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Flow Diversion for Intracranial Aneurysms A Review

Pietro I. D'Urso, MD; Giuseppe Lanzino, MD; Harry J. Cloft, MD, PhD; David F. Kallmes, MD

Abstract—The introduction of flow diverters for treatment of intracranial aneurysms represents a major paradigm shift in the treatment of these lesions. The theoretical hallmark of flow diverters is the treatment of the diseased segment harboring the aneurysm instead of treating the aneurysm itself. Flow diverters are designed to induce disruption of flow near the aneurysm neck while preserving flow into parent vessel and adjacent branches. After flow diversion, intra-aneurysmal thrombosis occurs, followed by shrinkage of the aneurysmal sac as the thrombus organizes and retracts. Preliminary clinical series document effective treatment of wide-neck and/or large and giant aneurysms with acceptable complication rates. However, several questions remain unanswered related to the incidence and mechanisms of aneurysm rupture after treatment with flow diverters, fate of small perforating vessels, and long-term patency rates. (*Stroke*. 2011;42:2363-2368.)

Key Words: flow disruption ■ flow diverters ■ intracranial aneurysms

With the approval of detachable coils in 1995, endovascular treatment of intracranial aneurysms has become an alternative to surgical clip ligation. Despite the introduction of “modified” coils and advanced techniques such as stent-assisted and balloon-assisted coiling, coil embolization has major limitations because of inability to completely and permanently occlude all aneurysms. The risks of incomplete treatment and recurrence are higher in complex large and giant aneurysms. As stents were being developed for intracranial use,¹⁻⁴ it was hypothesized that stents could be utilized to divert flow “away” from the aneurysm “back” into the parent vessel, and the concept of “endovascular flow diversion” was proposed. Early in vitro and in vivo studies showed this concept to be valid, but clinical application was limited because of high porosity of first-generation intracranial stents. With technological improvements, intracranial flow diverters have become available for endoluminal parent vessel reconstruction and early clinical experiences have been encouraging.

Flow diverters induce disruption of flow near the aneurysm neck, inducing thrombosis into the aneurysmal sac while preserving physiological flow in the parent vessel and adjacent branches (Figures 1 and 2). The development of flow diverters represents a classical example of technological evolution from a theoretical concept based on in vitro models, confirmed by experimental animal studies and eventually applied in clinical practice. In this review, we trace the development of flow diverters and summarize early clinical experiences with particular emphasis on complications encountered.

Flow Diverters: Evolution of a Concept

The concept of flow diversion comes from observations of intra-aneurysmal flow patterns in in vitro models of stented intracranial aneurysms using laser-induced fluorescence and particle image velocimetry. These studies suggested that placement of a stent across the aneurysm alters intra-aneurysmal flow patterns redirecting flow away from the aneurysm and back into the parent artery.⁵⁻⁸ Experimental studies paralleled in vitro studies and confirmed the validity of the theoretical concepts discussed.⁹⁻¹¹ Wakhloo et al¹⁰ demonstrated in a canine aneurysm model the feasibility of placing first-generation stents across experimental aneurysms in small arteries with resultant aneurysm occlusion, long-term stent patency, and absence of thromboembolic complications. Furthermore, they showed that a neointimal layer grew on the inner surface of stent with asymmetrical pattern of growth, probably reflecting local differences in wall shear stress.¹² Early clinical experiences demonstrated the ability of newly designed stents to navigate the tortuosity of the intracranial circulation and paved the way to a “new era” in the treatment of intracranial aneurysms.³ However, because of the high porosity of early available devices, the flow-diverting effect was limited and stents were used mostly as a scaffold to support endovascular coils in the treatment of wide-neck aneurysms.^{1,2}

Further theoretical in vitro studies suggested that stent porosity and local hydrodynamic conditions play an important role in uncoupling flow between the parent vessel and the aneurysmal sac.⁵⁻⁸ Porosity is the most common metrics used to quantify the amount of “coverage” with the metallic

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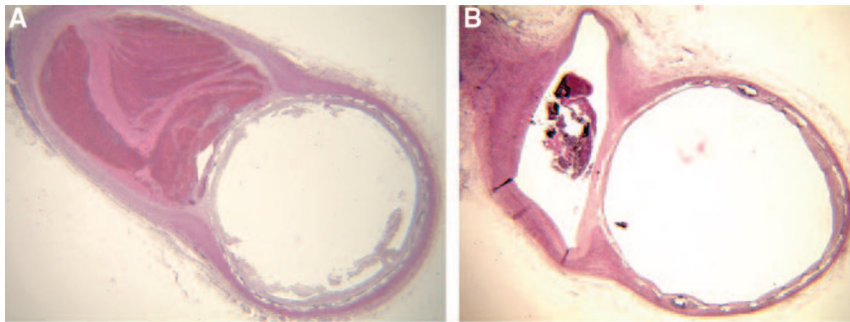


Figure 1. Photomicrographs of experimental aneurysms 1 (A) and 6 (B) months after flow diverter deployment. A, There is poorly organized thrombus throughout the dome (hematoxylin and eosin, original magnification $\times 20$). B, Progressive collagenization of intraaneurysmal clot (hematoxylin and eosin, original magnification $\times 20$). Reprinted with permission from Kallmes et al. *Stroke*. 2007;38(8):2346–2352.

implant in a stent; it is defined as the area percentage of metal over the neck. Another important metric is the “pore density,” defined as the number of pores per area. Lower porosity and increased pore density are design goals for devices aimed at occluding aneurysms. Using low-porosity stents, a reduction up to 90% of the original flow inside the aneurysmal sac was observed.^{6,13,14} Computational fluid dynamics studies confirmed the efficacy of low-porosity stents in pursuing intraaneurysmal flow disruption.^{13,15} These studies also clarified the role of parent vessel geometry, demonstrating that flow reduction is more significant in side wall aneurysms (in which shear-driven flow is dominant) than in aneurysms located on a curve of the parent vessel (in which inertia-driven flow is prevalent).^{16,17}

Animal studies have also confirmed the important role of device porosity in promoting complete aneurysm thrombosis.¹⁸ The concept of flow diversion was illustrated in some of these studies by catheter angiography showing intra-aneu-

rysmal flow rearrangements occurring after stenting.^{18–20} Kallmes et al^{21,22} in a series of experiments in rabbits showed a high rate of complete or near-complete occlusion with preservation of the patency of the parent vessel and side branches and no evidence of distal emboli (Figure 3A–C). Histopathologic analysis of the explants showed a neointimal layer covering the stent struts and the aneurysm neck while preserving the ostia of normal branches (Figure 3D). Long-term patency of these branches was also demonstrated.^{21,22} As the intraaneurysmal thrombus organizes and eventually retracts, progressive shrinkage of the aneurysm sac is observed. This effect was later confirmed by clinical experiences (Figure 4).

One of the major concerns related to the use of flow diverters is the potential occlusion of perforating arteries or other side branches, with secondary ischemic complications. A series of *in vitro* studies on models reproducing conditions in which a flow diverter is placed across aneurysmal neck and

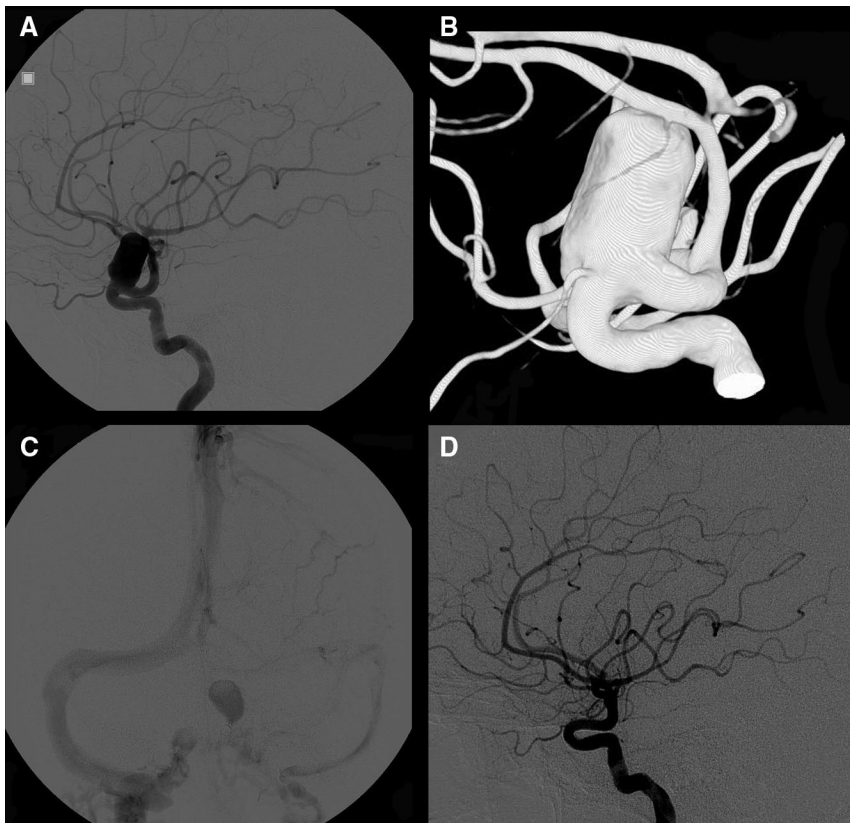


Figure 2. Arterial phase angiograms obtained in lateral projection (A) and three-dimensional rotational angiography image (B) showing a giant left carotid-ophthalmic aneurysm. C, Venous phase angiogram obtained immediately after flow diverter deployment showing contrast medium stasis into the aneurysmal sac. D, Arterial phase angiogram performed 6 months after the treatment showing complete occlusion of the aneurysm.

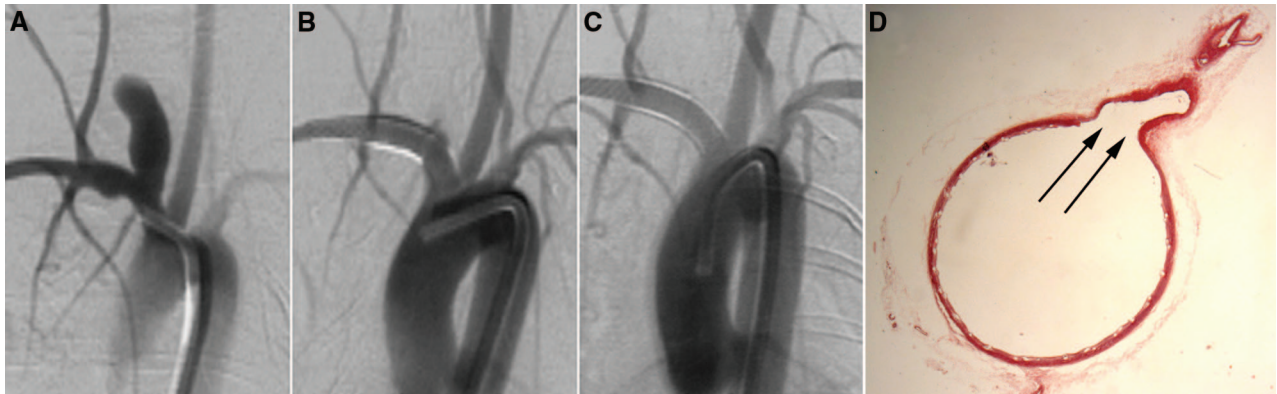


Figure 3. **A**, Angiogram obtained before device implantation showing a subclavian aneurysm in a rabbit model. **B**, Immediately after placement of a flow diverter there is significant modification of the intraaneurysmal flow dynamics. **C**, Follow-up angiography after 6 months demonstrates complete occlusion of the aneurysm. **D**, Photomicrograph of the parent vessel 6 months after implantation of the flow diverter showing patency of the ostium of a collateral branch (arrows) (hematoxylin and eosin, original magnification $\times 12$).

collateral branches has demonstrated that flow through perforators is usually preserved and that $>90\%$ coverage of the perforator inlet area resulted in a flow reduction into the simulated perforating vessel of $<10\%$.^{23,24} These results are not unexpected because flow through a perforator, whether “jailed” by a porous medium, is driven by a pressure gradient. These theoretical concepts developed in highly sophisticated in vitro models were confirmed by the animal studies previously mentioned.^{21,22} Based on these theoretical and animal studies, newer-generation flow diverters were designed with adequate low porosity and this opened the groundwork for the modern clinical experience.

Flow Diverters: Recent Clinical Studies

Results of treatment with flow diverters have been reported in a total of 242 patients in 10 case series^{25–34} and 9 case reports.^{35–43} Only 5 studies were prospective,^{26,30–33} and 4 of them included patients enrolled in multicenter studies/registries.^{26,30,32,33} Table 1 summarizes the results of the 5 prospective studies.

Most reported aneurysms treated in prospective series with flow diverters are unruptured (86%–100%) and located in the anterior circulation (71%–95%). Treated aneurysms included small and large and giant aneurysms, and selection varied among series.^{30–32} However, the majority of aneurysms were

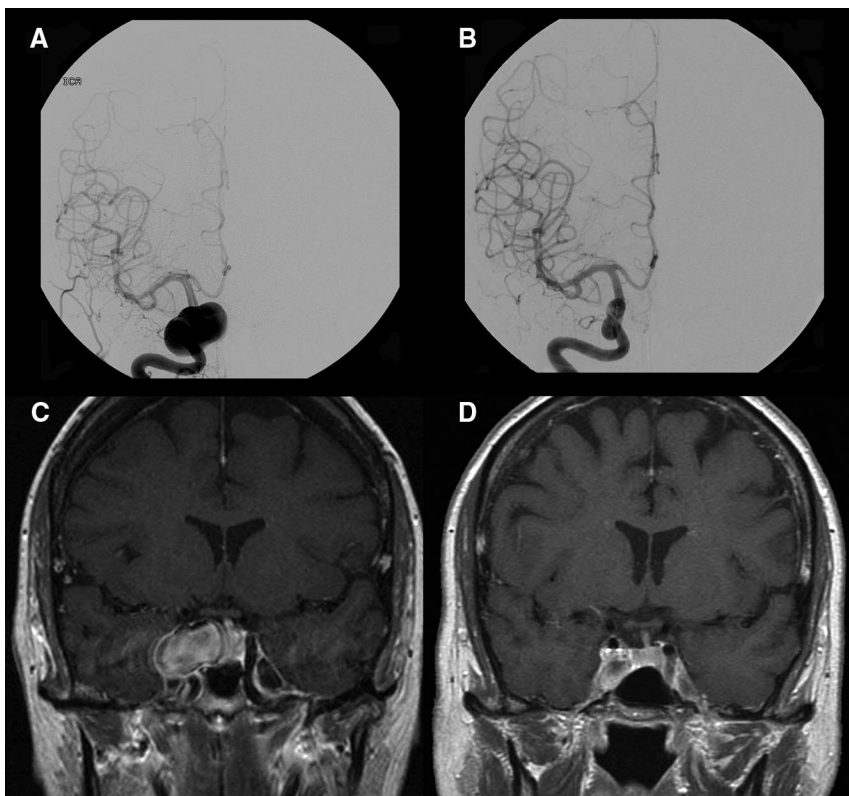


Figure 4. **A**, Anterior-posterior projection of arterial phase angiogram showing a giant right internal carotid artery aneurysm in the cavernous segment. **B**, Angiogram obtained 1 year after flow diverter deployment showing complete aneurysm occlusion. **C**, Postcontrast coronal T1-weighted magnetic resonance image demonstrating the compression of the aneurysm on the sellar structures. **D**, Postcontrast coronal T1-weighted magnetic resonance image obtained 10 months after treatment showing significant reduction of aneurysmal sac and resolution of the compression on the sellar structures.

Table 1. Published Prospective Studies of Flow Diversion for Intracranial Aneurysms

Author and Year	No. of Patients	No. of Aneurysms	Recurrence (%)	Location		Size			Device	Occlusion Rate (Complete)		
				AC (%)	PC (%)	S (%)	L (%)	G (%)		3 mo (%)	6 mo (%)	12 mo (%)
Lylyk et al, 2009	53	63	37	87	13	52	35	13	PED	56	93	95
Byrne et al, 2010	70	70	N/A	71	29	26	53	21	SFD	N/A	49	N/A
Lubicz et al, 2010	29	34	29	85	15	53	35	12	SFD	69		N/A
Szikora et al, 2010	18	19	5	95	5	26	53	21	PED	N/A	95	N/A
Nelson et al, 2011	31	31	39	94	6	64.5	29	6.5	PED	N/A	93	N/A

Six patients of the Lylyk et al series and 9 patients of the Szikora et al series have been included in the PITA trial (Nelson et al 2011).

AC indicates anterior circulation; DN, de novo; G, giant; L, large; N/A, not available; PC, posterior circulation; PED, pipeline embolization device; R, ruptured; REC, recurrence; S, small; SFD, SILK flow diverter; UR, unruptured.

wide-neck and many had a fusiform configuration or were recurrent aneurysms that had failed other treatments.

Preclinical technical refinement of the devices resulted in a high incidence (>90%) of successful deployment. As expected for a new device, technical complications were not uncommon in these earlier series. These are related to a combination of a steep learning curve and to technical limitations of the devices themselves. Technical complications included inadequate device apposition against the parent artery wall, a factor that may predispose to device thrombosis or late stenosis, and proximal migration of the device with subsequent “diversion” of flow within the aneurysm with resultant delayed rupture.³⁰ Future improvements of currently available devices and increased operator experience are likely to obviate some of these earlier issues.

Immediate angiographic exclusion of the aneurysm at the end of the original procedure is observed only in a minority of patients (8%–21%).^{26,31,33} One of the main advantages of flow diverters over more traditional endovascular techniques is the ability to promote total aneurysm occlusion, with rates of complete occlusion ranging from 69% at 6 months³⁰ to >90% at 1 year,³¹ even in large and giant aneurysms.

Periprocedural (within the first month) permanent morbidity and mortality have been reported in 1.4% to 7.6% and 4% to 8%, respectively (Table 2). Most common causes of permanent morbidity and mortality are periprocedural distal thromboembolic events, parent artery occlusion, wire/catheter perforations, and aneurysm rupture. Periprocedural adherence to strict pharmacological protocol is important to decrease the likelihood of device thrombosis.³³ Patients are pretreated with aspirin and clopidogrel and this regimen is usually maintained for 3 to 6 months after the procedure. After 3 to 6 months, aspirin alone seems to be sufficient.

Table 2. Mortality, Early and Late Complication Rate, and Delayed Rupture

Author and Year	Early Complications (%)	Late Complications (%)	Mortality (%)	Rupture Rate (%)
Lylyk et al, 2009	None	None	None	None
Byrne et al, 2010	1.4	4	8	2
Lubicz et al, 2010	7.6	7.6	4	4 (1/26)
Szikora et al, 2010	5.5	None	5.5	None
Nelson et al, 2011	7	None	None	None

Placing a device with high surface area coverage poses problems regarding potential occlusion of side branches. The majority of clinical cases reported involved the paraclinoid carotid artery, and immediate or delayed ophthalmic artery occlusion has been only rarely observed,³³ even when the artery is covered with multiple devices. Critical side branches such as the anterior choroidal, the posterior communicating, the anterior-inferior cerebellar artery, and the superior cerebellar artery have been reported to stay open after coverage with flow diverters, although larger numbers of patients are required before more definitive conclusions can be made. Furthermore, uncertainty exists about the fate of very small perforator branches covered with flow diverters.⁴⁴ Van Rooji et al,⁴³ after telescoping 2 pipeline devices, observed perforator occlusion secondary to unintentional metal coverage of tiny branches of the anterior cerebral artery with poor functional outcome.

A major concern with flow diverters is their inability to immediately occlude the aneurysm with the risk of aneurysm rupture during the “latency” period. A few cases of aneurysm rupture have been reported and raised concerns about the safety of these devices. In the prospective series reported, the incidence of hemorrhage after flow diversion was 2% (5 out of 242 aneurysms treated). This risk should be weighed against the high risk of rupture of giant and large aneurysms.⁴⁵ Moreover, some of these aneurysms are so “unstable” that rupture even has been reported after parent artery sacrifice with or without bypass.⁴⁶ It should be kept in mind that results of the reported studies refer to aneurysms treated with the 2 first commercially available flow diverters. New generation devices are being evaluated in ongoing clinical trials, and preliminary results have not shown cases of aneurysm ruptures.⁴⁷

When aneurysm rupture occurs after flow diversion, it is usually catastrophic and resulted in death of 4 out of 5 patients (Table 2). Several hypotheses have been advanced to explain these ruptures: proximal migration of the flow diverter with redirection of the jet inside the aneurysm sac instead of away from the aneurysm; inflammation related to the intra-aneurysmal clot burden with subsequent rupture of aneurysm wall;⁴⁸ and redirection of intra-aneurysmal flow into an unstable aneurysm. Close monitoring of this phenomenon is of paramount importance to assess the real safety of these promising devices.^{49,50} It remains questionable whether the addition of endosaccular coils is helpful in mitigating the

risk of aneurysmal rupture during the latency period; nonetheless, this practice is being adopted at many centers.

Late complications have been observed in 6% to 14% of patients (Table 2). Late complications are usually related to device occlusion, although exceptionally delayed hemorrhages have been observed up to 5 months after flow diversion.⁴⁸ Device occlusion with resultant death has been reported as late as 2 years after flow diversion in a patient with a vertebrobasilar aneurysm.³⁶ No long-term data exist regarding patency of the parent vessel, although midterm patency rates have been satisfactory and the incidence of device stenosis, although reported to be as high as 30% with 1 device, seems to be low with other devices available and is usually of no clinical significance.

Conclusions

Flow diverters represent a major paradigm shift in the endovascular treatment of intracranial aneurysms. These devices allow for reconstruction of the diseased segment by providing a scaffold for neointima formation while diverting flow away from the aneurysm into the parent vessel. This results in aneurysm thrombosis followed by shrinkage of the aneurysm as the clot organizes and retracts. After in vitro and in vivo extensive studies, early clinical experiences have been encouraging, with high rates of complete aneurysm occlusion. However, concerns exist regarding complications of these devices primarily connected to early aneurysm rupture during the latency period and thromboembolic complications. Moreover, questions persist regarding the fate of small critical perforators after coverage with flow diverters. Careful analysis and follow-up of treated patient are required to answer some of these pending issues.

Disclosures

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