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Design and biocompatibility of endovascular aneurysm filling devices

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Abstract

The rupture of an intracranial aneurysm, which can result in severe mental disabilities or death, affects approximately 30,000 people in the United States annually. The traditional surgical method of treating these arterial malformations involves a full craniotomy procedure, wherein a clip is placed around the aneurysm neck. In recent decades, research and device development have focused on new endovascular treatment methods to occlude the aneurysm void space. These methods, some of which are currently in clinical use, utilize metal, polymeric, or hybrid devices delivered via catheter to the aneurysm site. In this review, we present several such devices, including those that have been approved for clinical use, and some that are currently in development. We present several design requirements for a successful aneurysm filling device and discuss the success or failure of current and past technologies. We also present novel polymeric based aneurysm filling methods that are currently being tested in animal models that could result in superior healing.

Keywords

intracranial aneurysm; shape memory polymer; aneurysm filling device; endovascular; embolization

1. Introduction

Intracranial aneurysms are focalized dilations of an arterial wall, which tend to be spherical in shape and are associated with a weakening of the structure of the artery. These vascular malformations are located deep within the arteries of the brain and are highly susceptible to

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Conflicts of Interest

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rupture, resulting in high morbidity and mortality, making early diagnosis and treatment a necessity. The walls of cerebral arteries have a structural composition unlike the vasculature in other regions of the body. These arteries lack an external elastic lamina¹, which if present, would act as an extra elastic sheath within the wall of the artery. This reduced elasticity within the cerebral arteries causes them to be more susceptible to aneurysm formation.² Further, the aneurysm dome is structurally weakened as evidenced by a thicker adventitia and decreased thickness of the media.¹ Figure 1a and 1b illustrates the various layers composing an artery.¹ Additionally, arteries with aneurysms exhibit increased stiffness due to the presence of hyaline fibers.¹ The combination of reduced elasticity within an already compromised, or weakened vessel, makes these malformations susceptible to rupture due to the constant impinging blood flow to the area.

The two most common forms of intracranial aneurysms are fusiform aneurysms, a dilation of the full diameter in a straight segment of an artery, and intracranial saccular aneurysms (ISAs), which are spherically shaped and commonly occur at artery bifurcations within the Circle of Willis.³ Housepian et al. reported that fusiform aneurysms account for 9% and saccular aneurysms account for 85% of all aneurysms found at autopsy.⁴ This review focuses specifically on the development of devices for the treatment of ISAs. ISAs can be classified using characteristics of the dome, including the diameter at the widest portion of the aneurysm, the diameter of the neck (the interface between the dome and the parent vessel), and the height of the aneurysm (the distance from the neck to the most distal portion of the dome of the aneurysm). Subsequently, the dimensions are used to determine the dome-to-neck ratio (maximum dome width/maximum neck width), and aspect ratio (dome height/maximum neck width) of an aneurysm (Figure 1c). These ratios are used to describe the geometry of ISAs. For example, an ISA is classified as wide necked if it has a dome-to-neck ratio less than 1.6, an aspect ratio less than 1.6, and a neck width of at least 4.0 mm.⁵ These geometrical ratios are significant in that they greatly affect the design and variety of medical devices that can be used to treat these aneurysms.

Hemorrhagic stroke, known as subarachnoid hemorrhage (SAH), occurs when there is a rupture of an aneurysm or arteriovenous malformation (AVM) (a malformation involving both the arteries and veins). SAH is a medical emergency, which requires immediate treatment. SAHs are among some of the most debilitating morbidities that may be caused by an aneurysm. Between 35–50% of patients who experience an SAH die.^{3,6,7} Among the survivors, only 50% of patients regain normal mental and physical capabilities. Of the remaining 50% of survivors, 30% suffer irreparable damage, and a staggering 20% require hospice care for the remainder of their life.⁸ There are often more than one ISA per patient, which makes subsequent ruptures in survivors commonplace.⁹ Due to these dire statistics associated with SAH, ISA treatment and rupture prevention is necessary to decrease the potential morbidity and mortality of these events.

1.1 History of Aneurysm Treatment Methods

The study and treatment of aneurysms has improved throughout history; from limited observation, including visualization of aneurysms at autopsy or by palpitations of the skin for diagnosis, to advanced imaging techniques that facilitate endovascular treatments.

Historically, early diagnosis often involved observing dilatation and pulsations on the skin from large aneurysms caused by trauma or infectious disease, such as syphilis.¹⁰ Thus, surgical treatments of aneurysms were limited to large aneurysms found in the thoracic or abdominal aorta, proximal carotid artery, and peripheral vasculature.¹¹ Aneurysm treatments often focused on preventing rupture or reducing symptoms caused by mass effect; typical methods included wrapping or compressing the aneurysm or occluding a saccular aneurysm to reduce the blood flow into the sac.¹² In the late 18th century, Gilbert Blane first described clearly identifiable cerebral aneurysms in the course of performing autopsies¹³, however, viable diagnosis of intracranial aneurysms would not occur until the development of cerebral angiography in 1927.¹⁴ Effective early diagnosis of cerebral aneurysms enabled surgical interventions, including the first obliterative clipping of an aneurysm by Walter Dandy in 1937 using silver clips.¹⁵ As surgical clipping techniques improved, the method became the gold standard of intracranial aneurysm treatment until the development of endovascular coiling in the 1980's.¹⁶

Though endovascular treatments of intracranial aneurysms would not be introduced until the late 20th century, technological precursors to current aneurysm occlusion techniques date back to the late 18th century. Several early pioneers experimented with insertion of foreign bodies into thoracic or aortic aneurysms to induce thrombosis, including the use of metallic wires.^{11,17} Wiring techniques often implemented electrothrombosis, which aimed to induce clotting via an electrical current to improve the occlusion stability.¹⁸ However, these initial occlusion treatment methods resulted in high rates of morbidity and mortality.¹⁷⁻¹⁹ From 1969-1972, endovascular treatment of intracranial aneurysms was demonstrated using balloon catheterization and occlusion by Serbinenko et al.²⁰ The development of endovascular detachable balloon therapy led to treatment of various cerebrovascular lesions, including intracranial aneurysms.²¹ However, the detachable balloon method introduced a number of issues, including recurrence or rupture due to a “water-hammer effect” from the pulsating arterial flow, which illuminated the need for alternative solutions.²² Through the late 1980s and early 1990's, platinum coils were introduced²³, culminating in the detachable coil developed by Guglielmi and Target Therapeutics (Fremont, CA).²⁴ The Guglielmi Detachable Coils (GDC®) (Stryker Neurovascular / Boston Scientific Corp., Fremont, CA, USA) became the gold standard of endovascular embolization for intracranial aneurysms. The success of the detachable coils has led to the development of additional endovascular therapies for treating intracranial aneurysms implementing various device design and biomaterial solutions. A list of common devices used in endovascular embolization procedures is provided in Table 1, where the devices are categorized by the type of material used.

1.2 Types of Aneurysm Filling Devices

Based on the materials used, endovascular aneurysm treatment devices can be separated into one of three categories: metal, polymer, or a combination of the two, known as hybrid devices. The following is a summary of marketed and developing devices in both the United States and European Union.

1.2.1 Metal Devices

1.2.1.1 Coils: The first endovascular devices for aneurysm occlusion approved by the FDA were Guglielmi's detachable coils (GDC®) in 1995 (Figure 2).²⁴ These are soft platinum coils that have the ability to conform to the surrounding geometry and coil around themselves, allowing for multiple coils to be packed into an aneurysm dome. Due to the inherent risks and invasiveness of a full craniotomy surgery required for clipping, endovascular coiling was recognized as a major improvement in the treatment of aneurysms. Figure 3 is a summary of the methodology and potential treatment outcomes from endovascular coiling by platinum coils. Although these devices yielded lower occlusion rates when compared to clipping (77.6% vs 92.5%)²⁵, they have remained popular among clinicians. Bare platinum coils, such as GDCs®, are currently the gold standard for comparison to new devices because of their flexibility and the simple electrolytic nature of the release mechanism, which elicits a thrombogenic event around the coils.²⁶ They are also preferred by clinicians due to the low rates of procedural complications and patient recovery times.²⁷

The volumetric occlusion (the ratio of inserted coil volume to the total aneurysm volume) achieved by different coils is a strong indicator of long-term device efficacy; a higher volumetric occlusion leads to decreased coil compaction (i.e. shifting of implanted coils toward the aneurysm dome as shown in Figure 3) and lower aneurysm recurrence.^{28,29} Volumetric occlusion using GDCs ranges between 20-31%. To improve these percentages, larger coil diameters, and complex three dimensional coil shapes, such as spherical, (rather than two dimensional shapes, such as helical) have been investigated.³⁰ Slob et al., concluded that 0.012" (305 µm) diameter coils with a complex geometry achieved a higher aneurysm volumetric occlusion than 0.010" (254 µm) helical coils (30% vs. 23%) (Figure 2). He also discovered that comparable lengths of the larger diameter coils could be delivered because of the complex coil shape.^{28,31} Penumbra 400™ (Penumbra, Alameda, CA, USA) bare platinum coils feature a much larger coil diameter (0.020" or 508 µm) and offer a higher volumetric occlusion (33%) for large aneurysms (~11.3mm diameter).³² However, some neurointerventionalists have found these larger diameter coils as a quick means of achieving high volumetric occlusion in aneurysms as small as 4 mm.³³

1.2.1.2 Flow Diverters: A more recent development in the treatment of aneurysms has been the emergence of flow diverters (FDs), which have geometry similar to stents but with many more struts orientated to form a fine mesh. FDs are typically delivered in the parent artery, across the aneurysm neck, anchored by radial forces acting against the normal arterial wall.³⁴ FDs feature higher pore density than stents, which minimizes blood flow through the aneurysm neck and facilitates stagnation of blood within the dome of the aneurysm. Covidien's Pipeline™ Embolization Device (PED; Covidien, Irvine, CA) and Balt's SILK FD (Balt Extrusion, Montmorency, France) have effectively treated giant and uncoilable intracranial aneurysms, which typically have a diameter larger than 25 mm.^{35,36} However, studies have shown that with the use of FDs, there is difficulty in occlusion of curved, side wall, and bifurcation aneurysms in canine models.³⁷

1.2.2 Polymer Devices—The use of polymeric endovascular devices for treating arterial vascular malformations (AVMs) has been proposed as early as the 1970's.³⁸ Current FDA

approved polymer embolic devices consist of liquid polymer implants utilizing cyanoacrylates, such as n-butyl cyanoacrylate (n-BCA), and ethylene vinyl alcohol (EVOH). In 2000, Trufill® n-BCA (Codman Neurovascular, Raynham, MA) became the first FDA approved liquid polymer embolic system for treating cerebral ISAs and AVMs.³⁹ It consists of n-BCA liquid polymer, ethiodized oil, an injectable radio-opaque diagnostic agent, and tantalum powder. The liquid components are injected through a microcatheter and solidify when in contact with ions present in blood. The solidification time is controlled by adjusting the ratio of ethiodized oil in the liquid polymer mixture. Complications from using cyanoacrylates, such as n-BCA, include acute and chronic inflammatory reactions that can occur within the vessel walls or surrounding tissues and recanalization.⁴⁰

More recently, the FDA approved Onyx® (Covidien, Irvine, CA), a liquid embolic system consisting of an ethylene vinyl alcohol co-polymer dissolved in dimethyl sulfoxide (DMSO) to treat ISAs and cerebral AVMs.⁴¹ Onyx® incorporates tantalum powder for radio-opacity and has a slow solidification time for prolonged and controlled injection. Onyx® is currently used for presurgical embolization of AVMs and in the treatment of ISAs. A recent 4 year study evaluating the effectiveness of the Onyx® embolic system on the treatment of AVMs found a total occlusion rate of 53.9%, with a morbidity rate of 8%.⁴² A separate study, however, revealed a recurrence rate of 50% in completely occluded cerebral AVMs.⁴³ There are concerns regarding the angiotoxic, or vessel toxicity, effects that can occur when using DMSO as an organic solvent, primarily due to the possibility of vasospasms. However, studies conducted on the toxicity of DMSO revealed no harmful effects when used as directed.⁴⁴

In contrast to the liquid embolic systems used to treat cerebral AVMs and ISAs, the FDA recently approved the cPax Aneurysm Treatment System (NeuroVasx, Inc., Maple Grove, MN) for cerebral aneurysms larger than 10 mm in diameter.⁴⁵ The device functions much like metallic coils and can be positioned with either a permanent stent, or a temporary balloon catheter. cPax consists of a polymer strand that can be delivered through a microcatheter and has the ability to be detached at any point along the length of the device. The FDA approved the use of this device under a Humanitarian Device Exemption (HDE) that considers rare conditions that affect fewer than 4,000 people in the U.S. annually.

1.2.3 Hybrid Devices—Currently, the only hybrid devices on the market are coil-based treatments. Hybrid coils contain both metal and polymer components. The primary polymers used in these treatments include bioactive polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA) (Matrix® and Matrix2™ Detachable coils, Stryker Neurovascular, Fremont, CA; Cerecyte® Coils, Codman Neurovascular, Raynham, MA; Axium™ Detachable Coil System, Covidien, Irvine, CA.; Nexus™ Detachable Coils, Covidien, Irvine, CA), and hydrogels (HydroCoil® and HydroSoft®, MicroVention Terumo, Tustin, CA). Other polymers, such as nylon (Axium™ Helix Nylon Coil, Covidien, Irvine, CA), are also being investigated for these types of devices. These devices are considered bioactive because they are designed to interact with the body's natural foreign body response to elicit thrombogenesis, while at the same time utilizing biodegradable polymers.

Hydrogel coated coils aim to increase the volumetric occlusion compared to bare platinum coils (BPCs) through the use of a hydrogel coating that expands in the presence of blood.⁴⁶ MicroVention Terumo (Tustin, CA) manufactures a line of hydrogel coated platinum coils, including HydroCoil®s and HydroSoft®. HydroCoil®s feature an external hydrogel coating around a platinum coil and up to 900% volume expansion.⁴⁷ The coating makes them stiffer than BPCs, increasing the time it takes to properly place the coil in the aneurysm.^{46,48} While a study by Guo et al. noted many handling issues with HydroCoil®s, such as early hydrogel expansion, large amounts of friction, and catheter instability when inserting multiple coils,⁴⁶ researchers observed reduced recurrence rates compared to aneurysms treated with BPCs.⁴⁸ In a different design, HydroSoft® coils were designed to improve upon the HydroCoil® design, making them easier to handle. HydroSoft® coils are different in that they contain a hydrogel fiber and a stretch resistant filament within the lumen of a platinum coil, instead of an outer hydrogel coating, and exhibit a 40% volume expansion.⁴⁹ The lower volume expansion eliminates working time limitations of HydroSoft® coils. It was also found that the HydroSoft® coil was more compliant than HydroCoil®s and could even be used as finishing coils.⁴⁶ A finishing coil is typically very compliant and is used in the final steps of the coiling process to fill the aneurysm more completely.

Coils containing biodegradable polymers were introduced to promote a tissue response and reduce recanalization rates.^{50,51} Matrix® and Matrix2™ coils consist of a platinum coil core with a PLGA coating. Although approved by the FDA, the clinical results of the Matrix® coils were disappointing. Many studies have reported elevated recanalization rates compared to BPCs.⁵² Matrix2™ coils, designed to mitigate problems with the first generation coils, have shown improvement over Matrix® coils at eight months post procedure, but showed significant recanalization at long term follow up, approximately eighteen months, leading to durability concerns.⁵³

In contrast to polymer coated coils, Nexus™ and Axium™ coils consist of a platinum coil with PLGA and PLGA/nylon fibers intertwined within the coil respectively.^{32,54} Nexus™ coils have been deemed safe to use but do not offer significant advantages compared to GDCs and Truefill platinum coils.⁵⁴ The ACCESS study, which evaluated the safety in treating a small number (n=16) of aneurysms with Axium™ MicroFX PLGA coils, found Axium™ coils to be safe and durable at a four month follow up.⁵⁵ However, due to the similarities in design with Nexus™ coils, which had poor performance, and the short time to follow up in the ACCESS study, subsequent studies are necessary to determine the long term efficacy and durability of Axium™ coils.

Another study involving coils with polymers within the central lumen of the coil involved the Cerecyte® coils. Cerecyte® bioactive coils incorporate a PGA filament within the lumen of a platinum coil. Therefore, the coil volume does not change as the PGA degrades. Another advantage of these coils are the mechanical properties, which are identical to BPCs from Codman Neurovascular.⁵¹ Initial studies investigating Cerecyte® coils have been more promising than other bioactive coils and have exhibited similar procedural complication rates and improved implant durability when compared to BPCs.^{50,51,53,56,57} A prospective, randomized study performed by Molyneux et al. has shown that there is not a significant

difference in angiographic outcomes between Cerecyte® and BPCs when assessed at 6 months.⁵⁸

1.3 Developing Technology

There are many new approaches to aneurysm filling that are currently in the proof-of-concept stage of development. Some of the most promising new devices utilize shape memory polymer (SMP) foams, magnetic micro-particles (MMPs), or thermal ablation. Of these developing technologies, the most mature technology is the SMP foam. Consequently, there are multiple groups that are currently working towards refining SMP foam devices with animal studies.^{59,60} In general, these studies take advantage of the novel “smart” functionality of the SMP foams by deforming and programming the foam into a temporary compressed shape, delivering it through a catheter, and then restoring it to its original shape within the aneurysm via an external stimulus (Figure 4). When the shape is restored, the aneurysm is filled and a clot rapidly forms, allowing for healing to occur. Optimal aneurysm treatment involves endothelialization and neointima formation across the aneurysm neck, which isolates the aneurysm from the parent artery (Figure 4).^{27,61}

SMP foams have many favorable characteristics as an aneurysm filling material, such as tunable pore size for optimal cellular infiltration, excellent biocompatibility, radio-opacity, low circumferential recovery stress, exceptional volume occlusion, and device flexibility. Previously, Metcalfe et al. has shown that foam pore size may influence cellular infiltration and stable tissue integration within the foam.⁵⁹ Foams with a pore diameter of approximately 250-800µm have demonstrated effectiveness in occluding porcine side wall aneurysms and acting as an ideal scaffold for connective tissue deposition, resulting in favorable long-term healing.⁶⁰ The pore sizes of SMP foams can be tailored by altering the initial monomer concentrations during synthesis.⁶² This control allows for the fabrication of foams with pore sizes optimized for cellular infiltration, retention, and proliferation, which is a contributing factor to its excellent biocompatibility. Implanted SMP devices within a porcine vein pouch aneurysm model reported by Rodriguez et al. has shown that the foams are less inflammatory than traditionally used suture materials.⁶⁰ Additionally, the foams encouraged collagen formation, neovascularization, lack of fibrin and a complete endothelial layer across the ostium of the aneurysm as early as 90 days after implantation.⁶¹

Due to these promising healing responses, SMP foams are currently being designed and tested as a minimally invasive treatment of cerebral aneurysms in bench top studies, as well as porcine animal models.⁶³ These SMP foam devices are first shaped into a sphere, then temporarily programmed into a compressed cylindrical secondary shape via heating above their transition temperature and cooling under compression. This crimped device is then delivered through a catheter to the aneurysm site with the aid of fluoroscopy. When the foam is properly positioned within the aneurysm, it is thermally actuated to recover the primary, spherical shape (Figure 4). The recovered SMP conforms to and fills the aneurysm sac.

These SMP foam prototypes have been successfully delivered within *in vitro* aneurysm models for testing and validation of the treatment method. *In vitro* tests focused on determining the deliverability of the device through a catheter, recovery of the primary

shape by thermal actuation of the device, and fluoroscopic visualization during the delivery (Figure 4). Future studies will include deploying these devices within a sidewall porcine aneurysm model and a comparison of the healing response, safety, and efficacy of embolic foams to GDCs®.

A similar approach utilizing MMPs instead of SMP foam is currently being developed by Oechtering et al.⁶⁴ This method aims at obliterating the aneurysm by delivering these MMPs via a microcatheter to the inside of the aneurysm, with assistance of an external or intravascular magnetic field. In their study, they were able to achieve short-term success with an *in vivo* rabbit model, but failed to develop a long-term solution. However, in retrospect, they were able to identify areas of improvement for future studies. For example, they found that in order to successfully direct the MMPs to the inside of the aneurysm, a magnetic force that exceeds the local hemodynamic forces is required. In addition, they also suggested that future studies should investigate new coatings for the MMPs in order to reduce immunological reactions during treatment.

Another technology that is currently being developed by Qiao et al. utilizes thermal ablation.⁶⁵ In this approach, they combine catheter-based delivery of an antenna with microwave or radiofrequency heating. They hypothesize that if an antenna is properly placed within the aneurysm, its heating will induce cell death, and thereby cause clot formation inside the aneurysm. If the clot reaches an appreciable size, it is thought to be capable of occluding the aneurysm from its parent artery. Although, there have yet to be *in vivo* studies testing this methodology. If successful, this method is advantageous because it does not leave a foreign substance or device inside the patient. However, it is critical that the thrombus does not migrate out of the aneurysm and cause serious complications, including blocking blood flow of distal arteries and potentially causing an ischemic stroke. To ensure that this does not occur, they suggested using a stent to seal off the neck of the aneurysm prior to the heat treatment.

1.4 Analyzing and designing effective devices

1.4.1 How Current Treatments Fail—Current endovascular embolization techniques focus on occlusion of the aneurysm via reduction of blood flow and promoting thrombosis within the aneurysm sac. Ideally, a treated aneurysm is isolated from its parent artery by neointima formation across the neck of the aneurysm, preventing blood flow into the sac and aneurysmal rupture. However, various devices are prone to a number of issues, reducing the long-term effectiveness of the treatment.

Though safety and efficacy of endovascular coiling with the GDC® system has been proven more advantageous compared to surgical clipping,⁶⁶ coiling methods have demonstrated various drawbacks. Primarily, aneurysms treated with coils are prone to recanalization and recurrence, which can lead to aneurysm rupture due to renewed blood flow in the aneurysm sac (Figure 3).⁶⁷⁻⁷⁰ GDC® and other bare platinum coils exhibit coil compaction, low filling with volumetric occlusion ranging from 20-31%, and low material bioactivity, resulting in recanalization rates of 21-31%.^{29,52,69-72} Additional complications with bare platinum coils include approximately 2–5% chance of aneurysm rupture during an embolization procedure^{27,70} and the necessity for multiple coils per procedure, approximately one coil for

each millimeter of aneurysm diameter, which increases technical complexity and procedural risk.⁷³

In response to the drawbacks of bare platinum coils, hybrid metal/polymer embolization coils were developed, but long-term effectiveness has been limited. Hydrogel-coated coils have achieved a significant improvement over bare platinum coils in volumetric occlusions of 64-85%, but still result in unfavorable recanalization rates of 17-28%.^{47,74,75} Hydrogel-coated coils are also limited with a working time of 5 minutes to deliver the device through the microcatheter prior to hydrogel expansion, reducing the time available for the physician to deliver and properly position the device within the aneurysm sac.⁷⁶ Additionally, hybrid coils combining platinum with PLGA or PGA have exhibited volumetric occlusion of 23-43%, yet have resulted in recanalization rates of 15-37%.^{53,56,68,69} Higher recanalization rates have been attributed to the degradation of the bioactive polymer before a stable thrombus has formed, reducing coil volume and, ultimately, volumetric occlusion.^{53,68}

Flow diverters (FDs) are used as an alternative, or in conjunction with, endovascular coils, and although they have shown desirable thrombosis within the aneurysm sac, the devices exhibit similar complications seen in bare metal cardiovascular stents, such as restenosis. Flow diverters have mortality and morbidity rates of 8% and 4%, respectively⁷⁷, but devices such as the SILK FD and Pipeline™ Embolization Device, have also shown restenosis rates of 21.7%-33% in the parent vessel.^{78,79} Thus, although the probability of hemorrhagic stroke is reduced by the FDs, the risk of ischemic stroke increases with the introduction of restenosis.

Liquid polymer embolic devices have also presented a variety of technical limitations associated with their use. For example, there are possible toxicity effects caused by using organic solvents, such as DMSO.⁴⁴ Additionally, liquid polymer systems, such as Onyx®, utilize irreversible reactions. Therefore, it is not possible to reposition or retrieve the solidified polymer once it has been delivered into the aneurysm. Furthermore, the working time of the liquid polymer solution may be limited, and as a result, it can be difficult to prevent the liquid embolic polymer from migrating out of an aneurysm during delivery. Several studies performed by Murayama et al. have confirmed this with testing of Onyx's liquid embolic system. The results showed migration rates into the parent vessel ranging from 9-33%, which is an issue due to the possibility of embolizing the parent vessel and causing an ischemic stroke.⁸⁰

1.4.2 Why the Switch to Polymeric Devices?—Bioactive hybrid devices have some advantages over biologically inert bare platinum coils. The polymer coating of specific hybrid devices elicits a positive tissue response to promote healing and positive remodeling.⁸¹ An intra-aneurysmal inflammatory response can accelerate thrombus formation and assist in coil anchoring.⁸² The irregular geometries of aneurysms can lead to ineffective occlusion and failed treatments. Hybrid devices coated in expandable hydrogels, such as HydroCoils®, are advantageous over metal devices because of their ability to expand to fill these irregular shapes with fewer coils. Although the polymer coatings are not radio-opaque, the metal backbones used in hybrid devices allow imaging under fluoroscopy during surgery. However, hybrid devices do not have a reduction in recanalization rates and

are limited by working time.⁴⁶ These disadvantages have motivated a focus on novel polymer devices for aneurysm treatments.

Polymer devices share the bioactive advantages of hybrid devices, and can be radio-opaque with the inclusion of filler materials.⁶⁰ Versatile polymer devices, such as cPax (for its optimizable coil lengths) or the liquid embolic Onyx®, possess some advantages over hybrid and metal devices. Specifically, polymer foam devices have tunable pore sizes and the ability to achieve high occlusion percentages with fewer devices. Additionally, the polymer foam can be synthesized with biocompatible polymers that elicit minimal long-term inflammation while providing a scaffold for optimal cellular penetration and the subsequent deposition of connective tissue throughout the volume of the foam. Polyurethanes are well-known for their biocompatibility because their chemistry can be easily altered to promote or reduce thrombogenesis.⁸³ For instance, changing the chemical composition of traditional polyurethanes, by incorporating large non-polar, hydrophobic segments, can reduce platelet adhesion, thus making the compound less thrombogenic.⁸³ Alternatively, hydrophilic groups such as zwitterions, or negatively charged surfaces will increase platelet and fibrinogen adhesion.⁸⁴ Studies by Kipshidze and Metcalfe have yielded promising results in animal models using polymer foam devices to occlude the vasculature.^{59,61,85}

1.4.3 Design Requirements for an Optimal Device—The optimal aneurysm filling device is one that would promote rapid clotting (to initiate the healing process), remain stable over longer periods of time without migration into the parent vessel, and match the mechanical properties of the surrounding tissues. All of these properties lead to the isolation of the weakened portion of the aneurysm, preventing future rupture and SAH.

1.4.3.1 Mechanical Properties and Fluid Dynamics Considerations: There is a great deal of debate regarding the pathogenesis of aneurysm growth, initiation, and rupture. However, researchers have shown that hemodynamics, vessel wall biomechanics, mechanobiology, and the intracranial environment are the four primary concerns in understanding the pathogenesis of cerebral aneurysms.⁸⁶ All endovascular aneurysm treatment devices interact with, and alter, the blood flow and mechanical properties within aneurysms and the blood vessels surrounding the treatment region. This continuous interaction makes it imperative to design treatment devices that minimize disturbances in native blood flow patterns and match the mechanical properties of the cerebrovasculature.

Several hemodynamic factors are thought to influence the growth and rupture of intracranial aneurysms.⁸⁷⁻⁹⁰ The shear stress within blood vessels has proven to regulate coagulation cascades^{91,92}, cell proliferation⁹³, the release of vasodilators⁹⁴, the potential for hemolysis⁹⁵, and leukocyte and monocyte adhesion to endothelial cell surfaces.⁹⁶ Thus, abnormally high, or low, shear stresses contribute to aneurysm growth and rupture.⁹⁷ Also, it has been shown that the oscillatory nature of the wall shear stress on the aneurysm causes continuous damage to the endothelial lining of the sac.^{98,99}

Researchers have found a strong correlation between areas of high wall shear stress in the neurovasculature, typically located at flow impingement sites, and aneurysm initiation and rupture.^{97,100,101} There have also been studies showing that ruptured aneurysms experience

significantly greater shear stresses and unstable flow than unruptured aneurysms.¹⁰²⁻¹⁰⁴ Proposed mechanisms for aneurysm growth via areas of high shear stress focus mainly on the mechanically stimulated overproduction of molecules and proteins from endothelial cells, which leads to destructive remodeling and denudation of the aneurysm wall.^{86,105} In extreme cases, high wall shear stresses can cause cell injury and damage to the elastic lamina, which may also result in destructive remodeling of the wall.^{86,106,107}

Low shear stresses are also a factor leading to the growth and rupture of aneurysms.¹⁰⁸⁻¹¹⁰ Decreased wall shear stresses, such as those found in recirculation zones, can lead to inflammation, apoptosis of endothelial and smooth muscle cells, cell dysfunction, and localized degeneration as there is a reduction in the production of nitric oxide (NO), which causes aggregation of red blood cells and platelets and the eventual infiltration of leukocytes and fibrin.^{86,111-117} This mechanism likely occurs in the fundus of narrow-necked aneurysms where there is flow stagnation and reduced wall shear stresses.^{97,118} The effects of low shear stresses, as a result of turbulent flow, are shown in Figure 5.

Despite the contradicting theories regarding high and low shear stresses as the primary cause of aneurysm rupture, all researchers agree that extremes in shear stress have adverse effects on aneurysm pathology. Given the impacts of shear stress extremes, researchers must consider the potential effects of implanted devices on the fluid dynamics within a blood vessel. This includes avoiding abrupt changes in geometry and sharp edges that may induce unstable, turbulent flow in the vessels surrounding the aneurysm. Turbulent flow is not entirely a result of geometry, but also depends on the velocity of the fluid flowing around the device.¹¹⁹ However, the geometries shown in Figure 6 have demonstrated an affinity for generating turbulence in previous experiments and should be avoided when possible.¹²⁰⁻¹²³

Despite the role wall shear stress plays in aneurysm pathogenesis, it is believed that hemodynamic pressure within the aneurysm is the governing factor in stress-induced rupture.¹²⁴ Similarly, excessive pressures and forces exerted on the aneurysm wall by devices can increase medical complications. Thus, mechanical analysis and testing of devices is necessary to show stresses from device use are minimal. For example, Hwang et al. has shown that SMP foams do not impart a high stress on the aneurysm wall, which reduces the risk of stress-induced rupture. These studies observed and estimated the circumferential stress of foams in a latex model of a cylindrical aneurysm. ABAQUS simulations were performed to measure the circumferential stress imparted by foams that were oversized to 1.5x and 2x the diameter of the cylindrical aneurysm model. The results from these simulations estimated a circumferential stress of 350 kPa with a circumferential Green Strain of 0.21. This estimation is significantly less than the aneurysm wall breaking strength of 700 kPa.¹²⁵⁻¹²⁷ However, this critical strength varies based on gender, the test performed, and the size of aneurysms.¹²⁴ Due to the low amount of stress imparted on the aneurysm wall, the foams can be oversized and fully occlude the aneurysm without concern of rupture.¹²⁶

In general, endovascular aneurysm treatment devices should aim to reduce flow in the aneurysm and promote thrombus formation. This leads to the eventual exclusion of the aneurysm from the parent vessel via new endothelialization of the aneurysm neck; thereby

ensuring vessel patency and normal physiologic flow.^{99,128,129} Flow stagnation can be caused by disrupting and reducing flow in the aneurysm, leading to reduced shear stresses and long residence times of platelets, i.e. the time the platelets remain in the aneurysm volume. This increases the likelihood of platelet adhesion to the aneurysm wall and implanted device, thus promoting the formation of thrombus.¹³⁰⁻¹³² It can be inferred that the most successful device will produce long residence times and promote clot formation, while preventing damaging extreme shear stresses to the compromised endothelium.

Another critical criterion that must be considered when designing embolic devices for the treatment of aneurysms is the compliance of the device, or the amount of deformation that results from a given applied force.¹³³ In order to prevent rupture of the aneurysm, and damage to the adjacent blood vessels during delivery of the device, it is critical to match the compliance of the device to the compliance of the vessels within the cerebrovasculature. In other words, treatment devices should have high longitudinal flexibility, and low radial stiffness to allow navigation through highly tortuous, narrow vessels.^{134,135} Platinum coils have exhibited high compliance and Hwang et al. demonstrated that the flexural modulus of crimped SMP foams was compared to that of a 5Fr catheter (ENVOY 5 Fr, Codman Neurovascular, Raynham, MA) through a three-point bending test. The flexural modulus of the crimped foam was determined to be less than half that of the 5Fr catheter, indicating that device flexibility should not be an issue during delivery.¹²⁶ If these conditions are met, treatment devices can completely occlude the aneurysm by conforming to the precise geometry of various aneurysms. For example, in the case of embolic coils, the compliance of the devices is essential as it affects the volumetric occlusion that can be achieved within the aneurysm sac.⁷¹ Due to the variability in the size and shape of aneurysms between patients, this is an essential design consideration for coils or other devices.

1.4.3.2 Biocompatibility: Material properties unrelated to mechanical properties are critical to an aneurysm-filling device because they play a major role in the device's function, bioactivity, and toxicity after implantation. Previously, the relative biocompatibility of polymeric and hybrid aneurysm filling devices has been compared to bare platinum coils. These studies have encompassed evaluations of hydrogel-coated coils, polymer coils, and polymeric foam filling devices. A study conducted by Ding et al. in 2005, compared the performance of Microplex® (MCS) platinum coils (MicroVention Terumo, Tustin, CA), HydroCoil®s hydrogel coated metal coils, and 2D Matrix® Coils, platinum coils coated with a bioabsorbable polyglycolic acid/lactid copolymer known to induce a tissue reaction at two, six, and ten week follow-up.⁵² This study was completed to evaluate the tissue response of each device within an elastase-induced aneurysm rabbit model. Histological analysis of the HydroCoil®s at six weeks did not show a significant inflammatory response and there was a lack of compaction of the coils. Additionally, continuous unorganized thrombus was present in the dome and there was fibrous tissue formation across the aneurysm neck.⁵² HydroCoil®s provided better coil stability as shown in the angiographic and histological data. Mild inflammation was seen in seven of the HydroCoil® treated aneurysms. The aneurysm dome was mostly filled with polymer in these aneurysms rather than connective tissue.⁵²

Histological analysis of the Matrix® coils at ten weeks showed compaction of the coils, unorganized thrombus formation, and did not show tissue formation across the neck of the aneurysm. An increased tissue reaction was shown by cell infiltration around the coil surface in 60% of the aneurysms treated with Matrix® coils.⁵² It was believed that modification with a bioactive polymer was not enough to prevent recanalization within this study.

Additionally, increased amounts of inflammation were seen in the aneurysms treated with the Matrix® coils compared to the others studied.⁵² This study showed that a superior tissue response was consistently achieved with the Matrix® coils compared with platinum coils; however the angiographic outcome was worse, due to coil compaction. This is consistent with other studies' findings, which indicate that the outer PLGA coating degrades before an organized thrombus forms, leaving bare platinum coils which do not properly fill the aneurysm.^{56,57,82,136} These results suggest that the addition of polymer alone, is not sufficient to increase both volumetric filling and result in a superior healing response.

Mechanical stability of the filling device is required for proper healing. Ding et al. have suggested that mechanical stability of the neck may be the key to stable closure and healing of the aneurysm, which may be more important than bio-active/degradable components. It is believed that HydroCoil®s are successful due to the substantial volume filling of the aneurysm.⁵² The expansion of the hydrogel helps seal the aneurysm neck, potentially reducing recurrence.⁴⁶

Biocompatibility of an aneurysm filling device requires an initial active biological response, one in which clotting is initiated within the aneurysm. Not only must this device initiate clotting, but it must also remain stable long enough for cellular components to infiltrate the volume to begin the healing process, as demonstrated in Figure 4. Devices such as the PLLA/PLGA coils have not demonstrated promising results within rabbit models, despite containing bioactive surfaces. This lack of success is likely due to rapid degradation *in vivo*.⁵²⁻⁵⁴ These devices degrade prior to complete endothelialization, which further emphasizes the importance for stabilization of the aneurysm by an embolization device. Stabilization includes the initial clotting of the aneurysm, infiltration by cellular components within the first few months after treatment, and the complete endothelialization at the device and parent vessel interface. These studies further emphasize that the selection of the polymeric material is of utmost importance. The presence of PLLA/PLGA was not able to provide a stable structure on which platelets and erythrocytes could adhere and initiate clotting, thereby limiting the eventual deposition of fibrin and subsequent cellular infiltration, which is necessary for long-term healing and stabilization. These results suggest that a permanent, or slower degrading, polymer implant would be advantageous for aneurysm filling devices.

Contrary to the previously mentioned results within the rabbit model, human studies involving the Matrix® Detachable Coils have shown encouraging results *in vivo*. In a clinical study conducted using Matrix® Detachable Coils and bare platinum coils⁷², it was shown that the polymeric coated coils were covered with a thick tissue layer that was composed of fibro cellular tissue that lacked residual fibrin but contained collagen, smooth muscle cells, and small blood vessels at six months.⁷² These positive results were seen at

least three months after implantation *in vivo*. The superior healing seen in human trials using Matrix® Detachable Coils suggests that although the rabbit elastase-induced model, used in numerous preclinical studies of aneurysm-filling devices, closely mimics the coagulation cascade and blood pressure of humans^{137,138}, it may be a more rigorous model of healing and inflammation that provides conservative indications of success compared to human trials.

Previous biocompatibility research conducted on polyurethane based porous materials^{59,60,85,139} has shown promising histological findings, aneurysm void stabilization, endothelialization, and a fibrous cap at the device and parent vessel interface which is evident at 30 days and complete at 90 days *in vivo*. Cytotoxicity and mutagenicity studies performed by Metcalfe et al. on SMP foams in 2003 showed no evidence of toxicity or mutagenicity *in vitro*, and histological findings from a canine model displayed a minimal inflammatory reaction with tissue ingrowth throughout the foam and neointima formation across the majority of the neck of each aneurysm.⁵⁹ Additionally, in the study conducted by Rodriguez et al. in 2012, an ultra-low density polyurethane SMP foam was reported with less inflammation than commonly used suture materials, silk and polypropylene, which were positive and negative controls for inflammation respectively.^{60,62} These materials were also shown to induce healing which was evident by cellular infiltrates, the laying down of collagen, a lack of residual fibrin, neovasculature and a mature endothelial cell cap at the vessel and aneurysm interface.⁶¹ These results agree with the previous conclusions about stabilization being an important contribution toward healing proposed by Ding et al. in 2005.

The success of porous foam devices for aneurysm treatment using *in vivo* models suggests that porosity is an important material characteristic for optimizing the tissue response to a device. Metcalfe et al. suggested that smaller foam cell sizes might be advantageous for embolic procedures, because they do not allow for a large clot to form inside the foam, but still allow for cellular migration into the foam.⁵⁹ The theory supporting these conclusions is based on scaffolding for cell growth. SMP polyurethanes do not offer natural scaffolding for cells to grow on, but it is believed that the scaffold is generated from fibrin within the clot throughout the foam.⁵⁹ Previous studies support this showing that fibrin can provide the necessary scaffolding for cell binding.¹⁴⁰ As a result, it is critical that clot formation takes place within the foam, to allow migrating cells to bind to the newly formed attachment sites and induce tissue growth.

Previously, a vascular occlusion device (VOD)⁸⁵ and a type II endoleak treatment for abdominal aortic aneurysm (AAA)¹³⁹ filler have been made of a non-degradable, fully reticulated polyurethane foam material. These materials had pore cell sizes of approximately 250-600µm (Biomerix Corp., Fremont, CA). Other previous materials tested, have included SMP aneurysm devices made of partially reticulated polyurethane foams that had an average pore cell size of 800-1200µm.⁶⁰⁻⁶² All of these devices showed promising *in vivo* biocompatibility and cellular infiltration in animal models. These materials, with interconnected pores, acted as a scaffold for cellular infiltration that promoted healing evident by the presence of vascularized tissue and overall device stabilization.^{61,139}

Within the rabbit elastase model, performed by Ding et al., moderate inflammation was present in two of the platinum coil treated aneurysms, along with loose connective tissue and unorganized thrombus at ten weeks. Increased cellular infiltration was not seen in the bare metal groups.⁵² From the Szikora et al. study in humans, it was shown that at two months after treatment the bare platinum coils were covered with an incomplete fibrin layer and had a residual neck.⁷² After three years of treatment the aneurysm remained an open sac with both organized and unorganized thrombus that remained unstable. Another drawback, in terms of biocompatibility, associated with the use of GDC® coils includes the detachment system used for deployment. It has been shown that electrolytic detachment of GDC® coils has the potential to create bubbles, which may cause air embolisms.¹⁴¹ Lee et al. tested several types of coils, including GDC®, and found that each released a very small amount of gas (up to 23.42mm³) into the parent artery. Since multiple coils are used to fill an aneurysm, even this small volume could be a concern.¹⁴²

1.4.3.3 Radio-opacity: Endovascular devices are placed into the aneurysm via catheter with the aid of fluoroscopic imaging. Fluoroscopic imaging is an x-ray based projection imaging modality. This modality is dependent upon the attenuation of x-rays by the body or material between the projector and the detector. Metal devices are made of high-z element materials, or densely packed atoms, and therefore are visible under fluoroscopic imaging when compared to the density of the human head. Polymeric devices however are not made from high z-element materials and are less dense than the thickness of the surrounding tissue and skull. Due to this lack of visual differentiation between the device and the surrounding tissues via fluoroscopy, the polymeric device alone would not be able to be implanted via endovascular methods due to its lack of radio-opacity. For this reason, many polymeric materials are loaded or doped with high-z element particulates to make them visible under fluoroscopy. Previous devices proposed for aneurysm treatment have been loaded with tantalum and tungsten^{60,143} to induce radio-opacity (Figure 7). The Onyx® liquid polymer embolic device is doped with tantalum for visibility, and the cPax polymer strand device has a platinum band at the distal end for visualization similar to a standard catheter.

2. Summary and Remarks

Many methods have been developed to treat ISAs, such as platinum coil filling, flow diverting stents, injection of liquid polymer, polymer coiling, and combinations of metal and polymer coils. There are other approaches (e.g., SMPs, MMPs, and thermal ablations) that are currently being developed, each having advantages and disadvantages. However, all of the devices described strive to improve biocompatibility, device/thrombus stability, higher volume occlusion, and improved device compliance, while reducing adverse complications.

GDC® coils were the first FDA approved coiling method developed to treat ISAs and have recurrence rates of 21-31%^{67,69}, a mortality rate of 8%⁶⁶ and unable to treat wide neck aneurysms. Flow diverters were designed as a treatment for large, complex aneurysms, not amenable to treatment by traditional coiling methods. However, these types of devices have resulted in mortality and morbidity rates of 8% and 4%, respectively⁷⁷ and have demonstrated significant rates of restenosis.^{78,79}

Liquid polymer embolic devices offer advantages over metallic coils, such as the ability to inject a controlled amount of polymer necessary for complete filling of the aneurysm, minimizing device prolapse into the vessel lumen, and minimal circumferential stress imparted on the aneurysm sac. However, limitations include inability to reposition or retrieve the solidified polymer once it has been delivered and high rates of device migration into the parent vessel.^{44,80}

Hybrid coil aneurysm embolization is designed to solve some of the issues associated with bare metal coil embolization, such as poor aneurysm filling and tissue response, while maintaining mechanical and radio-opaque advantages of platinum coils. Hydrogel-coils incorporate a hydrogel coating that expands in the presence of blood, increasing the volumetric filling of the aneurysm compared to BPCs.⁴⁶ However, hydrogels have not shown a significant promotion of tissue response, and have short working times, the potential for the hydrogel to swell before the device is properly placed in the aneurysm.⁵² Biodegradable and bioactive coils incorporate a polymer to elicit a cellular response to encourage rapid clot formation and endothelialization.^{50,51} These coil types are designed to promote proper healing and tissue integration to reduce recanalization and reformation of the aneurysms. However, studies have shown that the outer polymer degrades more rapidly than the time required for an organized thrombus to form, resulting in incomplete filling and recanalization of the aneurysm.^{53,56,57,82,136} Despite these stabilization concerns, PLGA-coated coils have shown more favorable tissue response compared to BPCs.⁵² Contrary to the polymer coated coils, platinum coils with central strands of biodegradable polymer, serving as the inner core of the coil, have had more positive results. With these coils the volumetric occlusion does not change when the polymer degrades, and initial studies have shown promising results.^{50,51}

In summary, the devices mentioned attempt to improve interventional outcomes by using either biostable or biodegradable polymers, less invasive procedures, higher volume filling of the aneurysm, and filling materials with mechanical properties that more closely match the native vessel properties.

Due to the high mortality and morbidity rates associated with the rupture of intracranial aneurysms, it is imperative that minimally invasive treatment methods continue to be explored. The drawbacks of current “gold standard” devices have led to the commercialization of alternative embolic devices aimed at improving long-term efficacy and decreased procedural complexity. While some devices have demonstrated improvement over traditional platinum coils, there remains a necessity for novel technologies to enhance treatment outcomes. However, multiple design criteria must be considered during the device development process including device compliance, radio-opacity, novel materials and geometries that provide favorable biocompatibility and cellular infiltration. The goal of these requirements is to promote optimal long-term healing while preserving the ability for endovascular treatment methods. Current research suggests that polymer-based devices improve volumetric filling and subsequent stabilization of aneurysms, potentially leading to better patient outcomes and lower rates of morbidity and mortality.

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Figure 1.

(a) Diagram of normal arterial structure (b) Dimensions to determine dome-to-neck ratio and aspect ratio of aneurysms for treatment. (c) Example of locations for dimensions to determine dome to neck ratio and aspect ratio of aneurysms for treatment.

Figure 2.

A side-by-side comparison of GDC® coils having a (a) three-dimensional complex shape and (b) two-dimensional helical shape. Complex coils show multiple radii of curvature, while the helical coils maintain approximately the same radius of curvature.

Endovascular coiling:

Figure 3.
Schematic of endovascular coiling procedure and potential outcomes of treatment.

Figure 4. Schematic of endovascular deployment of SMP foam and summary of healing response within a porcine aneurysm model. Cellular infiltrates indicated via wound healing knowledge are summarized from Kumar et al.¹, and the aneurysm composition at thirty and ninety days are a summary of the results reported by Rodriguez et al. in 2013⁶¹.

Quiescent phenotype:

Coagulation:

↑ PGI₂, NO, tPA
↓ Platelet aggregation

Endothelium:

↓ Proliferation
↓ Apoptosis
↑ Alignment

Vessel wall:

↓ SMC proliferation
↓ Leukocyte adhesion
quiescent

Activated phenotype:

Coagulation:

↓ PGI₂, NO, tPA
↑ Platelet aggregation

Endothelium:

↑ Proliferation
↑ Apoptosis
↓ Alignment

Vessel wall:

↑ SMC proliferation
↑ Leukocyte adhesion
atherogenic

Figure 5.

Endothelial cell phenotypes depend on the hemodynamic environment. Quiescent cells are found in high shear stress environments, whereas activated cells are found in low shear stress environments⁹³.

Figure 6.

Cross-sectional view of geometries that induce turbulent flow. **(a)** Channel with semi-circular baffles within the lumen^{120,121}. **(b)** A device with an outlet containing a transverse bevel, like a hemodialysis needle¹²². **(c)** A reverse step, or rapid expansion in geometry¹²³. Arrows indicate the direction of fluid flow.

Fluoroscopy of crimped to expanded SMP foam in a silicone model

Fluoroscopy of expanded SMP foam in porcine aneurysm model

Figure 7.

Demonstrated radio-opacity of tungsten doped SMP foam in vitro and in vivo. A.1) The crimped SMP foam has been delivered and positioned in the aneurysm, A.2) The distal end of the delivery device actuated the crimped foam using Joule heating to ~50% expansion of primary shape within 1 minute, A.3) The SMP foam was fully expanded within 2 minutes from the initial actuation. Reprinted from Hwang et al. with permission from ASME, B)

Example of tungsten doped SMP foam implants within a porcine vein pouch aneurysm model.⁶³

Table 1

Historical development of intracranial aneurysm treatments. Metallic devices are shown in blue, hybrid devices are highlighted in green, and polymer devices are shown in yellow.

	Introduction Date	Device	Methodology	Clinical Outcomes
Metal	1864	Metallic Wires	Iron wires are delivered through needle into the aneurysm to induce embolization.	Weak clot formation achieved with temporary symptom reduction; emboli creation and aneurysm rupture events result in 7% survival rate. [1886 Ransohoff]
	1879, 1938	Electrically-conductive Wires	Wires constructed of silver and copper is delivered through needle into the aneurysm and electrical current is passed through them to induce electrothrombosis.	Reduction of pulsation and pain in most cases, though no benefit or readmitted in 32% of cases. Short-term mortality rate of 38% primarily due to infection or aneurysm rupture. [1912 Finney]
	1921	Collapsible Wire Mesh	Collapsible wire mesh is inserted via cannula into the aneurysm to induce embolization.	Pulsation and pain reduced in most cases, though 56% of patients died within 4 months of operation primarily due to infection or aneurysm rupture. [1921 Power]
	1938	Implantable Clip	A flat silver clip is surgically placed across the aneurysm neck, preventing flow into the aneurysm and isolating it from the parent vessel. Current versions use titanium clips.	Within 1 year of treatment, 21% patients dependent and only 10% dead. [Molyneux 2005] Current standard for invasive surgical treatment of intracranial aneurysms.
	1966	Magnetically-directed Iron-Acrylic Compound	The iron-acrylic compound is injected into intracranial aneurysms via needle and directed within the aneurysm via a magnetic stereotaxic probe.	Mortality rates of 33% primarily due to migration of injected compound or thrombus into parent vessel. [1971 Alksne]
	1974	Detachable Balloon-tipped Catheters	A detachable balloon, constructed of silicone or latex, is delivered endovascularly to the aneurysm or parent vessel and detached to induce embolization.	Arterial and aneurysmal occlusion achieved, though successful treatment dependent on location. Procedural complication included death in 10% patients and stroke in 8% patients. [1991 Higashida (Radiology)]
	1990	Detachable Platinum Coils	Platinum coils are delivered endovascularly to the aneurysm and detached to induce embolization.	Within 1 year of treatment, 16% patients dependent and only 8% dead. [2005 Molyneux] However, aneurysm recurrence occurs in 21-31% patients. [2003 Raymond, 2012 Piotin] Current standard for endovascular treatment of intracranial aneurysms.
	1999	Flow diverters	Stent-like device implanted across the neck of the aneurysm endovascularly to create hemodynamics favorable	Successful occlusion of aneurysms, including those failing alternative treatments. Reported improvement in 74 - 88%

	Introduction Date	Device	Methodology	Clinical Outcomes
			for embolization and are often used in conjunction with platinum coils.	aneurysms and complications for 6% lesions. [2013 Beckske, 2013 Ringelstein]
Hybrid	2001	Bioactive Polymer-Platinum Coils	Platinum coils with bioactive PLGA or PGA polymer coated or embedded within the coil are delivered endovascularly to the aneurysm and detached to induce embolization. The biodegradable polymer is designed to promote tissue response and rapid thrombus formation.	Aneurysm healing improved over bare platinum coils, though reported recurrence ranged 15 - 37% of patients. [2012 Piotin, 2006 Fiorella, 2008 Veznedaroglu]
	2002	Hydrogel-coated Coils	Hydrogel-coated platinum coils are delivered endovascularly to the aneurysm and detached to induce embolization. Blood contact causes the hydrogel to swell, increasing aneurysm filling.	Aneurysm volumetric occlusion improved over bare platinum coils with recanalization occurring in 22 - 28% patients. [2007 Cloft, 2008 Gunnarsson]
Polymer	2000	Liquid Embolics	Polymer suspended in solvent is injected into the aneurysm with balloon catheter blocking the aneurysm neck and the polymer precipitates and solidifies in the aneurysm. Often used in conjunction with stenting.	High volumetric occlusion of aneurysms achieved, but procedure is significantly more complicated. Recurrence shown in 5 - 13% aneurysms. [2006 Cekirge, 2009 Piske]