Stent-Assisted Reconstructive Endovascular Repair of Intracranial Aneurysms
Long-Term Clinical and Angiographic Follow-Up

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Abstract

**Background and Purpose:** The development of self-expanding stents dedicated to intracranial use has significantly widened the applicability of endovascular therapy to many intracranial aneurysms. The purpose of this study was to report the angiographic and clinical outcomes of wide-necked intracranial aneurysms treated with stent. **Methods:** Between January 2007 and October 2011 we deployed 22 stents in 20 patients with wide-necked cerebral aneurysms. Inclusion criteria restricted the group to adult patients with wide-necked intracranial aneurysms (ruptured and unruptured lesions). Immediate post-procedural angiographic studies were performed to evaluate successful occlusion of the aneurysm as well as patency of the parent vessel. We assessed long term angiography follow-up to detect in-stent stenosis, progressive thrombosis, recurrence and need for retreatment. Clinical outcome was assessed with the modified Ranking Scale (mRS). **Results:** Technical success was obtained in all 22 (100%) cases. Angiography immediately after treatment procedure showed complete occlusion in 7 aneurysms (35%), neck remnant in 11 (55%), incomplete occlusion in 1 (5%) and partial occlusion in 1 (5%). During the endovascular embolization procedure no rupture of the sac or bleeding complication occurred; none of the patients needed undergoing surgical crossover. Procedure-related adverse events occurred in one (5%) patient: a brachial artery pseudoaneurysm. Three (15%) patients had neurological complications after procedure, whose 1 (5%) transitory complication spontaneously resolved. Two patients (10%), had acute complete in-stent thrombosis which resolved after intraarterial administration of abciximab and placement of a new stent in-stent. Of the 20 patients treated with stent deployment, a follow-up imaging study was available in all 19 surviving patients (95%) at an average of 16.2 months (range, 6 to 50 months). The first follow-up DSA, compared with initial angiography, showed no changes in 14 aneurysms (73.7%), progressive thrombosis in 3 (15.7%), and major recurrence in 2 (10.5%). The overall rate of successful procedure to 6 months is 89.5%; there was 1 case of asymptomatic moderate endothelial hyperplasia. The further follow-up imaging study, showed no changes in 17 (89.5%) of the 19 surviving patients, 1 progressive thrombosis and 1 minor recurrence. One month- and long term (average of 16.2 months; range, 6 to 50 months) clinical follow-up showed no worsening in the mRS
in 18 (90%) of 20 patients, 1 (5%) mRS 2 and 1 (5%) mRS 6. All the survived patients are alive and we did not observe periprocedural or long-term intracranial bleeding events or symptomatic stent related stenosis/occlusion complication.

**Conclusions:** Our findings suggest that the endovascular treatment of intracranial aneurysms by stenting is feasible, effective and safe; follow-up results proved intact parent arteries and stable occlusion rates in the majority of treated aneurysms. Nevertheless, long-term data on safety and efficacy and larger patient groups are necessary.
CHAPTER 1: “INTRACRANIAL ANEURYSM AND ITS TREATMENT”.

1.1 INTRODUCTION

Subarachnoid hemorrhage (SAH) is the most serious presentation of ruptured intracranial aneurysms. Autopsy reports have shown that aneurysms are present in roughly 5% of the population, yet most are often asymptomatic (1). Estimated annual incidence rates of SAH range from 10 to 15 cases per 100,000, which translates to at least 30,000 annual cases of SAH in the United States. Two-thirds of patients with aneurysm rupture either die or have a disabling neurological deficit (2). In recent years, an increasing number of unruptured, incidental aneurysms are being detected due to increased availability of non-invasive imaging modalities. While it is clear that most ruptured aneurysms must be treated to prevent rerupture, the management of the unruptured intracranial aneurysms (UIA) is more complex both from treatment decision making perspectives. Aneurysms typically develop during adulthood and rupture risk increases with age. The mean age for aneurysmal SAH is about 50 years (3). Typical locations at risk for the development of aneurysms are branching points, where structural irregularities in the collagen matrix exist (4), and elevated hemodynamic stresses due to segments involving short radii of curvature are more observed. Studies have shown that abnormal hemodynamic stress plays an important role in aneurysm formation and growth (5).

Intracranial aneurysms can be classified using several schemes. The most obvious division is considering the ruptured and unruptured lesions separately. With respect to morphology, aneurysms are classified as saccular or non-saccular. Non-saccular intracranial aneurysms such as fusiform, dolichoectatic, and dissecting aneurysms are rare with an incidence of less than 0.1% (6). Another system of classification is by aneurysm location. The predominant location for saccular aneurysms is the anterior circulation (90%), with most arising from the circle of Willis. The anterior communicating complex (30–35%) is the most common location, followed by the internal carotid artery (30%). The basilar apex represents the most common location
in the posterior circulation and accounts for 10% of all intracranial aneurysms (7). Aneurysms are also classified by size into subgroups of small (< 10 mm), large (10–25 mm), and giant (> 25 mm) in diameter. According to Wiebers et al. (8), aneurysms smaller than 12 mm in dome size account for more than 75% of the unruptured aneurysms. The establishment of endovascular therapy has led to further classification of aneurysms based on the size of the neck. Management of UIA remains a topic of debate due to incomplete and often conflicting data relating to the natural history of aneurysms, along with the risks associated with treatment (9).

While published studies may present different aneurysm rupture risk levels, they all indicate that treatment is recommended due to the poor outcome of rupture. Ruptured aneurysms account for approximately 85% of non-traumatic SAH and are associated with a 30-day mortality rate of 45% and a morbidity rate of 25% (10). In a study of hospital discharge records for patients with ruptured and unruptured aneurysms, mortality rates for SAH demonstrated little change with the introduction of endovascular treatments (11). In addition to poor outcomes and co-morbidities resulting from SAH, economic burden associated with SAH must also be taken into consideration. Dodel et al. (12) recently published a study on the cost of illness due to SAH, the total accumulated costs in the first year were € 38,300 (95% CI, € 34,490 to € 43,100). Their data also indicate higher costs associated with younger patients. The method of treatment for ruptured intracranial aneurysms, however, remains a problem with no clear solution.

1.2 CEREBROVASCULAR ANATOMY AND PATHOPHYSIOLOGY OF ANEURYSMS

It is suggested that formation of an intracranial aneurysm is a consequence of a systemic vascular pathology, which is associated with pleomorphism in different candidate genes (13). A higher prevalence of aneurysms in the cerebrovascular system may also be due to alterations in hemodynamic and histological characteristics (4, 14). Cerebral arteries are particularly susceptible to aneurysm formation due to the absence of an external elastic lamina, paucity of supportive perivascular tissues, attenuated tunica media, and irregularities near bifurcations (4). The internal elastic lamina is an important layer of the arterial wall especially in the cerebral vessels. Thus, disruption of this layer would promote formation of aneurysms (15).
Particularly, the regions around the bifurcations have atypical wall structures with a discontinuity of the muscle cells of the tunica media as a medial defect in connection with a predominance of collagen fibers over the elastic ones (4). In addition to this specific structure, non-uniform collagen framework in the bifurcation region of brain arteries might further induce development of intracranial aneurysms (4). Swietaszczyk et al. (16) demonstrated that arterial blood flow disturbance and hypertension in the brain vessels lead to increased hemodynamic stress on arterial walls. Some studies also present strong association between wall shear stress (WSS) and initiation of cerebral aneurysm formation in experimental models (14). A prolonged high WSS induces matrix metalloproteinase production and fragmentation of the internal elastic lamina at, or immediately adjacent to the bifurcation (5, 14). Prolonged elevation of blood pressure leads to excessive mechanical loading and causes remodeling of the arterial wall. The exact mechanisms involved in this tissue remodeling are not completely understood, but the decreased structural integrity of the tissue may be one of the underlying reasons of aneurysm formation and growth.

1.3 RISK OF ANEURYSM RUPTURE

The International study of unruptured intracranial aneurysms (ISUIA) has been the most comprehensive clinical study of its kind to date (17). The study enrolled 4,060 patients from the US, Canada, and Europe. In phase II of ISUIA trial, there were a total of 6,221 unruptured aneurysms among different studied cohorts (i.e., operated and unoperated) (8). A higher rupture rate was reported to be associated with larger aneurysms, location in the posterior circulation, and previous history of SAH. The 5-year cumulative rupture rate, for patients with no history of SAH and aneurysm size between 7 and 12 mm, was 2.6 and 14.5% for aneurysms located in the anterior and posterior circulation, respectively. The greatest risk of rupture, for large size aneurysms in the posterior circulation, was 50% (8). Juvela et al. (18) followed 142 patients with 181 aneurysms for a total of 2,575 person years and reported a rupture rate of 1.46% per year (95% CI: 1.04–2.04). Rinkel et al. (19) presented data on nine studies, totaling 3,907 patient years and similarly concluded a rupture rate of 1.9% (95% CI: 1.5–2.4). Prevalence of aneurysms and rupture risks were shown to increase in both studies due to the factors such as size of the unruptured aneurysm, age of the patient, pre-existing familial conditions, and hypertension. Smoking has been also
associated with higher prevalence of aneurysms and rate of rupture (18). More recent studies have begun to focus on additional quantification methods of aneurysms to predict rupture risks. Several geometric indices, measured by using three-dimensional rotational angiography or digital subtraction angiography, have correlated to increased rupture rates. Ryu et al. (20) compared geometric indicators of 109 unruptured and 105 ruptured aneurysms to develop imaging predictor markers of aneurysm rupture. The two highest indicators were the aspect ratio (the ratio of the aneurysm’s height to its neck) and the volume to neck ratio. From the published data in the literature, larger aneurysms have an increased risk of rupture. Raghavan et al. (21) noted that two other factors, the undulation index and the non-sphericity index, are strong predictors of aneurysm rupture as well.

1.4 TREATMENT OPTIONS

1.4.1 SURGICAL CLIPPING

The first direct operation on an intracranial aneurysm was performed by Norman Dott in 1931 (22). In 1937, Walter Dandy performed the first operation for clipping an intracranial aneurysm, in which he applied a silver clip across the neck of a posterior communicating artery aneurysm (23). Introduction of operative microscopes, development of dedicated aneurysm clips and of advanced surgical approaches were instrumental to improving outcomes from aneurysm surgery. Factors such as site, size, and age-specific risks of repair for each patient should be considered in the treatment of UIA (8).

A detailed description of open surgical technique for aneurysm clipping is beyond the scope of this study. Some important steps include patient positioning, planning of the craniotomy, and a microsurgical approach to clipping of the aneurysm. Depending on the location of the aneurysm, specific arachnoidal dissection is necessary to obtain proximal control of the parent artery. Once this is achieved, the aneurysm can be exposed and dissected under high magnification. The middle cerebral artery (MCA) bifurcation aneurysms serve as examples of the various approaches available.

There are three different approaches to expose the MCA aneurysm in the sylvian fissure. The sylvian fissure can be opened from medial (proximal) to lateral (distal) or vice versa. The lateral to medial approach requires less brain retraction and is usually
more direct to these superficial aneurysms (24). Alternatively, an incision in the superior temporal gyrus with subpial resection can be used to expose the aneurysm (25). This approach may be particularly useful when there is an associated temporal lobe hematoma. Thereafter, routinely the parent artery is prepared for temporary clipping before deployment of the permanent clips (26). Temporary clipping of the parent artery is useful in the event of an intraoperative aneurysm rupture. Moreover, it is useful to reduce the turgor of the aneurysm and facilitate permanent clip application across the aneurysm neck. However, there may be a higher risk of ischemic complications with temporary clipping (27). Prior to temporary clipping, blood pressure may be elevated pharmacologically and cerebral protectants such as barbiturates, propofol, or etomidate can be administered to reduce the risk of ischemia. Finally, after placement of the permanent clip on the aneurysmal neck, intraoperative micro-Doppler, non-invasive near infrared indocyanine green videoangiography, or invasive intraoperative cerebral angiography are employed to assess the patency of the parent artery as well as the entire occlusion of the aneurysm neck (28).

1.4.2 ENDOVASCULAR COILING

In 1939, the first endovascular treatment of an intracranial aneurysm was performed, in which 30 feet of silver wire were placed into a giant cavernous carotid aneurysm that had eroded the orbit (29). Luessenhop and Velasquez (30) first described catheterization of the intracranial arteries and catheter based embolization of an intracranial aneurysm. In the early 1970s, Serbinenko (31), considered by many to be the founder of endovascular neurosurgery, developed a series of balloon mounted flow guided catheters and detachable balloons designed to occlude intracranial vascular lesions. In the 1980s and early 1990s, Guglielmi et al. (32, 33) combined the concepts of electrothrombosis and endovascular approaches to develop a detachable coil system. Guglielmi detachable coils (GDC) were approved by the Food and Drug Administration (FDA) and form the basis of contemporary endovascular treatment of intracranial aneurysms. Endovascular therapy for aneurysms is attractive because an effective and often equivalent result can be achieved with a less invasive method compared to traditional microsurgery. This may result in decreased hospitalization and faster recovery times for the patient (34).
The following is an overview of the key steps of the coil embolization procedure. It can be performed under general anesthesia or conscious sedation depending on the patient’s ability to cooperate, the complexity of the aneurysm, and the operator’s preference. Aneurysm coiling is typically performed using biplane fluoroscopic guidance. A typical procedure involves gaining access to the common femoral artery and navigating a guide catheter, ranging from 5 to 7 French in diameter, into the internal carotid artery or vertebral artery. A microcatheter, ranging in size from 1.7 to 2.3 French, is then advanced over a microwire (typically 0.014” ). Once the best projection of the aneurysm is obtained (i.e., a view that clearly delineates the aneurysm neck and surrounding arterial branches), the microcatheter is advanced into the aneurysm. Platinum coils of various configurations and sizes are deployed and detached through the microcatheter. The coils are detached using either a hydraulic or electrolytic mechanism.

In general terms, the first coil is either sized or slightly undersized to the maximum diameter of the aneurysm. For example, a 7-mm coil would be a reasonable first coil for a 7.3-mm diameter aneurysm. After framing coils are placed, the subsequent coils are two-dimensional “filling” or “finishing” coils. Additional coils are deployed until the aneurysm is no longer filling with contrast or until additional coils cannot be placed safely. The latter condition is often represented by either the final coil or the microcatheter protruding into the parent artery.

There are a variety of microcatheters, microwires, and coils available in the market. The choice of device depends on the vascular tortuosity, the navigability and stability of the catheter, and ultimately operator preference.

The early experience with coiling tended to be limited to aneurysms with narrow necks. Wide necked aneurysms, defined from an endovascular standpoint as those with a dome-to-neck ratio > 2 or an absolute neck diameter > 4 mm, were not amenable to coil embolization until technological advancements in the late 1990s and early 2000s. Three major advancements have expanded the indications for coil embolization of these wide-neck aneurysms. First, the introduction of three-dimensional coils has allowed for complex framing configurations to be achieved with less coil protrusion into the parent artery. Second, the development of balloon assisted coil embolization has allowed for improved packing density of coils and also reduces the risk of coil protrusion into the parent vessel. In this technique, a compliant balloon is navigated and inflated across the neck of an aneurysm as coils are introduced into
the aneurysm through the microcatheter. The balloon can also arrest flow in the parent artery in the event of an intraprocedural aneurysm rupture. Finally, stent-assisted coil embolization has allowed for treatment of the very wide necked aneurysms and diffusely diseased segments of arteries. The microcatheter can be navigated through the pores of the stent into the aneurysm or can be trapped between the artery wall and the stent. In addition to improving coil packing density and preventing coil protrusion, the stent may divert flow away from the aneurysm and allow vessel remodeling. Currently several stents are available, including Enterprise stent system (Codman, J&J, Raynham, MA, USA), Neuroform stent system (Stryker, Kalamazoo, MI, USA) and Leo stent system (Balt, Montmorency, France).

Murayama et al. (35) described a single center experience with GDCs during an 11-year period from 1990–2002. A total of 916 aneurysms in 818 patients were treated by coiling and results were separated into patients treated before and after FDA approval of coils. This study included patients with acute SAH (49%), unruptured aneurysms (42%), and non-acute SAH (9%). Three hundred thirty-four aneurysms (36.5%) were small, 198 (21.6%) were large, 73 (8%) were giant. The overall results were complete occlusion in 504 (55%) of 916 aneurysms, and a neck remnant was seen in 234 (35.4%). Complete occlusion was highest (86.2%) in small diameter and small neck aneurysms, the occlusion rate was reduced by approximately half in the other groups which subsequently had increases in the amount of neck remnants.

Another study by Gonzalez et al. (36) examined 247 UIA treated at the UCLA Medical Center during a similar time period (1991–2000). Of those UIA’s, 118 (54.4%) were found incidentally during angiography, CT angiography, or MR angiography, and 51 (23.5%) presented with mass effect. Angiographic results indicating complete occlusion were achieved in 138 (55%) of 247 aneurysms, incomplete occlusion in 3 (1.2%), and neck remnants in 92 (37.2%).

Further evaluation of the results, stratified into the aneurysm size groups described in the Murayama et al. (35) study, show higher success rates for complete occlusion in smaller aneurysms. Of the 83 small aneurysms with narrow necks, 63 (75%) were completely occluded, while 20 (23.8%) had a neck remnant. As aneurysm size increased, the likeliness of complete occlusion was greatly reduced, with success being achieved in 7 (24.1%) of 29 giant aneurysms. Wanke et al. (37) published endovascular treatment results of 39 patients harboring 42 unruptured aneurysms. The study included 18 small (0–5 mm), 11 medium (6–10 mm), 9 large (11–25 mm), and
4 giant (> 25 mm) aneurysms. Endovascular treatment was deemed technically feasible in 38 aneurysms, with 4 being unable to be treated due to an unfavorable dome-to-neck ratio. They reported complete (100%) or near complete (95–99%) occlusion in 34 (89.5%) aneurysms. Incomplete occlusion (< 95%) was achieved in four aneurysms (three large and one giant).

While endovascular coiling of intracranial aneurysms has offered an alternative treatment option to open surgery, there are serious risks to consider. Some of these risks overlap with those seen in open surgery and others are unique to endovascular therapy. Murayama et al. (35) reported procedural complications in 69 (8.45%) patients, the most common being thromboembolism in 24 (2.4%) patients. This percentage is also similar to the cerebral embolization reported by Gonzalez et al. (3.7%) (36). Other complications include aneurysm perforation, parent artery occlusion, coil migration, arterial dissection, and vasospasm. A major shortcoming of aneurysm coiling, especially in the early era of the therapy, was durability. The main etiology for recanalization is coil compaction. Another mechanism may be rearrangement of individual coil loops. Insufficient packing of the aneurysm neck increases the chances of aneurysm recurrence (38). The ability to increase packing density has improved with the introduction of three-dimensional coils and hydrogel coated coils that swell when exposed to blood. The clinical relevance of aneurysm recanalization for endovascular approach is not settled unless rerupture risks for coiled aneurysms and surgical clipping are comparable. Clinical outcomes of aneurysm coiling are superior for small to medium size aneurysms when compared to giant and fusiform aneurysms. (A review of 46 studies encompassing 8,161 coiled aneurysms showed a 91% rate of adequate occlusion at initial treatment (39). Recanalization was reported in 21% of aneurysms, and retreatment was performed in 10%). At our institution, we typically perform at least one follow-up angiogram in the first 6 months. The results of the follow-up angiogram determine the need for additional angiograms. We have also found magnetic resonance angiography (MRA) to be an useful alternative in detecting recanalization in majority of cases.

1.4.3 STENT-ASSISTED COILING

Stents have been developed as an endovascular approach to open blocked arteries in
patients for reestablishing normal blood flow to tissue at risk. The first coronary stent was implanted in a human in 1986, and by 1999 its use had increased to 83% of all endovascular interventions in the coronary arteries (40). The early stents were made of stainless steel and were deployed using a balloon catheter to mechanically force open the vessel to increase blood flow. The evolution of coronary stents eventually led to self-expanding stents, eliminating the need for balloon angioplasty to expand the stent against the arterial wall. Material advances also led to the development of stents comprised of super-elastic metals. The combination of these two technologies enabled stents to be extremely flexible and expand without the use of rigid balloon catheters, which in turn reduces the tendency of vessel rupture due to arterial wall damage during deployment. These improvements, in conjunction with the introduction of microcatheters and microwires, enabled clinicians to navigate and deliver stents to previously inaccessible areas, more specifically the cerebral vasculature. The first stent designed for treatment of aneurysms was the Neuroform stent, which received a Humanitarian Device Exemption from the FDA in late 2002 (41). The primary objective of a stent application is to provide a scaffold for coiling an aneurysm with difficult shapes and sizes with a wide neck. Fiorella et al. (41) were among the earliest to report results from stent-assisted coiling immediately following the FDA limited approval use of the device for broad-neck, fusiform, or giant aneurysms. The study included a total of 74 aneurysms in 64 patients, however only 61 aneurysms were treated with stent-assisted coiling. Follow-up angiographic (average 4.6 months) results were available for 48 aneurysms. Eleven patients showed an increase in residual aneurysm size, seven of which underwent additional coil embolization. Residual aneurysm decreased or resolved in 25 patients, while no change was observed in 12 patients. Similar results were shown by Lubicz et al. (42), who treated 15 unruptured aneurysms in 14 patients with stent-assisted coiling. All patients showed excellent (neurologically intact) clinical outcome after the procedure. Lubicz et al. (43) published another study, utilizing the Leo stent (Balt, Montmorency, France) and Enterprise stent (Codman, J&J, Raynham, MA, USA), on long term follow up of patients treated with stent-assisted coiling. Thirty-four aneurysms, all wide-neck (neck > 4 mm or neck/sac ratio > 0.7), were treated in 32 patients. Follow up was performed at 6 months (n = 4 patients), 12 months (n = 16 patients), and 36 months (n = 12 patients) with a mean of 20 months. Final angiographic results (performed between 6 and 36 months) showed that aneurysm
occlusion was complete in 27 (79%), neck remnant in 3 (9%), and incomplete in 4 (12%).
Favorable results were also shown by Weber et al. (44) for the treatment of 31 wide-neck saccular aneurysms in 30 patients. Successful stent placement with adequate coil positioning, without any procedural complications, was achieved in 28 (90%) of 31 aneurysms. At 6 months, they observed complete occlusion in 15 (50%) aneurysms, neck remnants in 8 (26.7%) aneurysms, and 7 (23.3%) residual aneurysms. Results also revealed that 29 (93.5%) of the parent arteries were unaffected, while 2 parent vessels had minor asymptomatic narrowing at the stent site.
Vendrell et al. (45) assessed stent-assisted coiling in 49 patients presenting a total of 52 unruptured MCA aneurysms. Fifty (96.2%) aneurysms were successfully treated; two were referred to surgery after catheterization of the parent vessel was unsuccessful. At a follow-up period of 14 ± 9 months, complete treatment was observed in 34 (71%) aneurysms, residual necks were present in 6 (12%), and incomplete occlusion in 8 (17%).
Biondi et al. (46) reported retrospective results of stent-assisted coiling in the treatment of 46 wide-neck aneurysms in 42 patients, however only 40 aneurysms were successfully treated with stents and coils. Follow-up results of 30 aneurysms treated by stent-assisted coiling showed 17 (57%) aneurysm occlusions, 7 (23%) presented neck remnants, and 6 (20%) had a residual aneurysm.
A recent study published by Piotin et al. (47) presented results on the endovascular repair of 1,325 aneurysms using coils, including 216 that were treated by stent-assisted coiling. One hundred eighty-one (83.8%) of the aneurysms receiving a stent were unruptured. The analysis of angiographic follow up showed that stented aneurysms had lower recurrence rates vs. non-stented aneurysms. The study showed that the use of stents was beneficial in terms of angiographic stability in both ruptured (P = 0.0339) and unruptured (P = 0.0073) aneurysms.
The analysis of treatment by endovascular approach of non-ruptured aneurysms (ATENA), published by Pierot et al. (48), has been one of the most comprehensive studies on the treatment of unruptured aneurysms. The study included 649 patients, harboring 739 aneurysms. Seven hundred twenty-seven aneurysms were treated using coils (98.4%). Coils alone were used in 396 aneurysms (54.4%), with balloon remodeling in 271 cases (37.3%), intracranial stents in 57 cases (7.8%), and the Trispan neck bridge in 3 cases (0.4%). Treated aneurysms were divided into four size
categories: 131 (17.7%) aneurysms were 1–3 mm, 304 (41.1%) aneurysms were 4–6 mm, 215 (29.1%) aneurysms were 7–10 mm, and 89 (12.0%) aneurysms were 11–15 mm. Fusiform and dissecting aneurysms were excluded from the study, as well as patients who had experienced a SAH from another aneurysm within the last month. Initial results indicated postoperative complete occlusion in 436 aneurysms (59.0%); neck remnant in 160 aneurysms (21.7%), and aneurysm remnant in 143 aneurysms (19.3%). Another study by Pierot et al. (49) further broke down the analysis of the ATENA results for each treatment technique. The ATENA study shows that the viability of endovascular treatment of unruptured aneurysms can be achieved in large number of cases (95.7%) with low mortality and morbidity (1.4 and 1.7%, respectively).

Stent-assisted coiling has improved the ability to treat difficult and complicated aneurysms since its FDA approval in 2002. New clinical techniques continue to emerge along with advances in-stent design. However, while these devices provide another treatment option for endovascular repair, additional risks are associated with stent placement compared to coiling alone. Placing a stent in the parent artery requires lifetime use of anti-platelet agents to reduce the risk of thrombosis based stenosis within the stent. Kanaan et al. (50) reported acute in-stent thrombosis or chronic stenosis in 9 of 133 stent-coil deployments (6.8%) during a mean follow up of 15.4 months. The need for anti-platelet therapy limits the role of stent placement in patients with ruptured aneurysms. These patients may need additional invasive procedures such as ventriculostomy, decompressive craniectomy, tracheostomy, or gastrostomy. The risk of these procedures is increased due to anti-platelet or anticoagulation therapy. Mocco et al. (51) showed a high rate of mortality in patients with SAH when compared to the unruptured cohort (12 vs. 0.8%, respectively). In the study reported by Piotin et al. (47), mortality rates were similarly high (6.0 vs. 1.2% in aneurysms treated with stent and without stent, respectively). Differences in procedural complications were also statistically significant (P = 0.027) when comparing results of aneurysms treated with stent (7.4%) and those treated without a stent (3.8%). The increase in complications translated into higher procedure related deaths (4.6 to 1.2%, P = 0.006). Long term studies are needed to further evaluate in-stent thrombosis or stenosis. Due to their high porosity, stents surface area coverage of aneurysm neck is relatively low (4 to 7%). Therefore while they may provide improved stability for coiling, they are not sufficient as a stand-alone therapy of the
majority of intracranial aneurysms.

### 1.4.4 FLOW DIVERSION

With advent of computational fluid dynamics over the past few decades, more and more research has begun focusing on advancing aneurysm treatment options. Improvement in imaging modalities has greatly influenced medical device design. The latest neuroendovascular devices for treating intracranial aneurysms to reach the market are flow diverters. So far, limited clinical approval has been achieved on any such device, but procedures are performed under FDA exemption for compassionate use (52). The primary goal of a flow diversion device is to divert flow away from the aneurysm by placing a mesh structure, similar to a stent, on the aneurysm neck along the parent artery. By decoupling blood flow between the parent artery and aneurysmal sack, a flow diverter can create blood stasis to allow for thrombus formation inside the aneurysm. Flow diverters are intended to be used in anatomical situations where stent-assisted coiling becomes difficult, such as giant or fusiform aneurysms. In terms of design, they are very similar to stents, consisting of a highly flexible tubular structure with a mesh. They differ in one major aspect, the porosity of the cells or mesh is less than typical stents. Therefore, the major focus in manufacturing design for flow diverters has been shift from radial force exerted by the stent on the vessel wall to flow alternation inside the aneurysm (from solid mechanics to fluid mechanics). These scaffolds, or constructs, are specifically designed for use in the neurovasculature, where as stent design evolved from its original coronary application. Many studies are available on flow-diversion (53, 54, 55, 43, 56).

Current research continues to materialize on the use of flow diverters to treat intracranial aneurysms. These devices are typically deployed in situations where established techniques, such as coiling and stent-assisted coiling, are not viable options. It is not surprising that with increased technical demands, comes increased technical complications with deployment of flow diverters. Lubicz et al. (43) reported an overall complication rate of 38%, including parent artery stenosis, distal embolism, in-device thrombosis, branch occlusion, and hemorrhage or mass effects. They also reported parent artery stenosis in eight cases (33%) at follow up. In another study, parent artery occlusion was seen in seven (14%) patients, with additional arterial narrowing in three (6%) patients (56).
Stents used for coil stability do not substantially reduce blood flow to the aneurysm sack as compared to flow diverters. Clinicians must use caution in deployment of flow diverters when aneurysms are located near regions of side branching arteries. Incorrect placement could prevent blood flow to an otherwise healthy artery. Another concern with flow diverters is the low porosity, needed to reduce blood flow, will be problematic if additional coiling is needed after deployment due to the small open spaces in the mesh. Anti-coagulants required for flow diverters may be beneficial for prevention of in-device thrombus, but could negatively impact the time for thrombus formation inside the aneurysm without the additional coil packing used with stents.

The interaction of thrombus formation inside aneurysms is not clearly understood and has been suggested it could lead to rupture after deployment of a flow diverter (55). The mechanisms behind this phenomenon could relate to a reduction in WSS below normal physiological values (57), leading to vessel remodeling and rupture.

Endovascular treatment of intracranial aneurysms using flow diverters is a relatively novel approach, with a small number of clinical results available, and more information is needed to fully evaluate the effectiveness. It should be noted that Pipeline Embolization Device (PED), owned by Covidien, Mansfield, MA, USA (previously owned by eV3, Inc./Chestnut Medical Technologies, Inc., Menlo Park, CA, USA) and SILK (eV3, Inc./Chestnut Medical Technologies, Inc., Menlo Park, CA, USA) has recently been approved by the FDA Neurological Devices Advisory Panel as flow diversion device for treatment of aneurysms, and is currently awaiting a final decision by the FDA committee.

1.5 COMPARISON OF SURGICAL CLIPPING AND COIL EMBOLIZATION

The advent of endovascular therapy has certainly reduced the role of open surgery. For some aneurysms, endovascular treatment is preferred, whereas for others surgery is still superior in both cost and outcomes (23). The choice of open surgery vs. endovascular surgery for aneurysms, whether ruptured or unruptured, remains an individualized decision. The following factors play a role in treatment decision making:

1) age, past medical history, and medical/neurological conditions help to determine the patient’s ability to tolerate a specific treatment. For example, a patient with a ruptured aneurysm in poor neurological condition likely has a diffusely swollen,
friable brain, and coil embolization may be superior to surgery in this setting. On the other hand, a young patient with an unruptured aneurysm may be a good candidate for open surgery in anticipation of achieving a durable result. In some instances, patient preference also plays a role in which treatment is chosen.

2) Aneurysm characteristics such as location (suitability for surgical access), morphology, and size. Basilar apex aneurysms are associated with higher surgical morbidity compared to other locations, so endovascular treatment is usually the preferred choice of treatment. On the other hand, MCA aneurysms tend to have complex morphologies with wide necks and important arterial branches may be incorporated into the aneurysm. These aneurysms tend to be more suitable for open surgery. A ruptured aneurysm with a large intracerebral hematoma and mass effect may be better suited for surgery.

3) Finally, operator preferences are often understated but equally important. This includes the operator’s bias toward a certain treatment because of experience and familiarity. Some complex aneurysms may require a combination of open and endovascular surgeries.

The International subarachnoid aneurysms trial (ISAT) was a randomized, multicenter study that compared clinical outcomes of patients presenting with ruptured aneurysms, and treated either by clipping or by coiling (17). A total of 9,559 patients with SAH were assessed, and 2,143 patients were ultimately enrolled and randomized. Initial clinical outcomes from ISAT indicated little difference between endovascular and surgical treatment. However, the results at 1 year follow up were convincing enough to lead to an early termination of the study, because those treated with endovascular coiling had a 6.9% absolute risk reduction and 22% relative risk reduction in poor outcome compared with surgical clipping (17). Long term follow-ups in ISAT indicated endovascular coiling had a higher risk of re-bleeding than clipping, but the risk was low and remained similar to risk of SAH from another aneurysm (58).

The ISAT study indicated that endovascular treatment was a safe and effective alternative to surgical treatment for certain ruptured aneurysms. However, the results were not sufficient to determine that endovascular treatment is superior to surgical treatment in all patients with ruptured aneurysms and cannot be applied to unruptured aneurysms. The trial demonstrated that coil embolization resulted in less peri-procedural morbidity in a selected group of patients. Retreatment was performed in
17.4% of the 1,096 patients who underwent endovascular therapy and in 3.8% of the 1,012 patients who underwent surgical clipping (59).

A recent study reported by Alshekhlee et al. (60) compared hospital mortality and complication rates associated with aneurysm clipping and coiling based on the National Inpatient Sample (NIS) between 2000 and 2006. A total of 3,738 patients had aneurysm clipping and 3,498 had endovascular coiling. For clipping vs. endovascular coiling, both median length of hospital stay (4 and 1 days, respectively, P < 0.0001) and mortality (1.6 vs. 0.57%, respectively) were higher. The study also presented data showing a trend in hospital use of endovascular coiling has increased during recent years.

Singh et al. (61) showed that increased clinician experience with endovascular coiling resulted in decreased risk of complications. The combination of these factors may be advantageous for endovascular treatment, but similar comparative studies have to be conducted.

In conclusion, literature data confirm:

- advances in imaging modalities and knowledge of natural history and prevalence of aneurysms have increased detection of unruptured asymptomatic intracranial aneurysms. An unbiased assessment of most appropriate course of treatment is crucial for achieving a favorable outcome;
- the size of an aneurysm has been associated with higher risk of complications for both surgical and endovascular treatment approach (62). Studies reporting on the risk of rupture and outcomes have provided much insight but the debate remains of how and when unruptured aneurysms should be managed;
- the studies reviewed here support the generalized notion that endovascular treatment of UIA provides a safe and effective alternative to surgical treatment. The risks associated with endovascular repair are lower and incur shorter hospital stays for appropriately selected patients;
- the method of endovascular treatment should be considered based on factors such as aneurysm size, location, patient medical history, and clinician experience. To date, there have been no randomized large studies comparing outcomes using different endovascular options. The likeliness of such a study appears slim as the variability in the use of devices is wide. Furthermore, the rapid development of endovascular technology often prevents adequate appraisal of existing devices and methods.
Currently, endovascular therapy and surgical therapy must be viewed as complementary rather than competitive in the treatment of intracranial aneurysms.
CHAPTER 2: “CLINICAL STUDY”.

2.1 MATERIALS AND METHODS

Between January 2007 and October 2011, we deployed 22 stents in 20 patients harboring wide-necked cerebral aneurysms. Inclusion criteria restricted the group to adult patients (>18 years old) with wide-necked intracranial aneurysms (ruptured and unruptured lesions) and follow-up imaging studies (DSA or MRA) performed at our Institution. A wide neck was defined as a dome-neck ratio of less than 2 or a neck that was 4 mm or wider as measured on angiograms.

The study consisted of 18 (90%) women and 2 (10%) men with a mean age of 56.2 years (range 37-83 years). Eleven (55%) aneurysms were located in the anterior circulation and nine (45%) in the vertebrobasilar system.

According to the ISUIA II (International Study of Unruptured Intracranial Aneurysms) classification (63), 4 (20%) aneurysms were characterized as small (< 7 mm), 11 (55%) medium (7-12 mm), 4 (20%) large (13-24 mm) and 1 (5%) giant aneurysm (>25 mm), with a mean size of 11.2 mm (range 4-26 mm).

Four aneurysms (20%) were ruptured with SAH, whereas 15 (75%) of them were incidental and one (5%) presented with compression symptoms.

Before all procedures, patients underwent complete 4-vessel digital angiography and 3-dimensional angiography in selected cases. Immediate postprocedure angiographic studies were performed to determine successful coil occlusion of the aneurysm as well as patency of the parent vessel.

Therapeutic strategy and endovascular procedure

All therapeutic procedures were conducted under general anesthesia and systemic heparinization. To evaluate morphological features of the aneurysm and parent vessel and to establish the optimal visual working projections for coil occlusion of the aneurysm a cerebral angiography was performed.

The stent-assisted coil delivery procedure consisted of the placement of the stent in the parent artery across the aneurysm neck. A microcatheter was then navigated through the stent interstices into the aneurysm sac, and coil embolization was performed. In a modified stent delivery procedure, the microcatheter was inserted into
the aneurysm sac first and then the stent was placed across the wide neck of the lesion. This “jails” the microcatheter in the aneurysm, helping to stabilize the microcatheter during delivery of the coils.

The stenting strategy varied as it follows:

- Stenting before coiling in 17 patients (85%). In 16 of these 17 aneurysms, the microcatheter was introduced through the interstices of the stent, whereas in the other one, the catheter was jailed between the stent and the artery wall.

- Stenting after microcoil embolization in 2 patients (10%). The stent was deployed across the aneurysm-neck immediately after the aneurysm coiling. Primary coiling or remodeling technique was first used and then the stent was deployed, aiming to reduce the late recanalization rate.

- Stenting without microcoil embolization in 1 patient (5%). Stent deployment across the aneurysm-neck as followed by difficult in introducing the microcatheter through the interstices of the stent. Therefore, the patient was treated with the technique of flow-diversion.

- Emergency stenting in 2 patients (10%). In these patients, presenting with evidence of acute complete in-stent-thrombosis which not resolving after intraarterial administration of Reopro, placement of a new stent in-stent was necessary.

Coiling procedure has already been published in the literature (7). Medical premedication (160 mg of ASA and 75 mg of clopidogrel per day) at least 3 days before the procedure in all unruptured patients, and a loading dose of 300 mg of clopidogrel was administered 2 hours before the procedure in ruptured aneurysms was administered. A bolus infusion of heparin (70 IU/kg body weight) was done during the procedure, and hourly. The adequacy of systemic anticoagulation was monitored by keeping the activated clotting time 2 to 2.5 times the baseline. Systemic heparinization was stopped immediately after the procedure in most cases and prolonged for 24 hours in selected cases. Unilateral femoral access was obtained through a percutaneous femoral artery puncture, and a 6F guide catheter was inserted into the parent vessel. When proper alignment was achieved, the microcatheter was gently pulled-back to unsheath the stent while gentle forward tension was maintained on the stabilizer to keep it in place. Positioning was confirmed by direct fluoroscopic visualization. Once the stent was fully deployed, the microcatheter and introducing system were removed. A smaller microcatheter, as Excelsior SL-10 (Boston Scientific, Natik MA, USA) or Prowler 14 (Codman e Shurtleff Inc., Raynham, MA,
USA), was then introduced through the guiding catheter and, with direct fluoroscopic visualization and road mapping, guided through the interstices of the stent and into the aneurysm. The coils were then delivered within the aneurysm through the microcatheter.

Immediately after EVT, patients were transferred to the intensive care unit for monitoring of blood pressure and neurologic status. Patients were maintained on clopidogrel (75 mg/d) for 2 months and ASA (160 mg/d) for 6 months. Clinical data were obtained from examinations conducted by stroke neurologists or neurosurgeons before and after the procedure. Patients were re-evaluated generally within 30 days after the intervention. Long-term clinical evaluations were acquired in conjunction with the follow-up imaging.

The clinical outcome measure used was the modified Ranking Scale. The scale runs from 0 to 6, running from perfect health without symptoms to death:

<table>
<thead>
<tr>
<th>mRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability. Able to carry out all usual activities, despite some symptoms.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability. Requires some help but able to walk unassisted.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability. Unable to attend own bodily needs without assistance, and unable to walk unassisted.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability. Require constant nursing care and attention, bedridden, incontinent.</td>
</tr>
<tr>
<td>6</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

Technical success was defined by correct placement of the stent and successful positioning of the coils into the body of the aneurysm without compromising the parent vessel. Successful stent placement was defined as stable placement with complete coverage across the aneurysm neck and patency of the parent artery. Satisfactory coil mass position was defined as the stent maintaining coil position within the aneurysm sac with parent artery patency.
Patients were evaluated by angiography at the end of the procedure to document aneurysm obliteration. Angiographic results were classified as complete occlusion (>99%) (no contrast filling the aneurysmal sac), neck remnant (91-99%) (residual contrast filling the aneurysmal neck), incomplete occlusion (70-90%) (residual contrast filling the aneurysmal body) and partial occlusion (<70%). Angiography follow-up was performed in all patients within 6 months after the intervention and further follow-up was performed by MRA or DSA with evaluation of stent stenosis, progressive thrombosis, recurrence and need for retreatment.

A recurrence was defined as any increase in the size of the remnant. The recurrence was qualified as major if it was saccular and its size would theoretically permit retreatment with coils; minor in the other cases.

All MR images were obtained on a GE 1.5T scanner (Signa HDxt; GE Healthcare, Milwaukee, WI, U.S.A.) with an 8 channel head-coil.

At first, we obtained a T2wi and a three-dimensional (3D) TOF-MRA with parameters as follows: spoiled gradient-echo sequence with TR/TE/FA, 30 msec/2.7 msec/20°; FOV/Matrix, 240 mm/384 × 224; slice thickness/slice overlap, 1.4 mm/50%; ASSET factor, 1; and actual bandwidth, 31.25 KHz.

In selected cases we perform a contrast-enhanced MRA (CE-MRA) with parameters as follows: Fast Spoiled gradient-echo sequence with TR/TE/FA, 30 msec/minimum/45°; FOV/Matrix, 240 mm/352 × 352; slice thickness/slice overlap, 1.0 mm/50%; ASSET factor, 1.75; and actual bandwidth, 41.67 KHz.

Contrast medium was gadolinium-chelate in all cases.

Source data of each imaging set were reconstructed with the maximal intensity projection (MIP) and volume rendering (VR) technique. All the image interpretation of MRA was performed on a PACS monitor by two board-certified neuroradiologists.

2.2 RESULTS

**Procedure**

The correct placement of the stent in the parent vessel across the aneurysm neck was obtained in all 22 (100%) case.

A satisfactory coil mass position was obtained in 19 (95%) of 20 patients; the only one case treated without coiling embolization is caused for impossibility to navigated through the stent interstices with microcatheter into the aneurysm sac.
Angiography immediately after treatment procedure showed complete occlusion in 7 aneurysms (35%), neck remnant in 11 (55%), incomplete occlusion in 1 (5%) and partial occlusion in 1 (5%).

During the endovascular embolization procedure no rupture of the sac or bleeding complication occurred, neither any patients needed to undergo to surgical crossover. Procedure-related adverse events occurred in one (5%) patient, treated by brachial arterial access: a postprocedural pseudoaneurysm presented, then resolved with glue embolization without clinical sequelae.

Three (15%) patients had neurological complications after procedure; in one patient there was a muscular overtone of the left arm at the end of general anestesia, spontaneously resolved without sequelae in 12 hours. Two patients showed a reduced consciousness 6 hours after the treatment. Emergency DSA was performed, demonstrating evidence of acute complete in-stent thrombosis, which resolved after intraarterial administration of Reopro (Eli Lilly and Co., Indianapolis, Ind.) and placement of a new stent in-stent. However one of this patients died 20 days after procedure for severe vasospasm; in the other one, follow-up MRI showed a midbrain ischemic lesion with gait disturbances.

Overall neurological complication rate is 15%, with only one case (5%) of major complication.

Of the 20 patients treated with stent deployment, a follow-up imaging studies was available in all 19 surviving patients (95%) at an average of 16.2 months (range, 6 to 50 months).

**Six months follow-up**

The first follow-up DSA, compared with initial angiography, showed no changes in 14 aneurysms (73.7%), progressive thrombosis in 3 (15.7%), and major recurrence in 2 (10.5%). The 6 months overall rate of succesful procedure is 89.5%.

Of the three aneurysms with progressive thrombosis, two initially displayed neck remnant and later exhibited spontaneous progression of thrombosis at the follow-up, while one underwent to stenting without coil embolization and was then treated with principle of flow-diversion; in this patient the follow-up angiography showed reduction in opacification of the aneurysmal body.

The two cases (10%) with major recurrence were those with stent placement after
coiling; in these patients, presenting with ruptured aneurysm, occurred a coil stretching with partial occlusion of parent vessels; DSA performed immediately after the procedure showed subtotal occlusion (neck remnant) of the aneurysm with patency of parent vessel; both patients were re-treated by endovascular coiling with complete occlusion of the aneurysms. The follow-up imaging exams did not demonstrate any recurrence.

In one (5%) of 20 patients the 6-months-follow-up-angiography showed an asymptomatic moderate endothelial hyperplasia in the stent; at the further DSA and MRA follow-up we observed a spontaneous progressive endothelial hyperplasia reduction.

**Long term follow-up**

The follow-up imaging study, compared with the first follow-up DSA (6 months after treatment), showed no changes in 17 (89.5%) of the 19 surviving patients. The patient treated with stenting alone demonstrated further progression of thrombosis during the follow-up.

One patient at 18-months follow-up MRA showed a minor recurrence; no further changes in size of the signal into the aneurysm sac was detected in the further follow-up MRA.

**Clinical Follow-up**

At 30 days clinical follow-up we did not observe any worsening in the mRS in 18 (90%) of 20 patients; in one case presented worsening of mRS (mRS 2) for stent-related midbrain ischemic lesion; the other case was a patient presenting with SAH, who died (mRS 6) 20 days after procedure for severe vasospasm.

Long term follow-up neurological examination were available in all of 19 surviving patients at an average of 16.2 months (range, 6 to 50 months); there were no changes in the mRS in all patients.

All the surviving patients are alive and we did not observe periprocedural or long-term intracranial bleeding events or symptomatic stent related stenosis/occlusion complications.
2.3 DISCUSSION

Since the introduction of GDC for treatment of cerebral aneurysms in 1991, numerous reports have been published to show its safety and efficacy, particularly in treating saccular aneurysms with small neck size. Unfortunately, for those aneurysms with large neck size or unfavorable neck-to-dome ratio, durable aneurysm occlusion has been more difficult to reach. For complex neck, large, and giant aneurysms, recanalization frequently result from unintentional or deliberate undercoiling of the neck region and involve a sequence of events leading to coil compaction, with or without true continued growth of the aneurysm.

After stenting, the increased resistance to high flow into the aneurysm dome due to the stent interstices is partly responsible for reduced intraaneurysm flow vortices and increased stasis (64). Besides this, the rationale for adjunctive stenting in the treatment of wide-necked cerebral aneurysms relies on the reestablishment of laminar flow patterns, which actually may heal the aneurysm at its neck (65, 66, 67, 68) and induction of more profound hemostasis within the aneurysm, contributing to intraaneurysmal thrombosis. The theoretical “vascular reconstruction” concept lies on the subintimal incorporation of the stent into the parent vessel wall, reinforcing the parent artery at the neck margins and potentially reducing the likelihood of recurrent aneurysm growth from the neck region and providing an organized substrate to support neointimal growth over the aneurysm neck.

Stented aneurysms had a low rate of immediate total circulatory exclusion, in our series 35%, but showed increased delayed occlusion between immediate control and the first follow-up angiogram. The fact that immediate total aneurysm occlusion was less frequent in the stented group can be explained by the fact that tight coiling is more difficult to obtain when the stent is implanted before coiling, giving less maneuverability to the coiling microcatheter and thus resulting in looser aneurysm packing. Previous published series have also reported a similar finding with a relatively low rate of immediate complete aneurysm occlusion with delayed sac thrombosis at follow-up (46, 69, 42). Moreover, the use of dual antiplatelet therapy during the procedure in addition to heparin did not favor immediate peri-procedural sac thrombosis.

The classification of angiographic results and the diagnosis of a recurrence are subjective evaluations. We have chosen to distinguish “minor” from “major”
recurrences. Minor changes from the initial or first follow-up angiogram can be detected objectively by a rigorous evaluation, but there might be concerns of increasing sensitivity of detection of recurrences at the expense of specificity by overcalling lesions that might show stability later on. The clinical significance of a nonprogressing residual neck, has not been determined certainly, although it is probably not without hemorrhagic risks (70). Major recurrences are more definitely of concern. Patients who bled during follow-up were shown to have unstable results, with residual aneurysms that had progressed since the previous angiographic study. In this series none of the patients had re-bleeding in the follow-up period.

Larger aneurysms are known to recur more frequently (71) and it’s known that there were less recurrences in the stented aneurysm despite that this group usually included larger aneurysms with lower packing densities than the aneurysms usually treated without stent (71); in our series we had found a complessive recurrence rate of 15%, with 2 cases of major recurrence at 6 months angiographic follow-up, and one case of minor recurrence at 18 months follow-up MRA. This finding shows that the key factor to prevent aneurysm recurrence is, aside from the packing density of the sac, better arterial wall reconstruction at the level of the neck. However, the duration of follow-up was shorter for stented aneurysms due to the fact that the majority of the stents were implanted during the last 3 years, and the duration of follow-up is obviously a key factor known to influence angiographic or imaging recurrence rate. Longer follow-up is mandatory to draw more definitive conclusions.

In our series of aneurysms treated with stent or stent-assisted coiling, major recurrence was observed in 2 (10%) patients and successful retreatment was accomplished in both cases. Recurrences seemed to be more frequent in posterior circulation aneurysms (all 3 cases) in agreement with other previous studies (72). This may be related to the size and etiology of the aneurysm.

Experience in cardiology teaches that it might be important to place stented patients on dual antiplatelet therapy to prevent thrombotic events.

There were more procedure-related complications in the stented patients. The conjunction of the use of antiplatelet drugs and guidewire exchange maneuvers explained overincidence of hemorrhagic complications in stented aneurysms compared with coiling aneurysms and more specifically vessel perforations. The necessity of dual antiplatelet therapy in stent-assisted coil embolization is known to increase the risk of hemorrhagic complications. However in our series we observed no
periprocedural bleeding complication and no rebleeding events in the clinical follow-up; this might be due to the small number of ruptured aneurysms (4 of 20, 20%) included in the study.

Particular care is necessary for patients presenting with SAH; this subgroup of patients with stented aneurysms wasn’t obviously placed on dual antiplatelet therapy. The protocol of pretreatment with an antiplatelet regimen for patients with acutely ruptured aneurysms is still controversial. Considering the inherent thrombogenicity of stent placement and risk of severe rebleeding after antiplatelet therapy, we administered antiplatelet drugs very shortly before stent placement, as advocated by some authors (65, 46); in our Institution we administrated 500 mg of ASA and 300-600 mg of clopidogrel by nasogastric tube immediately after procedure. Nevertheless, none of the cases had post-procedural bleeding or re-bleeding during the follow-up period. However, Katsaridis et al. (72), reported that stent-aided coiling without any pretreatment is safe in ruptured and unruptured aneurysms on the basis of experience in 54 cases. Therefore, further study is required to evaluate the benefit-risk balance for different protocols.

The only one case of procedure-related adverse event was a brachial-artery pseudoaneurysm occurred in a patients presenting with SAH; this might have been favored by antiplatelet therapy. Thromboembolic complications could be more frequent in the stented patients; this finding was similar in a previously reported series (73). However, dual antiplatelet drug administration before stent delivery had later diminished the occurrence of such complications.

We observed that both cases of stent thrombosis were patients presenting with SAH due to rupture of aneurysms of the posterior circulation and occurred within 6 hours after endovascular treatment; both cases required the intra-arterial use of abciximab (ReoPro) and subsequent placement of a new stent.

In our series permanent neurological deficits occurred in only one (5%) of stented patients, which is a similar rate compared with previously published series (65, 74, 46).

The incidence of in-stent stenosis is likely related to neoointimal growth as has been previously suggested (75), which might be secondary to endothelial injury. Due to shear stress of the stent deployment, new endothelial growth called “neoointima” occurs. The content of neoointima changes over time. The early neoointima contains a
large quantity of proteoglycans, which provide both the volume of the neointima due to high water content, and facilitate cell migration and proliferation. However, as the neointima ages, it loses the bulky, hydrated proteoglycans, which results in reduction in the neointimal volume and the stimulus for smooth muscle cell proliferation. Meanwhile, the collagen matures, transforming from the fibrillar type to the cross linked type and the smooth muscle cells also change their phenotype from synthetic to contractile cells, with the cell content remaining relatively stable. As a result, neointimal regression may occur after 6 months. Late angiographic improvement has been proposed to be probably due to fibrotic maturation of in-stent neointima (75).

Unlike coronary balloon-mounted stents, self-expanding intracranial stents such as the Enterprise (Cordis Neurovascular J&J, Miami Lakes, Fla) or the Neuroform (Stryker, Kalamazoo, MI, USA) have low radial force and are less traumatic. In our series, one patient (5%) with angiographic follow-up presented with an asymptomatic in-stent stenosis of 30% with the newer self-expanding stent designed for the neurovascular realm.

Great care is necessary to preserve perforators at the time of stent placement, because important perforators, that exit from the stented arterial segment during aneurysm embolization, may be occluded. As discussed in the coronary literature (76) future development of absorbable stents should be considered to prevent permanent jailing of important perforators.

The correct imaging follow-up protocol for the patients treated with intracranial stent remains unclear. Transfemoral cerebral arteriography has been considered as the method of reference for evaluation of the stented arteries and for detection of endothelial hyperplasia. However, it is invasive and could have the potential risk of neurological complications (77). Contrast-enhanced MR angiography (CE-MRA) seemed to be alternative to the arteriography in terms of detecting restenosis of stented large arteries such as carotid, iliac or femoral arteries (78, 79). However, CE-MRA requires the use of gadolinium contrast media, which presents the risk of anaphylaxis, renal complication, and nephrogenic systemic fibrosis (80).

Time-of-flight (TOF) MRA is a widely used and well-established MRA technique for evaluating intra- and extra-cranial arterial pathology without contrast media (81, 82). However, various metallic stents cause the variable degree of luminal signal loss of the stented artery due to susceptibility artifact or radiofrequency (RF) shielding artifact (82, 83). TOF-MRA can demonstrate pathology of the intracranial large
arteries that is less than 3 mm in diameter. However, it is difficult to interpret patency and/or degree of stenosis of stented artery on TOF-MRA because of susceptibility artifact or RF shielding effect of intracranial stents \((84, 85)\). It is known that wider BW can reduce susceptibility artifact and overcome RF shielding effect. However, this might reduce signal to noise ratio of the TOF-MRA \((86)\).

At our Institution, we decided to perform a DSA within 6 months in all patients to detect the presence of recurrence and endothelial hyperplasia; it is known that the intra-stent endothelial hyperplasia has its highest expression after 6 months and then tends to decrease, as previously discussed \((75)\). If the patient shows endothelial hyperplasia is always followed with angiographic follow-up. If at 6 months-angiography there are no signs of endothelial hyperplasia, the patient is monitored with 3D TOF-MRA, and CE-MRA in selected cases; if there are no signs of recurrence it continue the follow-up to 18 months and then every 3 years. If it’s detected a minor recurrence, the patient is monitored with annual MRA (3D TOF and CEMRA); in case of major recurrence a DSA is performed, also in anticipation of a possible re-treatment.

2.4 CONCLUSION

The use of the stent for intracranial aneurysms treatment integrates 3 principles:
- “endovascular bypass” with anatomic reconstruction of the diseased parent vessel;
- mechanical support for coil embolization;
- flow diversion.

Our findings suggest that the endovascular treatment of intracranial aneurysms using the stent is feasible, effective and safe. In addition, the use of stent allows to expand the pool of patients who benefits of endovascular treatment. The follow-up proved intact parent arteries and stable occlusion rates in the majority of treated aneurysms. Nevertheless, long-term data on safety and efficacy and larger groups of patients are necessary, as well as a universally shared follow-up protocol.
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PICTURE 1

a) and b) left internal carotid artery angiography showed carotid-ophtalmic wide-neck aneurysm.

c) Volume rendering of 3D rotational angiography allowed us to choose the best work-projection.
d) MIP reconstruction of 3D rotational angiography allowed us to measure body and neck of the aneurysm.
e) Roadmap picture: a small microcatheter positioned into the parent artery.
f) Roadmap picture: the stent positioned across the aneurysm neck.
g) and h) left internal carotid artery angiography showed correct stent placement with preserved patency of parent artery.
i) Roadmap picture: a guidewire passed through the interstices of the stent.
l) Roadmap picture: a small microcatheter passed through the interstices of the stent into the aneurysm body.
m) Partial coiling of the aneurysm body.
n) Cast of coils kept inside the body of the aneurysm by the stent.
o) and p) left internal carotid artery angiography showed complete occlusion of the wide-neck aneurysm.
PICTURE 2

a) left vertebral artery angiography showed basilar artery-apex wide-neck aneurysm.
b) left vertebral artery angiography showed complete occlusion of the wide-neck aneurysm.
c) and d) 6-months left vertebral artery angiography showed no recurrence.
e) 18-months axial 3D Time-Of-Flight MRA showed no flow signal into the treated aneurysm.
f) Volume Rendering reconstruction of the 3D Time-Of-Flight MRA confirmed the absence of the flow signal into the aneurysm; note the signal loss into basilar-artery stent.