The Use of Flow Diverters in the Intracranial Circulation

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A Thesis submitted in fulfilment of of the requirements for the gree of Doctor of Philosophy in Life Sciences and Medicine

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Declaration

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree. The work presented was carried out by the author.

Dedication

This work is dedicated to my Father who showed me the value of courage, to my Mother who showed me the value of compassion, to my Brother who showed me the value of perserverance, to my Sister who showed me the value of integrity, and to my Partner who showed me the value of kindness.

Summary

Intracranial aneurysms are common lesions with autopsy studies suggesting a prevalence of between 1-5% in the adult population. Intracranial aneurysms can be asymptomatic, present with acute subarachnoid haemorrhage or present due to mass effect, for example with cranial nerve palsies. The most common presentation of intracranial aneurysm is rupture leading to subarachnoid haemorrhage. With the increased access to advanced imaging modalities such as MRI and greater imaging of the brain for unrelated conditions such as headache aneurysms are increasingly detected prior to rupture. Following the publication of ISAT endovascular treatment of intracranial aneurysms was considered by many to be the gold standard of treatment. Flow diverters entered clinical use around a decade ago and have gained wide spread acceptance however, there remained numerous unanswered questions from the original trials on flow diversion.

The aim of this project was to compile real world published data to help answer some critical questions regarding the use of flow diversion.

The results show that flow diversion is safe to use beyond the circle of Willis in vessels such as the MCA and ACA, as well as to treat aneurysms of the anterior choroidal artery. Furthermore, the risk of covering side branches appears to be minimal. The combined use of flow diversting stents with endosaccular/intra-aneurysmal flow diverting devices can also be performed and appears to offer rapid occlusion of aneurysms which may be particularly useful in large or partially thrombosed aneurysms. Flow diversion in the posterior circulation is also feasible however, it is likely that any benefits seen from flow diversion for non-saccular posterior circulation aneurysms must take into account the clinical state and flow diversion should be performed prior to symptoms of brainstem compression.

Abbreviations

ACA	anterior cerebral artery
AChoA	anterior choroidal artery
AcomA	anterior communicating artery
ADC	apparent diffusion co-efficient
AICA	anterior inferior cerebellar artery
AVM	arteriovenous malformation
CE	Conformité Europienne
CFD	computational fluid dynamics
CT	computed tomography
DAPT	dual anti-platelet treatment
DSA	digital subtraction angiography
DWI	diffusion weighted imaging
ECA	external carotid artery
FDS	flow diverting stent
FLAIR	fluid attenuated inversion recovery
Fr	French
FRED	Flow Re-direction Endoluminal Device
FRED jnr	Flow Re-direction Endoluminal Device junior
GDC	Guglielmi Detachable Coil
HR	hazard ratio
ICA	internal carotid artery
IRB	institutional review board
ISAT	international subarachnoid aneurysm trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
IU	international units
IVH	intra-ventricular haemorrhage
MAFA	mean aneurysm flow amplitude
MCA	middle cerebral artery
MED	Medina Embolic Device
MRI	magnetic resonance imaging
mRRC	modified Raymond Roy classification
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale Score
OKM	O'Kelly Marotta
OR	odds ratio
PCA	posterior cerebral artery
PCom	posterior communicating artery
PD	packing density
PED	pipeline embolisation device
PICA	posterior inferior cerebellar artery
PITA	pipeline embolisation device for intracranial treatment of aneurysms
PUFS	pipeline for Uncoilable or Failed aneurysms
RCT	randomised controlled trial
RRC	Raymond Roy classification
SAH	subarachnoid haemorrhages (SAH)
SAPT	single anti-platelet treatment

ß-TG	beta-thromboglobulin
TAT	thrombin-antithrombin
TIA	transient ischaemic attack
WEB	woven endobridge
WSS	wall sheer stress

1 Chapter 1

1.1 Introduction

1.2 Epidemology and pathophysiology of aneurysms

Intracranial aneurysms are common lesions with autopsy studies suggesting a prevalence of between 1-5% in the adult population (1). Intracranial aneurysms are thought to be sporadically acquired lesions, although familial conditions have been described. Associated conditions include polycystic kidney disease, fibromuscular dysplasia, Marfan's syndrome and Ehler's Danlos type IV (2). Approximately 10-30% of patients have multiple aneurysms (3).

Intracranial aneurysms can be asymptomatic, present with acute subarachnoid haemorrhage or present due to mass effect, for example with cranial nerve palsies. The estimated incidence of subarachnoid haemorrhage from a ruptured intracranial is 1 case per 10,000 persons (3,4). Subarachnoid haemorrhage is more common in women (2:1) and the peak incidence is in the 6th decade of life, between 55 and 60 years old (5,6).

Little is known about the cause of intracranial aneurysms or the process by which they form, grow, and rupture although hypertension and smoking-induced vascular changes are believed to play a major role (3). Furthermore, inflammation is thought to play a key role in the rupture of aneurysms (7). Histologically, the most common finding in aneurysm walls is a decrease in the tunica media. This defect, combined with haemodynamic factors, is thought to lead to aneurysmal out-pouchings at arterial branch points.

1.3 Natural history and risk of rupture

The most common presentation of intracranial aneurysm is rupture leading to subarachnoid haemorrhage. With the increased access to advanced imaging modalities such as MRI and greater imaging of the brain for unrelated conditions such as headache aneurysms are increasingly detected prior to rupture.

Aneurysms presenting with subarachnoid haemorrhage tend to re-rupture. Between 2 and 4% of aneurysms bleed again within the first 24hrs after the initial haemorrhage with up to 20%

bleeding again within the first 2 weeks. Patients that present with symptoms of compression including cranial nerve palsies or brain stem dysfunction should also be treated promptly as the risk of rupture in this sub-group is higher (6% per year) (8).

In 1998 the International Study of Unruptured Intracranial Aneurysms (ISUIA) was published. This study involved 53 centres and 2621 subjects and challenged the belief that all unruptured aneurysms posed a high risk of rupture. In this large study of people with unruptured aneurysms selected for conservative management, the rate of aneurysm rupture for certain small aneurysms (<10mm) was found to be as low 0.05% per year. Amongst those patients with a history of a bleeding aneurysm, the risk of haemorrhage was 10 times higher than those without previous haemorrhage. Size and anatomical location were shown to be associated with the risk of rupture with aneurysms located in the posterior circulation, at the basilar apex or on the posterior communicating artery, and aneurysms >10mm having a higher rate of rupture. In the prospective arm of the ISUIA study, which involved 1692 patients, there were similar results. Patients with aneurysms ≤7mm, which represented 62% of the cohort, the 5-year cumulative rupture risk was 0% (9,10). However, this study has been criticised as the subjects entered into the study were pre-selected by the neurosurgeons of the basis that the aneurysms were less likely to rupture (11,12).

1.4 Management of Intracranial Aneurysms

There are three different treatment options for intracranial aneurysms: observation, craniotomy and clip ligation (clipping), and endovascular occlusion of the aneurysm typically with detachable coils (coiling). Unruptured aneurysms that are often discovered incidentally are either observed or treated electively. As mentioned earlier one of the key determinants in choosing to observe an aneurysm rather than treat an aneurysm is its size. Other factors that also play a role in predicting the risk of rupture include age, history of hypertension or subarachnoid haemorrhage, aneurysm location and geographical location (13). For ruptured aneurysms the treatment options remain the same with either an endovascular approach or a neurosurgical approach for patients with Hunt and Hess grade 1-4 subarachnoid haemorrhage. For patients with the severe grade, Hunt and Hess grade 5, there is still on-going debate as to whether treatment should be performed given the poor outcome in this cohort of patients.

Until the latter part of the 1990's neurosurgical clipping was the only real treatment option for aneurysms requiring treatment. The advent of the Guglielmi Detachable Coil (GDC) heralded a

revolution in the treatment of intracranial aneurysms (14,15) although there remained contention as to whether the endovascular approach was as safe and as robust as neurosurgical clipping.

1.4.1 The International Subarachnoid Aneurysm Trial (ISAT)

ISAT was a randomized trial comparing neurosurgical clipping with endovascular coiling in patients with ruptured intracranial aneurysms. Recruitment to the trial was halted after an interim analysis at 1 year showed a benefit of endovascular treatment on the primary outcome or death or dependency at 1 year. On the initial report of the trial, which included complete data for 1594 or the 2143 patients enrolled, there was a significant difference between the two treatments with an absolute risk reduction of death or dependence of 6.9% for endovascular coiling compared with clipping (16). Similar results were seen with the 1-year outcomes with an absolute risk reduction of 7.4% (95% CI 3.6-11.2, p=0.0001) in favour of endovascular coiling. Although these results were met with much controversy there was no clear evidence for an advantage of neurosurgical clipping versus coiling in any of the sub-groups (17). The results of this trial led, in many countries, to a change in practice with clipping becoming the mainstay of aneurysmal treatment for both ruptured and unruptured aneurysms.

More recently, the long-term follow-up results of UK cohort of ISAT were published (18). At 10 years, 674 patients (n=809, 83%) allocated to coiling and 657 patients (n=835, 79%) allocated to clipping were alive (OR 1.35, 95% CI 1.06-1.73). Of 1003 patients questioned, 435 that were coiled (82%) and 370 that were clipped (78%) were independent (modified Rankin scale Score 0-2; OR 1.25, 95% CI 0.92-1.71). Patients in the endovascular treatment group were more likely to be alive and independent at 10 years than were patients in the neurosurgery group (OR 1.34, 95% CI 1.07-1.67). A repeat haemorrhage from the treated aneurysm was more common after endovascular coiling and at the end of follow-up the cumulative risk was 0.0216 (95% CI 0.0121-0.0383) for coiling and 0.0064 (95% CI 0.0024-0.0173) for clipping. Meta-analyses have also demonstrated a higher independent outcome and lower outcome after coiling (19).

Overall, after the publication of ISAT, there has been a trend towards treating aneurysms via an endovascular approach. This change in treatment encouraged the development of new endovascular equipment that included initially laser cut stents and later braided stents and flow diverters.

1.5 Flow Diverters

Flow diverters are fine mesh stents that are endovascularly implanted into cerebral arteries across the neck of aneurysms. As their name suggest their function is to divert the blood flow away from the aneurysm and into the parent artery in which they are implanted and thereby reduce flow within the aneurysm. In the earlier post-implantation stage the reduced flow within the aneurysm promotes the formation of thrombus. In the longer term the fine mesh structure of the flow diverter acts as a scaffold on which new endothelial cells can reconstruct the parent artery and occlude the aneurysm (20). There is concomitant resorption of the thrombosed aneurysm with the end result being complete remodelling of the parent vessel and a return to its normal physiological state.

1.5.1 Flow diverter structure

The currently commercially available flow diverters all share a similar structure. The devices are tubular structures made of braided (helically wrapped) wires. The wires themselves can be made of different materials with both nickel titanium alloy (Nitinol) and cobalt chromium alloys used. As mentioned earlier the devices act as a porous screen at the neck of an aneurysm and as such it is important to define certain characteristics of the devices. Porosity is defined as the percentage ratio of the metal free surface area (total surface area-metal surface area) to the total surface area. The percentage metal coverage is also often frequently used in literature and is the opposite of porosity. Pore density is the number of pores per unit surface area of the device. The variables governing the design of these devices include the device diameter, wire diameter, and the braiding angle (the angle that the wire makes to the axis of the device). The nominal pore density and porosity - the porosity and pore density of the design in its unconstrained state - can be mathematically expressed in terms of these variables.

The braided design of flow diverters allows the wires to slip over one another and this feature allows the device to be implanted into vessels whose diameter varies. When deployed in vessels smaller that the nominal diameter of the device the flow diverter will elongate and vice versa. Similarly, during deployment of the devices, the surgeon can apply longitudinal pressure on the device and compress the flow diverter, called ‘packing’, and this allows superior apposition of the device to the vessel wall. The braided structure of the devices means that the porosity of the device can vary along its length dependant on numerous factors such as the diameter of the

vessel, the curvature of the vessel, the size of the aneurysm neck, and manipulation of the stent when deployed by the surgeon.

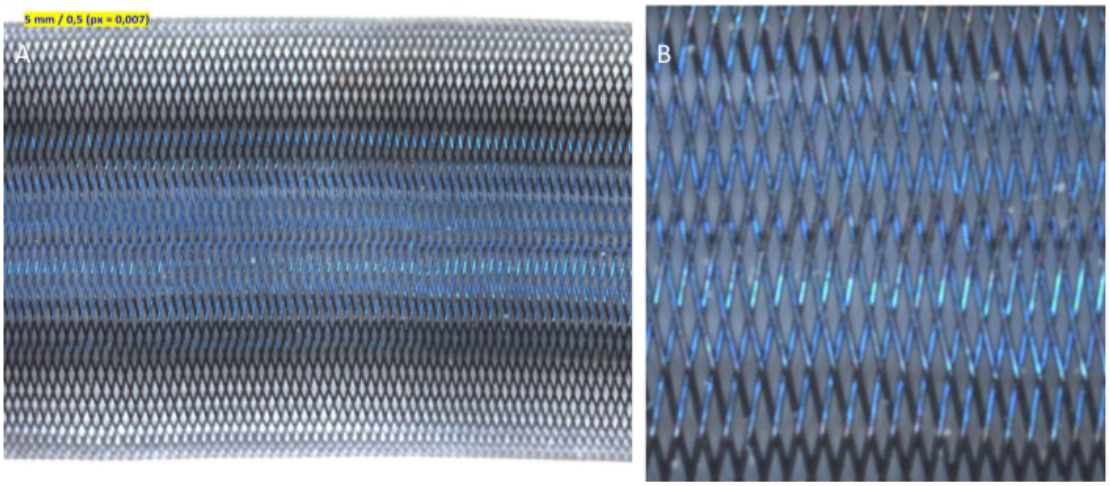

Figure 1

Flow diverters are made from braided metallic alloys to construct tubular structures that can be placed within vessels. They are of low porosity and high metal surface coverage relative to traditional laser cut stents. The braided structure of the device can be seen in Fig. 1a with the device seen side-on. A magnified view of the braided structure can be seen in Fig. 1b (Images courtesy of phenox Gmbh, Bochum, Germany)

1.5.2 The effect of pore structure

The existing devices all share a porosity of approximately 30-40% (21) however, as mentioned earlier the pore density can be altered by a variety of factors. The porosity and pore structure of the devices is the primary method by which flow diverters alter intra-aneurysmal flow. Naturally, by lowering pore density the intra-aneurysmal flow can be reduced and this is the reason for 'packing' the devices at the aneurysm neck. At the moment it is unclear whether a uniform porosity threshold exists, given that approximately 90% of aneurysms are excluded at 12 months after implantation of a flow diverter it is thought that the current porosities are within the correct range. Although decreasing the porosity of the devices further may reduce intra-aneurysmal flow further this needs to be balanced against the practical considerations of increased device stiffness, trackability of the devices through microcatheters and in tortuous vessels, as well as the potential for an increased risk of in-stent thrombosis and occlusion of covered side branches.

Each of the pores of a flow diverter can be thought of as a deformable rhombus. When a flow diverter is placed into a vessel smaller than the nominal size of the device e.g. a 3.5mm diameter device is placed in a 2mm diameter vessel, the angles of each rhombus changes in proportion to the degree of constraint. The area of the rhombus is related to the length of the side of the rhombus (a) and the angle made by two adjacent sides (b) and is maximal when the angle is 90 degrees. For increasing and decreasing angles the area of the rhombus decreases. This alteration in the area of a rhombus forms a parabolic curve and therefore, the porosity and metal surface coverage will also follow parabolic curves. Put alternatively the porosity vs. device diameter forms a parabola (22). It is therefore important to appropriately size each device to the parent vessel. Similarly, in curved vessels the porosity and metal surface coverage alter significantly. The pores on the outer curve will be larger with smaller, compressed pores on the inner curve as the braided wires slide over one another in order to conform to the curved tubular shape. This has the effect of increased porosity on outer curves and simultaneously decreasing porosity along inner curves (22,23) (Fig. 2).

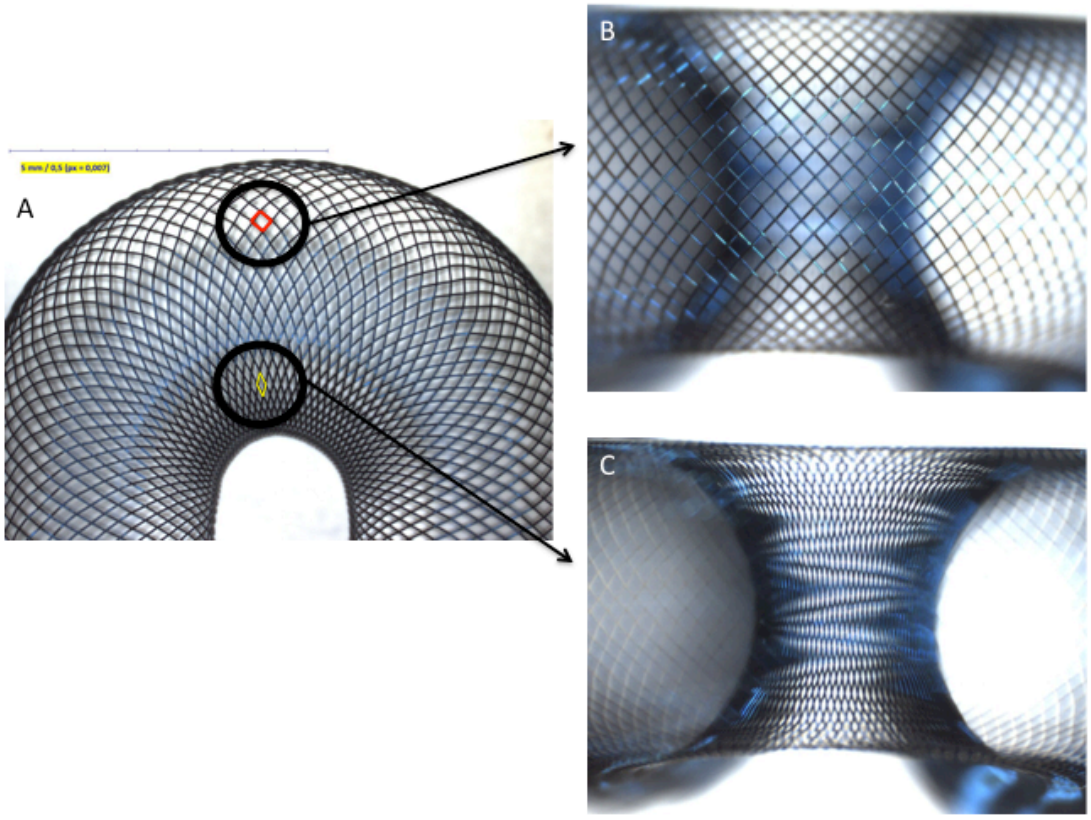

Figure 2

The braided structure of flow diverters allows them to conform to the curvature of the vessels however, this also results in a change in the shape and size of the pores. As the braids on the outer curve open up the pore size increase (Fig. 2a, red square and Fig. 2b, magnified image of the outer curve of the flow diverter). In the inner curve the braids are compressed together resulting in smaller pores (Fig. 2a, yellow rhomboid, Fig.2c, magnified image of the inner curve of the flow diverter). This results in varying degree of flow diversion on the inner and outer curves of blood vessels. (Images courtesy of phenox Gmbh, Bochum, Germany)

1.5.3 Intra-aneurysmal flow changes

It is traditionally believed that the inflow into idealized, untreated side wall aneurysm enters the aneurysm at the distal neck and travels along the distal wall to the dome of the aneurysm and then exits near the proximal neck of the aneurysm and thereby forming a vortex. In reality this pattern is likely to depend greatly on the various different anatomical features of an aneurysm and the parent vessel along side other factors such as the blood pressure, compressibility of the parent artery etc. The placement of a flow diverter across the neck of an aneurysm alters the in and outflow patterns. In general the flow into the aneurysm adopts the direction of the flow within the parent artery with inflow at the proximal neck and outflow at the distal neck (24–27). These studies have analysed a variety of different flow characteristics including inflow rate, kinetic energy, average velocity, maximal velocity, vorticity, and wall shear stress being amongst the most common. Although a variety of different effects have been shown in general flow diversion results in a reduction of intra-aneurysmal flow of approximately 75-95% for idealised side-wall aneurysms (25,28–31) with lower reductions in simplified bifurcation aneurysms (28,32). This change in flow after flow diversion also alters the viscosity of the blood within the aneurysm since blood, as a non-Newtonian fluid, increases in viscosity as the velocity over a given distance (shear rate) decrease. It is important to realise that although flow within the aneurysm is substantially reduced and there is an increase in the pressure gradient across the neck of the aneurysm after placement of the flow diverter, as the flow diverter is porous the intra-aneurysmal pressure is essentially unaltered (33).

1.6 Clinical Trials Using Flow Diverters

1.6.1 The Pipeline Embolization Device for the Intracranial Treatment of Aneurysms Trial (PITA)

PITA (34) was the first prospective multicentre trial of the Pipeline Embolization Device (PED). This single arm trial was conducted at 3 centres in Europe and 1 in South America. Subjects were enrolled if they had wide necked intra-cranial aneurysms (>4mm or dome to neck ratio <1.5) or if the aneurysms had failed previous endovascular treatment attempts. Exclusion criteria included patients with recent sub-arachnoid haemorrhage (<60days), unstable neurological deficit, or >50% stenosis of the parent artery. The average maximum aneurysm size was 11.5mm (range 2.5-26.6mm) with the majority of aneurysms being smaller than 10mm (n=20, 64.5%) with a further 9 aneurysms being between 10 and 25mm (29%). Only two aneurysms (6.5%) were ≥25mm in maximum dimension.

All patients were given aspirin and clopidogrel prior to treatment. All procedures were performed under general anaesthesia. All angiographic data was reviewed by an independent experienced neuroradiologist and aneurysm occlusion was graded on a three point modified Raymond Roy Scale (35). Similarly, in stent stenosis was calculated based on the luminal diameter and graded as none (0to <25%), mild (>25 to <50%), moderate (>50 to <75%), and severe (>75 to 100%).

In total 31 patients were enrolled between January and May 2007, 25 of whom were women. The average age was 54.6 (range, 35-76 years). Twelve of the patients had undergone previous treatments. In total 47 devices were placed (1.52 per aneurysm). In 18 cases a single PED was placed. Adjunctive coiling was used in 16 aneurysms (51.6%) and the remaining 15 aneurysms were treated with PED alone. Forty-six of the 47 PED's were implanted successfully. In 1 unsuccessful PED implantation there was reduced flow in the parent ICA after deployment and coiling of the aneurysm sac. Angioplasty was performed to improve the flow within the parent vessel but this resulted in rupture of the ICA distal to the PED. During the subsequent surgical repair both the coils and the PED were removed and ultimately the parent ICA was ligated. In the remaining aneurysms the entire neck of the aneurysm was covered by the PED.

Clinically two patients had a major stroke during the peri-operative period that included the patient with iatrogenic ICA rupture secondary to angioplasty. Another patients suffered a stroke within the deep gray matter after telescoped PED's were placed in the M1 segment and this was thought to be due to excessive coverage across the lenticulostriate vessels.

Angiographic assessment at 180 days, available in 30 patients, showed complete aneurysm exclusion in 28 patients (93.3%) with residual aneurysm filling seen in 2 remaining patients (6.7%). In 28 patients there was no stenosis, in 1 patient there was mild stenosis and in the remaining patient the parent vessel could not be assessed due to an overlying coil ball mass. Clinically at 180 days there were no delayed neurological events.

The authors report that the most important observations from the PITA trial were:

- The treatment of intracranial aneurysms with PED alone (alone or adjunctively in support of aneurysm coiling) was feasible with a high rate of technical success.
- Definitive endoluminal reconstruction of the parent artery with PED was achieved with a level of procedural safety analogous to that reported for the conventional coil-based endosaccular treatment of complex intracranial aneurysms.
- Parent artery reconstruction with PED yielded a rate of complete aneurysm at 180 days that approached 100% and exceeded that traditionally reported after conventional endosaccular aneurysm treatment
- PED implantation was not associated with a high prevalence of delayed in-construct stenosis or thrombosis during the study interval.
- PED was not associated with delayed clinical neurologic events following treatment.

Following on from the success of the PITA trial, the pivotal Pipeline for Uncoilable or Failed aneurysms (PUFS), continued to demonstrate the safety and efficacy of the PED for the treatment of intracranial aneurysms.

1.6.2 Pipeline for Uncoilable and Failed Aneurysms

This multicentre, prospective, interventional, single arm trial of PED for the treatment of uncoilable or failed aneurysms of the internal carotid artery. Between November 2008 and July 2009 108 patients from 10 centres were prospectively enrolled. The study was conducted according to U.S FDA regulations regarding investigational device exemption. To be included in the study the patients had to have an aneurysm arising from the ICA (petrous through to the superior hypophyseal segments) that measured at least 10mm in maximal diameter and had a

neck of at least 4mm. Patients were excluded if they had subarachnoid haemorrhage in the previous 60 days, any intracranial haemorrhage or major surgery within the last 42 days, a history of a bleeding disorder or a low platelet count, previously placed stent at the target aneurysm, known allergy to cobalt or chromium alloys or platinum, evidence of infection and a major stenosis in the ipsilateral ICA. All patients were started on aspirin and clopidogrel prior to the procedure with all patients continuing aspirin and clopidogrel for at least 3 months (most were maintained for 6 months).

All patients underwent neurological assessment prior to the procedure and as baseline with subsequent neurological testing at 30 and 180 days after the treatment. Further periodic follow-ups were scheduled for up to 5 years. Additionally, patients underwent conventional angiography and a focused neuro-ophthalmalogical examination at 180 days. An independent core lab, made up of three interventional neuroradiologists, reviewed and reported on the imaging data with the degree of occlusion based on the Raymond Roy occlusion score. These interventional neuroradiologists reviewed the imaging data and determined the degree of aneurysm occlusion.

The primary efficacy end point was complete occlusion (Y/N) of the target aneurysm without major (>50%) stenosis of the parent artery or adjunctive use of complementary embolic agents as seen on the 180 day angiogram. A case was considered successful if at least 2 members of core lab agreed that the aforementioned efficacy endpoints had been met. The primary safety endpoint was the incidence of major ipsilateral stroke (increase of ≥4 points on the National Institute of Health Stroke Scale Score [NIHSS]), as adjudicated by the independent clinical events committee, or neurological death within 180 days. The major secondary end-points of the study included complete occlusion of the target aneurysm at 1, 3, or 5 years, and change in the modified Rankin Scale (mRS) score of more than 2 points at 180 days.

Of the 108 patients enrolled the vast majority were female (96, 88.9%) with mean age of 57 years. The mean aneurysm size was 18.2mm with just over one fifth (n=22, 20.4%) being >25mm in maximum dimension. In total 107 patients underwent PED treatment and completed discharge. In one patient the parent artery could not be catheterised and therefore PED placement was not attempted. Three patients died on post-operative days 4, 11, and 14 leaving 104 alive at 180 days. Complete scheduled clinical follow-up was performed in 100 patients and 180 day catheter angiography was performed in 97 patients with 99 treated aneurysms.

Four of the 108 patients were excluded from the efficacy cohort however, two additional qualifying contralateral aneurysms were identified and treated meaning 106 aneurysms in 104 patients were available for efficacy assessment. In total 78 aneurysms (73.6%) met the study's combined efficacy endpoint. In 14 of the remaining aneurysms there was residual filling and a variety of reasons including death, carotid occlusion etc. that excluded others from reaching the primary efficacy endpoint.

Recently, the results from the 5-year follow-up of the PUFS trial have been published. These showed progressive aneurysm occlusion reaching 95.2% (60/63) (36).

Despite the success of the PUFS trial and the numerous papers published subsequently there remain numerous unanswered questions. Some of these include:

The use of flow diversion beyond the circle of Willis, for example within the middle cerebral artery. (Chapters 2 and 3)

The use of flow diverters to treat bifurcation aneurysms rather than sidewall aneurysms. (Chapter 4)

The effect flow diverters have on the side branches that are covered by them. (Chapter 5)

The effect of flow diverters on the anterior choroidal artery. (Chapter 6)

The use of flow diverters to treat non-saccular aneurysms of the posterior circulation. (Chapter 7)

The combined effect of intra-luminal flow diverters with intra-saccular flow diverters. (Chapter 8)

2 Chapter 2

2.1 The Use of Flow Diverters in the treatment of unruptured saccular aneurysms of the anterior cerebral artery

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MAP serves as proctors and consultants for phenox GmbH with moderate financial compensation. HH is a co-founder and shareholder of phenox GmbH. The other authors declare no conflict of interest.

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2.1.1 Abstract

Background and Purpose
Few publications have dealt exclusively with the use of flow diverter stents for the treatment of aneurysms of the anterior cerebral artery (ACA). We sought to determine the efficacy of flow diverting stents to treat small, unruptured aneurysms of the ACA.

Methods
We retrospectively reviewed our database of prospectively collected information for all patients treated with flow diversion for an unruptured saccular aneurysm of the ACA between September 2009 and July 2016. The aneurysm fundus size, neck size, number and type of flow diverting stent (FDS), complications and follow-up data was recorded.

Results
In total 26 patients, with 27 aneurysms were identified that matched our inclusion criteria (11 male and 15 female). The average age of the patients was 59.3 years old (range 27-77yrs). All patients except one had a single aneurysm affecting the ACA. Fourteen aneurysms were located on the left (51.8%). The average aneurysm fundus size was 2.9mm (range 2-6mm). Twenty patients have had follow-up angiographic studies. In total, 16 aneurysms have been completely excluded, 1 aneurysm shows a very small remnant, with no follow-up angiographic data available for the remaining patients. One patient suffered a treatment related complication.

Conclusion
Treatment of aneurysms arising from the ACA with flow diverters is technically feasible and carries a high degree of success with low complication rate.

2.1.2 Introduction

The introduction of flow diverting technology represented a monumental advancement in our ability to not only exclude aneurysms from the circulation but also to reconstruct the parent vessel. These new stents were originally tested in previously un-treatable aneurysms or those in which previous endovascular treatments had failed (1). The exact mechanism of action of aneurysm exclusion is slowly being elucidated and likely involves reduced intra-aneurysmal flow, stasis, and thrombosis, with neo-endothelialisation of the stent to finally reconstruct the

parent vessel (2). This process occurs slowly and usually spares covered perforator branches such as the anterior choroidal artery or the lenticulostriate arteries (3–5). These devices have an increased metal coverage compared to conventional stents with an optimal porosity of between 60-76% according to some studies (6,7).

A variety of different flow diverting stents (FDS) are currently available and these include the Pipeline Embolisation Device (PED) (Covidien, Irvine, California), Silk (Balt Extrusion, Montmercy, France), Surpass (Stryker Neurovascular, Fremont, California), p64 (phenox, Bochum, Germnany) and the Flow Re-direction Endoluminal Device (FRED) (Micorvention, Tustin, California). Newer derivations of these devices, such as the Pipeline FLEX have also entered the market and offer added advantages such as near complete re-sheathability.

The PED is one of the most widely studied devices and is made of 25% platinum and 75% nickel-cobalt chromium alloy with a porosity of 65-70%. Its is available in a variety of different sizes and diameters and multiple telescoped PED's can be used to alter the porosity (8). The Pipeline for Uncoilable or Failed aneurysms study (PUFS) (1) showed an aneurysm occlusion rate of 73.6% at 6 months and major ipsilateral stroke or neurological death rate of 5.5% whilst the Pipeline embolisation device for the Intracranial Treatment of Aneurysms (PITA) showed a 6month aneurysm occlusion rate of 93.3% and ischaemic stroke risk of 6.5% (8). More recently Griessenauer et al. (9) published their multicentre results on the use of the PED for small (≤7mm) aneurysms and showed a complete occlusion rate of 87% and symptomatic procedural complication rate of 6%.

The Silk flow diverter has a porosity of 45-60% and can be re-sheathed even up to 90% deployment. The Silk is made up of 48 braided Nitinol strands and was the first device to enter clinical use for the treatment of intracranial pathologies. In the recent systematic review performed by Murthy et al (10) a 12 month aneurysm occlusion rate of 81.8% was seen with ischaemic complications occurring in 10% of patients and a cumulative mortality of 4.9%. Similarly the recently published results of a Canadian registry showed that 83.1% of aneurysms treated with the Silk flow diverter were either completely or nearly completely occluded at last follow-up with a peri-operative morbidity of 8.7% and mortality of 2.2% (11).

The SURPASS flow diverter employs a different design in order to maintain pore density at close to 70% across different device diameters. The construction of the device has a varying number of

metal struts increasing in number from 48 (2mm diameter devices) to 96 (5mm diameter devices) at larger diameters. It is made of a cobalt-chromium alloy and contains 12 platinum wires to aid radio-opacity. Wakhloo et al. (12) recently reported the preliminary angiographic and clinical results from a multicentre study. They showed complete occlusion in 75% of patients that had follow-up angiography (158 of 186 aneurysms). Ischaemic stroke was seen in 3.7% of patients in ≤30days with intra-parenchymal haemorrhage and subarachnoid haemorrhage (≤7 days) seen in 2.5% and a mortality of 1.6% for aneurysms in the anterior circulation.

The FRED flow diverter is a unique dual layer design that consists of a low porosity inner mesh and higher porosity outer mesh. The device is composed of 48 braided nitinol inner strands and 16 outer struts with 4 interwoven marker strands as well as proximal and distal markers. The dual layer is restricted to the midsection and covers approximately 80% of the device length with the aim of increasing coverage across the aneurysmal neck. Kocer et al. (13) published their initial experience of the FRED flow diverter and showed progressive occlusion of aneurysms upto 12 months with low rates of morbidity and mortality. Similarly, Möhlenbruch et al. (14) showed progressive aneurysmal occlusion with 73% of aneurysms completely occluded at 6 month follow-up whilst Briganti et al. (15) had occlusion rates of 83%. The safety profile also seems comparable to the other devices with no mortalities seen in the studies and morbidity of seen in 10% of cases in the series by Möhlenbruch and 8% in that of Briganti et al. (15).

The p64 is a braided flow diverting stent composed of 64 nitinol wires. Two platinum wires wrapped around the shaft assist in radio-opacity. The 64 wires are grouped into 8 bundles proximally, with each bundle consisting of 8 wires. A radio-opaque marker is attached to end of each of these bundles. The porosity of the device is 51-60%. The p64 is unique amongst flow diverters in that it is mechanically detached and can be resheathed even after complete deployment. Fischer et al. (16) published their intial experience and showed, similar to other flow diverters, a progressive occlusion with an overall occlusion rate of 85.7% at last follow-up and a good safety profile (permanent morbidity 1.7%, and mortality 0.8%). Briganti et al. (17) have also reported their experience with the p64 and showed occlusion rates of 88% and 2.5% permanent morbidity with no mortality.

With the introduction of flow diversion into clinical practice, previously untreatable or difficult to treat aneurysms are now amenable to endovascular treatment approaches. Until recently little has

been published on the use of flow diverters above the level of the circle of Willis and especially their use in the anterior cerebral artery (18). The purpose of our study is to report our experience with flow diverters in the management of aneurysms of the anterior cerebral artery (ACA), excluding the anterior communicating artery (AcomA), including the safety and effectiveness of this strategy.

2.1.3 Materials and Methods

Patient Population

Between September 2009 and February 2016, 26 patients with un-ruptured ACA aneurysms were admitted to our institution for endovascular treatment. For each patient we recorded demographic data, clinical presentation, location of the aneurysm, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information. The data was entered into our prospectively collected computer database.

Classification of ACA segment aneurysms

All aneurysms were evaluated and anatomically located based in the position of the aneurysmal neck. The A1 segment was classified as the segment extending from the termination of the internal carotid artery to the AcomA. The A2 segment was defined as the segment of the vessel extending from the AcomA to the region between the rostrum and the genu of the corpus callosum. The A3 portion of the vessel was defined as that portion of the vessel lying anterior and curving around the genu of the corpus callosum. There were no documented aneurysms arising from the A4 segment or distal. We purposefully excluded aneurysms of the AcomA itself as we feel these aneurysms warrant separate attention and alternative treatment strategies.

Endovascular Treatment

All treatments were performed under general anaesthesia. Two commercially available FDS were used: Pipeline Embolisation Device (PED) (Medtronic) and p64 (phenox, Bochum, Germany). Patient informed consent was obtained before the procedure in all cases. The selection of FDS was dependent upon the operators' judgement. A single FDS was placed in all patients.

All patients received dual antiplatelet therapy (aspirin 100mg daily and clopidogrel 75mg) prior to the treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche). Patients found resistant to clopidogrel received 2x 90 mg ticagrelor daily. The post-procedural antiplatelet regimen consisted of clopidogrel continued for 12 months following treatment and aspirin continued for life.

All procedures were performed via the right common femoral route using a 6Fr access system as standard and either a Marksman (Covidien) catheter or XT27 (Stryker Neurovascular) catheter to deploy the FDS. All procedures were performed under heparin anticoagulation with a 5000 IU bolus dose at the start of the procedure and subsequent 1000 IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline.

Procedural Assessment and Follow-Up

Patency and flow characteristics within the ACA and any cortical branches were assessed angiographically immediately after placement of the FDS and during follow-up. Procedural follow-up (digital subtraction angiography) was performed initially at 3-6 months, again at 9-12 months and then once per year. Standard angiographic projections were used to assess the patency of the vessels and the aneurysms in addition to angiographic projections that repeated those used during the treatment. Aneurysm occlusion was graded as either completely excluded, minor remnant, major remnant, or unchanged (patent).

Neurological examinations were performed to evaluate for potential ischaemic or haemorrhagic complications in the post-operative period (<24hours post procedure) and at each subsequent follow-up.

2.1.4 Results

Patient population

We identified 26 patients with 27 aneurysms. Eleven patients were male and the average of the patients was 59.3 years old (range 27-77). Fourteen patients had left sided aneurysms. There were 9 aneurysms located on the A1 segment, 15 aneurysms located at the A1/A2 junction, 2

aneurysms on the A2 segment and 1 aneurysm located at the A2/A3 junction. The average aneurysm fundus size was 2.9mm (range 2-6mm). The results are summarised in Table 1.

Patient No.	Location	Number of aneurysms on the ACA	Laterality	Aneurysm Neck (mm)	Aneurysm Dome (mm)	other treatment	Flow Diverter	First F/U (months)	occluded at F/U	Covered Branch Patent?	mRS pre-intervention	mRS post-intervention
1	A1	1	l	2	2	0	2 x PED	3	Y	Y	0	0
2	A1/A2	1	r	2.5	2.5	0	1 x p64	2	Y	Y	0	0
3	A1	1	r	2	2	0	1 x p64	3	Y	Y	0	0
4	A1/A2	1	r	2	3	0	1 x p64	3	Y	Y	0	0
5	A1/A2	1	l	2	3	0	1 x p64	3	Y	Y	0	0
6	A1/A2	1	r	3	3	0	2 x PED	4	Y	Y	1	1
7	A1 A1/A2	1 1	l l	2 2	4 2	coils 0	2 x p64 telescoped	4 5	Y Y	Y Y	0 0	0 0
8	A1	1	l	2	4	0	1 x p64	4	N/A	Y	1	1
9	A1/A2	1	l	2	2	0	1 x p64	1	Y	Y	1	1
10	A1	1	r	1	2.5	0	1 x p64	3	Y	Y	0	0
11	A1	1	l	2	2	0	1 x p64	1	Y	Y	0	0
12	A1/A2	1	l	3	6	Solitaire stent	1 x PED	N/A	N/A	Y	0	3
13	A1	1	r	4	2	0	1 x p64	3	Y	Y	0	0
14	A1/A2	1	r	2	2	0	1 x p64	3	N/A	Y	0	0
15	A1/A2	1	l	0	0	0	1 x p64	3	N	Y	0	0
16	A1	1	l	2	4	coils	1 x p64	N/A	N/A	Y	0	0
17	A1	1	r	2	4	0	1 x p64	3	N	Y	0	0
18	A1/A2	1	l	3	4	coils	1 x p64	3	N/A	Y	1	1
19	A1/A2	1	l	2	5	0	1 x p64	N/A	N/A	Y	0	0
20	A2/3	1	l	4	2.5	coils	1 x PED	5	Y	Y	0	0
21	A2	1	l	1	2	0	1 x p64	3	Y	Y	1	1
22	A1/A2	1	r	2	2	0	1 x p64	N/A	N/A	Y	0	0
23	A1/A2	1	l	3	2	Enterprise stent	1 x p64	3	Y	Y	0	0
24	A1/A2	1	r	2	2	0	1 x p64	N/A	N/A	Y	0	0
25	A1/A2	1	r	3	6	0	1 x p64	N/A	N/A	Y	0	0
26	A2	1	r	2	2	0	1 x PED	4	Y	Y	1	1

Table 1

Background demographics, aneurysm characteristics, clinical and radiological follow-up

Feasibility

Delivery of the flow diverter was possible in all cases. Six aneurysms had adjunctive devices used, 4 had coils in the aneurysms and two patients had stents. A single type of flow diverter e.g. either a p64 or PED, was used in 23 patients and 2-telescoped stents were used in 3 patients. Delivery of the flow diverter was possible in all cases.

Angiographic Follow-Up

At least 1 follow-up angiogram was available in 20 patients at an average of 3.1months (range 1-5months) (Fig. 1). Delayed follow-up was available in 13 patients at an average of 27.25 months (range 7-66 months). Of all patients with at least 1 follow-up angiogram 16 aneurysms were completely occluded (80% occlusion) and 1 patient had a minor remnant (5%). All covered branches remained patent at follow-up (Fig. 2).

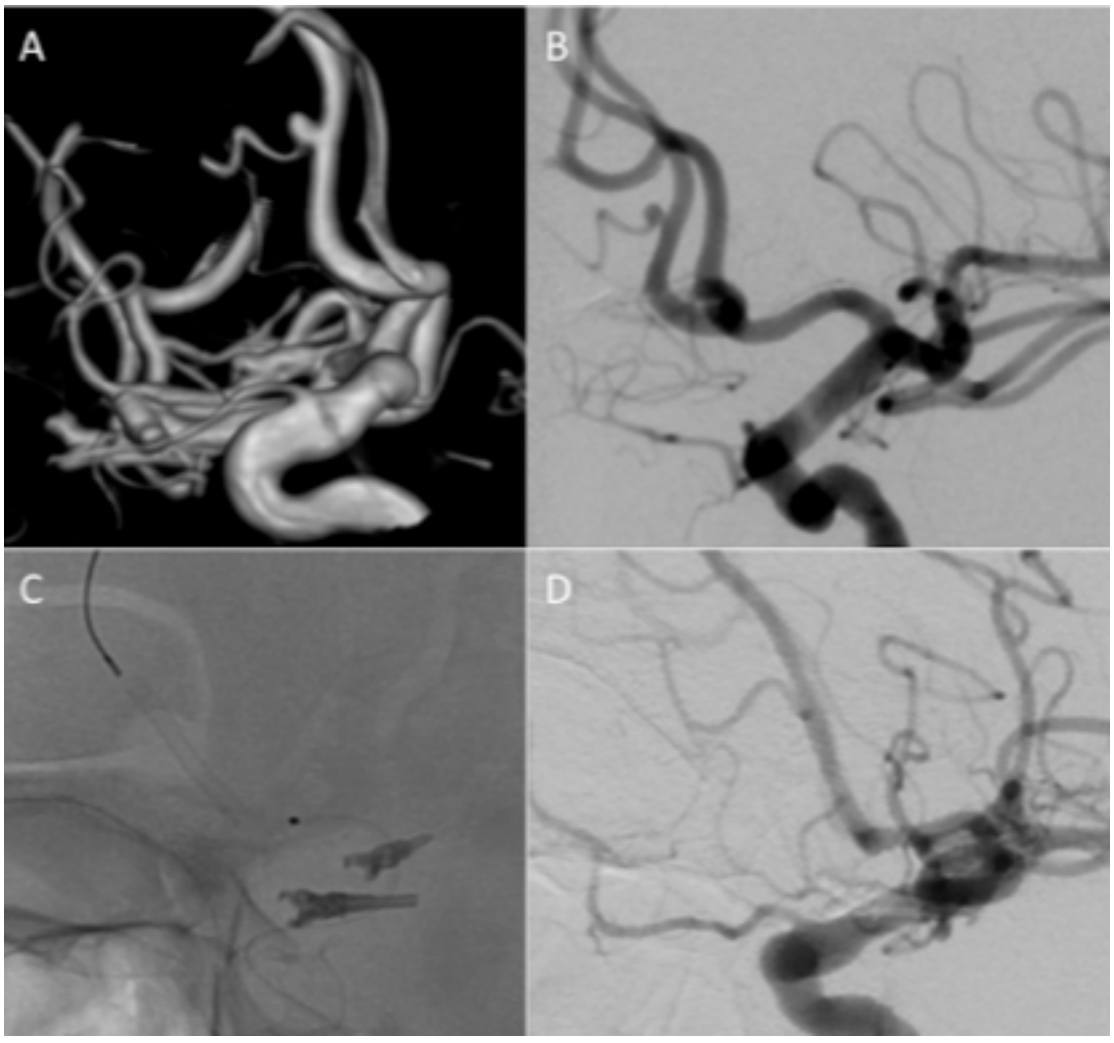

Figure 1

A patient in their twenties presented with an unruptured aneurysm of the A2 segment (Fig 1a and b) that was treated with a single PED (Fig. 1c). Catheter angiography performed at 3 months showed complete exclusion of the aneurysm from the circulation and patency of the fronto-polar branch (Fig. 1d).

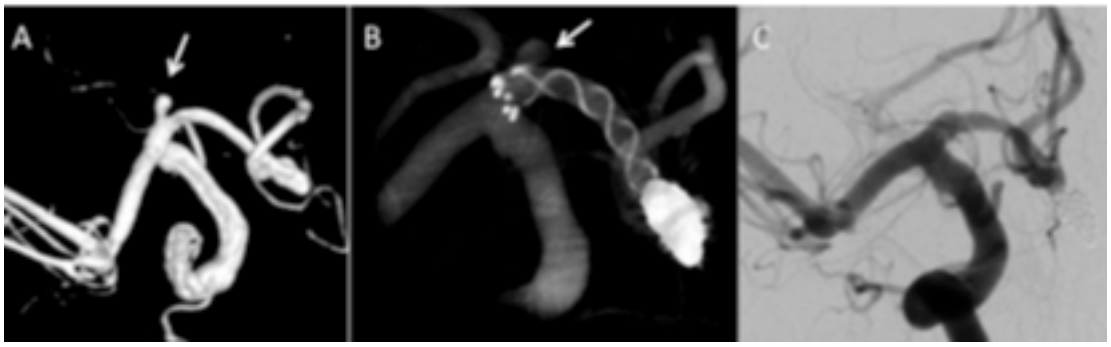

Figure 2

A patient in their early teens was treated with a single p64 flow diverter for an unruptured aneurysm arising from the proximal A1 segment of the right ACA (Fig. 2a and b, white arrow). An angiogram performed at 3 months post-treatment showed complete exclusion of the aneurysm from the circulation (Fig. 2c).

Complication Rate

A single case of mortality was seen in our series (patient 12). In this patient a left A1/A2 aneurysm had previously been coiled after a SAH. Follow-up DSA showed a progressive reperfusion of the aneurysm. Catheterization of and FD deployment into the left ACA were straightforward. DSA thereafter revealed a wire dissection of the left pericallosal artery, with a minor leakage. The perforated vessel was occluded with glue, with an instantaneous interruption of the extravasation. During the following night, the patient deteriorated clinically and CT showed a massive ICH, which eventually caused the death of this patient.

2.1.5 Discussion

Flow diverters are a new generation of stents that cause disruption of intra-aneurysmal blood-flow and changes in the transmural pressure gradient. Progressive intra-aneurysmal stasis and thrombosis occurs as does neo-endothelialisation of the stent to finally exclude the aneurysm from the circulation and reconstruct the parent artery (2). Even though these devices have recently entered the interventional sphere a large body of evidence regarding the effectiveness,

safety profile and technical limitations has already been amassed with several systematic reviews already available. The review by Briganti et al. (19) included 18 studies for a total of 1704 aneurysms in 1483 patients. Unruptured aneurysms accounted for 90% of aneurysms treated and 87.5% of aneurysms were located in the anterior circulation, the majority being located on the internal carotid artery upto the bifurcation (1368 aneurysms) with only 135 located on either the ACA or MCA. This group reported an overall rate of occlusion at final follow-up of 81.5% (range 69-100%). This study also showed progressive occlusion of the aneurysm with occlusion of 74.5% of aneurysms at 6-month follow-up (nine studies) and 89.6% occluded at 12 months (eight studies). The overall rate of ischaemic complications was 4.1% and haemorrhagic complications 2.9% and mortality reported at 3.4%.

Lv et al. (20) published the result of their meta-analysis and systematic review which included 1524 patients with 1732 aneurysms, 87.5% unruptured and 85.3% located in the anterior circulation blow the level of the ICA bifurcation. This group focused principally on complication rates, morbidity and mortality. They showed that the overall technical failure rate and complication rate was 9.3% with incomplete deployment of the stents accounting for the majority of the technical complications (5.2%), and vessel perforation, misplacement dissection, wire fracture and stent migration all accounting for less than 1% of technical complications. In this study the overall favourable clinical outcome was reported as 88.2% (mRS<2) and complete or near complete aneurysmal occlusion rate of 84.4%. They reported morbidity and mortality of 6.6% and these results are comparable with those of other analyses performed by Brinjikji et al. (21) who reported aneurysmal occlusion rates of 76%, morbidity of 5% and mortality of 4% in the 29 studies they evaluated. Similarly Arrese et al. (22) (15 studies, 897 patients with 1018 aneurysms) reported early mortality of 2.8% and late mortality of 1.3% with early morbidity 7.3% and late morbidity 2.6% with overall occlusion rates of 76.2%. Interestingly they showed a difference in the occlusion rate between the Silk flow diverter and the PED (68% occlusion vs. 88% respectively) but no increase in the rate of haemorrhagic complications between the devices. The rates of occlusion, morbidity and mortality from the major series using individual flow diverters (PED, Silk, SURPASS, p64 and FRED) are summarised in Table. 2.

Study	**Year of Publication**	**No. Of Patients**	**No. Of aneurysms**	**Flow Diverter**					**Morbidity**	**Mortality**	**Occlusion rate at Last FU**
				PED	Silk	SURPASS	p64	FRED			
Berge et al (23)	2012	65	77		73				7.80%	3%	84.50%

Wagner et al (24)	2012	22	26		23				5%	5%	86%
Maimon et al(25)	2012	28	32		31				7.20%	3.60%	83.30%
Lubicz et al(26)	2015	58	70		54				5.50%	0%	73%
Strauss et al(27)	2016	60	67		62				10%	6.67%	88%
Mpotsaris et al(28)	2015	25	28		28				8%	4%	59%
Shankar et al(11)	2016	92	92		92				8.70%	2.20%	83.10%
Briganti et al(29)	2012	273	295	182	151				3.70%	5.90%	85%
Yu et al(30)	2012	143	178	213					3.50%	3.50%	84%
O'Kelly et al(31)	2013	97	97	156					4.30%	6.40%	90%
Saatci et al(32)	2012	191	251	324					1%	0.50%	94.60%
Fischer et al(33)	2012	88	101	235					5.60%	1.10%	52%
Wakhloo et al(12)	2015	165	186			165			4.20%	2.40%	75%
De Vries et al(34)	2013	37	49			38			13.5%	0%	94%
Fischer et al(16)	2015	121	130				127		1.70%	0.80%	85.70%
Möhlenbruch et al(14)	2015	29	34					35	10.30%	0%	73%
Poncyljusz et al(35)	2013	6	8					8	0%	0%	100%
Briganti et al(15)	2016	20	24					24	0%	0%	83%
Kocer et al (13)	2014	35	37					35	2.80%	0%	100% (at 12 months)
Average									**5.41%**	**2%**	**81.8%**

Table 2

Summary of the different flow diverters, complication rates, and occlusion rate

The ACA is an extremely important artery that supplies eloquent brain territories with numerous small perorating branches (36,37). Some of these arteries can be derived from the AcomA when this vessel is present. Damage to these small vessels can result in devastating effects including hemiparesis, anosmia, amnesic syndromes and psychiatric conditions (38,39). Therefore, it is perhaps not entirely unexpected that the treatment of aneurysms arising from this vessel has followed standard endovascular and neurosurgical approaches. The patency of covered branches has naturally been of major concern when considering the use of flow diverters despite evidence

from animal models suggesting that even multiple telescoped flow diverters do not result in occlusion of perforating vessels (40). Neki et al. (3) recently published the results of their study evaluating the patency of the anterior choroidal artery following coverage by a flow diverter and they showed that in all cases with angiographic follow-up the artery remained patent and this is something we have seen in our department (unpublished results).

However, infarction after placement of a flow diverter in the distal anterior circulation has been seen with early reports published by Nelson et al (41) who reported a left basal ganglia infarction secondary to two PED's placed in the M1 segment of the left MCA with a pre-existing stent. Van Rooij and Sluzewski (42) reported a further case of left basal ganglia infarction after two telescoped PED's were placed in the A1 segment of the ACA. Recently larger series have been published in the scientific literature. Zanaty et al (43) described 10 patients with MCA aneurysms treated with flow diversion and they showed an occlusion rate of 77.7% (mean follow-up of 7.55 months) with 1 peri-procedural stroke (10%). One branch occlusion and 1 parent vessel occlusion, both of which were asymptomatic, were also seen in this group. Similarly Yavus et al. (4) used the PED to treat 25 aneurysms of the MCA with a complete occlusion rate of 84% with no mortalities and only one morbidity which was deemed to be secondary to vasospasm. In this series, of the 9 cortical branches that were covered and showed either reduced filling or complete occlusion, all were clinically asymptomatic. Caroff et al. (44) performed a retrospective analysis of 14 patients with 15 aneurysms of the MCA bifurcation, all treated with flow diversion and in this series although there were no mortalities, morbidity was 21% at follow-up and 43% of patients showed ischaemic lesions on MRI that was deemed secondary to the treatment. Similarly Briganti et al. (45) in their series showed a high rate of ischaemic complications (27%) with permanent neurological deficit in 21%. Pistocchi et al (46) published their series of 30 aneurysms treated with either the Silk or PED. Of these 30 aneurysms 21 were located in the ACA's. At mean follow-up of 13 months 79% of aneurysms were occluded with neurological complications seen in 11.1% (3.7% permanent). Lin et al. recently published their series of 28 patients with 28 aneurysms distal to the ICA bifurcation all of which were treated with the PED. In this study, of the 27 patients with angiographic follow-up, 21 had complete aneurysm occlusion. The peri-procedural complication rate was 10.7% with good outcome (mRS≤2) in 96.4%. Gawlitza et al. (47) published their series of 17 patients with 18 aneurysms, 13 of which were present on the MCA. In total 19 cortical branches were covered. Of these 'jailed' branches 3 were immediately occluded with a further 3 showing reduced blood flow (15.8% each) however, at latest follow-up only 2 branches were completely occluded although 47.4% of covered

branches were of reduced calibre. This demonstrates that changes in the flow pattern can occur rapidly and can adjust over time to changes in flow demand. There were no deaths in or permanent morbidity however, 2 patients had symptomatic perforator territory infarctions and asymptomatic lacunar infarctions were seen in 29.4% of patients. It is also worth noting that the in the recent meta-analysis performed by Lv et al. (20) only posterior circulation aneurysms and peripheral location had a statistically significant increased odds ratio for morbidity and mortality however, this was not seen on the multivariate analysis conducted by Brinjikji et al. (48). In our series none of the covered branches were occluded at follow-up.

Several reports have recently been published that deal specifically with the issue of flow diversion in the ACA territory. Clarencon et al (49) recently reported their results of treating ACA aneurysms with flow diverters. In this study of seven patients with eight aneurysms, 3 were located on the A1 segment and 2 on the A2-A3 segment with the remainder located on the AcomA. Three of the treated aneurysms showed complete occlusion at follow-up (grade A on the Raymond-Roy classification) and two showed grade B occlusion on the Raymond-Roy classification at follow up. There were no acute or delayed clinical complications and they noted that treatment with flow diverting stents was feasible in all patients. Dabus et al. (50) published the largest series to date of aneurysms in the ACA territory treated with the PED. In their series of 20 patients with 20 aneurysms they showed an aneurysm occlusion rate of 68.7% (11 of 16 patients with angiographic follow-up data at a mean of 10 months). There was one mortality secondary to early post-operative haemorrhage that the authors could not easily explain and one minor infarction (5% morbidity and 5% mortality). Taken together these results suggest that flow diverters can be used in the distal circulation with high success rates for aneurysm occlusion however, the risk of perforator infarction is present and although does not often lead to permanent morbidity there is a definite risk of this occurring. The predisposing factors for perforator infarction e.g. fusiform aneurysm, stent type etc. are yet to be elucidated and larger studies are required. In our series there was a single case of mortality and this was secondary to haemorrhage that occurred secondary to wire perforation of a vessel during deployment of the flow diverter. Even though the vessel was glued intra-operatively and the haemorrhage controlled a repeat haemorrhage occurred during the night and led to the death of the patient. It is difficult for us to explain this. Vessel perforation has been noted during balloon inflation to remodel implanted flow diverters as well as during wire manipulation (34,41). Delayed haemorrhage is generally considered to be one of two different types – either subarachnoid or intraparenchymal

and each occurs with a risk of 3% (51) and the exact underlying mechanism is still to be elucidated. Distant haemorrhages may be caused by haemorrhagic transformation of infarctions that occurred during the procedure (52,53) whereas subarachnoid haemorrhage is thought to occur secondary to degradation of the aneurysm wall by enzymes triggered during thrombosis (54,55).

Aside from flow diversion alternative endovascular treatment strategies are available. Cavalcanti et al (56) published their single centre experience of 22 consecutive patients with distal ACA aneurysms and they managed to achieve 95% or greater initial occlusion in all aneurysms, including in the 13 patients that presented with subarachnoid haemorrhage. Of the 13 patients that had radiographic follow-up complete occlusion was seen in 11 patients and recoiling was required in two cases. Prior to this Menovsky et al (57) presented their series of coiled distal ACA aneurysms and they achieved initial complete occlusion in 91.7% of patients with 66.7% of aneurysms remaining completely occluded at last follow-up. Similarly Yamazaki et al. (58) achieved complete occlusion in 19 of 27 coiled pericallosal aneurysms with a neck remnant in 6 aneurysms. Overall using coiling as the primary treatment modality for the treatment of ACA aneurysms, both ruptured and unruptured, the mean morbidity stands at 8.8% (range 0-17.2%) with a mean mortality of 8.8% (range0-20.7%) (57,59–63). Neurosurgical treatment is also an option and the de Sousa et al. reported a 100% rate of complete occlusion on routine post-operative angiography after the treatment of 74 distal ACA aneurysms. Lehecka et al (64) et al. reported an occlusion rate of 95% of 362 patients undergoing micro-neurosurgical treatment.

This paper is one of the first to exclusively deal with aneurysms arising from the ACA. Our results suggest that this treatment option is technically feasible and carries a low risk of transient and/or permanent clinical complications.

Our study has several limitations. First it is a retrospective analysis of data prospectively collected from a single centre. The relatively small population and lack of long term follow-up are further limitations.

2.1.6 Conclusion

Our series suggest that the treatment of ACA aneurysms with flow diverters is technically feasible, has a good safety profile and can result in exclusion of the aneurysms arising from these vessels.

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3 Chapter 3

3.1 The management of unruptured saccular aneurysms of the M1 segment with flow diversion - a single centre experience.

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3.1.1 Abstract

Purpose

The optimal strategy for the treatment of M1 segment aneurysms has not been determined as both standard microneurosurgical and endovascular techniques can pose challenges. We sought to determine the efficacy of flow diverting stents to treat small, unruptured aneurysms of the M1 segment.

Methods

We retrospectively reviewed our database of prospectively collected information for all patients treated with flow diversion for an unruptured saccular aneurysm of the middle cerebral artery (MCA) between February 2009 and February 2016. The relationship to early cortical branches, aneurysm fundus size, number and type of flow diverting stent (FDS), complications and follow-up data was recorded.

Results

In total 15 patients were identified that matched our inclusion criteria (11 female and 4 male). The average age of the patients was 58.3 years old (range 14-76yrs). All patients had a single aneurysm affecting the M1 segment of the MCA, 10 (66.6%)of which were related to early cortical branches. Ten aneurysms were located on the left (66.6%). The average aneurysm fundus size was 3mm (range 2-9mm). Thirteen patients have had follow-up angiographic studies. In total, 8 aneurysms have been completely excluded, and 6 remain incompletely occluded (3 = mRRC II and 3 = mRRC IIIa). One patient suffered a stroke and another patient had an iatrogenic vessel dissection that was non-flow limiting.

Conclusions

Flow diversion can be used to treat small, unruptured aneurysms of the M1 segment of the MCA and even though side vessel occlusion can occur clinically relevant infarction occurs infrequently.

3.1.2 Introduction

The middle cerebral artery (MCA) can be considered as the continuation of the internal carotid artery. Phylogenetically it is a relative new artery and appeared as a dominant branch in higher species as the telencephalon enlarged (1). MCA aneurysms make up approximately one fifth of all intracranial aneurysms (2) and when considering aneurysms in this location one often thinks of bifurcation aneurysms. However, another group of aneurysms that involve the pre-bifurcation segment exist and although less common, account for up to 16% of MCA aneurysm and up to 6% of all intracranial aneurysms (3). As the majority of MCA aneurysms occur at the bifurcation with a relatively easy neurosurgical approach many centres employ a clip first policy for aneurysms of the MCA. However, as endovascular neurosurgery has evolved, MCA aneurysms should no longer be considered the sole territory of microneurosurgery. This is especially true of M1 segment aneurysms, which require a deeper dissection, and their intimate relationship with small branches can make clipping more complex. Conversely the M1 segment of the MCA is readily accessible to the endovascular surgeon and its morphology may make it suitable to for flow diversion.

In this article we review our experience of the management of M1 segment aneurysms treated with endoluminal flow diverter stents (FDS).

3.1.3 Methods

Patient Population

We searched our prospectively maintained database, for patients treated in our institution between February 2009 and February 2016, with unruptured, saccular aneurysms arising from the M1 segment of the MCA and treated with flow diverting stents. Using these inclusion criteria we identified 15 patients. For each patient we recorded demographic data, clinical presentation, location of the aneurysm, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information.

Classification of M1 segment aneurysms

Although there is disagreement on what constitutes the M1 and M2 we chose to categorise the M1 segment as pre-bifurcation. Small cortical branches arising prior to the division of the MCA into a superior and inferior trunk or into three divisions and relationship between these branches and the aneurysm were noted.

Endovascular Treatment

All treatments were performed under general anaesthesia. Two commercially available FDS were used: Pipeline Embolisation Device (PED) (Medtronic) and P64 (Phenox, Bochum, Germany). Patient informed consent was obtained before the procedure in all cases. The selection of FDS was dependent upon the operators' judgement. Selection of the FDS was initially based on availability. Initially only the PED was available however, after the p64 gained the CE mark it was also available for use in our department. Furthermore, in our experience, the p64 offers advantages in that it can be completely deployed and resheathed to allow repositioning alongside improved visibility compared to the PED.

A single FDS was placed in 14 patients and multiple telescoped FDS were placed in 1 patient. In three patients the aneurysms were coiled. In one of these patients there was an aneurysm recurrence secondary to coil compaction. In another case there was a neck residual and in the final case coils were initially placed in the aneurysm however, a satisfactory packing density could not be safely achieved and therefore, it was decided place a FDS across the aneurysm neck.

All patients received dual antiplatelet therapy (aspirin 75mg daily and clopidogrel 75mg) started 7 days prior to the planned treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche) within 24 hours of the planned procedure. In patients who demonstrated resistance to clopidogrel, ticagrelor (180mg) was used as a substitute. Four patients received aspirin and ticagrelor and eleven patients received aspirin and clopidogrel. The post-procedural antiplatelet regimen consisted of clopidogrel/ticagrelor continued for 3 months following treatment and aspirin continued for life.

All procedures were performed via the right common femoral route using a 6Fr access system as standard. All procedures were performed under heparin anticoagulation with a 5000IU bolus dose at the start of the procedure and subsequent 1000IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline.

Procedural Assessment and Follow-Up

Patency and flow characteristics within the MCA and any cortical branches were assessed angiographically immediately after placement of the FDS and during follow-up. Procedural follow-up was performed initially at 3-6 months, again at 9-12 months and then once per year

until aneurysm occlusion. Standard angiographic projections were used to assess the patency of the vessels and the aneurysms in addition to angiographic projections that repeated those used during the treatment. Aneurysm occlusion was graded as either completely excluded, minor remnant, major remnant, or unchanged (patent) and additionally using the modified Raymond-Roy classification (4).

Neurological examinations were performed to evaluate for potential ischaemic or haemorrhagic complications in the post-operative period (<24hours post procedure) and at each subsequent follow-up.

IRB approval was not required for this article.

3.1.4 Results

Population

In total, 15 patients were identified that matched our inclusion criteria (11 female and 4 male). The average age of the patients was 58.3 years old (range 14-76yrs). All patients had a single aneurysm affecting the M1 segment of the MCA, 10 (66.6%) of which were related to early cortical branches (Fig. 1).

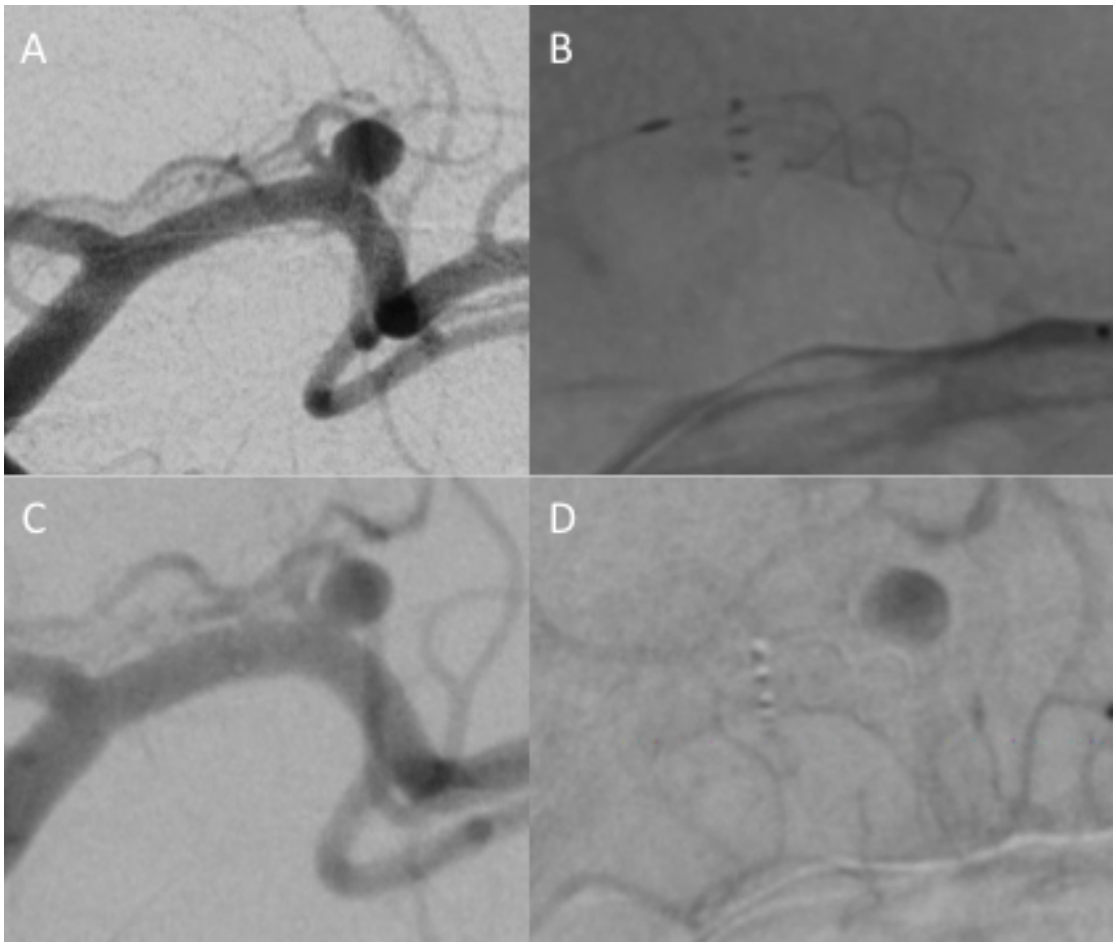

Figure 1

A saccular aneurysm associated with an early cortical branch (Fig. 1a) was treated with a singular p64 flow diverter (Fig. 1b). Early arterial phase angiography following stent deployment shows filling of both the aneurysm and the cortical branch (Fig. 1c) however, marked intra-aneurysmal stagnation is noted on delayed phase imaging (Fig. 1d). There is no follow-up imaging available yet.

Ten aneurysms were located on the left (66.6%). The average aneurysm fundus size was 3mm (range 2-9mm). The results are summarised in Table 1.

Patient Number	Related to Cortical branch	Side	Fundus size (mm)	Aspect ratio	Other treatments	Flow Diverter	Complications	Last follow-up	Side vessel occlusion	Aneurysm status	Modified Raymond-Roy score
1	Y	L	3	1.5	0	p64 x 1	N	7 months	N	minor remnant	IIIa
2	Y	R	2	1	0	p64 x 1	N	3 months	N	minor remnant	II

3	Y	R	2	1	Solitaire	PED x 1	N	44 months	Y	excluded	I
4	Y	L	3	1.5	0	p64 x 1	N	N/A	N/A	N/A	N/A
5	Y	R	2	1	0	p64 x 1	N	16 months	Y	minor remnant	IIIa
6	Y	L	2.5	1.25	coils	p64 x 1	asympt. ICA dissection; anaphylactic reaction	21 months	N	excluded	I
7	Y	L	4	1	coils	PED x 1	N	52 months	N	exlcuded	I
8	N	L	2	2	0	PED x 1	ischemic - stroke in MCA territory both perforator and cortical territory	18 months	N	excluded	I
9	N	L	2.5	1	0	p64 x 1	N	14 months	N	minor remnant	II
10	N	L	2	1	0	p64 x 1	N	4 months	N	excluded	I
11	Y	L	2	1	0	p64 x 1	N	22 months	N	minor remnant	IIIa
12	Y	R	3	1	0	p64 x 1	N	16 months	N	minor remnant	II
13	Y	R	2	1	coils	p64 x 1	N	21 months	N	excluded	I
14	N	L	4	1	0	p64 x 1	N	21 months	N	excluded	I
15	N	L	9	1.125	0	p64 x 2, PED x 1	N	3 months	N	excluded	I

Table 1

Summary of the aneurysm characteristics and follow-up angiographic status of all patients with M1 segment aneurysms treated with FDS.

Feasibility

Delivery of the flow diverter was possible in all cases. Fourteen patients were treated with a single type of flow diverter (p64, n=11; PED, n=3) and one patient had multiple telescoped flow diverters (2 p64 and 1 PED) (Fig. 2).

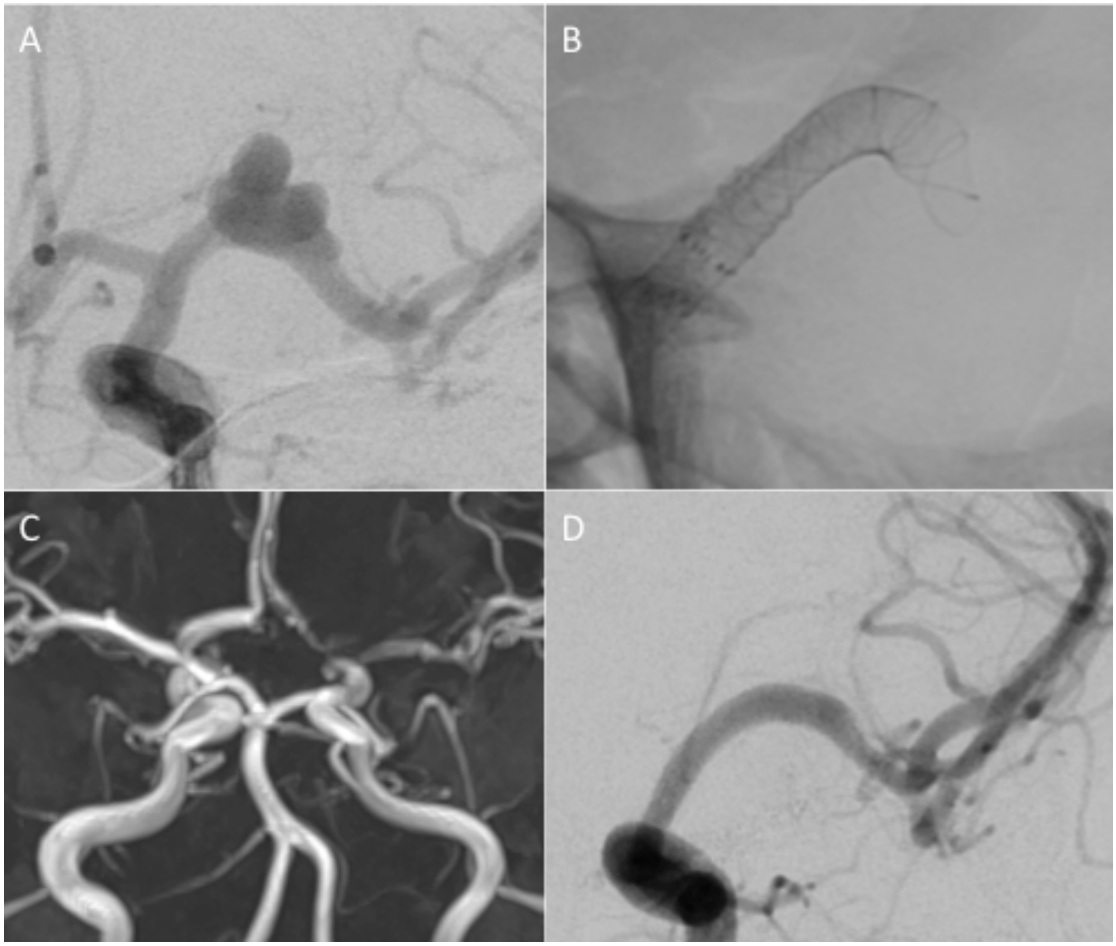

Figure 2

A patient with a large multi-lobulated aneurysm of the M1 segment that does not appear related to an early cortical branch (Fig. 2a). This was treated with telescoped flow diverters (Fig. 2b). A TOF MRI can be seen to show persistent filling of the left ACA via the anterior communicating (Fig. 2c) with exclusion of the aneurysm seen on follow-up imaging at 3 months (Fig. 2d).

Three patients had the aneurysm previously coiled. In two of these patients there were aneurysmal remnants and in the third patient the aneurysm had recurred. All of these aneurysms were successfully treated with flow diversion. In one patient a stent assisted coiling was planned and a solitaire was implanted however, the aneurysm was still uncoilable as the coils continued to prolapse and risk a side branch. Therefore, a single flow diverter was implanted at a later date (1month later)

Angiographic Follow-Up

Fourteen patients have had follow-up angiographic studies (median 18.7months) with the most recent angiographic results documented. In total 6 patients have aneurysms that are not

completely excluded (three of which are classified as mRRC II and the remaining three classified as mRRC IIIa) whereas 8 aneurysms have been completely excluded (Fig. 2 and 3). A decrease in contrast opacification was seen in all of the aneurysms that remain incompletely excluded. Only 2 side vessels that were covered by the FDS were occluded, in one case the aneurysm is excluded and in the other the aneurysm is not excluded from the circulation.

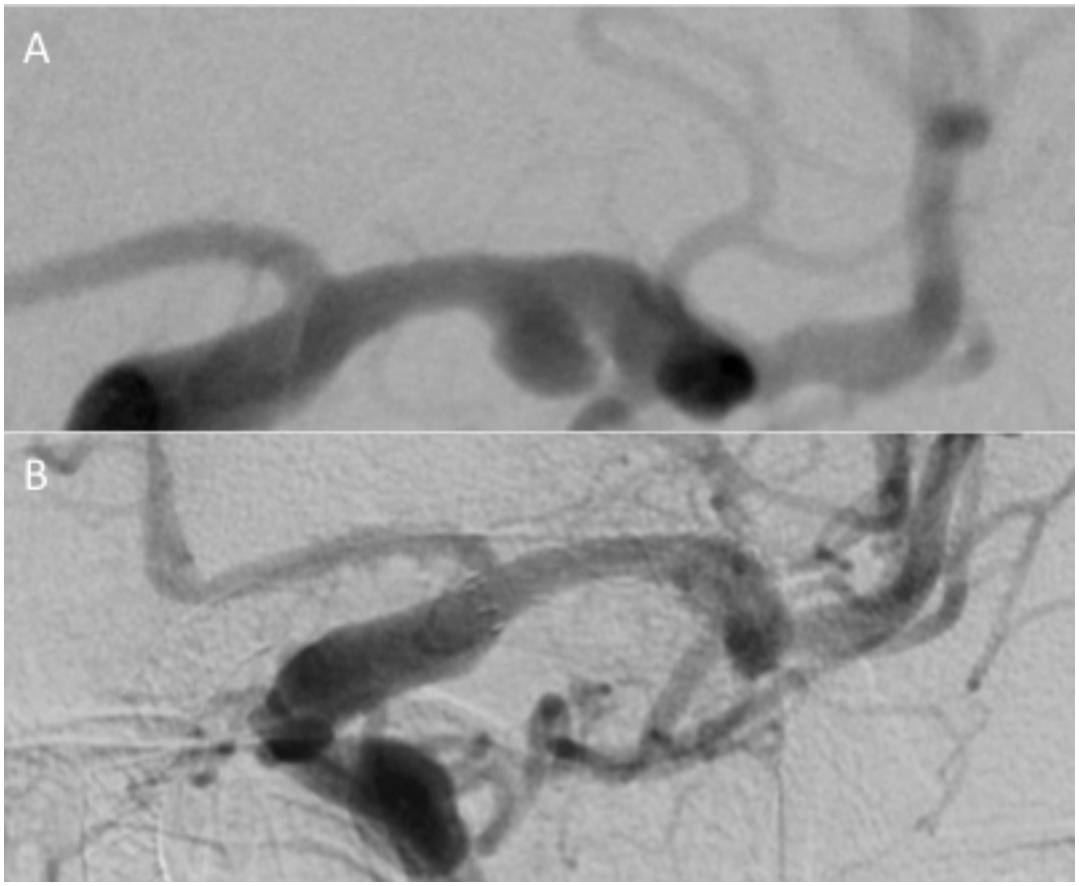

Figure 3

A patient with a saccular aneurysm arising from the inferior aspect of the M1 segment and treated with a single FDS. Angiography at 3 months showed complete exclusion of the aneurysm from the circulation.

Complication Rate

In one patient the procedure was a technical success with no intra-operative complications however, three days following the procedure the patient developed an acute right-sided hemiparesis and aphasia. An MRI demonstrated restricted diffusion within the MCA territory however, there was no evidence of in-stent luminal narrowing or thrombosis (Fig. 4).

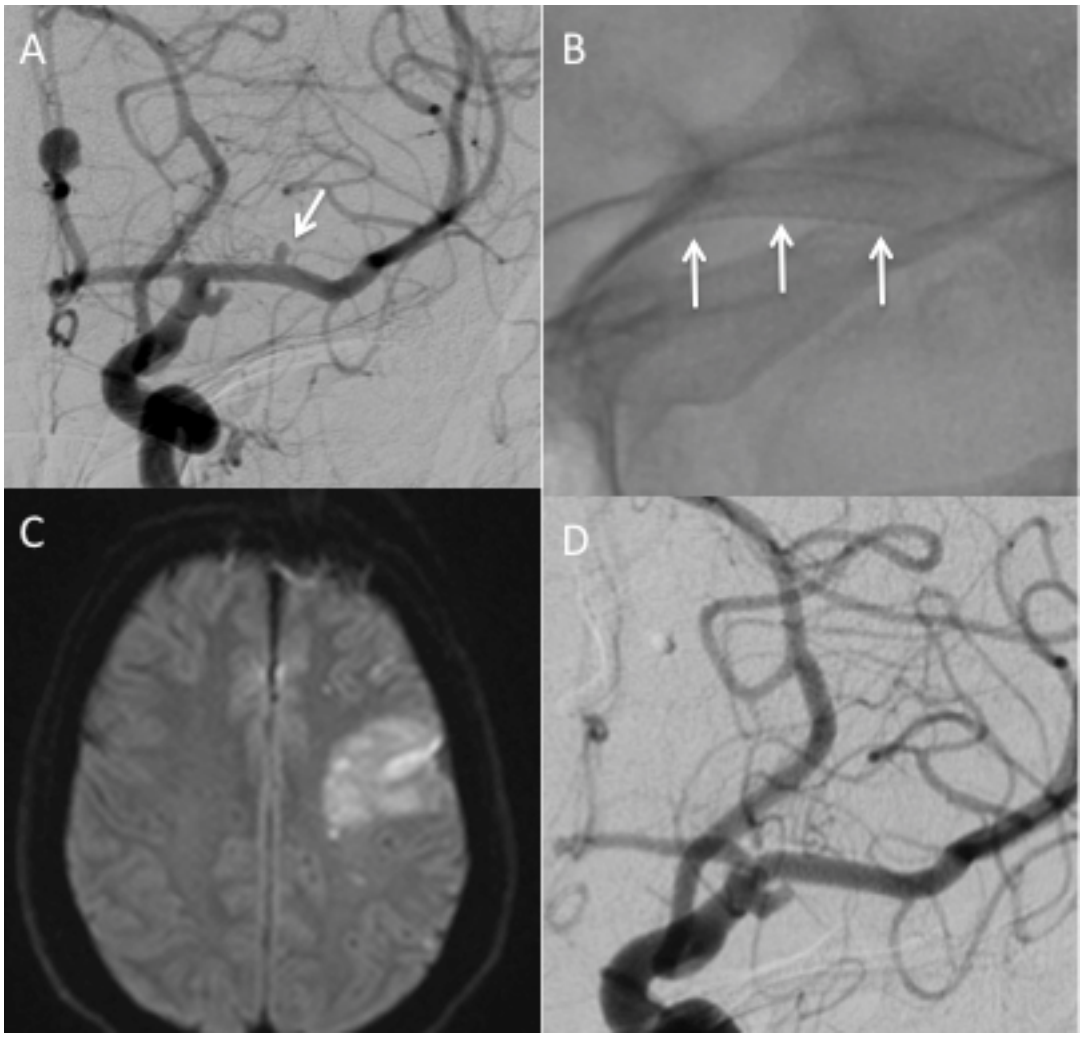

Figure 4

A patient with multiple aneurysms and a history of polycystic kidney disease. The M1 segment aneurysm (Fig. 4a) was treated with a single PED (Fig. 4b). There were no intra-operative complications. Three days after the procedure she developed acute neurological symptoms and MRI showed restricted diffusion (Fig. 4c). Angiography at the same time (not shown) did not reveal in stent stenosis/thrombosis or vessel occlusion. The most recent follow-up angiogram (21months) shows complete exclusion of the aneurysm (Fig. 4d)

It is possible that a thrombus formed and caused a cortical vessel occlusion, enough to cause ischaemia but that the vessel had recanalised prior to the angiogram being performed.
Another patient had a small asymptomatic iatrogenic ICA dissection that was not flow limiting.

3.1.5 Discussion

Aneurysms arising from the M1 segment are relatively uncommon and they can be challenging to treat. These aneurysm are often small, intimately related to one or more arterial branches and may be thin walled (5). Although some would consider MCA aneurysms to be suitable for microneurosurgical clipping, this presumption is based primarily upon the relatively easy access to MCA bifurcation aneurysms. Aneurysms arising from the M1 segment represent more of a challenge to the neurovascular surgeon (6). In addition to the more difficult and deeper dissection, one must preserve the numerous cortical arteries that may arise from the M1 segment as well the lateral lenticulostriate arteries. Türe et al. (7) divided the M1 segmental arteries into:

Cortical branches – often the temporopolar, frontotemporal and orbitofrontal
Lateral lenticulostriate arteries.

A cadaveric study performed by Ulm et al. (8) showed that 39% of MCA aneurysms arise from early cortical branches rather than at the true bifurcation of the MCA. It is possible that previous reports have confounded these two distinct aneurysmal locations. In the recent paper by Topcuoglu et al. (9), 62.5% of patients had aneurysms associated with early cortical branches which they termed 'variant bifurcation'. This result is similar to our own experience where 66.6% of aneurysms were associated with an early cortical branch. Preservation of these branches during clipping procedures is essential. The same meticulous preservation of vessels is required during endovascular coiling procedures. In the case series presented by Doerfler et al. (10) of the 18 patients with unruptured MCA aneurysms treated with endovascular coiling the permanent procedural morbidity was 6.6% which was comparable to that of clipped unruptured aneurysms in the meta-analysis of King et al. (11). However, in this series only 3 of these 18 patients harboured M1 segment aneurysms. In the study of Zhou et al. (12) successful treatment was achieved in 96.6% of cases and 2 (n=28, 6.9%) patients had procedure related complications one of which resulted in hemiparesis.

The introduction of flow diverting stents has provided an alternate treatment method for aneurysms. This is particularly true for aneurysms where standard coiling procedure could be anatomically or technically challenging such as those arising from the M1 segment. These aneurysms are often small and have a relatively wide neck. In addition since they are often related to early cortical branches that may be small (less than 1mm in diameter), can supply eloquent brain territory and have acute angles, and protecting these branches can be difficult. For

these reasons FDS may be a suitable alternative treatment strategy. Previous groups have documented their experience with the management of MCA aneurysms with FDS (13) however, none to our knowledge, have dealt exclusively with aneurysms arising from the M1 segment. A particular concern when dealing with MCA aneurysms is the fate of covered cortical branches, which is of particular concern in the MCA since the distal collateral pathway is based purely on leptomeningeal vessels and there is no definitive way to ensure that these will provide adequate circulatory capacity if a jailed vessel is occluded. Although, as has been reported by others, covered arteries tend not to close unless there is competing flow downstream (14). Perforator infarction is also of concern and small clinically silent infarctions have been seen by other groups (15) The recently published results of the IntrePED study (16) showed that higher rates of acute stroke were seen in patients with hypertension and aneurysms of the MCA however, these did not reach statistical significance.

Zanaty et al (17) described 10 patients with MCA aneurysms treated with flow diversion and they showed an overall occlusion rate of 77.7% (mean follow-up of 7.55 months) with 1 peri-procedural stroke (10%). One branch occlusion and 1 parent vessel occlusion were seen neither of which were symptomatic. Of the five patients in this group with aneurysms located on the M1 segment, 3 had complete occlusion and 2 had near complete occlusion. In the series of Topcuoglu et al (9) of 29 aneurysms in 28 patients, 10 were located on the M1 segment, 50% of which presented with SAH. In this series 8 of the aneurysms were fusiform or dissecting and 2 were saccular however, 8 of the aneurysms demonstrated complete occlusion at follow-up, 1 showed near total occlusion and 1 remained unchanged. Gawlitza et al. (18) published their series of 17 patients with 18 aneurysms, 13 of which were present on the MCA. In total 19 cortical branches were covered. Of these 'jailed' branches 3 were immediately occluded with a further 3 showing reduced blood flow (15.8% each) however, at latest follow-up only 2 branches were completely occluded although nearly half of the covered branches were reduced in calibre demonstrating that changes in the flow pattern can occur rapidly and can adjust over time to changes in flow demand. Two patients had symptomatic perforator territory infarctions and asymptomatic lacunar infarctions were seen in 29.4% of patients although there was no permanent morbidity or mortality. It is also worth noting that in the recent meta-analysis performed by Lv et al. (19) only posterior circulation aneurysms and peripheral location had a statistically significant increased odds ratio for morbidity and mortality however, on the multivariate analysis conducted by

Brinjikji et al. (16) this was not evident. In our series two of the covered branches were occluded at follow-up but neither of these resulted in infarction.

The average size of the aneurysm in our cohort was 3mm (2-9mm). The data from ISUIA (20) would suggest these aneurysms have a very low risk of rupture. However, there is evidence contrary to this data, for example 15% of the ruptured aneurysms arising from the MCA in the study of Elsharkawy et al (21) were <7mm. Similarly, Forget et al (22) also showed that 15% ruptured aneurysms in their cohort were smaller than 7mm. Bansal et al. showed an even higher rupture rate with 45.2% of ruptured aneurysms that presented to their institution being <5mm (23). In the prospective 10-year cohort study of Murayama et al (24) 69.6% of the aneurysms that ruptured during follow-up were <7mm and the mortality of those with ruptured aneurysms <5mm was 18%. Additionally, small aneurysms can show relatively rapid growth. Ramchandran et al (25) showed 10.1% of aneurysms <7mm showed growth over mean follow-up of 4 years whilst Zylkowski et al (26)showed growth in 21% of <7mm aneurysms. Chalouhi et al (27) identified a variety of risk factors that should be considered when deciding to treat small aneurysms that include amongst others presence of multiple aneurysms, previous SAH, patient age, location and familial history of SAH. For these reasons we evaluate each patient independently and offer treatment to some even when the aneurysm is <7mm.

Our study has several limitations. We have dealt solely with unruptured, saccular aneurysms and therefore it is not clear whether the results could be extrapolated to fusiform aneurysms although if the results of Topcuoglu et al (9) are considered, fusiform aneurysms of the M1 segment may be amenable to flow diversion treatment. Additionally, as some of the aneurysms have not occluded after several months it may not be suitable to use FDS for M1 segment aneurysms in the acute ruptured state. In this regard the multi-step process reported by Yavuz et al. (13) suggests that up to 18 month may be required to for complete aneurysm occlusion. Similarly Briganti et al. reported that only 17% of aneurysms showed complete occlusion at 3month angiography compared to 100% at 24 months. However, it is worth pointing out that, at least in the study of Yavuz et al. the aneurysms presented appear to be true bifurcation aneurysms and given that it has been suggested the occlusion effect of flow diversion is less when branching vessels are larger, it may be that for M1 aneurysms associated with smaller early cortical branches the occlusion would be more rapid. The relatively small number of patients in this series is a reflection of our strict inclusion criteria however, we feel that this is important to clarify the possibility of FDS as a treatment option in different anatomical and clinical settings

3.1.6 Conclusion

The treatment of M1 segment aneurysms with both the p64 and PED flow diverting stents is technically feasible and carries a good safety profile. Further larger studies would be of use to determine their efficacy in this specific anatomical location.

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4 Chapter 4

4.1 Flow diversion for the treatment of MCA bifurcation aneurysms

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4.1.1 Abstract

Background

Intracranial aneurysms located at the bifurcation of the middle cerebral artery (MCA) can often be challenging for the neurointerventionalist. We aimed to evaluate the efficacy and safety of flow diverting stents (FDS) in the treatment of these aneurysms.

Material and methods

We retrospectively reviewed our prospectively maintained database to collect information for all patients with unruptured saccular bifurcation MCA aneurysms treated with FDS between January 2010 and January 2016. In addition to demographic data we recorded the location, aneurysm characteristics, previous treatments, number and type of FDS, complications and clinical and angiographic follow-up.

Results

Our search identified 13 patients (7 male) with an average age of 61.7 years (47-74yrs). All patients had a single bifurcation aneurysm of the MCA and none of the aneurysms were acutely ruptured. The average fundus size of the saccular aneurysms was 3 mm (range 1.5-10 mm). Follow up studies were available for 12 patients. Based on the most recent follow-up angiograms, 6 aneurysms (50%) were totally occluded; 5 aneurysms (41.7%) showed only a small remnant and 1 aneurysm (8.3 %) remained unchanged. One patient suffered from an ischemic stroke with resultant permanent hemiparesis (mRS 3). In another case there was an in-stent thrombosis during the intervention, which resolved upon intra-arterial infusion of Eptifibatide (mRS 0). There were no intra-operative vessel or aneurysm ruptures and no mortalities. Angiography of the covered MCA branches showed no change in the caliber or flow of the vessel in 6 (50%), a reduction in caliber in 5 (41.7%) and a complete occlusion in 1 (8.3%). All caliber changes and occlusions of the vessels were asymptomatic.

Conclusions

In our series 91.7% of treated MCA bifurcation aneurysms were either completely occluded or showed only a small remnant with a good safety profile. Flow diversion of MCA bifurcation aneurysms should be considered as an alternative treatment strategy when microsurgical clipping or alternative endovascular treatment options are not feasible.

4.1.2 Introduction

Since the publication of the International Subarachnoid Aneurysm Trial (ISAT) intracranial aneurysms are being increasingly treated via the endovascular approach as an alternative for craniotomy and surgical clipping (1). Aneurysms of the middle cerebral artery (MCA) remain, however, challenging for the neurointerventionist as they most commonly arise at a bifurcation of the vessel and frequently have a wide neck that can incorporate one or more branches (2), rendering traditional coiling difficult and necessitating the use of adjunctive devices such as balloon remodelling (3–7) or stent assisted coiling (8–12). Over the last few years flow diversion has proved to be a feasible and efficacious approach for the treatment of sidewall and dissecting aneurysms (13–19) even though long term clinical data is still unavailable. The role of flow diverter stents (FDS) in treating bifurcation aneurysms remains, however, unclear. In this report we review our experience in treating MCA bifurcation aneurysms with flow diversion as the primary approach or secondary therapy after previous coiling or clipping with subsequent recanalization/aneurysm residual.

4.1.3 Materials and Methods

Population

We retrospectively reviewed our prospectively maintained database to identify patients with aneurysms of the MCA bifurcation who were treated with flow diversion. Records were made of demographic data, clinical presentation, location and morphology of the aneurysms, the endovascular procedure, the postoperative complications and the latest angiographic and clinical follow-up.

Definition of MCA bifurcation aneurysm

We chose to categorize aneurysms arising at the first main division of the M1 trunk and those arising at an early division of a dominant superior or inferior trunk as MCA bifurcation aneurysms. Aneurysms of the M1 segment and distal to the MCA bifurcation were excluded.

Endovascular Treatment

Informed consent was obtained prior to the intervention in all patients. A loading dose of two antiplatelet agents (aspirin 100mg per day and clopidogrel 75 mg per day) was administered in every case and the adequacy of the antiplatelet therapy was measured using the Multiplate Analyzer (Roche, Germany). Patients found resistant to clopidogrel received 2x90 mg ticagrelor

daily. All therapeutic interventions were performed under general anesthesia. Arterial access was carried out through a standard 6Fr right common femoral route in all cases. A bolus dose of heparin (5000IU) was administered after securing the introducer sheath followed by repeat bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline. The post-procedural antiplatelet regimen consisted of clopidogrel/ticagrelor continued for 12 months following treatment and aspirin continued for life.

A Pipeline embolization device (PED) was used in one case (Covidien, Irvine, California), the p64 flow modulation device (Phenox, Bochum, Germany) was used in all other cases. The choice of flow diverter was down to the operator and we only have the p64 and PED available in our department. The PED is one of the most widely studied devices and is made of 25% platinum and 75% nickel-cobalt chromium alloy with a porosity of 65-70%. It is available in a variety of different sizes and diameters and multiple telescoped PED's can be used to alter the porosity (20). The p64 is a braided flow diverting stent composed of 64 nitinol wires. Two platinum wires are wrapped around the shaft and assist in the radio-opacity of the device. The 64 wires are grouped into 8 bundles proximally, with each bundle consisting of 8 wires. A radio-opaque marker is attached to end of each of these bundles. The porosity of the device is 51-60%. The p64 is unique amongst flow diverters in that it is mechanically detached and can be resheathed even after complete deployment.

Clinical and angiographic Follow-Up

All patients were evaluated clinically and neurologically prior to the treatment and during the postoperative hospital stay, another clinical and neurological evaluation was performed at every follow up as well. Initial follow-up catheter angiography was performed at 3 months. The extent of the aneurysmal occlusion was graded as:

1 total occlusion, no contrast filling of the aneurysm sac (Raymond Roy I)

2 subtotal occlusion, minor residual sac filling or neck remnant (Raymond Roy II)

3 incomplete occlusion, substantial residual sac filling (Raymond Roy III)

4 unchanged, patent aneurysmal sac with constant morphology compared to the pretreatment angiogram

4.1.4 Results

Population

There were 13 patients matching our inclusion criteria (7 male) with an average age of 60 years (42-76yrs). The treated aneurysms were equally distributed between right and left. Three patients had a second aneurysm at a different location, one patient had two and another patient had four other intracranial aneurysms located elsewhere. All aneurysms were saccular with a fundus size ranging from 1.5-10 mm (average fundus size 3mm) and with the exception of one case all aneurysms had a dome/neck ratio of less than 1.5. Twelve aneurysms were located at the fist main MCA-bifurcation (early bifurcation in two cases), one aneurysm was located at the bifurcation of each of the superior and inferior trunk. All patients were treated on an elective basis. The two fusiform aneurysms were previously clipped with incomplete occlusion. Four of the saccular aneurysms were previously treated by other modality (three were coiled and in one case there was an enlarging neck remnant after clipping and then coiling). The results are summarized in table 1.

Patient No.	Gender	Age	Side	Dome (mm)	Neck (mm)	Previous treatments	FDS (No. + Type)	Occlusion	Covered Branch	Complications	Change in Baseline mRS
1	m	60	L	2	2	surgery, coils	1 x p64	2, RRC II	Unchanged	N	N
2	m	64	R	2	2	N	1 x p64	1, RRC I	Asymptomatic occlusion	N	N
3	f	47	L	1.5	1.5	coils	1 x p64	1, RRC I	Unchanged	N	N
4	f	50	L	2	2	coils	1 x p64	1, RRC I	Reduction in caliber	N	N
5	f	60	R	4	4	N	1 x p64	2, RRC II	Reduction in caliber	N	N
6	m	58	R	2	3	N	1 x p64	2, RRC II	Reduction in caliber	N	N
7	m	60	L	3	4	N	1 x p64	1, RRC I	Unchanged	N	N
8	m	76	R	10	3.5	N	1 x p64	2, RRC II	Reduction in caliber	N	N
9	f	74	R	4	1.5	N	1 x p64	4	Reduction in caliber	N	N
10	m	58	L	2	2	N	1 x p64	NA	NA	N	N
11	m	71	L	2	3	N	1 x p64	2, RRC II	Unchanged	stroke	Y (mRS 3)
12	f	59	L	3	1	N	1 x p64	1, RRC I	Unchanged	asymptomatic thrombosis	N
13	f	65	R	2	2	N	1 x PED	1, RRC I	Unchanged	N	N

Table 1.

Demographics, aneurysm characteristics, clinical and radiological follow-up.

Feasibility

The delivery of the FDS was unproblematic in all cases. A single flow diverter was used in all cases. A Pipeline embolisation device (PED) was used in one case; all other patients were treated using the p64 flow modulation device.

Angiographic follow up

Follow up studies were available for 12 patients with first follow up catheter angiography performed at mean 3.1 months after treatment. Delayed angiography was performed at mean 15.8 months. There was complete aneurysmal occlusion in 6 cases (50%) (Fig.1). Near complete occlusion with only a neck remnant was achieved in a further 5 cases (41.7 %). A single case remained unchanged in our series therefore, complete or near complete occlusion was achieved in 91.7% of our cases.

The covered branches remained unchanged in calibre and flow in 6 cases (50%). In 5 cases there was a reduction in the calibre of the covered branch but the vessel remained patent with anterograde flow (Fig. 1). There was a single case of asymptomatic occlusion of the covered branch (8.3%). All the cases where the covered vessel calibre was reduced or completely occluded were clinically asymptomatic.

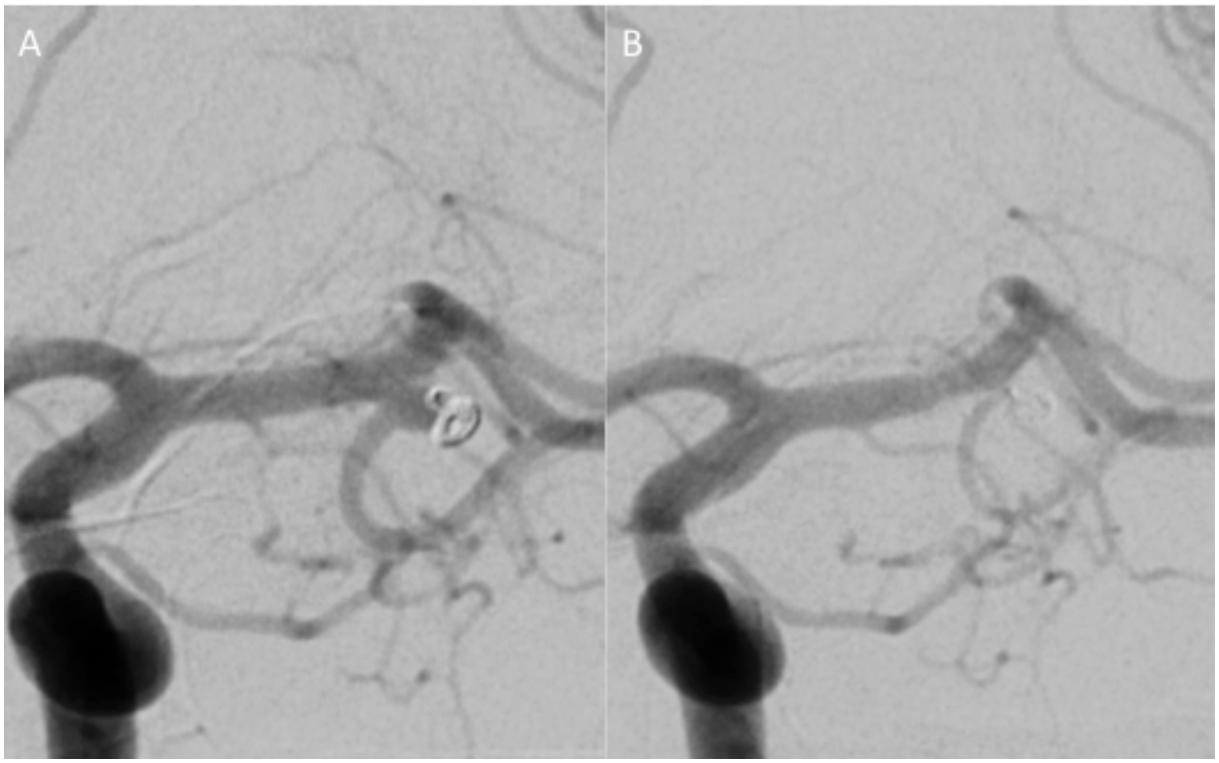

Figure 1

A small neck recurrence after a previous coiling (Fig. 1a). Repeat treatment using coils would have necessitated a stent into the inferior branch and therefore, it was felt an alternative strategy would be to place a single p64 FDS into the superior MCA trunk. A follow-up angiogram performed 3 months later (Fig. 1b) showed on contrast enhancement of the aneurysm and a reduction in the caliber of the size of the inferior trunk but with persistent anterograde flow. The patient was neurologically intact and there were no clinical consequences of the vessel modification.

Complications

There was one case of an immediate thrombosis of the FDS, which resolved secondary to intra-arterial infusion of Eptifibatide and the patient recovered without neurological sequelae. One patient developed hemiparesis four days after the implantation of the FDS. The emergent MRI showed restricted diffusion in the basal ganglia and centrum semiovale. The immediate angiogram showed no in-stent thrombosis or vessel occlusion. Although the exact cause of the infarction in this case is not know it is possible that a drop in blood pressure plus reduced flow through the FDS may have resulted in decreased perfusion to the infarcted region (Fig. 2).

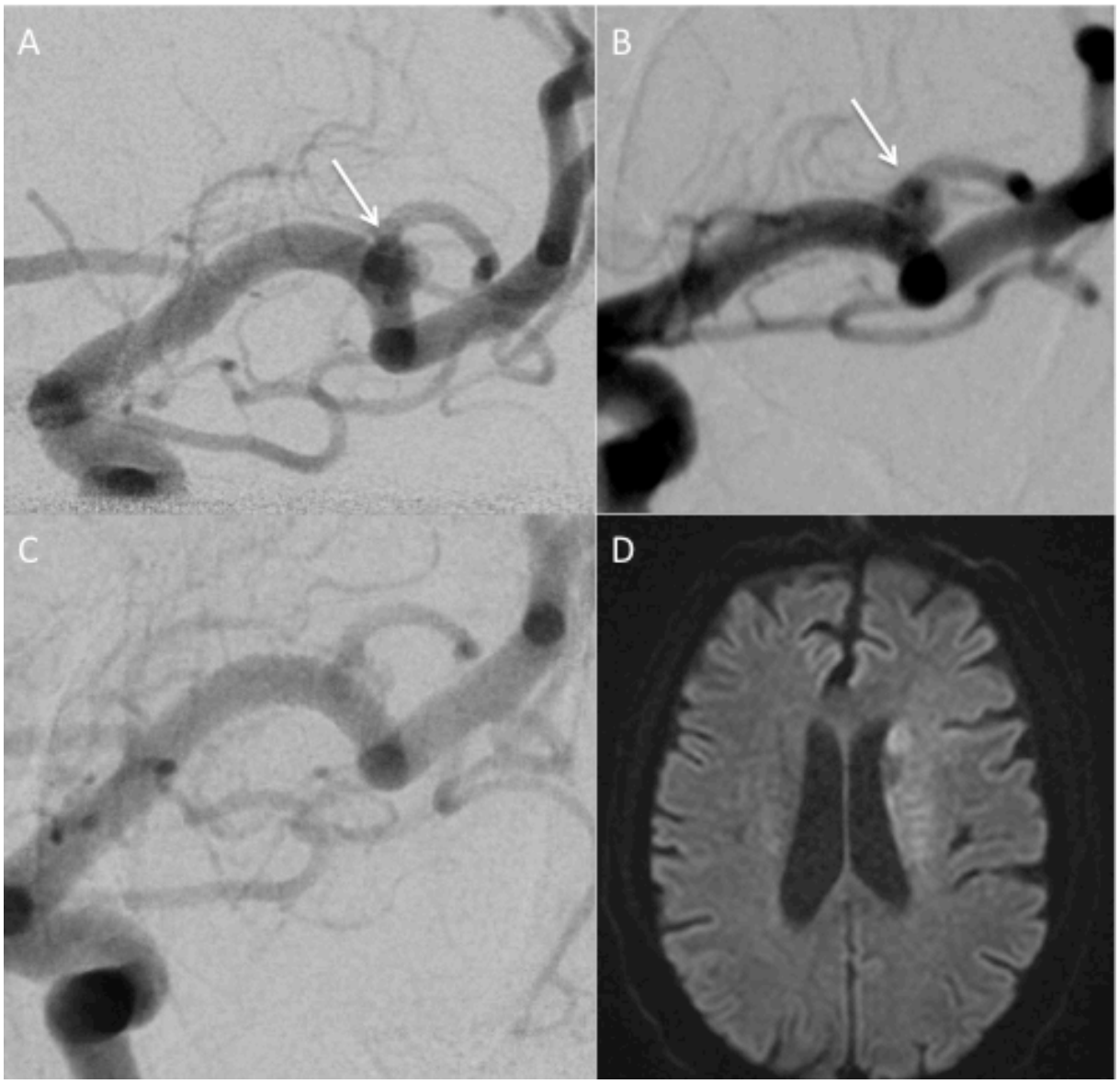

Figure 2

A patient treated with a single p64 FDS for an MCA bifurcation anerurysm. There were no intra-operative complications and immediately post-procedure the patient awoke with baseline neurology. 5 days post procedure the patient developed a right hemiparesis. Catheter angiography at this time (Fig. 2c) showed all branches were patent with anterograde flow and minimal filling of the aneurysm. An MRI showed restricted diffusion (Fig. 2d).

4.1.5 Discussion

The middle cerebral artery (MCA) is the larger of the two terminal branches of the internal carotid artery. Over its course the MCA is divided into four segments: the M1 (sphenoidal) segment, the M2 (insular) segment, the M3 (opercular) segment and the M4 (cortical) segments

(21). The branching pattern of the main trunk of the MCA is variable with a bifurcation being the most common: absence of a main division in 6%, bifurcation in 64%, trifurcation in 29% and quadrifurcation in 1% of people. The location of the bifurcation depends on the length of the M1 Segment. The main divisions are of equal diameter in only 15% of the cases with the inferior trunk being dominant in 50% (22).

Aneurysms of the middle cerebral artery occur most often at the main division point (23). In a review of a population-based series of 3005 patients with 4253 intracranial aneurysms, 1704 were MCA aneurysms, of which 1385 (81%) were located at the main bifurcation of the MCA. The percentage of aneurysms located at the main bifurcation was even higher among ruptured MCA aneurysms (89%)(2). Elsharkawy et al (24) analysed 1009 aneurysms located on the MCA to determine if there were particular risk factors associated with a risk of rupture. In this study location at the MCA bifurcation, wall irregularity and non-spherical shape were all identified as risks for rupture. Interestingly, it was also seen that 26% of patients with ruptured MCA bifurcation aneurysms were classified as small (<7mm) and that this was significantly greater than the percentage of patients with large (15-24mm) and giant (≥25mm) aneurysms, which presented with rupture in 15% and 2% of cases respectively. This highlights, that at least in this location, small aneurysms carry a not insignificant risk of rupture.

From an anatomical perspective MCA bifurcation aneurysms are often wide necked and may incorporate one or more branches. This can be challenging for traditional endovascular approaches such as coiling without adjunctive devices (2,25,26). In the study of Jin et al (27) 103 aneurysms of the MCA bifurcation were treated with only coiling. The post-coiling angiogram in these patients showed a complete occlusion in 27.2% and residual neck in 58.3%. At follow-up angiography (mean 30 months) recanalization was seen in 25% of cases and just over 20% of these recanalised aneurysms were deemed completely occluded on post-coiling angiography. Other authors have also published their experience of MCA aneurysm treatment involving endovascular techniques; for example Bracard et al reviewed 152 MCA aneurysms treated by coil occlusion. They showed complete or near-complete occlusion in 84.2% of aneurysms, of which 80.2% persisted at the 5 year follow up (28). In a large retrospective analysis of 300 consecutive endovascularly treated MCA aneurysms (80% ruptured), complete or near total occlusion was achieved in 91% of cases (25). Similarly Zaidat et al. (29) reviewed their endovascular treatment of 161 consecutive MCA aneurysms and reported technical feasibility of 98.8% and a retreatment

rate of 11%. In the meta-analysis of 12 studies performed by Brinjikji et al. they noted an overall occlusion rate (complete or near complete occlusion) of 82.4% with an overall procedure related permanent morbidity/mortality rate of 5.1% for unruptured aneurysms. Whilst these latter studies are useful a major difficulty in their interpretation is they include all MCA aneurysms together with no separation based on anatomical location.

In order to address the various anatomical abnormalities that may be encountered when treating MCA bifurcation aneurysms a variety of techniques have been developed and include: balloon remodeling(3–7), stent-assisted coiling (7–9,11,12), neck bridging devices (30,31) and intra-aneurysmal flow disrupters (32–35).
Eboli et al. (36) recently published their series of 184 MCA bifurcation aneurysms treated endovascularly. In this series stent assisted coiling was required in 70 cases (38%) and only 3 cases (1.6%) required 'Y' stenting. They achieved an initial total occlusion rate of 59.8% however, on follow-up angiography (mean 41 months) complete aneurysm occlusion was seen in 90.1% of patients with a further 6.1% of patients having a stable remnant. The overall peri-procedural morbidity was 3.8% and the mortality rate in the unruptured cohort was 0%.

The Woven EndoBridge, WEB (Sequent Medical, Aliso Viejo, California) is an intra-saccular device designed to disrupt the intra-aneurysmal flow at the level of the neck to encourage intra-aneurysmal thrombosis. Although some authors reported high feasibility of this device with promising early and midterm post-procedural angiographic results (32–34) the follow up study by Cognard and Januel reported worsening at follow up in 71.5% in their series of 14 patients with wide neck bifurcation aneurysms (of which 11 were at the MCA bifurcation) with compression of the cage demonstrated in 8 of the 14 cases (37). Additionally, the available sizes of the WEB device may render it unsuitable to small wide necked aneurysms. The pCONus (Phenox, Bochum, Germany) device is an electrolytically detachable self-expanding nitinol implant with 4 distal petals designed to open inside the aneurysm providing support for coiling of wide neck bifurcation aneurysms. Aguilar-Perez recently published their experience with the pCONus neck-bridging device for the treatment of wide necked aneurysms. This series included 11 MCA aneurysms with complete occlusion of 6 aneurysms (54.5%) at follow up and only neck remnant in 3 cases (27.2%). (30)

Since their introduction, flow diverter stents (FDS) have gained popularity for the treatment of intracranial aneurysms. The occlusion of an aneurysm by FDS is initially by the promotion of intra-aneurysmal thrombosis through induced flow stasis. The blood's flow though the struts of a FDS depends on flow demands and thus preserving the patency of covered branches where flow is needed (38). For example, even relatively small arteries such as the anterior choroidal artery remain patent after coverage by FDS as was recently shown by Neki et al (39). Covered branches with an adequate collateral arterial supply, such as the ophthalmic artery, where the orbit enjoys a rich collateral blood supply through branches of the external carotid artery, frequently undergo spontaneous, asymptomatic occlusion (40). Rangel-Castilla et al recently published their longer-term results of 82 aneurysms treated with FDS with an emphasis on covered branches (41). In this study of 76 covered ophthalmic arteries 10.5% were occluded (clinically asymptomatic), 28 posterior communicating arteries were covered with 10.7% of the vessels occluded (clinically asymptomatic), and 21 covered anterior choroidal arteries with no evidence of occlusion. This study also reported 2 cases where the anterior cerebral artery was covered and there was occlusion with filling of the A2 segment via the contralateral anterior cerebral artery. Therefore, there is evidence that branch occlusion can be asymptomatic. However, this may not necessarily be the case in more distal locations such as at the MCA bifurcation.

Yavus et al. (42) used the PED to treat 25 MCA aneurysms located at or distal to the bifurcation in 21 patients and reported a complete occlusion in 21 of the cases (84%). There were no mortalities, and apart from one patient who developed ischemia several days after the procedure (which was attributed to vasospasm by the authors) there were no significant peri-procedural morbidities. There was reduced filling of 6 and total occlusion of 3 of the covered branches, all of which remained clinically asymptomatic. The authors concluded that the PED is a safe and feasible option in treating aneurysms arising at the MCA bifurcation. The results reported by Caroff et al. (43) were not so promising. In their retrospective review of 14 patients harboring 15 saccular MCA bifurcation aneurysms treated with FDS, the authors reported ischemic complications in 43% of the cases detected on MRI, and although there were no mortalities, procedure related morbidities reached 21% on follow up, most of these were related to occlusion or slow flow in the covered branches. Complete occlusion was, however, achieved in only 62% of the treated aneurysms. In another report by Briganti et al. (44) total occlusion of the MCA bifurcation aneurysms was achieved in 80% with the rest of the aneurysms being partially occluded. This series included 14 patients harboring 15 MCA-aneurysms of which 13 were

located at the MCA bifurcation, all of which were treated using the PED. Of the thirteen side branches covered by the PED, follow up angiographic studies showed reduced flow in 6 and total occlusion of 3 of them. The authors reported ischemic complications in 27% of the cases with permanent neurological deficient in 21%. Topcuoglu et al (45) recently published their series of 29 aneurysms of the MCA treated with flow diversion, 6 of which occurred at the true bifurcation of the MCA (defined as the division of the MCA in an superior and inferior trunks). Of these 6 cases, all of which were treated with the Silk FDS (Balt, Montmercy, France), occlusion of the covered branch occurred in 50% of cases, none of which resulted in morbidity or mortality. In our series we achieved a complete occlusion in 50% of patients and near complete occlusion in 41.7%. We had no mortalities and only one case of permanent morbidity. We believe, as with flow diversion used in other sites, that the aneurysms with near complete occlusion will continue to occlude over time as neo-endothelialisation occurs however, longer-term follow-up is required. In a single case the aneurysm showed no change at delayed angiography (9 months) and we are unable to explain this phenomenon. The patient had no background medical conditions that could potentially interfere with neo-endothelialisation nor did they demonstrate any abnormal response to the anti-platelet medication.

Saleme et al. (46) sought to clarify the role of covered branches and collateral supply. They compared remodelling of the side braches covered after the deployment of flow diverters dividing the aneurysms in two groups based on whether the territory supplied by the side branch received a direct collateral supply or not. This study included the placement of FDS across the anterior cerebral artery, the anterior communicating artery, the terminal ICA and the MCA (51.4% of cases). They showed that in the group with a direct collateral supply 78.5% of covered branches had undergone narrowing or occlusion at 6 months, although no new strokes were seen on MR imaging. Hence, the authors suggest that symptomatic remodelling of covered side braches depends on the extent and type of collateral supply and this is similar to the findings reported earlier by Rangel-Castilla et al (41)[41][40][39]. One explanation of the lower occlusion rate observed with flow diversion for bifurcation aneurysms might be the persistent flow through the covered braches incorporated by the aneurysm. Fahed et al. (47) compared flow diversion with and without occlusion of the jailed branch in 14 wide neck aneurysms induced in 8 canines and found that occlusion of the jailed branch resulted in better occlusion rates of aneurysmal occlusion. Patent aneurysms were associated with leaks or holes in the neo-intima covering the aneurysm neck. The authors concluded that persistent flow to the jailed branch is a potential

cause of treatment failure after flow diversion for bifurcation aneurysms. Furthermore, it is also worth remembering that the porosity of FDS is known to alter with curves and this appears to be most marked for FDS deployed across bifurcation aneurysms and on the outer edge curves of vessels (48,49). This effect has been studied for both the PED and the Silk flow diverters with similar results and it is likely that the same effect will be seen with the p64.

Despite the plethora of currently available modality for the treatment of MCA-aneurysms, considering the relatively straight forward access, the good outcome after clipping and the ability for simultaneous removal of a space occupying hematoma in cases of ruptured aneurysms, a surgical approach remains the principal treatment of MCA aneurysms in many centers (2,50,51). In their series of 282 ruptured and 261 unruptured MCA aneurysms Rodríguez-Hernández and colleagues reported complete aneurysm obliteration in 98.3% and good clinical outcomes in 92 % of patients with unruptured and 70.2% with ruptured aneurysms (52). In a review of the literature by Wuyang Yang and Judy Haung the authors favoured the microsurgical approach for the definitive management of MCA aneurysms. The reviewed surgical series reported occlusion rates between 90-89.3% with good clinical outcomes in 92-100 % of unruptured and 70-80 % of ruptured MCA aneurysms treated with clipping. The authors also suggested that the significantly higher retreatment rated and lower occlusion rates of the endovascular approach would offset the favourable clinical outcome in the short term of the less invasive approach. (53)

Our study has several limitations. The sample size is small and the treated aneurysms are heterogeneous. Another limiting factor is that flow diversion was not the primary treatment in 6 cases (42.8%), rather implemented as a secondary therapy for persistent aneurysmal perfusion after coiling or clipping. The results are also limited by the relatively short follow up period (13 months on average), especially because the definitive results of this modality depend on the progressive reduction of flow inside the aneurysmal sack. Although one type of flow diverter stents, namely the p64 was used in all but one case in our series, we believe that the relatively inferior results in comparison to other endovascular or surgical modalities are related to the special anatomic consideration of the MCA bifurcation, rather than the technical specification of the flow modulation device.

4.1.6 Conclusion

Based on our small series, flow diversion for the treatment of bifurcation MCA-aneurysms is feasible with good angiographic results and acceptable complication rates. However compared to the results of other endovascular techniques and to surgery, total occlusion of bifurcation MCA-aneurysms seems to be less frequent with flow diversion. We therefore believe that flow diversion should be reserved for cases where other treatment modalities are deemed unfeasible or carry excessive risk.

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5 Chapter 5

5.1 The Fate of Side Branches Covered by Flow Diverters – results from 140 patients.

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MAP and PB serve as proctors and consultants for phenox GmbH, with moderate financial compensation.

HH is a co-founder and shareholder of phenox GmbH.

The other authors have no potential conflict of interest.

5.1.1 Abstract

Background

Flow diverter stents (FDS) are a recognised treatment option for intracranial aneurysms. There remain on-going concerns regarding the safety of FDS especially when it comes to the fate of covered side branches. We sought to report on the patency of side branches covered by FDS.

Methods

We retrospectively reviewed our database of prospectively collected information for all patients treated with FDS for an unruptured saccular aneurysm of the clinoid, ophthalmic, and terminating segments of the internal carotid artery between September 2009 and July 2016. The aneurysm location, fundus size, and the state of covered branches at last angiography were recorded in comparison to pre-operative angiography.

Results

We identified 140 patients, with 147 aneurysms, that met our inclusion criteria. Five patients had bilateral aneurysms. There were 31 male patients in our cohort (21.9%) and the mean average age was 56.2±13.7-years. Sixty-seven aneurysms arose from the communicating, 58 from the ophthalmic and 22 from the clinoidal segments. At last follow-up (mean 22.3months) 116 aneurysms were completely occluded (78.3%). On the most recent angiogram 7 ophthalmic (5.3%), 20 posterior communicating (42.6%), 0 anterior choroidal (0%), and 2 anterior cerebral arteries (14.3%) were completely occluded. Reduced vessel calibre was seen in 11 ophthalmic (8.3%), 3 posterior communicating (6.4%), 0 anterior choroidal and 6 anterior cerebral arteries (42.9%). One patient died during follow-up.

Conclusion

The side branch occlusion rate was 20% and included ophthalmic, posterior communicating and anterior cerebral arteries. Consistent with other studies we did not see occlusion of the anterior choroidal artery.

5.1.2 Introduction

Flow diverter stents (FDS) have gained increasing acceptance amongst the interventional and neurosurgical communities as an alternative treatment options for saccular intra-cranial aneurysms (1–13). Similarly they have also shown benefit in previously difficult to treat diseases such as posterior circulation non-saccular aneurysms (14). To date the majority of studies have focused on the occlusion rate of the treated aneurysms alongside complications (15). However, there is little literature on the fate of side branches that have been covered by the FDS secondary to the treatment of an aneurysm. Although small studies have looked at the fate of individual branches such as the anterior choroidal artery (16) or the ophthalmic artery (17) we are aware of only a single study that has reviewed the fate of all the major branches of the distal internal carotid artery (ICA) (18).

We sought to determine the fate of covered branches in our institution.

5.1.3 Methods

Study Design and Patients

This is a single centre retrospective case series analysis of consecutive patients with aneurysms arising from the clinoid (C5), ophthalmic (C6) or communicating (C7) segments of the ICA and treated with at least one FDS at our institution between September 2009 and July 2016. Data for all patients undergoing treatment with flow diversion is entered into our prospectively maintained database. From this database we identified all patients with aneurysms of the clinoid, ophthalmic and communicating segments as defined by Bouthillier et al (19). We chose these segments because aneurysms arising from any of these locations will likely cover at least one major side branch (e.g. ophthalmic, posterior communicating, or the anterior choroidal artery) and in certain circumstances may cover the origin of the anterior cerebral artery (ACA). Two types of flow diverter were used – the Pipeline Embolization Device (PED) (Medtronic, Irvine, California) and the p64 (phenox, Bochum, Germany).

All patients received dual antiplatelet therapy (aspirin 100 mg daily and clopidogrel 75 mg daily) for at least 5 days prior to the treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche, Basel, Switzerland) and since 2016 the VerifyNow test (Accumetrics) was also used. Patients found resistant to clopidogrel received 2x90 mg ticagrelor daily. The post-procedural antiplatelet regimen consisted of clopidogrel (or ticagrelor) continued

for 12 months following treatment and aspirin continued for life. Procedures were performed via the right common femoral route using a 6Fr access system as standard and either a Marksman (Medtronic, Dublin, Ireland) catheter or an Excelsior XT27 (Stryker Neurovascular, Kalamazoo, USA) catheter to deploy the FDS. All procedures were performed under heparin anticoagulation with a 5000 IU bolus dose at the start of the procedure and subsequent 1000 IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline.

Because of the retrospective study design, approval by a medical ethics committee was not necessary according to local regulatory requirements.

Imaging Analysis

All patients treated with FDS undergo routine 4 or 6 vessel catheter angiography prior to the procedure. Routine follow-up angiography is performed at 3-6 months, 9-12 months and then each year until the aneurysm is excluded from the circulation.

The native arterial configuration was based on the pre-operative angiography. Where a vessel was not seen on the pre-operative angiography e.g. the posterior communicating artery, it was recorded as 'not present'. Any patients that did not have a conventional catheter angiogram prior to the treatment with FDS were excluded from the study. The location and size of aneurysms was based on catheter angiography.

The termination of the FDS was reviewed in all cases and recorded based on the catheter angiography. For each potentially covered vessel – ophthalmic, posterior communicating, anterior choroidal, and anterior cerebral artery, a status was recorded as:

Not Present (NP) – based on the native pre-operative angiogram
Not Covered (NC) – not covered by the FDS on angiography
Patent (P) – no change in flow or calibre of a covered vessel
Reduced calibre (RC) – a reduction in the calibre of the covered vessel
Occluded (O)– no anterograde flow seen in the covered vessel

Clinical outcome data was recorded in our database. For all patients with an occluded or reduced calibre vessel follow up CT and MR imaging was also reviewed to determine the presence of territorial infarctions.

5.1.4 Results

We identified 140 patients, with 147 aneurysms, that met our inclusion criteria. Five patients had bilateral aneurysms. There were 31 male patients in our cohort (21.9%) and the mean average age of the patients at treatment was 56.2±13.7 years. In terms of aneurysm location, 67 arose from the communicating segment, 58 from the ophthalmic segment and 22 arose from the clinoidal segment. The average aneurysmal fundus size was 4.2mm for aneurysms arising from the ophthalmic and communicating segments and 5.1mm for those arising from the clinoidal segment. On average 1.1 p64 FDS were implanted (range 1-3) and 1.9 PED's were implanted (range 1-3). No patients had both a p64 and a PED implanted. At last follow-up (mean 22.3months) 116 aneurysms were completely excluded from the circulation (78.3%). The results are summarised in Table 1.

Characteristic	**Result**
No. Patients	140
No. Aneurysms	147
No. Of patients with bilateral aneurysms	5
Mean Age ± SD	56.2±13.7
Male	31 (21.9%)
Aneurysm location	
Clinoid (C5)	22
Ophthalmic (C6)	58
Communicating (C7)	67
Average Aneurysm Size	
Clinoid (C5)	5.1mm
Ophthalmic (C6)	4.2mm
Communicating (C7)	4.2mm
No. Of Aneurysms Occluded at Follow-up	116 (78.3%)

(RRC 1)	

Table 1.

The baseline demographics and aneurysm characteristics

(RRC – Raymond Roy classification)

The pre-operative catheter angiograms in each patient were used to determine the native state of the side branch anatomy and configuration of the circle of Willis. On angiography, we identified 144 ophthalmic arteries (one patient did not have an ophthalmic artery arising from the ICA). All patients had an identifiable anterior choroidal artery (145 in total) and 75 posterior communicating arteries were seen. Of these branches, 133 ophthalmic arteries, 91 anterior choroidal arteries, 47 posterior communicating arteries and 14 anterior cerebral arteries were actually covered by at least one FDS. On the most recent angiogram (average 22.3 months post-op) 7 ophthalmic arteries (5.3%), 20 posterior communicating arteries (42.6%) (Fig. 1), 0 anterior choroidal arteries (0%), and 2 anterior cerebral arteries (14.3%) were completely occluded. Reduced anterograde flow and/or vessel calibre was seen in 11 ophthalmic arteries (8.3%) (Fig. 1), 3 posterior communicating arteries (6.4%), 0 anterior choroidal arteries and 6 anterior cerebral arteries (42.9%). The results are summarised in table 2.

Characteristic	**Result**
Number of Side Branches	
Ophthalmic	144
Posterior Communicating Artery	75
Anterior Choroidal	145
Number of Stents Terminating in Segments	
C6	54
C7	76
M1	15
Number of Covered Branches	
Ophthalmic	133

Posterior Communicating Artery	47
Anterior Choroidal	91
Anterior Cerebral Artery	14
Number of Arteries with Reduced Flow After Coverage	
Ophthalmic	11
Posterior Communicating Artery	3
Anterior Choroidal	0
Anterior Cerebral Artery	6
Number of Arteries Occluded Flow After Coverage	
Ophthalmic	7
Posterior Communicating Artery	20
Anterior Choroidal	0
Anterior Cerebral Artery	2

Table 2

Summary of the baseline status and most recent angiographic status of covered branches.

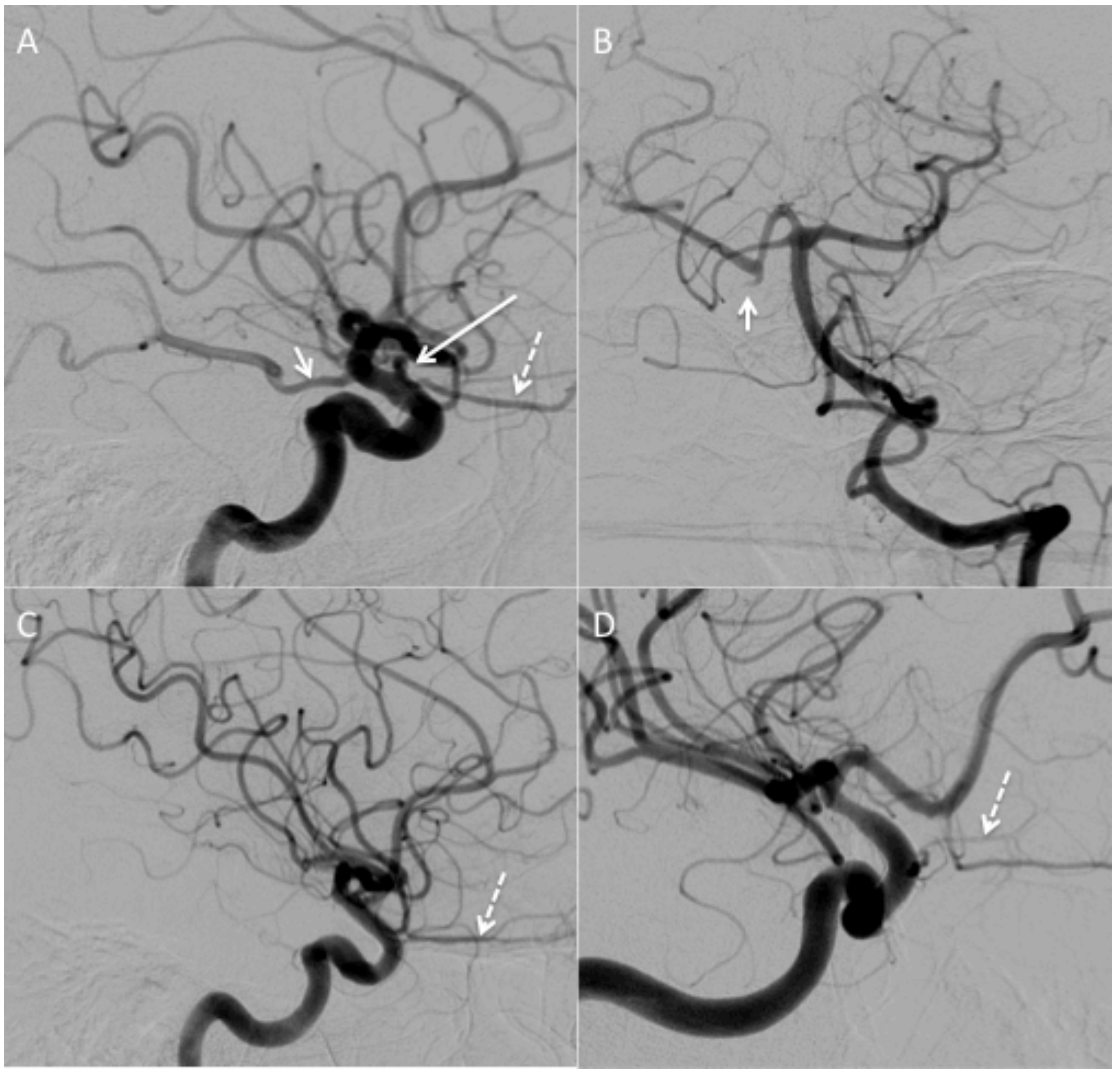

Figure 1

A patient with a 3mm aneurysm (long white arrow) arising from the ophthalmic segment (C6) of the ICA (Fig. 1a). A prominent posterior communicating artery (Short white arrow Fig. 1a and 1b) is noted although the calibre was smaller than the P1 segment. A single p64 was implanted to treat the aneurysm and follow-up angiography performed 3 months later showed occlusion of the PComA and reduced calibre of the ophthalmic artery (Fig. 1c and 1d) with complete exclusion of the aneurysm from the circulation (Fig. 1c and 1d).

In all of the patients with reduced flow/occluded anterior cerebral arteries an anterior communicating artery was present and flow into the distal ACA was maintained via the AComA (Fig. 2).

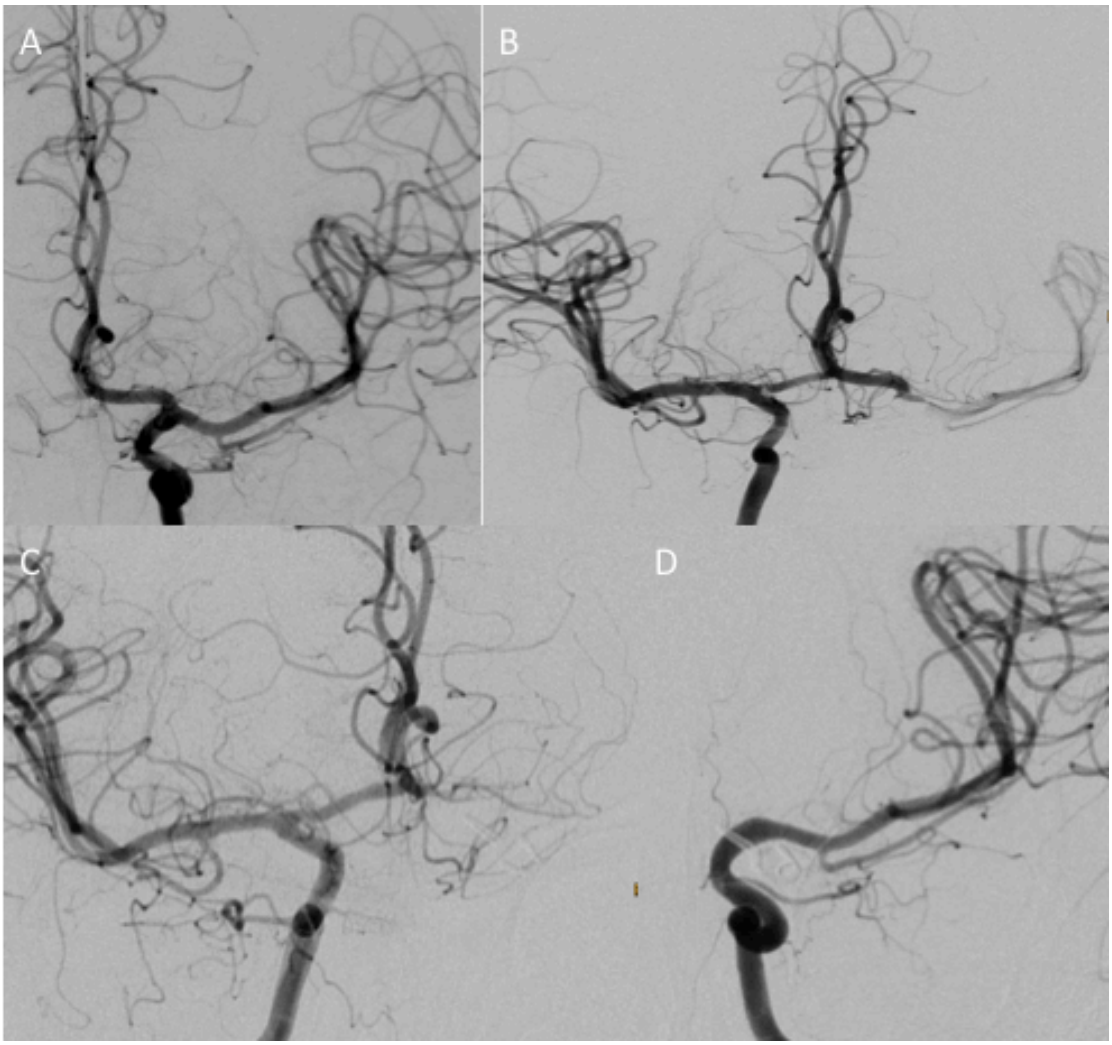

Figure 2

A patient with an aneurysm arising from the communicating C7 segment with a normal calibre left A1 segment (Fig. 1a) was treated with a single FDS that terminated in the M1 segment and crossed the ICA bifurcation. Angiography at the end of the procedure in the right ICA shows good cross flow across the AComA. A follow-up angiogram shows complete occlusion of the covered left A1 segment (Fig. 1d) however, there is excellent flow in the left A2 and beyond via the AComA (Fig. 1c). Similarly there is visible flow in the Heubner and medial lenticulostriate arteries (Fig. 1c). There was no evidence of infarction on MR imaging.

Similarly 18 of the occluded posterior communicating arteries did not have a foetal anatomical configuration. In one case a P1 segment was not visible on the pre-operative angiogram and there was a large posterior communicating artery that appeared to be the only supply to the ipsilateral posterior cerebral artery. However, on delayed angiography the PComA had reduced in

calibre and there was hypertrophy of the P1 segment (Fig. 3). We do not believe this phenomenon has been reported for this anatomical location.

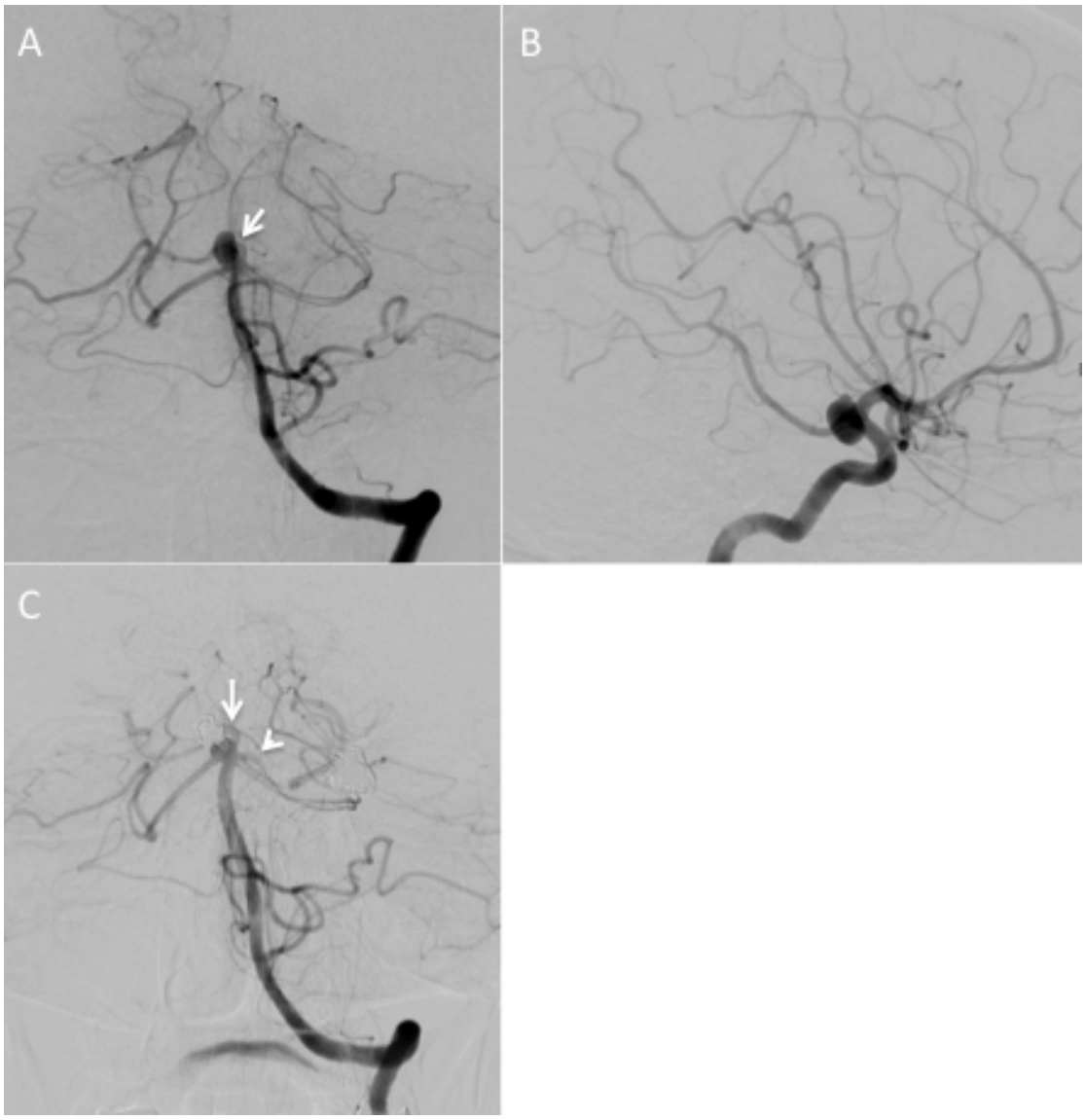

Figure 3

A patient with multiple aneurysms including a communicating segment aneurysm on the left and a right superior cerebellar aneurysm. The right PCA can be seen to curl behind the aneurysm (Fig. 3a, short white arrow) however, there is no evidence of a P1 segment on the left and the pre-operative angiography was suggestive of a true foetal PComA configuration on the left (Fig. 3a and 3b). Both aneurysm were coiled however, a FDS was placed across the communicating segment aneurysm at a later date for an aneurysm recurrence. This covered the origin of the PComA. An angiogram performed 8 months after the FDS treatment showed a reduced calibre

of the PComA and the ophthalmic artery (not shown) and a prominent left P1 segment (Fig. 3c, white arrow head) with filling of the left PCA.

Complications

In total there were 5 ischaemic events all of which are discussed in detail below.

Case 1

A 74-year-old patient with an incidental right PCOM aneurysm was originally treated with endovascular coiling in 2012. After routine follow-up an aneurysm recurrence was seen and therefore she was planned for re-treatment with further coiling and placement of a flow diverter. The FDS was positioned across the aneurysm and terminated in the terminal ICA. Post-operatively she had developed a facial palsy, which resolved completely (mRS 0) and the MRI showed a basal ganglia infarction. The lenticulostriate arteries were not covered by the FDS and the complication was likely embolic during the procedure (Fig. 4a, b).

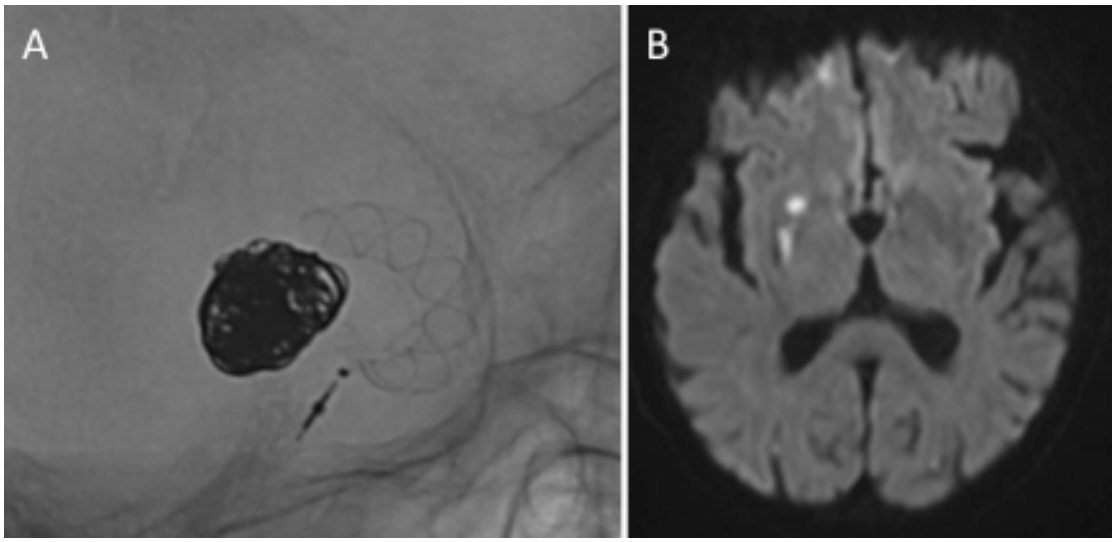

Figure 4

A right PCOM aneurysm in a 74 year old patients was coiled but showed a recurrence on follow-up angiography. It was re-treated with repeat coiling and a FDS (Fig. 4a). Post-operatively the patient developed a facial palsy with embolic infarctions on the DWI sequence. The lenticulostriate arteries were not covered by the FDS.

Case 2

A 62 year old patient with an incidental para-ophthalmic aneurysm of the right ICA was treated with 3 x PED's (Fig. 5a, b). The follow-up MRI showed multiple small embolic lesions (Fig. 5c) that were believed to have occurred secondary to the extreme tortuosity of the vessels and difficult access as well as peri-interventional spasm that occurred during deployment of the FDS. The patient had a transient left leg weakness but made a complete recovery (mRS 0).

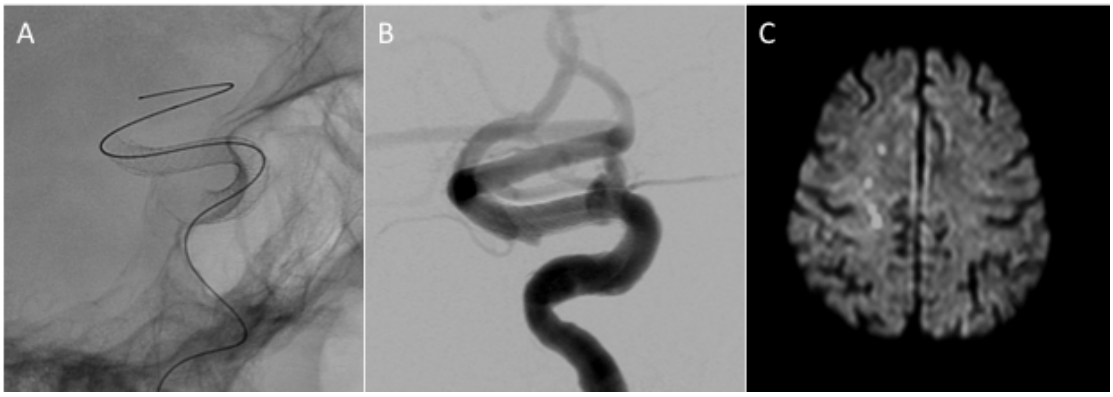

Figure 5

A 62 year old patient treated with multiple telescoped PED's (Fig. 5a, b). Multiple small emboli were seen on the post-operative MRI and these were thought to be due to the difficult access and intra-procedural vasospasm.

Case 3

A 45 year old patient with an incidental AchoA aneurysm (Fig. 6a) was treated with 2x PED's, after the first PED was improperly positioned. There were no immediate complications. Approximately 18 months following treatment the patients was advised to stop clopidogrel and there were no complications following this. One year later the patient discontinued aspirin and reported vague visual symptoms. Angiography demonstrated minor thrombi adherent to the posterior-inferior wall of the PED (Fig. 6b). An MRI performed on the same day showed multiple restricted diffusion deficits consistent with emboli (Fig. 6c). The patient was immediately re-started on aspirin and prasugrel with a repeat angiogram one week later showing resolution of the thrombus. The patient was asymptomatic (mRS 0).

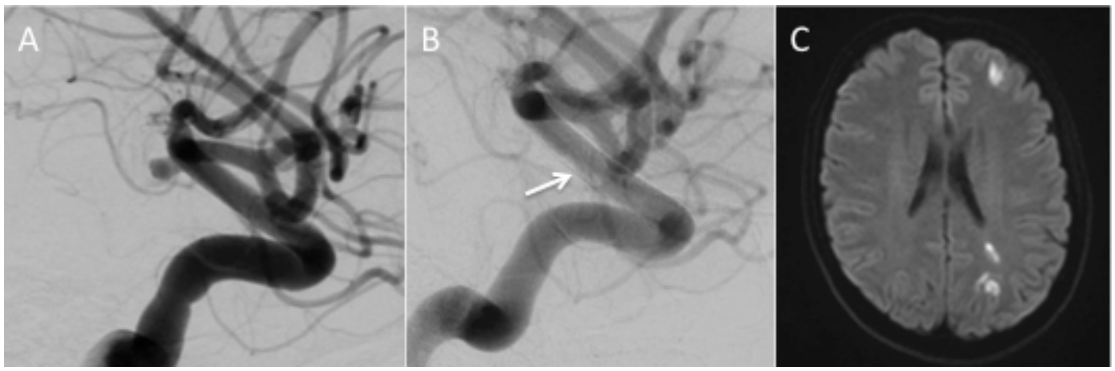

Fig. 6

A 45 year old patient treated with an AChoA aneurysm (Fig. 6a) and treated with 2 telescoped PED's. After discontinuing clopidogrel there were no complications however, the patient inadvertently stopped aspirin. The patient presented with visual symptoms and an angiogram demonstrated adherent thrombus on the posterior inferior aspect of the FDS (Fig. 6b, white arrows). The MRI showed multiple embolic infarctions (Fig. 6c).

Case 4

A 65 year old with an incidental para-ophthalmic aneurysm (Fig. 7a) underwent treatment with a single p64 flow diverter without immediate complication. One month later the patient returned with right hand weakness and an MRI revealed several small embolic lesions in the peri-Rolandic region (Fig. 7b). An angiogram showed the proximal ends of the p64 had collapsed and this was thought to have occurred because of the stenosis in the ICA (Fig 7c). This was also felt to be the cause of the emboli. A balloon angioplasty was performed to open the proximal end of the FDS (Fig. 7d) and then a coronary stent was inserted to prevent the FDS from collapsing again (Fig. 7e). The patient

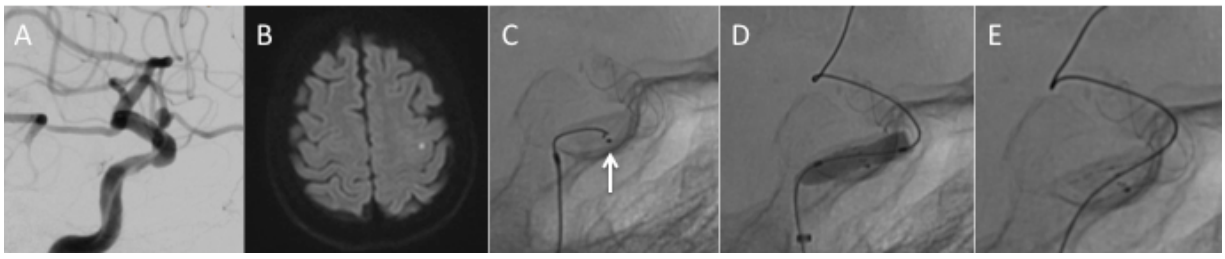

Fig. 7

A 65 year old with a para-ophthalmic aneurysm (Fig. 7a) was treated with a single p64 flow diverter. One month later the patient developed right hand weakness and an MRI revealed several small embolic lesions in the peri-Rolandic region (Fig. 7b). Angiography showed the proximal ends of the p64 had collapsed (Fig. 7c, white arrow) and this was thought to have

occurred because of the stenosis in the ICA. A balloon angioplasty was performed to open the proximal end of the FDS (Fig. 7d) and then a coronary stent was inserted to prevent the FDS from collapsing again (Fig. 7e).

Case 5

A 63 year old patient with an incidental right anterior choroidal aneurysm was treated with a single p64 flow diverting stent after treatment with coiling failed due to the wide neck of the aneurysm (Fig. 8a, b). The patient reported new numbness of the left arm post-operatively and an MRI showed several small embolic lesions (Fig. 8c). The symptoms resolved completely (mRS 0).

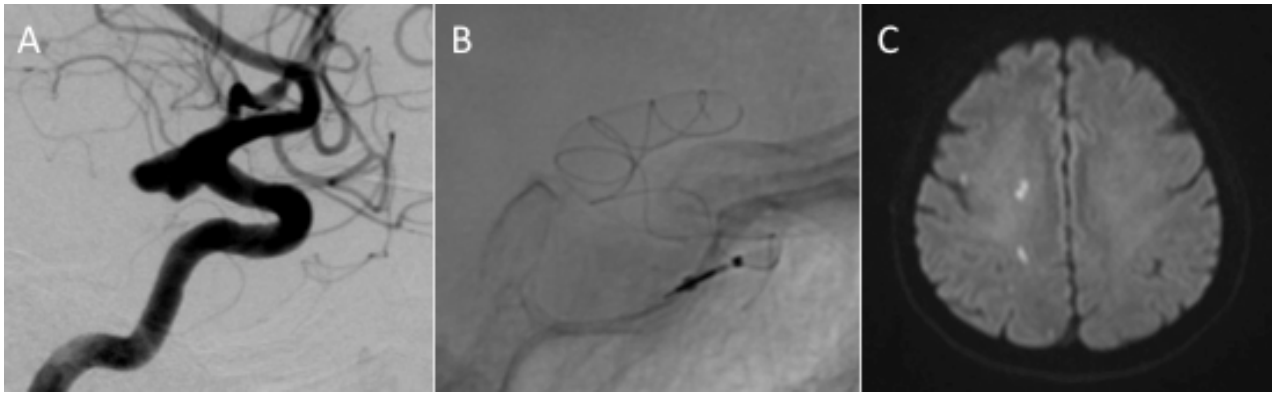

Figure 8

A 63 year old patient right AChoA treated with a single p64 flow diverting stent after treatment with coiling failed due to the wide neck of the aneurysm (Fig. 8a, b). The patient reported new numbness of the left arm post-operatively and an MRI showed several small embolic lesions (Fig. 8c).

Five patients had haemorrhagic events during the post-operative follow-up period. Three of these were subarachnoid haemorrhages (SAH), two of which were traumatic but asymptomatic. The remaining SAH was also asymptomatic but the cause was unknown. One patient had an intra-ventricular haemorrhage (IVH) that was secondary to uncontrolled hypertension and another patient had both an intra-cerebral and intra-ventricular haemorrhage that resulted in death.

5.1.5 Discussion

The use of FDS has rapidly gained acceptance as an alternative treatment option in both saccular and fusiform intracranial aneurysms. Although the use of these stents has been predominantly for unruptured aneurysms reports on their use in ruptured aneurysms have also been published. Initially the stent acts to redirect flow away from the aneurysm with consequent flow stasis in the aneurysm fundus and the progressive development of thrombus. Over time neo-endothelialisation across the aneurysm neck occurs with complete exclusion of the aneurysm from the circulation (20), however, in animal studies this neo-endothelialisation does not extend over the ostia of covered branches (21). Despite this there was initial trepidation in covering side branches particularly those with extremely eloquent territories such as the anterior choroidal artery. This initial reservation appeared justified after the reports of infarctions within the territories of covered perforator branches (22,23).

The ophthalmic artery is frequently covered during treatment of FDS treatment and Puffer et al (17) were amongst the first to report the patency of covered ophthalmic arteries. In this study 21% of ophthalmic arteries were occluded although the number of patients studies was small (n=20). More recently Burrows et al. (24) reported an incidence of 21.6% for ophthalmic artery occlusion in their study that looked only at para-ophthalmic aneurysms treated with FDS. The occlusion of the ophthalmic artery was clinically well tolerated and this was also reported in the study of Rangel-Castilla et al(18), who reported the incidence of ophthalmic artery occlusion of 10.5%. These studies suggest that occlusion of the ophthalmic artery is relatively benign however, it should be noted that the exact method for investigation of the visual field was not documented and that the standard method of bedside visual field assessment (kinetic finger-wiggle confrontation method) is relatively insensitive for detecting a field defect (25). Rouchaud et al (26) sought to determine the visual outcomes in relation to the exact anatomical location of the aneurysm and the ophthalmic artery. They showed that in patients with the ophthalmic artery arising from the aneurysm sac 80% of patients developed new clinical visual symptoms (3/4 of which were permanent) and this was believed to be due to small retinal emboli derived from the thrombosing aneurysmal sac and travelling down the patent ophthalmic artery. This shows that a patent ophthalmic artery is synonymous with normal vision and that detailed ophthalmological investigations should be conducted both prior to and after FDS treatment. Furthermore, one should carefully consider the exact anatomical situation in individual patients in order to provide a tailored treatment for each patient.

The posterior communicating (PComA) artery is variable in its presence and can either communicate with the posterior cerebral artery (PCA) or take over the territory of the PCA, the so-called foetal posterior communicating artery. Occlusion of the PComA has been previously reported. Vedantam et al (27) reported a single case of PComA occlusion (n=14, incidence 7.1%). Brinjikji et al. (28) reported 5 cases (n=11) of PComA occlusion or diminished anterograde flow, none of which resulted in clinical symptoms. Rangel-Castilla et al (18) reported 3 occlusions (n=28) at long term follow-up and all of these cases were non-foetal PComA's.

The anterior choroidal (AChoA) supplies an extremely eloquent region of brain that includes the posterior limb of the internal capsule and infarcts within its territory can result in a devastating outcome for patients. Distal anastomoses are formed with the lateral posterior choroidal artery, the posterior cerebral artery and the posterior communicating artery (29,30). These collateral pathways have been observed in cases of chronic occlusion (31). Coverage of the origin of the anterior choroidal artery should therefore be avoided whenever possible and this is also our policy. However, recent data suggests that coverage of the anterior choroidal artery is unlikely to result in occlusion. Neki et al. (16) recently published their retrospective analysis of 20 patients in whom the AChoA was unavoidably covered during the endovascular management of intracranial aneurysms. In this study none of the patients developed AChoA territory infarctions and none of the patients developed either permanent or transient symptoms that could be related to occlusion of the AChoA. Furthermore, in the patients with follow-up angiography (85%) the artery remained patent and they did not report any anterograde flow changes. Similarly Raz et al identified 29 patients in whom the AChoA origin was covered by at least one FDS. They showed that at angiographic follow-up (mean 15.8 months) 28 patients had anterograde flow in the artery and in one patient there was occlusion of the vessel and reconstitution distally by the collateral postero-lateral choroidal arteries and medial lenticulostriate arteries. This patient developed very transient symptoms (5 minutes) consistent with an AChoA syndrome. Similarly in the study of Brinjikji et al (32), which included 15 patients with 3 ruptured cases, there was only 1 occlusion seen at delayed angiography and this was asymptomatic. In the 8 patients in whom CT or MR imaging was available there were no radiological signs of infarction within the AChoA territory. In the recent study by Rangel-Castilla et al (18) there were no occlusions of the artery and this mirrors our own results as well as those of Vedantam et al (27).

Reports of occlusion of the anterior cerebral artery (ACA) are limited and to our knowledge the only report that documents the flow status of the ACA following coverage with FDS is that by Rangel-Castilla et al. (18) who reported two cases of occlusion of the A1 segment after a FDS was placed across the ICA bifurcation and into the M1 segment. In both cases flow into the A2 segments and distally was maintained by the contralateral A1 segment of the ACA and across the anterior communicating artery (AComA). Again this phenomenon can be explained by the presence of collateral arterial supply that can take over the distal territory.

Early on the use of flow diverters there was concern that the coverage of side branches may result in occlusion of these vessels and this phenomenon has certainly been seen. It is believed that occlusion of covered branches is the result of the presence of distal collaterals and the suction effect created by lower pressure in these vessels (33). In the presence of collateral flow a 'flow equalisation point' may occur that results in the slow flow and occlusion of the proximal vessel proximal to the collaterals (34,35). This is our belief and we believe this explains the difference in the occlusion rates of the various covered branches. For example in the case of ophthalmic artery there is a rich collateral source from the external carotid artery (ECA) and an adequate supply from these branches may promote ophthalmic artery occlusion. Similarly, a patent contralateral A1 and ACOM may takeover the supply of the distal ipsilateral ACA territory as was seen in the case represented in Fig. 2. This slow occlusion and redirection of flow that occurs as neo-endotehlialisation of the flow diverter occurs is completely distinct to acute occlusion that may have a completely different effect. This slow adaptation is well represented by the case shown in Fig. 3. A P1 segment could not be visualised in angiography pre-operatively and the anatomical configuration appeared consistent with a foetal PCOM disposition. However, on angiography the calibre of the 'foetal' PCOM had reduced and flow via a P1 segment could be readily seen. This phenomenon has not been described to our knowledge and attests to the fact that flow diverters can modify the intracranial cerebrovascular architecture. Although there is a collateral supply to the anterior choroidal artery via the medial and lateral posterior choroidal arteries it is possible that these vessels are unable to provide a significant enough collateral supply to enable endothelialisation across the ostium of the anterior choroidal artery however, in a single case of the study by Raz et al. (36) retrograde reconstitution of the anterior choroidal after occlusion was reported as mentioned earlier. Additionally, at nominal diameter the PED pore size is between 0.02-0.05mm^2 (13). The area of the AChoA origin varies from 0.4 to 1.1mm^2 (mean 0.9mm^2) (30) and therefore, even though the flow diverter struts will certainly

cross the origin of the AChoA as long as adequate flow is maintained in the parent artery and a pressure difference persists occlusion of the AChoA is unlikely to occur. Saleme et al. (37) sought to clarify the role of covered branches and collateral supply. They compared remodelling of the side braches covered by flow diverters, dividing the aneurysms in two groups based on whether the territory supplied by the side branch received a direct collateral supply or not. This study included flow-diverting stents crossing the ACA origin, the AChoA, and the MCA. They showed that in the group with a direct collateral supply 78.5% of covered branches had undergone narrowing or occlusion at 6 months, with no new strokes identified on MR imaging. The authors suggest that symptomatic remodelling of covered side braches was dependant on the extent and type of collateral supply and we would concur with this as do other authors (18)[18].

A factor that has been suggested to play an important role in the occlusion of aneurysms arising from jailed branches, based on computational fluid dynamics studies and animal studies, is continued flow into the jailed branch (38–40). The occlusion of aneurysms at branch points has also been investigated. Fahed et al. (41) compared flow diversion with and without occlusion of the jailed branch in 14 wide neck aneurysms induced in 8 canines. They found that occlusion of the jailed branch resulted in better occlusion rates of aneurysmal occlusion whereas patent aneurysms were associated with less dense neointimal coverage and persistent holes in the neointima. The authors suggest that occlusion of the side branch assists in the occlusion of aneurysms at bifurcations, which may be especially relevant for aneurysms of the PCOM where the neck of the aneurysm may incorporate the PCOM and ICA in a similar configuration to bifurcation aneurysms.

Overall it can be said that whilst side branch occlusion of the terminal carotid and ACA does occur after coverage with FDS this rarely results in clinical symptoms. However, individual anatomical considerations should be borne in mind. It should also be noted that this phenomenon may not represent what occurs in the distal intracranial circulation e.g. FDS placed across the middle cerebral artery bifurcation, and dedicated studies in these anatomical locations is required.

Study Limitations

This study has the inherent limitations of a retrospective study. Not all patients had follow-up angiography of the vertebral arteries or the ECA and so assessment of the collateral supply could not be accurately documented. In our institution we use only the p64 and PED flow diverters and

therefore, the applicability of our results to other flow diverters is unknown. Similarly, in some cases the follow-up period is relatively short. Posterior circulation aneurysms were excluded from this study and we are unsure whether the results can be extrapolated to the posterior circulation.

5.1.6 Conclusions

This represents the largest study to date on the status of branches covered by FDS and arising from the clinoid, ophthalmic and communicating segments of the ICA as well as the ACA. The overall side branch occlusion rate was 20% and this included ophthalmic arteries, PComA and the ipsilateral A1 segment of the ACA however, consistent with other reports we did not observe any occlusions of the AChoA. Further studies are required to determine if this information can be extrapolated to the distal intracranial circulation and the posterior circulation.

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6 Chapter 6

6.1 The Treatment of Unruptured, Saccular, Anterior Choroidal Artery Aneurysms with Flow Diversion – A Single Centre Experience

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6.1.1 Abstract

Background

The region of the brain supplied by the anterior choroidal artery (AChoA) is exquisitely eloquent. Aneurysms arising at or close to the origin of the vessel are not uncommon and damage or occlusion to the vessel can result in devastating consequences. The optimal treatment strategy is yet to be determined.

Objective

We sought to determine the efficacy of flow diversion for the treatment of unruptured anterior choroidal artery aneurysms.

Methods

A retrospective review of our prospectively maintained database was performed to identify all patients with unruptured aneurysms of the anterior choroidal artery between March 2009 and May 2017. The fundus size, number and type of flow diverting stent (FD), complications and follow-up data were recorded.

Results

We identified 30 patients (60% female), average age of 52.8±10.8 years (range 27-73), with 30 aneurysms. The aneurysms were generally small with a mean fundus diameter of 3.4 mm (range, 1-7 mm). Early angiographic follow-up data was available for all patients at which point 15 aneurysms were completely occluded (50%). Delayed angiographic follow-up was available in 24 patients and occlusion was seen in 21 patients (87.5%). One patient developed transient ischaemic symptoms after interruption of the antiplatelet medications and another patient had a small embolic infarct with transient symptoms in the peri-procedural period.

Conclusion

Flow diversion can be used to successfully treat aneurysms of the anterior choroidal artery. The treatment carries a high rate of technical and radiological success with a good safety profile.

6.1.2 Introduction

The anterior choroidal artery (AChoA) supplies an extensive and eloquent territory, which includes the posterior two-thirds of the internal capsule, the adjacent optic radiations, medial portion of the globus pallidus, caudate tail, uncus, hippocampal head, amygdala, piriform cortex and part of the lateral geniculate nucleus (1–5). Occlusion of the AChoA can therefore result in severe neurological deficits for patients with the development of hemiparesis, hemi-hypesthesia, and hemi-anopsia with motor and sensory deficits being most common (2,6–10).

AChoA aneurysms account for 4% of all intracranial aneurysms (11). As with aneurysms elsewhere both surgical clipping and endovascular treatment options are available. Surgical clipping of AChoA aneurysms carries a high mortality and morbidity with rates varying between 5% to 50% in the literature, and principally due to ischaemic stroke (12–18). In 2004 Piotin et al. (11) published their series of 18 patients with AChoA aneurysms treated endovascularly with coils (n=12), balloon remodelling technique (n=4) or stent assisted coiling (n=1). In this series there was one treatment related death secondary to aneurysm perforation and one transient contralateral hemiparesis that resolved within 24hrs. This paper demonstrated that standard endovascular techniques were amenable to the treatment of AChoA aneurysms with a good safety profile.

More recently the introduction of flow diverters (FD) has increased the armamentarium of interventional neuroradiologists. Naturally there was initial trepidation regarding the coverage of small vessels and their potential occlusion, especially important vessels such as the AChoA, despite animal data to the contrary. Neki et al. (19) recently published their retrospective analysis of 20 patients in whom the AChoA was unavoidably covered during the endovascular management of intracranial aneurysms. They showed that no patients complained of transient or permanent clinical symptoms related to AChoA occlusion and that the vessel remained patent without any flow changes.

With the goal of assessing the efficacy and complication rate of flow diversion treatment for un-ruptured AChoA aneurysms we retrospectively studied 32 consecutive patients treated endovascularly with either the Pipeline Embolisation Device (PED, Medtronic, Minnesota, USA) or the p64 flow remodelling device (phenox, Bochum, Germany).

6.1.3 Methods

Patient Population

We searched our prospectively maintained database, for all patients treated in our institution with unruptured, saccular AChoA aneurysms between March 2009 and May 2017. For each patient we recorded demographic data, clinical presentation, location of the aneurysm, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information. The data was entered into the prospectively collected computer database for each institution.

Classification of AChoA aneurysms

The analysis of the aneurysm characteristics was performed by the senior neurointerventionist (HH). The AChoA aneurysms were lesions that could be seen arising directly from the AChoA or adjacent to the AchoA at the branch point. The size of the aneurysms was recorded as their greatest sac diameter. Aneurysms were carefully assessed and aneurysms of the posterior communicating artery or terminal ICA were excluded.

Endovascular Treatment

All treatments were performed under general anaesthesia. Two commercially available FD were used: PED and p64. All the aneurysms were treated with only a single type of FD, either a PED or a p64 (there were no cases where both types of FD were used in the same patient) although in four cases the aneurysms had been previously unsuccessfully treated with coils and one with the Medina embolic device (Medtronic). In two patients coils were used during the same procedure. Patient informed consent was obtained before the procedure in all cases. The selection of FD was dependent upon availability the operators' judgement. Selection of the FDS was initially based on availability. Initially only the PED was available, however, after the p64 gained the CE mark it was also available for use in our department. Furthermore, in our experience, the p64 offers advantages in that it can be completely deployed and re-sheathed to allow repositioning alongside improved visibility compared to the PED (20).

All patients received dual antiplatelet therapy with either 100 mg ASA daily and 75 mg clopidogrel for at least three days or a loading dose of 500 mg ASA and 600 mg clopidogrel on

the day prior to the treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche) and/or VerifyNow (Accumetrics). The post-procedural antiplatelet regime consisted of 75 mg Clopidogrel per day continued for 12 months following treatment and 100 mg ASA per day continued for life. Patients resilient to clopidogrel received either 10mg prasugrel or 2x 90mg ticagrelor per day.

All procedures were performed via the femoral route using a 6 Fr access system as standard. All procedures were performed under heparin anticoagulation with a 5000 IU bolus dose at the start of the procedure and subsequent 1000 IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline.

Procedural Assessment and Follow-Up

Patency and flow characteristics within the internal carotid artery (ICA) and AChoA were assessed angiographically immediately after placement of the FD and during follow-up. In-stent stenosis with neointimal hyperplasia was graded as none (0%), mild (<50%), moderate (50-75%) and severe (>75%) (21). Aneurysms were graded using the 3-point Raymond-Roy classification (22). Grading was performed by a diagnostic neuroradiologist within the department that was not involved with the procedure itself.

Neurological examinations were performed to evaluate for potential ischaemic or haemorrhagic complications in the post-operative period (<24hours post procedure) and at each subsequent follow-up. The neurological assessment was performed by a member of the neurosurgical team and a member of the interventional neuroradiology team. The modified Rankin Score (mRS) was recorded pre-operatively, immediately post-operatively and at all subsequent follow-ups.

6.1.4 Results

We identified 30 patients that met our inclusion criteria. Of the 30 patients 18 were female (60%) with an average age of 52.8±10.8 years (range, 27-73 years) at presentation. A total of 30 saccular aneurysms were treated, 16 (53%) of which were on the left side. In four cases the aneurysm had been previously unsuccessfully treated with coils. The aneurysms were generally small with a mean average maximum fundus diameter of 3.4 mm (range 1-7 mm).

PEDs were used to treat 4 of the aneurysms and the p64 was used to treat the remaining 26 aneurysms. There were no cases where both a PED and a p64 were used. In 3 patients treated with the PED more than 1 stent was used (3 telescoped PED in 2 patients and 2 telescoped PED in 1 patients). In 5 patients treated with the p64, 2 telescoped stents were placed one of which was due to inappropriate position of the first p64. In the remainder of the cases only a single p64 was placed.

Early angiographic follow-up data was obtained for all aneurysms at a mean average of 3.1 months after the procedure. At initial follow-up 15 of the aneurysms showed complete occlusion (RRC I) (Fig. 1) and 8 aneurysms showed a small neck remnant (RRC II).

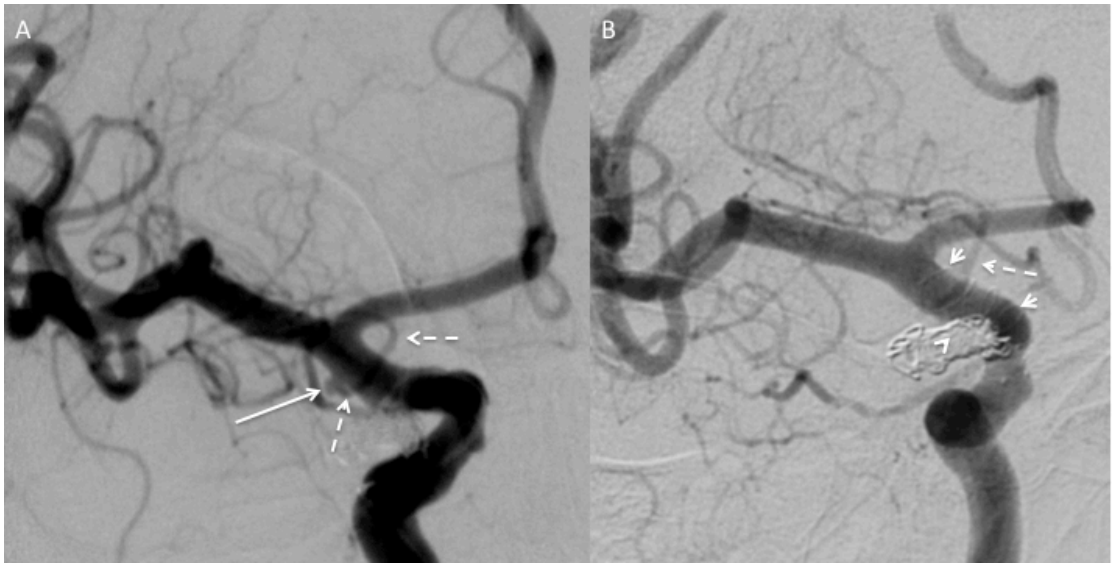

Figure 1.

A patient with a right-sided AChoA aneurysm treated with a single p64. The pre-operative angiography (Fig. 1a) shows the small 2mm aneurysm (white arrow) with the AChoA clearly visible (dashed white arrows). The post-operative follow-up angiogram (Fig. 1b) performed 3 months later shows complete occlusion of the aneurysm (white arrow head) and a patent AChoA (dashed white arrow). The markers for the p64 can also be seen (short white arrows).

The remaining aneurysms showed continued contrast opacification (RRC III). At mid-term follow-up at a mean average of 9.9 months after treatment, available for 24 patients, 19 aneurysms showed complete occlusion (RRC I) and 2 showed a small remnant (RRC II). The remaining 6 patients did not attend for follow-up angiography. At delayed follow-up available in

14 patients and performed at mean average of 31.9 months, complete occlusion was seen in all the aneurysms (Fig. 2).

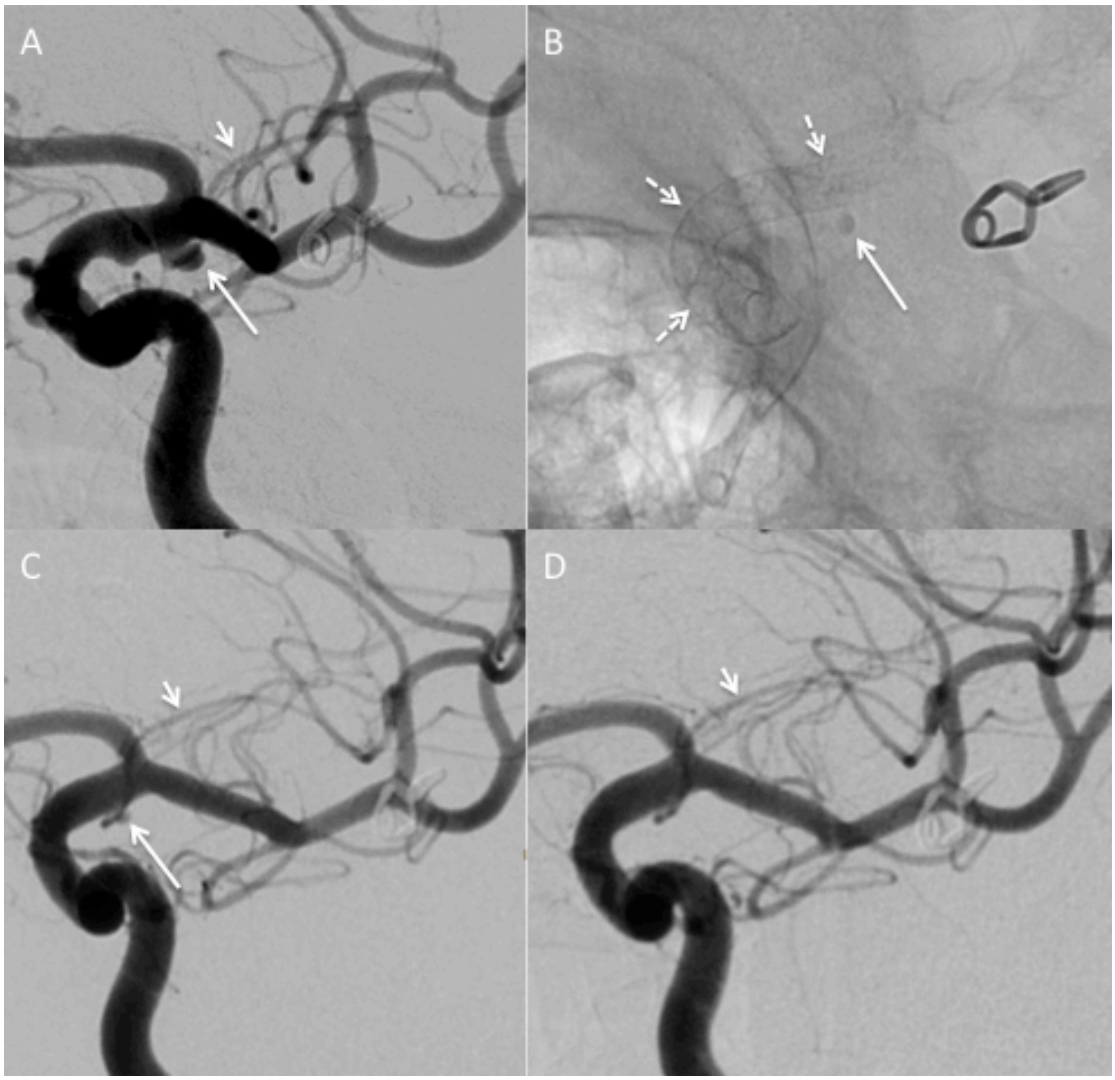

Figure 2

A patient treated with a single PED for a 3mm AChoA aneurysm. The pre-operative angiogram (Fig. 2A) shows the aneurysm (long white arrow) with the AChoA clearly seen (short white arrow). The unsubtracted image (Fig. 2B) following deployment of the PED (dashed white arrows) shows contrast stagnation within the aneurysm (long white arrow). Follow-up angiography at 3 months shows a small remnant (Fig. 2C) with complete occlusion of the aneurysm at delayed angiography performed after 15 months (Fig. 2D).

In total 23/30 aneurysms were occluded on follow-up angiography (76.6%). Of the 24 patients with delayed angiography 21 aneurysms were occluded (87.5%). The AchoA was patent in all cases. The results are summarised in Table 1.

		Aneurysm Characteristic											
Patient	Age	Sex	Laterality	Fundus Max. Dimension	Neck Width	Previous Treatment	No. FD's	First F/U (months)	Last F/U (months)	Occluded	AChoA Patent	mRS Pre-op	mRS Post-op
1	73	f	l	5	3	0	1 p64	2 months	9 months	Y	Y	2	2
2	43	f	l	2	2	0	1 p64	3 months	20 months	Y	Y	0	0
3	53	m	l	4	3	coils	1 p64	3 months	25 months	Y	Y	0	0
4	40	f	l	6	6	coils	1 p64	3 months	9 months	Y	Y	2	2
5	53	f	r	2	2	0	1 p64	3 months	21 months	Y	Y	0	0
6	60	f	l	3	3	0	1 PED	3 months	15 months	Y	Y	0	0
7	56	f	r	4	2	0	2 PED	4 months	54 months	Y	Y	0	0
8	46	m	l	3	2	0	1 p64	3 months	12 months	Y	Y	1	1
9	68	f	l	3	3	0	1 p64	4 months	10 months	N	Y	1	1
10	58	f	r	5	3	0	1 p64	3 months	10 months	Y	Y	0	0
11	45	m	l	3	3	0	3 PED	3 months	32 months	Y	Y	0	0
12	61	f	r	5	5	0	1 p64	4 months	NA	N	Y	0	0
13	57	m	r	4	3	0	1 p64	3 months	10 months	Y	Y	0	0
14	41	f	l	4	3	0	1 p64	3 months	8 months	Y	Y	0	0
15	64	m	l	3	2	0	1 p64	3 months	10 months	N	Y	0	0
16	64	m	r	4	2	0	1 p64	3 months	NA	N	Y	0	0
17	27	f	r	3	4	0	1 p64	3 months	21 months	Y	Y	0	0
18	53	m	l	2	2	0	2 p64	3 months	12 months	Y	Y	2	2
19	47	f	r	2	3	0	1 p64	3 months	NA	Y	Y	0	0
20	61	f	l	2	3	0	2 p64	6 months	11 months	N	Y	0	0
21	52	m	r	2	1.5	0	1 p64	3 months	10 months	Y	Y	0	0
22	30	f	r	2.5	2.5	coils	2 p64	3	9 months	Y	Y	0	0

								months					
		m	l	1	1	0	2 p64	3	11	Y		0	1
23	39							months	months		Y		
		f	l	3	3	0	3	4	47	Y		0	0
24	53						PED	months	months		Y		
		m	r	7	6	coils	1 p64	3		Y		2	2
25	62							months	NA		Y		
26	64	f	r	7	5	0	1 p64	6 days	NA	N	Y	0	0
		m	r	2	2	0	1 p64	5				0	0
27	61							months	NA	N	Y		
		f	l	2	2	0	2 p64	2		Y		0	0
28	47							months	7 months		Y		
		f	l	2	2	0	1 p64	2		Y		1	0
29	59							months	6 months		Y		
		m	r	4	2	0	1 p64	4	10	Y		2	2
30	42							months	months		Y		

Table 1

Patient demographics, aneurysms characteristics and follow-up data

Nine patients demonstrated intimal hyperplasia on initial follow-up angiography (8 patients <50%, 1 patient 50-75%, all asymptomatic). In 5 cases the intimal hyperplasia resolved and in one patient the intimal hyperplasia improved during the follow-up period, in two it remained stable (<50%) and one follow-up is pending.

Complications

In one patient there was a small embolic ischaemic lesion that represented the only case of peri-procedural morbidity. A further patient developed transient ischaemic embolic symptoms during the follow-up period after a transient interruption of the antiplatelet medication. Both patients returned to baseline neurology. There were no cases of vessel rupture or dissection. There were no cases of delayed rupture or morbidity.

6.1.5 Discussion

The AChoA artery supplies an extremely eloquent area of the brain with several potential anastomotic pathways known to exist with the posterior choroidal arteries, the interpeduncular plexus and the posterior communicating arteries (4,23). These anastomotic connections are not easily assessed and therefore their presence or ability to undertake supply of the AChoA territory, if this vessel is impaired, is difficult to judge. For these reasons the most feared consequence of

treatment of aneurysms arising from AChoA is infarction within the territory of this vessel that can, but does not always, result in a devastating outcome for patients (24,25). Friedman et al. (17) reported their case series of 51 AChoA aneurysms in 50 patients, 33 of whom presented with acute subarachnoid haemorrhage (SAH). Three patients died, two from treatment related complications. Eight patients (16%) demonstrated clinical and CT evidence of infarction within the AChoA territory. Li et al. (13) more recently presented their single centre experience of 102 patients with AChoA aneurysms treated with microneurosurgical clipping. In total 106 aneurysms were treated with an overall surgical mortality of 7% and major surgical morbidity of 12%. A similar rate of AChoA infarction (15%) to that by Friedman et al. (17) was reported. To our knowledge Bohnstedt et al. (26) have published the largest surgical series in the English literature. Of the 127 aneurysms treated 112 underwent microsurgical clipping, 5 aneurysmal wrapping and 2 surgical exploration. The remaining 8 aneurysms were treated endovascularly with coils. The post-operative ischaemic complication rate in those patients that underwent microneurosurgical treatment was 12.6% (15 of 119 patients), 4 of whom died during hospitalisation or shortly thereafter. Interestingly, just over half of the patients (8 of 15) that demonstrated AChoA territory infarction showed persistent flow within the artery. This group also reported that the use of temporary clipping more often led to post-operative ischaemia and that the average number of the times the ICA was temporarily occluded was statistically significant in leading to post-operative ischaemia 1.51 for non-ischaemic, 2.56 for ischaemic, p=0.007). Clip repositioning was also statistically significantly associated with postoperative ischaemia. This goes to show that even temporary interruptions to the flow with the AChoA can have disastrous effects likely due to the inability of collateral supply to supply the metabolic demands of the territory. However, we acknowledge that a direct comparison with our results, or the results from other studies using flow diversion, could be erroneous and a well designed RCT would be the only way to provide an accurate answer on the merits of the

The endovascular management of AChoA aneurysms has naturally until recently consisted principally of coiling. In 2004 Piotin et al. (11) published their series of 18 consecutive patients that underwent endovascular treatment of AChoA berry aneurysms. In this series 14 patients presented with SAH and two of the aneurysms were associated with arteriovenous malformations (AVMs). There was one death secondary to rupture of the aneurysm during the coiling procedure with another patient developing a transient contralateral hemiparesis. More recently Gimonet et al (27) described a three catheter technique to treat AChoA with coils. This involved placing one

catheter in the aneurysm, one inside the AChoA itself to protect it and finally a balloon catheter in the ICA. This technique was used to treat 6 aneurysms, all of which were small (mean fundus size 2x2x2mm), and in all patients the aneurysms were successfully occluded with no ischaemic complications or aneurysm rupture. Other endovascular coiling techniques have also been described (28) as have single centre series looking at the risk of complications from the treatment of these aneurysms (29).

Kim et al. (30) sought to compare the outcomes of patients undergoing either surgical or endovascular treatment of AChoA aneurysms. In their retrospective study 38 patients were treated with coiling and 35 clipping. Four patients in the clipping cohort developed permanent contralateral hemiparesis due to AChoA infarction with a further patient developing a 3rd cranial nerve palsy. In the coiling cohort 2 patients developed temporary contralateral hemiparesis that resolved completely. The authors suggest that the overall outcome and prevention of repeat haemorrhage for both groups was similar but with a significantly lower incidence of AChoA territory infarction within those patients treated endovascularly.

The advent of FD has provided a new treatment option for these aneurysms and although there was initial concern that covering the AChoA may result in infarction this does not seem to be the case. In the series by Neki et al. (19) there were no documented cases of AChoA territory infarction and in all the cases (85%) with follow-up angiography the AChoA remained patent. This is in agreement with our study and whilst the AChoA is a small artery is still larger than the pore sizes of FD (4,31,32). At nominal diameter the PED pore size is between 0.02-0.05mm^2 (31) with the area of the origin of the AChoA varying from 0.4 to 1.1mm^2 (mean 0.9mm^2) (4). Therefore, even though the stent struts are likely to cross the origin of the AChoA as long as adequate flow is maintained in the parent artery and the AChoA occlusion is unlikely to occur. The alteration in flow within the aneurysms that allows occlusion to occur with the simultaneous preservation of flow within the AChoA, as shown in our study, highlight the potential for this treatment option for these otherwise difficult to treat and high risk aneurysms. Other groups have also recently published their results of flow diversion involving the anterior choroidal artery. Raz et al (33) analysed 157 patients that had at least PED covering the origin of the AChoA with 29 patients meeting this criteria. At angiographic follow-up (mean 15.1 months) 28 AChoA were patent with anterograde flow. In a single case there was occlusion of the artery and retrograde reconstitution via the medial lenticulostriate and posterolateral choroidal arteries. Interestingly

the artery in this case arose from the fundus of the aneurysm and 3 PED's were used for the treatment of the aneurysm and although the patient had very transient symptoms consistent with a AChoA syndrome, these symptoms lasted for 5 minutes only. Similarly Brinjikji et al (34) presented the findings of 15 consecutive patients where a PED was placed covering the ostium of the AChoA. In this series none of the aneurysms treated actually arose from the AChoA and 12 of the aneurysms were unruptured. In this study, immediate post-operative angiography showed anterograde flow in all the covered AChoA. One patient died 10 days after treatment secondary to an intra-parenchymal haemorrhage but angiography performed 1 day after the procedure showed patency of the AChoA. Of the remaining 14 aneurysms, the AChoA remained patent in 13 and in one patient the artery was occluded (mean F/U 12 months) with no symptoms reported in this patient. Eight patients had follow-up MRI or CT imaging and none of the patients demonstrated infarction within the AChoA territory. The study of Rangel-Castilla et al (35) also reviewed the occlusion of the AChoA as well as other covered branches. In their series of 82 patients, none of the covered AChoAs were occluded at follow-up however, they reported occlusion of other covered branches such as the ophthalmic artery (10.5%), posterior communicating artery (10.7%, all adult type) and all the covered ACAs (n=2). Although there were no clinical consequences to the occlusion of any of these branches the authors suggest that the use of multiple FDS may contribute to branch occlusion. In our series none of the covered AchoAs were occluded at follow-up and there was no evidence of infarction within the territory of the artery.

The main limitations of our study are its retrospective design and the relatively small number of patients. Additionally, as the aneurysms in our case series are all <7mm, the applicability to larger aneurysms is uncertain. Furthermore, as all the aneurysms are saccular we are unsure of the applicability of the technique to fusiform aneurysm. We also acknowledge that a direct comparison with our results and the results from other studies using flow diversion with surgical series could be erroneous and a well designed RCT would be the only way to provide an accurate answer on the merits of either technique to treat these lesions.

6.1.6 Conclusion

The results of this study suggest that the use of FDS for the treatment of unruptured AChoA aneurysms is safe and carries a high rate of technical and radiological success.

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7 Chapter 7

7.1 Treatment of Posterior Circulation Non-Saccular Aneurysms with Flow Diverters – A Single Centre Experience and Review of 56 Patients

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There is no further data or information available to share at this time.

7.1.1 Abstract

Background and Purpose

Non-saccular aneurysms of the posterior fossa are an uncommon pathology with no clear treatment strategy. The use of flow diverting stents (FDS) has had mixed results. We sought to evaluate our experience of FDS for the treatment of this pathology.

Methods

We retrospectively reviewed our database of prospectively collected information for all patients treated only with flow diversion for an unruptured non-saccular aneurysm of the posterior circulation between February 2009 and April 2016. The aneurysms were classified as dolichoectasia, fusiform or transitional and imaging characteristics including maximal diameter, disease vessel segment, MRI features (intra-aneurysmal thrombus, T1 hyperintensity in the aneurysmal wall, infarctions in the territory of the posterior circulation, and mass effect) were recorded alongside clinical and follow-up data.

Results

We identified 56 patients (45 male) with 58 aneurysms. The average of the patients was 63.5 yrs. Twenty-two patients were symptomatic from the aneurysms at presentation. The majority of the lesions were vertebra-basilar in location (44.8%) with isolated vertebral lesions representing 29.3% of aneurysms. Transitional aneurysms were the most common (48.2%). The mean maximal diameter of the aneurysms was 11mm. Angiographic exclusion of the aneurysms was seen in 57.4% of aneurysms with follow-up (n=47). During the follow-up period 9 patients died.

Conclusion

Treatment of non-saccular aneurysms of the posterior fossa is technically possible. Early treatment particularly of the fusiform and transitional subtypes is recognised as is treatment prior to the development of symptoms. A 'watch and wait' strategy with regular imaging follow-up could be employed for asymptomatic dolichoectasia.

7.1.2 Introduction

In 1922, Wells was the first to describe a non-saccular aneurysm of the basilar artery upon surgical exploration in a patient with obstructive hydrocephalus and paresis of cranial nerves VI-VIII (1) with further reports published later by Walter Dandy (2) as well as Greitz and Lofstedt (3). Non-saccular aneurysms of the posterior circulation are uncommon with an incidence of less than 1%. In an autopsy series from Columbia University the incidence of aneurysms was 0.1% (4) and a similar series from a VA hospital series showing an incidence of 0.07% (5). These aneurysms can manifest with a variety of different symptoms ranging from asymptomatic and incidental findings on routing imaging, posterior circulation ischaemic strokes, brainstem compression, cranial nerve palsies - most commonly V-VIII (6), obstructive hydrocephalus and haemorrhage (7–14).

The natural history of these lesions is fateful and a mortality of up to 30% has been reported (14–16) with the recent review by Shapiro et al. suggesting that the mortality could be even higher at 43% (17). If left untreated they carry significant morbidity with growth of these aneurysms seen in 46% of patients over a median interval period of 8.5 years (6,10,18,19) and according to the findings of Mangrum et al (18) this particular phenomenon is associated with a 5.7 times increase in mortality relative to those patients with aneurysms that were stable.

It is not surprising then that the advent of endoluminal reconstruction with flow diverting stents (FDS) was met with much fanfare and the promise of providing a potential new treatment option for a group of patients that carry a generally poor prognosis and few other suitable treatment options. Unfortunately this initial optimism quickly reverted to pessimism after preliminary experiences suggested that the use of flow diverting stents in the posterior circulation would not yield similar results to those in the anterior circulation (20–25). However, more recent reports have shown promise for example in the publication of Phillips et al. (26) there were no treatment related deaths and an overall morbidity of 9.4% with all patients having good functional outcome (mRS 1), being independent and returning to work.

In this study we present our single centre experience of the use of FDS in non-saccular posterior circulation aneurysms, which we believe is the largest series to date of non-saccular aneurysms of the posterior circulation treated with flow diverters and the first to detail the specific locations and morphological features as has been shown to be important in prognosis.

7.1.3 Methods

Patient Population

We retrospectively reviewed our prospectively maintained database and identified 56 patients with 58 un-ruptured intradural fusiform aneurysms of the posterior circulation that were admitted to our institution for endovascular treatment between September 2009 and April 2016. For each patient we recorded demographic data, clinical presentation, location of the aneurysm, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information.

Classification of non-saccular aneurysms

All aneurysms of non-saccular appearance arising from the V3/4 segment or distally within the posterior circulation and not representing acute dissecting pseudoaneurysms were included in this analysis. This was determined through the clinical resentation and the radiological appearance. The imaging features used to exclude potential dissecting aneurysms included T1 hyperintensity on fat suppressed MRI (in those patients that underwent MR imaging), visualisation of a dissection flap, the 'bead and string' sign and narrowing of the parent artery proximal to a dilated segment.

The anatomical location was determined by the extent of the lesion (where the abnormality was thought to begin and where it appeared to end) and classified into 5 different groups:

- Vertebral only
- Basilar only
- Vertebrobasilar
- Vertebrobasilar-posterior cerebral
- Basilar –posterior cerebral

The aneurysms were classified as either dolichoectactic, fusiform or transitional as per the classification of Flemming et al (6) with the definition of each sub-type based on the following imaging appearance (Fig.1):

- Fusiform – dilatation >1.5 times normal involving a part of the vertebral or basilar artery, without any discernible neck and with any degree of tortuosity
- Dolichoectatic – uniform dilatation >1.5 times normal involving the entire basilar artery, vertebral artery or both with any degree of tortuosity

- Transitional – uniform dilatation of an entire arterial segment >1.5 times normal involving the vertebral artery, basilar artery or both with a superimposed dilatation of a portion of the involved arterial segment

This anatomical classification was chosen since the recent work of Nasr et al (27) has demonstrated a marked difference between these aneurysm subtypes with regard to their propensity to enlarge as well as the Kaplan-Meier survival curves for each of these aneurysmal subtypes. Therefore, we feel it is important to classify these aneurysms appropriately in order that we can determine if treatment may alter the natural history of the disease.

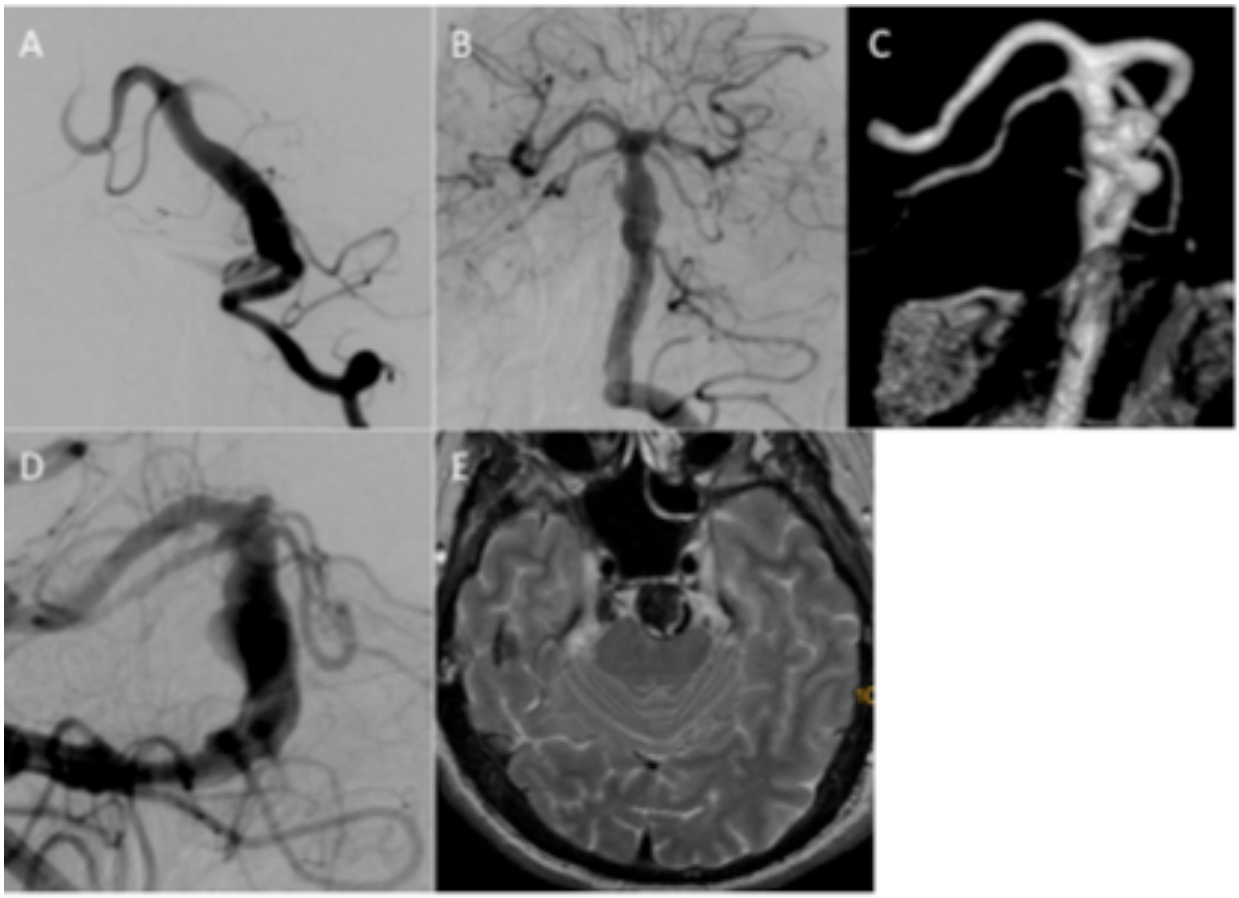


Figure 1

Examples of the different sub-types of aneurysm. Fig 1a shows dolichoectasia, smooth dilatation of the basilar artery. Fig.1b and 1c show fusiform dilatation of the distal basilar. This aneurysm shows partial thrombosis on the MR imaging (not shown). Fig. 1d and 1e show a transitional aneurysm of the basilar artery which is grossly dilated with a more focal abnormality that also shows thrombosis on MR imaging.

Imaging Characteristics

The maximum diameter of the vessel was measured on axial imaging at the point of maximal dilatation. For those patients with MR imaging prior to intervention note was made of:

- The presence of thrombus within the aneurysm
- The presence of T1 hyper-intense signal within the aneurysmal wall
- The presence of mass effect on the nearby structures of the posterior fossa.
- Any infarctions seen within the territory of the posterior circulation seen on either T2/FLAIR sequences or DWI sequences.

These characteristics were also shown to be more common in different aneurysmal subtypes and therefore, were included in our evaluation.

Endovascular Treatment

All treatments were performed under general anaesthesia. Two commercially available FDS were used: Pipeline (Medtronic) and P64 (Phenox). Patient informed consent was obtained before the procedure in all cases. The selection of FDS was dependent upon the operators' judgement.

All patients received dual antiplatelet therapy (aspirin 75 mg daily and clopidogrel 75 mg) prior to the treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche). The post-procedural antiplatelet regime consisted of clopidogrel continued for 12 months or longer following treatment and aspirin continued for life. Ticagrelor was substituted for patients non-responsive to clopidogrel.

All procedures were performed via the right common femoral route using a 6Fr access system as standard and were performed under heparin anticoagulation with a 5000IU bolus dose at the start of the procedure and subsequent 1000IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times compared to the baseline.

Procedural Assessment and Follow-Up

Patency and flow characteristics within the parent artery and aneurysm were assessed on follow-up catheter angiography. MR imaging was performed in most patients.

Neurological examinations were performed to rule out potential ischaemic or haemorrhagic complications in the post-operative period (<24hours post procedure) and at each subsequent follow-up.

IRB approval was not required for this study.

7.1.4 Results

Patient Population (Table 1)

We identified 56 patients that met our inclusion criteria with 58 aneurysms (two patients had bilateral aneurysms of the vertebral arteries). Just over 80% of patients were male and the average age at first treatment was 63.5yrs (±9-96, range 49-86). Patients that were symptomatic from the aneurysm (n=22) accounted for 37.9% of patients with the rest presenting incidentally or for reasons thought not related directly to the aneurysm. At presentation 50 patients had an mRS ≤2 with the remaining 6 patients presenting with an mRS ≤5.

BASELINE CHARACTERISTICS	**RESULT**
No. Patients	56
No. Aneurysms	58
Mean Age (SD)	63.5 (9.96)
Male, N (% of patients)	45 (80.3%)
Symptomatic at Presentation (% of aneurysms)	22 (37.9%)
Aneurysm Location	
Vertebral	17 (29.3%)
Basilar	11 (18.9%)
Vertebro-basilar	26 (44.8%)
Vertebro-basilar-posterior cerebral	3 (5.17%)
Basilar-posterior cerebral	1 (1.72%)
Type of Aneurysm	
Dolichoectactic	6 (10.3%)
Fusiform	24 (41.3%)

Transitional	28 (48.2%)
mRS at presentation (no. of patients)	
0	25
1	15
2	10
3	4
4	1
5	1
6	0
mRS at last F/U	
0	21
1	14
2	6
3	2
4	2
5	2
6	9
Mean Angiographic F/U in months	25.2
Mean Max. Diameter (SD)	11mm (5.48)
Max. Diameter ≥10mm	25 (43.1%)
Mass effect on MRI/CT	28 (48.2%)
T1 hyperintensisty in aneurysm rim	13 (22.4%)
Thrombus in Aneurysm	15 (25.8%)

Table 1

Baseline characteristics of patients

Imaging characteristics and anatomical localisation (Table 1 and 2)

The most common anatomical location of aneurysms in our cohort was vertebra-basilar (44.8%) with vertebral location the second most common location (29.3%) and basilar the third (18.9%). Location extending from the vertebral artery into the posterior cerebral arteries and extending from the basilar artery into the posterior cerebral arteries was relatively uncommon.

	Dolichoectasia	**Fusiform**	**Transitional**

Characteristic			
Location (n=58)			
Vertebral	0	17	0
Basilar	4	3	4
Vertebrobasilar	2	3	21
Vertebro-basilar-cerebral	0	0	3
Basilar-Cerebral	0	1	0
Percentage	10.30%	41.30%	48.30%
Max. Diameter			
Vertebral	N/A	8.8mm (6-12.5mm)	N/A
Basilar	7.6mm (5.5-10mm)	11.7mm (8.5-14mm)	13.6mm (7-19mm)
Vertebrobasilar	11.5mm (7-16mm)	8mm (7-9mm)	13.5mm (5.5-20mm)
Vertebro-basilar-cerebral	N/A	N/A	10.1mm (8-13mm)
Basilar-Cerebral	N/A	5mm	N/A
MRI Findings (n=53)			
Mass Effect	2 (33.3%)	10 (41.6%)	16 (57.1%)
T1 Hyperintensity	1 (16.6%)	4 (16.6%)	8 (28.6%)
Thrombus	0 (0%)	7 (29.1%)	8 (28.6%)
Established Infarcts In the Posterior Circulation Territory	2 (33.3%)	6 (33.3%)	14 (50%)

Table 2

Imaging and anatomical characteristics

The mean maximal diameter of the aneurysms was 11mm (±5.48, range 5.5-30mm). The maximal diameter of 25 aneurysms was 10mm or larger (43.1%).

The majority of aneurysms in our cohort were transitional, with 28 aneurysms (48.2%) having this anatomical classification. There were 24 fusiform aneurysms (41.3%) and 6 were dolichoectactic (10.3%). Of the dolichoectactic aneurysms 4 (66.6%) involved only the basilar artery, with the majority of fusiform aneurysms, 17 (70.8%) involved only the vertebral artery (Fig. 2) and of the transitional aneurysms 21 (75%) were vertebra-basilar in location.

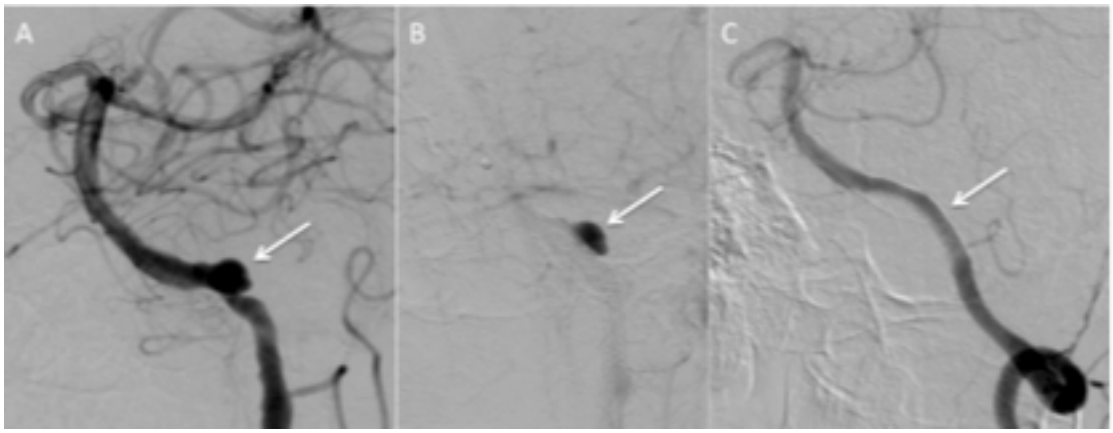


Figure 2

A patient with an asymptomatic V4 fusiform aneurysm (Fig. 2a white arrow). Two telescoped PEDs were placed in situ with stagnation of contrast medium seen in the aneurysm at the end of the procedure (Fig. 2b, white arrow). A follow-up angiogram performed 4 months after the procedure confirmed closure of the aneurysm and patent vertebrobasilar system (Fig. 2c).

Transitional aneurysms were the largest of the three subtypes with the maximum diameter seen in the basilar (13.6mm, range 7-19mm) and vertebra-basilar locations (13.5mm, range 5.5-20mm). For fusiform aneurysms the basilar location showed the largest maximal diameter (11.7mm, range 8.5-17mm) and for dolichoectasia disease affecting both the vertebral and basilar arteries showed the largest diameter (11.5mm, range 7-16mm).

Most patients (n=53) had MR imaging at initial presentation. This was performed to assess for the presence of mass effect, infarction, intra-aneurysmal thrombus and any other intracranial pathology that may preclude treatment. In those patients with transitional aneurysm subtypes were seen to have mass effect on neighbouring structures, T1 hyperintensity within the wall of the aneurysm, thrombus and posterior circulation territory infarcts more frequently than either the fusiform or the dolichoectactic subtypes. Conversely these features were least common amongst patients with dolichoectasia.

Treatment and Follow-up (Table 3)

All patients were treated with FDS of the aneurysmal segment. None of the patients had coils placed in the aneurysmal sac (if present). In disease that crosses the vertebrobasilar junction, after treatment with FDS, coil occlusion of the contralateral vertebral artery is required in order to stop the otherwise persistent endoleak around the new flow diverter construct. This is an

essential part of the treatment plan. In total 338 FDS were implanted in the 56 patients (163 p64 stents, 175 PED's).

Characteristic	Dolichoectasia	Fusiform	Transitional
Average No. Of FDS (range)			
Vertebral	N/A	2.8 (1-3)	N/A
Basilar	4.5 (2-6)	8.3 (1-19)	4 (3-5)
Vertebrobasilar	5 (4-6)	3.6 (1-7)	8.2 (1-18)
Vertebro-basilar-cerebral	N/A	N/A	5 (2-8)
Basilar-Cerebral	N/A	1 (1)	N/A
Average No. Of Treatment episodes (range)			
Vertebral	N/A	1.35 (1-3)	N/A
Basilar	1 (1)	3.66 (1-5)	1 (1)
Vertebrobasilar	1.5 (1-2)	1.66 (1-2)	1.86 (1-5)
Vertebro-basilar-cerebral	N/A	N/A	2 (1-3)
Basilar-Cerebral	N/A	1 (1)	N/A
Angiographic F/U status			
Minor Remnant/filling	1	3	7
Major remnant/filling	0	0	5
Occluded	4	18	5
Unchanged	0	1	2
	1 No F/U available	1 No F/U available, 1 died	1 No F/U available, 8 died
MRI F/U of those without angiographic occlusion (n=18)	n=1	n=4	n=13
Stable	1	1	3
New Infarcts	0	0	3
Increased intra-aneurysmal thrombus	0	3	6
Increased Mass effect	0	0	3
Decrease in max. diameter of aneurysm	0	3	1

No change in max. diameter of aneurysm	0	1	8
Increase in max. diameter of aneurysm	0	0	4

Table 3

Treatment and imaging outcomes of patients

Fusiform aneurysms of the basilar artery and transitional aneurysms of the vertebrobasilar arteries required the most FDS in order to reconstruct the vessels (on average 8.3 and 8.2 respectively) (Fig. 3).

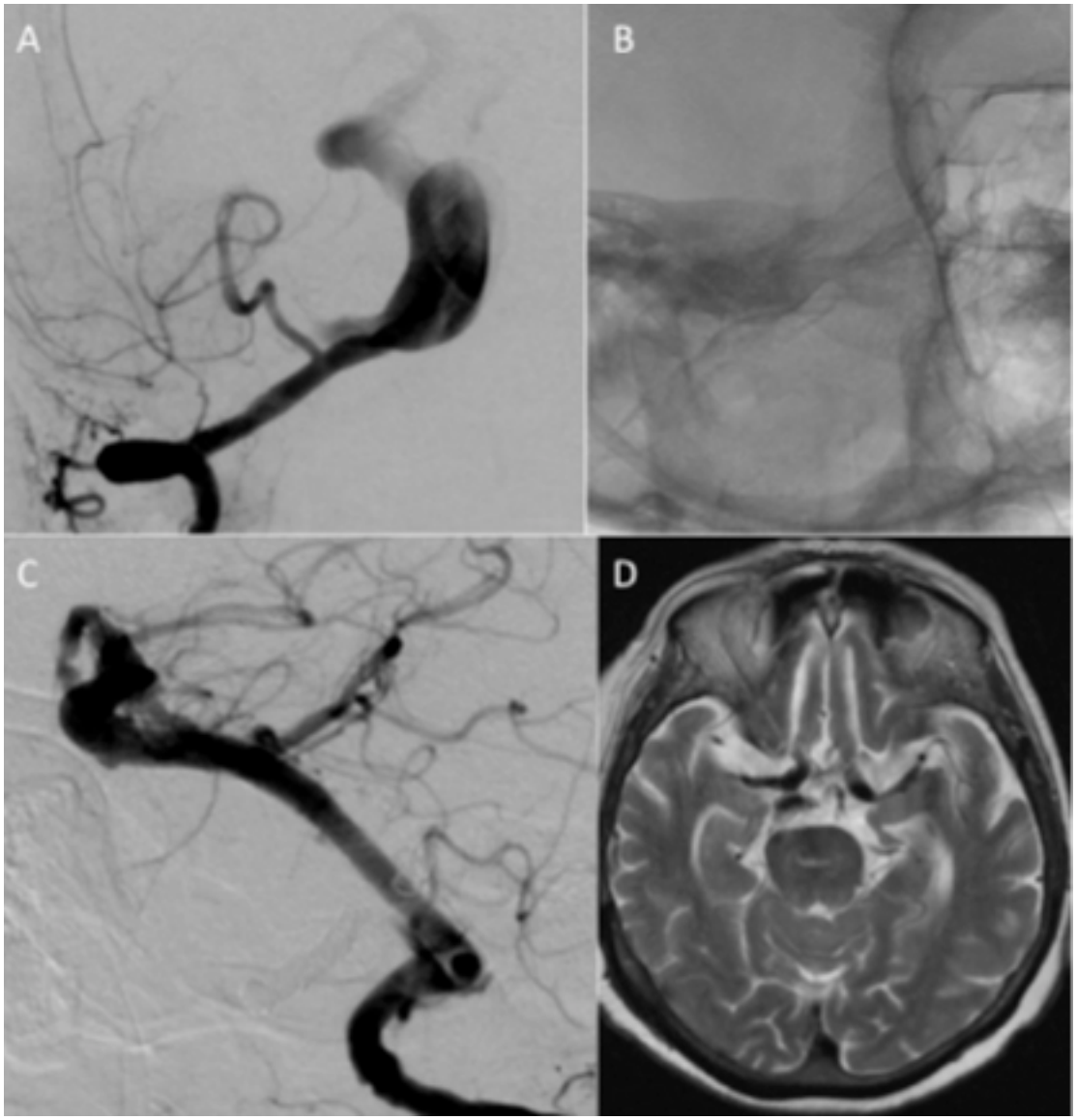


Figure 3

A patient with symptoms of mass effect from a vertebra-basilar transitional aneurysm (Fig. 3a) underwent treatment with 16 telescoped PED's (Fig. 3b). The procedure was noted to be technically difficult but there were no procedural complications. Follow-up angiography performed 16 months after the procedure showed good reconstruction of the vessel with only a small remnant aneurysm (Fig. 3c). There was no evidence of pontine infarction on MR imaging.

In circumstances that required multiple telescoped FDS up to 19 were used to treat a basilar fusiform aneurysm in a single patient, where as significantly fewer were used for disease that was confined to the vertebral artery (mean 2.8, range 1-3). Treatment was carried out in a multi-stage process with up-to 5 treatment sessions required in some patients. The more complicated aneurysms required more procedures (mean 3.66 for basilar fusiform aneurysms, 1.86 for vertebrobasilar transitional aneurysms).

The last angiographic follow-up was performed at 25.2 months (mean, range 1-72 months). In our cohort 9 patients died and 3 had no angiographic follow-up. Of the remaining patients, there was complete restoration of normal angiographic appearance for 66.6% of those with dolichoectasia (Fig. 4) with only minor flow in the remaining patient with angiographic follow-up. In those patients with fusiform aneurysms there was complete aneurysm occlusion in 18 patients (75%) with a minor remnant seen in in 3 patients (12.5%) and an unchanged appearance in 1 patient (4%). There was 1 death and 1 patient without angiographic follow-up in this group. In the patients with transitional aneurysms, 5 were completely occluded (17.8%) (Fig. 5) with 7 showing only minor remnants (25%). In 5 patients there was still a major remnant although in all of these aneurysms flow reduction could be seen on angiography. In 2 aneurysms there was no change in the appearance of the aneurysms although flow into the aneurysmal sac had been reduced.

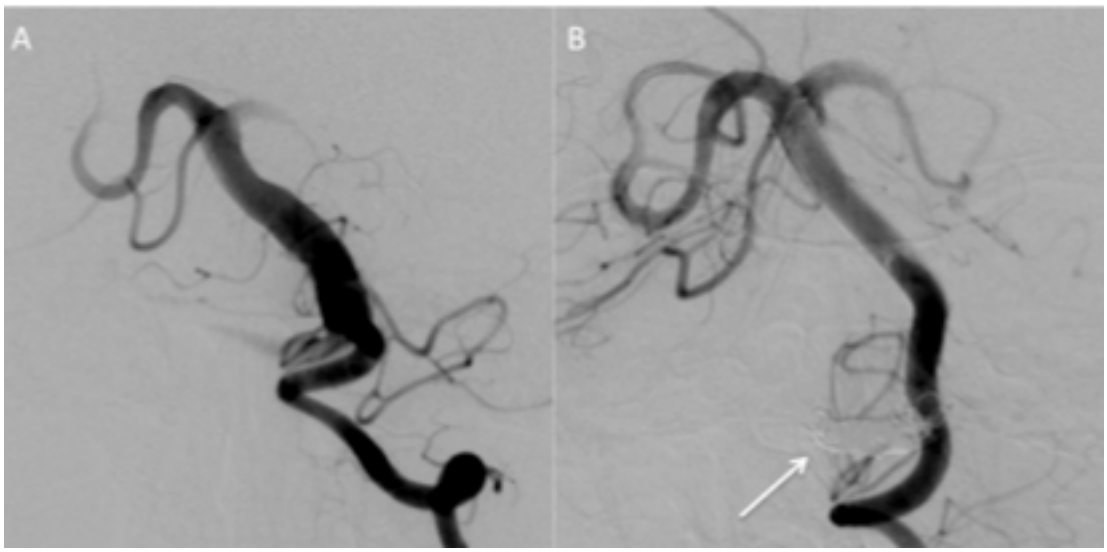


Figure 4

A patient with dolichoectasia of the basilar artery (7mm) treated with telescoped PED's showed no progression of the disease on the follow-up angiogram performed at 14 months.

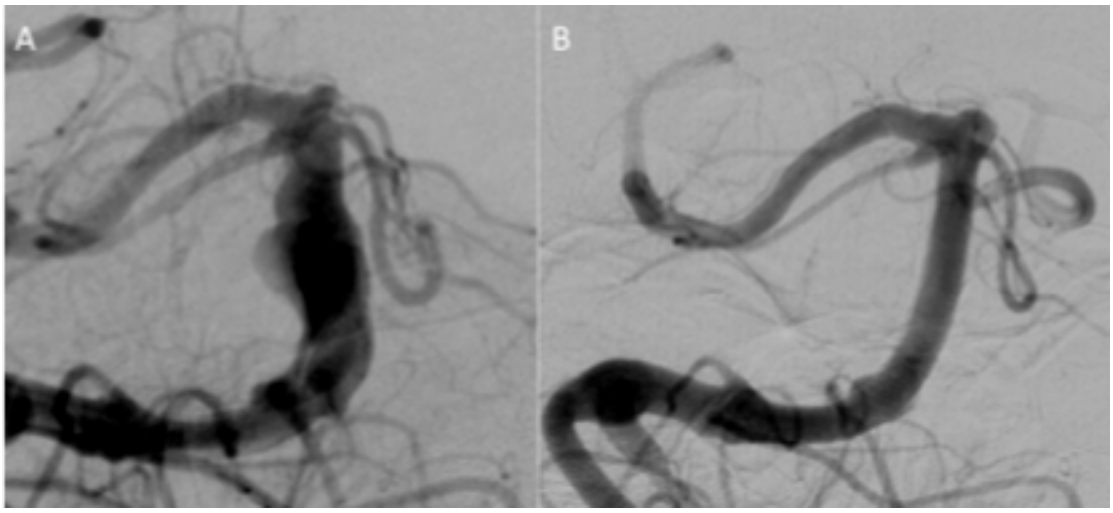
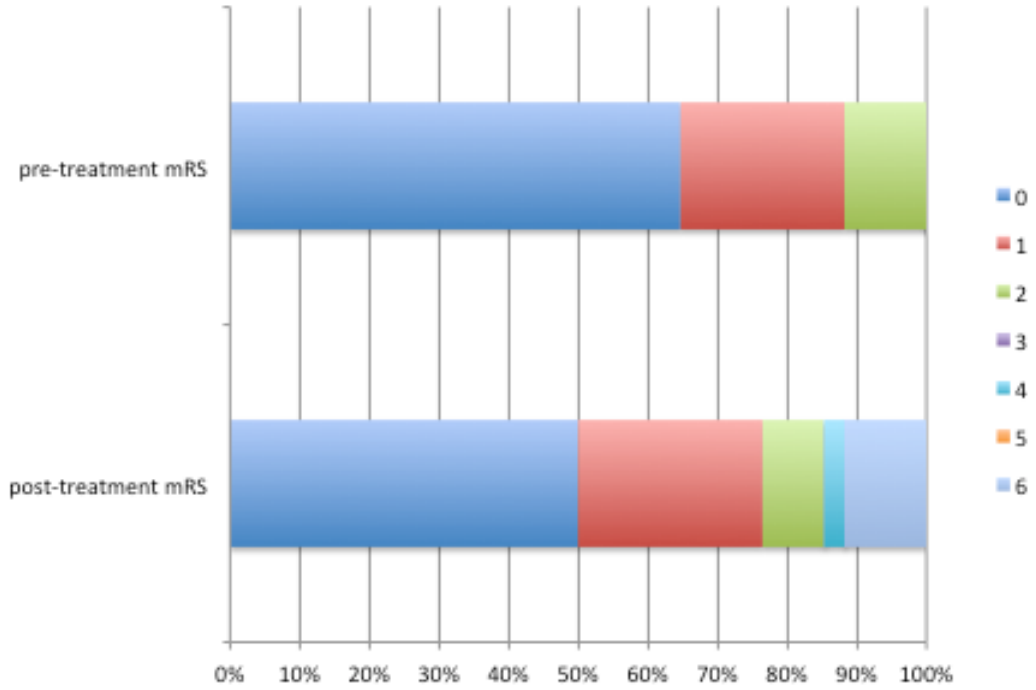


Figure 5

A patient with a transitional basilar artery aneurysm 4 months after treatment with 3 telescoped PEDs showing complete reconstruction of the vessel with no further filling of the aneurysm.

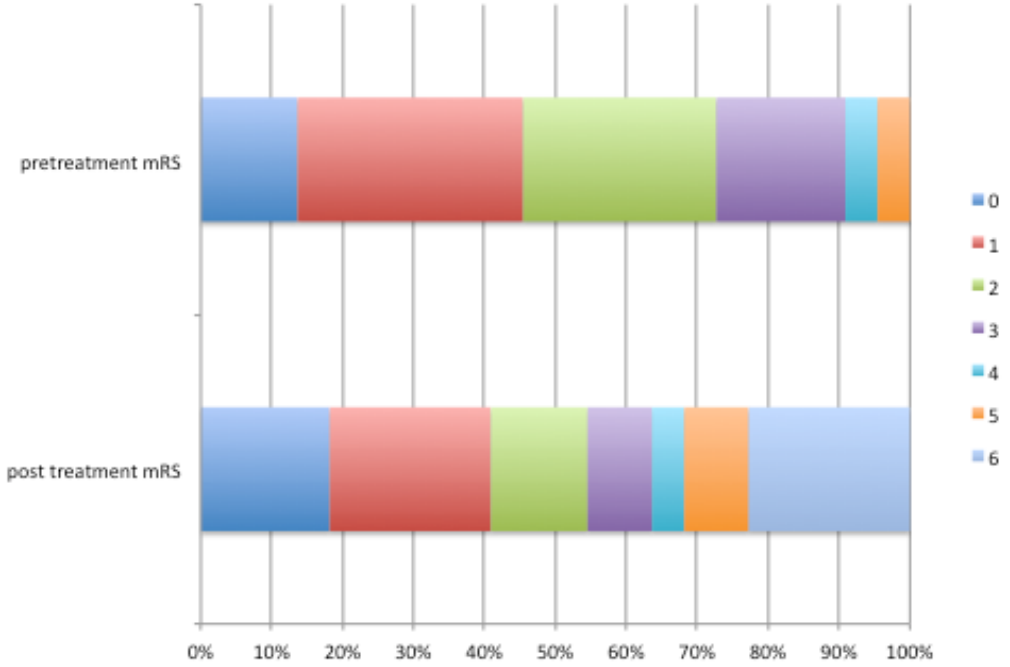
The initial and final mRS of patients was recorded and analysed according to the initial presentation of patients e.g. whether the aneurysm was symptomatic or not at presentation. In those patients that were initial asymptomatic all patients presented with a mRS ≤2 and 82.8% of patients had a final mRS of ≤2 (Graph 1). However, in the symptomatic group 72.7 of patients presented with a mRS≤2 and only 54.5% had mRS≤2 at last follow-up (Graph 2). Similarly the

incidence of mRS 6 was just over double in the symptomatic group (22.7%) compared with the asymptomatic group (11.1%)



Graph 1

A breakdown of the mRS pre and post intervention for patients that did not present with symptoms related to the aneurysm.



Graph 2

A breakdown of the pre interventional and post interventional mRS for patients that presented with symptoms related to the aneurysm.

Complications and deaths

In total 7 patients had ischaemic symptoms, one of whom inappropriately stopped taking clopidogrel, which resulted in thrombosis of the SCA's bilaterally and the left PCA and a final mRS of 5. Four of these patients had a final mRS ≤2 with the remaining two patients mRS 4. One patient had a traumatic intra-ventricular haemorrhage and one other patient had a cerebellar haemorrhage. Overall the complication rate was 15.5%.

In total 9 patients in our cohort died (15.5%), 5 of which were symptomatic at presentation (Fig. 6 and 7), which represents death in 22.7% of patients that were symptomatic at presentation. In stent thrombosis occurred in 3 patients, secondary to stopped medication in one patient, inappropriate use of ibuprofen which antagonised aspirin in another and loss of platelet inhibition secondary to a platelet transfusion required for uncontrollable inguinal haemorrhage in another. In the remaining patients there was one fatal sub-arachnoid haemorrhage, 2 cases of progressive mass effect (one in which the patient refused to have the contralateral vertebral artery coil

occluded following FDS treatment resulting in persistent endoleak and aneurysm enlargement) (Fig. 8), 2 ischaemic events and one patient died of unrelated causes.

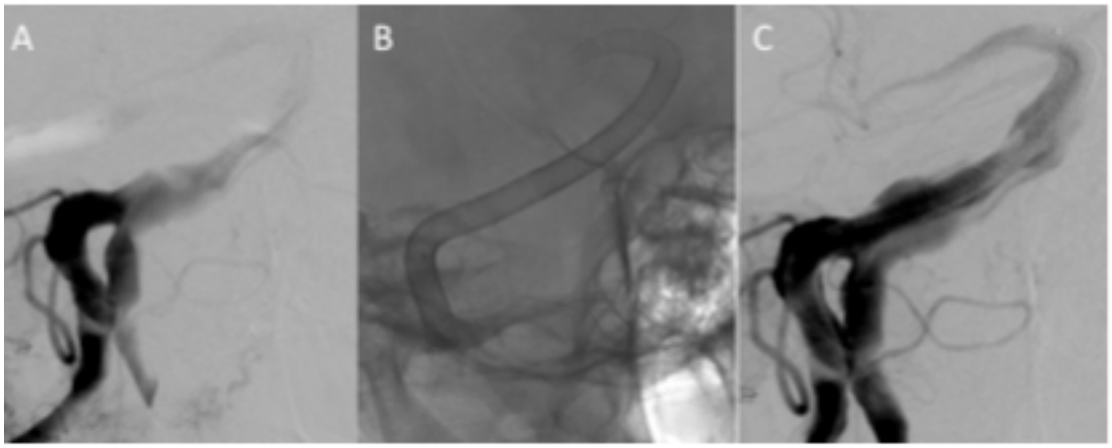


Figure 6

A patient that presented with recurrent posterior fossa strokes was found to have a transitional vertebrobasilar aneurysm (Fig. 6a). He underwent treatment with 18 telescoped PEDs that extended from the P1 segment to the vertebral artery (Fig 6b). Flow through the PEDs into the aneurysm and distally into the PCA's could be demonstrated at the end of the procedure (Fig .6c)

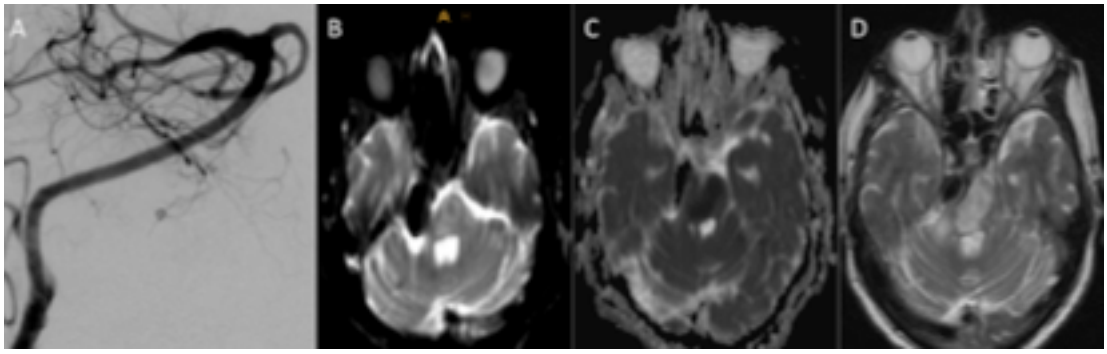


Figure 7

The same patient as in Fig. 6, acutely deteriorated 24 hours post procedure. An angiogram confirmed patent basilar artery and good flow distally (Fig. 7a). MRI DWI and ADC showed restricted diffusion in the pons (Fig. 7b and 7c). A T2 weighted MRI scan performed 5 days later showed a pontine infarction (Fig.7d) and the patient died shortly thereafter.

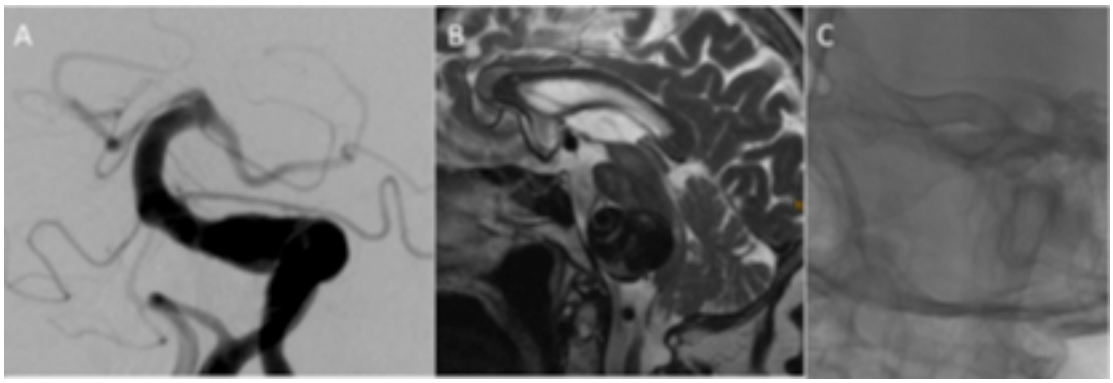


Figure 8

A patient that presented with symptoms of mass effect from a partially thrombosed vertebrobasilar transitional aneurysm was initially treated with 5 telescoped PEDs placed in the left vertebral artery. The patient was due to have coil occlusion of the contra-lateral vertebral artery but refused further treatment and later died from progressive mass effect.

7.1.5 Discussion

Non-saccular aneurysms of the vertebrobasilar tree are characterised by elongation, dilation and/or tortuosity of the vessel. The end appearance, which can be striking, is likely due to a variety of different processes and this may account for the difference seen in the natural history and prognosis. Flemming and colleagues (6) reported the most thorough longitudinal evaluation with 159 patients and 719 patient years. In this study, which excluded dissecting aneurysms, the lesions were defined radiologically as fusiform, dolichoectactic, or transitional (see earlier for definition). Using this classification, 45% of patients in the Flemming cohort had dolichoectasia, 19% had a transitional aneurysm and 15% had a fusiform aneurysm with 21% having an indeterminate type. In this cohort the transitional and fusiform types were more likely to be symptomatic with dolichoectatic aneurysms appearing more benign in clinical course. After age adjustment, fusiform type, transitional type and basilar involvement all had increased hazard ratios for mortality (HR 7.7, 3.56, and 8.77 respectively). Furthermore asymptomatic patients did not often become symptomatic with stroke seen in 7.8%, mass effect symptoms in 3.1% and haemorrhage in 1.6%. Mizutani et al (28) proposed a different classification in 1999 however, they also showed that dolichoectactic aneurysms found incidentally had no significant neurological sequelae in follow-up and neither group reported a transformation from dolichoectasia to fusiform type. Recently Nasr et al (27) published their analysis on the imaging characteristics associated with growing and ruptured non-saccular and dolichoectatic aneurysms

of the vertebrobasilar tree. They showed that whilst transitional aneurysms (56.3%) and fusiform aneurysms (24.4%) were the most likely to grow, dolichoectactic aneurysms also grew (8%) during the follow-up period (mean 40 months for dolichoectactic aneurysms). These results are similar to Passero et al (10) who found approximately 5% of dolichoectactic aneurysms progressed (defined as either increasing tortuosity and/or enlargement) over a 5 year follow-up period. The study by Nasr et al (27) also showed a significant difference in the Kaplan-Meier survival curves for the various sub-types with approximately 90% survival at 100 months for patients with dolichoectasia and less than 30% for those with transitional morphology.

The natural history of these lesions is extremely variable and is dependant upon their initial presentation, which in all likelihood is also related to their morphological appearances. Flemming et al (6) found that the ischaemic stroke risk was higher than the risk of haemorrhage and the rate of infarction related to the aneurysms rose from 2.7% at 1 year to 15.9% at 10 years. The risk of a recurrent stroke, for patients initially presenting with stroke, was calculated as 6.7% per year (median time of 1.73 years). Symptomatic lesions, previous ischaemia secondary to the aneurysm and transitional aneurysmal type were all seen to increase the factors for stroke (HR 16.2, 3.88, 3.2 respectively). Similarly 18.8% of patients with transitional aneurysms in the cohort of Nasr (27) developed new infarcts. For dolichoectactic aneurysms the risk of infarction is not negligible with 14.7% in the Nasr et al cohort having new infarctions. The exact cause of the ischaemia is not fully elucidated however several mechanisms have been put forward. These include occlusion of the small perforating vessels caused by the significant distortion of the parent basilar artery, embolisation of thrombus within the parent artery and/or in-situ thrombus formation within the small perforating vessels as well as the parent artery.

Compressive symptoms were seen in 22% of patients in cohort of Fleming et al. (6) and approximately three quarters of these patients had only mild or no disability. At 1 year only 46% of patients had mild or no symptoms and importantly 7.5% who did not initially have compressive symptoms developed them. The growth of aneurysms is associated with development of compressive type symptoms and in the Mayo Clinic cohort approximately half of all patients demonstrated enlargement, which was statistically associated with the transitional and fusiform sub-types, larger size (15 vs. 8 mm) and symptomatic presentation. Furthermore, T1 weighted high signal within the vessel wall was more commonly in enlarging aneurysms and in the Nasr et al cohort 54% of aneurysms that enlarged showed T1 hyperintensity compared to only

20% of those without enlargement. Aneurysm growth also affects mortality with the 5 year mortality of enlarging aneurysms being 56.5% compared with 3.7% for stable aneurysms (18).

As with other aneurysmal pathologies rupture is also a risk although it appears that the risk of rupture is less than that of ischaemia/compression. In the cohort of Nasr et al (27) rupture was seen in 12.5% of patients with a transitional aneurysm, 6.7% of those with fusiform aneurysm and 1.3% of those with dolichoectasia. They also showed that for those aneurysms that were ≥10mm the annual rupture rate was 6.8% compared to 2.5% for those <10mm. Similarly in the cohort of Flemming et al (6) the annual risk of rupture for fusiform and transitional aneurysms was 2.3% whilst that of dolichoectatic aneurysms was 0.4%. As with compressive symptoms larger size was also associated with rupture and in the multi-variate analysis of Passero et al. (11) a median basilar artery diameter of 6.8mm was associated with intracranial haemorrhage.

Given the prognosis it is no wonder then that management options have been aggressively sought. Surgical treatment of these lesions often involved either flow reduction if inadequate collateral supply was available, flow reversal if adequate collateral supply was available, or trapping with haematoma decompression for lesions that presented with acute mass effect. In the series published by Drake et al. (29,30) 63% of patients that had flow reduction had an excellent/good outcome with 74% of those undergoing flow reversal having a excellent/good outcome. Similarly, 71% of patients that had trapping and thrombectomy achieved good outcomes (30). As might be suspected the likelihood of success following ligation is related principally to the supply from the posterior communicating arteries (PComA) with a 6.7% chance of ischaemia in patients with at least one large PComA (>1mm) compared to 43% in patients with 2 small PComAs (<1mm). In the case of poor collaterals bypass surgery can be performed prior to flow reversal/reduction and this is often achieved via superficial temporal artery to superior cerebellar/posterior cerebral artery bypass. Kalani et al (31) reported their series of 11 patients using these bypass techniques and despite the fact that the mortality at 1 month was 45% the remaining patients achieved an average mRS of 2.5 (mean follow-up 71.6%). Vessel sacrifice can also be achieved endovascularly. For example Leibowitz and colleagues (32) reported their results of 13 cases, 10 of which represented fusiform aneurysms of the vertebrobasilar system. In 6 patients flow reduction was attempted via dominant vertebral artery occlusion for patients with either vertebrobasilar junction or basilar aneurysms. Four of the patients died, 1 patient deteriorated clinically and the other remained stable. The remaining four

patients had disease confined to the vertebral artery and these patients all improved clinically. Similarly Sluzewski et al (33) reported 6 cases of basilar fusiform aneurysms treated with bilateral vertebral occlusion. Of these cases, the three patients that presented in good condition did well post-operatively and the 3 patients that presented in poor condition had a poor post-operative outcome. Again, these authors noted that the presence of large PCom's was predictive of a good functional outcome.

The advent of FDS heralded a significant advancement in the management of intracranial aneurysmal disease. This was initially met with great enthusiasm in the neuro-interventional community and it was believed that the ability to reconstruct diseased vessels would offer a particular advantage for the treatment of fusiform aneurysms of the posterior circulation.

In 2012 Siddiqui et al (25) reported their experience of treating fusiform vertebrobasilar aneurysms. In their case series FDS were used to treat 7 patients all of whom also received dual antiplatelet therapy. Similar to many of our cases several telescoped stents were used (3-9 stents). In this relatively small series 4 of the 7 patients died and a further patient had severe neurological disability. The remaining two patients had a good outcome and the authors concluded that the treatment of vertebrobasilar aneurysms with FDS carries a significant morbidity and mortality. Similar poor results were also reported by Raphaeli et al (16) who reported a 25% mortality. Better results were reported by Chalouhi et al (34) who used the PED to treat 3 aneurysms with no reported complications or mortality at follow-up of 5.5 months. More recently Munich et al (35) published their series of 12 patients that were treated with FDS. Excluding the two patients that presented with SAH, 7 patients showed complete occlusion with 1 case showing persistent filling and an endoleak. One patient in this series died although this was secondary to acute respiratory distress and pneumonia. There were no cases of acute in stent thrombosis in this series. Phillips et al (26) published their series of 32 patients with an overall rate of permanent neurological complications of 9.4% (3/32). However, they reported that all three patients had only mild residual symptoms and good clinical outcome with mRS 1 and a return to independent living and work. The aneurysm occlusion rate in this series was 96% at >1 year follow-up but it is important to note that this study did not deal exclusively with non-saccular aneurysms, with 12 of 32 aneurysms classified as berry aneurysms. Natarajan et al (36) also recently published their series of 12 patients only one of whom suffered a perforator territory infarction with poor clinical outcome (mRS = 4). There were no deaths in this cohort and the

results of this study are considerably better than previously reported by the same group in 2012 (25). The improvement in the results is attributed to several factors:

- A strict anti-platelet regimen with confirmation of the therapeutic effect of the anti-platelet therapy prior to the intervention.
- Patient selection - the authors note that patients in this latter cohort presented earlier when compared to those in the series of 2012 with only 25% of the patients in the most recent series presenting with ischaemic symptoms but none had evidence of ischaemia on MRI, therefore in this series the patients presented earlier than in the authors original series. The authors also state that patients presenting with acute ischaemic symptoms from brainstem infarction or compression carry a bad prognosis. This may be due to already compromised perforator ostia as well as a larger number of devices required to treat these vessels.
- A decreased number of flow diverters was used in the latter series and this is at least in part because longer PEDs have become available that allow easier reconstruction of diseased vessel.
- Adjunctive coiling was used in 50% of the cases and the authors now place coils in all the aneurysmal sacs if possible. They believe that the addition of coils in the aneurysmal sac helps to act as a scaffold for the PED and prevent foreshortening of the PED construct. Furthermore, they believe that the addition of coils will help protect against haemorrhagic complications and promote thrombus formation within any saccular components of the aneurysm.

We concur with some of these findings and believe that early management prior to infarction or compressive symptoms is extremely important to achieve a good clinical outcome. In our data the mortality is double in those patients that were symptomatic at presentation (22.7% compared to 11.1%). We also agree with these authors with regard to a strict anti-platelet regimen as in-stent thrombosis or thrombo-emboli are a significant risk as highlighted by several of our cases. Platelet function is tested routinely in our clinical practice. Additionally, since 2016 we have added direct oral anti-coagulants (e.g. 2x100mg Dabigatran daily) for patients with large fusiform or transitional type aneurysms involving the basilar trunk. We believe that coils within an aneurysmal sac may be a useful but in our experience do not appear to be necessary and this needs to be based on individual anatomy. The number of FDS required to obtain a good result is

difficult to determine. This will be, at least in part, based on the longitudinal extent of the disease. The target of the treatment should be to redirect flow away from the diseased vessel wall and this, in our opinion is most important at the level of a saccular aneurysm. Furthermore, as is discussed later, neo-endothelialisation commences from the site of contact with the parent artery. Therefore, we believe it is important to land the FDS in a portion of the vessel that demonstrates a normal appearance, both at the proximal and distal end. We believe this will assist neo-endothelialisation. A summary of the published literature is provided in Table 4.

Authors	**No. Patients with non-saccular aneurysms**	**Morbidity**	**Mortality**	**Follow-Up**
Narata et al(37)	2	0	0	6-9 months
Fiorella et al(21,38)	2	50%	50%	12-28 months
Ducruet et al(39)	1	0	0	6 months
Tan et al(40)	1	0	0	6 months
Chalouhi et al(34)	3	0	0	5.5 months
Siddiqui et al(25)	7	14%	57%	NA
Gong et al(41)	1	0	0	6 months
Nelson et al(42)	1	0	0	NA
Szikora et al(43)	1	0	0	6 months
Ertl et al(44)	1	0	100%	17 months
Raphaeli et al(16)	4	0	25%	NA
Munich et al(35)	12	25%	8.30%	11 months
Toth et al(45)	2	50% (patient discontinued anti-platelets)	50%	NA
Natarajan et al(36)	12	8.30%	0%	12-43 months
Ahmed et al(46)	4	25%	75%	12-25months

Table 4

Summary of the published literature on the use of FDS in posterior circulation fusiform aneurysms.

The recent work of Kardivel et al. (47) is important to acknowledge when considering fusiform aneurysms. In this elegant animal study it was shown that the formation of neointima is required to cause complete exclusion of aneurysms from the circulation and this process of neointimal formation begins at the site of contact between the flow diverter stent and the parent artery. The process then proceeds from site until it covers the aneurysmal neck. During this process only scattered inflammatory cells were seen on the flow diverter stent struts that cover the aneurysmal neck. If this process is similar in fusiform aneurysms, and there is no reason to our knowledge to suspect that it is not, then it stands to reason that longer diseased segments will require a much longer time to neo-endothelialise. With regard to antiplatelet medication this means that a tailored approach is required with some patients likely to require lifelong double antiplatelet medication. This is likely to be true for those with non-saccular aneurysms, which may endothelialise very slowly. Some evidence to support this view recently came from Szikora et al. (48) who performed a histopathological analysis of five deceased patients treated with FDS in both the anterior and posterior circulation for fusiform aneurysms. In 3 patients the flow diverter had been present for over 6 months yet in only one patient was neo-endothelialisation and intimal hyperplasia identified and this was only seen on the section of flow diverter that was in the normal artery proximal to the aneurysm. In the remaining patients a thin layer of fibrin without smooth muscle cells was seen covering the inner layer of the flow diverter. This small but important study appears to support the work of Kadirvel and colleagues although further evidence is required. Neo-endothelialisation may not occur even after 12 months however, the angiogram can demonstrate lack of contrast entering the aneurysm (48). It is important to realise though that lack of contrast entering the aneurysm does not mean endothelialisation of the flow diverter has occurred. Under these circumstances, a lack of platelet inhibition could result in either thrombosis of the flow diverter or distal embolism. Therefore, it is important to tailor the antiplatelet regime to the patient and the disease process. Long segments of disease may require lifelong dual antiplatelet medication.

The telescoping method used in our patients was similar to that described previously by Siddiqui et al.(25), and was modified during the last seven years. In general we aimed to obtain maximal coverage at the site of maximal diameter and looked for flow redirection into the FDS construct and away from the vessel wall. We prefer telescoping from proximal to distal with about 30% overlap of the implanted FDS. The diameter of the most proximal stent should be slightly larger than the diameter of the landing zone (e.g., 4 mm). Subsequent FDS should have the same or

larger but never smaller diameters, since smaller diameters will result in FDS displacement. Since PED comes with a heat pretreatment while p64 does not, the coverage of the unrestrained PED is less than with p64. This aspect influences which implant will be used: PED for less and p64 for more coverage. A combination of PED and p64, devices with non-matching braiding patterns, will result in more coverage than telescoping of devices of the same kind. These technical aspects leave plenty of space for the intuition of the operator. The procedure is usually stopped as soon as a hemodynamic effect becomes visible through repeated catheter angiography. The patient would return for repeat angiography and MR imaging after approximately 6 - 12 weeks, to observe for flow changes and changes in size of the aneurysm. If no significant flow redirection had occurred compared to the original pre-treatment angiography then more FDS were placed inside the construct. Similarly, if an adequate amount of flow redirection into the FDS had occurred then coil occlusion of the contralateral vertebral would be performed (if required). This procedure was repeated until a satisfactory degree of flow redirection into the FDS construct had occurred. In some cases stagnation of flow between the FDS and the aneurysmal wall could be seen almost immediately and in these cases the procedure was stopped at this point with repeat MR and angiography imaging performed after 3 months. If the follow-up DSA revealed continued flow through the FDS into the aneurysm, which is mostly confined to certain focal points rather than affecting the entire length of the implants, additional FDS were deployed. The aim remains the gradual reconstruction of a smooth vessel lumen with a maximum diameter between 4.5 - 5 mm, avoiding both proximal and distal endoleaks as well as contrast exit at any point of the FDS construct.

Gradual vessel reconstruction obviously allows for the development of collateral brainstem circulation, eventually with no opacification of pontine basilar artery branches but without signs of brainstem ischemia, neither clinically nor on MR. In our experience, gradual adaption of the local circulation through staged FDS implantation, confirmed dual anti-aggregation and mild oral anticoagulation are key.

In our experience disease of the basilar trunk and disease that crosses the vertebral basilar junction can be the most difficult to treat. In addition to the flow diverters, coil occlusion of the contralateral vertebral artery is required to prevent a persistent endoleak around the flow diverter (49). This is important since continued flow from the contralateral vertebral artery between the FDS construct and diseased wall may result in disease progression as was seen in one of our patients that refused occlusion of the contralateral vertebral artery. Furthermore, we are unsure

of the changes in haemodynamic stress that will be exerted on the diseased wall by flow between the FDS construct and diseased segment however, we do not believe this would be conducive to healing. Whether the coil occlusion should be performed before the flow diverter is implanted, simultaneously or after is open to conjecture and we have no experience to promote a particular chronological order. We favour implanting the flow diverters initially and then at a later date coil occluding the contralateral vertebral artery as the flow diverters will prevent distal migration of the coils. We have also seen that despite dense coil packing, flow through the contralateral vertebral artery may continue and therefore, newer endovascular closure devices such as the UNO (Covidien) (50) should be considered as alternatives for vessel occlusion, although our experience with these devices is limited (Fig. 9). Furthermore, in some cases where the aneurysm sac is positioned at or very close to the AICA or AICA/PICA there is persistent filing of the aneurysm via the flow into these arteries (Fig. 10). Therefore, in this anatomical disposition a combined surgical and endovascular procedure with surgical bypass of these arteries followed by flow diversion may be an alternative strategy although we have no experience of this.

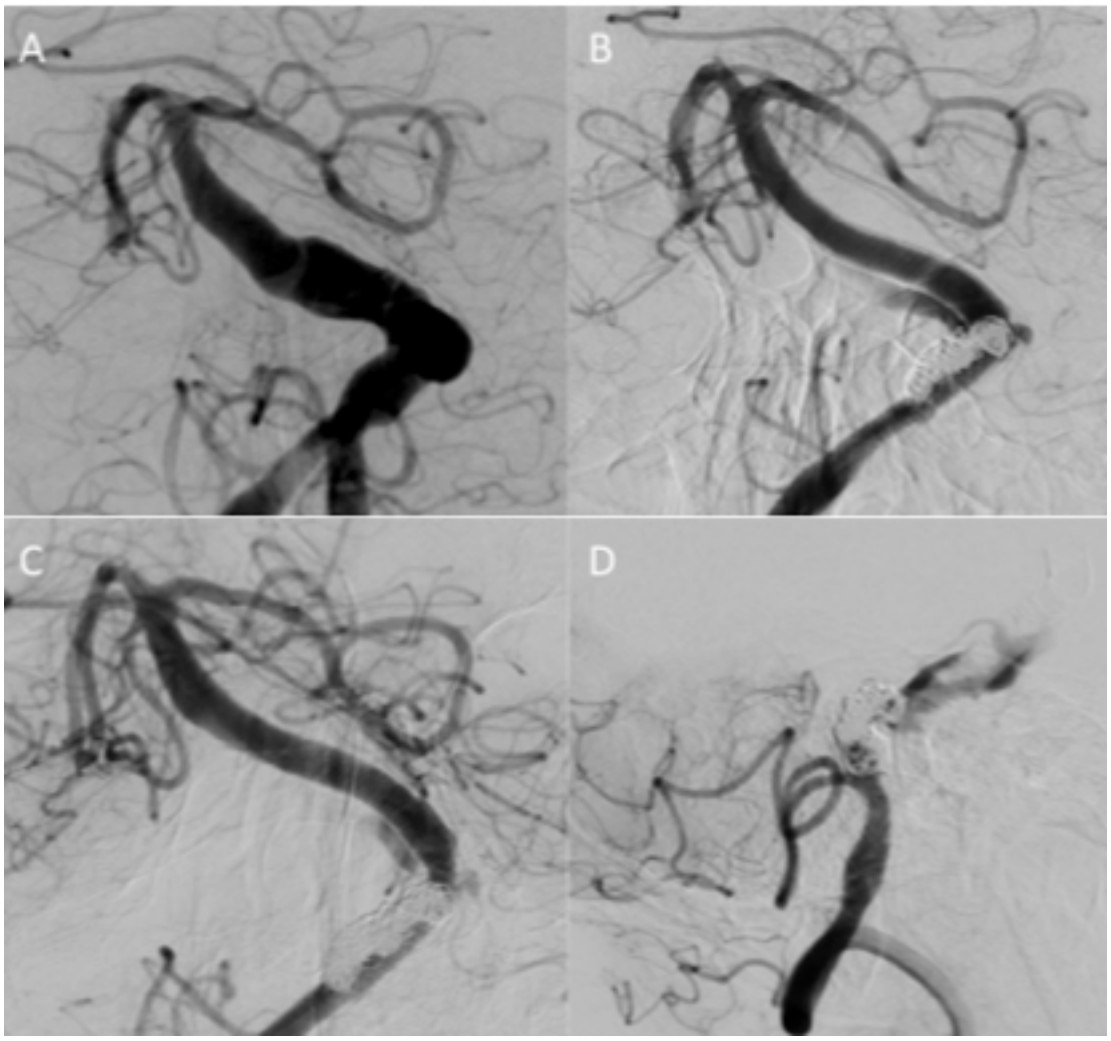


Figure 9

A patient with a vertebrobasilar transitional aneurysm (Fig. 9a) treated with 14 FDS (5 x PEDs, 9 x p64) and coiling of the contralateral vertebral artery. There has been good reconstruction of the vertebral and basilar artery with a decrease in the aneurysmal filling seen on follow-up angiography (Fig. 9b, 22 month angiography following initial treatment; Fig. 9c, 28 month angiography). However, despite dense coil packing in the contralateral vertebral artery a persistent leak into the aneurysm can be seen through the coil ball mass (Fig. 9d) warranting repeat occlusion of the vertebral artery.

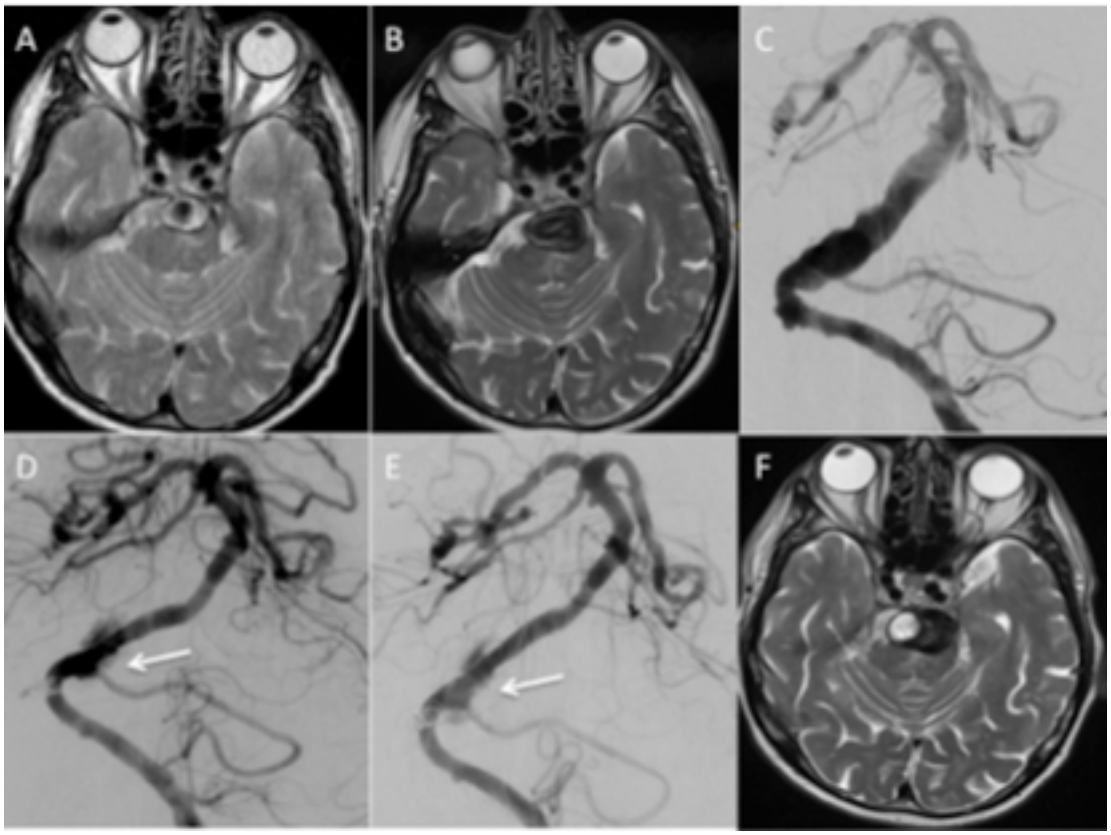


Figure 10

A patient was incidentally found to have dilatation of the basilar artery on routine MR imaging (Fig. 10a). At this point the patient refused further investigation. The patient had repeat MR imaging 26 months later (Fig. 10b) and the aneurysm had significantly increased in size with mass effect and small pontine infarction. An angiography performed at this time revealed a transitional vertebrobasilar aneurysm. The patient was treated with FDS and coil occlusion of the contralateral vertebral artery. A follow-up angiogram performed 24 months later shows good reconstruction of the basilar artery but persistent filling in the region of a large AICA-PICA (Fig. 10d, white arrow). A repeat angiogram after a further 6 months shows slightly slower, but persistent filling (Fig. 10e, white arrow). An MRI performed at the same time showed no significant increase in the aneurysm size or mass effect but increasing thrombus within the aneurysm (Fig. 10f).

A major difficulty in these cases comes from the timing of the treatment. In asymptomatic patients one cannot be reliably sure that the aneurysm is stable unless serial imaging is performed. This inherently carries a risk that the patient will become symptomatic either with new infarctions or progressive mass effect and the consequent deterioration in operative outcome. If one opts for an aggressive treatment strategy then one may treat patients with otherwise stable

aneurysms. This is not *per se* a problem especially for patients with fusiform or transitional subtypes as well as those with basilar involvement since we know these carry a poor prognosis overall. For dolichoectasia, where the risk of growth is relatively low, regular serial imaging could be considered in the first instance and as soon as growth is seen treatment could be considered. Additionally, if the results of Kardivel et al. (47) and Szikora et al (48) are accurate then it stands to reason that treating shorter diseased segments will likely result in a more rapid exclusion of the aneurysm from the circulation as bridging of the aneurysm neck with neointima will occur more rapidly.

Overall a criticism of the previously reported studies is that they have not clearly defined the aneurysms and yet it is now clear that location, aneurysmal subtypes, MRI characteristics and clinical presentation all have a major impact on the prognosis of the disease. Our study is the first to analyse non-saccular aneurysms treated with FDS in this manner in order to gain a greater understanding of which aneurysms should and should not be treated. A detailed analysis of the morphology of the aneurysm (subtype, size, side branches etc.) as well as assessing for both clinical and radiological signs of ischaemia, mass effect etc. will help guide treatment plans and hopefully improve patient outcomes in this often aggressive disease.

Limitations

Our study has several limitations. It is retrospective in nature and has a relatively small number of patients with varying aneurysms in different locations. Similarly the staging of treatments was based upon individual parameters and not upon a pre-determined timescale. MR imaging is not complete and in order to determine if treatment of these pathologies is of benefit longer term follow-up is required.

7.1.6 Conclusion

Flow diversion represents a promising treatment option for non-saccular aneurysms of the posterior circulation however, longer-term studies are required. We propose that early treatment prior to the development of symptoms and when the maximum diameter and length of diseased segment is minimised. Both transitional and fusiform aneurysmal sub-types should be managed aggressively given their poor prognosis however, a 'watch and wait' strategy could be used for

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8 Chapter 8

8.1 The Combined Use of Intraluminal and Intrasaccular Flow Diversion for the Treatment of Intracranial Aneurysms: Report of 25 Cases

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Conflict of Interests

PB, MAP serve as proctors and consultants for phenox.

HH is a co-founder and share-holder of phenox.

The other authors report no conflict of interest

8.1.1 Abstract

Background

The Medina Embolic Device (MED) is a new intrasaccular device with promising early results. Previously we documented our initial experience of this device both alone and in combination with other devices including flow diverters (FDS). We sought to determine the effect of the MED + FDS strategy for the treatment of selected aneurysms.

Methods

We performed a retrospective analysis of prospectively collected data to identify all patients with aneurysms treated using both the MED and intraluminal FDS. We present our technical success rate, early and mid-term angiographic follow-up, and clinical outcome data.

Results

We identified 25 non-consecutive patients. The treatment was staged in 9 patients and in a single session 16 patients. The average age was 61±12.8 years (range 40-82). The average fundus height was 11±3.6mm and average fundus width was 10.1±3.4mm. In the staged cohort (n=9) at delayed angiography (mean 10mths) 8 aneurysms (89%) showed complete exclusion (mRRC 1) and in one patient there was a parent vessel occlusion. In the simultaneous cohort delayed angiography (n=10, mean 8.1mths) demonstrated complete occlusion (mRRC 1) in 6 aneurysms (60%), 3 neck remnants (mRRC 2) (30%) and 1 patient (10%) showed persistent aneurysmal filling (mRRC 3a). There were 5 complications with permanent morbidity (mRS>2) in two patients. There were no mortalities.

Conclusion

The MED can be successfully used in combination with intraluminal FDS and in selected aneurysms this may represent an alternative to FDS and adjunctive coiling.

8.1.2 Introduction

The Medina Embolic Device (MED) is a new generation of intrasaccular flow diverter. The device has been granted CE mark in Europe and consists of a 3-dimensional layered structure

made from a radiopaque shape set core wire, and shape memory alloy filaments, which form a self-expanding mesh. Although there is limited experience of the device the available evidence suggests that it has a good safety profile and there is a negligible learning curve (1–3).

In our previous publication we documented the use of the MED both alone and in conjunction with other devices such as standard intraluminal flow diverters (3). In this publication we documented the potential short-comings of the MED when used as a stand-alone device however, we suggested that the device if used in combination with other devices may allow for extremely rapid occlusion of aneurysms, especially large aneurysms.

In this paper we document our experience on use of the MED with intraluminal flow diversion both sequentially and simultaneously using a jailing technique. We discuss the potential advantages of this technique and provide early follow-up on the use of both intraluminal and intrasaccular flow diversion in combination.

8.1.3 Methods

Patient selection

We retrospectively searched our prospectively maintained database to identify patients treated with both the MED and an intraluminal FDS between September 2015 and September 2017.

Endovascular treatment

We offered the use of MED to selected patients with unruptured aneurysms with a fundus diameter of ≥5 mm. The decision was based on individual aspects such as anticipated feasibility of this kind of treatment, propensity to coil compaction or aneurysm reperfusion. Patient informed consent was obtained before the procedure in all cases. All treatments were performed under general anaesthesia.

All patients received dual antiplatelet therapy (aspirin 100 mg daily and clopidogrel 75 mg daily) for at least 5 days prior to the treatment. The effectiveness of the antiplatelet regime was tested using the Multiplate analyser (Roche, Basel, Switzerland) and since 2016 the VerifyNow test (Accumetrics) was also used. Patients found resistant to clopidogrel received 2x90 mg ticagrelor daily. The post-procedural antiplatelet regimen consisted of clopidogrel (or ticagrelor) continued for 12 months following treatment and aspirin continued for life.

Procedures were performed via the right common femoral route using a 6Fr access system as standard. For deployment of the MED a 0.021´´ID Prowler Select Plus (Codman) microcatheter was used. The framing MED was chosen based on a similar sizing method used for standard coils. In spherical saccular aneurysms with a fundus diameter of 9 mm or less the size of the first framing MED was purposely undersized by about 1 mm. After forming a spherical shape and adequate positioning of the framing MED it was mechanically detached and the requirement for further occlusion was assessed. Two commercially available intraluminal FDS were used: the Pipeline Embolisation Device (PED) (Covidien, Irvine, California) and p64 (phenox, Bochum, Germany). The selection of FDS was dependent upon the operators' judgement.
For deployment of the intraluminal flow diverter either a Marksman (Medtronic, Dublin, Ireland) catheter or an Excelsior XT27 (Stryker Neurovascular, Kalamazoo, USA) catheter was used. In cases where a jailing technique was used the aneurysm was first catheterised followed by partial deployment of the intraluminal FDS to cover the neck. The MED was then deployed with the neck protection provided by the intraluminal FDS. After deployment of the MED the intraluminal FDS was fully deployed and detached.

All procedures were performed under heparin anticoagulation with a 5000 IU bolus dose at the start of the procedure and subsequent 1000 IU bolus doses every hour to maintain the activated clotting time between 2-2.5 times the baseline.

Procedural assessment and follow-up

Patency and flow characteristics within the aneurysm was assessed angiographically immediately after placement of the MED and the FDS and during follow-up. Procedural follow-up with digital subtraction angiography (DSA) is routinely performed initially at 3-6 months, again at 9-12 months and then once per year usually for 3 years or until the aneurysm was excluded from the circulation. In our early experience with the MED very early DSA follow-up was performed within the first two weeks.
Standard angiographic projections were used to assess the patency of the vessels and the aneurysms in addition to angiographic projections that repeated those used during the treatment. Aneurysm occlusion was graded using the modified Raymond-Roy classification (mRRC) (4) or unchanged (patent).

8.1.4 Results

We identified 25 patients, 21 of which were female (84%) with 25 aneurysms that were treated with the MED and FDS. The average age of the patients was 61±12.8 years (range 40-82). Eleven aneurysms were located on the left, one aneurysm was in the midline the remaining 13 aneurysms were on the right.

Aneurysm location was the para-ophthalmic segment of the ICA (n=8), the cavernous ICA (n=4), the supra-clinoidal segment (n=3), posterior communicating artery (n=5), ICA bifurcation (n=1), the M1 segment (n=1), the A1 segment (n=2), and anterior communicating artery (n=1).

The average dome height was 11±3.6mm (range 5.9-17.2mm), average dome width was 10.1±3.4mm (range 6-17.5mm) and average neck width was 5.6±1.8mm (range 2-9.7mm). The average aspect ratio was 2.1 and the average bottleneck ratio was 1.9. Three of the aneurysms presented with mass effect symptoms and the remaining were incidental. The aneurysm characteristics are summarised in Table 1.

	Aneurysm Characteristics							
Patient Number	Location	Laterality	neck width (mm)	fundus width (mm)	fundus height (mm)	Aspect ratio	Bottle neck factor	Presentation
1	paraophthalmic	L	3.5	8.5	6.5	1.9	2.4	incidental
2	PcomA	L	5	9	11.2	2.2	1.8	incidental
3	AcomA	Midline	4.5	8	9	2.0	1.8	incidental
4	ICA bifurcation	R	4	6	6.3	1.6	1.5	incidental
5	paraophthalmic	R	6.6	9	12	1.8	1.4	incidental
6	cavernous	R	8	16	16	2.0	2.0	incidental
7	paraophthalmic	R	3.8	7	5.9	1.6	1.8	incidental
8	PcomA	R	3.9	6	11.5	2.9	1.5	incidental
9	cavernous	R	6	10	10	1.7	1.7	incidental
10	paraophthalmic	L	5	12.6	17.2	3.4	2.5	incidental

11	paraophthalmic	L	7.7	9	11	1.4	1.2	incidental
12	ICA, suprac	L	4	10.8	13.6	3.4	2.7	incidental
13	MCA, M1	R	7.6	11.3	14.1	1.9	1.5	incidental
14	paraophthalmic	L	9.7	15.5	15.5	1.6	1.6	mass effect
15	PcomA	L	4.5	8.6	9.4	2.1	1.9	incidental
16	A1	L	8.5	9.4	14.5	1.7	1.1	mass effect
17	PcomA	R	2	5	9.4	4.7	2.5	incidental
18	cavernous	L	5	16.2	13.6	2.7	3.2	mass effect
19	cavernous	R	6	9.3	6.8	1.1	1.6	incidental
20	paraophthalmic	R	4.6	6.5	7.8	1.7	1.4	incidental
21	supraclinoid	R	7.5	9.5	8	1.1	1.3	incidental
22	supraclinoid	R	7	8.5	7.8	1.1	1.2	incidental
23	PcomA	L	4.5	13.3	16	3.6	3.0	incidental
24	paraophthalmic	R	4.6	9.5	7	1.5	2.1	incidental
25	A1	L	6	17.5	15	2.5	2.9	incidental

Table 1

Aneurysm size, location, and clinical presentation

Sequential Treatment

In total 9 patient were treated sequentially with MED's placed in the aneurysm and then at a later date an intraluminal FDS was implanted (Fig. 1).

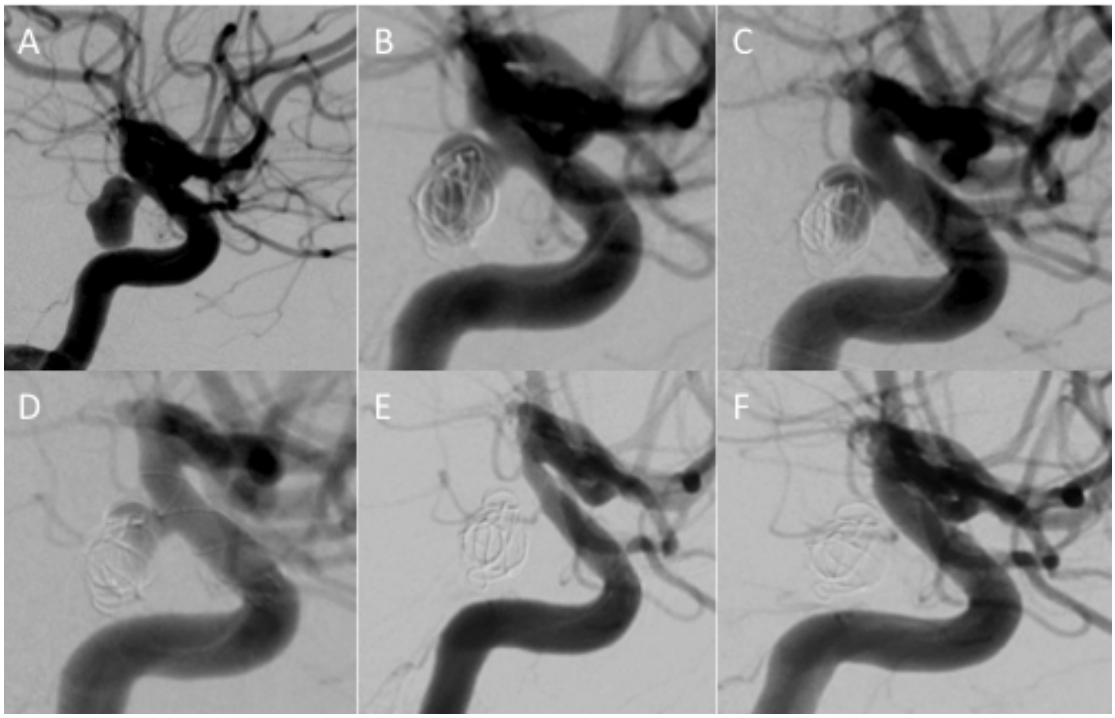

Figure 1

A patient in their 30's with an unruptured incidental right PComA aneurysm that measured 9x5mm (Fig. 1a). At the initial treatment two MEDs were placed in the aneurysm sac and at the end of the procedure sub-total opacification of the aneurysm was seen (Fig. 1b). At initial follow-up (1 month) there was a significant neck remnant and filling of the proximal fundus (Fig. 1c). At this stage a single p64 FDS was implanted (Fig. 1d). Follow-up 3 months after implantation of the FDS showed complete exclusion of the aneurysm from the circulation (mRRC 1) and mild, asymptomatic, in-stent stenosis (Fig. 1e) that spontaneously resolved on delayed angiography (Fig. 1f).

An average of 4.3 (range 1-9) MEDs were placed in each aneurysm and a single FDS was implanted to treat 8 of the aneurysms. At the end of the MED implantation three patients had persistent neck remnants (mRRC 2) and the remaining 6 patients demonstrated persistent filling of the aneurysm sac (mRRC 3a). The FDS was implanted at an average of 1.6 months (range 0.25-7 months) after the MED's were implanted. Two intraluminal FDS were implanted in a single patient. The p64 FDS was used in all cases.

At initial follow-up performed on average 2 months after implantation of the FDS (range 0.5-3months) 4 aneurysms showed complete exclusion (mRRC 1), 4 showed neck remnants (mRRC 2) and one parent vessel occlusion had occurred. At the last follow-up performed on average 10

months (range 7-15 months) after the initial treatment 8 aneurysms showed complete exclusion of the aneurysm. The results are summarised in Table 2.

Patient Number	Number of MED's*	mRRC post MED	Type +Number of FDS†	Time between Med and FDS (months)	Initial follow-up (months) after MED*+FDS†	mRRC ‡	Delayed follow-up (Months)	Delayed mRRC‡	Complication	mRS §
1	1	3a	1 p64	1	3	1	7	1		0
2	3	3a	1 p64	1.5	1.5	2	7	1		0
3	2	3a	1 p64	1.5	1.5	2	10	1		0
8	5	2	2 p64	0.5	1	2	15	1		0
9	9	3a	1 p64	7	3	1	10	1		0
12	5	3a	1 p64	0.5	0.5	2	10	1		0
15	6	2	1 p64	0.5	3	1	10	1		0
16	6	2	1 p64	0.25	NA	NA	9	1	Occlusion of the FD after 6 days	1
17	2	3a	1 p64	1	2	1	9	1		0

Table 2

Clinical and radiographic outcome of patients treated using a staged method

** - MED (Medina Embolic Device)*

† - FDS (Flow Diverter Stent)

‡ - mRRC (modified Raymond Roy Classification)

§ - mRS (modified Rankin Score)

Simultaneous Procedure including Jailing Technique

In total 16 patients the aneurysms were treated with MED and an intraluminal FDS during the same treatment session. In 4 cases a jailing technique (Fig. 2) was used and in 12 cases the MEDs were placed and detached inside the aneurysm followed by deployment of the intraluminal FDS (Fig. 3). An average of 3.9 MEDs were deployed (range 1-13) and an average of 1.2 intraluminal FDS were placed (range 1-4). The p64 was used alone in 14 cases, the p48 in one case and a PED was used in conjunction with the p64 in one case.

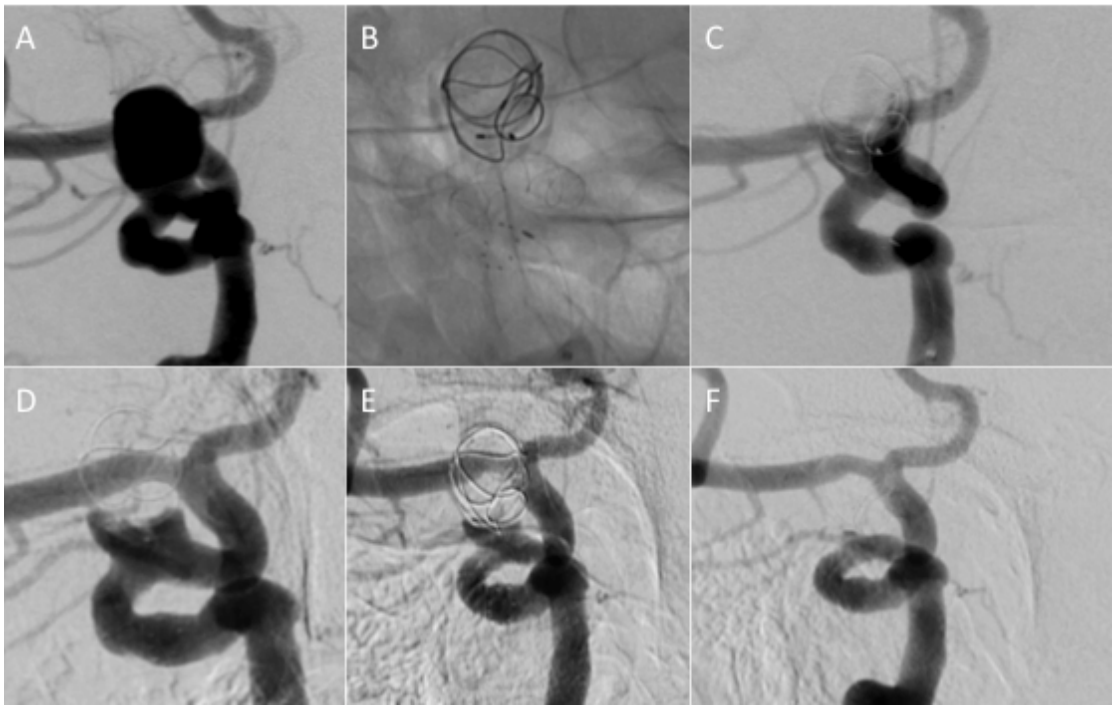

Figure 2

A patient in their 70's with an incidental 9 x 12mm para-ophthalmic aneurysm (Fig. 2a) was treated initially with a MED with a p64 FDS deployed during the same procedure (Fig. 2b). At the end of the procedure there was persistent filling of the aneurysm (Fig. 2c). Early follow-up angiography (2 months post-procedure) showed a persistent neck remnant (Fig. 2d), which gradually decreased over time (Fig. 2e). At delayed angiography (8 months) there is complete exclusion of the aneurysm from the circulation (mRRC I) (Fig. 2f).

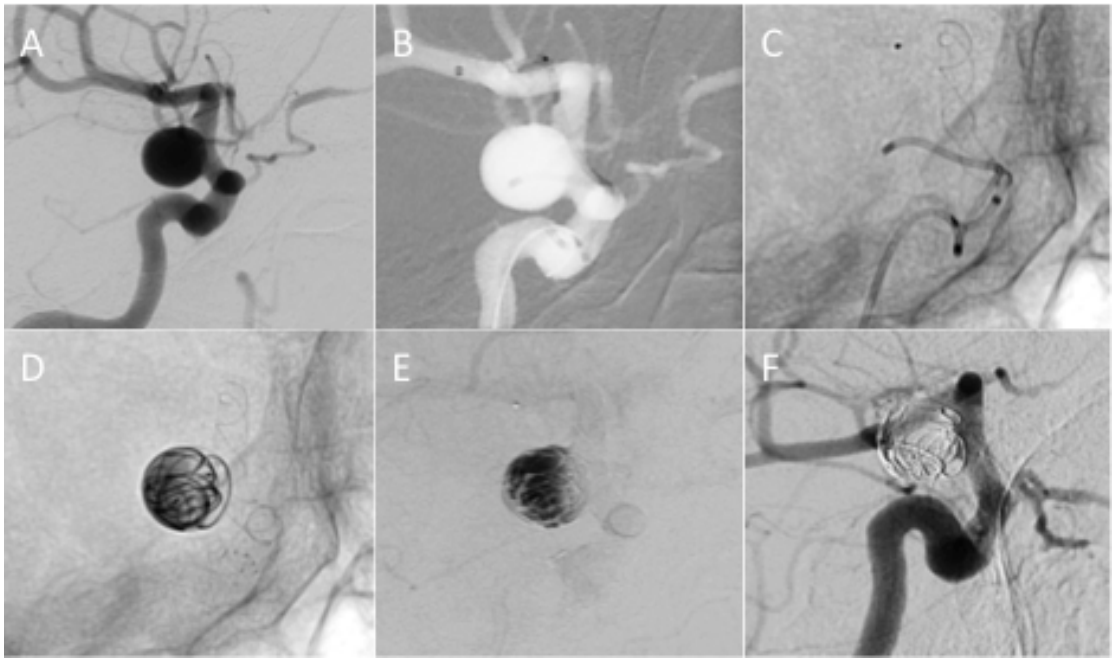

Figure 3

A patient in their 70's with an incidental 8 x 8mm of the supraclinoid ICA (Fig. 3a) was treated with the MED and a p64 FDS using a jailing technique. After the catheterisation of the aneurysm and the M1 segment (Fig. 3b) the p64 was partially deployed until it completely covered the neck of the aneurysm (Fig. 3c). Subsequently, three MEDs were deployed in the aneurysm (Fig. 3d) and the p64 was fully deployed and detached. Angiography at the end of the procedure showed marked contrast stagnation within the aneurysm (Fig. 3e). Angiography performed 7 months post-procedure demonstrated complete exclusion of the aneurysm from the circulation (mRRC 1) (Fig. 3f).

Initial follow-up angiography was available for 13 aneurysms. One patient had an occlusion of the FDS at 4months. Of the remaining 12 aneurysms angiography was performed on average at 2.8 months post-procedure, 6 (50%) aneurysms showed complete occlusion (mRRC 1), 3 aneurysms (25%) showed neck remnants (mRRC 2), and the remaining 3 patients (25%) showed persistent but subtotal filling of the aneurysm fundus (mRRC 3a).

Delayed angiographic follow-up was available in 10 patients and performed on average 8.1 months after the procedure at which point 6 aneurysms (60%) showed complete occlusion of the aneurysm (mRRC 1), 3 aneurysms showed neck remnants (30%) showed neck remnants (mRRC 2) and 1 patient (10%) showed persistent filling of the aneurysm fundus (mRRC 3a). The results are summarised in Table 3.

Patient Number	Number of MEDs*	Type and Number of FDS†	Jailing Technique	Immediate post-op mRRC‡	Initial follow-up (months)	mRRC	Delayed follow-up (months)	mRRC	Complications	mRS§
4	1	1 p64	N	3a	1.5	3	301	1		0
5	1	1 p64	N	3a	1.5	2	257	1		0
6	4	1 p64	Y	3a	10.5	1	463	1	Occlusion of the FD after 4 months	4
7	1	1 p64	N	3a	2.5	1	284	1	Occlusion of the FD after 5 days	0
10	9	1 p64	N	3a	2	2	392	2		0
11	2	1 p64	Y	3a	3	1	288	1		0
13	1	1 p64	N	3a	3	3	299	2		0
14	6	1 p64	N	3a	3	1	325	1		1 (unchanged)

18	10	3 p64, 1 PED	N	3a	2.5	3	291	2		2 (unchanged)
19	1	1 p64	N	3a	3	1	267	1		0
20	1	1 p64	N	3a	3	2	249	2	SAH - asymptomatic	0
21	2	1 p64	Y	3a	4.5	1	136	2		0
22	3	1 p64	Y	3a	3	1	90	1		0
23	13	1 p64	N	3a	NA	NA	NA	NA	ICH	4
24	1	1 p64	N	3a	NA	NA	NA	NA		0
25	7	1 p48	N	3a	NA	NA	NA	NA		0

Table 3.

Clinical and radiographic outcome of patients treated with MED and FDS in the same sitting

** - MED (Medina Embolic Device)*

† - FDS (Flow Diverter Stent)

‡ - mRRC (modified Raymond Roy Classification)

§ - mRS (modified Rankin Score)

Complications

There were 5 complications, two of which led to permanent morbidity. There were no cases of mortality.

In three patients there was thrombosis within the FDS. In one patient this was asymptomatic (patient 16). Patient 6 developed an in-stent thrombus 4 months after the patient inadvertently stopped taking their prescribed anti-platelet medication. The patient was successfully treated with mechanical thrombectomy was left with permanent morbidity (mRS 4). In patient 7 in-stent thrombosis occurred 5 days post-procedure. The patient was successfully treated with mechanical thrombectomy and returned to baseline neurology (mRS 0). In one patient there was an asymptomatic sub-arachnoid haemorrhage, detected on routine post-operative imaging, the cause of which was unknown. In patient 23 after deployment of the MED, a MED coil loop protruded into the parent artery prior to the implantation of the FDS. The patient had been placed on dual antiplatelet medication prior to the operation however, a bolus dose of eptifibatide was given. Post-operatively there was a large intra-parenchymal haemorrhage that was thought to be due to haemorrhagic conversion of an ischaemic lesion.

8.1.5 Discussion

The MED represents a major advancement in the design of endosaccular flow diverters. In the first publication on the use of the MED, Turk et al. (2) included 9 patients, 7 of whom were treated solely with the MED with aneurysms varying in size from ≈4.5mm to 17mm. Only three of the aneurysms had early follow-up at 1 month, all three showed >95% occlusion and the authors state that this limited follow-up provided an early indication that the device caused progressive aneurysm occlusion over time.

In our own publication on the use of the MED (3) we presented the results of 15 consecutive patients with 16 aneurysms were reported. In this series 3.4 MED's per aneurysm were used (range 1-9). Adjunctive devices were used to treat several of the aneurysms. In this original publication we discussed in detail the potential advantages and disadvantages of the device including the problems regarding aneurysmal shape. The MED is designed to form a spherical shape however, many aneurysms are not spherical (5) which could create a problem regarding the applicability of the device to many aneurysms. The device can and has been used in non-spherical aneurysms (2,3) and can cause flow disruption however, the exact shape of the MED in the aneurysm may be difficult to assess. This difficulty in assessing the position of the leaflets of the MED within the aneurysm comes from the fact that these leaflets are almost radiolucent, even when using magnified exposures. Therefore, it can be difficult to determine the positioning of the leaflets particularly at the neck of the aneurysm. The most recent publication regarding the MED (1) evaluated twelve patients with 13 aneurysms. In this series the authors used a single MED framer to obtain a basket in 12/13 aneurysms. They then proceeded to implant further MED fillers, standard coils or both. The authors state that, as this was their first experience with the device, even if total exclusion of the aneurysm was seen coils were used to fill the basket in order to prevent any retraction of the MED.

The introduction of intraluminal flow diversion (FDS) represented a major advancement in the management of intracranial aneurysmal disease that allowed not only the occlusion of aneurysms but also the reconstruction of the parent artery. Intraluminal FDS are likely to promote the occlusion of aneurysms via a combination of effects. Initially intra-aneurysmal flow alteration promotes thrombosis however, the complete exclusion of the aneurysm from the circulation does not occur until after neointima has covered the neck of the aneurysm (6–10). The intra-aneurysmal thrombosis will depend on the flow conditions created within the aneurysm after implantation of an intra-aneurysmal FDS. Aneurysm morphology, aneurysm location, neck size,

angulation and many other factors may play a role in determining the inflow stream into the aneurysm. Similarly, the individual characteristics of flow diverters and the implantation strategy e.g. compressed, appropriately sized etc. will also play a role in the intra-aneurysmal haemodynamic flow post-operatively. Pereira et al (11) used dynamic DSA images to estimate the mean aneurysm flow velocity (mean aneurysm flow amplitude, MAFA) before and after FDS treatment. They demonstrated a larger decrease in mean aneurysm flow in patients that had occluded aneurysms at follow-up compared to those in whom the aneurysms remained patent. Other investigators have reported similar results of attenuated inflow and aneurysm occlusion (12,13) and in clinical cases the average reduction in intra-aneurysmal flow is in the region of 50-60% (14–22). Although there have been no studies looking at the MAFA ration with intrasaccular flow diverting devices recent bench side studies have demonstrated that coverage at the neck is extremely important. Frölich and colleagues (23) assessed the MED in aneurysm models. They showed that the degree of intra-aneurysmal flow disruption significantly correlated with the neck coverage ($p=0.002$) and the size of the neck ($p=0.024$). This data goes some way to confirming the clinical suspicion raised by others (24,25).

This process of aneurysm exclusion post FDS occurs gradually over time and the in the recent meta-analysis of Brinjikji et al. (26) the complete aneurysm occlusion rate of aneurysms treated with intraluminal FDS was 76% at 6 months. The occlusion rate was slightly higher for small aneurysm (<10mm) at 80% and 74% for large aneurysms (>10mm). In a more recent meta-analysis of Zhou et al (27) that looked at the results of 59 studies and the treatment of 2263 patients with 2493 aneurysms a 6 month occlusion rate of 80.1% was documented that rose 90.8% at longer term follow-up (>12 months). Whilst these results are impressive approximately 10% of aneurysms will remain patent at 12 months and therefore, there is a potential risk posed by these aneurysms. Delayed aneurysm rupture post intraluminal FDS is well documented (28,29) and in a recent meta-analysis of 53 studies 81 cases of delayed aneurysms rupture were reported (30). The authors found that in cases when the rupture was documented the majority of cases or delayed rupture occurred within the first 1month after the treatment (77.58%). The majority of the delayed ruptured aneurysms, as would be expected, were located in the anterior circulation and the majority of the aneurysms were not giant aneurysms (53.7% of the aneurysms <25mm). This result was similar to the results of the IntrePED study where 3/5 spontaneous ruptures occurred in giant aneurysms (31). The outcome in cases of delayed rupture was poor with just under 75% of delayed aneurysm ruptures resulting in death. The exact mechanism

behind the delayed aneurysm rupture is incompletely understood. Some studies have demonstrated that intra-aneurysmal flow changes post FDS implantation may result in either an increase in intra-aneurysmal pressure (32) or no significant decrease in pressure (21). Shobayashi et al (21) suggested that because of the persistent intra-aneurysmal pressure contrast stagnation or even the immediate disappearance of the aneurysm on post-treatment angiography does not necessarily mean that the aneurysm is protected against rupture. Other studies have suggested a potential role for intra-aneurysmal thrombus as a source for proteolytic enzymes that can break down the arterial wall and result in rupture (33). It has also been shown recently that flow conditions within the aneurysm lumen are associated with differences in aneurysm wall histology (34). It is not entirely inconceivable that based on the pre-operative flow conditions certain aneurysms will not favour treatment with flow diversion alone due to the dramatic change in intra-aneurysmal flow induced by the FDS however, this is yet to be ascertained.

In order to try and minimise the risk of delayed rupture, especially in large or giant aneurysms, concomitant coiling has been recommended by several authors (28,35,36). Of note, 20% of the delayed ruptures in the meta-analysis of Rouchaud et al (30) occurred in aneurysms that were coiled. Unfortunately the packing density of the coiling was not recorded and therefore, further analysis is difficult however, it was suggested that a higher packing density might protect against rupture.

In order to quantify the different effects of FDS, coiling and FDS + Coiling Damiano et al (37) used finite element modelling and computational fluid dynamics (CFD) to compare the intra-aneurysmal haemodynamics of coiling, of various packing density, single FDS, multiple overlapping FDS, and FDS + coiling. This study showed that coils disrupt and impinge the inflow jet and that with increasing packing density (PD) there is decreased flow penetration into the aneurysm. A single FDS did not disrupt the vortex-like flow pattern but it does decrease the velocity of the inflow jet and of the impingement of the jet on the aneurysm wall. A single FDS accomplished a greater inflow rate reduction than coiling (PD<30%) however, coils at PD>30% results in a greater reduction in aneurysm–averaged inflow velocity than a single FDS. The adjunctive use of coils, upto a PD of 30%, in addition to a single FDS reduces average intra-aneurysmal velocity and wall shear stress (WSS) beyond that achieved by a single FDS alone. However, the addition of coils produced no further inflow rate reduction until the PD exceeded 11%. At low PD, <11%, the coils may act as a scaffold for intra-aneurysmal thrombus but they

will have a limited haemodynamic effect. Similar additive effects of FDS and coiling have been seen by other groups (18). These studies may help to explain why even with adjunctive coiling some aneurysms rupture (29) as well as the higher occlusion rate and lower risk of retreatment seen in patients treated with both FDS and coils compared to FDS alone (38) since it is likely that a threshold of coil PD is necessary to achieve a meaningful clinical effect.

Although the work of Fröhlich (23) did not compare the MED with standard coiling we believe that the flow disrupting effect of a single MED is likely to be significantly greater than that of a single coil. This is likely to reduce the inflow velocity as well as intra-aneurysmal flow characteristics that will protect the wall and promote thrombosis. Furthermore, the MED leaflets may provide a greater stabilisation of thrombus within an aneurysm as well as greater attenuation of the WSS due to their larger surface. We believe that this combination treatment may be particularly useful in partially thrombosed aneurysms. The flow redirection effect of the intraluminal FDS and the flow disrupting effect of the intrasaccular MED, along with the more even distribution of force afforded by the MED leaflets, may prevent the device being engulfed in the thrombus as may happen with coils.

Although in-stent thrombosis was seen in several of our cases we do not believe that there is an increase in the thromboembolic risk from this technique. In one of these cases this was caused by the patient inadvertently stopping their anti-platelet medications. In the other two cases the exact cause for the in-stent thrombosis was unknown although it is know that other medications can alter the effectiveness of anti-platelet agents (39). We test all patients for anti-platelet activity prior to the implantation of FDS however, it is impossible to monitor the response of patients post-operatively and we believe that it is imperative for the general physicians to be aware of possible drug interactions with the commonly used anti-platelet medications. Similarly, although more complications occurred in the 'simultaneous' treatment cohort we do not believe that this technique is inherently more dangerous. This technique is similar to stent assisted coiling which has been shown to have a similar safety profile to standard coiling (40) however, larger studies are required to prove the technique is safe. As with wide necked aneurysms, jailing with the FDS may provide security and prevent the MEDs from prolapsing into the parent vessel. However, it is possible that jailed microcatheter does not allow the intraluminal FDS to properly open and abut the arterial wall. This is a hypothetical risk and not something we have seen but we do believe it could occur and therefore, careful assessment of the FDS at the end of the procedure is

required. When the aneurysm neck is relatively narrow, but the aneurysm is non-spherical, it may be more appropriate to deploy the MEDs followed by the FDS but not use a jailing technique as it is not required.

We believe this is the first paper to look at the combination of intraluminal and intrasaccular flow diversion. Although these results are preliminary we believe that the additive effects of these two strategies may promote safe occlusion of aneurysms, particular large aneurysms that may otherwise carry inherently greater risk of rupture post FDS implantation. We believe aneurysms best suited to this treatment strategy include large aneurysms (>10mm), multi-lobulated aneurysms and non-spherical aneurysms where there is a risk of a neck remnant after treatment with MED alone, and partially thrombosed aneurysms.

Our study has several limitations including those inherent to a retrospective design. In addition aneurysm location is varied as is the number of devices. In order to determine the effects of intraluminal and intrasaccular flow diversion on aneurysm filling and luminal flow we plan to perform bench side studies in the near future to evaluate the effects of MED and MED+FDS and hope to provide an indication as to the optimal number and combination of devices.

8.1.6 Conclusion

The use of intraluminal and intrasaccular flow diversion appears to be an effective treatment strategy for the treatment of aneurysms that can lead to rapid aneurysm exclusion. We believe that this may provide a useful alternative strategy in large and partially thrombosed aneurysms. Further studies are required to determine the usefulness of the techniques in ruptured aneurysms as well as the optimal combination of devices.

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9 Chapter 9

9.1 Discussion

Flow diversion has become an accepted treatment for intracranial aneurysms and has been shown to provide stable aneurysm exclusion. There has been a continual development of these devices and the future of endovascular aneurysm treatment with flow diversion is continually evolving. In addition to the standard indications for the use of flow diverters numerous reports have described the use of these devices beyond the Circle of Willis (37–53). Ravindren et al (54) recently reported their multi-cohort study of FDS use distal to the circle of Willis defined as at or beyond the A1, M1 and P1 segments of the ACA, MCA and PCA respectively. They identified 46 patients with 46 aneurysms all treated with either the PED or the FRED from 3 centres. Just under three quarters of the aneurysms (74%) were located in the anterior circulation. The mean follow-up time was 13.0 months at which time complete or near complete occlusion was seen in 36 aneurysms (76.1%). All patients had a good functional outcome (mRS 0-2) and there were 2 cases of perforator vessel stroke (4.3%) but no haemorrhagic complications. Yan et al. (55) sought to determine the efficacy of flow diversion in small calibre vessels. In their meta-analysis, comprising 26 non-comparative studies and 572 aneurysms, the overall technical success rate of the FDS treatment reached 96% (95% CI =0.93-1.00) with good long-term clinical outcome seen in 96% (95% CI=0.93-0.99). At last follow-up the complete occlusion rate was 70% (95% CI= 0.64-0.76). Procedure related morbidity was 9% (95% CI= 0.07-0.12) and mortality was 4% (95% CI=0.00-0.08). Interestingly, there was no statistically significant difference in aneurysms treated with a single FDS or overlapping FDSs although rates of occlusion were higher for the overlapping FDS's (68% vs. 85%, p=0.07) and this would suggest that the design of the stents could be better optimised to target the smaller vessels. It should be noted that the devices used in these studies are likely to have been oversized.

In the past flow diversion was not routinely considered for the distal circulation due to the relatively superficial anatomy and good accessibility for neurosurgical clipping. Similarly, the delivery of devices via larger delivery catheters, typically 0.027inch ID, to the distal circulation was considered technically challenging (56). Several devices have recently entered clinical use specifically targeting smaller vessels. These include the FRED Jnr, the Silk Vista Baby, the Evolve, and the p48. These devices are designed to pass through either 0.017inch or 0.021inch ID microcatheters rather than the 0.027inch ID microcatheters that were originally required for

deployment of these devices. The ability to pass these newer devices through smaller microcatheters allows aneurysms in the distal vasculature to be accessed and treated. To date, there is limited data on both the FRED Jnr and the Silk Vista Baby. Möhlenbruch et al. (57) published their multicentre results of 42 patients with 47 aneurysms. The FRED Jnr was successfully deployed in 39/42 (93%) and the vast majority of the aneurysms treated arose from the anterior circulation (42/47, 89.4%) with 18 aneurysms located on the MCA and 24 located on the ACA. The majority of the aneurysms were saccular (n=35) with 9 fusiform aneurysms and 2 giant aneurysms. One aneurysm was treated in the sub-acute period following subarachnoid haemorrhage. Five of the aneurysms represented recurrences following previous coiling, 4 were re-growths following aneurysm clipping, and 2 had been previously treated with the PED but had failed to occlude. The median diameter of the aneurysms was 6mm (range1.3-25.2mm) with median neck diameter of 4mm (range 1.3-14.5mm). The median parent vessel diameter was 2.4mm (range 1.4-3.6mm) proximally and 2.1mm (range 1.5-3.4mm) distally. Angiographically, complete occlusion of the 70% of the aneurysms (19/27) was seen at 6 months. Complete occlusion of the 73% (8/11) of the aneurysms was seen at 12 months and near complete occlusion was seen in 27% (3/11) of aneurysms. Overall, 78% of aneurysms showed complete or near complete aneurysms occlusion at any time-point post-operatively. In terms of safety, the primary endpoint of the study was the absence of mortality, stroke (major or minor), and TIA, with 93% of patients (39/42) achieving the primary end-point. Side-branch occlusion was documented in two patients and in both cases IV tirofiban injection was successful in achieving recanalization. Rautio et al (58) recently published their results with 6 month follow-up (n=15, 11 female). Of the 15 aneurysms, 8 had previously ruptured and been treated with coiling (n=7) or neurosurgical clipping (n=1) with retreatment required for neck residuum or aneurysm regrowth. In all cases the procedure was technically feasible. Adequate wall apposition was seen in all cases and contrast stagnation (O'Kelly Marotta grade B) at the end of the procedure was seen in 2 of the aneurysms (13%). The NIHSS and mRS remained stable in all patients during the follow-up period. At the 3-6 month follow-up 9 aneurysms (60%) showed complete occlusion and based on the most recent angiographic results for each patient (6-24 months) the number of aneurysms that had been completely occluded reached 13/15 (87%). The remaining 2 aneurysms had decreased in size. It is of note that the authors report no branch occlusions or significant calibre reductions in the stented vessels although this remains of concern (46,59,60). Early results on the Silk Vista Baby device have also recently been published (61,62). Martinez-Galdámez et al (61) recently reported the results of a multi-centre study involving 41 patients (28 female, average age 50.5years) with

43 aneurysms. The majority of the aneurysms were saccular (n=30, 69.76%) and <10mm (n=30, 69.76%). The average artery diameter was 2.28mm (range 0.9-3.6mm), the proximal parent artery diameter was 2.8mm and 2mm distally with the majority of the aneurysms located in the anterior circulation (n=34, 79.1%). An average of 1.19 stents were deployed. Multiple devices were used in 6 cases and adjunctive coiling was performed in 13 cases. There were 5 intra-procedural complications, none of which resulted in permanent clinical sequelae. Immediately after stent deployment, 8 aneurysms (18.6%) were classified as completely occluded (OKM D), 5 (11.6%) were near complete occlusion (OKM C), 4 (9.3%) showed incomplete filling (OKM B), and 26 (60.4%) showed complete filling (OKM A). Longer term follow-up data is awaited and in the only other available publication regarding the Silk Vista Baby both aneurysms were completely occluded by follow-up (62).

In addition to the development of newer devices that can be deployed through small microcatheters another major step forward has been the introduction of devices with surface modification. In order to safely prevent thromboembolic complications there is a need for dual anti-platelet treatment (DAPT) when using flow diverters and neurovascular stents in general. This can cause issues in certain circumstances such as in patients with acute subarachnoid haemorrhage or in patients with pre-existing conditions such as gastric ulcers. Similarly, there are potential drug interactions which may interfere with the effectiveness of the antiplatelet therapy (63). One way to negate these potential issues has been to develop surface coated flow diverters and stents. The PED Shield was the first surface modified flow diverter. It has a 3 nm phosphorylcholine coating covalently bound to the braid wires. Phosphorylcholine is a major component of the membranes of red blood cells and has been shown to reduce platelet adhesion and activation (64). *In vitro* studies have suggested that the PED Shield has lower thrombogenicity than other flow diverters with similar thrombogenicity to stents with lower metal coverage such as the Solitaire AB (Medtronic, Dublin, Ireland) and Leo (Balt, Montmercy, France) (65). An *in vitro* study by Girdhar et al. (66) has shown reduced thrombogenicity of PED Shield compared to the uncoated PED Flex and FRED flow diverters. In this study, that utilised a flow loop containing 5.0 ml of human blood connected to a pulsatile drive system, the thrombogenicity of the different FDSs was tested. Thrombin generation was tested using assays to assess thrombin-antithrombin (TAT) complex and platelet activation assessed using beta-thromboglobulin (ß-TG). Thrombin generation (TAT) was measured as FRED (30.3 ± 2.9], PED (13.9 ± 4.4), PED Shield (0.4 ± 0.3), and negative control (no device) (0.1 ± 0.0). Platelet

activation (ßTG) was measured as FRED (148 ± 45), PED (92.8 ± 41), PED Shield (16.2 ± 3.5), and negative control (2.70 ± 0.16). The FRED was significantly more thrombogenic than PED and PED Shield ($p < 0.05$) for TAT. Furthermore, on gross analysis there was significant accumulation of thrombus on both the PED and the FRED but not on the PED Shield. When multiple PEDs and PED Shields were tested there remained a significant decrease in TAT (39.1 ± 12 vs. 0.63 ± 0.6, $p < 0.05$) and ßTG (146 ± 24 vs. 23.6 ± 17, $p < 0.05$) as well as minimal thrombus on gross evaluation. The authors state that the PED Shield has the lowest thrombogenicity of the devices tested even when multiple PED Shield devices were tested that increased the metal surface exposed to the blood six-fold.

Marosfoi et al. (67) compared the thrombogenicity of the classic PED to the PED Shield in a rabbit model. Using optical coherence tomography (OCT) they assessed *in vivo* the presence or absence of clots along the length of the implanted flow diverters both before and after angioplasty of the implanted FDS. Additionally, clot formation was assessed at the origin of covered side branch arteries. They showed that there was no difference in the aneurysm occlusion rate between the two different FDS's at 30 days. They showed prior to angioplasty, the number of FDS segments with clots were not associated with the type of FDS ($p = 0.8279$), DAPT (0.5177) or aneurysmal neck size ($p = 0.4363$). After angioplasty the number of flow diverter segments with clots was significantly associated with the type of flow diverter ($p < 0.0001$), but still not with DAPT ($p = 0.3872$) or aneurysmal neck size ($p = 0.8555$). Similar results were seen with regards to clots located at the ostia of covered branches. Although the authors state in their conclusion that 'phosphorylcholine surface modified flow diverters are associated with less thrombus formation on the surface of the device' it may, in fact, be more accurate to say less thrombus formation occurs on phosphorylcholine surface modified flow diverter after angioplasty but there is no significant difference between coated and uncoated devices if angioplasty is not performed. Similarly, as all the animals were on DAPT for the duration of the study the formation of thrombus on either device under single anti-platelet treatment (SAPT) conditions cannot be determined.

To date there are limited publications on the clinical efficacy of the PED Shield device. One of the first publications was by Hanel et al. (68) where the device was used to treat an acutely ruptured fusiform aneurysm of the right V4 segment of the vertebral artery with concomitant coiling. The patient was treated with aspirin monotherapy. There were no intra-operative

complications and despite the patient being on aspirin the stents were thrombosed at day 10 and anti-platelet testing at this time revealed the patient to be non-responsive to aspirin. More recently, Manning et al. (69) published the results of their multicentre retrospective analysis on the use of the PED Shield in patients with aneurysmal SAH and treated with SAPT. They identified 14 patients (12 female) with 7 saccular aneurysms, 5 blister aneurysms, and 2 fusiform aneurysms. All patients were treated, at a median of 1 day post-ictus, with the PED Shield (mean 1.2 ± 0.7 devices) and 12 of the patients had adjunctive coiling. All of the patients were treated with aspirin with one having a bolus dose of IV abciximab intra-operatively. Six of the patients had intra-operative heparin and 5 of these had a continued heparin infusion post-procedure although the reason for this is not clearly documented. There was no evidence of intra-operative stent thrombosis, platelet aggregation or haemorrhage. At follow-up one patient (7.1%) was seen to have complete stent thrombosis (day 1 post PED Shield implantation) and was treated with thrombectomy. Two further patients (14.3%) demonstrated minor non-flow limiting platelet aggregation and were commenced on P2Y12 inhibitors at day 8-9 post-ictus. There were two cases of repeat aneurysmal haemorrhage, one of which resulted in death and both these patients had been continued on heparin infusion post-operatively. At early follow-up 12/14 aneurysms were classified as complete/near complete occlusion (Raymond Roy 1 or 2 occlusion). In total there were 5 complications, 4 of which (80%) occurred in patients on post-operative heparin infusion, including 2 haemorrhagic and 3 ischaemic complications. The use of heparin post-operatively was associated with all complications combined ($p=0.028$). This preliminary data suggests that surface coated devices may play an important role in the management of aneurysms, particularly acutely ruptured aneurysms, but that the anti-platelet regime must be meticulous. Even in the publication of Manning et al. the authors have more recently switched to a twice daily aspirin regimen as this may reduce complications and platelet function recovery (69–71).

In addition to the PED Shield other surface modified flow diverters are being developed including the p48 HPC (phenox, Bochum, Germany) but as of yet there is limited published literature regarding the clinical experience of this device (72). Similar surface modified devices are currently in development by other companies.

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