatham has received honoraria for consulting from Abiomed, Atricure, Biotronik, Biosense Webster, Boston Scientific, Medtronic, Spectranetics, St. Jude Medical, Sanofi, Wolters Kluwer, and Elsevier; and he is a co-holder of a patent and may receive future royalties from Aegis for appendage ligation. Dr. Holmes, along with Mayo Clinic, has a financial interest in technology that has been licensed to Boston Scientific. Ole De Backer, MD, PhD, served as Guest Editor for this paper.

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**ABBREVIATIONS
AND ACRONYMS**

- AF** = atrial fibrillation
- CT** = computed tomography
- DAPT** = dual antiplatelet therapy
- EP** = electrophysiologist
- FDA** = U.S. Food and Drug Administration
- IC** = interventional cardiologist
- ICE** = intracardiac echocardiography
- LAA** = left atrial appendage
- NOAC** = novel oral anticoagulant agent(s)
- OAC** = oral anticoagulant agent(s)
- TEE** = transesophageal echocardiography

**POTENTIAL OPPORTUNITIES AND
BENEFITS OF LAA OCCLUSION**

Although device-maker Boston Scientific highlighted the “first-of-its-kind alternative to long-term warfarin” (Coumadin) in announcing the approval of the LAA occlusion device (9), the indication was only for patients with nonvalvular AF who are at increased risk for stroke and systemic embolism on the basis of CHADS₂ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism) or CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≤75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65 to 74 years, sex category) scores and deemed by their physicians to be suitable for

warfarin, but who “have an appropriate rationale to seek a nonpharmacological alternative to warfarin” (10). Apart from this current indication, there are several other possible indications for use of this device:

Possible clinical scenarios (Table 1)

1. As an alternative to oral anticoagulation in patients intolerant to oral anticoagulant agents (OACs). Current estimates suggest that up to 40% of people with AF and an indication for OAC have a relative or absolute contraindication to the use of warfarin, and <50% of eligible patients are being treated because of medication intolerance or noncompliance (10-13). Whether this pattern of underutilization will be similar with the several new OACs that are now approved is unknown. These agents have their own unique concerns, such as continued issues with gastrointestinal bleeding, cost, lack of antidotes, and for some of them, the need for twice-a-day dosing. Patients with previous intracranial bleeds, recurrent gastrointestinal bleeds, coagulopathies, and intolerance to NOACs/warfarin will still present clinical challenges. Unfortunately, there is a lack of randomized clinical trial data for use of the LAA occlusion device in these patients. The most robust data available for LAA device occlusion in this group comes from the European PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) study (14) and the ASAP (Aspirin Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology) registry (15). In the ASAP registry, the predicted stroke rate depending on the CHADS₂ score was 7.3% per year

TABLE 1 Possible Clinical Scenarios for LAA Occlusion With the Watchman Device

1. As an alternative to oral anticoagulation in patients intolerant of OACs
2. Patients with high stroke and concomitant high bleeding risk
3. Patients with thromboembolic events while on OACs with therapeutic INR or on a NOAC and no other etiology for the clinical event
4. Patients that can tolerate oral anticoagulation and are also candidates for LAA device occlusion
5. Patients undergoing AF ablation or MitraClip implantation that may qualify for concomitant LAA occlusion at the same time of the original procedure

AF = atrial fibrillation; INR = international normalized ratio; LAA = left atrial appendage; NOAC = novel anticoagulant agent(s); OAC = oral anticoagulant agent.

and the observed stroke rate was 2.3%. It must be pointed out that these patients were on dual antiplatelet therapy (DAPT) for a duration of approximately 6 months and on aspirin indefinitely thereafter. Potential patients who would be enrolled into this pathway must be able to tolerate short-term DAPT and indefinite use of aspirin.

2. Patients with high stroke and concomitant high bleeding risk. A HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR [International Normalized Ratio], Elderly, Drugs/Alcohol Concomitantly) score ≥3 would suggest a high bleeding risk (16,17). In these cases, individual patient-level assessment is warranted to accurately quantify the stroke and bleeding risk; a trial of warfarin or NOACs may still be warranted, especially if the risk of intracranial hemorrhage is relatively low. Patients with high stroke risk, but unacceptable bleeding risk, should be considered for LAA device occlusion. Similarly, patients on triple anticoagulant therapy (DAPT and an OAC drug), such as those with atrial fibrillation who receive a drug-eluting stent, have an elevated bleeding risk; they may be considered for LAA device occlusion. Finally, patient subgroups with comorbidities associated with a high bleeding risk not captured by the HAS-BLED score, such as malignancy and inflammatory bowel disease, may also be considered for LAA device occlusion.
3. Patients with thromboembolic events while on OACs with therapeutic international normalized ratio or on a NOAC when no other etiology for the clinical event can be identified. In this group, LAA device occlusion may potentially be used as an adjunct to anticoagulation.
4. Patients that can tolerate oral anticoagulation and are also candidates for LAA device occlusion. This

is the group in which the randomized clinical trial was conducted. On the basis of the randomized trial results, LAA device occlusion is noninferior to warfarin therapy and appears to be a safe alternative to warfarin in these patients. This has been proven in the initial trials of this device and in long-term follow-up studies. Holmes et al. (4) published the initial PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) trial that documented the noninferiority of device occlusion using the Watchman device compared with oral anticoagulant therapy with warfarin. A recently published long-term follow-up study on this group of patients revealed continued noninferiority of LAA occlusion with the Watchman device, as compared with warfarin (8). Concerns about the early procedural safety events seen in the initial PROTECT AF study were alleviated in the second randomized study, the PREVAIL trial, which revealed significant reductions in periprocedural events/complications (7). This would be a rather large population and issues of cost effectiveness, device safety, and efficacy when compared with the NOACs would be important here. In these patients, the risks and benefits of anticoagulant agents and LAA device occlusion should be presented so that they can make well-informed decisions regarding their preferred therapeutic option.

5. Patients with atrial fibrillation undergoing AF ablation or MitraClip procedures—here, LAA occlusion can be an adjunct procedure while these other procedures are being performed. A recent paper by Swaans et al. (18) revealed that LAA occlusion with the Watchman device and AF ablation can be successfully and safely combined. Patients with significant mitral insufficiency and AF undergoing the MitraClip (Abbott Vascular, Santa Clara, California) procedure may also plausibly benefit from concomitant LAA occlusion at the time of the MitraClip procedure. A recent case report documented the first combined LAA occlusion and MitraClip implantation (19). Pros and cons of this combined procedure are numerous: it may be cost effective and provide the dual benefits to the patient; however, it may expose the patient to potential complications of both approaches and may result in somewhat prolonged procedure and fluoroscopy times.

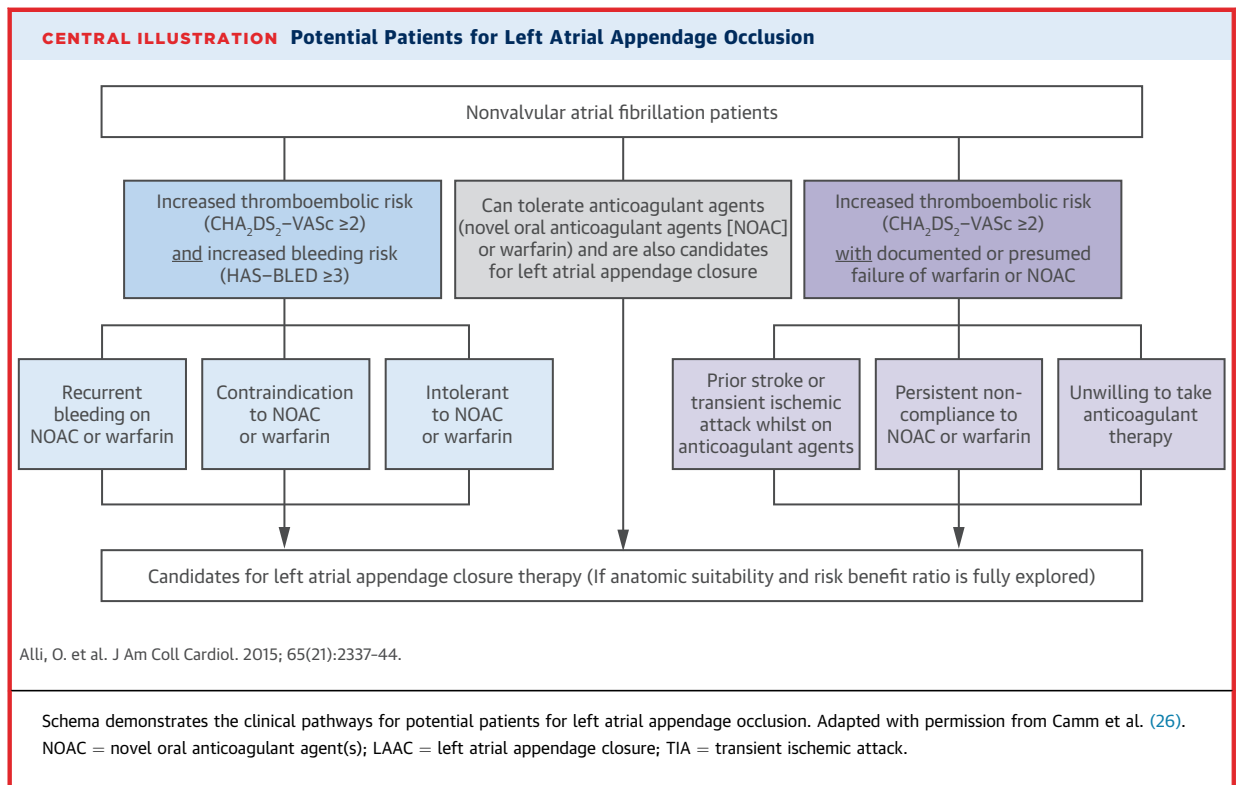
Outside of the United States, LAA device occlusion is being performed (20-26). The current European Society of Cardiology guidelines on AF (20) recommend that LAA closure may be considered in patients

with high stroke risk, but with contraindications for long-term oral anticoagulation (Class IIb recommendation). On the basis of this recommendation, the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions drafted the first European consensus statement on catheter-based LAA occlusion (21). This document provides guidance for clinicians in Europe regarding evaluation and management of thromboembolic protection in patients with AF. A recent European survey examined data from 24 centers that performed LAA occlusion procedures. In this survey, the majority of procedures were performed by interventional cardiologists (ICs) and each center performed an average of 10.6 ± 11.7 (range 1 to 50) LAA procedures per year. The most common indication was “patient has absolute contraindication to long-term anticoagulants.” Complication rates varied widely, but included pericardial tamponade (1% to 10%), major bleeds (0% to 8%), thromboembolism (0% to 10%), and device dislodgement (0% to 5%). The majority of the centers (65%) reported a 0% complication rate.

The Amplatzer Cardiac Plug is the other commonly used endocardial LAA occlusion device. Data on this device have been limited to single-center studies, case series, and small registries (22-25). The largest clinical study to date on the use of the Amplatzer Cardiac Plug (St. Jude Medical, Minneapolis, Minnesota) for LAA device occlusion was recently published by Tzikas et al. (25), who analyzed 1,047 patients from 22 centers. These investigators reported a 97.3% success rate with a 1-year all-cause mortality of 4.2%. There was a 59% risk reduction in thromboembolism and a 61% risk reduction in bleeding events. The **Central Illustration** illustrates the clinical pathways for potential patients for LAA occlusion.

OPERATORS/PERSONNEL/ INSTITUTIONAL CONSIDERATIONS

Similar to other structural heart procedures, LAA device occlusion will benefit from a multidisciplinary team approach to maximize program success. ICs with structural heart training experience and electrophysiologists (EPs) with training and experience in performing AF ablation both have an interest in performing this procedure. Each group brings a different skill set that should be used in a collaborative fashion to maximize procedural safety and efficacy. As procedures are planned and performed with echocardiographic guidance, cardiac imaging specialists will be essential members of the team. We suggest a



collaborative approach, with ICs and EPs working together in tandem, similar to current collaborations between ICs and CV surgeons to ensure procedural and institutional success and excellent patient outcomes with transcatheter aortic valve replacement. Although not all institutions have IC and EP expertise, we believe that optimal care should involve both specialties.

Specific training requirements must be met by operators interested in performing this procedure, regardless of their specialty: knowledge of LAA anatomy, experience with interpreting echocardiographic images, and experience in performing transseptal puncture and pericardiocentesis are all essential.

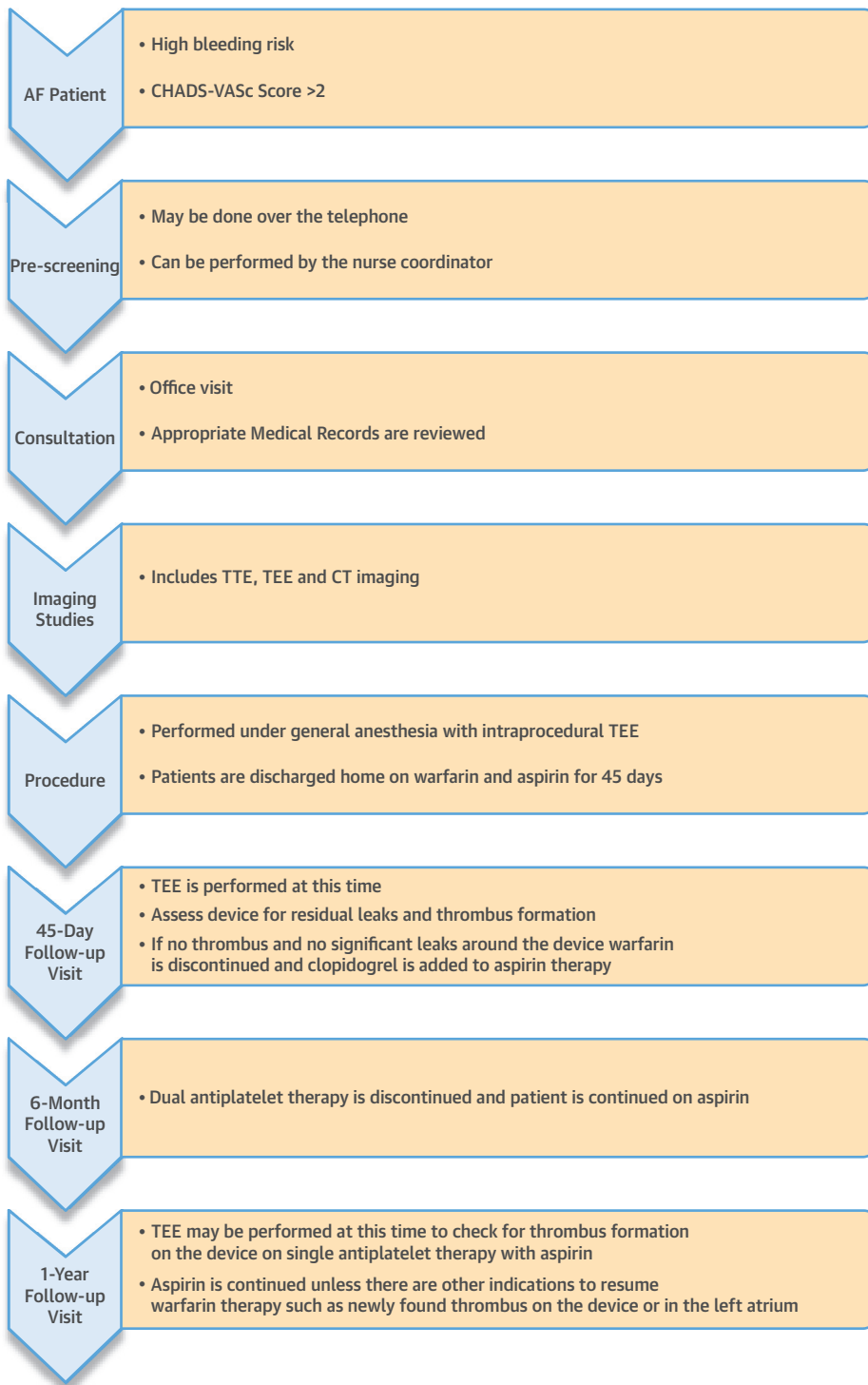
We recommend that operators and teams undergo a rigorous, structured training program. This could be provided by the relevant professional societies, as well as by the device manufacturer, and would include patient selection, adjunctive medications, LA/LAA anatomy, specific device characteristics, procedural techniques, and management of complications. Practical hands-on training would also be important; this could involve simulators to practice procedural steps and device deployment, as well as live case demonstrations by experienced centers and operators. Finally, we suggest that each team be proctored for a minimum of approximately 5 to 10 cases, or until the team is comfortable with all aspects

of the procedure, device deployment, and recognizing/managing complications.

Imaging experts with expertise in transesophageal echocardiography (TEE) and computed tomography (CT) imaging are also an invaluable part of the team. TEE would be needed for pre-procedure assessment, intraprocedural guidance, and post-procedure follow-up. Personnel performing TEE for device occlusion must be familiar with LAA anatomy, the procedure, and required measurements for device selection and delivery. We suggest a dedicated group of imagers for this procedure; this may be the same group that supports transcatheter aortic valve replacement and percutaneous mitral valve repair procedures (sometimes called interventional echocardiography). They should be familiar and experienced in supporting procedures in the cardiac catheterization laboratory, electrophysiology laboratory, or hybrid operating rooms with real-time online imaging, particularly the use of real-time 3-dimensional echocardiography. These imaging specialists should also participate in dedicated training sessions, with particular attention paid to knowledge and techniques for acquisition of baseline pre-procedural images, guidance during device delivery, and post-procedural imaging.

Some of the barriers to having a dedicated imaging specialist in each case have been reimbursement; these procedures can be time-consuming and there is

FIGURE 1 Outline of the Evaluation and Therapy Process, as Patients Are Seen and Treated



AF = atrial fibrillation; CT = computed tomographic imaging; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

currently no adequate reimbursement for the time spent by operators and echocardiographers in procedural performance. In groups where productivity is measured using relative value units, physicians involved in this procedure may have to develop other ways to account for the time spent supporting the procedure (i.e., “virtual relative value units”).

Anesthesia support is another component of the personnel team that must be involved with this procedure; traditionally, anesthesia support comes with the operating room, but is becoming more frequent in the cardiac catheterization and electrophysiology laboratories due to the increasing number of procedures being performed in these laboratories that require general anesthesia. To coordinate all the groups and personnel involved and to optimize efficiency and safety, a dedicated LAA procedure day(s) might be considered.

ALTERNATIVES TO ENDOCARDIAL LAA OCCLUSION

The Lariat device (SentreHeart, Redwood City, California) is currently approved for use in the United States for opposing tissue planes and has been utilized for suture closure of the LAA; it combines both endocardial and epicardial approaches. The PLACE-2 (Percutaneous Left Atrial Appendage Suture Ligation Using the LARIAT Device in Patients with Atrial Fibrillation) trial (6) was pivotal in documenting the safety and efficacy of the Lariat device. Use of the Lariat device may also be incorporated into the overall LAA occlusion program, because candidates may benefit from its use on the basis of anatomic variation. By contrast, patients may not qualify for use of the Lariat device because of previous cardiac surgery, prior pericarditis, and/or a large and superiorly directed LAA (>40 mm) in close proximity to the left superior pulmonary vein. A potential benefit of the Lariat device is the ability of suture ligation to aid in reduction of arrhythmia burden, which may be useful in patients with recurrent AF following ablation (27). Potential issues include endothelial or pericardial trauma and the lack of clarity on anticoagulation post-procedure. Using the Lariat device in a recently published real-world multicenter registry, Price *et al.* (28) documented an 85% success rate and a 9.7% major complication rate. There have not been any studies comparing suture ligation with the Lariat device versus endocardial LAA occlusion devices, and it is unclear if such studies will be conducted, but real-world use of both devices may shed some light on the efficacy of either strategy.

Surgical LAA occlusion using sutures or staples at the time of heart surgery (coronary artery bypass graft, heart valve replacement) is also frequently performed. The efficacy of this procedure is being evaluated in the ongoing LAAOS III (Left Atrial Appendage Occlusion Study III) study (29), which will follow patients undergoing surgical LAA occlusion at the time of open-heart surgery over time to determine the continued occlusion of the structure, efficacy, and safety outcomes.

PATIENTS/REFERRAL BASE/ TARGET POPULATION

The initial target population will depend on the FDA-approved indication for use; once this is formulated, several questions would need to be addressed by operators/institutions. These include: patient referral; where these patients would come from; who will see them initially as outpatients; and how will they move from the initial evaluation period up until procedural performance. Patients could be referred from several sources, (general cardiology, primary care, hospitalists), and may need to be seen in a dedicated clinic with a dedicated nurse/clinic coordinator. There may be a large volume of potential patients with a significant “screen fail” rate, and these patients would need to be seen using a streamlined, efficient approach. One potential patient flow system might function as follows: an initial call to scheduler or clinic coordinator to make arrangements for the patient to be seen; the patient is seen by a physician, either IC or EP, who screens for eligibility; if the patient qualifies, a pre-procedure TEE is performed. If the patient is eligible, detailed risk/benefit sessions with the patient and family need to be performed before performance of the planned procedure.

The goal would be to perform this procedure in appropriate patients who may benefit from a device-based strategy with high success rates and low complication rates, avoiding patients who are too sick, too old, or too frail, which may lead to high complication rates.

IMAGING

Imaging remains central and essential to the development of a successful LAA occlusion program. The ability to assess the LAA using imaging modalities is essential for pre-procedural assessment, during device delivery and deployment, and during follow-up. The use of transthoracic and transesophageal imaging techniques allow for adequate assessment of the LAA. CT, magnetic resonance imaging, and

intracardiac echocardiography (ICE) may also be useful.

TEE remains the central imaging technique for adequate visualization of the LAA; when used for pre-procedural assessment, it is essential to demonstrate adequate visualization to exclude LAA thrombus. Adequate interrogation of the LAA is performed using multiple views from 0° to 145°, where LAA morphology is adequately characterized, with measurements of the LAA ostium and neck. Intra-procedural imaging is also usually accomplished using TEE; it aids with transseptal puncture, device sizing and deployment, and detection of complications, such as pericardial effusion.

The accessibility of other imaging modalities, such as ICE, is also important; occasionally patients may not be able to undergo TEE or sedation under general anesthesia. In such cases, ICE imaging may play an important role. The ICE probe can be inserted directly into the LA to obtain a closer imaging assessment of the LAA, or it may be directed into the right ventricle and the pulmonary artery, which also gives excellent visualization of the LAA.

PROGRAM EVALUATION/ DATA COLLECTION/PATIENT FOLLOW-UP

This should be an ongoing effort between the administrative leadership and the clinical leadership; assessment would include quality measures, outcomes, length of stay, resource utilization, and cost effectiveness. It would be beneficial to develop a standard methodology for assessment of perioperative and post-operative complications, such as the VARC 2 (30) criteria used for transcatheter aortic valve replacement. Adequate data collection would be a very important component of the program; a national post-approval registry is currently being considered. Regardless, individual institutions should track their own data and continually assess and track their success and complication rates. Maintenance of a post-approval registry is extremely important, because it enables collection of additional data that will shed more light on device performance in the real world.

PRACTICAL CONSIDERATIONS

Incoming referrals to the center must be carefully screened and evaluated before their appointment; a screening checklist may be utilized to ensure that the appropriate candidates are being selected for appointments. The initial clinic visit will include a comprehensive history and physical examination, assessment of stroke and bleeding risk, basic laboratory testing, and review of imaging studies (transthoracic

echocardiography, CT, and TEE, if performed). At this visit, frailty assessment, quality of life metrics, and mental status assessment may also be conducted.

Patients are likely to come into the facility before the procedure, at which time, a history and physical is performed, basic blood work is obtained, and risk-benefit considerations are discussed fully with the patient and family. The goal of the procedure is the successful delivery of a LAA occlusion device and prevention/rapid management of potential complications. For the procedure, sedation and general anesthesia is initiated, appropriate arterial and venous lines are placed, and a TEE probe is inserted. The procedure is then performed using standard techniques with TEE imaging.

Post-procedure, patients can be managed in a cardiac step-down unit; care is taken to ensure close observation, with attention to blood pressure and early detection of complications. Most patients would be expected to spend between 1 and 2 days in the hospital following an uncomplicated procedure; for patients intolerant of OACs, DAPT with aspirin and clopidogrel is used. Follow-up at 45 days is recommended. At this visit, a TEE is performed to assess device position, check for peri-device LAA flow, and assess device-related thrombus. Patients are seen at 6 months, when clopidogrel may be discontinued for those who were on DAPT, and aspirin is continued indefinitely. Patients undergoing AF ablation or MitraClip implantation along with concomitant LAA occlusion may be referred from specialty AF or valve clinics, but will follow a similar pathway post-procedure as the general patient. **Figure 1** provides a schematic diagram of a typical patient pathway from evaluation to therapy and follow-up.

CONCLUSIONS

LAA occlusion for stroke prevention in patients with AF represents a tremendous opportunity to change the landscape of stroke prevention in patients with nonvalvular AF. Several devices have CE-mark approval and the Watchman device was recently approved in the United States. As we discussed, in order to ensure success of the device/procedure, operators/institutions must commit to a strong collaborative approach to optimize outcomes and resource utilization.

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KEY WORDS anticoagulant agent(s), atrial fibrillation, stroke prevention, thromboembolism