Ali Massumi Cardiac Arrhythmia Symposium

Closure of Left Atrial Appendage to Prevent Stroke: Devices and Status

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Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, is diagnosed in 2% to 3% of the general population.[1] It causes blood to stagnate in the atrial chamber, which leads to thrombus formation. The risk of stroke is 4 to 5 times higher in persons with AF than in those without.[2] More than 90% of thrombus accumulation occurs in the left atrial appendage (LAA).[3] Left atrial appendage closure is an alternative treatment to prevent strokes in high-risk patients with nonvalvular AF who are not candidates for oral anticoagulation (OAC) therapy or in whom OAC therapy has failed.[4]

Evolution in Device Design for Left Atrial Appendage Closure

Several endocardial LAA closure devices have been developed over the years. A first-generation device, the Percutaneous LAA Transcatheter Occlusion system (PLAATO) (ev3 Inc.), never reached commercial production.[5] One second-generation device is the WATCHMAN™ Left Atrial Appendage Closure Implant (Boston Scientific Corporation); another, the AMPLATZER™ Cardiac Plug (Abbott), is not yet commercially available in the United States.

Four next-generation endocardial closure devices have been created. One, the WaveCrest® Left Atrial Appendage Occlusion System (Coherex Medical, Inc.),[5] received the Conformité Européene (CE) mark of approval in 2013, but it is not commercially available in the U.S. This device advantageously has a very short landing zone, and the sheath does not have to be introduced deeply into the LAA.

A second device, the *ultrasept* Left Atrial Appendage Closure Device (Cardia, Inc.),[6] is fully retrievable, which enables repositioning as often as necessary during deployment.

A third device, the LAmbre™ LAA Closure System (Lifetech Scientific Corporation),[7] is a nitinol-based, fabric-covered, hook-embedded self-expanding umbrella that is connected to a short central waist. This product has the CE mark of approval for LAA closure.

Finally, the Occlutech LAA Occluder (Occlutech International AB)[8] is a self-expanding, conical, nitinol wire-mesh device that is anchored with distal closed loops. Flexible and self-adjusting, it earned the CE mark of approval in 2016 for LAA closure.

A transcatheter epicardial LAA closure device, the LARIAT® Suture Delivery System (SentreHEART, Inc.), is used to ligate the LAA via the endocardial and epicardial approaches. Placement of a surgical knot around the LAA ostium and approximation of all walls removes the LAA.

Clinical Studies

Several studies have been conducted to evaluate LAA closure in patients with and without contraindications to OAC therapy. In patients without such contraindications, 3 studies are of note.

PROTECT AF. After 3.8 years of monitoring, results from this prospective randomized trial[9] showed that LAA closure is noninferior to warfarin therapy alone in preventing cardiovascular death, stroke, or systemic embolism in patients with nonvalvular AF. The investigators recruited 707 patients at 59 sites, randomizing 463 to the device group and 244 to warfarin therapy. The rate of adverse events (transient ischemic attack or stroke) was 3.6 events per 100 patient-years in the device group versus 3.1 in the warfarin group. This study raised some concerns, however, including the high initial

rate of procedural complications, failure to implant the device in some patients, and a low $CHADS_2$ score of the patients after treatment.

PREVAIL. The PREVAIL study[10] was performed to confirm the results of the PROTECT AF study regarding the efficacy of the WATCHMAN procedure, and to find answers to the concerns about that study's outcomes. The PREVAIL study maintained a design similar to PROTECT AF, with slight modifications to the patients' inclusion criteria. In total, 407 patients were randomized at a ratio of 2:1 (device vs warfarin). A significant increase in the implantation success rate (95.1%) was found in PREVAIL versus that in PROTECT AF (90.9%), and the rate of complications was lower. Seven-day procedure- or device-related severe vascular complications occurred among 4.5% of patients in PREVAIL, in comparison with 8.7% in PROTECT AF. Trial results failed to show that the WATCHMAN procedure was superior to warfarin at preventing cardiovascular/unexplained death, stroke, or systemic embolism at 18 months; however, the device was not inferior to warfarin at preventing stroke and systemic embolism from 7 days up to 18 months.

Five-Year Outcomes after Left Atrial Appendage Closure. The 5-year follow-up analysis of the PROTECT AF and PREVAIL trials[11] showed that the WATCHMAN procedure had similar all-cause stroke rates, fewer cardiovascular deaths, superior efficacy, lower mortality rates, and similar overall safety in comparison with warfarin.

Four major studies have focused on LAA closure in patients who have contraindications to OAC therapy.

Five-Year Results of the PLAATO Study. Investigators recruited 64 patients who had permanent or paroxysmal AF for the observational, multicenter, prospective Percutaneous Left Atrial Appendage Occlusion for Patients in Atrial Fibrillation Suboptimal for Warfarin Therapy Study and monitored them for 5 years.[12] The stroke and transient ischemic attack rate among these patients was expected to be 6.6% per year on the basis of the $CHADS_2$ scoring system; however, the rate improved to 3.8% per year after percutaneous LAA occlusion.

ASAP. The ASAP study (ASA Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology)[13] focused on LAA closure with use of the WATCHMAN. In this multicenter, prospective, nonrandomized study, 150 patients with nonvalvular AF, $CHADS_2$ scores ≥1, and contraindications for warfarin underwent the WATCHMAN procedure. The rate of ischemic stroke, expected to be 7.3% per year on the basis of $CHADS_2$ scores, improved to 1.7% after the procedure.

Multicenter Experience with the AMPLATZER Cardiac Plug. In this study of LAA occlusion for stroke prevention in AF with use of the AMPLATZER Cardiac Plug,[14] 1,047 patients were recruited from 22 centers. The procedural success rate was 97.3%, and 52 periprocedural major adverse events were reported. The rate of ischemic stroke, an expected 5.62% per year on the basis of

TABLE I. Comparison of Results of the LARIAT Trials[5]

Variable	LARIAT Place II Bartus K, et al.[15]	LARIAT Massumi A, et al.[16]	LARIAT Stone D, et al.[17]	LARIAT No OAC Sievert H, et al.[4]	LARIAT Cumulative
Patients (n)	89	21	27	143	280
Intent to treat	85 (96)	20 (95)	25 (93)	139 (97)	269 (96)
Procedural closure among intent-to-treat population	82 (96)	19 (95)	25 (100)	138 (99)	264 (98)
>60-d closure among pts who had follow-up TEE	81 (95)	16 (94)	22 (100)	126 (91)	245 (91)
$CHADS_2$ score	1.9 ± 0.95	3.2 ± 1.2	3.5 ± 1.4	2.4 ± 1.2	2.6 ± 1.2
Sequelae*					
Access-related	3 (3.4)	1 (4.8)	1 (3.7)	3 (2.1)	8 (2.9)
All-cause death	2 (2.2)	1 (4.8)	0	6 (4.2)	9 (3.2)
All-cause stroke	2 (2.2)	0	1 (3.7)	4 (2.8)	7 (2.5)
Major bleeding	0	0	1 (3.7)	2 (1.4)	3 (1.1)
Pericardial or pleural effusion	1 (1.1)	3 (14.3)	2 (7.4)	1 (0.7)	7 (2.5)

OAC = oral anticoagulation; pts = patients; TEE = transesophageal echocardiography

Data are presented as number and percentage or mean ± SD.

*No patient experienced a device-related sequela.

Adapted with permission from Safavi-Naeini P, Rasekh A. Tex Heart Inst J 2016;43(4):320-3.[5]

$CHADS_2$ scores, improved to 2.3% postprocedurally. The expected 5.34% rate of major bleeding on the basis of the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol use) improved to 2.1%. Patients who underwent single LAA occlusion on aspirin or no therapy had fewer cerebral and bleeding events upon longer follow-up.

LARIAT Use. Although the LARIAT device has not been evaluated in prospective randomized trials, data in retrospective published studies[5] showed the efficacy of the LARIAT procedure for LAA closure and preventing AF-related stroke (Table I).[4,15-17]

Combined Ablation and LAA Exclusion

The aMAZE trial,[18] an ongoing prospective, multicenter, randomized (2:1) controlled study, is designed to determine the safety and effectiveness of the LARIAT procedure to percutaneously isolate and ligate the LAA from the left atrium as an adjunct to planned pulmonary vein isolation catheter ablation in the treatment of patients with symptomatic or longstanding persistent AF.

Challenges and Unanswered Questions

Several challenges and questions remain regarding LAA closure. First, the data on stroke reduction are not robust given the inconsistency between the PROTECT AF and PREVAIL results,[10,13] and the studies with positive results are nonrandomized.[5] Second, how can the severe procedural complications be reduced? Third, the target population is not well defined: should all AF patients undergo LAA closure, or only patients in whom OAC therapy is contraindicated? Finally, do all devices have similar efficacy? Are comparative studies needed?

The initial results of LAA closure and ligation procedures to prevent AF-related stroke are encouraging. However, only the WATCHMAN is approved in the U.S. for LAA exclusion to prevent stroke, while clinical trials of the AMPLATZER Cardiac Plug and WaveCrest are ongoing. The role of the LARIAT in persistent AF also needs to be determined. In the meantime, no device is approved for use in the U.S. for patients with AF and contraindications to OAC therapy.

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