Chapter

Endovascular Treatment of Brain Aneurysms

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Abstract

Topic: Chapter discussing the indications for treatment of brain aneurysms, endovascular techniques, tips and tricks. 1. Pathophysiology of aneurysms: Discuss the formation of aneurysms, current thinking of aneurysm development 2. Prevalence/Incidence of aneurysms: Discussion of current state of aneurysm prevalence and how it differs in different populations 3. Unruptured Aneurysms: Diagnosis, Management and Treatment: Imaging paradigms of brain aneurysms, current thoughts on how to follow aneurysms which are being observed, different treatment options for unruptured aneurysms, including clipping, coiling, stent assisted coiling, flow diverter stent, flow disruptors, including the medical management of stent placement 4. Ruptured Aneurysms: Diagnosis, Management and Treatment: Imaging paradigms of ruptured aneurysms, management options for co-morbidities associated with aneurysm rupture, treatment options including coiling, clipping, flow diverter stents, flow disruptors 5. Complication Avoidance: Tips and tricks to avoid complications in the treatment of brain aneurysms.

Keywords: brain aneurysms, subarachnoid hemorrhage, coils, flow diversion, flow disruption

1. Pathophysiology of aneurysms

A cerebral aneurysm is defined as a local outpouching of an intracranial artery and can either be saccular or fusiform. The formation of aneurysms is an incompletely understood gradual process [1] involving genetics, epidemiology and pathobiology, in conjugation with the study of biophysics provides a more complete picture on how these factors interact [2]. The natural history of saccular intracranial aneurysms consists of three phases: initiation, growth, and either stabilization or rupture, and the application of scientific principles to biological processes has made it easier to understand the behavior of aneurysm formation and rupture.

1.1 Genetic factors

Various genome studies and subsequent replication case control studies suggest genetic components in the formation of intracranial aneurysms (IA), no specific genes strongly associated with formation have yet been identified. A meta-analysis [3], identified three single nucleotide polymorphisms (SNPs) located on chromosome 9 within the *CDKN2B-AS1* gene, on chromosome 8 near the *SOX17* transcription regulator gene, and on chromosome 4 near the endothelin receptor gene associated with the presence of sporadic IAs. A new IA susceptibility locus on 13q

was identified [4]. Subsequent genome-wide association studies [5, 6] have found additional loci on chromosome 7 near *HDAC9*, as well as in chromosomal regions 1p34.3–p36.13, 19q13.3, Xp22 and 7q11. The strongest evidence for linkage was with a locus on 7q11 near the perlecan gene that encodes elastin, a protein that is involved in the preservation of vessel wall integrity.

1.2 Structural changes and hemodynamics

Cerebral arteries are prone to aneurysm formation due to presence of cerebrospinal fluid, sparse tunica adventitia, lower proportion of elastic fibers and disruption of internal lamina at bifurcation [7–9]. Blood is an active participant in the formation of aneurysms, its flow provides the mechanical triggers for reactions in the vessels at the level of the endothelium, while it is also a biological participant in the inflammatory cascade [10, 11]. This dual function of blood contributes significantly to the degradation of the arterial wall in the formation of aneurysms [2].

Cohort studies on people with a familial preponderance to saccular aneurysm have shown that the geometry of bifurcations around the circle of Willis adds additional stress to the vessel walls, given the significant shifts in flow velocity, dynamic forces, and shear stress. Thus, high flow across a wall that is not "designed" for the exposed pressures results in tissue injury and remodeling. The biological result may be plaque or may be an aneurysm, depending on the presence (or absence) of an intact media [2]. Fluid-dynamic models calculate and visualize wall shear stress or wall shear gradients, intra-aneurysmal flow, impingement zones, and flow patterns or velocities. Wall shear stress constitutes the degree of friction in the intracranial aneurysm wall that results from blood inflow and impingement into the aneurysm. High and low wall shear stress can both be present during aneurysm formation but the relevance of these flow conditions to the pathogenesis, growth and rupture of an aneurysm remain unclear [12]. The role of shear stress is very controversial, responsible for damage at specific phases of aneurysmal development and rupture. Some studies suggest the direct effect of shear stress on the vessel wall resulting in injury and degeneration of the wall's media, leading to aneurysm formation. Others suggest that low shear stress in the aneurysm and the vessel wall may result in small thrombus formation, endothelial reactivity, and inflammation at the site, thus weakening the vessel.

Data generated from fluid-dynamic models could help improve our understanding of aneurysm formation patterns and potential structural deficiencies in aneurysms. The relevance of existing data derived from computational fluid modeling is limited, however, because the majority of studies compared ruptured with unruptured aneurysms. An ideal approach would be to compare the same aneurysm before and after rupture [13–16].

1.3 Molecular changes

In response to internal elastic lamina disruption and the subsequent mechanical overload and shift in tensile forces, vascular smooth muscle cells and fibroblasts synthesize collagen types I and V, which are the main molecular constituents of intracranial aneurysms [17].

Once the molecular mechanisms fail to compensate for the mechanical overload of the vessel wall and myo-intimal injury, cellular and humoral inflammatory responses become the main drivers of aneurysm formation [17–20]. These responses are mediated by inflammatory cytokines such as tumor necrosis factor (TNF), IL-1β and matrix metalloproteinases (MMPs), promote influx of macrophages and continuous degradation of collagen and elastin fibers. Wall shear stress might also contribute to cellular inflammatory responses during aneurysm formation.

1.4 Can aneurysm rupture be predicted?

Aneurysm rupture has been suggested to occur as aneurysm expansion approaches and exceeds the physical limits of the tissue. It has also been suggested that the vibrations induced by pulsatile flow and the subsequent resonant frequency may promote aneurysmal rupture [21, 22]. Although not directly resulting in aneurysmal rupture, vibrational irregularities secondary to the presence of the aneurysm may accelerate the degeneration of the aneurysmal wall and subsequently lead to rupture. A shift to quantitative and not just qualitative analysis, and a focus on flow and flow dynamics as a force of influence in rupture have changed the landscape of research for cerebral aneurysms [2].

2. Prevalence and incidence of aneurysms

Although Unruptured Intracranial Aneurysms (UIA) are common [23, 24]. Their prevalence is subject to changes due to the improvements in invasive and non-invasive imaging techniques, the increasing knowledge about the related factors that determines screening in asymptomatic populations and the increase in the life expectancy. Historically, the methods used to address prevalence were retrospective or prospective autopsy studies in the decades from 1950's to the earliest 2000's [25] but non-invasive imaging studies have demonstrated higher prevalence and prevalence ratios compared to autopsy studies (PR 3•5, 95% CI 2•1–6•1)3. To study UIA, the Magnetic Resonance Angiography (MRA) is the most common method for detection in asymptomatic patients [26] and compared to Intra-Arterial Digital Subtraction Angiography (IA-DSA), systematic reviews have found no significant differences in the prevalence reported between these two imaging techniques (more details will be elucidated in the next section of this chapter). However, it's important to highlight that prevalence reported in non-invasive imaging studies can present limitations due to the interobserver agreement, training, experience, quality of equipment and expert's judgment [27].

The IA characteristics are also a major concern in prevalence studies; technical limitations in regard to location, size and morphology can decrease the sensitivity and specificity of the diagnostic methods. Both, large and relatively small [28] cohort's studies had shown that saccular morphology is the most common form of presentation and that among patients without history of subarachnoid hemorrhage (SAH) the distribution of IA in the internal carotid artery (ICA) and middle cerebral artery (MCA) are 24.8 and 22.7% [29] respectively, however in patients with previous history of SAH, the prevalence is higher in the MCA. In regard to the size, modern imaging techniques can easily detect aneurysms from 2 mm, which is extremely important to determine the risks of possible treatments or natural history, so far, the current evidence is that UIA > 5 mm, location in basilar artery apex and decrease in BMI over the follow-up period are related to speed up the 2.9% of aneurysm growth per year. However, irrespective of aneurysm size, the irregular shape and daughter sac are more likely to rupture [30, 31]. Although we know these are contributing factors, there is still a need to understand better the contribution of aneurysm related factors.

The prevalence of UIA among the general population is 3–5% [32] but there are several differences between populations that increase the risk for having a IA or a SAH. The risk factors commonly associated to IA development and rupture whether there's a previous history of SAH or not, are age > 30, female sex, African-American race, smoking, alcoholism, hypercholesterolemia, high blood pressure, first and second-degree relatives with SAH history, and other comorbidities as polycystic kidney disease, connective tissue disorders and brain tumors [33–36]. However,

lifelong follow-up studies of UIA suggested that only female sex and smoking status were significant risk factors for aSAH [37]. Across countries, compared to USA prevalence, China, Japan, European countries including (UK, Netherlands, Finland, Germany and Italy) had no significant differences in the prevalence ratios adjusted to age, sex and comorbidities [38–41]. Other studies in Iranian population [42] have shown a prevalence of 3.2% but more studies in non-Caucasian populations are still required to further understand the impact of genetics and cultural practices.

The incidence of aneurysmal SAH (aSAH) reports are questionable, first, in average 20% of the aSAH deaths occur suddenly, away from hospital or in emergency rooms [43]. Therefore, incidence can vary between countries with different autopsy rates and medical study protocols. In the case of Finland, the PHASES study showed a 3–6 times increased risk of aneurysm rupture in compared to other European nations and USA [44]. However, these findings can be a proof of how epidemiological studies need to improve their parameters more than a proof that Finnish people have more risk of aSAH. Finland has high rates of autopsy studies in sudden deaths [45] and all nonhospital deaths and moreover, longer life expectancy and pyramid shrinking due to the increasing of elderly population [46]. So, there's no currently strong evidence to conclude that aSAH in Finland cohorts is truly higher than the other countries included in the PHASES study.

In spite of this evidence, careful consideration must be taken when we think about the pros and cons to treat a patient based on their personal risk factors. Most of the large cohort's publications and meta-analysis have been done in populations where ethnicity diversity was limited, the impact of social stratus had not been assessed and criteria for collecting data and analysis was not standardized. Therefore, perfect epidemiological studies do not exist so, great efforts will be necessary to determine inclusion and exclusion criteria in future prospective cohorts.

3. Unruptured intracranial aneurysms

Diagnosis of unruptured intracranial aneurysms (UIA) in most of the cases is incidentally during evaluations of other conditions [44] because the vast majority are asymptomatic or have subtle manifestations. Only, 10 to 15.5% of patients have symptoms related to UIA [45]. These symptoms generally are associated to mass effect due to the aneurysm size and growth, rarely cranial neuropathy or even more rare with sentinel hemorrhage, due to minimal blood leaking with the consequent meningeal irritation [45]. Symptomatic UIA often present with neurological deficits as visual dysfunction, ocular nerve palsy, bilateral temporal hemianopsia and other neurological symptoms as headaches, embolic cerebral ischemia, poorly defined spells, and seizures [46, 47]. Patients with symptomatic UIA need more attention because this can be a manifestation about riskier distribution and morphological [45] characteristics of the aneurysm, and a warning sign of an impending rupture [48]. The diagnoses modality after incidental discovery of an UIA, is based on which imaging modality is more sensitive depending on aneurysms characteristics, patients related factors, medical history and moreover, methods available in each center. Therefore, there is no specific diagnoses algorithm for UIA. The decision of screening or further imaging after finding an incidental aneurysm is still on the specialist judgment. These considerations are discussed below:

It has been mentioned that most of the UIA are diagnosed incidentally, and some of the non-invasive imaging methods have also been mentioned in the "prevalence" section of this chapter. However, there are still different evidences about the rates of diagnosis and prevalence reported through these non-invasive imaging methods as the MRA or CTA and IA-DSA, the current gold standard [22, 49]. Many authors had

suggested that the MRA and CTA to be the best methods for preliminary screening of IA [50, 51], the sensitivity and specificity of both methods are 87 and 95% for MRA and 90 and 86% for CTA [47]. But the effectiveness of the diagnoses can decrease depending on the IA characteristics; in UIA < 3 mm, MRA and CTA sensitivity plummet to 38 and 61%, respectively [52]. Moreover, the high rates of comorbidities in people with UIA product of common pathophysiology (like hypertension with the consequent kidney failure) or to the old age of patients can limit the use of the contrast dye in CTA for screening. Therefore, MRA is the most frequent tool for screening nowadays. Other non-invasive techniques like transcranial Doppler (TCD) have been explored, but whether power Doppler is done with or without contrast enhancement, it's sensitivity and specificity together are not superior to MRA and CTA [51]. Nevertheless, TCD can be a screening tool in countries were the expensive costs of MRA or CTA makes them inaccessible.

Sensitivity and specificity of imaging methods for diagnostic are important, but more considerations should be taken to study UIA characteristics. IADSA, provides the better spatial resolution than other techniques [44], but this method may not provide a good sense of aneurysm volume and can present difficulties when vessels are overlapped, and therefore 3D reconstructions are often needed to fully evaluated for intracranial aneurysms. Moreover, IADSA as an invasive method, can carry risks; 2.3% of patients can present transient neurological complications, 0.4% permanent neurological complications and 14.7% of non-neurological complications [52]. Novel imaging methods as the Optical coherence tomography (OCT) can be useful to assess key factors in aneurysm structure due to the power to increase 10 times image resolution compared to other current techniques [44] and furthermore, OCT has a nearly-biopsy resolution [53] and enhance resolution of birefringent tissues as artery laminas [54] which is major concern in pathophysiology, as mentioned before in this chapter.

Furthermore, considerations need to be taken as to imaging modality if the patient has had previously treated aneurysms. MRA is not sensitive for patients with previously treated clipped aneurysms. For these patients CTA is preferred. MRA is still sensitive for previously coiled aneurysms. For patients treated with flow diverter stents either MRA with contrast or CTA can be used. If the patient had coils with any kind of stent, then MRA with contrast is the preferred modality.

Taken together the results of imaging for UIA, the neuro-interventional team consider the possible treatments for each patient based on the risks and benefits between prevent treatment and natural history, however due to lack of evidence of the natural history in some categories of UIA is not uncommon to balance the pros and cos between prevent treatment and aSAH outcomes. Some of the current available treatments will be discussed below.

3.1 Conservative management

First of all, having an aneurysm does not imply always the need to undergo surgical or endovascular treatment. Most of the UIA will never cause symptoms neither rupture or at least the probability of this events will not be over 1% per year. Therefore, many patients decide to take the risk of conservative management over the risks of preventive treatments. However, conservative management is not equal to doing nothing, this management bear intervention from the physician to educate well the patient about the risk factors that will increase the probabilities of rupture and an active participation of the patients to modify their risky habits. There is strong evidence that supports the conservative management when lifetime risk of morbidity and mortality is low [42] as represented in **Figure 1**.

Nevertheless, in patients under conservative management, imaging follow-ups at 1 year intervals have been recommended with CTA or MRA [25] to assess aneurysm

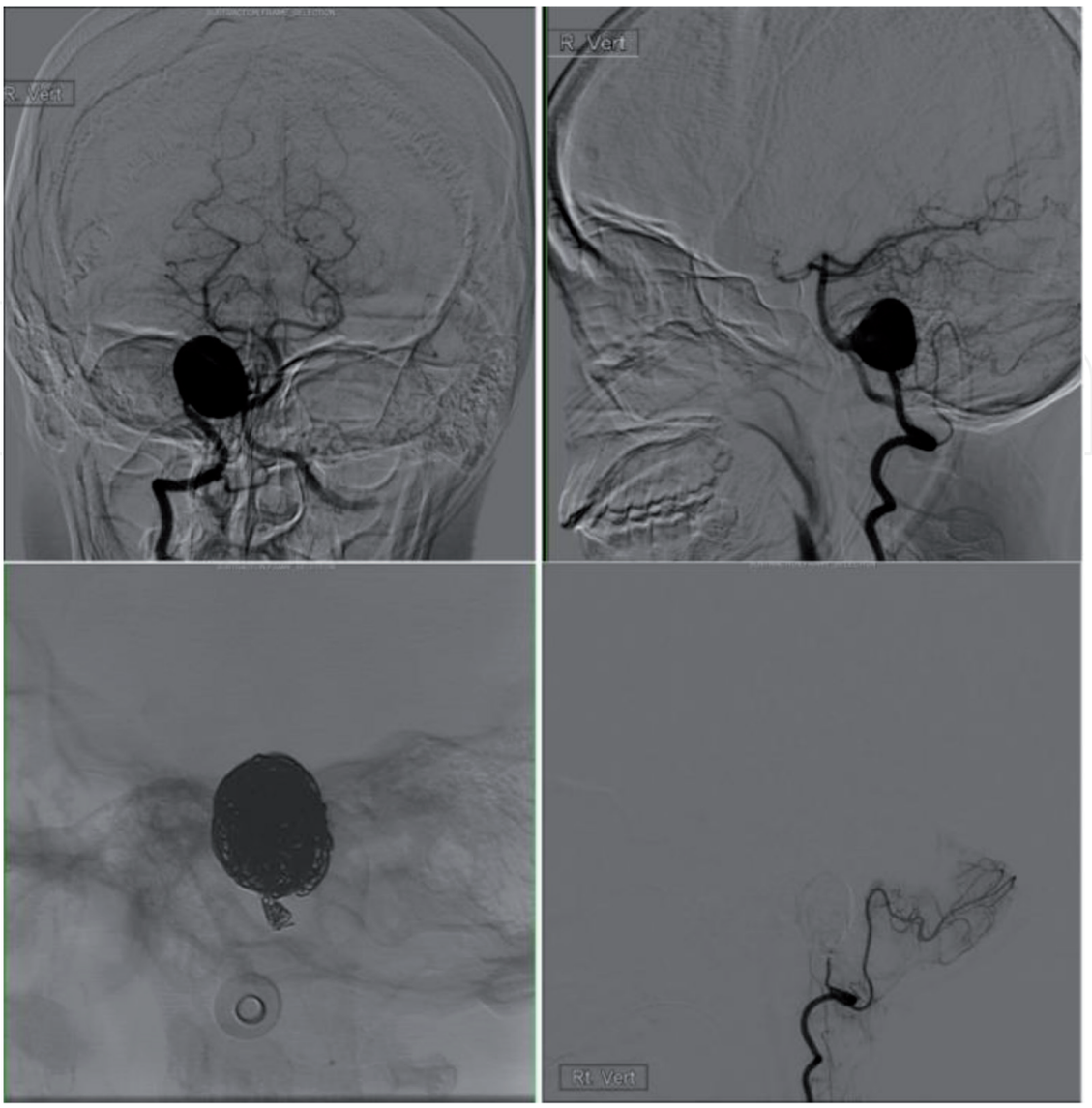

Figure 1.
Giant right vertebral aneurysm before and after coiling.

growth, although it is unclear whether this frequency of time-interval is truly necessary. However, is not uncommon to have mixed factors in UIA patients, to make it clear, a systematic review showed that if hypertension and history of SAH are present (considering this both as major risk factors) in a patient under 70 years, with an <10 mm UIA in the anterior circulation, we will still be talking about a probability of risk of ~1% per year [24]. So, a standardized timing for imaging follow-ups according to each patients and aneurysm related factors does not exist, in part because aneurysm growing is discontinuous but the ELAPSS score (mentioned in **Figure 1**) can be helpful to determine the need of follow-up at 3 or 5 years based on the risk of aneurysm growth [55]. These patients who choose conservative management live with a small very definite risk of rupture. Recently, a study showed that patients with untreated UIA, may decrease their quality of life (QoL) and moreover, trigger mental disorder as anxiety and depression [56, 57] possibly due to the uncertainty of whether their aneurysm is going to burst and when.

3.2 Surgical management

Successful surgery is achieved in most of the cases by excluding aneurysms from circulation but currently, there is a lack of prospective, multicenter and randomized

trials that report outcomes in a uniform way. Moreover, most of the studies were done in patients with previous aSAH like the ISAT trial [58], which makes difficult to extrapolate those results to patients with UIA and no history of aSAH. The ISUIA-2 study did evaluate the surgical outcomes of nearly 1500 patients. They reported a mortality rate of 2.7% at 1 year and poor outcome (mRS 3–5) of 1.4% at 1 year. In this study, age > 70, posterior circulation and giant aneurysms were all associated with higher surgical morbidity and mortality. A meta-analysis done in the US with patients without previous history of aSAH that underwent to elective surgical clipping (SC) 14,411 and to endovascular treatment (EVT) 16,659 reported that iatrogenic stroke, intracranial hemorrhage, pulmonary complications, sepsis and status epilepticus were significantly higher after SC [59]. Moreover, the reduced recovery time and shorter stays in hospital [60] play a major role in the final decision of patient to avoid surgery. Nowadays, SC is usually reserved to younger patients that will benefit more from an immediate occlusion of the aneurysm, less need to have follow-up imaging, less probability of retreatment and the ones with large and giant aneurysms or locations in the MCA.

3.3 Endovascular treatment (EVT)

Since its conception, endovascular treatment has rapidly taken over as the major treatment for most intracranial aneurysms. While there is supporting data for ruptured intracranial aneurysms from the ISAT trial, there is no randomized controlled trial comparing surgery and endovascular treatment to surgical clipping for unruptured aneurysms. Relative indications for endovascular treatment are poor surgical candidate, favorable aneurysm and vascular anatomy, high risk for anesthesia complications and posterior circulation aneurysms. In 2012, a systematic review and meta-analysis reported different outcomes between endovascular treatments; >52 years, >10 mm and posterior circulation location were main risk factors to poor outcomes [61]. Coiling alone was safer compared to the percent of complications reported with balloon-assisted coiling 7.1% (99% CI 3.9–12.7), 9.3% (99% CI 4.9–16.9) with stent-assisted coiling and 11.5% (99% CI 4.9–24.6) with flow-diverting stents. However, the increase of the complications reported with additional devices can be due to the more-complex aneurysm cases or due to the number and type of devices placed. Furthermore, in the last decade the neuro-interventional procedures have improved their outcomes with increased understanding of the various treatments and technological innovation improving safety and efficacy.

3.4 Coiling

EVT emerged in the 1990's with coiling [62]. Since then, technological advances in coil properties made neuro-interventional procedures safer with improved outcomes. Recently, a single center study reported 0% of poor outcomes when coiling was used [25], however >20% of poor outcomes have been reported after coiling in aneurysms >10 mm size, with wide necks, unfavorable dome-to-neck ratio < 2 and fusiform configuration [63]. So, using coiling alone must be used just in aneurysms with specific characteristics, otherwise new devices must be considered.

3.5 Stent assisted coiling

This method represents a solution for aneurysms in which coiling alone will not be the best option (mentioned in **Figure 1**), as coiling this endovascular technique has the same concerns about patient selection, recovery and risks. However, when leaving a stent placed in the artery it is important to manage the tolerance and adherence of the patient to dual anti-platelet therapy (DAPT) (**Figure 2**) [64].

3.6 Flow diversion

This method was developed in the 2000s. The concept of Flow Diversion is that a high-mesh density stent placed in the parent artery will disrupts blood flow into the aneurysm with the subsequent thrombosis of the aneurysm, this process takes 6 weeks to 6 months in average in radiographic follow-ups. Moreover, the stent in parent artery provides a scaffold for which endothelium can grow [62]. In 2011, the FDA approved the Pipeline Embolization Device (PED) for large or giant (≥10 mm) wide-necked intracranial aneurysms from the petrous to the superior hypophyseal segments of the ICA [65]. Since then, a second flow diverter stent (Surpass) has come to market. Flow diverter stents now have expanded indications, including smaller aneurysms, and aneurysm up to the internal carotid artery bifurcation. Recently, a multicenter group published a retrospective study of follow-ups after PED placement [66], in this report overall complications were 3.4% and in multivariate analysis older age > 70, larger diameter > 15 mm and fusiform were identified as independent variables with higher rates of incomplete occlusion in 6-month follow-up. However, currently there is not a standardized scale to report

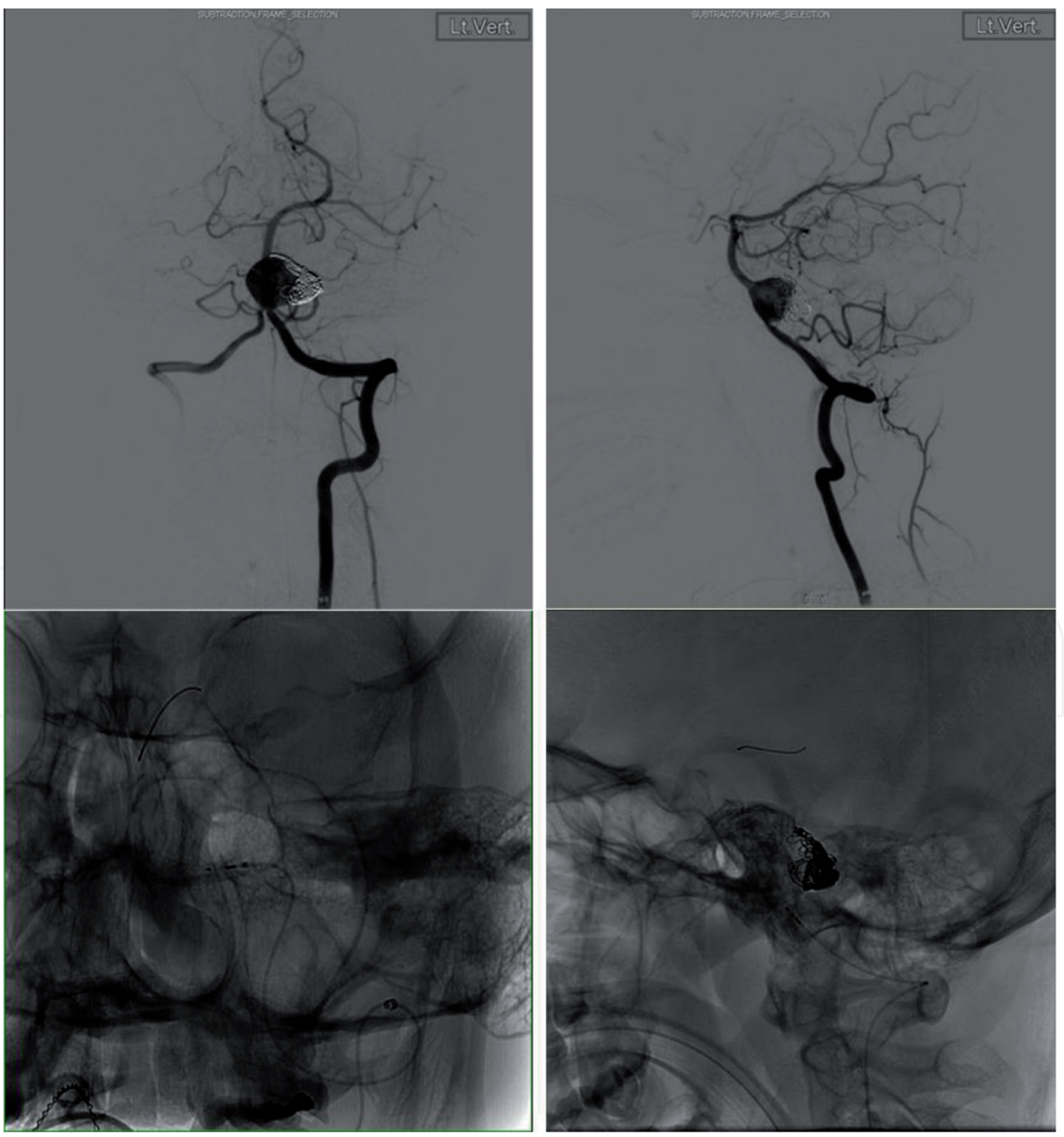

Figure 2.
Pipeline placement in a wide neck aneurysm in the left vertebral artery.

radiographic outcomes that can be useful to meta-analysis studies or to new prospective randomized cohorts. Flow diverter stents are currently also limited usually to unruptured aneurysms, given the need for DAPT, however their use has found a niche in the treatment of ruptured blister aneurysms. Consequently, the next generation of this technology is looking into the possibility of special coating to mitigate the need for DAPT. Further investigation is still needed before this advancement will come to market.

3.7 Flow disruptors and web endoluminal bridge (WEB)

Although flow diversion devices can work out for many types of aneurysms as off-label uses; aneurysms located in bifurcations with wide neck and dome-to-neck ratio > 1 and < 2 remains a challenge for this technology. Therefore, the WEB device was created in regard of these concerns in flow diversion and has proven promising to overcome those limitations. The WEB device is placed intra-aneurysm with a subsequent change in the blood flow at the aneurysm neck [67]. In European multicenter prospective studies, the WEB device placed in basilar, MCA, Acomm and ICA bifurcation showed 2.7% of morbidity and at 1 year of follow-up, 56% of aneurysm complete occlusion [68]. Owing this method does not require to put the patient under DAPT unlike the PED, it can be used also in aSAH cases. Further investigation is needed as to the long-term outcomes for this device (**Figures 3** and **4**).

3.8 Medical management after flow diverter placement

All the patients that can be good candidates for PED placement based on their UIA characteristics needs also to be eligible for prolonged DAPT. Acetylsalicylic acid (ASA) plus clopidogrel is the DAPT of reference used for preventing thrombosis in such procedures [69]. The laboratory tests pre and post-procedure are yet to be standardized; due to the risk of clopidogrel resistant (28–68%) [70], is has been considered necessary to assess platelet reactivity. High platelet reactivity (HPR) is related with thromboembolic evens after stenting arteries [71]. Depending on institutional protocols, some neuro-interventional teams use the VerifyNow P2Y12 assay which has been widely studied however, the results of this tests may not be completely reliable [72] due to the fact that P2Y12 response units (PRU) cannot differentiate aspirin-induced platelet inhibition in patients administered clopidogrel. Other studies recommend the use of the Thromboelastography (TEG), which is dynamic and real time tool to measure clot formation. The advantages of VerifyNow assay is that can be done very fast with instant results, however in patients with programed procedures for UIA stenting this concerning may not be transcendental.

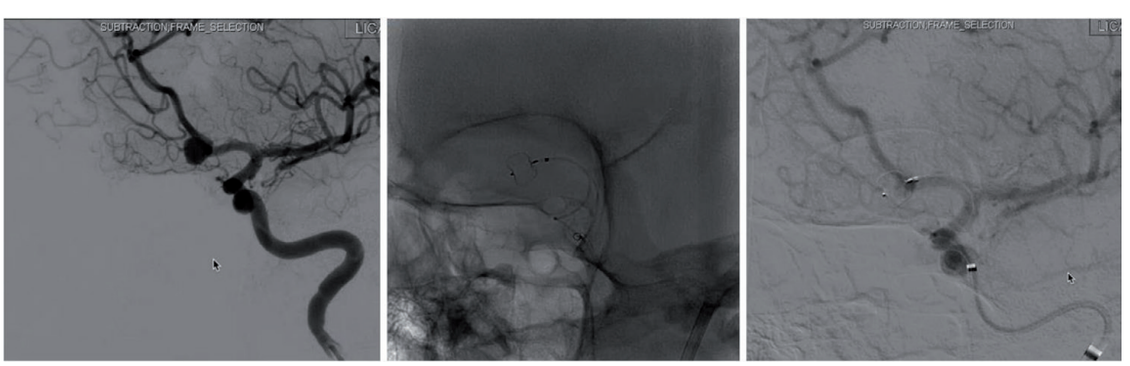

Figure 3.
Web Endoluminal bridge placement in left ICA bifurcation.

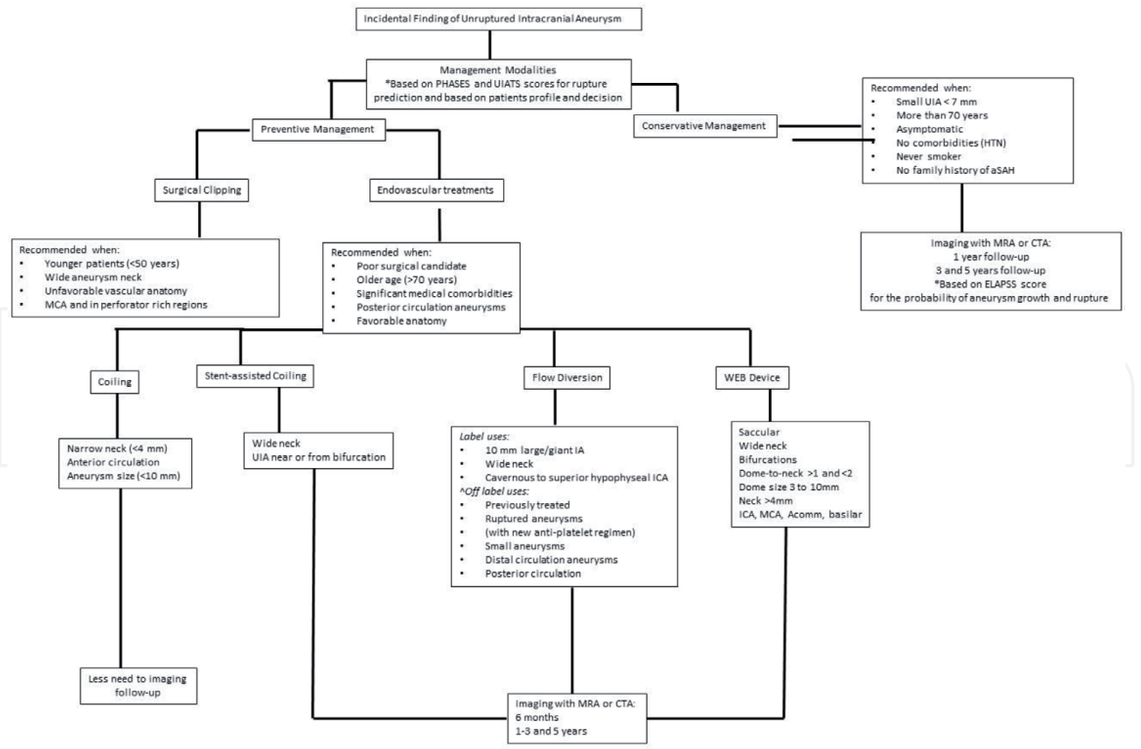

Figure 4.
Flowchart of management after incidental UIA diagnosis.

VerifyNow can overestimate the rate of clopidogrel resistance when compared to TEG. However, there is currently no randomized trials that have assessed the utility of this tests. Moreover, there's no strong evidence to support that the assessment of platelet reactivity improves clinical and imaging outcomes after stent placement. Nevertheless, the neuro-interventional teams at these days usually starts the DAPT with 325 mg of ASA and 75 mg of clopidogrel 7 days prior and maintain for 3–6 months after PED placement.

4. Ruptured intracranial aneurysms

A 50-year-old female was preparing her children for school when she experienced a headache severe enough to make her lie down on the sofa. She managed to get the children off to school, but the headache did not abate. She was used to headaches, as she had migraines periodically that were controlled with over-the-counter medications, but this one was different and much more intense. She took a couple of acetaminophen, and when the pain was not relieved, she brought herself to the emergency department (ED) [73].

Headache is seen in up to 2% of patients, presenting to the emergency department (ED). Most are benign, but it is imperative to understand and discern the life-threatening causes of headache when they present. Headache caused by a subarachnoid hematoma (SAH) from a ruptured aneurysm is one of the deadliest, but fortunately, also rare, comprising only 1% of all headaches presenting to the ED [74].

Rupture is the most serious consequence of intracranial aneurysms. Subarachnoid hemorrhage (SAH) from a leaking aneurysm is a neurological emergency. While SAH is typical of aneurysmal rupture, it is also associated with intraventricular hemorrhage, intracerebral hemorrhage, and subdural hematoma. The force of rupture and location of an aneurysm determine the presence of the other types of hemorrhage. Although the prevalence of aneurysms is high, the

global annual incidence of subarachnoid hemorrhage is 10/100,000person years, so the best possible treatment plan would be to determine exactly those aneurysms that will rupture and the ones that never will.

4.1 Presentation

The presenting symptom of SAH is acute headache, generally described as "the worst headache of my life."

Some cohort studies mention it as "thunderclap" headache that peaks at headache onset or reaches severity within minutes to an hour of onset [75].

1. Signs of meningeal irritation-meningismus, photophobia

2. Signs of intracranial hypertension-nausea, vomiting, diminished level of consciousness

3. Epileptic seizures

4. Focal neurological deficits

5. Intraocular hemorrhage [76, 77]

    - Terson syndrome: hemorrhage in vitreous humor, associated with high mortality [78]

    - Subhyaloid (pre-retinal) hemorrhage [79].

4.2 Scoring system

Several scoring systems have been developed to predict patient outcomes for those with aneurysm related sub-arachnoid hemorrhage (a-SAH). The Hunt and Hess score and World Federation of Neurological Surgeons grading system are both used to predict patient outcome, and the Fisher grade helps to predict vasospasm [80, 81].

The severity of neurologic impairment and the amount of subarachnoid bleeding on admission are the strongest predictors of neurologic complications and outcome [82]. Therefore, it is essential that patients with SAH be scored promptly after arrival and stabilization. The World Federation of Neurological Surgeons Scale (WFNSS) and the modified Fisher Scale are the most reliable and simple to perform [74, 75]. Higher WFNSS and modified Fisher Scale scores are associated with worse clinical outcome and a higher proportion of neurologic complications. The modified Fisher scale is designed to predict the development of delayed cerebral ischemia (DCI) which is the most common cause of disability secondary to rupture next the actual rupture itself (**Tables 1**–**3**).

4.3 Initial imaging

With such a large number of patients presenting to the ED with a chief complaint of headache [79–84], the description of headache can help differentiating those with a benign cause from those with an emergent etiology such as SAH. The diagnosis of SAH should be considered in any patient with a severe and sudden onset or rapidly escalating headache (**Figure 5**).

Grade	Glasgow coma scale (GCS)	Neurological exam
1	15	No motor deficit
2	13–14	No motor deficit
3	13–14	Motor deficit
4	7–12	With/without motor deficit
5	5–6	With/without motor deficit

Table 1.
World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage - (WFNS) scale.

Grade	Criteria	Survival
I	Asymptomatic, mild headache, slight nuchal rigidity	70%
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	60%
III	Drowsiness/confusion and mild focal neurological deficit	50%
IV	Stupor, moderate to severe hemiparesis	20%
V	Coma, decerebrate positioning	10%

Table 2.
Hunt and Hess scale.

Grade	Appearance of blood on CT	Risk of cerebral hemorrhage
0	No sub arachnoid hemorrhage (SAH) or ventricular hemorrhage (VH)	0%
1	Minimal SAH, No VH in 2 lateral ventricles	6%
2	Minimal SAH, VH in 2 lateral ventricles	14%
3	Large SAH, No VH in 2 lateral ventricles	12%
4	Large SAH, VH in 2 lateral ventricles	28%

Table 3.
Modified fisher grading system [82].

4.4 Management

Once the patient has been diagnosed with an SAH, treatment should focus on limiting secondary neurologic injuries to improve the patient's functional outcome.

- Resuscitation of a patient with SAH should follow all established protocols with immediate attention to airway and circulatory support.

- After stabilization of the airway and circulation, treatments specific to SAH can begin.

4.5 Pharmacologic treatments

4.5.1 Antiepileptic drugs

In patients with a suspected ruptured aneurysm, seizures can lead to aneurysmal rebleeding and result in intracranial hypertension and herniation, the

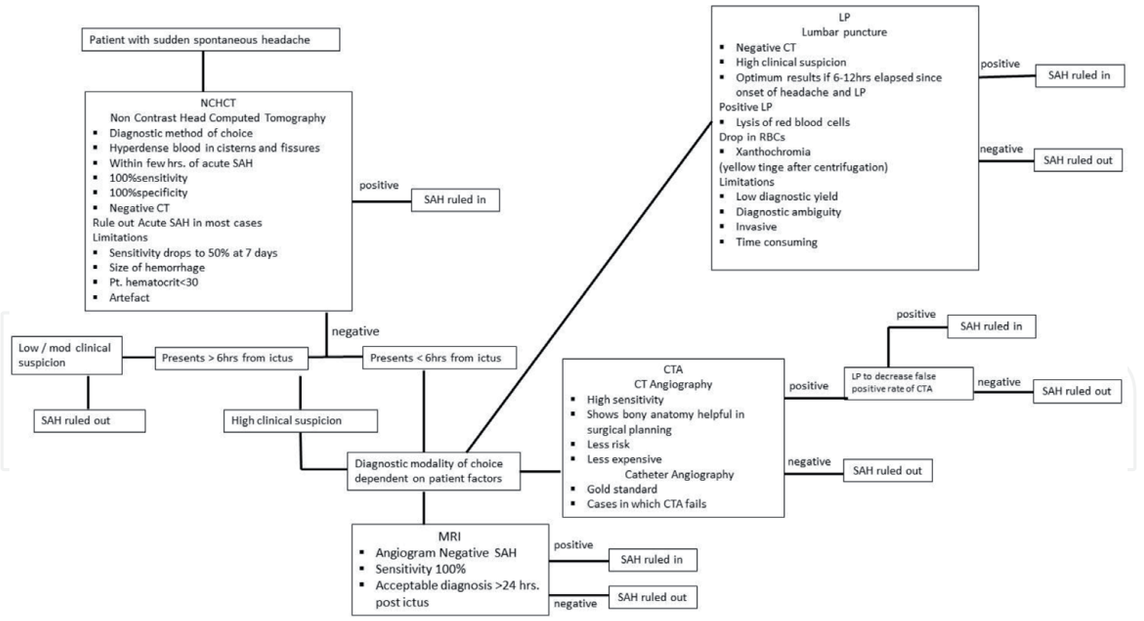

Figure 5.
Flowchart of management aSAH [1, 10–12].

risk of being highest in patients with poor Hunt and Hess grade and those with thick subarachnoid blood [85]. Routine prophylactic antiepileptic drug use in patients with SAH is a common practice despite limited evidence The American Stroke Association (ASA) guideline recommends consideration of short-term prophylactic antiepileptic drug use in the immediate post hemorrhage period [86]. No randomized controlled trials have investigated the safety and effectiveness of antiepileptic drugs in SAH [87].

4.6 Nimodipine

Delayed cerebral ischemia (DCI) is one of the most serious complications associated with SAH, occurring in one-third of patients surviving the initial hemorrhage and results in poor outcome in half of the patients with this complication [86]. Nimodipine is a calcium antagonist that is thought to reduce the rate of cerebral vasospasm by reducing the influx of calcium into the vascular smooth muscle cells. The administration of nimodipine to reduce the risk of poor outcome and DCI is the only level IA evidence recommended by the ASA [86].

4.7 Blood pressure management

There is general consensus that hypertension should be controlled after SAH and until the ruptured aneurysm is secured. However, specific parameters for blood pressure have not been defined and data are sparse. Early retrospective studies suggest a higher rate of rebleeding with SBP greater than 160 mm Hg and severity of initial hemorrhage [88]. Therefore, the ASA and Neurocritical Care Society recommend maintaining SBP less than 160 mm Hg and mean arterial pressure less than 110 mm Hg before the ruptured aneurysm is secured to reduce the risk of rebleeding [86, 87, 89, 90]. The ideal antihypertensive to use in SAH would be a parenteral agent that produces a rapid and reproducible dose response while concurrently minimizing adverse cerebral effects. Labetalol, nicardipine, and clevidipine are agents recommended by the ASA [86].

4.8 Antifibrinolytics

When early definitive treatment of the ruptured aneurysm is not possible, antifibrinolytic therapies such as amino epsilon caproic acid or tranexamic acid can be considered to reduce the risk of early aneurysmal rebleeding. Early studies showed a reduction in rebleeding but an increase in cerebral ischemia with prolonged use of antifibrinolytics [88]. Neither aminocaproic acid or tranexamic acid is approved by the US Food and Drug Administration for prevention of aneurysmal rebleeding, thus the use of antifibrinolytic therapies should be discussed on a case-by-case basis.

4.9 Rebleeding

Rebleeding can occur before the ruptured aneurysm is secured, and is associated with significant mortality and poor prognosis for functional recovery, most common within the first 24 hours, with some studies reporting peak time of rebleeding within 2 hours [88]. Factors associated with rebleeding include longer time to aneurysm treatment, worse neurologic status on presentation, initial loss of consciousness, previous sentinel headaches, larger aneurysm size, and possibly SBP greater than 160 mm Hg [91]. Although early definitive treatment of ruptured aneurysms can reduce the risk of rebleeding, approximately 12–15% of patients die before reaching the hospital [90].

4.10 External ventricular drainage

Acute hydrocephalus is common in patients with SAH and is a common cause of early neurologic decline. Treatment of symptomatic hydrocephalus often requires placement of an external ventricular drain, which allows ICP monitoring as well as CSF drainage. Untreated hydrocephalus can lead to intracranial hypertension and cerebral ischemia with potential cerebral herniation. Identification of the presence of hydrocephalus on CT and communication of this finding with neurosurgical consultants are key steps in the management of SAH.

4.11 Microsurgical clipping versus endovascular coiling

Definitive treatment of SAH is early microsurgical clipping or endovascular coiling of the ruptured aneurysm to prevent rebleeding and its associated complications. Choice of treatment modality depends on aneurysm size, characteristics, and location, as well as the patient's clinical grade and comorbidities [92]. The International Subarachnoid Aneurysm Trial (ISAT) [93] is a multicenter, randomized clinical trial, which compares a policy of neurosurgical clipping with a policy of endovascular treatment with detachable platinum coils in patients with ruptured intracranial aneurysms considered suitable for either treatment. The results show that endovascular intervention with detachable platinum coils in patients with ruptured intracranial aneurysms can improve the chances of independent survival compared with neurosurgical intervention to clip the neck of the aneurysm.

4.12 Pipeline embolization device

The PED has mostly been used to treat unruptured aneurysms, whereas its use for acutely ruptured aneurysms has been limited and is theoretically contraindicated, given the need for dual antiplatelet therapy as it increases the risk of re-hemorrhage [94].

However, in certain cases of complex ruptured aneurysms, the PED may still serve as a good alternative (and sometimes may be the only available option) because these aneurysms are anatomically and technically more difficult to treat using standard techniques [93]. Furthermore, certain anticoagulation protocols can be put into place to prevent the feared consequences associated with PED placement in ruptured aneurysms due to dual antiplatelet therapy. The standard management for the prevention of thromboembolic events when using flow diverters is pretreatment with aspirin and clopidogrel for 7–10 days prior to the procedure. When treating ruptured aneurysms with the PED in conjunction with this dual antiplatelet therapy, there is a concern for hemorrhagic complications. Chalouhi and colleagues [95] described a new regimen for anticoagulation that was recently implemented in the hope of minimizing the risk of thromboembolic and hemorrhagic complications. In summary, the PED may be particularly helpful in acutely ruptured aneurysms that are not amenable to coiling or clipping. It can also be used in a staged fashion 1 or 2 weeks after partial coiling of the aneurysm dome. It is generally preferable to place an external ventricular drain if treatment with the PED is contemplated [96].

5. Future directions

The future of neuroendovascular surgery is bright. The technology platforms for access, delivery and treatment continue to improve at exponential rates. As it is there has been a rapid change in the number of brain aneurysm patients treated with endovascular treatment versus open surgical clipping. With this change comes a great void in experience and skill in the open surgical management of brain aneurysms. It remains to be seen whether this skill will be needed in the future [97].

5.1 Flow disruptor

Currently there is only one flow disruptor available in the US market; the WEB device. Currently, its limitations lie in the fact that it is only available in sizes to treat aneurysms 3–10 mm in size. The second limitation exists in its delivery system which, at larger sizes requires a 33-microcatheter, and at smallest sizes requires a 21-microcatheter. As newer generations come to market over the next 5 years, we expect there to be improved deliverability, different shapes available, and smaller designs for smaller ruptured aneurysms [98].

5.2 Flow diverter

Currently there are two flow diverter stents available in the US Market, the Pipeline Flex (2nd generation), and the Surpass. Currently the bulk of innovation required with this technology is in finding a coating for the stent that might mitigate the need for dual anti-platelet therapy. The second area of innovation is in the deliverability of the stents, currently needing 27-microcatheter for delivery, there is an expectation that these stents can be delivered through a 21-microcatheter in the near future, with also smaller diameter stent sizes available to treat more distal aneurysms. We fully expect the indications on which type of aneurysms can be treated in the near future.

5.3 Endosaccular coiling

Coiling has likely reached its technological pinnacle. There has been little advancement in this technology over the last 5 years. One area of interest is in

endosaccular flow disruptor type coils such as the Medina system. This is not as of yet FDA approved and remains to be seen whether this is efficacious or safe. Also the adjunctive tools for coiling continue to improve such as the Atlas stent, Pulserider stent and barrel stent which all are improvements for the treatment of bifurcation aneurysms and make difficult to coil aneurysms easier. We expect further improvements in these designs, and with improvements in deliverability. In addition to stents, the balloons available for balloon assisted coiling continue to improve in shape, design and deliverability which are particularly helpful in the setting of a ruptured small or wide necked aneurysm [99].

5.4 Imaging and aneurysm rupture prediction

Currently other than aneurysm size, and certain bio-social risk factors, there is no way to accurately predict which aneurysms are at risk for rupture. Over the next 5 years we expect to see, further advancement in the arena of MR vessel wall imaging, and flow-modeling. We hope that this will help improve our predictive models.

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