

# EDITORIAL: WHAT IS THE FUTURE OF THE ENDOVASCULAR TREATMENT OF INTRACRANIAL ANEURYSMS?

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*Intracranial aneurysms rupture is a common cause of mortality or morbidity worldwide. For this reason, in case of rupture, early treatment of the aneurysm is mandatory. The evaluation of unruptured intracranial aneurysms continue to increased due to the improvements in invasive and non-invasive neuroimaging. Securing of this life-threatening condition, considering all demographical and procedural factors is necessary for improving treatment results and patients outcome. The endovascular treatment has become frontline therapy of cerebral aneurysms treatment during the last 20 years, and without a doubt its recent advances shifted this boundary even further. Nowadays endovascular armamentarium continues to grow rapidly. Neuro-interventional procedures have tremendously improved their efficiency and continue to improve device's safety. However some types of aneurysms are not really easy to treat with ordinary endovascular technique as it can result in devastating consequence, Firstly, it is not always applicable to complex aneurysms or very large neck aneurysms. Secondly, durability of the of the aneurysm occlusion is not guaranteed in all cases even after usage of the remodeling technique or regular stenting. New devices are introduced to decrease these limits. Two new innovative techniques that are increasingly used for endovascular occlusion of the complex aneurysms are flow diversion and intrasaccular flow disruption. The objective of this review is to provide a comprehensive overview of novel paradigms and latest research of flow diversion and intrasaccular flow disruption devices, its current application, limitation and future prospective. The obvious advantages of these new technologies proved progressive expansion of their utilization to the extent that they will ultimately replace standard coiling in an increasing number of cases going forward.*

*The future of the endovascular treatment of intracranial aneurysms is bright. Fast growing improvement in vascular access, treatment modalities and device delivery continue*

*to increase number of patients with intracranial aneurysms treated with endovascular approach versus surgical clipping.*

**Key words:** intracranial aneurysms; endovascular treatment; flow diversion; intrasaccular flow disruption.

The prevalence of intracranial aneurysms (IA) in the population is high, close from 3 % [1]. The major risk of an IA is its rupture leading to intracranial bleeding (subarachnoid, parenchymal, and/or intraventricular hemorrhage), which is associated with a high case fatality (between 40 to 50 %) [2].

After the initial aneurysm rupture, the aneurysm wall is fragile and a re-rupture with a new bleeding can be observed, singularly in the days following the initial event. For this reason, in case of rupture, early treatment of the aneurysm is mandatory. After publication of ISAT (International Subarachnoid Trial) results, treatment of ruptured aneurysms has progressively shifted from surgical approach (clipping) to endovascular treatment (EVT) with intrasaccular coiling [3]. EVT is now the first-line treatment in the management of ruptured aneurysms [4].

With the development of non-invasive vascular imaging (Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA)), aneurysms are more and more discovered before any rupture. The treatment of such unruptured aneurysms is still a matter of debate as the individual risk of bleeding is very difficult to evaluate. From large studies, the risk of rupture is increasing with aneurysm size and in some aneurysm locations (posterior circulation) [5, 6]. Subsequently the strategy of treatment of patients with unruptured aneurysms is defined on an individual basis taking into account several factors including patient's age, aneurysm's size and location, patient's risk factors, etc [7, 8].

#### **IA coiling: limits and additional techniques (balloon-assisted coiling and stent-assisted coiling)**

The first endovascular approach used on a large extent for the treatment of IA was coiling using controlled-detachable coils [9]. However

as several types of aneurysm can be encountered according to their shape (sacciform/fusiform), size (small/large/giant), neck size (narrow/wide neck), and location, this treatment was rapidly facing some limitations. Wide-neck and fusiform aneurysms are not really easy to treat with coils that have a tendency to migrate into the parent vessel with a risk of parent vessel occlusion.

The remodeling technique or balloon-assisted coiling (BAC, temporary inflation of a balloon in front of the neck during deposition of the coils) was subsequently developed for such wide neck aneurysms with quite good results [10–12]. An alternative approach for wide-neck aneurysms was subsequently proposed with stenting that was used to support the coils placed in the aneurysm. Initial evaluation showed a good efficacy at the price of a relatively high morbimortality rate [13]. Further developments of intracranial stents and increased skills of the physicians using them, was progressively associated with a decreasing morbidity and mortality [14].

Despite these technical developments, the endovascular treatment of IA still has some limitations. First of all, it is not always applicable to complex aneurysms such as fusiform aneurysms or very large neck aneurysms. Secondly, even if the endovascular treatment of some complex aneurysms is now feasible using the remodeling technique or regular stenting, the long-term stability of aneurysm occlusion is not guaranteed in all aneurysms. Thus large and giant aneurysms, wide neck aneurysms, and also more regular aneurysms are candidates for aneurysm reopening (recanalization) [15].

The difficulties encountered in the treatment of some complex IA with coils has lead to the development of 2 new techniques that are progressively increasingly used in their management: flow diversion and intrasaccular flow disruption.

#### **Flow Diversion**

Flow diverters are stents with a very dense mesh. Their goal is primarily to reconstruct the diseased vascular segment harboring the saccular or fusiform aneurysm pouch. The device used for parent vessel reconstruction produces hemodynamic and biological effects:

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- flow redirection: the flow diverter crosses the aneurysm neck and diverts the blood flow from the aneurysm sac, thus reducing shear stress on the aneurysm wall and promoting intra-aneurysm flow stasis and thrombosis. This phenomenon is affected by the amount of metal surface area coverage provided by the stent;
- tissue overgrowth: the flow diverter provides scaffolding for the development of endothelial and neointimal tissue across the aneurysm neck.

The first prospective, multicenter study evaluating flow diversion was PUFS (Pipeline for Uncoilable or Failed Aneurysms) conducted with a first-generation device (Pipeline Embolization Device, Medtronic, Minneapolis, Minnesota, USA) [17]. This study was showing an acceptable safety and efficacy in the treatment of large and giant unruptured internal carotid artery (ICA) aneurysms (see below). Subsequently initial indications were focused on large and giant unruptured ICA aneurysms as well as recanalized or residual aneurysms.<sup>18</sup> The great efficacy of this treatment demonstrated in further studies (see below) and the development of new-generation flow diverters including small diameters devices (FRED/FREDJr, Microvention, Aliso Viejo, CA, USA; p64/p46-MW/p64-MW, phenox, Bochum, Germany) was leading to the progressive enlargement of indications to small aneurysms, distal aneurysms, and bifurcation aneurysms [19, 20]. One major limitation in the use of flow diverters is the need of using dual antiplatelet treatment (DAPT) preoperatively and in the months (usually 3 to 6 months) following the procedure (see below). Accordingly ruptured aneurysms are not considered as an appropriate indication, except in some specific situations [21].

Complications encountered when treating an aneurysm with flow diverters are, as for coiling, thromboembolic events and intraoperative rupture [22]. Other complications rarely encountered can be seen after aneurysm flow diversion like delayed aneurysm rupture and delayed remote hematoma [23, 24]. As after aneurysm coiling, delayed thromboembolic complications can occur after aneurysm treatment with flow diversion, but on the contrary to coiling these delayed events can occur very late [25, 26].

Initial studies dedicated to aneurysm treatment with flow diversion were showing relatively high morbidity and mortality [17, 27]. Pipeline embolization device was the first to be evaluated

in large, multicenter series including PUFS. In the cumulated population of 3 multicenter series (1092 patients with 1221 aneurysms), the major neurological morbidity was 5.7 %, whereas neurological mortality was 3.3 % [28]. Surpass flow diverter (Stryker Neurovascular, Fremont, CA, USA) was also evaluated in a multicenter trial (SCENT = Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms) that included 180 patients with 180 aneurysms. 12-month major ipsilateral stroke or neurological death rate was 8.3 % [29]. These morbidity and mortality rates are clearly higher to what is reported with coiling (1.7 % and 1.4 %, respectively, in Analysis of Treatment by Endovascular Approach of Non ruptured Aneurysms [ARETA] study) [30].

With more recent flow diverter generations, the safety was improving probably due to several factors including improvement of flow diverter design, increased skills of the physician, and change in the use of medications used. In SAFE study evaluating FRED/FREDJr flow diverters, cumulative 1-year morbidity and mortality rates were 1.9 % and 2.9 %, respectively [31].

Initial experience with p64 and p48 flow diverters was reported in several single-center and multicenter series showing low morbidity and mortality. Fischer et al. reported a series of 121 patients with 130 aneurysms treated with p64 device with transient and permanent morbidity and mortality in 5.0 %, 1.7 %, and 0.8 %, respectively [32]. Briganti et al. reported a multicenter series of 40 patients and 50 aneurysms treated with p64 with low morbidity (2.5 %) and no mortality [33]. In Morais et al. series, 35 patients with 41 IA were treated with p64 with no permanent morbidity or mortality and 5.7 % transient neurological morbidity [34]. Finally in a large single-center series of 108 patients with 109 aneurysms permanent morbidity was 1.9 % and no mortality was reported [35]. Clinical experience with p48 reported in the literature is more limited with one single-center series of 25 patients with 25 aneurysms treated with the device with no mortality or morbidity related to the device [36].

Regarding efficacy, the experience with flow diverters reported in the literature has shown two important things:

1) Flow diversion is associated with a very high rate of complete aneurysm occlusion at 6-month or more follow-up (Table). At 6 months rate of complete aneurysm occlusion is between

61.1 % and 82 %, whereas at one year it is between 66.1 % and 88.0 %.

2) On the contrary to what is observed with coiling, aneurysm occlusion after flow diversion is a slow process. When an aneurysm is treated by selective occlusion using coils, intraaneurysmal thrombosis will rapidly occur affording immediate protection against bleeding or rebleeding. On the contrary, complete occlusion is rarely obtained at the end of the flow diversion procedure and will take few months to occur. As demonstrated for instance in PUFs, the rate of complete aneurysm occlusion after flow diverter treatment is 73.6 % at 6-month, 86.8 % at 1-year, 93.4 % at 3-year, and 95.2 % at 5-year [37].

To overcome the limitation represented by the need of DAPT, flow diverters with surface modification associated with less platelet aggregation are available and have been used clinically:

1) Pipeline with Shield technology: the Shield technology is a surface modification where a synthetic phosphorylcholine polymer is covalently bonded to the strands that make up the Pipeline braid [38]. A preliminary evaluation of the device was conducted in a prospective, single arm, multicenter study (PFLEX = Pipeline Flex Embolization Device with Shield Technology study) showing a good safety under DAPT in 50 patients [38]. Another single-arm study conducted under DAPT (SHIELD = Pipeline Flex with Shield Technology Embolization – An International, Multicenter Observational Post-Market Study) showed in a population of 205 patients 2.9 % major stroke leading to 1.0 % neurological death [39]. Complete aneurysm occlusion was obtained in 70.8 % at 6-month and 77.2 %

at 12-month. In a non-industry-sponsored study (PEDSU = Pipeline Embolization Device with Shield Technology in Unruptured Aneurysms) with DAPT, the cumulative morbidity and mortality at 1-year were slightly higher (6.8 % and 2.3 %, respectively) [40]. Complete aneurysm occlusion was reported in 69.2 % at 6-month and 82.7 % at 18-month. A limited evaluation was conducted in a small group of 14 patients with ruptured aneurysms treated in the acute phase of bleeding with SAPT (aspirin) [41]. Permanent treatment-related morbidity and mortality occurred in 7.1 % and 7.1 %, respectively, which is quite high in comparison with the worse results of bare Pipeline treatment with DAPT. As of now, no comparative study involving Pipeline Shield has been published.

2) p48-MW and p64-MW with HPC (Hydrophilic Polymer Coating) surface modification: Hydrophilic Polymer Coating is a newly developed glycan-based multilayer hydrophilic polymer coating that has been shown to reduce thrombogenicity when applied to nitinol surface [42]. Limited clinical experience with p48-MW-HPC and p64-MW-HPC has been published. In a small series of 8 patients with ruptured aneurysms treated with p48-MW-HPC under SAPT (aspirin or prasugrel), intraprocedural transient thrombus formations was observed in 50 % of patients, whereas intra-stent thrombus formation was observed at day 3 [43].

#### Intrasaccular flow disruption

Intrasaccular flow disruption (IS-FD) is an innovative approach that involves the placement of a self-expanding, roughly spherically-shaped, cage-like device within the aneurysm [44–49].

**Table.** Rate of complete aneurysm occlusion in different flow diverter series, %

Series or Authors	Device	3-month	6-month	1-year	3-year	5-year
DIVERSION [27]	Multiple	–	–	68.4	–	–
PUFS [37]	Pipeline	–	73.6	86.8	93.4	95.2
PUFS+IntrePED+ASPIRe [28]	Pipeline	–	75.0	85.5	–	–
SCENT [29]	Surpass	–	–	66.1	–	–
SAFE [31]	FRED/ FREDJr	–	61.1	73.3	–	–
Fischer [32]	P64	–	79.6	85.7	–	–
Briganti [33]	p64	60.0	82.0	88.0	–	–
Bhogal [36]	P48	–	75.0	70.0	–	–

This construct disrupts blood flow at the level of the aneurysm neck and induces intra-aneurysmal thrombosis. Only one intra-saccular flow diversion device, the Woven EndoBridge (WEB), is currently commercially available worldwide (Sequent Medical, Aliso Viejo, CA). The WEB device has been extensively evaluated in several high quality, prospective trials (WEB-CAST, WEBCAST-2, US WEB-IT, the French Observatory and CLARYS) [50–56].

The WEB was initially designed to treat wide-neck bifurcation aneurysms arising at the proximal bifurcations, including the internal carotid artery terminus (ICAt), basilar artery (BA), anterior communicating artery (Acom), and middle cerebral artery (MCA). The progressive improvement of the technology (dual-layer to single-layer devices, enhanced visualization, reduction in size of the microcatheter) has led to an expansion of the potential clinical indications to more distal aneurysms (i.e. pericallosal) and sidewall aneurysms (i.e. carotid siphon) in the EU [57, 58].

WEB treatment is associated with an extremely high level of procedural safety, which has been consistently observed in all of the existing prospective trials. In the cumulative population of the 3 GCP studies conducted in Europe (168 patients/169 aneurysms), the rate of any thromboembolic (TE) event was 14.4 %, but TE events with permanent deficit were reported in only 3.0 % of cases [55]. Hemorrhagic complications (intraprocedural rupture or intracranial hemorrhage) were reported in 1.8 % and were all asymptomatic. Finally, the mortality at one month was 0.0 % and the morbidity was 3.0 % [55]. Very similar results were reported in the US WEB-IT trial with one-month mortality at 0.0 % and morbidity at 0.7 % [56].

WEB treatment is also associated with a good efficacy in term of anatomical results. In the cumulative population of the 3 European GCP stu-

dies (which included primarily wide neck bifurcation aneurysms), anatomical results at one year were complete occlusion in 52.9 %, neck remnant in 26.1 %, and aneurysm remnant in 20.9 % [55]. The rate of adequate occlusion (complete occlusion or neck remnant) was 79.1 %. Long-term anatomical results (2 years for the 3 European GCP, 3 years for WEBCAST and WEBCAST-2) were recently published showing the great stability of WEB aneurysm treatment [59, 60].

### Conclusions

The tools for the endovascular management of intracranial aneurysms continue to evolve rapidly. Flow diversion and intrasaccular flow disruption are the most recent innovation in the field.

Flow direction is the endovascular technique that is associated with the highest rate of complete aneurysm occlusion in long-term follow-up with no aneurysm recanalization observed in the long term. If the safety of this technique was at its beginning relatively worse compared to coiling with or without balloon- or stent-assistance, the recent development of new generation flow diverters, the improved skills of the physicians, and the optimization of perioperative medications has conduced to the decrease of complications and improved morbidity and mortality rates. Development of surface-modified flow diverters will potentially enlarged indications for this technique, singularly for ruptured aneurysms.

Intrasaccular flow disruption is associated with a great safety and a good efficacy in comparison to aneurysm coiling for similar aneurysms.

According to the great safety and good efficacy of intrasaccular flow disruption and the great efficacy and good safety of flow diversion, there will very likely be a progressive expansion of the indications for both techniques to the extent that they will ultimately replace standard coiling in an increasing number of cases going forward.

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## ОТ РЕДАКЦИИ: КАКОЕ БУДУЩЕЕ У ЭНДОВАСКУЛЯРНОГО ЛЕЧЕНИЯ ВНУТРИЧЕРЕПНЫХ АНЕВРИЗМ?

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Разрыв внутричерепной аневризмы часто приводит к смерти или инвалидизации пациентов. Поэтому в случае разрыва обязательным и неотложным является раннее лечение аневризмы. Распространенность асимптомных внутричерепных аневризм в популяции продолжает увеличиваться благодаря усовершенствованию инвазивных и неинвазивных технологий нейровизуализации. Учитывая все демографические факторы, сопоставление рисков наличия аневризмы и хирургии, выключение аневризмы является необходимым и положительно влияет на исход лечения у этих пациентов. Эндоваскулярные методы при лечении аневризм головного мозга стали ведущим направлением в течение последних 20 лет и последующие достижения закрепили этот статус еще больше. В настоящее время эндоваскулярный арсенал продолжает стремительно увеличиваться. Нейроинтервенционные операции становятся все более эффективными, повышается их безопасность, совершенствуются методы. Однако использование стандартных эндоваскулярных методов для лечения некоторых типов аневризм может привести к неблагоприятным последствиям. Во-первых, их не всегда можно применить в случае сложных и больших аневризм с большой шейкой. Во-вторых, не во всех случаях можно достичь долговременной радикальности окклюзии аневризм после использования техники ремоделирования и протекционного стентирования. Применение новых устройств расширяет возможности эндоваскулярного лечения. Двумя новыми инновационными методами, которые все чаще используют в эндоваскулярной практике, являются потокоотклонение (Flow Diversion Device) и интрасаккулярные окклюзирующие устройства с потококотклоняющими свойствами (Intrasaccular Flow Diversion Device). Цель этого обзора – всесторонне проанализировать применение этих устройств, выявить ограничения и перспективы. Очевидное



преимущество новых технологий обосновывает их более частое использование, что в будущем позволит в большинстве случаев заменить стандартную технику койлинга. Усовершенствование инструментов для внутрисосудистого доступа, навигации и доставки различных окклюзионных устройств способствует увеличению количества пациентов, у которых используют интервенционные методы, а не микрохирургическое клипирование.

**Ключевые слова:** внутречерепные аневризмы; эндоваскулярное лечение; потокоотклонение; интрасаккулярные окклюзирующие устройства с потококклоняющими свойствами.

## **ВІД РЕДАКЦІЇ: ЯКИМ Є МАЙБУТНЄ ЕНДОВАСКУЛЯРНОГО ЛІКУВАННЯ ВНУТРИШНЬОЧЕРЕПНИХ АНЕВРИЗМ?**

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Розрив внутрішньочерепної аневризми часто призводить до смерті або інвалідизації пацієнтів. Тому в разі розриву обов'язковим і невідкладним є раннє лікування аневризми. Поширеність асимптомних внутрішньочерепних аневризм у популяції продовжує збільшуватися завдяки вдосконаленню інвазивних і неінвазивних технологій нейровізуалізації. З огляду на всі демографічні чинники, зіставлення ризиків наявності аневризми і хірургії, виключення аневризми є необхідним і позитивно впливає на наслідок лікування у цих пацієнтів. Ендоваскулярні методи при лікуванні аневризм головного мозку стали провідним напрямом протягом останніх 20 років і наступні досягнення закріпили цей статус ще більше. Нині ендоваскулярний арсенал продовжує стрімко збільшуватися. Нейроінтервенційні операції стають дедалі ефективнішими, підвищується їх безпечність, удосконалюються методи. Однак використання стандартних ендоваскулярних методів для лікування деяких типів аневризм може призвести до несприятливих наслідків. По-перше, їх не завжди можна застосувати в разі складних і великих аневризм з великою шийкою. По-друге, не в усіх випадках можна досягти тривалої радикальності оклюзії аневризм після використання техніки ремоделювання і протекційного стентування. Застосування нових пристроїв розширює можливості ендоваскулярного лікування. Двома новими інноваційними методами, які дедалі частіше використовують в ендоваскулярній практиці, є потіскерування (Flow Diversion Device) та інтрасаккулярні оклюзійні пристрої з потіскерувальними властивостями (Intrasaccular Flow Diversion Device). Мета цього огляду – всебічно проаналізувати застосування цих пристроїв, виявити обмеження і перспективи. Очевидна перевага нових технологій обґрунтовує їх частіше використання, що в майбутньому дасть змогу в більшості випадків замінити стандартну техніку койлінга. Вдосконалення інструментів для внутрішньосудинного доступу, навігації та доставки різних оклюзійних пристроїв сприяє збільшенню кількості пацієнтів, у яких використовують інтервенційні методи, а не мікрохірургічне кліпування.

**Ключові слова:** внутрішньочерепні аневризми; ендоваскулярне лікування; потіскерування; інтрасаккулярні оклюзійні пристрої з потіскерувальними властивостями.