Review: Flow Diversion for the Treatment of Middle Cerebral Artery Aneurysms

Übersichtsarbeit: Flow Diversion zur Behandlung von Aneurysmen der A. cerebri media

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ABSTRACT

Background The invention of flow diverting stents (FDS) is a novel milestone in the field of endovascular aneurysm therapy, promoting physiological healing of the vessel segment contrary to prior deconstructive treatment strategies, such as coiling. The effects of FDS are based on changes in flow patterns, segmental wall stabilization, and the growth of a neointima. Although flow diversion is already well established for cerebral aneurysms in proximal segments, peripheral locations remain challenging. Especially the middle cerebral artery (MCA) with its predominance of non-collateralized perforators and functional end arteries that supply the eloquent areas of the brain is of major concern.

Methods The literature was reviewed for flow diversion of the MCA and antiplatelet therapy.

Results and Conclusion Resulting from the special anatomical characteristics of the MCA, FDS implantation in this territory is completely different from the proximal vessel segments. Still, flow diversion represents an effective endovascular strategy, especially in otherwise non-accessible or sufficiently treatable lesions. However, the risk of ischemic adverse events might be increased. Special attention to the individual decision regarding device selection, antiplatelet regimen, and exact definition of the proximal and distal landing zone considering the jailed side branches is essential for a good angiographic and clinical outcome.

Key Points

- MCA aneurysms can be sufficiently treated by FDS.
- The anatomic and hemodynamic characteristics of the MCA result in an increased risk of thromboembolism.
- Individual device selection and antiplatelet regimen are essential for treatment success.

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ZUSAMMENFASSUNG

Hintergrund Die Einführung flussmodulierender Stents ist als neuer Meilenstein für die zerebrale Aneurysmatherapie zu betrachten. Anders als beispielsweise bei der Coil-Okklusion wird über die Veränderung der lokalen Hämodynamik, die Stabilisierung der erkrankten Gefäßwand und die Bildung einer neuen Intima der Aneurysmaverschluss schrittweise erzielt. Obgleich flussmodulierende Stents bereits für die Behandlung von proximalen hirnversorgenden Gefäßabschnitten etabliert sind, stellen periphere Segmente distal des Circulus Willisii eine Herausforderung dar. Insbesondere die Arteria cerebri media, welche zahlreiche nicht kollateralisierbare Perforatoren und für eloquente Hirnareale essenzielle Endarterien trägt, nimmt in diesem Zusammenhang eine besondere Stellung ein.

Methode Es erfolgte die Literaturrecherche zu flussmodulierenden Stents für die Aneurysmatherapie der Arteria cerebri media mit besonderem Augenmerk auf der Thrombozytenaggregationshemmung in diesem Kontext.

Ergebnisse und Schlussfolgerung Resultierend aus den anatomischen Besonderheiten der Arteria cerebri media unterscheidet sich die Implantation hämodynamisch aktiver Implantate wesentlich vom Einsatz in weiter proximal gelegenen Gefäßsegmenten. Trotz dessen stellt diese Therapieoption einen effektiven Behandlungsansatz für anderweitig nicht oder lediglich schwer behandelbare Aneurysmen in diesem Gefäßterritorium dar. Jedoch ist das Thromboembolierisiko vergleichsweise hoch. Besonderer Beachtung bedarf die Implantatarchitektur- und Oberfläche, die notwendige Thrombozytenaggregationshemmung und die genaue Definition der proximalen und distalen Landezone mit Verweis auf überlegte Seitenäste, um ein gutes hämodynamisches Ergebnis und klinisches Outcome zu ermöglichen.

Kernaussagen

- Aneurysmen der A. cerebri media können suffizient mittels flussmodulierender Stents behandelt werden.
- Die anatomischen und hämodynamischen Besonderheiten der Arteria cerebri media bedingen ein erhöhtes Ischämierisiko.
- Die sorgfältige Implantatauswahl und angepasste Thrombozytenaggregationshemmung sind wesentlich für den Behandlungserfolg.

The concept and basic mechanisms of flow diversion

The treatment of cerebral aneurysms has rapidly evolved in the past decades. From primary microsurgery, as pioneered by Yasargil [1, 2], a significant shift towards endovascular therapy has been seen.

The success of the Guglielmi detachable coils in the 1990s, which made it possible for the first time to occlude a good proportion of saccular aneurysms without craniotomy, prompted the further development of numerous additional endovascular tools. Among those were self-expanding stents, which are used to bridge the neck of unfavorably broad-based aneurysms in order to make them amendable for coiling without compromise to the parent vessel. Growing clinical experience suggested that such stents not only protect the parent vessel from coil dislocation ex aneurysm, but also influence the hemodynamic situation in the aneurysm-harboring vessel in a beneficial way. Increased metal surface coverage due to dual layer or triple layer stent constructs showed enhanced flow modifying properties [3, 4], and braided stents, with even greater surface coverage than combined laser-cut stents, already demonstrated a moderate flow redirecting effect [5, 6]. Further developing this concept, densely braided flow diverting stents were introduced and became one of the cornerstones of modern endovascular therapy for cerebral aneurysms.

The philosophy of flow diversion (FD) is to mechanically stabilize a weak brain vessel segment, promote the hemostaseological occlusion of the aneurysm and start the formation of a proper sealing vessel wall along the interface between the parent artery and the aneurysm, instead of directly occluding the aneurysm with a foreign material implant. The degree and speed of endothelialization of a flow diverter stent depends on sufficient wall apposition and consequently the ingrowth of endothelial cells from the adjacent parent artery [7].

The technique does not require the direct microcatheterization of the aneurysm. Being a delicate maneuver mandatory for coiling and technically similar endosaccular filling procedures, direct probation of the aneurysm harbors the risk of procedural rupture in up to 9% of procedures with a potentially fatal outcome in almost two thirds of those cases [8]. This consideration is even more important for the treatment of pseudoaneurysms that result from dissections of intradural arteries, which are exceptionally fragile lesions with an inherently higher risk for rupture and unfavorable outcome [9]. In addition, as revealed by histological studies, the vessel remodeling effect based on flow diversion is superior to aneurysm coiling in regards to residual aneurysm perfusion and aneurysm relapse [10]. However, in contrast to prior established therapies such as coiling and clipping, the effects of FD manifest less suddenly and the exact mechanisms associated with the apparent angiographic changes until complete aneurysm occlusion still remain incompletely understood [11].

Aneurysm occlusion is commonly achieved over time and is the consequence of different interacting processes, including changed flow patterns, aneurysmal thrombosis, and the formation of a neointima. Permanent aneurysm occlusion is the consequence of a complete layer of neointima covering the flow diverter mesh [7, 11].

Immediately after implantation, changes in hemodynamics can be observed and are visible on digital subtraction angiography. On the one hand, redirection of blood flow along the parent artery, as the result of the circumferentially implanted mesh, causes an immediate drop in intra-aneurysmal pressure. Simultaneously, the flow pattern itself, which has a main impact on aneurysm growth and rupture, undergoes pivotal changes in the sense that its risk profile is downgraded [12]. For example, early and prolonged intra-aneurysmal stagnation were determined as reliable predictors for occlusion [13, 14]. In detail, Mut et al. determined that decreased flow velocity, decreased shear rates, and laminar flow immediately after FD significantly promote aneurysm occlusion [15]. Reduction of intraaneurysmal flow furthermore facilitates intra-aneurysmal coagulation and a decrease in size up to occlusion [16].

At the same time, however, sudden aneurysm thrombosis was described as potential risk factor for delayed, post-procedural aneurysm rupture as a rare but severe complication. Kulcsár et al. proposed intramural inflammation due to intra-aneurysmal thrombus formation as a main factor responsible for aneurysm wall degradation, and thus, a probable cause for delayed rupture [17]. As a side note, the aneurysms of the study investigated by Kulcsár and colleagues had high risk profiles. They were either large in size, clinically symptomatic, present in study subjects with explicit vascular risk factors, or a combination of these.

The controversies regarding thrombus formation as a conceivable cause for either occlusion or rupture at the same time might be explained by considering the histology of thrombi. On the one hand, the luminal thrombus site is acting pro-coagulatory, encouraging platelet activation and aggregation. The intermediate and abluminal thrombus formations, in contrast, are thought to promote fibrinolysis and thus may cause inflammatory degradation of the aneurysm wall [18]. As a consequence, the risk of aneurysm rupture may potentially increase during the early process of thrombus formation [19].

Furthermore, thrombosis and inflammation are inherently linked mechanisms. Among other mechanisms, activated platelets, for example, regulate the recruitment and activation of neutrophils [20] resulting in the formation of neutrophil extracellular traps [21], which have been tied to aneurysm rupture [22].

Flow diversion and antiplatelet therapy

A main limitation of flow diversion is the need for dual antiplatelet therapy (DAPT), in order to prevent distal thromboembolism from the treated segment or its thrombotic occlusion [23]. The great surface area of flow diverter stents results in significant thrombogenicity in vivo and additionally triggers inflammatory responses following their implantation, until neo-endothelialization is finished. For example, plasma levels of nucleotides are increased after flow diverter implantation, mediating platelet adhesion, and aggregation [24].

To date, the administration of dual anti-aggregation combining COX- and P2Y12-inhibitors is the established regimen aiming to decrease the risk of thromboembolic events. Initial multicentric flow diverter studies were emphasizing the administration of ASA and clopidogrel. The Pipeline for Uncoilable or Failed Aneurysms trial as one of the first studies used dual anti-platelet medication, comprising ASA 325 mg and 75 mg Clopidogrel daily for at least 3 to 6 months [25].

Ischemic complications, however, may still occur as a result of clopidogrel hypo- or nonresponse, which may affect up to 67 % of patients [26, 27]. Platelet testing should, therefore, consequently be considered in order to identify and address inadequate response, but actually has not been routinely added to the clinical standard [28].

The variability of individual clopidogrel responses may turn the focus to other anti-platelet agents becoming the standard of care. Prasugrel and ticagrelor are considered more potent inhibitors of platelet activation and aggregation. Both act as P2Y12-inhibitors, comparable to clopidogrel, but differ with regard to their pharmacokinetics. Whereas clopidogrel and prasugrel are prodrugs, irreversibly binding to the ADP-receptor, ticagrelor is an active metabolite with a reversible effect. The individual properties of those drugs need careful consideration in the context of neurovascular stenting and comorbidities.

As an exemple, subacute ischemic stroke poses a contraindication for prasugrel and the dose requires adaption to the individual body weight. Ticagrelor necessitates a high level of pharmacovigilance and patient compliance, as its effect is reversible and the drug has a very short half-life period, thus requiring consistent administration every 12 hours.

Recent cardiological studies comparing the abovementioned P2Y12 inhibitors conclude that ticagrelor and prasugrel are superior to clopidogrel [29]. Whether this is applicable for neurovascular stenting remains to be elucidated.

Advancements in flow diversion over the past decade

In recent years, general interest in endovascular techniques using flow diverting stents (FDS) has rapidly increased. Consequently, the major issues and pitfalls of the method (sizes, device delivery, and hemocompatibility) were addressed in order to enhance safety and feasibility and furthermore to expand the indications.

The Pipeline Embolization Device (PED, Medtronic, Dublin, Ireland) was the first established FDS entering the European market in 2008. However, it was only approved for the treatment of unruptured anterior circulation aneurysms arising from the petrous to the clinoid segment of the internal carotid artery. The Pipeline for Failed or Uncoilable Aneurysms (PUFS) trial was a multicentric clinical study reporting complete aneurysm occlusion of nearly 87 % after one year and a risk of treatment-related major adverse events of less than 6 % [25]. These results were also confirmed by the Aneurysm Study of Pipeline in an Observational Registry (ASPIRe) trial in which occlusion rates of 75 % were observed eight months post-intervention and morbidity and mortality of 8.4 % were seen [30]. Comparable devices, such as the Derivo (Acandis, Pforzheim, Germany), the Flow Redirection Endoluminal Device (FRED, MicroVention, California, USA), and the SILK flow diverter (Balt, Montmorency, France) were soon introduced and expanded the field of available devices. Although the indications for implantation were rapidly expanding after the introduction of flow diversion, the clinical application remained limited to the proximal segments of the circle of Willis for quite some time. This limitation had mostly technical reasons. The microcatheters used for deployment of first-generation flow diverter stents had to have a large caliber resulting in significant stiffness, thereby impeding access to smaller and more tortuous peripheral intracranial vessel segments.

Aside from that, the peripheral cerebral hemodynamic situation is distinctly different from the situation in the segments of the circle of Willis. For example, collateralization of jailed branches via the anterior and posterior communicating arteries can compensate for altered perfusion after flow diverter implantation in the circle of Willis [31], whereas segments distal to the circle represent end arteries that cannot be collateralized in a comparable manner. Furthermore, small perforator branches essential for the perfusion of eloquent regions are at risk for occlusion after being overstented with a flow diverter stent [32].

Nevertheless, the use of FDS for the treatment of distal cerebral aneurysms has gained significant momentum over the past years. Initially, the established devices – like the PED – were implanted in peripheral segments in case the anatomy allowed probation with the required endovascular armamentarium. Initial studies showed promising results: Atallah et al. compared complication rates and the angiographic outcomes in proximal versus distal segments using the PED [33]. In their study, no statistically

significant differences were observed between the two groups, confirming the safety and reliability even of off-label use in peripheral branches. Notably, the rate of complete aneurysm occlusion was 78 % in distal cerebral aneurysms (versus 68 % in proximal locations) without a statistically increased risk of thromboembolic adverse events (6 % versus 8.6 %). However, within this single-center study, the great majority of treated aneurysms were proximal ICA aneurysms (n = 414), compared with only a small minority of 23 distal aneurysms. These results were further confirmed by the actual literature focusing on flow diversion in small caliber cerebral vessels in comparison to larger parent arteries, further validating sufficient occlusion rates without an increased risk for adverse events [31, 34, 35, 36, 37, 38].

Accompanying the learning curve of flow diversion, smaller devices and application systems were soon developed. Among these, the p48MW (phenox, Bochum, Germany) and the Silk Vista Baby (Balt Extrusion, Montmorency, France) were the forerunners with adequate results [39, 40]. Most importantly, the required microcatheters for the implantation of this new generation of devices had smaller calibers with a diameter of 0.021 inches or even less, consequently affording less traumatic probation and enhanced access to tortuous anatomies.

A further milestone in FDS development was the introduction of anti-thrombotic coatings for flow diverter stents [41, 42, 43]. As discussed above, DAPT is generally required for 3 to 12 months after FDS implantation in order to prevent ischemic complications at the cost of increasing the risk for hemorrhage. The use of anti-thrombogenic coatings has shown very promising results and can allow the reduction of aggressive anti-platelet medication in selected cases, even for acutely ruptured aneurysms [44]. In this regard, studies on flow diversion using only a single anti-aggregant have shown interesting and promising results, with prasugrel showing a very good safety profile with a 3.9 % thromboembolic complication rate [45], in contrast to ASA, which resulted in a thromboembolic complication rate of approximately 20 % [46]. Using appropriate medication regimens, recent reports observed comparable outcomes for single anti-platelet therapy or dual anti-platelet therapy after FD [47, 48, 49]. However, the use is still off-label.

The conquest of more distal target segments: Anatomical characteristics of the MCA requiring special attention

Despite recent and ongoing optimization of flow diverter stents for the treatment of distal cerebral vessels, the anatomical peculiarities and functional significance of the middle cerebral artery (MCA) require specific attention. Language and speech are located in the MCA territory. In right-handed individuals, areas in the left frontal and temporal lobes are responsible for producing and understanding language. Usually, the superior M2 division supplies the lateral inferior frontal lobe, which contains the Broca area, and the inferior division supplies the lateral superior temporal lobe, which contains the Wernicke area as well as Heschl's gyrus [50]. The supply of most of the motor areas is also provided by branches of the MCA, most importantly the Rolandic artery. Jailing of one of those branches with a flow diverter stent may result in impeded perfusion of the respective, highly eloquent area and manifest with aphasia, dysphasia, hemiparesis, or visual field defects [51, 52]. Those symptoms can be transient in nature or manifest as permanent disabilities, even months after treatment [53].

As a consequence, considering the segmental anatomy of the MCA and its functional importance is paramount for good treatment outcomes. The commonly accepted anatomical concept of the MCA is related to adjacent structures and differentiates the M1 or sphenoidal segment, the M2 or insular segment, the M3 or opercular segment, and the M4 or cortical segment [54]. The horizontally oriented M1 segment mainly divides into a bifurcation in two thirds of cases or trifurcates in up to one third. However, it may also separate into four or more trunks prior to the genu of the MCA – the anatomical transition zone to the M2 segment [55].

Unfortunately, the exact definition of the MCA segments is inconsistent, which complicates the clinical routine and the comparability of scientific studies. With distinct interindividual variation, the trunks can be equal in diameter, or present with one dominant branch. The MCA can bifurcate, trifurcate, or quadrifurcate in healthy individuals.

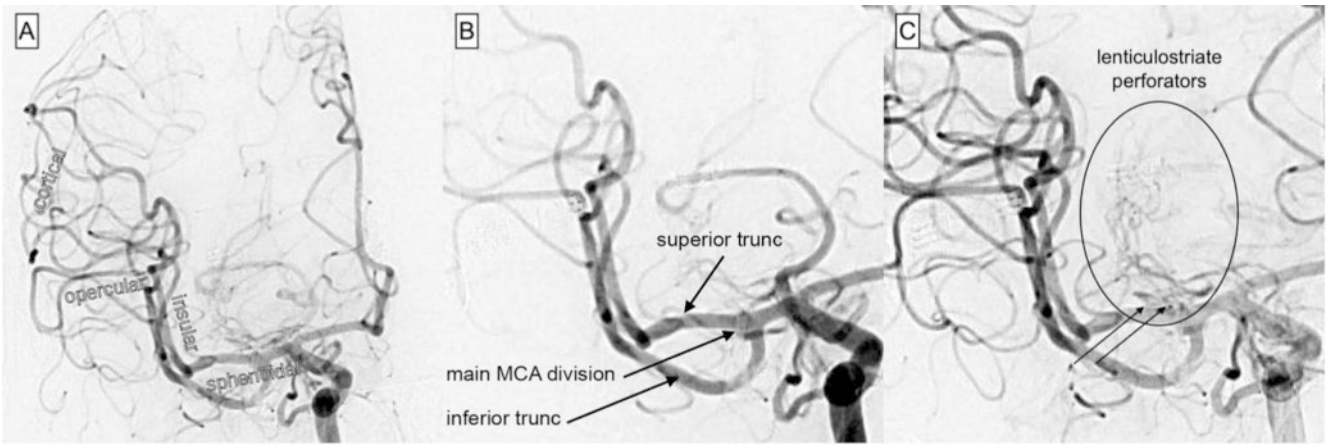
▶ **Fig. 1** visualizes anatomical key features of the middle cerebral artery.

The inequality of the branches has an impact on flow patterns and has been tied to an increased risk of aneurysm formation. Also, the angle of the MCA bifurcation has been reported to be of key importance in this regard [56, 57, 58, 59]. Resulting from the anatomical constitution of the bifurcation segments of the MCA, wall shear stress is comparatively high, which impairs the elasticity of the vessel wall, specifically causing a continuous loss of smooth muscle cells at the M1 division, resulting in endothelial damage at the same time. The increased hemodynamic stress can trigger the development of cerebral aneurysms. Hence, bifurcation segments are more prone to the development and growth of aneurysms [56, 60, 61].

The M1 division is a frequent location for aneurysm formation and may require flow diversion in the acute or elective setting when insufficiently accessible for neurosurgery and not amendable for coiling [62, 63]. Besides its accessibility, the presence of lenticulostriate perforators, representing end arteries, complicates treatment of the M1 segment, as over-stenting them may result in strategically significant infarction [55].

As an example, ▶ **Fig. 2** shows an example for flow diversion for the treatment of an M1 aneurysm.

Resulting from the special characteristics of involved bifurcation vessels, MCA bifurcation aneurysms often present with a wide neck and thus are not well suited for sufficient coil occlusion. Studies reporting the efficacy of endovascular coiling in MCA bifurcation aneurysms present highly varied results with rates of insufficient occlusion or recurrence at follow-up ranging from 6 % to 35 % [64, 65, 66]. As a result of the anatomic burden, the aneurysm neck cannot be completely secured, the aneurysm is more prone to relapse or coils may protrude into the parent artery. Assisted strategies for coiling using either stents or balloons were invented but are not yet routinely integrated into the clinical setting [67]. Although the angiographic outcome might be improved, stent or coil assistance increases the risk of peri-interventional adverse events [64].



▶ **Fig. 1** gives an overview of the anatomical key points of the middle cerebral artery. The left image shows the segments of the MCA (**A**). The following images detail the branching pattern: (**B**) shows a co-dominant superior and inferior trunk of an early MCA bifurcation. As a consequence, the lenticulostriate perforators arise from the short pre-bifurcational M1 segment and the proximal superior trunk (**C**).

The implantation of a flow diverting stent is, therefore, an important therapeutic option with better long-term occlusion rates. However, it often necessitates the coverage of – partially – non-collateralized side branches in this location. Preclinical data published by Kalmes et al.

suggest the long-term patency of covered side branches together with sufficient aneurysm occlusion in 88 % of cases [68]. The authors attribute this effect to the persistent flow of jailed branches in contrast to the stagnant perfusion of the aneurysm dome. In concordance with these findings, Dai et al. presented data on multiple FDSs in rabbit models [69]. Despite the coverage with up to three overlapping devices and an increased amount of neointimal hyperplasia, the jailed branches remained patent on angiography until the last follow-up after 12 months.

Resulting from the anatomic characteristics, branch occlusion versus patency in the course of flow diversion might be in line with the aneurysm outcome. Topcuoglu et al. pointed out the impact of jailed branches [70]. Aneurysm occlusion might coincide with increased rates of obliteration of covered side branches. Conversely, patency of jailed bifurcation segments might result in insufficient aneurysm occlusion. The authors conclude that FDS is the preferred endovascular therapy for variant MCA cortical branches and fusiform or dissecting lesions but is not the best option for MCA bifurcations. In line with these findings, studies in experimental bifurcation aneurysms have so far also failed to report sufficient FDS treatment at mid-term follow-up for single and even combined device implantation strategies [71].

The physiological collaterals ensuring perfusion of the MCA territory can be a double-edged sword. On the one hand, leptomeningeal collateral vessels may ensure perfusion of distal regions of covered branches. However, collateral perfusion can also manifest with competitive flow, causing retrograde blood stream via the leptomeningeal anastomoses and at the same time a reduced antegrade flow in the treated segment with a consequently decreased flow gradient [36, 72]. Resulting from these opposing mechanisms, the risk of occlusion can be significant.

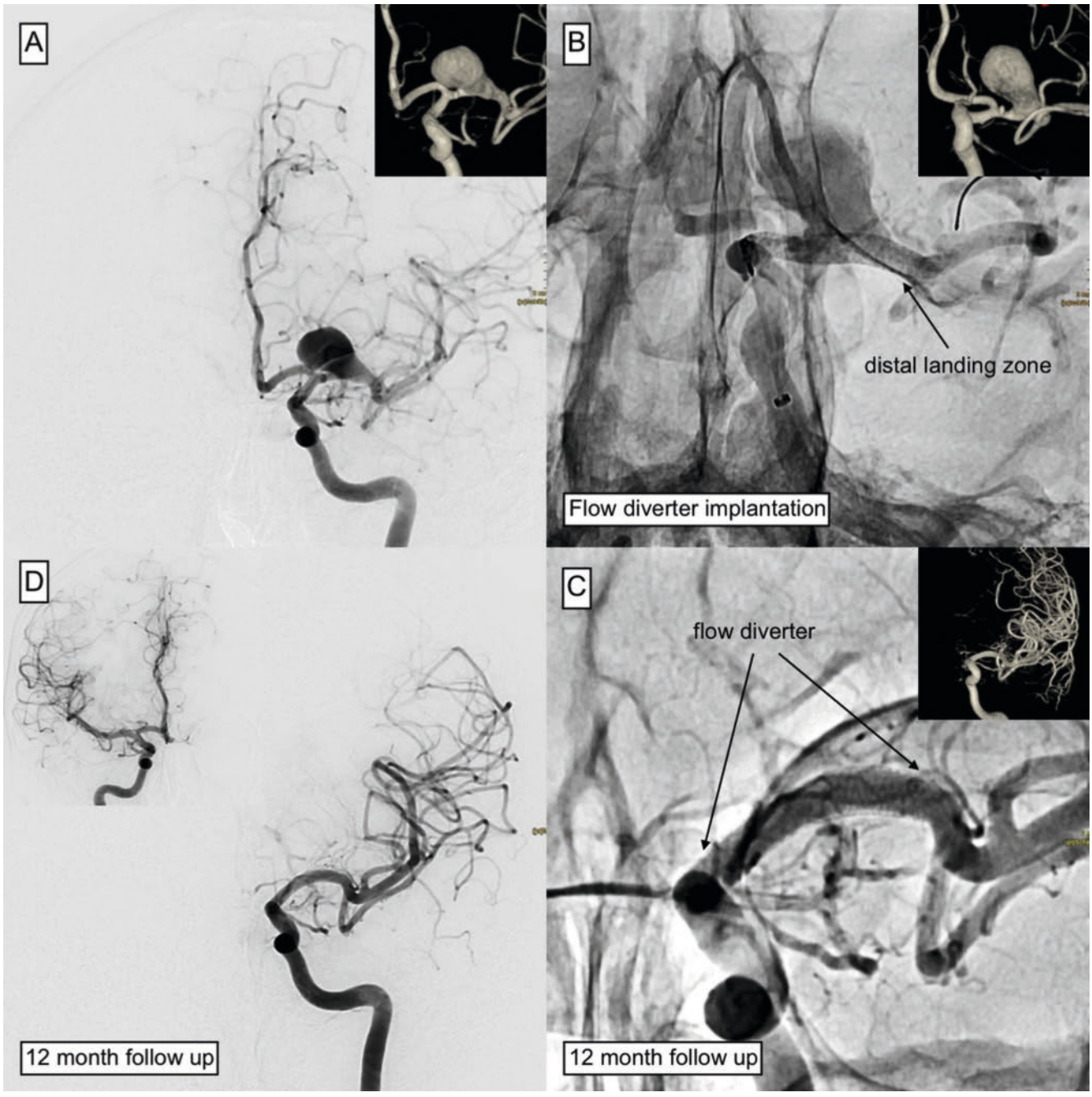
Apart from the aneurysms originating from the MCA main stem, lesions arising from early frontal or cortical branches are to be considered separately [62]. With regard to the vulnerable perforators arising from the M1 segment at risk for acute thrombosis or gradual occlusion over time, the subgroup of aneurysms arising from those branches should also be accurately distinguished. As of today, literature review is reporting controversial outcomes of covered side branches and perforators of the MCA after flow diversion. Although the blood flow of the perforators can most commonly be preserved, the risk of ischemia has to be taken into account and weighed against the risk of other treatment options [73]. The metal coverage of the hemodynamic implant should consequently be chosen deliberately [60].

Therefore, implantation of hemodynamically active devices and flow diverting stents in the MCA is completely different from the treatment of primary indications such as the ICA. The predominance of bifurcation segments within the MCA territory as well as non-collateralized vessels impair endovascular procedures and may include an increased risk for thromboembolism, especially in regard to the vulnerable lenticulostriates.

▶ **Fig. 3** illustrates an example of flow diversion necessarily involving the main MCA bifurcation segment.

Boghal et al. presented a series of 13 bifurcation aneurysms with sufficient occlusion of nearly 92 % at follow-up [74]. MRS-relevant morbidity was only seen in one case. All changes in perfusion of dependent side branches were asymptomatic, either presenting with reduced blood flow or gradual occlusion over time. According to these findings, effects on covered side branches including a decrease in caliber as well as complete occlusion were completely asymptomatic in the study by Yavuz et al. [75]. Promising occlusion rates after flow diversion of 54 MCA bifurcation aneurysms were also observed by Diestro et al. [76]. However, contrary to the prior studies, the rate of thromboembolism was distinctly increased up to nearly 17 %.

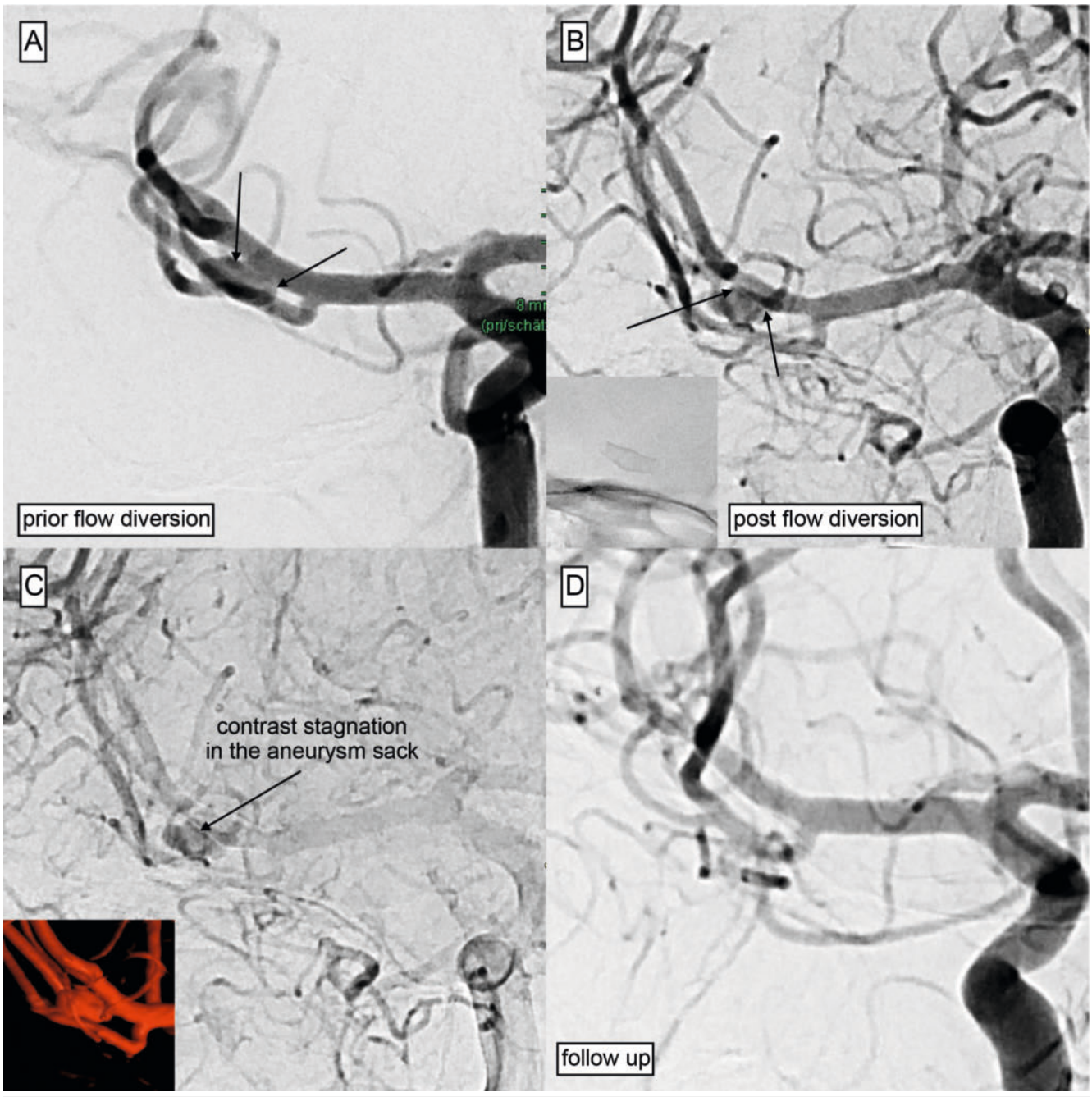
Another series of MCA bifurcation aneurysms treated with flow diversion was published by Caroff et al. [77]. Contrary to the previously mentioned studies, insufficient occlusion rates were reported in 38 % of the cases at follow-up. As the rate of 21 % of treatment-related adverse events was comparably high, the authors do not suggest flow diversion for this subtype of aneurysms. However,



▶ **Fig. 2** provides an example of flow diversion for the treatment of a large aneurysm arising from the distal M1 segment of the left-hand side MCA in a young athlete (**A**). There is an additional, very proximal, smaller aneurysm at the M1 origin, requiring the placement of the flow diverting stent in such a way that the proximal landing zone covers the origin of the ipsilateral anterior cerebral artery (**B**). The follow-up studies reveal the occlusion of the aneurysm and the shrinking of the jailed A1 segment, which was compensated via the anterior communicating artery (**C, D**).

the patients included in this study were treated with a high dose of ASA (160 mg) together with 75 mg clopidogrel for only 3 months without testing the efficacy of the antiplatelet medication. Considering the notoriously high rates of clopidogrel "resistance" [27] and the comparatively short duration of DAPT [78], high treatment platelet reactivity together with associated thromboinflammation [79] are a potential explanation of those results.

The abundance of segmental perforators and the combination of complex, serially connected bifurcations supplying eloquent brain areas complicate endovascular treatment of the MCA and distinguish the vessel from other targets like the ICA or ACA. The MCA should consequently be treated with extraordinary caution and be considered a higher-risk vessel compared to the ICA or ACA. In accordance, Briganti et al. reported an increased risk for thromboembolism with clinical sequalae in the early post-interventional phase after the treatment of MCA bifurcation aneurysms in comparison to non-bifurcation aneurysms [80].



▶ **Fig. 3** provides an example of flow diversion for the treatment of a saccular M2 aneurysm involving the origin of an M2 branch (**A**). The flow diverter was placed in such a way that only the segment with the aneurysm and its associated branch were covered (**B**). Immediately after implantation, perfusion of the aneurysm and the associated branch was decreased, as reflected by contrast stagnation in the aneurysm sack and a slightly delayed filling of the dependent branch compared to the other M2 branches (**C**). After 18 months, the aneurysm was occluded, all M2 branches remained patent (**D**).

The meta-analysis by Cagnazzo et al. summarizes the controversial outcomes after flow diversion for MCA bifurcation aneurysms [81]. Although occlusion rates may vary significantly from 67.8 % to 89.7 %, treatment effect was sufficient as (re-) rupture was only reported in 0.4 % of cases. Treatment-related adverse events, however, were distinctly higher with rates up to 27.5 % (averaged 20.7 %) and were predominantly related to ischemic complications (16.3 %). Compared to flow diversion in other segments of the circle of Willis, the authors conclude the MCA bifurcation is more prone to ischemic events in the course of FDS treatment. Considering jailed branches, a decline in perfusion was achieved in a quarter of the cases, and occlusion was observed in 10 %.

▶ **Table 1** summarizes the outcomes of flow diversion of the middle cerebral artery.

Based on the currently available clinical evidence, flow diversion for the treatment of MCA bifurcation aneurysms is feasible

▶ **Table 1** Summary of study outcomes.

Source	Functional aneurysm occlusion*	Fate of covered side branches	Adverse events
Zanaty et al. [60]	78 %	Patency or asymptomatic occlusion	30 %
Topcuoglu et al. [70]	78 %	69 % patency 31 % occlusion	14 %
Boghal et al. [74]	92 %	Patency or asymptomatic decrease in perfusion up to occlusion	15 %
Yavuz et al. [75]	84 %	Patency or asymptomatic decrease in perfusion up to occlusion	12 %
Diestro et al. [76]	80 %	n.a.	17 %
Caroff et al. [77]	70 %	17 % occlusion 50 % caliber reduction	21 %
Briganti et al. [80]	80 %	8 % asymptomatic occlusion 15 % symptomatic occlusion 46 % decrease in perfusion	27 %
Cagnazzo et al. [81]	67.8 % to 89.7 %	25 % decrease in perfusion 10 % occlusion	averaged 20.7 %

*Complete occlusion or small neck remnant

and effective, but ischemic complications remain a significant concern. Applying current knowledge and biotechnological innovations in order to enhance the safety of flow diversion for MCA bifurcations is therefore paramount to avoid thromboembolic adverse events and achieve better neurological outcomes. To do so, the use of long known, but in a significant number of cases insufficient standard regimens such as the combination of acetylic salicylic acid and clopidogrel, especially without testing its efficacy, must be avoided [82, 83]. Instead, more reliable anti-aggregants, such as prasugrel, in combination with platelet function testing, should be considered, although large-scale clinical evidence is scarce [45]. Furthermore, the use of flow diverter stents with antithrombogenic surface modifications has shown promising results with regard to increased hemocompatibility, applicability of single antiplatelet therapy, and low rates of ischemic and hemorrhagic complications, especially in the early, vulnerable phase of vascular healing [23, 43, 84, 85].

Summary

Flow diversion has changed the landscape of aneurysm therapy and enables endovascular therapy of previously inaccessible lesions like giant and wide-necked or even instable, high-risk aneurysms with a comparatively low procedural risk. From the initial focus on proximal locations, distal aneurysms can now also be reliably treated by FDS. Nevertheless, the MCA still represents a challenge in different ways. On the one hand, covering perforators arising from the M1 and M2 segments with a flow diverter stent poses an increased risk for thromboembolic adverse events. Secondly, the bifurcation segments and the potential need to cover an eloquent side branch demands special attention, as an overstented eloquent MCA branch can result in significant permanent disability, such as hemiparesis and aphasia. For the MCA, the rate of perforator or side branch occlusion following distal flow diversion is increased. Consequently, devices should be chosen deliberately under consideration of their metal coverage, hemocompatibility, and the required anti-aggregant medication.

In regard to aneurysm occlusion, the location has a main impact on occlusion rates and tends to be more important than the aneurysm morphology. In contrast, whether the lesion has a saccular, fusiform, and/or dissecting morphology might primarily impact the rate of adverse events [32].

Conflict of Interest

The authors declare that they have no conflict of interest.

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