Original research

A novel intrasaccular aneurysm device with high complete occlusion rate: initial results in a rabbit model

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ABSTRACT:

Background Intrasaccular flow-disrupting devices are a safe and effective treatment strategy for intracranial aneurysms. We utilized high-frequency optical coherence tomography (HF-OCT) and digital subtraction angiography (DSA) to evaluate SEAL Arc, a new intrasaccular device, and compare the findings with the well-established Woven EndoBridge (WEB) device in an animal model of saccular aneurysms.

Methods In a rabbit model, elastase-induced aneurysms were treated with SEAL Arc (n=11) devices. HF-OCT and DSA were performed after implant and repeated after 12 weeks. Device protrusion and malapposition were assessed at implant time and scored on a binary system. Aneurysm occlusion was assessed at 12 weeks with the WEB Occlusion Scale and dichotomized to complete (A and B) or incomplete (C and D) occlusion. The percentage of neointimal coverage after 12 weeks was quantified using HF-OCT. We compared these data to previously published historical controls treated with the gold-standard WEB device (n=24) in the same model.

Results Aneurysm size and device placement were not significantly different between the two groups. Complete occlusion was demonstrated in 80% of the SEAL Arc devices, which compared favorably to the 21% of the aneurysms treated with WEB devices (P=0.002). Neointimal coverage across SEAL Arc devices was 86±15% compared with 49±27% for WEB (P=0.001). Protruding devices had significantly less neointimal coverage (P<0.001) as did incompletely occluded aneurysms (P<0.001). Histologically, all aneurysms treated with SEAL Arc devices were completely healed.

Conclusion Complete early aneurysm occlusion was frequently observed in the SEAL Arc treated aneurysms, with significant neointimal coverage after 12 weeks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Translational large animal models of saccular aneurysms enable the study of factors related to complete, early occlusion. Previously, in this model, it has been shown that Woven EndoBridge (WEB) treatment revealed complete occlusion in approximately one of five cases, and that protrusion was an independent predictor of failed early, complete occlusion.

WHAT THIS STUDY ADDS

⇒ We tested a novel new intrasaccular device (SEAL Arc) that is a double layered, neck bridging, hybrid nitinol mesh device designed to disrupt blood flow inside aneurysms. We found a very high rate of complete, early aneurysm occlusion on angiography (80%) that histologically was actually 100%. We confirmed that protruding devices had significantly less neointimal coverage (P<0.001) as did incompletely occluded aneurysms (P<0.001).

HOW THIS MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The design of the SEAL Arc flow disruptor with minimal protrusion shows a very high rate of early complete aneurysm occlusion in a translational model.

INTRODUCTION

Intrasaccular devices have become a widely accepted treatment strategy for intracranial aneurysms. Due to their minimal exposure to the parent artery circulation, intrasaccular devices have some advantages over endoluminal flow diverters and stents. Mainly, they do not require dual antiplatelet therapy and can be deployed with reduced concern of disrupting flow or shedding platelet aggregates in small perforators.[1] The Woven EndoBridge (WEB, Microvention, Aliso Viejo, CA) device is the most well studied and shows promise with wide-neck aneurysms that have otherwise proven difficult to treat endovascularly.[2] These devices are designed to disrupt blood flow inside the aneurysmal sac, promote thrombosis, and provide a scaffolding across the neck of the aneurysm to promote neointimal growth, achieving the goal of permanent exclusion of the aneurysm from circulating blood flow.[3] WEB is currently the only intrasaccular flow-disrupting device cleared by the US Food and Drug Administration (FDA). It has demonstrated an excellent safety profile[4]; however, despite promising long-term results,[5] some studies have raised concerns regarding the efficacy of the device, highlighting a need for further research.[6–8] Similar

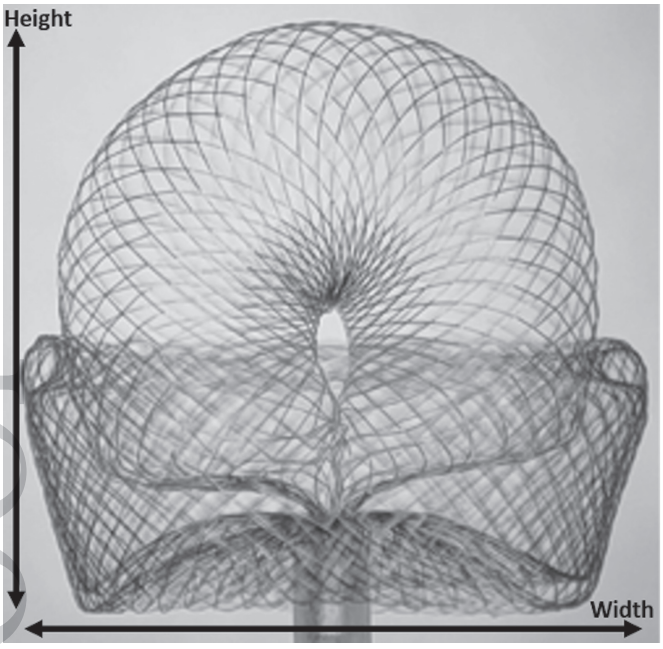

Figure 1 The SEAL Arc aneurysm occlusion device has double layer coverage at the base with an anchoring tube in the dome limiting the need to oversize.

devices have been approved in other countries and are under clinical trial for FDA clearance. The novel Saccular Endovascular Aneurysm Lattice Arc configuration (SEAL Arc) (Galaxy Therapeutics, Inc, Milpitas, CA) device is a double layered, neck bridging, hybrid nitinol mesh device designed to disrupt blood flow inside aneurysms. It consists of a horn torus-like structure that meets the aneurysm neck connected to an atraumatic anchoring tube that contacts the dome with radial force designed to allow the device to conform to various aneurysm shapes (figure 1).

High-frequency optical coherence tomography (HF-OCT), specifically designed for the tortuous anatomy of the neurovasculature,[9] is a relatively new technology for interrogating endovascular devices. It has shown value in addition to digital subtraction angiography (DSA) for evaluating the placement of intravascular devices.[10 11] HF-OCT provides a uniquely detailed view of the neointimal growth on device struts and is comparable to histopathology.[12–14] Given these attributes, HF-OCT can be used in place of other postmortem imaging modalities.[11]

We leveraged this technology to study the occlusion rates and neointimal growth for SEAL Arc devices in a leporine model and compared them to an identical experiment previously reported with the WEB device. We hypothesized that the unique multilayered design of the SEAL Arc device, with added tube structure increasing the metal density at the aneurysm's neck, would lead to high neointimal coverage and occlusion rates.

METHODS

Experimental procedures

All animal research procedures were approved by our university's Institutional Animal Care and Use Committee. Elastase-induced aneurysms were created in a New Zealand White rabbit model (n=11) (sex: either; weight 3.0–4.0 kg).[15] After a minimum of 3 weeks from aneurysm creation, the rabbits were implanted with the SEAL Arc devices.

All procedures were performed under general anesthesia. The animals were pre-anesthetized by subcuticular injection of atropine (0.01 mg/kg) and given an intramuscular dose of sustained release buprenorphine (0.03 mg/kg) for pain management. Anesthesia was induced by intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg) and maintained with mechanical ventilation of 1–3% isoflurane. The physiologic status of the animal was assessed using continuous monitoring of respiration rate, heart rate, oxygen saturation level, end-tidal carbon dioxide level, and temperature every 15 min. Periprocedural heparin was used (100 U/kg); however, no antiplatelet therapy was provided before or after implantation.

Catheter angiography was used to measure the aneurysms and select the device. The devices were delivered via microcatheter with an internal diameter of 0.021–0.027 inches. The device was deployed by a trained interventional neuroradiologist (VA, 11 years of experience) via a right transfemoral approach. The device's position was confirmed with DSA before detachment. All procedures were performed by the same operator. Following detachment, DSA was acquired. HF-OCT (Vis-M; Gentuity LLC, Sudbury, MA) was then used to interrogate the position of the device with respect to the neck.[9] After 12 weeks, DSA and HF-OCT were repeated to evaluate healing and device occlusion, after which all the animals were humanely euthanized (160 mg/kg sodium pentobarbital IV), receiving cardiac perfusion first with saline and then paraformaldehyde under physiologically relevant pressures. The aneurysms with SEAL Arc devices were explanted and placed in 4% paraformaldehyde for histological analysis. The samples were processed through a series of graded alcohols and embedded in Spurr resin blocks. The blocks were cut into wafers that were ground and micropolished with the Exakt Grinding System to a thickness of 100 µm. They were then stained with hematoxylin and eosin before being evaluated.

Image analysis

Baseline aneurysm characteristics before device implantation were measured at time zero (neck width, aneurysm dome height, and width). After device implantation, placement was evaluated with HF-OCT and DSA which were both repeated at the 12-week endpoint. HF-OCT was used to determine device apposition and protrusion based on a previously validated binary scoring system by two investigators,[10] who in cases of disagreement reached consensus (RMK, an engineer with 12 years of experience with DSA and OCT image analysis; VA, an interventional neuroradiologist with >15 years assessing DSA and 4 years analyzing OCT data). A device that was protruding into the lumen past the neck and <50% apposed to either wall of the aneurysm neck was assigned a score of 1 in each category. HF-OCT images from the 12-week follow-ups were used to determine the percentage of the device covered with neointima at the aneurysm neck. This was calculated manually using ImageJ (NIH, Bethesda, MD) by a research fellow (CZ) with a year of experience. Although originally reported by Vardar *et al* for the WEB data,[10] CZ repeated neointimal measurements for these data along with the data from the SEAL Arc device. DSA was used to determine aneurysm occlusion using the WEB Occlusion Scale as described by Fiorella *et al*.[16] Aneurysm occlusion was dichotomized to complete occlusion (grades A and B) or incomplete occlusion (grades C and D). On histology, the neointimal covering on the devices was closely analyzed to determine whether or not the aneurysm had healed histologically.

Statistical analysis

Previously reported WEB implants in the same model (with the same personnel for both the implant and data analysis) with identical outputs on DSA and OCT were used for comparisons.[10]

The Kolmogorov-Smirnov test was used to determine whether data followed a normal distribution. Student's unpaired two-tailed t-test was used to compare continuous normally distributed data. Analysis of variance was used to compare continuous data between multiple groups. Discreet data were compared with a Fischer's exact test due to sample sizes. Statistical tests were performed with GraphPad Prism (Dotmatics, San Diego, CA) and Excel (Microsoft Corporation, Redmond, WA). An α of 0.05 was used to determine statistical significance. Histological data were not compared between aneurysms treated with different devices as different histological techniques were deployed in the studies.

RESULTS

Our data analysis consists of 11 rabbit aneurysms treated with SEAL Arc. One rabbit in the SEAL Arc group was euthanized 2 weeks after implant for bilateral hind limb paralysis. This animal was excluded from analysis. Of the included animals, seven were female and the average weight was 3.5 kg. The mean±SD aneurysm width was 3.4±0.64 mm, aneurysm height was 6.8±1.5 mm, and aneurysm neck diameter was 2.6±0.53 mm.

Thirty percent (n=3) of the SEAL Arc devices were found to be protruding and 20% (n=2) demonstrated good apposition at both walls of the aneurysm on HF-OCT. Immediately following implant, none of the treated aneurysms demonstrated occlusion. At 12 weeks, complete occlusion was found in 80% (n=8) of aneurysms (figure 2).

The 12-week HF-OCT from one animal was eliminated due to poor image quality. At this time point, the average neointimal coverage for the remaining nine devices was 86±15% (figure 3). Devices that were protruding on HF-OCT did not demonstrate a statistically significant difference in neointimal growth compared with those that were not (74.3±23% vs 91.4±9%, P=0.135). There was no statistical difference in neointimal coverage between well-apposed devices and those that were not. Devices that were completely occluded also did not demonstrate significantly greater neointimal coverage compared with those that were incompletely occluded (89.1±9% vs 73.7±34%, P=0.253).

Macroscopically, all aneurysms treated showed full occlusion of the neck and coverage by a thin layer of tissue. The two cases with incomplete occlusion on follow-up DSA showed a dense fibromuscular neointima within the device spanning the entire neck of the aneurysm (figure 4). Histopathology revealed minimal to no inflammatory reaction to the mesh.

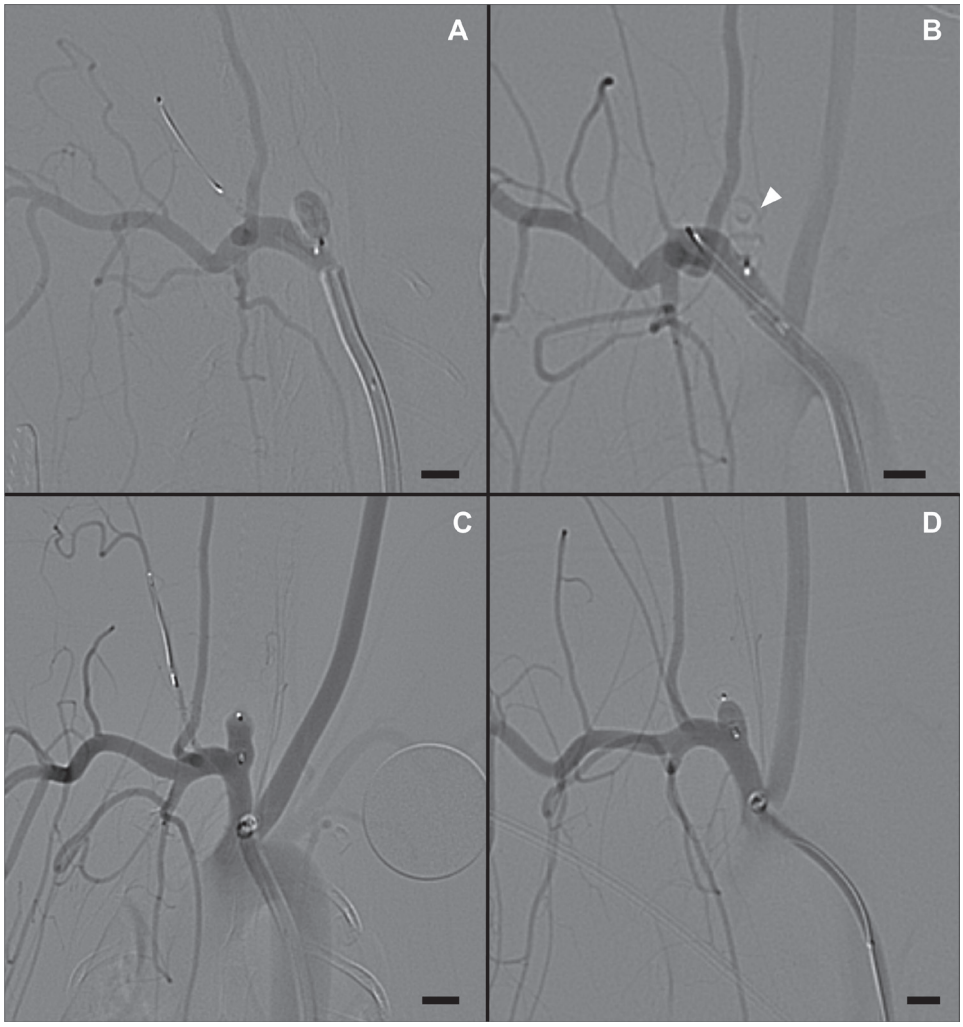

Figure 2 (A) Digital subtraction angiography (DSA) showing a SEAL Arc device in an aneurysm shortly after implant. (B) DSA obtained 12 weeks later showing the same SEAL Arc device (arrowhead) and a completely occluded aneurysm. (C) DSA of a Woven EndoBridge (WEB) device shortly after deployment in an aneurysm. (D) DSA of the same WEB device obtained 12 weeks later showing contrast filling and an incomplete aneurysm occlusion. Scale represents approximately 5 mm.

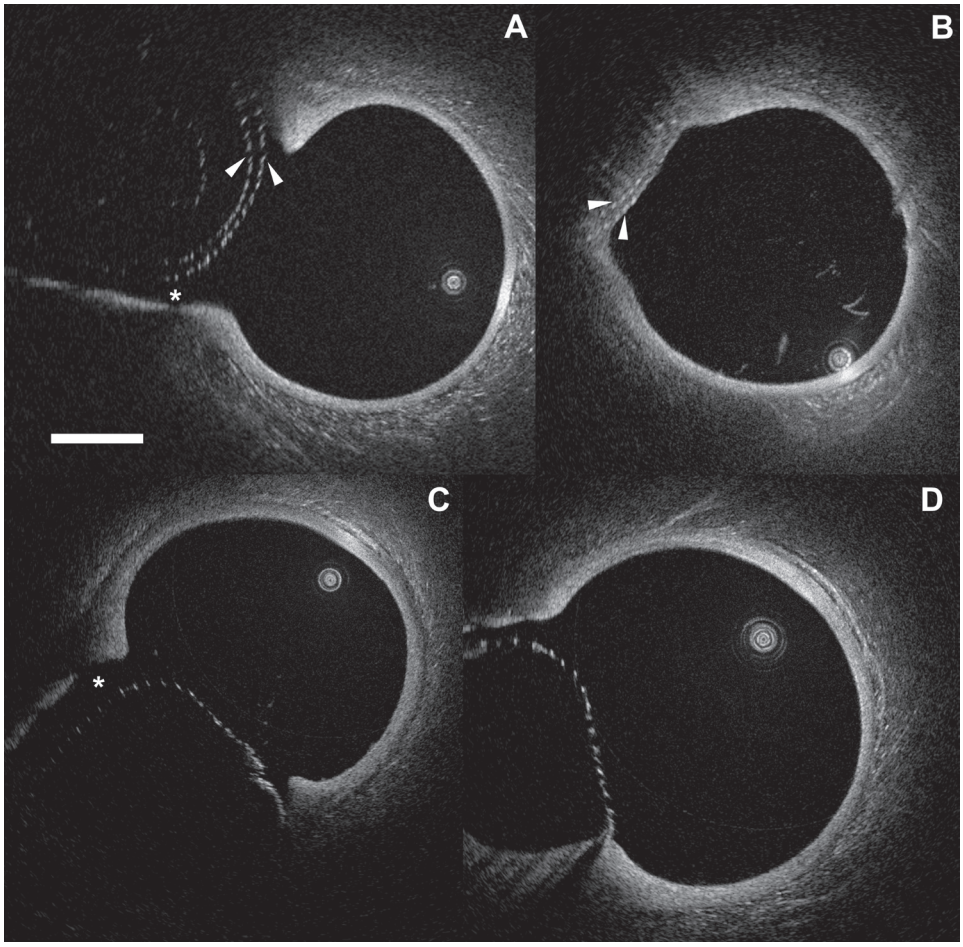

Figure 3 (A) High frequency optical coherence tomography (HF-OCT) image of a SEAL Arc device shortly after implant. The multilayered design is evident (arrowheads), as is the malapposition at one wall (asterisk). (B) The same SEAL Arc device can be seen 12 weeks later with the exposed portion now completely covered by neointimal growth. This device also demonstrated complete occlusion on digital subtraction angiography (DSA). (C) HF-OCT shows a Woven EndoBridge (WEB) device shortly after implant; malapposition at one wall can be appreciated (asterisk). (D) The same WEB device is seen 12 weeks later at the study endpoint with limited neointimal growth. This device did not demonstrate complete occlusion on DSA. Scale bar represents approximately 1 mm.

Comparison with historical controls

We compared these results to a historical cohort of 24 animals treated with the WEB device and studied under identical conditions at our center previously,[10] with no statistical difference in aneurysm dimensions. The incidence of protrusion of WEB (63%, n=15) trended higher as compared with the Arc SEAL device (P=0.057), whereas the rate of good apposition for WEB (21%, n=5) was nearly identical. The rate of complete aneurysm occlusion when treated with WEB (21%, n=5) on 12-week DSA was lower compared with Arc SEAL treated aneurysms (P=0.02). Taking all the data together from both cohorts, protruding devices were significantly less likely to demonstrate complete aneurysm occlusion at the study endpoint (P=0.001). This relationship was not observed for poorly apposed devices.

On HF-OCT, devices that were protruding had significantly less endothelial growth (40.7±22% vs 82±21%, P<0.001) for devices that did not protrude in the pooled data. There was no statistical difference in neointimal coverage between well-apposed devices and those that were not. Compared with WEB, the SEAL Arc devices had significantly more neointimal coverage 12 weeks after implant (P=0.001). At this time point, the average neointimal coverage for SEAL Arc devices was 86±15% compared with 49±27% for WEB devices. The positive relationship between neointimal growth and SEAL Arc trended to remain, even after controlling for the greater percentage of protruding WEB devices (P=0.001); however, this subgroup analysis is not adequately powered. Devices that were completely occluded demonstrated significantly greater neointimal coverage (90.9±7% vs 41.3±21% for incompletely occluded devices, P<0.001).

DISCUSSION

Our previous findings on the occlusion produced by the single layer WEB devices are largely congruent with other translational studies in the same model. Previous studies have demonstrated complete occlusion in 29% of barrel shaped devices[3] and 35% of single layered spherical devices, compared with the 21% of cases we noted to be completely occluded in a similar timeframe.[17] Double layered versions of the WEB device have also been tested in the model, with 33% of devices demonstrating complete occlusion at 1 month and 67% by 12 weeks.[18] This can be compared with the double layered SEAL Arc device we tested which demonstrated complete occlusion in 80% of cases at this time point. Though it was not the primary focus of their paper, Ding *et al* also investigated single- and double-layer devices in a rabbit model. They compared single layer barrel shaped and spherical devices with the double layered WEB device. The double layer devices demonstrated complete occlusion in 67% of

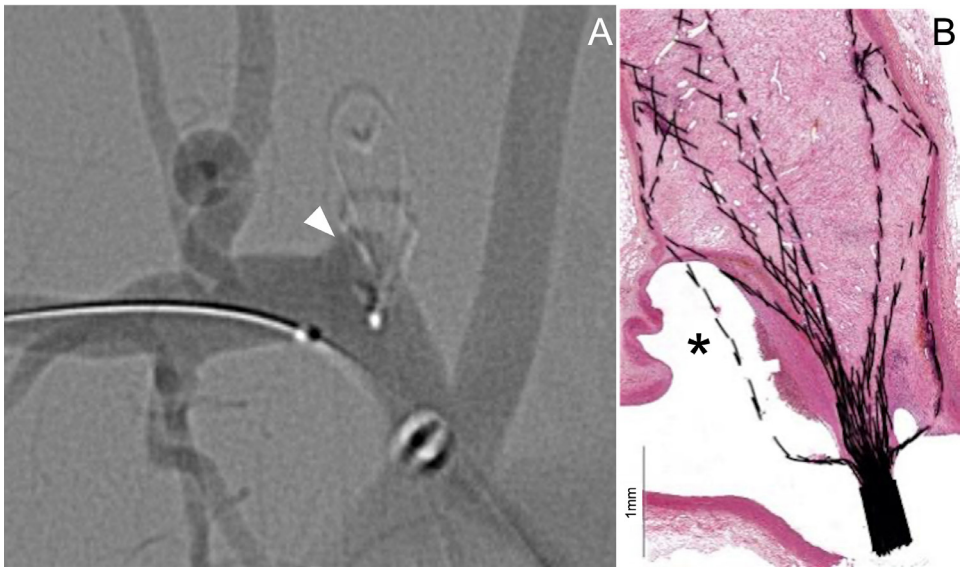

Figure 4 (A) Digital subtraction angiography (DSA) of a SEAL Arc device in an aneurysm 12 weeks after implant. This aneurysm was graded class C on the WEB Occlusion Scale due to what appears to be residual neck filling (white arrowhead). (B) The same SEAL Arc device shown on DSA is seen here sectioned and stained with hematoxylin and eosin. The recess responsible for the continued contrast filling seen on DSA is evident (asterisk). On closer inspection, the aneurysm demonstrates complete neointimal coverage with exclusion of the aneurysm from the circulation.

cases at 3 months compared with 41% with the combine single layer devices.[19] The results presented here and those previously published in the literature suggest a link between the double layer devices and complete aneurysm occlusion.

The histopathology results from the SEAL Arc devices further support this link. Close inspection of the two SEAL Arc devices with incomplete occlusion on DSA revealed that the aneurysms were fully healed with dense neointimal coverage preventing any blood flow in the parent artery from contacting the aneurysm wall.

On HF-OCT we also found significantly more neointimal coverage on the SEAL Arc devices compared with WEB after 12 weeks, potentially explaining the difference in occlusion rates on DSA. It has been shown that device placement, specifically lack of protrusion, may play a role in aneurysm occlusion.[10] Protrusion may negatively impact neointimal growth with higher shear forces and complex flow patterns delaying cell proliferation and attachment.[10 20]

Our analysis of the SEAL Arc devices alone did not find a difference in neointimal coverage between devices that were protruding compared with those that were not, or between devices that demonstrated complete occlusion compared with those that did not. While it is possible that these previously described relationships are not applicable with SEAL Arc given the unique design, it is much more likely that the small sample size resulted in inadequate power to detect such differences. While not significant, our data did trend toward a difference in these groups. In addition, in the pooled analysis we did observe that protruding devices were less likely to be completely occluded and had significantly less neointimal growth, supporting the importance of device placement at the level of the aneurysm neck.

WEB comes with the recommendation to oversize the device for the aneurysm to reduce the risk of compaction, which may lead to protrusion.[21] Following these recommendations, we observed that 62% of the WEB devices were protruding compared with just 30% of the SEAL Arc devices. Although this difference was not statistically significant, it is important to consider given the strong relationship we and others have observed between protruding devices and reduced neointimal growth.

Both devices were sized based on the manufacturers' recommendations. It is possible that with a larger sample size we would have observed SEAL Arc to protrude less often than WEB. However, even after statistically controlling for differing rates of device protrusion, the relationship between SEAL Arc devices and significantly greater neointimal growth remained. This indicates that there are other factors related to the SEAL Arc device design that explain the observed differences.

When deployed in the aneurysm, the multilayered design of the SEAL Arc allows for more mesh to be exposed at the neck and improved packing which is apparent on HF-OCT (figure 4). This produces an environment inside the aneurysm more conducive to occlusion and neointimal growth over the device. The closely approximated layers of nitinol mesh at the aneurysm neck likely create a microenvironment that favors endothelial growth and proliferation. The literature supports this, showing a correlation between the amount of exposed metal and development of neointima.[22 23]

One possible drawback of some dual layer designs is that they can lead to a stiff and inflexible device, potentially hindering delivery. The single layer WEB devices we tested in this study were developed as a lower-profile alternative to earlier double layer designs. They were created for improved navigation and delivery with a wider range of sizes.[24] The design of the SEAL Arc seems to allow for a double layer of mesh without compromising the overall profile of the device and the ease of navigation. Ongoing clinical case series also demonstrate SEAL Arc can be used to treat complex aneurysms.[25]

It is also important to consider the possible safety implications that may come with the design of the SEAL Arc device. The double layered version of the WEB device, while shown to be safe overall and comparable to the single layer design, did trend towards an increase in thromboembolic complications.[26] The intrasaccular factors that lead to the superior occlusion and endothelial growth can also promote clot formation, an important consideration without dual antiplatelet therapy. Ultimately, the speed with which the exposed portion of the SEAL

Arc device is covered by endothelium and the superior occlusion rate may lead to reduced complications and increased safety.

This study does have several limitations to consider. The experiments were performed in healthy rabbits, and although a validated model, the unique process of aneurysm formation in human patients may lead to different results. With the introduction of HF-OCT clinically, validation will hopefully soon be possible. HF-OCT can offer detailed assessment of these devices, but it is limited in that the resolution approaching 10 µm is not sufficient to study single cell layers like the endothelium.[27] The sample size for the subgroup analyses was too small, particularly for the correlation of occlusion as a function of apposition. This potentially increases the possibility of a type II error. Finally, although the aneurysms treated with SEAL Arc were examined histologically, these findings could not be compared with the WEB controls as these samples were instead prepared for evaluation with scanning electron microscopy.

CONCLUSION

We observed in a translational preclinical model that a flow-disrupting intrasaccular device with a unique multilayer design and an atraumatic leading anchoring tube shows a very high rate of complete aneurysm occlusion on DSA at 12 weeks (80%). In all cases, histological cure of the aneurysm was demonstrated. Using HF-OCT, SEAL Arc devices were found to have substantially more neointimal growth independent of differences in protrusion rate between the different devices. These results suggest that advancements in the design of intrasaccular flow-disrupting devices may improve efficacy to achieve complete aneurysm occlusion, which requires clinical validation.

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Competing interests CTZ, JK, RMK, ME, and VA declare no competing interest. TW, AB, EP, and OZ: co-founders of Galaxy Therapeutics. ASR: employee of Galaxy Therapeutics. BP: Consultant for Medtronic, Microvention, Cerenovus and MIVI NeurosciencesGJU: Employee of Gentuity LLC. MJG: 1. Consultant on a fee-per-hour basis for Alembic LLC, Astrocyte Pharmaceuticals, BendIt Technologies, Cerenovus, Imperative Care, Jacob's Institute, Medtronic Neurovascular, Mivi Neurosciences, phenox GMbH, Q'Apel, Route 92 Medical, Scientia, Simcerre, Stryker Neurovascular, Stryker Sustainability Solutions, Wallaby Medical; holds stock in Imperative Care, InNeuroCo, Galaxy Therapeutics, Neurogami and Synchron; 2. Research support from the NIH, the United States–Israel Binational Science Foundation, Anaconda, ApicBio, Arsenal Medical, Axovant, Balt, Cerenovus, Ceretrieve, CereVasc LLC, Cook Medical, Galaxy Therapeutics, Gentuity, Gilbert Foundation, Imperative Care, InNeuroCo, Insera, Jacob's Institute, Magneto, MicroBot, Microvention, Medtronic Neurovascular, MIVI Neurosciences, Naglreiter MDDO, Neurogami, Q'Apel, Philips Healthcare, Progressive Medical, Pulse Medical, Rapid Medical, Route 92 Medical, Scientia, Stryker Neurovascular, Syntheon, ThrombX Medical, Wallaby Medical, the Wyss Institute and Xtract Medical; 3. Associate Editor of Basic Science on the JNIS Editorial Board. OOZ: Consultant for: Stryker, Cerenovous, Penumbra, Medtronic; Research Grant: Stryker, Cerenovous, Penumbra, Medtronic, Genentech, MicroVention; PI: Investigator Initiated trials: TESLA Trial, PI: PICASSO Trial, NIH StrokeNet: Endovascular Committee, StrokeNet Steering Committee; PI: Sterling Aneurysm Registry; Steering Committee: ASSIST Registry, EXCELLENT Registry; Investor: Neuro Technology Investors (NTI)Co-Founder: Galaxy Therapeutics.

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