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Evolution of Catheter Based Therapies for Persistent and Long-Standing Persistent Atrial Fibrillation: The Amaze Trial

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia of man and the incidence of AF increases with age. AF is known to increase the risk of stroke, heart failure and death. Patients with persistent and longstanding persistent AF generally do not respond to medications. Catheter ablation of AF is associated with a high rate of success in patients with paroxysmal AF. However, once a patient develops persistent or longstanding persistent AF, the outcomes of curing AF drop dramatically with catheter ablation. The development of new technologies and procedures has allowed physicians to perform catheter-based procedures that could previously be done only with cardiac surgery. One such technological development is the LARIAT procedure that allows cardiac electrophysiologists and surgeons to percutaneously exclude the left atrial appendage (LAA) and perform catheter ablation resulting in a percutaneous alternative to the open-chested surgical procedure, the Cox-Maze procedure. The AMAZE trial is a prospective, multi-center trial that was designed to evaluate the safety and effectiveness of the LARIAT procedure to percutaneously exclude the LAA; and to determine if LAA exclusion combined with catheter based pulmonary vein isolation improves maintenance of sinus rhythm in patients with persistent or long standing persistent AF. The mini-review will describe the epidemiology of AF, review current treatment of AF and provide the rationale and status for the AMAZE trial.

Keywords: Atrial fibrillation; AMAZE trial; Catheter ablation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1]. It may cause debilitating symptoms of palpitations, fatigue, exercise intolerance and shortness of breath. AF exponentially increases with age; and there is a 5 to 6-fold increase in stroke, a 3-fold increase in heart failure, a 2-fold increase in dementia, and an overall increase in death [2-6]. AF is a major public health concern. The cost of treatment of AF and loss of productivity in the work force due to morbidities associated with AF result in costs to society estimated to be over 26 billion dollars per year [7]. The treatment of AF is focused toward reducing symptoms, and the prevention of stroke and heart failure. Much of the pharmacological treatment of AF has targeted rate control, conversion to sinus rhythm, maintenance of sinus rhythm, and prevention of cardioembolic stroke and systemic embolic events. Medical therapy includes: 1) beta-blockers and calcium channel blockers for rate control, 2) antiarrhythmic drug therapy to maintain sinus rhythm, and 3) oral anticoagulation (OAC) therapy for the prevention of cardioembolic events. Additionally, external cardioversion is commonly needed to convert AF to sinus rhythm. Medical management of AF is limited due to low efficacy, drug toxicities and in the case of OAC therapy, associated bleeding problems.

The non-pharmacological "Gold Standard" for the treatment of AF is the surgical Cox-MAZE procedure [8]. Results from the surgical Cox-Maze III procedure demonstrated maintenance of sinus rhythm of greater than 96% at 10 years with freedom from cardioembolic stroke exceeding 99% [9]. Few surgeons currently perform the "cut and sew" Cox-Maze III due to the complexity and morbidities associated with the surgery. However, due to the success of the surgery in treating AF, minimally invasive Maze procedures have been developed [10]. Although the minimally invasive Maze procedure has been reported to have better clinical outcomes then catheter ablation, there was a significantly greater amount of procedural adverse events with the minimally invasive surgical procedure (23%) compared to catheter ablation (3%) [11].

Radiofrequency catheter ablation was developed as an alternative to surgery and used for the treatment of AF when long-term medications or electrical cardioversion were not effective. AV node ablation with pacemaker implantation was commonly used for patients who failed medical therapy for maintenance of sinus rhythm and whose rate could not be controlled by medications. Although shown to be beneficial in some patients with persistent and longstanding persistent AF, the concern for the development of heart failure do to RV pacing and a finite risk of sudden cardiac death has lead to AV node ablation and pacemaker implantation as a treatment of last resort [8,12,13]. The observation that ectopic beats originating from the pulmonary veins contributed to the therapeutic development of catheter ablation based pulmonary vein isolation (PVI) for the treatment of AF [14]. Catheter ablation for paroxysmal atrial fibrillation (PAF) is the least invasive treatment of AF with acceptable efficacy rates of approximately 80% after a single procedure [8]. The success of PVI by catheter ablation has led to PVI becoming first line therapy for PAF. Despite the success with PVI for PAF, the results of catheter ablation in persistent AF approaches 45-50% after a single procedure at 12 months; while 5 year efficacy rates of 20% after a single procedure and less than 50% after multiple procedures are common [15,16].

Multiple catheter ablation strategies in addition to PVI have been used to try and increase the efficacy of catheter ablation for the treatment of persistent and long-standing persistent AF [15,17-19]. These additional strategies include the addition of ablation of complex abnormal fractionated electrograms, addition of linear ablation lines,

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targeting rotors and elimination of ectopic atrial tachycardias and/or atrial flutters [17-21]. Regardless of the ancillary approach to PVI, PVI alone appears to be as efficacious to PVI combined with additional catheter ablation strategies [17,18]. Therefore, catheter ablation alone is marginally effective for the treatment of persistent and long-standing persistent AF. A desirable target in addition to PVI to improve catheter ablation of persistent and long-standing persistent AF is epicardial left atrial appendage (LAA) exclusion. The primary source of cardioembolic events is thought to originate as thrombus formation in the LAA [22-24]. Additionally, atrial tachycardias originating from the LAA can initiate AF, while the heterogeneous muscular structure of the LAA provides the necessary substrate to allow for re-entrant circuits that propagate and maintain AF [25-27]. Elimination of the LAA is a critical step in the surgical Cox-MAZE III procedure, leading to its success in reduction of stroke and maintenance of sinus rhythm. With the development of the percutaneous LARIAT procedure to eliminate the LAA, realization of the potential to perform a percutaneous alternative to the "cut and sew" Cox-Maze procedure was appreciated [28,29].

The LARIAT Procedure

Prophylactic LAA exclusion for recurrent arterial emboli in humans was first reported by Madden in 1949, and has since been advocated as an approach for the prevention of cardioembolic events [24]. Prophylactic surgical exclusion of the LAA is recommended in the ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation during mitral valve surgery as a means of eliminating a potential source of thromboembolic events [30]. The LARIAT device obtained FDA 510K approval in 2006 for delivery of a suture or knot to approximate and/or ligate soft tissue structures with updates in 2009 and 2014 [31-33]. The LARIAT device was originally FDA approved for a general tool kit use approval that did not indicate a specific tissue type. The LARIAT suture delivery device was adapted to develop a percutaneous procedure as an alternative to surgical LAA ligation [34,35]. The initial clinical experience demonstrated the efficacy of LAA closure with an acceptable safety profile [36]. The initial report was corroborated in 2 small single center studies that also demonstrated efficacy in LAA closure and safety with the LARIAT suture delivery device [37,38]. A prospective, multicenter observational study was initiated to assess whether LAA ligation in non-valvular AF patients at high risk for embolic events with ineligibility for oral anticoagulation would be a beneficial approach to reduce the risk of embolic events in this patient cohort [39]. The study demonstrated a stroke and systemic embolism rate of 1.0% per year in this patient population representing an 84% reduction in risk, while only having a 2.8% incidence of adverse events needing a corrective intervention. Although promising results, future prospective randomized studies are required to validate the stroke reduction. Despite the initial efficacy of LAA closure and procedural safety with the LARIAT suture delivery device, the dissemination of the use of the LARIAT to a wider and more diverse group of interventional cardiologists and cardiac electrophysiologists resulted in increased adverse events and greater post-LAA ligation leaks [40,41]. Potential reasons for the increased adverse events include procedural deviation from a prescriptive approach to exclude the LAA with the LARIAT suture delivery device and closure of LAAs with anatomies that were not compatible with the LARIAT procedure. The LARIAT suture delivery device did not have specific FDA labeling for stroke prevention, but was used out of medical necessity to treat AF patients at high risk for cardioembolic stroke and limited options due to contraindication to OAC therapy. The use of the LARIAT suture delivery device for stroke prevention is considered an off-label use for stroke prevention. Since the LARIAT suture delivery device was being used for off-label purposes, the FDA issued a safety alert based on the MAUDE report [42]. Although there were 35 reported adverse events, the number of procedures was not indicated. It was estimated that over 4,000 LARIAT cases were performed at the time of the MAUDE report, placing the incidence of adverse events similar to other common cardiovascular interventions [43,44]. A recent US multicenter registry of 712 consecutive patients reported adverse event and LAA closure rates before and after implementing technical improvements of the LARIAT procedure (ie the use of a micro-puncture needle for pericardial access and the use of anti-inflammatory agents as colchicine) that has led to an overall acute procedural adverse event rate of 2.1% [45]. This compares favorably with an overall worldwide survey of major procedural adverse events of 4.5% during AF ablations [46].

Rationale for the AMAZE Trial

The hypothesis being tested in the AMAZE trial is that the LAA is a critical structure in the maintenance of persistent and long standing persistent AF; and LAA ligation combined with catheter ablation PVI will decrease the recurrence of AF in patients with persistent and long standing persistent AF. The ability to eliminate the LAA with the LARIAT procedure allows for the development of a percutaneous MAZE procedure. The hypothesis was based on the ability of the LARIAT procedure to: 1) electrically isolate the LAA, 2) reduce the volume of the LA leading to favorable electrical remodeling of the LA and 3) enable a more complete catheter ablation of the LAA of which is known to be a source of triggers causing recurrence of AF. Another benefit is the reduction of thrombus formation in the LAA, thus the potential to reduce stroke. Although stroke prevention is not a primary endpoint of the study, the incidence of stroke will be a secondary endpoint.

The LAA has long been recognized as a source of atrial tachycardias that can initiate AF [25,47]. Recent studies have demonstrated the value of electrically isolating the LAA to decrease the recurrence of AF [26,48]. Electrically isolating the LAA with catheter ablation results in mechanical standstill of the LAA and severely reduces flow into the LAA. One of the potential iatrogenic consequences of LAA electrical isolation with catheter ablation is the propensity of thrombus formation and strokes despite therapeutic doses of OAC therapy [49]. The implantation of an LAA occluder device as the Watchman has been employed as a strategy to combat the potential of strokes from occurring after LAA electrical isolation [50]. Although the Watchman device may reduce the potential for strokes, all LAA implants do not eliminate electrical activity to the LAA. Therefore, LAA implants do not reduce AF burden.

In contrast, it has long been known that arrhythmias originating from the LAA that are unresponsive to catheter ablation can be cured by epicardial exclusion of the LAA [25,51,52]. LAA ligation results in a permanent transmural lesion with atrophy of the LAA, achieving mechanical and electrical isolation of the LAA [28,53]. Permanent closure of the LAA results in a decrease in AF burden, and results in conversion of persistent AF to sinus rhythm in 8% of patients [54,55]. LAA ligation addresses the LA "mass" hypothesis in which the propensity to have AF increases with the size of one's LA [56]. LAA exclusion via the epicardial approach causes a debulking of the LA that favorably reduces the LA size and also results in electrical remodeling [29,57].

In addition to the LAA electrical isolation and decreasing the mass of the LA, LAA ligation enables the electrophysiologist to more effectively and safely perform catheter ablation at the LAA os and left lateral ridge between the left superior pulmonary vein (LSPV) and

the LAA [29]. The ability to produce more complete ablation lesions without concern of LAA perforation leads to a more durable PVI of the LSPV, and the elimination of irritable foci located at the LAA os and adjacent structures [58-60].

The above observations lead to the initial combined LAA ligation and PVI study for the treatment of persistent and long-standing persistent AF [29]. The LAALA-AF Registry was an observational study in patients with persistent or long-standing persistent AF comparing LAA ligation and PVI to a matched group of patients undergoing only PVI that demonstrated over a 60% improvement from recurrence of AF, and was the basis for the AMAZE trial [61].

AMAZE Trial Design

The study design of the AMAZE trial has been previously reported [61]. The AMAZE trial is a Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) approved Investigational Device Exemption (IDE) study. The AMAZE trial is a randomized, prospective, multicenter study with the primary endpoints of: 1) Recurrence of AF and 2) Safety of the LARIAT procedure. Recurrence of AF as defined by the current HRS guidelines is freedom from episodes of AF>30 s and no requirement for new Class I or III AAD therapy at 12 months post PVI, measured by 24 h holter or symptomatic event monitoring [8,30]. The safety endpoint assesses the incidence of significant LARIAT device or procedure-related serious adverse events (SAEs) occurring within 30 days after the LAA ligation procedure. The study cohort includes patients between the ages of 18 to 80 years old who have persistent or long-standing persistent AF. The patients have to have previously failed antiarrhythmic therapy. The study uses a Bayesian design with a 2:1 randomization of the LAA ligation combined with PVI to PVI alone; and is powered for superiority. The AMAZE trial is one of the few superiority studies involving catheter ablation for AF treatment.

To assess the safety of the LARIAT device and procedure, the study is composed of 2 stages. Stage 1 will enroll 100 patients and undergo interim safety and performance analysis by an independent data safety monitoring board (DSMB) who will submit their analysis to the FDA. If the DSMB deems that the LARIAT device and procedure is safe as defined by a predetermined performance goal, the AMAZE trial will be allowed to complete its full enrollment. Stage 2 will continue to enroll up to 600 patients for determining efficacy of preventing AF. The Bayesian design allows for periodic examination of the data by an independent statistician team once 400 patients are enrolled. If during one of these periodic examinations it is determined that the LAA ligation combined with PVI is statistically more effective then the PVI alone group, the study will be stopped and considered successful.

Current Status of the Trial

The AMAZE trial was initiated in 15 US sites on October of 2015. Completion of phase I randomization of 100 patients was completed in December 2016. There has been no notifications from the DSMB regarding concerns regarding safety of the LARIAT device or procedure. Expansion of the number of sites up to 50 sites (US and OUS) is in progress. The expected completion of enrollment is December 2018 (earlier if primary endpoint of efficacy is met).

Conclusion

Persistent and long standing persistent AF is difficult to treat with medical therapy and catheter ablation. LAA ligation is a desirable means to exclude the LAA resulting in the elimination of triggers originating from the LAA, improvement of electrical remodeling of the LA and the ability to perform a more durable PVI. Enrollment in the AMAZE trial is currently ongoing with no safety concerns noted through stage 1. The AMAZE trial will definitively determine the benefit of LAA ligation for the treatment of persistent and longstanding persistent AF; and is the initial step for the development of a percutaneous alternative to the surgical Cox-Maze procedure.

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