

UMBRELAA: DESIGN OF A VARIABLE-SIZED LEFT ATRIAL APPENDAGE OCCLUSION DEVICE FOR STROKE PREVENTION

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ABSTRACT

Blood clots originating in the left atrial appendage (LAA) are the leading cause of ischemic stroke in patients with nonvalvular atrial fibrillation (AF). Complications from and contraindications to oral anticoagulants (OACs), in addition to the recent successes of endocardial LAA closure devices, have driven increased interest in mechanical LAA occlusion. However, current devices are limited in their abilities to accommodate diverse LAA anatomies, motivating the development of a novel endocardial LAA occluder that supports more anatomical variability. We present the design of an in-situ expandable plug as well as an accompanying pacifier module for LAA occlusion. The final design accommodates LAA diameter ranges of 14 millimeters for each device size (10-24mm and 24-38mm), double that of any approved device. This adaptability can help to overcome imperfect pre-procedural imaging and suboptimal device fit. Benchtop tug and leak tests demonstrate the stability and sealing capacities of the design.

Keywords: left atrial appendage, left atrial appendage occlusion, atrial fibrillation, stroke;

NOMENCLATURE

AF	atrial fibrillation
LAA	left atrial appendage
OAC	oral anticoagulant
TEE	transesophageal echocardiography

1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is estimated to affect 37 million people

worldwide [1]. During AF, abnormal electrical activity in the atria of the heart causes irregular atrial contraction. The lack of organized contraction pattern can lead to blood stasis in certain areas, increasing the risk of thrombus formation [2]. If these thrombi dislodge, they may precipitate ischemic stroke; hence, AF patients have a five-fold increased risk of ischemic stroke compared to their age-matched peers [3].

90% of thrombi in patients with nonvalvular AF originate in the left atrial appendage (LAA), and up to 15% of AF patients have an LAA thrombus at any given time [4,5]. In order to mitigate the risk of thrombus formation and subsequent stroke in patients with AF, several interventions, both pharmacological and nonpharmacological, have been developed.

Oral anticoagulants (OACs) persist as the standard of care for the prevention of stroke in patients with nonvalvular AF, but suboptimal patient compliance with these drug regimens and their potential complications, including major bleeds [5,6], have led to increasing interest in alternative stroke-prevention strategies. To this end, LAA occlusion devices have been developed to remove the LAA from blood circulation in an attempt to completely block the release of thrombi from the LAA. Broadly, these devices mechanically occlude the LAA through transcatheter endocardial plugs, such as the WATCHMAN FLX (Boston Scientific, Marlborough, USA) and Amulet (Abbott, Chicago, USA), or epicardial sutures (LARIAT by SenteHeart, Pleasanton, USA). Although many strategies have been explored for LAA occlusion, only the WATCHMAN FLX and Amulet are currently FDA approved, and the WATCHMAN FLX captures about 90% of market share [7]. Both the WATCHMAN FLX and Amulet are based around self-

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expanding nitinol cages. Permeable polyester (PET) meshes over these cages encourage endocardialization. Both devices also use fixation anchors to secure themselves to the walls of the LAA.

The WATCHMAN FLX and Amulet each enable minimally invasive delivery, have relatively high success rates, and have good safety profiles (detailed clinical trial data can be found in [8]), suggesting the promise of LAA plugs. However, both devices have shortcomings, including limited supported ranges of patient LAA geometries. LAA occlusion has remained a challenge in large part due to the complex and variable geometries of the appendage seen in patients. LAAs can take on a wide array of different shapes, from “windsock” to “cauliflower,” and sizes, with openings, or ostia, recorded in the literature between 5mm and 40mm in “diameter” (though most ostia are ovular [9]) [4,5].

In attempts to accommodate this variability, the WATCHMAN FLX comes in five different sizes to fit LAA ostia between 14mm and 31.5mm in diameter, and the Amulet comes in eight sizes to accommodate ostium diameters between 11mm and 31mm. Because these devices are only effective for certain LAA geometries, a physician must first image the patient’s LAA, often using transesophageal echocardiography (TEE), before choosing and inserting the device that they believe to be appropriate for the patient. TEE has been shown to underestimate LAA dimensions [10], increasing the risk of potentially choosing an inappropriately sized device. Other risks associated with these devices include device embolization and device-related thrombosis [11].

The present article describes a novel innovation on endocardial plugs, with a focus on fitting a wider range of LAA geometries. In the sections that follow, we describe the design of a LAA occluder that can be controllably expanded *in situ* to more closely match and occlude diverse LAA geometries with fewer device sizes. Throughout, we reference the WATCHMAN FLX for comparison.

2. MATERIALS AND METHODS

The design team followed an engineering design process, beginning with considering prior art; proceeding to establishing functional requirements and design parameters; and subsequently iteratively designing, analyzing, prototyping, and testing devices. The team considered three approaches to remove the LAA from circulation: ablation, ligation, and mechanical plugging, the third being the approach shared by the WATCHMAN FLX and Amulet. A plug-type device was selected as the most promising strategy based on a combination of its favorable relative invasiveness (low), safety (high), and procedural novelty (low).

Next, the functional requirements and corresponding design parameters in Table 1 were identified based upon the literature and limitations of currently available LAA plugs.

TABLE 1: FUNCTIONAL REQUIREMENTS (LEFT) AND DESIGN PARAMETERS (RIGHT) DETERMINED FOR A LAA OCCLUDER

<i>The device must...</i>	<i>by...</i>
prevent the release of clots from the LAA	adequately sealing the LAA, blocking as much or more blood/thrombus flow as current devices
be adaptable to a large anatomical range	accommodating a larger range of LAA diameter/depth combinations than current devices per plug size
be minimally invasive	being deliverable via commercially available catheters
minimize the risk of device embolization	anchoring stably in the LAA, per standard (tug) tests
be easy to position and deploy	using a procedure of similar length and complexity to existing devices
avoid damage to cardiac and adjacent structures	not including more traumatic features than current devices
promote endocardialization	using established biocompatible materials

Guided by the requirements in Table 1, focusing on the first four early in the design process and with particular emphasis on improving anatomical accommodation ranges, the team generated several varied concepts and down selected them using preliminary analyses and Pugh charts. Concepts were iteratively rapid prototyped using available proxy materials, and these prototypes informed a final design (Figure 1).

2.1 Device Design

The final design consists of a controllably *in-situ* expandable plug module and a pacifier module (Figure 1). Similar to the WATCHMAN FLX and Amulet, the system can be delivered to the LAA via a transcatheter approach through the femoral vein using a transseptal puncture. The proximal side of the plug has a round central silicone base with a surgical steel nut in the center. This nut is threaded onto a surgical steel central threaded sleeve. Twelve silicone arms radiate from the center, and twelve surgical steel wire prongs further extend radially from these arms. The ends of the prongs are curved into a j-shape, forming hooks that anchor the plug in the LAA.

The silicone base collapses around the nut at its center to fit within existing 14 French (4mm) catheters by virtue of the material being thinner at elastic joint locations around the center of the base. Upon release from the catheter, these joints return to their molded position. Each of the twelve prongs is also attached to the base at a silicone joint and thus can be rotated about the points where they connect to the base.

The distal side of the plug serves to radially expand the prongs by shortening its depth, analogous to how an umbrella opens, thus giving this device its name. This side also has a nut threaded onto the threaded sleeve at its center and twelve shorter steel wire prongs, which are adhered at their ends to the longer prongs on the proximal side. Both the proximal and distal sides of the plug are thermoformed in thermoplastic polyurethane (TPU), which prevents clots from crossing the plug and promotes plug endocardialization.

The depth and diameter of the plug are controlled by the central sleeve that threads into the two nuts in the centers of each side of the plug. The proximal nut is fixed relative to the sleeve, while the distal nut can move along it. The operating physician can position the plug within the ostium after catheter delivery and then manually turn the central sleeve to rotate the distal nut closer to the proximal side and radially expand the prongs, thereby increasing the plug's diameter. The operator may expand the plug until a satisfactorily tight seal of the LAA is achieved, as judged by in-procedure imaging and operator tactile feel. This controllably expandable design allows for large ranges of LAA diameters to be accommodated by a single device size. The ability to adjust the plug size *in situ* also allows the operator to fit patients' true LAA geometry, despite potential limitations in pre-procedural TEE [10]. Once correctly situated and sized, the operator can pull the plug slightly toward the left atrium to engage the anchoring hooks.

The pacifier sits in the left atrium just outside the ostium and serves as an additional layer of protection against clot embolization from the appendage, including clots that may form on or around the proximal side of the plug. The pacifier has a silicone frame with a round center, onto which one side of a snap fit is adhered, sized to fit in a catheter. Flexible silicone prongs with elastic joints where they meet the center ring extend radially outward, with a thermoplastic elastomer (TPE) covering heat sealed over them. The joints allow the prongs to collapse around the center for catheter delivery. After the plug has been deployed in the ostium, the pacifier can be attached to the end of the threaded sleeve at the center of the plug's base through a snap fit mechanism. When snapped onto the head of the plug's threaded sleeve, the pacifier takes on a satellite shape, convex from the perspective of the LAA, to seal off the ostium. Since the pacifier is a separate module, the operator can select a pacifier size that is not coupled to the plug size and customize the joined device to each patient's unique geometry.

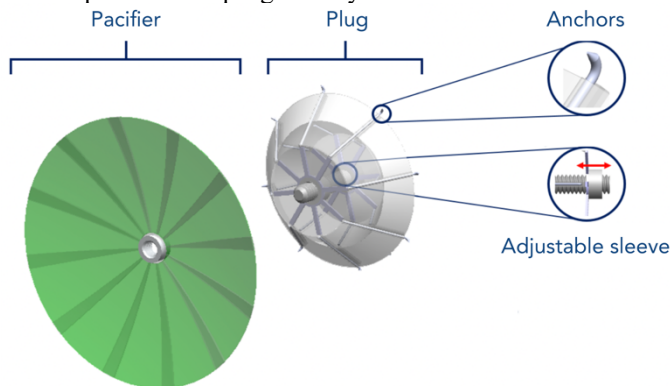


FIGURE 1: EXPLODED VIEW RENDERING OF THE PLUG-PACIFIER DESIGN

Plug prototypes (Figure 2) were based around laser cut PETG frames onto which the proximal and distal wire prongs and nuts were adhered due to unavailability of precision silicone manufacturing capacity. Likewise, pacifier frames were prototyped in PETG. In the prototypes, the pacifier is threaded

onto the same threaded sleeve that goes through the plug as opposed to attached through a snap fit for ease of prototyping. As shown in the model Figure 1, protrusion into the atrium of the component connecting the pacifier and plug is minimized in the final design.

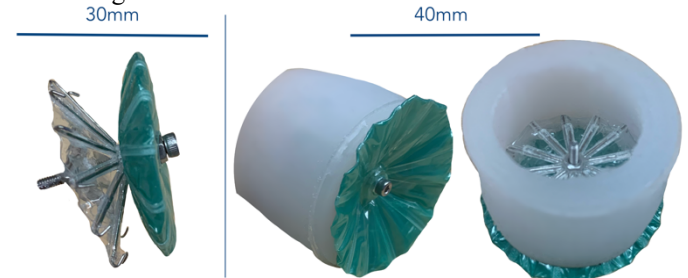


FIGURE 2: PLUG-PACIFIER PROTOTYPE (LEFT) AND ANOTHER PLUG-PACIFIER PROTOTYPE SITUATED IN AN ECOFLEX OSTIUM MODEL (RIGHT)

2.2 Test Methods

The design team conducted tug tests and leak tests to verify that the device could anchor securely into tissue and demonstrate low peri-device leakage. To perform these tests, round (as in Figure 2) and 1.6 diameter ratio ovular ostium models were created using 3D printed molds in sizes that can be occluded by the WATCHMAN FLX. 1.6 diameter ratio ovular molds represent the extreme end of the physiological range of ostium shapes [12]. Molds were made from Ecoflex 00-30 because its stiffness is within the range of heart tissue stiffnesses [13]. Tests were conducted with a plug prototype sized 32mm when fully radially expanded and pacifiers sized between 22mm and 42mm. WATCHMAN FLX devices were also tested for comparison.

To perform the tug test, Ecoflex ostium models were placed in a 3D printed fixture on an Instron universal testing machine (Figure 3, left). Plug prototypes were deployed near the bottom of the ostium models and pulled from the proximal side at 25mm/minute until the device was dislodged from the model. The force required to dislodge the device was recorded in Newtons. Tests were performed in this "static" condition as well as with 25% compression applied around the mold by a pneumatic actuator at a rate of 1Hertz to simulate compression due to a 60 beat-per-minute heartbeat ("dynamic" condition).

Two WATCHMAN FLX devices were tested in addition to early and final UmbreLAA plug prototypes (with eight and 12 prongs, with and without hooks), in order to justify design changes. Each test was performed three times, and mean and standard deviation values were calculated. Statistical significance was evaluated using Kruskal-Wallis tests (significance at $p < .05$).

To test for peri-device leakage, plugs were deployed in ostium models, and five grams of fine sand was poured over the devices from the proximal side (Figure 3, right). For tests on plug-pacifier combinations, pacifiers were connected to plugs and situated just outside the end of the ostium models, and sand was poured from the distal side. These leak tests simulate whether a device impedes the passage of small clots. The sand that leaked around or through the devices was collected in a cup

and weighed with a benchtop scale. Tests were performed in the same “static” and “dynamic” conditions as the tug tests three times for each device. Mean and standard deviation were calculated. Tests were replicated only three times to maintain the integrity of the limited supply of devices.

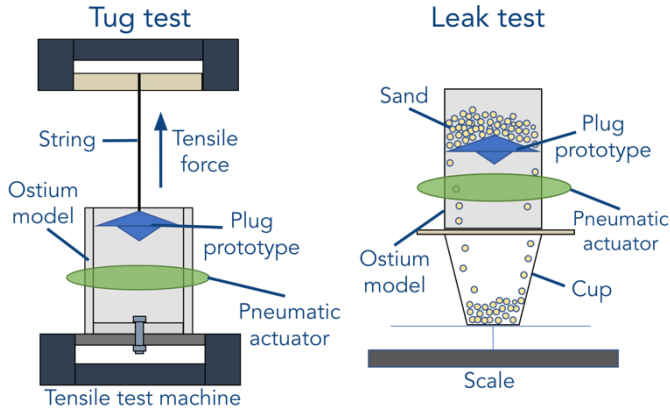


FIGURE 3: ILLUSTRATION OF THE TUG (LEFT) AND LEAK (RIGHT) TEST SET UPS (FOR PLUGS ALONE)

3. RESULTS AND DISCUSSION

3.1 Tug Tests

The two WATCHMAN FLXs tested dislodged under tensile tug forces of 1.9N (+/-0.1N) and 2.2N (+/-0.4N) under static conditions and 1.6N (+/-0.3N) and 2.7N (+/-0.1N) under periodic compression. UmbreLAA's anchoring hooks are larger than those on the WATCHMAN FLX, and the umbrella shape offers further resistance to displacement, resulting in higher required tug forces (Figure 4). The differences between the devices are statistically significant in both static and dynamic conditions ($p = 0.0073$ in both conditions). The results also demonstrate the stabilizing effects of the anchoring hooks and the increased stability provided by twelve compared to eight prongs. More and larger hooks add stability but could pose greater risk of trauma to tissue, a tradeoff that will be carefully considered in future work.

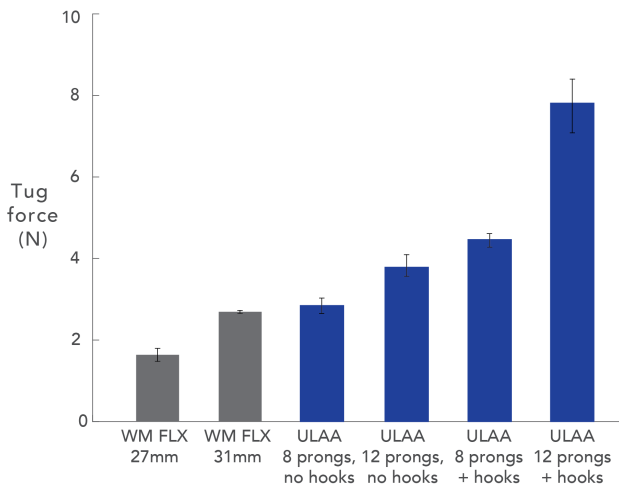


FIGURE 4: MEAN +/- STANDARD DEVIATION DYNAMIC TUG TEST RESULTS. STATIC TEST RESULTS WERE VERY SIMILAR.

3.2 Leak Tests

Peri-device leak around WATCHMAN FLXs as well as our devices was quantified in round ostium models, and UmbreLAA leakage was also quantified in ovalar models. In the round models, both the WATCHMAN FLX and the UmbreLAA (plug only) exhibited low peri-device leak (less than 1% of poured sand) when the devices were radially compressed by between 10-30%. In some unusual cases (e.g. under very low compression), peri-device leakage was significant around the UmbreLAA, reaching over 37%. In ovalar models, modest peri-device gaps around the UmbreLAA were apparent (Figure 5). Although LAA plugs are generally intended to be compressed by at least 10% and 1.6 diameter oval ratio ostia are extreme, this leakage potential motivated the addition of the pacifier to the UmbreLAA for more robust sealing. The addition of the pacifier mitigated leakage to essentially zero in all test conditions and models.

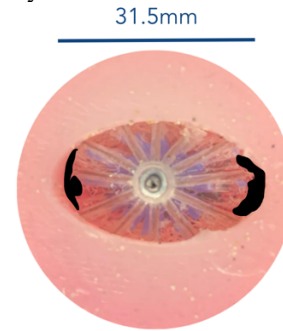


FIGURE 5: PERI-DEVICE GAPS (BLACK) VISIBLE AROUND A 32MM UMBRELAA PLUG IN 1.6 DIAMETER RATIO OVALAR OSTIUM MODEL

3.3 Final Dimension Specification

For ease of manual manufacturing, 32mm maximum diameter plugs and several pacifier sizes were fabricated and used for testing, and final device dimensions were optimized analytically. The length and diameter of the plug are interdependent and dynamic, so we denote the actual diameter of the device expanded to the appropriate extent for a given LAA as the “effective diameter” and the length of the device at this diameter as the “effective length.” Based on the geometry of the design, where l is the length of the unexpanded device, d is the diameter of the unexpanded device, and $l_{effective}$ and $d_{effective}$ represent the effective length and effective diameter respectively, the effective length is defined by equation 1:

$$l_{effective} = \sqrt{\left(\frac{l}{2}\right)^2 - \left(\frac{d_{effective} - d}{2}\right)^2} \quad (1)$$

The team utilized reports of LAA dimensions from several studies to qualitatively optimize the effective diameter and effective length ranges (which are constrained by ostium diameter and LAA depth), for two device sizes. Various imaging and interpretation techniques used to determine different LAA dimensions suggest that LAAs as short as 7mm before a significant bend and with short diameters as small as 5mm may be encountered [4,9,10,12,14,15].

Assuming that LAA depth and diameter are independent of one another and using versions of the plot in Figure 6, various length and diameter combinations were examined. Two adjacent optimal combinations were identified visually, pictured in Figure 6. The smaller size is 7mm long and has a diameter of 10mm in its compressed but out-of-catheter state (diameter of the silicone base), before any radial expansion. The prongs are sized such that it can expand to a maximum diameter of 24mm. The larger size is also 7mm long and has a diameter of 24mm in its fully compressed state, with prongs that enable radial expansion to 38mm.

The gray area shows the range of depth-diameter permutations that the five sizes of the WATCHMAN FLX device can accommodate, with the dark lines separating each size. The coverage of the two sizes achieved by our design at the two sets of dimensions selected are shown in blue. The curved lines at the low effective length ends of these ranges reflect the relationship between effective length and effective diameter. With only two sizes, our design substantially increases LAA geometry coverage compared to the WATCHMAN FLX.

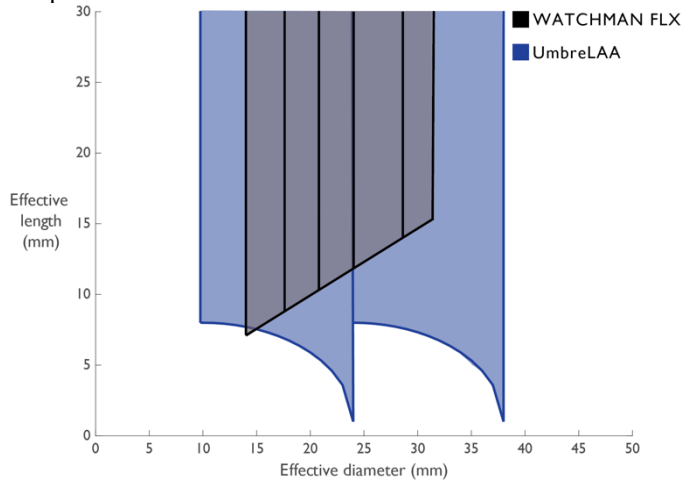


FIGURE 6: LAA DEPTH AND DIAMETER ACCOMMODATION BY WATCHMAN FLX AND UMBRELAA, WHERE EFFECTIVE LENGTH AND DIAMETER FOR THE WATCHMAN FLX ARE ITS NOMINAL DIMENSIONS

Increasing interest in mechanical LAA occlusion and the limited applicability of current devices motivated the development of a novel, controllably *in-situ* expandable endocardial LAA occluder. The design process for this device focused on the following functional requirements: preventing the release of clots from the LAA, fitting a large anatomical range, being compatible with transcatheter delivery, and minimizing the risk of device embolization.

The expandability of our occluder design enables theoretical accommodation ranges of 14mm in diameter, a significant increase from the WATCHMAN FLX's 4-7mm ranges per device size. The ability of the device to be expanded inside the LAA increases the flexibility of the surgical procedure and can help the operator compensate for potential inaccuracy in pre-procedural TEE imaging, possibly improving device sizing and ultimate fit [10]. "Landing zone," or LAA depth requirements,

are also reduced by our design, increasing the range of patient geometries eligible for occlusion. Moreover, the operator has the freedom to select any accompanying pacifier size based on unique patient anatomy and clinical needs. For example, a pacifier could be sized up in order to bolster protection from clot escape before endocardialization for a patient with contraindications to post-procedural OACs.

The tug and leak tests validated that the device meets key functional requirements and supported the team's hypotheses and design decisions. Preliminary leak tests before the addition of a pacifier and the formal tests of the plug-pacifier prototypes demonstrated the value of the pacifier and the effectiveness of the combination in sealing ostium models. Similarly, the tug tests proved the value of the anchoring hooks and validated the hypothesized increase in stability provided by 12 prongs and hooks compared to eight, with a larger difference in stability seen in the dynamic tests. The data suggests that device compression and the prongs alone provide some stability but that the addition of hooks significantly increases stability and enhances the effect of additional prongs. The forces required to dislodge the final 12-prong, hooked prototypes compared to those of the WATCHMAN FLX show that the stability of our device exceeds what the market considers sufficient. This stability indicates that the size of the hooks could potentially be decreased, reducing trauma to the LAA during anchorage while maintaining stability.

The precision manufacturing required to fabricate the fine features of the silicone base of the plug were not accessible to the design team during the early phases of the design process. Time and resources were also limited in the pacifier development due to its late addition to the design. Thus, the plug and pacifier frames and the attachment mechanism in the fabricated prototypes differ slightly from the final proposed design. The plug hooks and pacifier size and shape were the primary drivers of the results of the tug and leak tests, so we do not anticipate that these minor alterations would significantly affect these test results; the design changes are rather motivated by decreasing the size of the delivery catheter to enable minimally-invasive deployment. Thus, the final design satisfies the first four design requirements.

Limitations of the proposed design include the increased procedural complexity compared to the WATCHMAN FLX due to the manual adjustability of the plug and the separate pacifier module. Several aspects of the design, including some of the materials, are novel and have yet to be validated for use in LAA occlusion, which adds some risk.

Future work will focus on the last three design requirements and will include prototyping the final design with the intended final, non-thrombogenic materials and more robust testing with these new prototypes. Additional tests should include accelerated aging and fatigue testing. A precise deployment procedure and any necessary supporting surgical tools are also yet to be developed. We plan to integrate the UmbreLAA with femoral catheter delivery, the current delivery method for LAA occlusion devices. The interventional procedure and any accessory devices should be designed in consultation with interventionalists and human factors experts and should undergo usability testing. *Ex*

vivo and *in vivo* animal model testing will follow. Validating the safety and security of the anchoring hooks in heart tissue will be especially important, as the prototyped hooks are substantially larger than those on existing occluders.

4. CONCLUSION

This study describes the design and performance of a novel endocardial LAA occluder for stroke prevention in AF. The UmbreLAA, consisting of a plug and separate pacifier module, improves upon current devices by offering *in-situ* radial expansion capabilities, allowing it to adapt to a wide range of LAA geometries. Benchtop tug and leak tests demonstrate that the design can secure itself in and seal a synthetic LAA. Future work will include higher-fidelity prototyping, procedure development, and animal model testing.

ACKNOWLEDGEMENTS

We thank Dave Custer, the rest of the MIT 2.75 teaching team, the MIT Therapeutic Technology Design and Development Lab, and Patrick Willoughby and Brian Tischler of Boston Scientific for their support and contributions to this work.

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