6th Risk, Diagnosis and Treatment of Cardiovascular Disease in Women

Where We Stand on Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

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Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia—found in 1% to 2% of the general population.[1] It is also a major cause of ischemic stroke. Patients with AF are 4 to 5 times more likely to have an ischemic stroke.[2] Their annual rate of stroke is 5%, which accounts for 15% of all strokes in the United States.[2,3] The left atrial appendage (LAA) is a trabeculated cul-de-sac that is responsible for more than 90% of thrombus formations in AF patients.[4] Because of these findings, LAA closure devices have been developed as an alternative to oral anticoagulant (OAC) therapy.

The first generation of endocardial LAA occluders comprised 3 devices: the Percutaneous LAA Transcatheter Occlusion system (PLAATO) (ev3 Inc.; Plymouth, Minn), the WATCHMAN™ Left Atrial Appendage Closure Device (Boston Scientific Corporation; Natick, Mass), and the AMPLATZER™ Cardiac Plug (ACP) device (St. Jude Medical, Inc.; Minneapolis, Minn). PLAATO withdrew from the market in 2006, and the ACP is not yet available for commercial use in the U.S.[5]

The newer generation of endocardial LAA occluders comprises the WaveCrest® LAA Occlusion System (Coherex Medical, Inc.; Salt Lake City, Utah), the LAmbre™ Left Atrial Appendage Occluder (Lifetech Scientific [Shenzhen] Co., Ltd.; Shenzhen, PRC), and the Ultrasept LAA Closure Device (Cardia Inc.; Eagan, Minn), none of which is available for commercial use in the U.S.[6] If you prefer to perform LAA closure through an epicardial approach, the LARIAT® Suture Delivery Device (SentreHEART, Inc.; Redwood City, Calif) and the Aegis device (Aegis Medical Innovations Inc.; Vancouver, Canada) will permit that. But the Aegis device is available for investigational use only.[6]

The WATCHMAN Clinical Trial Experience

The WATCHMAN LAA Closure Technology for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) clinical trial was designed to examine the safety and efficacy of the WATCHMAN device in patients with nonvalvular AF who were eligible for warfarin therapy and had a $CHADS_2$ stroke-risk score of 1 or greater.[7] From February 2005 through June 2008, 707 patients at 59 centers in the U.S. and Europe were enrolled in the PROTECT AF study. The patients were randomly assigned in a 2:1 ratio to percutaneous closure of the LAA and subsequent discontinuation of warfarin (n=463), or to warfarin treatment. All patients were monitored for 12 months.[7] The PROTECT AF trial showed that the WATCHMAN LAA Closure is noninferior to warfarin for the combined endpoint of stroke, systemic embolism, and death, and it is a safe and effective alternative to OAC therapy in decreasing the risk of AF-related stroke.[7,8] The PROTECT AF trial showed a high rate (8.7%) of implant device-related sequelae, including perforations and pericardial effusions, and had a procedural failure rate of around 9%. However, most of these events occurred during the early stages of the trial, and procedural failure rates declined as surgeons became more experienced with the operation.[9]

According to the PROTECT AF trial, the U.S. Food and Drug Administration (FDA) review panel required a 2nd trial to show that the lower procedural failure rate at the late stages of the study could be maintained across various hospitals and with new operators. In order to respond to the FDA panel's concerns, a 2nd trial, The Prospec-

tive Randomized EVAluation (PREVAIL), was designed, involving 407 patients randomly distributed in a 2:1 ratio to warfarin (as a control group) or to WATCHMAN LAA Closure. These 407 patients were warfarin-eligible and had a mean $CHADS_2$ score of 2.6 ± 1.[10] The PREVAIL study showed an overall 95% success rate for implanting the device (93.2% for new surgeons), and the overall 7-day serious procedure- or device-related complication rate was 4.4% (a 49% relative reduction rate) in comparison with PROTECT AF, which had an 8.7% device-related complication rate.[10]

The PROTECT AF/PREVAIL meta-analysis (2,406 patients and 5,931 years of patient follow-up) showed that rates of hemorrhagic stroke, nonprocedural bleeding, and cardiovascular and unexplained deaths were decreased among patients who had LAA closure with use of the WATCHMAN, versus patients who were on long-term OAC therapy.[11] It bears mention, however, that if periprocedural complications were included, there would be no significant differences in rates of all-cause death or major bleeding.[12]

LARIAT Studies

The LARIAT is a minimally invasive procedure to tie off the LAA and remove the main source of AF-related stroke for patients who are at high risk of stroke and are not suitable candidates for OAC therapy. A single-center, nonrandomized study (PLACE II) showed about a 96% incidence of effective LAA closure (85 of 89 procedures). Three adverse events (3.3%) were reported, including bleeding (2 pericardial and 1 transseptal). The study investigators determined that the LARIAT procedure can effectively close the LAA, with acceptable low-access sequelae and periprocedural adverse events.[13]

To date, the LARIAT has not been involved in any prospective randomized trials, but published clinical results for single-center studies (together with a recent multicenter study) provide insight into the potential of the LARIAT as a method of LAA closure, as well as insight into the potential for protection against stroke (Table I).[13-17] These study results indicate consistent trends of efficacy and safety for LAA closure, which warrant further evaluation of the LARIAT in a multicenter prospective randomized trial. Sievert and colleagues[17] conducted a 5-center study that evaluated the use of LARIAT for patients who had contraindications to OAC therapy, such as histories of bleeding, stroke/transient ischemic attack, or cerebral aneurysm. There were 6 deaths during this study's 2-year follow-up period, one of them procedure-related because of a pulmonary embolus one day after the procedure. Sievert and colleagues' study provides promising insight into the potential of LARIAT's percutaneous, nonimplant approach in high-risk patients for whom there are no other options.[17]

Impact of LARIAT LAA Exclusion on Atrial Fibrillation Burden

Lakkireddy and colleagues[18] compared the AF burden over a period of 3 months, before and after LAA ligation. Among the 18 patients in that study, the AF bur-

TABLE I. Efficacy and Sequelae of the Lariat Procedure[14]

Study	LARIAT PLACE II Bartus K, et al.[13] (2013)	LARIAT Massumi A, et al.[15] (2013)	LARIAT Stone D, et al.[16] (2015)	LARIAT No OAC Sievert H, et al.[17] (2015)	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-day closure among patients 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					
Device-related	0	0	0	0	0
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)	4 (1.4)
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/pleural effusion	1 (1.1)	3 (14.3)	2 (7.4)	1 (0.7)	7 (2.5)

OAC = oral anticoagulation; TEE = transesophageal echocardiography

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

Adapted with permission from *J Tehran Heart Cent 2015;10(2):69-73*.[14]

den decreased from a baseline of 81% to 47% after ligation (P <0.01).[18] Afzal and associates[19] recorded the AF burden before LAA exclusion (baseline), and twice later, at 3 and 12 months after exclusion. According to this study, the AF burden at the 3-month follow-up evaluation was 42% ± 34%, significantly lower than that at baseline (76% ± 33%; P <0.0001); and the reduction of AF burden was fairly well sustained at 12 months (59% ± 26%; P <0.001).[19]

The aMAZE Trial

The LAA Ligation Adjunctive to PVI for Persistent or Long-Standing Persistent Atrial Fibrillation (aMAZE) Trial to Evaluate LARIAT Ligation of the Left Atrial Appendage is a prospective, multicenter, randomized (2:1) controlled study.[20] This trial was designed to evaluate the safety and effectiveness of the LARIAT, which percutaneously isolates and ligates the LAA from the left atrium as an adjunct to planned catheter ablation of the pulmonary vein in isolation, in the treatment of patients who manifest symptomatic persistent or long-standing persistent AF. This study will be conducted in 2 stages: in Stage 1 (the Limited Early Stage), there will be as many as 175 patients at up to 15 sites; and in Stage 2 (the Pivotal Stage), there will be as many as 600 patients at up to 50 sites. All patients from both stages will be included in the primary analysis.

Conclusion

The WATCHMAN is the only LAA closure device approved by the FDA for LAA exclusion in the U.S. Moreover, there are still no approved devices for patients who have AF and a contraindication to OAC therapy. Several retrospective multicenter studies of experiences with the LARIAT device have confirmed high acute procedural success rates.[13,15-17] The role of LAA ligation in reducing AF burdens in patients who display persistent AF must be further evaluated in a multicenter prospective study. The role of LARIAT in the treatment of a targeted population with persistent AF is currently under investigation.[20]

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