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Original Research

Preliminary clinical experience with the pipeline vantage 21 flow diverter for embolization of aneurysms in small diameter parent vessels

M.Harrison Snyder, Anthony J. Yu, Taylor Ferraro, Adel.M. Malek *

Cerebrovascular and Endovascular Division, Department of Neurosurgery, Tufts Medical Center, Boston, MA 02111, USA

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ABSTRACT

Background: The Pipeline Vantage 21 flow diverter is a 4th generation 48-braid stent recently introduced in the United States that is intended for small parent vessel diameter (<3.5 mm) wide-necked aneurysm treatment. We report our clinical and angiographic outcomes in an initial case series.

Methods: Twenty patients with 22 aneurysms (6 pericallosal, 13 anterior communicating, 2 V4, and 1 middle cerebral) underwent Vantage 21 treatment using 22 stents between April 2024 and January 2026. All procedures were performed via transfemoral triaxial access with platelet function testing on day of procedure. Mean aneurysm size was 3.7±1.5 mm. Aneurysm occlusion status was reported by modified Raymond Roy classification (mRRC).

Results: Vantage 21 deployed successfully in all cases with excellent vessel wall apposition. Median clinical follow-up at 12 months (patients, n = 20) revealed one symptomatic stroke and two asymptomatic strokes. Median 4-month follow-up angiography for 20/22 stents revealed complete occlusion (mRRC 1) in 16/20 evaluated aneurysms (80%), accompanied by in-stent luminal stenosis (ISS) in 10/20 stents (50%), exceeding ≥ 50% (severe) in 7/20 stents (35%). All 10 cases of ISS had intimal hyperplasia, and two cases had fishmouth braid deformity with concurrent intimal hyperplasia. Of a total 38 arterial branches covered by Vantage 21 stents with DSA follow-up, 6 progressed to occlusion, and 21/38 (55.3%) demonstrated significant caliber reduction on cone-beam computer tomography angiography with maintained antegrade patency, resulting in two asymptomatic caudate infarcts on follow-up MRI with evidence of narrowed or occluded ipsilateral artery of Heubner.

Conclusions: This early US-based single-center series noted rapid aneurysm involution rates for the Pipeline Vantage 21 flow diverting stent. However, this is accompanied by a robust intimal hyperplastic vascular response in small parent vessels leading to frequent ISS and side-branch attenuation warranting longer-term clinical follow-up and caution if considering coverage of critical branch vessels. Larger samples with longer term follow-up are needed to validate these findings.

1. Introduction

Flow diverting stents have advanced the treatment of intracranial aneurysms, particularly those with wide necks, with high rates of occlusion and a favorable safety profile.[1–3] In small and distal parent vessel aneurysms beyond the internal carotid artery (ICA), low-profile flow diverting stents have also shown promise but ischemic risk has limited their use.[4,5].

The Pipeline Embolization Device (PED; Medtronic Neurovascular, Irvine, CA, USA), the first US-approved flow diverting stent, has undergone stepwise alterations in its design, surface modification, and delivery system leading to the current 4th generation 48-braid Vantage 21 designed for delivery through 0.021″ inner caliber microcatheters for treatment of aneurysms originating from parent vessels having diameters up to 3.5 mm.

The Pipeline Vantage with Shield Technology family of devices was previously studied in Europe and Australia with promising results in its safety and efficacy for endovascular aneurysm treatment.[6–12] The device was recently released in the United States (US) in both its Vantage 27 and 21 variants; however, the larger diameter Vantage 27 was recalled for safety concerns associated with braid deformity and issues with incomplete stent apposition (ISA).[13,14] In the present study, we describe our initial clinical and angiographic experience with the Vantage 21 device in a retrospective review of a prospectively collected

* Corresponding author at: Department of Neurosurgery, Tufts Medical Center, 800 Washington Street, Proger 7, Boston, MA 02111, USA.
E-mail address: adel.malek@tuftsmedicine.org (Adel.M. Malek).

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single-center US cohort of patients with aneurysms involving small and distal parent vessels.

2. Methods

2.1. Pipeline Vantage

The Vantage flow diverting stent shares with its 3rd generation predecessor (PED-Shield) the phosphorylcholine-based surface modification (Shield Technology) intended to reduce thrombogenicity, but in lieu of the prior 36 cobalt-chromium and 12 platinum wire design, Vantage uses drawn-filled tube (DFT) design wires containing a platinum inner core within a cobalt-chromium shell (Fig. 1A).[7,10] Its small size (<3.5 mm diameter) Vantage 21 variant utilizes a 48 DFT design and the larger size (≥3.5 mm diameter) Vantage 27 variant uses 48 DFT wires and 16 chromium cobalt wires; the latter was recently recalled for safety concerns due to increased risk of ISA and braid deformation.[13] The lower diameter of the DFT wires used in the Vantage 21 device, compared to previous PEDs, reduces the profile of the stent while improving its radiopacity and fluoroscopic visualization.[10] The device has previously been reviewed favorably for its resheathing ability, visibility, and wall apposition (Fig. 1B-D).[8,9,12] At the time the Vantage 27 was recalled, the instructions for use (IFU) were updated for Vantage 21. The revised IFU emphasized that Vantage deployment technique differs from prior PED-Flex deployment, particularly with respect to minimizing device loading and longitudinal braid deformation. Updated recommendations discouraged aggressive forward push, stretching, distal braid repositioning under tension, and repeated "massaging" opening maneuvers after partial deployment. Operators were advised to use balanced microcatheter retraction and more gentle delivery-wire loading to achieve gradual opening and wall apposition, especially in tortuous anatomy and across vascular curves. The revised IFU also discouraged telescoping an additional flow diverter to correct mid-stent braid narrowing and instead recommended guidewire manipulation and/or balloon angioplasty for incomplete apposition. A more detailed sizing guide was included, and greater emphasis made on accounting for vessel shape and tapers in lumen diameter.[13].

2.2. Patients and study design

All patients harboring an aneurysm treated with Vantage 21 were retrospectively reviewed in a prospectively collected cohort, non-industry sponsored study with Tufts institutional review board (IRB) approval; informed consent for participation was waived by the IRB given the study focused on retrospective, fully de-identified data. Patients underwent Pipeline Vantage 21 and 27 embolizations between the device's US release in April 2024 through January 2026; all consecutive patients with Vantage 21 implants were included from this group. Small intracranial aneurysms (<5mm) in our cohort were generally recommended for treatment in cases where current or prior subarachnoid hemorrhage (SAH) had occurred, the aneurysm had recurred after prior treatment or increased in size on serial imaging, in cases of irregular aneurysm morphology (such as daughter sacs or multiple lobules), or in cases with multiple aneurysms or family history of SAH. Adverse and periprocedural (<30 days after procedure) events were considered neurologic (intracranial hemorrhages, ischemic stroke, cranial neuropathies) or non-neurologic and were stratified as permanent (present at last follow-up) or not permanent (resolved since onset). Imaging data included angiographic aneurysm occlusion status, as well as in-stent/luminal stenosis (ISS) secondary to stent deformity and/or intimal hyperplasia; the imaging outcomes were reported according to the guidelines described by Fiehler et al. and endorsed by multiple international neurointerventional societies.[15] Fishmouthing was defined as a delayed braid narrowing at the proximal and/or distal tines of the stent without ISA according to the F2B2 braid deformity classification; filling defects lining the lumen of the stent on follow-up DSA were considered consistent with intimal hyperplasia, an abnormal proliferation and migration of vascular smooth muscle cells along the luminal arterial wall.[15] ISS referred mainly to the state of angiographic narrowing of the patent parent vessel lumen regardless of cause (this could occur dur to intimal hyperplasia, braid deformity, or both). ISS was computed by one author using biplane high-magnification angiography as the ratio comparing the diameter of the narrowed lumen to the diameter of the closest proximal or distal healthy parent vessel, mathematically expressed as the difference between the normal and narrow diameters as the numerator and the normal diameter as the denominator, as

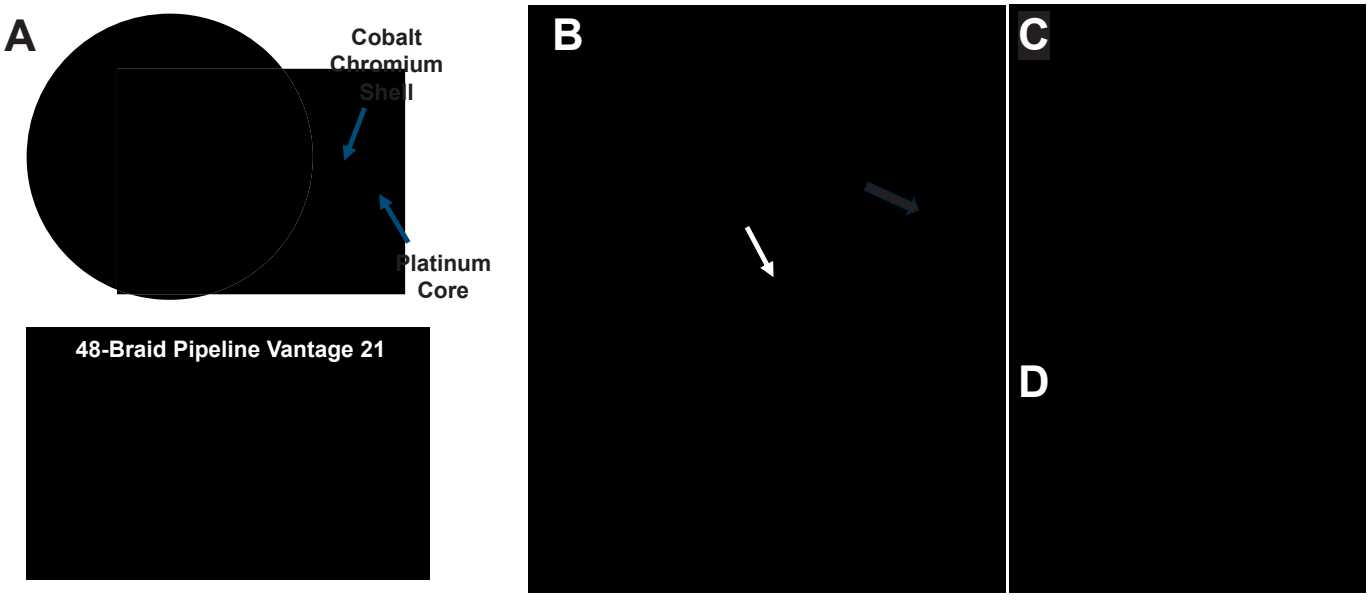


Fig. 1. Pipeline Vantage 21 flow-diverting stent detail showing Drawn-filled tube (DFT) construction (A) with radio-opaque platinum core and cobalt-chromium shell wires (top) forming a 48-braid flow diverter construct with a new delivery system enabling use of 0.021″ inner diameter microcatheter (bottom). Left pericallosal artery aneurysm with Vantage 21 partially deployed showing distal edge (black arrow) and Phenom 21 delivery microcatheter tip (white arrow) (B) and post-deployment imaging with dual-volume 3-dimensional rotational angiography (C) and cone-beam CT computed tomographic reconstruction in sagittal projection (D) showing excellent vessel wall apposition.

described in the North American Symptomatic Carotid Endarterectomy Trial and international neurointerventional societies' FD imaging analysis recommendations.[15,16] Jailed sidewall branches were evaluated and counted based on cone beam CT angiography (CBCT-A) immediately post-deployment, and on follow-up angiography, CBCT-A, 3D rotational DSA, and biplane runs were used to determine any decrease in caliber or occlusion.

2.3. Procedures

Dual antiplatelet therapy (DAPT) with Aspirin 81 mg daily and prasugrel 10 mg daily was initiated ~ 7 days prior to the procedure, with platelet function testing using VerifyNow (Accumetrics, San Diego, CA) P2Y12 reactivity units (PRUs) performed the day of procedure to ensure therapeutic effect at time of treatment. Prasugrel is preferentially used at our institution as a risk-mitigation strategy due to relatively common resistance to clopidogrel, which can be as frequent as 28–60% in some populations.[17,18] Embolization was performed using a transfemoral triaxial system consisting of a 6-french shuttle sheath (Cook Medical Inc., Bloomington, IN, USA), Phenom Plus intermediate catheter and Phenom 21 microcatheter (Medtronic Neurovascular, Irvine, CA, USA) after intravenous heparin administration for a goal activated clotting time (ACT) of ≥ 220 s with intraprocedural monitoring every 15–30 min. Selection of Vantage 21 size and length was estimated based on 3D rotational angiography as well as CBCT-A. Patients were observed in intensive care overnight and were discharged 2 days post-procedure with clinic follow-up visits and platelet function testing at 1 week followed by 3- and 6-month timepoints. Patients routinely underwent 3-Tesla magnetic resonance imaging and angiography (MRI/A) at post-procedure day 1, then at 3 and 6 months, to increase the sensitivity of detecting thromboembolic events for PRU testing periprocedurally with DAPT titration as needed. Follow-up catheter digital subtraction angiography (DSA) was performed when MRI/A suggested aneurysm involution, usually in the 3–6 month time range to rule out ISS related to stent deformity or intimal hyperplasia prior to initiating DAPT wean. DAPT was generally weaned after the first DSA, unless severe luminal narrowing (≥50% stenosis) was encountered, in which case it was continued for another 3–9 months on a case-by-case basis after follow-up with noninvasive imaging. Occlusion status was reported according to the modified Raymond-Roy classification (mRRC).[19] Analysis was performed with JMP statistical software, version 19.1.2 (SAS Institute, Cary, NC, USA). T-test was performed on continuous variables and Fisher's exact test on nominal variables when comparing differences where indicated.

3. Results

Twenty patients underwent 22 embolization procedures to treat 22 aneurysms using Vantage 21 with demographic and procedural characteristics summarized in Table 1. Mean age was 58.8 ± 9.8 years (range, 34–74), with 16/20 (80%) being female. Five of 20 (25%) were active and 7/20 (35%) former smokers; 11/20 (55%) had a history of hypertension. Six aneurysms (27.3%) were pericallosal, 13 (59.1%) anterior communicating (ACOM), 2 (9.1%) in the V4 segment of the vertebral artery, and one (4.6%) was a middle cerebral artery (MCA) sidewall aneurysm and the single ruptured case in the series. Most aneurysms were morphologically saccular (12/22, 54.6%) or lobulated (6/22, 27.3%), and 4 (18.1%) were for recurrences of previously coiled aneurysms. The mean size was 3.7±1.5 mm (range, 1.4–7.7). One patient underwent staged bilateral Vantage 21 stent placements for an ACOM aneurysm after the first stent failed to reduce the aneurysm's size; this patient had a follow-up DSA after having undergone both procedures, while 2 patients (each with 1 stent treating 1 aneurysm) had yet to undergo follow-up DSA. One patient underwent two separate Vantage 21 embolizations to treat two separate aneurysms (bilateral pericallosal aneurysms). Finally, one patient had two separate aneurysms, opposed ACOM aneurysms, treated with a single Vantage 21 stent in one procedure.

Table 1
Baseline Patient Demographics, Aneurysm Characteristics and Procedural Descriptors.

Variable	Patients n = 20, Procedures n = 22
Age (years)(n = 20), mean±SD (range)	58.8 ± 9.8(34–74)
Female gender (n = 20), n (%)	16 (80)
Past Medical History (n = 20), n (%)	
Hypertension	11 (55)
Diabetes Mellitus	2 (10)
Coronary Artery Disease	1 (5)
Prior Ischemic Stroke	1 (5)
Former Smoking	7 (35)
Active Smoking	5 (25)
Aneurysm locations (n = 22), n (%)	
Pericallosal	6 (27.3)
Anterior communicating	13 (59.1)
Middle cerebral	1 (4.6)
V4	2 (9.1)
Aneurysm morphologies (n = 22), n (%)	
Lobulated	6 (27.3)
Saccular	12 (54.6)
Neck recurrence	4 (18.1)
Greatest dimension of aneurysm (mm)(n = 22), mean ±SD (range)	3.7±1.5(1.4–7.7)
Ruptured at time of treatment (n = 22), n (%)	1 (4.6)
Previous endovascular treatment of target aneurysm with coiling (n = 22), n (%)	5 (22.7)
Previous endovascular treatment of target aneurysm with flow diversion (n = 22), n (%)	1 (4.6)
Procedures	**n = 22**
Technically successful deployment, n (%)	22 (100)
Total procedural time, minutes (mean±SD, range)	60.2±13.2, 37–87
Adjunct coiling performed, n (%)	2 (9.1)
Procedures treating 2 aneurysms with one Vantage	1 (4.6)
Vantage stent diameter, median (range)	2.5 (2.5–3.5)
Vantage stent length, median (range)	20 (14–25)
Size discrepancy between Vantage diameter and smallest parent vessel diameter, mm (mean±SD, range)	0.6±0.3, 0.16–1.07
Balloon angioplasty performed for incomplete apposition, n (%)	0 (0)

Abbreviations: mm = millimeters; SD = standard deviation

3.1. Procedures

Mean procedural time was 60.2 ± 13.2 min (range, 37–87). Vantage 21 stents were successfully deployed in all procedures with good stent-vessel wall apposition, and none required adjunctive balloon angioplasty or stenting. All stents were slightly oversized to allow for proper apposition; the mean difference between the Vantage stents and the parent vessels at their smallest calibers was 0.6±0.3 mm (range, 0.16–1.07). Two of 4 (50%) recurrent neck cases were treated with adjunctive coiling at the time of index procedure before finishing with the Vantage 21 placement.

Radiologic and clinical outcomes are summarized in Table 2. Of 22 procedures performed with 22 separate stents placed, all had available clinical and non-invasive imaging follow-up both at a median of 12 months, and 20/22 (90.9%) stents and aneurysms had follow-up DSA at a median of 4 months postoperatively (range, 2–18; mean 5.5 months).

3.2. Occlusion on DSA

Last follow-up DSA demonstrated complete occlusion (mRRC 1) in 16/20 (80%) and adequate occlusion (mRRC 1 or 2) in 17/20 (85%) aneurysms. By location, the adequate occlusion rates were as follows: MCA, 1/1 (100%, mRRC 2); pericallosal, 5/5 (100%, all mRRC 1; one

Table 2
Post-procedural Outcomes.

Variable	Procedures, n = 22
Neurologic complications, n (%)	
Symptomatic stroke or TIA	1 (4.6)
Asymptomatic stroke	2 (9.1)
Complications occurring within 30 days of procedure, n (%)	0 (0)
Non-neurologic complications, n (%)	
Groin hematoma	1 (4.6)
Hematuria	1 (4.6)
Persistent neurologic deficit at 7 days post-procedure, n (%)	0 (0)
Persistent, new neurologic deficit after stent placement at last follow-up, n (%)	0 (0)
Duration of latest clinical follow-up, months (median, range)(patients, n = 20)	12 (3–24)
Duration of latest DSA follow up, months (median, range)(stents, n = 20)	4 (2–18)
Duration of latest MRA or CTA follow-up, months (median, range)(patients, n = 20)	12 (3–24)
mRRC occlusion status of aneurysm on last DSA follow-up, n (%)(aneurysms, n = 20)	
1	16 (80)
2	1 (5)
3a	0 (0)
3b	3 (15)
Adequate occlusion (mRRC 1 or 2) at follow up DSA, n (%)(aneurysms, n = 20)	17 (85)
mRRC occlusion status of aneurysm on MRA or CTA follow-up, n (%)(aneurysms, n = 22)	
1	19 (86.4)
2	1 (4.6)
3a	1 (4.6)
3b	1 (4.6)
Repeat treatment for target aneurysm, n (%)(n = 22)	4 (18.2)
	Individual stents with DSA follow-up, n = 20
Presence of luminal stenosis from any cause, n (%)	10 (50)
Degree of luminal stenosis, n (%)	
1–25%	0 (0)
26–49%	3 (15)
≥50%	7 (35)
Causes of luminal stenosis, n (%)	
Intimal hyperplasia with fishmouth braid deformity	2 (10)
Intimal hyperplasia without any braid deformity	8 (40)
Status of covered branch vessels on DSA follow-up, n (%)	**Branches, n = 38**
Occluded	6 (15.8)
Reduced caliber	21 (55.3)
Status of stenosis on last MRA or CTA, n (%)	**ISS cases, n = 10**
Worsened	0 (0)
Stable	3 (30)
Improved	2 (20)
Resolved	4 (40)
Unable to discern	1 (10)

Abbreviations: CTA = computed tomography angiography; DSA = digital subtraction angiography; ISS = in-stent stenosis; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; mRRC = modified Raymon-Roy Classification; SD = standard deviation; TIA = transient ischemic attack.

pericallosal had not undergone DSA). Among ACOM aneurysms, 7/12 (58.3%) were mRRC 1 on the first post-Vantage DSA, while 5/12 (41.7%) remained mRRC 3b (1 ACOM patient has still not undergone DSA). One previously mentioned ACOM patient was re-treated with a contralateral Vantage 21 stent, while 2 other ACOM patients were re-treated with coil embolization from a contralateral approach from the original Vantage 21 stent. All three of these salvage cases were mRRC 1 at last DSA follow-up. One of 2 (50%) V4 aneurysms achieved mRRC 1, while the other grew in diameter and underwent subsequent treatment with a concentric Pipeline Shield device. Fig. 2 depicts three cases of mRRC 1 occlusion in pericallosal vessels.

3.3. In-Stent/Luminal Stenosis and Side Branch Attenuation

ISS secondary to intimal hyperplasia and/or stent deformity was noted in 10/20 stents at angiographic follow-up (50%), with severe stenosis (≥50%) present in 7/20 (35%) cases; Fig. 3 shows three examples of this phenomenon. Two of 20 stents (10%) demonstrated fishmouth deformity (one case having deformities at both the proximal and distal ends, and one case with deformity at the proximal end only) with concomitant intimal hyperplasia, and 8/20 (40%) developed intimal hyperplasia causing ISS without stent deformity. We did not find statistical differences for sex, age, aneurysm size, baseline PRU at stent placement, duration of procedure, stent length or diameter, or difference between the stent diameter and smallest parent vessel diameter between the stenosis and no-stenosis groups (Table 3).

A total of 38 branch vessels were covered by the Vantage 21 braid at time of placement; on angiographic follow-up, 27/38 (71.1%) demonstrated some degree of caliber reduction. Six of 38 (15.8%) progressed to complete asymptomatic occlusion (example of an occluded pericallosal branch in Fig. 4A-D) while 21/38 (55.3%) showed significant caliber reduction with maintained antegrade patency (Fig. 4E-H). Thirty-five of 38 (92.1) covered branches were clinically asymptomatic without evidence of ischemia or infarction on follow-up MRI/A. Two covered arteries had evidence of asymptomatic strokes, both asymptomatic artery of Heubner infarcts after ACA stent placement for ACOM aneurysms evidenced by volume loss of the caudate head and increased DWI and T2 signal in this area on 3-month follow-up MRI/A; there had been no evidence of ischemia on the post-procedural MRI/A (one example shown in Fig. 4I-L). DSA revealed artery of Heubner occlusion in one case and decreased caliber of the artery of Heubner with antegrade flow maintained in the other. These patients reported no facial weakness, language, or neurocognitive symptoms and remained neurologically intact. One patient who had a V4 stent placed for a posterior inferior cerebellar artery (PICA) aneurysm subsequently suffered a PICA territory stroke after having a lapse in DAPT adherence. DSA showed that although the PICA branch was stable in caliber, the PICA aneurysm had enlarged significantly, prompting re-treatment with a concentric PED-Shield stent as mentioned previously. The neurologic symptoms associated with the stroke resolved fully by the time of discharge.

3.4. Follow-up

No patients had permanent neurologic deficits at median 12 months clinical follow-up. There was one groin hematoma associated with femoral access which resolved without transfusion or treatment. Non-invasive imaging at last follow-up (median 12 months) showed mRRC 1 in 19/22 (86.4%) aneurysms and residual neck in 1/22 (4.6%), 1 patient (4.6%) had a small amount of residual flow within the center of the coil pack just past the neck (mRRC 3a), and 1/22 (4.6%) was fully patent (mRRC 3b) at last non-invasive imaging follow-up. While limited compared to DSA, the cases with ISS were assessed for changes in severity on their last non-invasive imaging follow-up. Of the 10 cases where luminal stenosis was identified, 3 (30%) remained approximately stable, 2 (20%) were improved, 4 (40%) were resolved, and 1 (10%) could not be determined due to imaging quality issues (examples shown in Fig. 5).

4. Discussion

The utility of treatment in small and distal parent-vessel aneurysms has been debated, with recent *meta*-analysis of high-quality studies demonstrating a rupture rate of 1.8% over 3.9 years in aneurysms ≤ 10 mm.[20] However, certain aneurysm- and patient-specific factors must be accounted for in individual cases. For example, a retrospective risk assessment by Sauvigny et al. suggests that tiny (<3mm) aneurysms are more likely to rupture if displaying irregular morphology or high size ratio to aspect ratio; further, most of the small aneurysms which

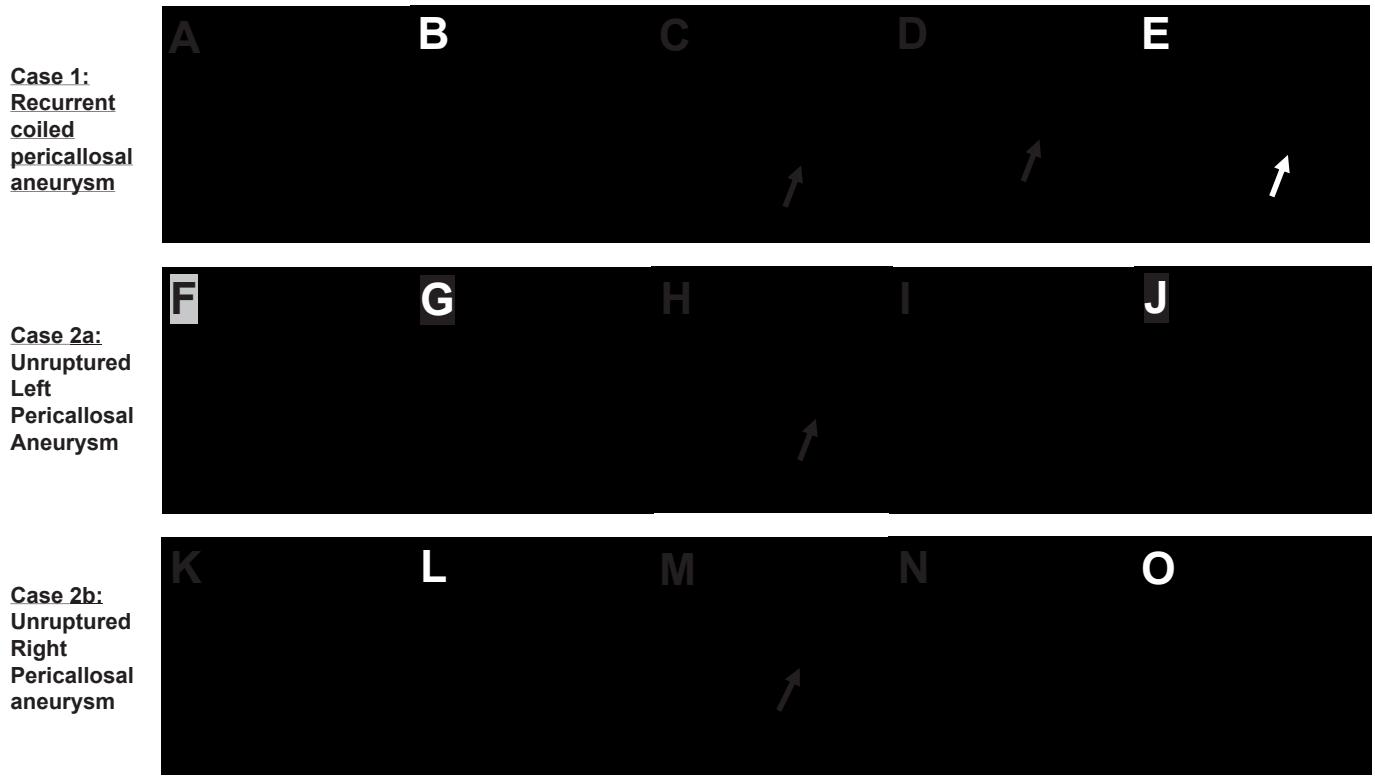


Fig. 2. Complete involution with Vantage 21. Case 1: a previously ruptured and coiled left pericallosal aneurysm developed recurrent growth (A) and was treated with adjunctive coiling and Vantage 21 (B). Follow-up DSA at 1 month showed complete involution with mildly decreased caliber of the associated frontopolar branch (arrows; C, D, E). Case 2a: A patient with bilateral pericallosal aneurysms is treated first for the left-sided aneurysm (F) with a single Vantage 21 (G). This was completely involuted on 6-month DSA (H, I, J) with decreased caliber of the frontopolar branch (arrow). Case 2b: The same patient's right pericallosal aneurysm (K) was treated with a single Vantage 21 (L) 3 months after the left-sided procedure. This was completely involuted at 3-month follow-up DSA (M, N, O) with decreased caliber of the associated frontopolar branch (arrow).

ruptured (79.7%) in their study would not have been recommended for treatment according to the Unruptured Intracranial Aneurysm Treatment Score.[21] In well-selected cases, flow diversion has demonstrated good outcomes for such aneurysms in prior studies. A *meta*-analysis of flow diverter use in small (<2.5 mm) parent vessels identified 19 studies, comprising 580 patients with 604 aneurysms, treated with multiple stents including PED, Flow Redirection Endoluminal Device (FRED; Terumo MicroVention, Aliso Viejo, CA, USA), Silk (Balt Group, Montmorency, France), Surpass (Stryker Neurovascular, Fremont, CA, USA), and p48 MW (Phenox GmbH, Bochum, Germany).[4] The analysis reported pooled complete angiographic occlusion (O'Kelly-Marotta [OKM] grade D or equivalent) rates of 70.4% and 77% at 6- and 12-month timepoints, respectively, with a re-treatment rate of 3.7%. Two percent of patients had permanent neurologic deficits at last follow-up. Procedural complications (device migration, thromboembolic events, procedural hemorrhage) occurred in 9.8% of cases overall, while total and symptomatic strokes occurred in 8.1% and 7.5%, respectively. Regarding prior studies on Vantage FD, most did not stratify their outcomes by internal carotid versus other locations or by Vantage 21 versus 27 stents, hindering direct comparison.[8–12] The Vanguard study reported 9/16 (56.3%) ACOM aneurysms and 7/25 (28%) MCA aneurysms remained patent at 6-month angiographic follow-up. A majority of the residual aneurysms in this study (16/21, 76.2%) were thus distal to the circle of Willis in small parent vessels, making the overall small-vessel aneurysm occlusion rate 40/56 (71.4%).[7].

Relative to prior studies, Vantage 21 performed well overall for aneurysm repair in small parent vessels in our experience. At a short median angiographic follow-up of 4 months, 85% of aneurysms were adequately embolized, with 16 (80%) achieving complete occlusion despite patients remaining therapeutic on DAPT at the time of follow-up angiography. The stent demonstrated particular efficacy in sidewall aneurysms of the pericallosal arteries, with a 100% adequate occlusion rate in these locations. ACOM aneurysms were less responsive to this technique in our series, with only 7/12 aneurysms (58.3%) demonstrating complete occlusion at first angiographic follow-up and with 2/3 re-treatment cases occurring in this subgroup. This is slightly better than the occlusion rate of 43.7% for ACOM aneurysms seen in the Vanguard study.[7] This is not unexpected, as the treatment of ACOM aneurysms relies on indirect flow diversion, a technique that Schob et al. described as placing a flow diverting stent proximal to the aneurysm neck rather than directly covering the neck (as is typical in sidewall aneurysms).[22] In their series with a median angiographic follow-up of 4 months (n = 17), 8 patients (47.1%) achieved complete occlusion (OKM D), 5 had small residual perfusion in the dome (OKM B1-3), 2 fully filled but with delay into the venous phase (OKM A3), and 2 had no response to the flow diverting treatment. Our results are similar to slightly improved, confirming that the lower rates of complete occlusion in this group are consistent with the literature and that indirect flow diversion requires a longer period to achieve complete involution. The ACOM complex is prone to this effect due to normal anatomic configuration, with contralateral A1 flow contribution and a dynamic response following unilateral A1-A2 segment flow diverter placement.

Vantage 21 elicited a strong response from the parent vessel, evidenced by a 35% (7/20) rate of severe ≥ 50% ISS secondary to significant intimal hyperplasia and 2 fishmouth deformities in our cohort (see Fig. 3). This occurred more frequently than prior similar studies on Vantage FD elsewhere, which noted ISS rates of 0 to 9.9%.[6–12] The stent also tended to affect the jailed side branches, leading to 6 completely occluded arteries and a 71.1% combined rate of decreased caliber or occlusion, with two artery of Heubner strokes attributed to

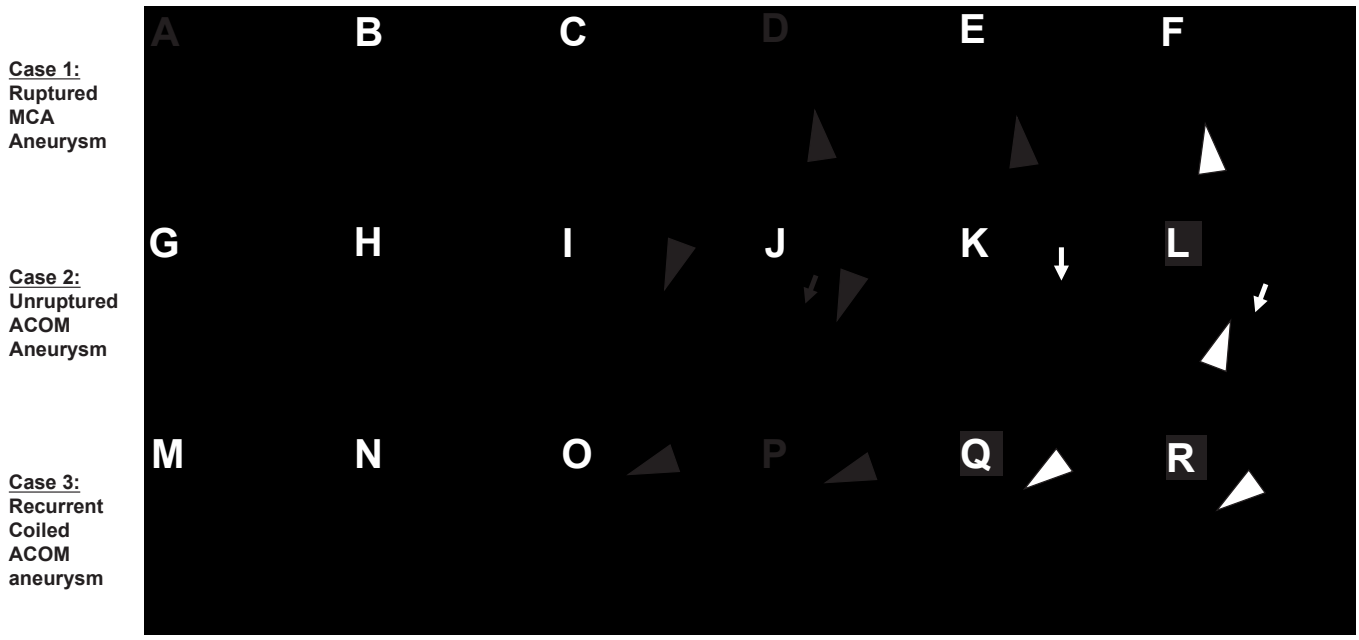


Fig. 3. Pipeline Vantage 21 vascular intimal response. Case 1: Ruptured left MCA aneurysm (A, B) with anteriorly oriented daughter sac, treated with a Vantage 21 (C). 3-month follow-up angiography (D, E, F) shows intimal hyperplasia (arrowheads) causing 62% luminal stenosis. A small residual neck can be seen in the aneurysm's place with complete occlusion of the daughter sac, the presumed rupture site. Case 2: Unruptured anterior communicating aneurysm supplied by a dominant right A1 at time of Vantage 21 right A1-A2 placement (G, H). 3-month follow-up angiogram (I, J, K, L) revealed complete aneurysm involution, but mild proximal fishmouth deformity (arrows) and robust proximal intimal hyperplasia (arrowheads) causing 63% ISS. Case 3: Recurrence of a coiled previously ruptured anterior communicating artery aneurysm; this was initially treated with coil embolization, and 4 months later had coil compaction and neck recurrence (M) treated with repeat coiling and Vantage 21 (N). DSA at 4 months (O, P, Q, R) showed persistent occlusion of the aneurysm but 84% ISS of the distal stent caused by intimal hyperplasia (arrows). Fishmouthing: stent deformity involving the converging of a focal proximal or distal end of a flow-diverting stent, with $\geq$ 25% decrease in the stent's diameter compared to the expected continuation of the stent's shape; indicated with arrows in this figure. Intimal hyperplasia: abnormal proliferation and migration of vascular smooth muscle cells along the luminal arterial wall; indicated with arrowheads in this figure.

Table 3
Comparison of Cases with and without In-Stent Luminal Stenosis.

Variable	No Stenosis (n = 10)	Stenosis (n = 10)	p-value
Gender (n, female)	9 (90%)	7 (70%)	0.58
Age (mean)	61.3 ± 9.9	56.9 ± 11.3	0.37
Aneurysm size (mean, mm)	4.2 ± 1.7	3.5 ± 1.1	0.36
Baseline PRU at time of embolization (mean)	34.3 ± 41.1	55 ± 35.6	0.25
Length of procedure (mean, minutes)	66 ± 12.8	57.1 ± 11.3	0.12
Stent diameter (mean, mm)	2.7 ± 0.4	2.7 ± 0.3	0.75
Stent length (mean, mm)	18.4 ± 2.1	18.7 ± 3.2	0.81
Difference between stent diameter and smallest parent vessel diameter (mean, mm)	0.66 ± 0.26	0.47 ± 0.23	0.11

vessel occlusion or diminished branch size (Fig. 4I-L). In comparison, a prior study on flow diverters used for MCA bifurcation aneurysms which examined jailed arterial branch response noted a decreased caliber rate of 28.6% and asymptomatic occlusion rate of 14.3%.[23] Because our angiographic follow-up was performed earlier than in most centers, these luminal stenoses and decreases in jailed vessel sizes prompted us not to pursue early (<6 months) DAPT wean in cases where they were observed. Stent oversizing could play a role in the elevated ISS rate; prior data has suggested that this correlates with an increased risk and severity of ISS.[24,25] It is hypothesized that this occurs due to a number of factors, including endothelial cell dysfunction secondary to mechanical stress exerted by the stent, disruption of regulatory vasoactive substance production, and inflammation with pathological reparative processes leading to aggressive neointimal proliferation.[24,26,27] The stents in this cohort were slightly oversized for the parent vessel, which is expected given non-ICA parent arteries are often smaller than the smallest-available diameters for existing FD and some oversizing is required for strong stent-wall apposition; however, the mean difference in our study was only 0.6 mm, and there was no statistically significant difference between the average mismatch for parent vessel and stent diameters in the stenosis and no-stenosis groups (Table 3).[4,24] These factors may be exacerbated with the Vantage stent in particular due to its altered construction compared to prior PED iterations, as it achieves higher braid density and uses a DFT design not present in prior generations which may change its interaction with the endothelium.[14,26,28] While its now-recalled, 64-wire Vantage 27 variant was prone to overt stent deformities, it is possible that the Vantage 21 may have this issue to a less perceptible extent; two cases of fishmouth deformities similar to those previously described were also observed in this cohort.[14] Focal areas of ISA can lead to higher-than-physiologic levels of shear stress, which can predispose to intimal hyperplastic responses; even if the smaller stents in this cohort did not display stent deformity as prominently as the larger Vantage 27 stent, it is possible that imperceptible foci of ISA with resulting shear stress could contribute to a similarly robust intimal response in Vantage 21.[14,26,27,29] Small, distal cerebral vessels also include several branch points, which contribute to inconsistent, oscillatory shear stress patterns that can provoke proliferative responses from endothelium, a mechanism that could also explain the high rate of side branch attenuation.[30].

In contrast to these findings, a *meta*-analysis of FD in distal parent vessels noted a pooled ISS rate of 3% and pooled branch occlusion rate of 5.5%, although these did not stratify by which specific flow diverting stent was used; older PED devices made up 126/184 (68.5%) of the included cases.[31] Analysis of FRED Jr. devices in small parent vessels noted an ISS rate of 10.7%, and of 17 jailed side branches observed reduced size in 10 (58.8%) and occlusion in 3 (17.6%).[32] Previous

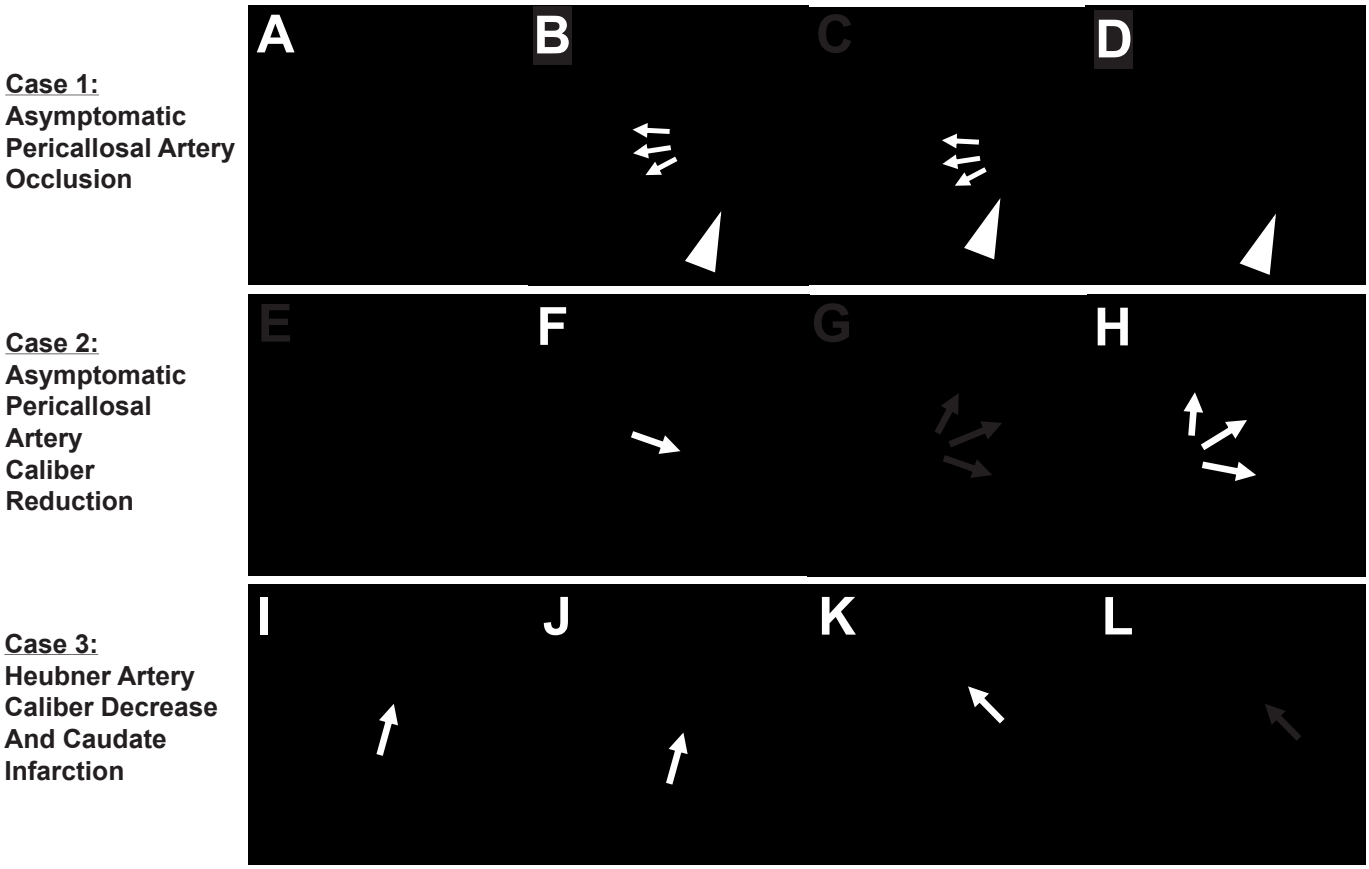


Fig. 4. Pipeline Vantage 21 effect on jailed side-branches. Case 1: A left pericallosal aneurysm (A) treated with Vantage 21 (B) spanning the origin of the aneurysm and the associated pericallosal branch (white arrows) as well as a frontopolar branch (white arrowhead). Follow-up angiography at 3 months (C, D) demonstrated complete occlusion of the aneurysm and its associated pericallosal branch, and a significant decrease in caliber of the jailed frontopolar branch (white arrowhead). The patient was asymptomatic without evidence of diffusion restriction on follow-up MRIs. Case 2: Right pericallosal aneurysm treated with Vantage 21 crossing the aneurysm and its associated pericallosal branch (E, F; white arrow indicates jailed pericallosal artery). Follow-up DSA at 9 months (G, H) shows complete aneurysm involution with faint outline of the diminished pericallosal artery (arrows). No ischemic events occurred during follow-up. Case 3: Anterior communicating aneurysm treated with staged bilateral Vantage 21 (right followed by left) with 3D reconstructions of left ICA injection at time of left stent placement (I) and at 3-month follow-up DSA (J) showing decreased caliber of the artery of Heubner (arrow). Compared to T2-weighted axial MRI performed on post-embolization day 1 (K) showing normal caudate head volume (arrow), 3-month follow-up MRI (L) noted caudate head volume loss on T2-weighted imaging (not shown) and increased diffusion signal of the left caudate head (arrows) on DWI indicative of evolving subacute infarct. Fishmouthing: stent deformity involving the converging of a focal proximal or distal end of a flow-diverting stent, with $\geq$ 25% decrease in the stent's diameter compared to the expected continuation of the stent's shape. Intimal hyperplasia: abnormal proliferation and migration of vascular smooth muscle cells along the luminal arterial wall.

literature has also examined this phenomenon in older iterations of the PED in small parent vessels. One notable study examining intimal hyperplasia rates on 6-month DSAs after FD with PED in anterior circulation aneurysms noted a higher rate of intimal hyperplasia in ACA (21.4%) and MCA (61.1%) stents than in ICA stents (15.9%); interestingly, 5/26 (22.7%) of the ICA cases with intimal hyperplasia had the distal stent seated in the proximal M1, with focal intimal hyperplasia occurring only in that part of the stent.[27] However, the severity of luminal narrowing was not defined in that study, precluding comparison to the severities seen in our patients. Another cohort of uncoated PED-Flex devices in distal parent vessels noted intimal hyperplasia in 31/85 cases (36.5%), with 13/85 (15.3%) having $>$ 50% luminal narrowing.[25] Finally, a third study analyzing PED-Flex in parent vessels sized $<$ 2 mm noted an ISS rate of 12.7%, with pre-existing parent vessel stenosis being expectedly associated with ISS.[33] These findings somewhat lend support to the idea that the distal location predisposes to intimal hyperplasia, but they probably do not fully explain the increased ISS rates among Vantage stents since these effects were also observed at much higher rates than prior PEDs in ICA aneurysms treated with Vantage 27.[14] The Shield surface modification also may not fully explain the variance in intimal hyperplasia rates seen in Vantage, as a prior analysis showed that both the original uncoated PED-Flex and coated PED-Shield stents had similar rates of ISS (14.2% vs 14.6%, $p = 0.927$).[34] This leaves biomechanical stent properties as a possible explanatory mechanism, although the exact underlying processes remain unclear and require further research.

Given flow diversion in small parent vessels may increase the risk of clinically significant flow limitation secondary to intimal neoplastic response, effective platelet inhibition becomes paramount to prevent complications in cases of ISS after flow diversion. The balance between ischemic and hemorrhagic complications is debated in FD, with data suggesting that most ischemic complications occur early while continuing DAPT for $>$ 6 months increases hemorrhage risk.[35] However, our outcomes were achieved with zero major neurological morbidity or mortality with median 12 months follow-up, with 1 minor neurologic complication (symptomatic stroke with full resolution of symptoms in a patient with lapsed DAPT coverage) and 2 asymptomatic neurologic complications, as well as two minor non-neurologic complications. A possible explanation for this low rate of ischemic events despite a higher-than-expected stenosis rate could be attributable to strong DAPT adherence, with therapeutic PRUs on the day of procedure (mean, 42.1) and at time of follow-up angiogram (mean, 51.7; median 4-months post-procedure). Over a longer follow-up period (mean of 10.6 months) in the small-parent vessel *meta*-analysis, symptomatic strokes

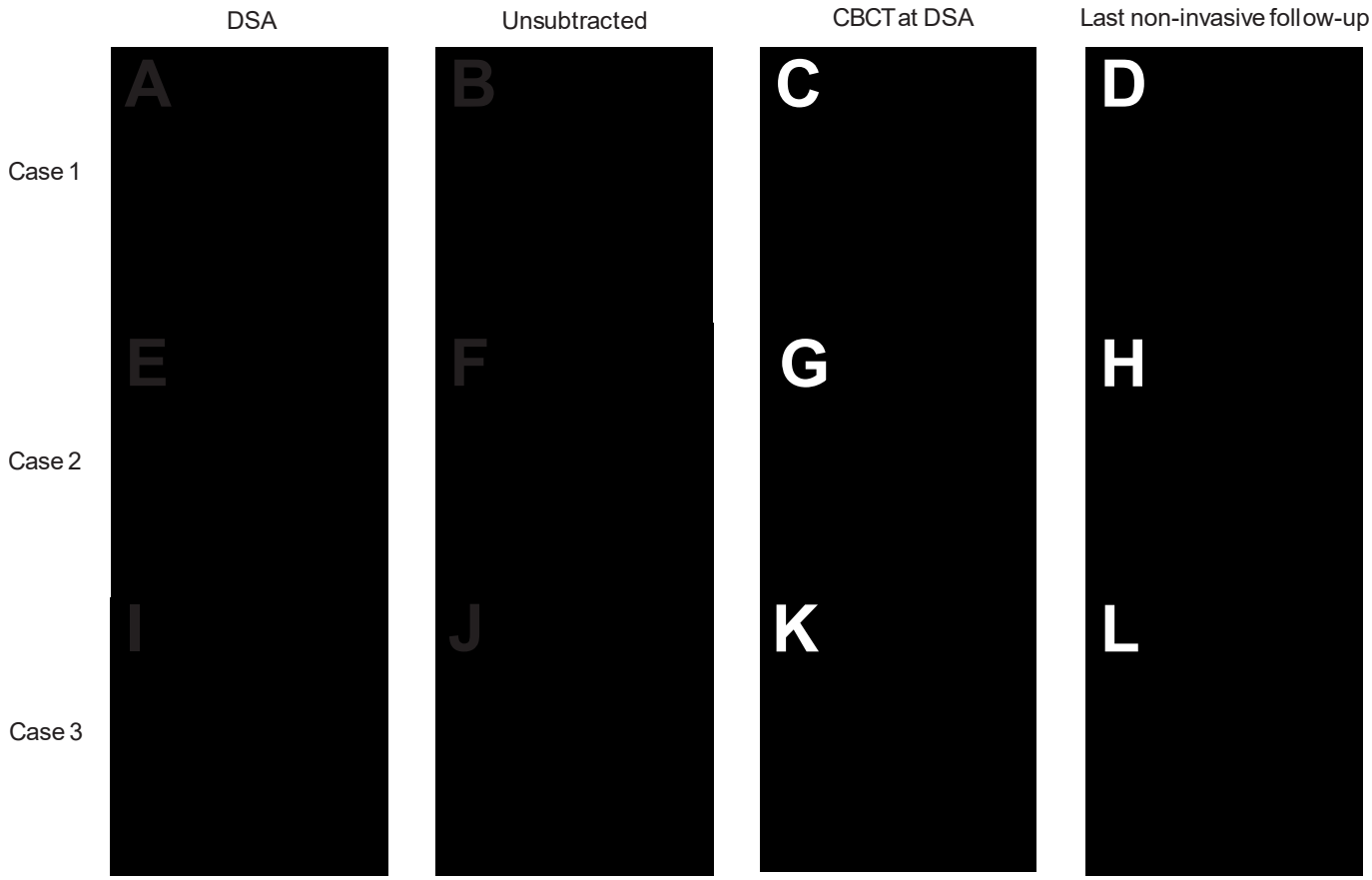


Fig. 5. Comparison of in-stent stenosis seen on DSA and last follow-up imaging. Views chosen to best illustrate the same area of stenosis on both studies. Case 1: Ruptured MCA aneurysm with severe stenosis on 2-month DSA (A, B); CBCT at DSA (C) vs CTA at 18 months (D) shows some improvement in lumen size and some reduction in intimal hyperplasia. Case 2: Left ACA stent with severe intimal hyperplasia on 4-month DSA (E, F); CBCT at DSA (G) vs follow-up MRA (H) at 13 months with resolved hyperplasia and stenosis. Case 3: Right-sided ACA stent placed for an ACOM aneurysm with intimal hyperplasia and mild proximal fishmouth deformity (I, J); CBCT at DSA (K) and on follow-up MRA performed at 18 months (L) shows resolution of intimal hyperplasia.

occurred in 7.5% and permanent neurologic deficits were present in 2% of cases. However, these results should be interpreted cautiously given the study heterogeneity. Many flow diversion treatments are carried out on DAPT regimens without platelet function testing to confirm adequate therapeutic effect, which could predispose to strokes if DAPT response is inadequate.[10] Management of severe FD-related ISS with DAPT has been documented previously, although there is no consensus on the duration of treatment required after ISS is identified; however, existing literature suggests that intimal hyperplasia is a transient phenomenon which peaks from 4-6 months and then improves between 12–24 months post-deployment.[24,27,35–40] In our cohort, the response over time was mixed, with 6/10 (60%) cases showing some degree of discernable improvement of the known ISS on final imaging follow-up. Despite lack of consensus over DAPT duration in FD-associated stenosis, DAPT with PFT appears to reduce thromboembolic risk overall, and poor response to DAPT may also increase risk for ISS.[40–42].

This study is limited by its retrospective design and small sample size compared to previous larger European and Australian cohorts. Our series may underestimate the true risk of thromboembolism and clinical morbidity from the ISS and jailed vessel narrowing caused by Vantage 21. For example, although the Heubner infarcts in this series were considered a "minor" neurologic event due to their asymptomatic nature in these specific patients, it does warrant greater concern given caudate head infarctions can produce neurologic morbidity in many patients, and these asymptomatic outcomes cannot be assumed to generalize to all patients suffering from a side-branch infarction related to the Vantage 21 stent. It is also unclear the exact role our DAPT protocol had in mitigating ischemic events and their resulting morbidity given the small sample size, as we use prasugrel preferentially and perform VerifyNow PRU testing regularly, a practice not seen at all institutions. However, the series is strengthened by its close clinical follow-up, with 90% of patients having undergone DSA as the primary determinant of occlusion status and stent-related complications. Our practice of early angiographic follow-up relative to other studies (3 vs $\geq$ 6 months) lends unique insight into the earlier occlusion rates of the Vantage 21, although this can overestimate ISS during the early intimal response to the stent. Conversely, the uniform single-center technical and treatment protocol may have helped reduce variability of the non-implant related variables in the dataset.

5. Conclusions

As an aneurysm repair device, the Pipeline Vantage 21 stent performs well in small- and distal parent vessels, achieving acceptable occlusion rates in most locations within a relatively short period of 4 months. However, a high ISS rate from a significant intimal response remains a major concern. There were prevalent jailed vessel caliber reductions in over half the cohort, with six complete occlusions and two caudate head infarcts secondary to reduced caliber or occlusion of the artery of Heubner. Although the latter are currently asymptomatic, they nevertheless represent high-risk events with unpredictable and potentially catastrophic consequences. These results may indicate a requirement for protracted DAPT to mitigate ischemic events and warrant significant caution in the use of this stent in small parent vessel aneurysms, particularly if the stent covers critical side branches. Additional research is required on the Vantage 21 stent's biomechanical properties

and their effects on parent vessels to better understand the strong parent vessel response and the resulting jailed side branch narrowing with potential thromboembolic/ischemic events.

CRediT authorship contribution statement

M.Harrison Snyder: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anthony J. Yu:** Writing – review & editing, Formal analysis, Data curation. **Taylor Ferraro:** Writing – review & editing, Data curation. **Adel.M. Malek:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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