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Safety and Efficacy of Left Atrial Appendage Closure Devices: In-Vitro Controlled Simulations and In-Vivo Correlations

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ABSTRACT

The "Left Atrial Appendage Closure (LAAC) Device" is specifically designed to address the problem of stroke prevention in patients with atrial fibrillation (AF). In individuals with AF, the heart's atria (upper chambers) do not beat effectively, allowing blood to pool and potentially form clots, particularly in the left atrial appendage (LAA). These clots can then travel to the brain, causing a stroke. The purpose of the Left Atrial Appendage Closure Device is to mechanically seal off the left atrial appendage, preventing blood clots from forming there and reducing the risk of stroke in patients with atrial fibrillation who are at high risk of stroke but cannot tolerate long-term anticoagulation therapy. Hence Patients with atrial fibrillation frequently develop thrombus in the Left Atrial Appendage (LAA), which significantly increases their risk of stroke. LAA closure devices block the appendage, providing a percutaneous method of lowering this risk. With an emphasis on current developments, this research article examines the history, development effectiveness, delivery & deployment and safety of LAA closure devices via in-vitro simulation testing with controlled conditions.

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KEYWORDS:

Left Atrial Appendage Closure (LAAC) Device, Atrial fibrillation Development, Delivery, Deployment and Simulation Testing

1. INTRODUCTION

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia associated with an increased risk of stroke, primarily due to thrombus formation in the Left Atrial Appendage (LAA) [2]. The LAA is a small, sac-like structure extending from the left atrium, which can trap blood clots and potentially lead to embolic events. For patients with AF, especially those who are at high risk of stroke or who cannot tolerate long-term anticoagulation, addressing LAA thrombus risk becomes a critical component of stroke prevention.

Traditionally, stroke prevention in AF patients has been managed with oral anticoagulants, such as warfarin and direct oral anticoagulants (DOACs). While effective, these medications are associated with risks of bleeding and may not be suitable for all patients. In response to these challenges, LAA closure devices have been developed as an alternative strategy. These devices are designed to occlude the LAA, thereby preventing thrombus formation and reducing the risk of stroke.

The concept of LAA closure has evolved significantly since the introduction of the first devices. Modern LAA closure devices are designed to provide safe and effective occlusion of the appendage through a minimally invasive percutaneous procedure [2].

The use of LAA closure devices offers patients with AF who are not able to take anticoagulant therapy or who are looking for a substitute for lifetime medication a beneficial option. This represents a significant improvement in stroke prevention measures. Nonetheless, there is still much to learn and discuss about the safety and efficacy of these devices.

In this research study, we have described about the development of a device that will be used to seal the LAA to prevent blood clots from traveling to the brain, prevent brain stroke, and lessen patient burden. In addition, an in-vitro study of the device was conducted to evaluate its deployment, trackability, stability, and sealing capacity using a silicon model. [3]

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1.1 Literature Review

The article by Brüggenjürgen et al. (2010) offers a detailed examination of the burden of atrial fibrillation, encompassing epidemiological data, economic costs, and individual patient impact. The findings underscore the increasing prevalence of AF and its significant economic and personal consequences. The review emphasizes the need for continued research and development of effective management strategies to alleviate the burden of AF and improve patient outcomes. Addressing the multifaceted challenges associated with AF requires a comprehensive approach involving both healthcare providers and policymakers [3].

Atrial fibrillation (AF) is a prevalent arrhythmia associated with a significant risk of stroke, primarily due to the potential for thrombus formation in the left atrial appendage (LAA). The management of stroke risk in patients with AF has evolved considerably over time, with ongoing research aimed at improving both prevention and treatment strategies. This review synthesizes key insights from the article by Holmes DR (2010) regarding current practices and future directions in managing stroke risk associated with AF [5].

(Tu et al). suggests that future research should focus on developing targeted therapies that address the specific pathophysiological factors contributing to worse stroke outcomes in AF patients. The findings emphasizes the need for a comprehensive approach to managing AF patients, including addressing inflammatory and coagulation abnormalities and monitoring for underlying cardiac conditions that may impact stroke outcomes [6].

2. MATERIAL AND METHODS

The durability and effective functioning of the device depend heavily on the materials chosen for the frame design. This structural material must be biocompatible, have sufficient elasticity to be compressed for loading into the tubular delivery system, and be able to afflict sufficient radial force upon expansion to re-establish patency of the vessel.

The main metal used in SEMS (Self Expanding Medical System) manufacture is Nitinol. Nickel titanium, also known as Nitinol, is a metal alloy of nickel and titanium, where the two elements are present in roughly equal atomic percentages. Nitinol alloys exhibit two closely related and unique properties: the shape memory effect and superelasticity (also called pseudo elasticity). Shape memory is the ability of Nitinol to undergo deformation at one temperature, stay in its deformed shape when the external force is removed, and then recover its original, undeformed shape upon heating above its "transformation temperature". Super elasticity is the ability of the metal to undergo large deformations and immediately return to its undeformed shape upon removal of the external load. Nitinol can deform 10–30 times as much as ordinary metals and return to its original shape.

Nitinol is a nickel-titanium alloy capable of undergoing austenitic transformation from a deformed monoclinic (martensitic) phase to an ordered cubic (austenitic) phase across a given temperature range. This shape-memory effect is initiated at a working temperature above that at which martensitic transformation occurs in nitinol devices are manufactured to specific dimensions, then annealed at 500ºC - 510ºC, cooled and compressed, and stored as per requirement.

This frame can be easily loaded into the loader and delivered through a delivery sheath. This not only reduces the risk of infection but reduces the time a patient is under sedation or anesthesia. Nitinol has high fatigue resistance and ductility properties that make Nitinol advantageous for this type of frame as it enables increased flexibility for obstructions in curved and kinked locations and allows for repetitive muscle contraction.

2.1 Construction Method

The flexibility, migration resistance, and accuracy of medical device are critically dependent on their construction method and design architecture. Braided frames or structures offer significant flexibility, while laser-cut frames are known for their high radial expansive force while maintaining flexibility. The design allows to move relative to each other at their contact points, enabling them to conform to the dynamic changes during muscle contractions. The manufacturing process involves several key steps, including braiding, tube mounting, cutting, arc welding, molding, secondary annealing, pre-cleaning, fabric stitching, jacketing, spot welding, and primary packaging.

Braiding machines vary in complexity, ranging from simple hand-operated devices to advanced automated systems. These machines use multiple carriers (also known as bobbins or spools) to hold and manage the tension and positioning of the wires during the braiding process. In braiding, the carriers move in a precise pattern around a central core (mandrel), interlacing the wires in a specific geometric configuration. This process creates a tubular structure with reinforced walls that provide both axial strength and radial flexibility.

The primary heat setting process refers to heating the mesh at 490-520°C temperature for 3-8 minutes to achieve the desired shape and allowing it to cool completely at room temperature. The mandrel is subsequently immersed in distilled water for a process known as quenching. Following this, it is moved to the tube mounting and cutting phase.

The mesh is visually inspected for any damage or kink. The parafilm is winded over the mesh at both ends. The tube is then mounted on the mesh in a clean room environment. Thereafter, the mesh is measured and cut as per the required length. Then it is transferred for the arc welding process.

After the cutting process, both the ends of mesh are welded using an arc welding machine in the clean room environment. Thereafter, the mesh is transferred for molding and secondary annealing process.

The mesh is subsequently molded by positioning it within the designated mold and subjecting it to high temperatures ranging from 490°C to 520°C for duration of 10 to 18 minutes to attain the desired shape and dimensions. This operation is conducted in a controlled clean room environment. Following the molding process, the mesh undergoes a pre-cleaning procedure, which involves the use of an air gun. Upon completion of the pre-cleaning, the mesh is then moved to the fabric stitching phase.

According to the required size, polyethylene terephthalate (PET) fabric is cut. The fabric is stitched into the mesh with the help of a surgical suture. This process is carried out in a clean room environment. The mesh is then transferred for the jacketing and spot welding process. The jacket is inserted at both ends of the mesh and further, it is spot welded using a spot welding machine to form an occluder. Thereafter, the closure device is transferred for the primary packaging process.

The occluder is packed in a tyvek pouch. The tyvek pouch is visually inspected for sealing integrity, dents, holes, or damage, and a product identification label is applied to it. Further, it is transferred for the sterilization process. The primary packed occluder is sterilized to achieve the desired sterility assurance level of 10-6. The sterile product is tested for in-house tests including microbiological, analytical, and performance tests.

A Product label is affixed on the outer side of the tyvek pouch. The sterilized product is placed into the product's outer box along with instructions for use and a silica gel pouch. The finished product label is affixed on the product's outer box. The product box is placed in a polypropylene bag which is then sealed and further stored in the finished product store. The developed LAAC Occluder has been depicted in the figure 01.

Figure 01: Left Atrial Appendage Closure (LAAC) Device

Table 01: Size Matrix of LAAC Device

Device Compatibility	Available Device Diameter (mm)	Available Access Sheath Diameter (F)
Guidewire Compatibility 0.035 (0.89mm), Usable Length (750mm)	18	**14**
	20	
	24	
	28	
	32	
	36	
	38	

2.2 In-Vitro Assessment of Left Atrial Appendage Closure Device Delivery and Deployment in Simulated Models.

Figure 02: This simulation model extends from the femoral vein to the left auricle. The model includes the femoral vein, iliac vein, inferior vena cava, right atrium, foramen ovale, left atrium, and left auricle.

2.3 Preparation Procedure of Circulating Fluid:

i. **Phosphate Buffer Saline (PBS):** 0.1M Phosphate buffer saline (PBS) of pH 7.4 ± 0.2

Prepare 0.1M Phosphate Buffer Saline (PBS) solution as follows:

The salts used for the preparation of PBS solution were of analytical grade.

Solution A: 1/10 mol/litre KH_2PO_4, was prepared by dissolving 6.805 gm Potassium dihydrogen phosphate (KH_2PO_4) in 500 ml of distilled water.

Solution B: 1/10 mol/litre Na_2HPO_4, was prepared by dissolving 28.392 gm dibasic Sodium hydrogen phosphate anhydrous in 2000 ml of distilled water.

A total of 2000 ml of buffer solution was prepared by mixing 364 ml of solution A (18.2% v/v) and 1636 ml of solution B (81.8% v/v). 11.7 gm (0.585% w/v) of Sodium chloride was dissolved in this buffer solution. The pH value of this buffer solution was 7.42.

A calibrated pH meter was used to measure the pH of the Phosphate buffer saline (PBS).

ii. **Digital Thermometer:** Digital thermometer to monitor the temperature of phosphate buffer solution over the course of the entire study.

iii. **pH Meter:** A pH meter device is sensitive in the physiological range i.e. pH 6 to pH 8 with a precision of 0.02. Over the course of the study, the pH should be monitored on a daily basis for at least three assemblies.

2.4 Test Procedure:

The Left Atrial Appendage (LAA) model was first set up. The compatible guide wire of the delivery system was inserted and placed at the target location. Subsequently, the delivery system was advanced over the guide wire. Following this, the LAA device was deployed, and the LAA was expanded from the delivery system at the center of the appendage. A continuous flow circulation of 72 ml/min of phosphate buffer saline was maintained at 37°C ± 2°C. The LAAC and delivery system were visually inspected and examined under a microscope.

2.5 Study Set-up step-by-step:

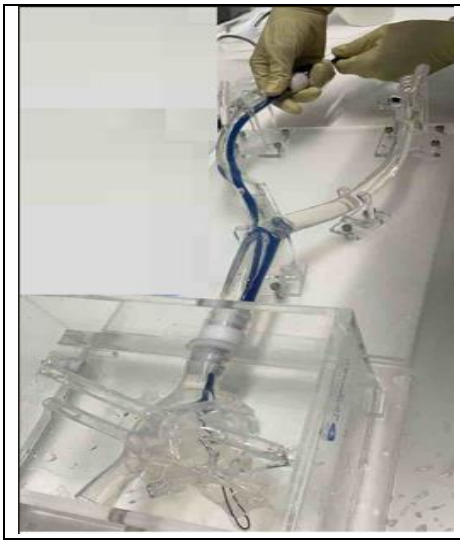

Figure: 03 Model set-up.

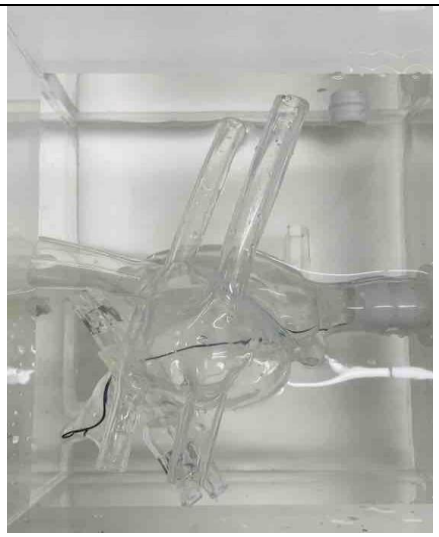

Figure: 04 Insertion and placement of a guidewire.

Figure: 05 Navigation to target location

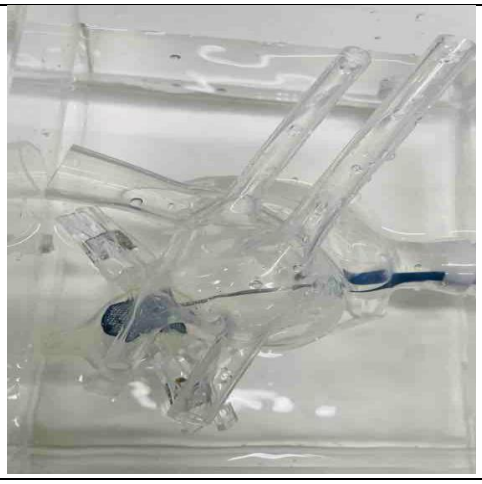

Figure: 06 Deployment of LAAC Device

The LAA sample was removed from the appendage and inspected visually on an optical microscope. The diameter of the LAAC occlude was measured at around the shape. The device was also inspected for any kind of fracture.

3. RESULTS AND DISCUSSION

3.1 Phosphate Buffer Saline Preparation and Testing Conditions:

The circulating fluid used in this study was a 0.1M Phosphate Buffer Saline (PBS) with a pH of 7.42 ± 0.2, closely simulating physiological conditions. The preparation followed standard analytical procedures, with the precise composition ensuring the appropriate ionic concentration and pH stability throughout the experiment. The buffer solution remained stable over the course of the study, with the pH continuously monitored using a calibrated pH meter with a precision of 0.02, which confirmed the solution's stability within the desired physiological range (pH 6 to pH 8). No significant deviations in pH were observed during the testing period.

The temperature of the circulating PBS was maintained at 37°C ± 2°C, using a digital thermometer for real-time monitoring. This temperature range effectively mimicked human body conditions, ensuring that the performance of the Left Atrial Appendage Closure (LAAC) device could be assessed under near-physiological conditions.

3.2 Delivery System and Guidewire Insertion:

The delivery of the LAAC device through the guidewire was successfully executed in all trials. The guidewire was accurately placed at the target location within the left atrial appendage (LAA) model, and the delivery system was advanced smoothly over the guidewire. This part of the procedure demonstrated the reliability and compatibility of the guidewire with the delivery system, suggesting that the device can be deployed with high precision in simulated anatomical models.

3.3 Device Deployment and Occluder Expansion:

Once the delivery system was positioned correctly, the LAAC was deployed at the center of the appendage. The occluder expanded uniformly within the model under the continuous flow of 72 ml/min of phosphate buffer saline.

The controlled flow rate simulated the conditions found within the left atrium during diastolic relaxation, replicating the forces acting on the device during actual clinical use.

Visual and microscopic inspections of the deployed occluder revealed a consistent shape with proper expansion. The LAAC maintained its form without visible deformation, indicating successful deployment under simulated in-vitro conditions. These observations suggest that the mechanical performance of the LAAC device is robust and capable of achieving the desired occlusion of the LAA.

3.4 Device and Delivery System Integrity:

After deployment, the device was removed from the LAA simulation model and visually inspected under an optical microscope. The diameter measurements around the occluder showed uniformity, confirming that the device had expanded symmetrically in all trials. No fractures, cracks, or other signs of mechanical failure were observed on the device or the delivery system during or after deployment.

The structural integrity of the delivery system was also verified, with no visible damage to the components, further confirming its suitability for repeated use in percutaneous procedures. The absence of fractures in the delivery mechanism underscores the reliability of the device's design and its potential for safe use in in-vivo applications.

3.5 Discussion:

The in-vitro performance assessment of the LAAC device in simulated models demonstrated its effective delivery and deployment, closely mimicking real-life clinical conditions. The use of phosphate buffer saline at a physiological pH and temperature provided an accurate environment to evaluate the device's performance. The successful guidewire insertion, deployment, and post-deployment evaluations highlight the device's potential for reducing stroke risk in atrial fibrillation patients who cannot tolerate long-term anticoagulation therapy.

The occluder’s symmetrical expansion and the intact structural integrity of both the device and delivery system suggest a high level of mechanical reliability, critical for ensuring that the LAA is securely occluded. These results support the device’s efficacy in safely sealing off the left atrial appendage, thereby preventing the formation of clots that could lead to stroke.

4. CONCLUSION

The in-vitro assessment of the Left Atrial Appendage Closure (LAAC) device under simulated physiological conditions provided valuable insights into its delivery, deployment, and mechanical integrity. The study demonstrated that the device can be successfully delivered to the target location via a compatible guidewire system and deployed with precision. The uniform expansion of the device and its consistent structural integrity across all trials highlight the robustness of the LAAC device in achieving effective occlusion of the left atrial appendage. The use of phosphate buffer saline (PBS) at physiological pH and temperature ensured that the simulated environment closely replicated human cardiac conditions, contributing to the reliability of the test results. The absence of mechanical failure, such as fractures or deformations, further reinforces the device’s potential for in-vivo applications, particularly for patients with atrial fibrillation who are at high risk of stroke but are unable to tolerate long-term anticoagulation therapy. In conclusion, this study suggests that the LAAC device is a promising intervention for stroke prevention in atrial fibrillation patients, offering an alternative to anticoagulant therapy. While the in-vitro tests have demonstrated the mechanical efficiency of the device under simulated conditions, in-vivo testing is still necessary. Factors such as the body’s inflammatory response and circulatory behavior must be assessed during pre-clinical evaluations. Once these are confirmed, we can make informed decisions regarding clinical trials.

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