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EDITORIAL COMMENT

Clinical Significance of Leaks Following Left Atrial Appendage Ligation With the LARIAT Suture Delivery Device*

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The LARIAT device (SentreHeart, Redwood City, California) utilizes a combined endocardial and epicardial approach to place an epicardial suture to ligate the left atrial appendage (LAA) (1). The initial prospective efficacy and safety study on the LARIAT device demonstrated an acute closure rate of 96% and a 1-year closure rate of 98% (1). The overall adverse event rate was 3.3%. Subsequent single-center studies supported these initial findings (2,3).

The early promising results led to a wider use of the LARIAT for LAA exclusion in patients with contraindications to oral anticoagulation (OAC) therapy. As with the adoption of any new interventional technology, there was a learning curve with reports of higher adverse events and leak rates (4,5), which can be attributed to small sample size, operator experience, patient selection, and training (6). In a multicenter registry involving 712 patients, the LARIAT procedure was found to have a long-term LAA closure efficacy rate of 93.3%, with a major adverse event rate of 3.6% that decreased to 1.0% with the use of the micropuncture needle for pericardial access (7). The safety of the LARIAT procedure compares favorably with other interventional and electrophysiological procedures performed; and will be verified in the aMAZE trial (8).

The LARIAT device is Food and Drug Administration–approved for delivery of a suture or knot to approximate and/or ligate soft tissue structures. For stroke prevention, the LARIAT device is being used off-label, advocated for only patients who have contraindications to OAC therapy (6). The medical rationale for advocating the use of the LARIAT procedure is reasonable on the basis of the assumption that LAA closure will prevent LAA thrombus formation, thus leading to a decrease in cardioembolic events in patients with AF. In this issue of *JACC: Cardiovascular Interventions*, Gianni et al. (9) report their results from a retrospective, multicenter study on the incidence of leaks and the clinical implications of leaks following LAA ligation with the Lariat device in patients with intolerance to long term anticoagulation therapy. The study raises an important question, namely, are LAA leaks resulting from a LARIAT procedure associated with thrombus formation and thromboembolic events.

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The authors were from 4 centers in the United States involving 98 consecutive patients who underwent a successful LAA ligation procedure with the LARIAT device. Leaks were assessed by 3-dimensional (3D) transesophageal echocardiography (TEE) imaging. Acute LAA closure was achieved in 95% of patients, while leaks were detected in 15% of patients at 6 months and 20% of patients at 12 months. Five neurological events occurred during the mean follow-up period of 16 months. A brain computed tomography/magnetic resonance imaging (CT/MRI) scan was done acutely in all patients and did not reveal hemorrhage. However, there was no independent review of the brain CT/MRI by a neurologist to determine whether the distribution of the stroke was consistent with a thromboembolic event. Additionally, the retrospective nature of the

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study did not exclude other potential thromboembolic sources as atheromatous plague in the aorta or carotids. Three neurological events were seen in patients with leaks, but no evidence of thrombus formation. The other 2 patients had acute LAA closure, but no follow-up TEE. Three of 19 patients with a leak had a thromboembolic event versus none of 77 with persistent LAA closure. However, 2 of the patients with neurological events had acute LAA closure and may not have had a leak at the time of their neurological event.

Although the study highlights the importance of investigating the relationship between leaks and stroke, any conclusions from this study needs to be taken in context with the limitations of the study and in relationship to other published reports. Inherent limitations to any retrospective analysis are the potential to introduce unintentional bias in the collection of data, reporting of results, and interpretation of results. If there are selective preconceptions between groups of patients about the risk factor of a leak and the outcome of a thrombotic event, recall bias will be present. Bias will be magnified with incomplete TEE data, differences in which patients received OAC therapy following LAA ligation and variation in site reporting. Cause and effect relationships are difficult to assess with a retrospective study due to the inability to control standardization of the procedure, imaging and outcome assessment. The small cohort, lack of pre-specified outcomes, and center variability prevented the investigators from performing any meaningful statistics. Therefore, only the suggestion of an association and not causation that leaks are related to thromboembolic events can be inferred from the results of the study.

In a multicenter prospective observational study reported by Pillarisetti et al. (10) comparing leaks and their clinical implications in 478 patients (219 with the WATCHMAN device [Boston Scientific, Marlborough, Massachusetts] and 259 with the LARIAT device) who had successful LAA closure, there was not an association of leaks and thrombotic events following LAA ligation with the LARIAT device. Gianni et al. (9) suggest the differences in results are due to the under detection of leaks assessed with 2-dimensional (2D) TEE. Although 3D TEE has been used to assess LAA orifice size before LAA closure (11,12), it has not been compared to 2D TEE for the assessment of leaks. Without standardization of 2D and 3D TEE imaging within each study and between the 2 studies, comparisons between the 2 studies regarding leaks and thromboembolic events cannot be made.

Corroborating the results of Pillarisetti et al. (10), a multicenter registry of 712 consecutive patients undergoing the LARIAT procedure did not demonstrate that leaks were associated with thrombus formation or thromboembolic events (7). There was an acute LAA closure rate of 98%. Follow-up TEE revealed that 6.5% of patients had leaks of 2 to 5 mm and 1 patient (0.2%) with a leak >5 mm. Thrombus was seen in 2.5% of patients. There were no thromboembolic events reported. The incidence of thrombus formation associated with the LARIAT device has been reported to be between 1.1% and 2.5% and are not limited to patients with leaks (1,7,13). A potential etiology for thrombus formation is that LAA ligation causes necrosis and an inflammatory response that could result in endothelial dysfunction and thrombus formation (14). Additionally, irregularities of the tissue surface due to the suture ligation and/or stagnant flow could also contribute to thrombus formation.

The only prospective study to date assessing clinical outcomes of stroke and death following the LARIAT procedure is from Sievert et al. (15). In this multicenter study, 139 patients were followed on average 2.9 years, with the longest patient followed for over 5.5 years. There was no transition OAC therapy after LAA ligation. Acute LAA closure was obtained in 138 of 139 patients. Follow-up TEE revealed a 10% incidence of leaks, with no leaks >4 mm. Two LA thrombus occurred in patients without a leak. Five adverse events (3.6%) required corrective interventions. The thromboembolic stroke rate was 1.0% constituting an 80% reduction compared to a historical National Registry of Atrial Fibrillation. There was no association of thromboembolic events and leaks.

The range of LARIAT associated LAA leaks reported in the published data with over 20 patients range from 0% to 24% (1-5,7,10,15). The large variation in the rate of leaks is due to technique, closure site, and lack of standardized imaging to detect leaks. The final diameter of the deployed suture loop determines the size of the leak. Deployment of the suture around too much tissue, that commonly occurs when the suture is deployed near atrial tissue on the neck of the LAA, will lead to a larger diameter suture loop due to closing of the suture around more tissue. As the ischemic LAA tissue leads to necrosis and remodeling, shrinkage of the tissue or migration of the suture knot to a narrow aspect of the LAA could result in a leak following the LARIAT procedure. Additionally, all leaks are not equal. Leaks <2 mm may close spontaneously (1,7,15), while leaks 3 mm or greater generally do not close spontaneously. LAA 3D geometry assessed by CT imaging revealed a range of LAA remodeling after a leak with all having a

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reduction in LAA volumes (16). There were no thromboembolic events in patients with LAA leaks during the follow-up period of 842 ± 338 days post-LAA ligation.

The significance of a leak and how to address a leak following the LARIAT procedure is unresolved. OAC therapy is generally not an option in patients undergoing a LARIAT procedure for stroke prevention. The central concentric leak associated with a LARIAT procedure can be effectively closed with endovascular closure devices and should be considered a permanent solution to residual leaks following LAA ligation, but potentially unneccessary. The initial prospective observational study by Sievert et al. (15) for stroke prevention with the LARIAT device in patients with contraindications to OAC therapy is promising. However, there is a need for validation of these initial observations and need to clarify the clinical significance of a leak. This can only be done with well-designed, prospective trials and registries that standardize patient eligibility, procedural aspects of the LARIAT procedure, imaging of the closure site, and clinical outcomes.

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