

1 **Definition of anterior-circulation aneurysm and posterior-circulation aneurysm**

2 Aneurysms located at the internal carotid artery, anterior communicating artery, posterior
3 communicating artery, anterior cerebral artery, and middle cerebral artery were defined as
4 anterior-circulation aneurysms. Aneurysms located at the vertebral artery, basilar artery,
5 posterior inferior cerebellar artery, and posterior cerebral artery were defined as
6 posterior-circulation aneurysms.

7

8 **Definition of aneurysm and parental artery morphology parameters**

9 The morphology parameters assessed in this study were defined as follows:

10 *Aspect ratio*: aneurysm height \div aneurysm width;

11 *size ratio*: maximum diameter of aneurysm \div parental artery diameter;

12 *height/width ratio*: perpendicular height of aneurysm \div aneurysm width;

13 *bottle/neck factor*: aneurysm neck length \div aneurysm width;

14 *neck ratio*: aneurysm neck length \div parental artery diameter;

15 *mean artery diameter*: (distal artery diameter + proximal artery diameter) \div 2;

16 *artery difference*: proximal artery diameter – distal artery diameter;

17 *proximal-distal ratio*: proximal artery diameter \div distal artery diameter.

18 All parameters were measured and calculated based on original digital subtraction
19 angiography photographs.

20 **Study Size Calculation**

21 No sample size calculation was performed and the sample size was established by the
22 time window of the study.

23

24 **Platelet function test statement**

25 The experimental diagnostic center at our hospital does not support PRU (P2Y12
26 reaction units) testing at present. Instead, all patients in our study underwent platelet function
27 monitoring 1 day before PED placement. Platelet function was assessed by standard light
28 transmittance aggregometry (LTA) to measure platelet aggregation. Light transmittance
29 aggregometry was conducted using platelet-rich plasma using the turbidimetric method in a
30 4-channel aggregometer (AG800; Techlink Biomedical, Inc., Beijing, China). Maximal
31 platelet aggregation (MPA) was defined as the percentage change in light transmittance.
32 Subsequently, non-responders were defined as having an MPA response to ADP (adenosine
33 diphosphate) of >50%. For those patients, clopidogrel was switched to one dose of ticagrelor
34 (180 mg) before the procedure, followed by twice daily doses of ticagrelor (45 mg) after the
35 procedure combined with aspirin (100 mg) for 6 months.

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37 **Statement for generation of PED used in this study**

38 Pipeline Embolization Device and Pipeline Flex Embolization Device were used in our study
39 without include PED Shield (Pipeline embolization device with Shield technology).

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41 **PED implantation procedure**

42 The PED was delivered and deployed through a Marksman™ microcatheter (Medtronic,
43 Irvine, CA) or an Excelsior™ XT-27™ microcatheter (Stryker, Kalamazoo, MI).
44 PED-assisted coiling was considered if there was (a) a risk of shortening and displacement of
45 the PED after release or (b) rapid blood flow (jet) at the aneurysmal neck on angiography,
46 which was expected to pose a high risk of recurrence and postoperative bleeding with FD
47 implantation alone. The brands of coil included Axium™ (Medtronic, Dublin, Ireland),
48 Microplex™ (Microvention, Aliso Viejo, CA), Target™ (Stryker, Kalamazoo), and Orbit™
49 (Johnson & Johnson, New Brunswick, NJ). When full vessel wall apposition was not

50 achieved, stent massage or balloon angioplasty was performed.

51

52 **Antiplatelet therapy after PED implantation**

53 The duration of dual antiplatelet therapy (DAPT) after PED implantation was 6 months for
 54 aspirin (100 mg/day) combined with clopidogrel (75 mg/day), and aspirin (100 mg/day) was
 55 continued for at least 1 year. For patients with inadequate platelet inhibition with clopidogrel
 56 (platelet function test showed maximal platelet aggregation of >50%), clopidogrel was
 57 switched to one dose of ticagrelor (180 mg) before the procedure, followed by twice daily
 58 doses of ticagrelor (45 mg) for 6 months after the procedure. In fact, some patients with poor
 59 adherence spontaneously withdrew the antiplatelet drugs. We have added these data to our
 60 revised manuscript. The duration and type of antiplatelet therapy have been included in the
 61 manuscript and analyzed as variables

62 **Analysis for drug withdraw between Non-ISS and ISS group**

	No-ISS	ISS	Total	P value
Drug withdraw	82 (21.03%)	21 (30.43%)	103 (22.44%)	0.116

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Univariate logistic regression	OR	95% CI	P value
Drug withdraw	1.641	0.932—2.903	0.116

64

65 **Analysis for clopidogrel switched to ticagrelor between Non-ISS and ISS group**

	No-ISS	ISS	Total	P value
Clopidogrel switched to ticagrelor	58 (14.9%)	14 (20.3%)	72 (15.7%)	0.254

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Univariate logistic regression	OR	95% CI	P value
Clopidogrel switched to ticagrelor	1.457	0.762—2.789	0.256

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69 **Subgroup analysis**

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71 **Subgroup analysis for the average duration of follow-up between resolution**
 72 **group vs non-resolution group in ISS patients**

73 There was a significant difference between the resolution group and the non-resolution group
 74 (25 [14–36] months vs. 14 [9–20] months; $P = 0.005$) in terms of the average duration of
 75 follow-up in patients with ISS. According to the ST-T curve, patients who developed ISS
 76 showed a clear trend toward resolution 24 months after PED implantation, which is in line
 77 with the statistical data.

78

79 **Subgroup analysis for the difference in resolution and progression to artery**
 80 **occlusion between ISS patients who were on DAPT and non-DAPT**

81 Patients who had ISR had a higher rate of resolution if they extended their dose or resumed
 82 DAPT (4 [7.8%] vs. 5 [27.8%]; $P = 0.045$). For patients with ISS who developed parental
 83 artery occlusion, there was no significant difference between the aspirin group and the DAPT
 84 group (12 [22.6%] vs. 6 [26.1%]; $P = 0.240$).

	Non-DAPT	DAPT	Total	P value
ISS to resolution	4 (7.8%)	5 (27.8%)	9 (13.0%)	0.045
ISS to occlusion	12 (22.6%)	6 (37.5%)	18 (26.1%)	0.240

85

86 **Subgroup analysis for the difference between responders and non-responders**
 87 **(according to the platelet function test) respect to ISR**

88 There was no difference between responders and non-responders with respect to ISR in the
 89 subgroup analysis (55 [14.2%] vs. 14 [19.4%]; $P = 0.254$)

	Responders	Non-responders	Total	P-value
In stent-stenosis	55 (14.2%)	14 (19.4%)	69 (15.0%)	0.254

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91 **Evaluation of the ISS patients for proximal or distal "fishmouthing" and diffuse**
 92 **or focal mechanical distortion of the actual Pipeline Embolization Device**

93

Types of in-stent stenosis	Numbers of patients (%)	Numbers of patients developed to parental artery occlusion (%)
Tissue growth in normal appearing PED	40 (57.97%)	0 (0.00%)
Proximal distortion (fish-mouthing) of the PED	9 (13.04%)	8 (44.4%)
Distal distortion (fish-mouthing) of the PED [#]	14 (20.29%)	8 (44.4%)
Distortion of the mid-portion of the PED	3 (4.35%)	1 (5.56%)
Tissue growth with distal distortion of the PED	2 (2.90%)	1 (5.56%)
Tissue growth with proximal distortion of the PED	1 (1.45%)	0 (0.00%)
Total	69 (100%)	18 (100%)

94 [#]The type of ISS was evaluated as distal distortion (fish-mouthing) of the PED in two patients that
 95 died.

96

97 After further back-to-back blinded review of follow up angiography of 69 patients with ISS,
 98 we found that 40 (57.97%) patients presented with tissue growth in normal appearing PED,
 99 nine (13.04%) patients had proximal distortion (fish-mouthing) of the PED, 14 (20.29%)
 100 patients had distal distortion (fish-mouthing) of the PED, and three (4.35%) patients had
 101 distortion of the mid-portion of the PED. Furthermore, two (2.90%) patients had normal
 102 tissue growth with distal distortion of the ISS, and one (1.45%) patient had tissue growth with
 103 proximal distortion of the PED. For the 18 patients who developed parental artery occlusion,
 104 dynamic assessment of postoperative follow-up angiography showed eight (44.44%) patients
 105 with proximal distortion (fish-mouthing) of the PED, eight (44.44%) patients with distal
 106 distortion (fish-mouthing) of the PED, and one (5.56%) patient with distortion of the
 107 mid-portion of the PED. One (5.56%) patient presented with normal tissue growth with distal
 108 distortion of the PED.

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110 Interestingly, we found that nearly 2/3 of patients presenting with late stent distortion had
 111 their procedure between 2015–2018, with many Chinese physicians having only 1–3 years of

112 experience in using PEDs. At that time, some of the physicians used the biaxial system (e.g., a
113 6F guiding catheter combined with a Marksman micro catheter) to deliver and deploy the
114 PEDs. Although the biaxial system is the classic approach in cerebrovascular interventions, it
115 has poor support in curved vessels, which can lead to poor PED apposition. Furthermore,
116 even if the PED achieves an adequate apposition, the operator has to perform more pushing
117 and pulling maneuvers, which can increase the risk of irreversible damage to the PED
118 structure (e.g., twisting in the middle of the stent). Finally, the distal or proximal part of the
119 PED can be occasionally or inevitably placed into the curved vessel area of patients with a
120 tortuous blood vessel. All these factors can lead to late distortion of the PED.

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122 When selecting the PED size, the operator will often measure the proximal and distal parental
123 artery diameters. However, to achieve adequate proximal wall apposition, the operator often
124 prefers to accommodate the proximal parental artery diameter. This inevitably results in a
125 ‘mismatch’ between the PED size and the distal vessel diameter, while the pressure from stent
126 expansion can result in intima damage at the distal part of the stent. We believe that these
127 factors may account for the greater number of patients with distal distortions than proximal
128 distortions.

129

130 To prevent the late mechanical distortion of the PED, we recommend that the operator use a
131 triaxial system to deliver and release the PED (e.g., the Neuron MAX 088 catheter combined
132 with the Navien intracranial support catheter and the Phenom-27 microcatheter). If poor wall
133 apposition is identified intraoperatively, the microguide wire massage stent should be used
134 carefully (careless handling can cause damage to the proximal part of the stent and may lead
135 to proximal distortion), and balloon-angioplasty or even further stent deployment (e.g.,
136 Neuroform EZ) should be used to achieve adequate apposition. Note that this additional
137 manipulation is also associated with increased risk of ISS.

138

Supplementary Table 1-1. Aneurysm characteristics of patients after PED treatment

Characteristics	Non-ISS (n=390)	ISS (n=69)	Total (n=459)	P value
Aneurysm location				0.008
ACA	2 (0.5%)	0 (0%)	2 (0.4%)	
AComA	1 (0.3%)	0 (0%)	1 (0.2%)	
BA	10 (2.6%)	2 (2.9%)	12 (2.6%)	
ICA	298 (76.4%)	40 (58%)	338 (73.6%)	
MCA	8 (2.1%)	2 (2.9%)	10 (2.2%)	
PCA	2 (0.5%)	1 (1.4%)	3 (0.7%)	
PComA	2 (0.5%)	0 (0%)	2 (0.4%)	
PICA	0 (0%)	2 (2.9%)	2 (0.4%)	
VA	67 (17.2%)	22 (31.9%)	89 (19.4%)	
Aneurysm position				0.390
middle	11 (2.9%)	2 (2.9%)	13 (2.8%)	
left	207 (53.1%)	30 (43.5%)	237 (51.6%)	
right	172 (44.1%)	37 (53.6%)	209 (45.5%)	
Aneurysm type				0.001
saccular	316 (81.03%)	44 (63.77%)	360 (78.43%)	
fusiform	74 (18.97%)	25 (36.23%)	99 (21.57%)	
Aneurysm in bifurcation	16 (4.1%)	5 (7.2%)	21 (4.6%)	0.401
Aneurysm with lobulation	43 (11.0%)	8 (11.6%)	51 (11.1%)	0.890
Aneurysm with daughter sac	28 (7.2%)	5 (7.2%)	33 (7.2%)	1.000
Multiple aneurysms	116 (29.7%)	18 (26.1%)	134 (29.2%)	0.538
Symptomatic aneurysms	172 (44.1%)	35 (50.7%)	207 (45.1%)	0.308
Recurrent Aneurysms	7 (1.8%)	2 (2.9%)	9 (2.0%)	0.890

139 ACA: anterior cerebral artery; AComA: anterior communicating artery; MCA: middle cerebral artery; ICA:

140 internal carotid artery; VA: vertebral artery; BA: basilar artery; PICA: posterior inferior cerebellar

141 artery; PComA: posterior communicating artery; PCA: posterior cerebral artery

Supplementary Table 1-2. Aneurysm characteristics of patients after PED treatment

Characteristics	Non-ISS (n=390)	ISS (n=69)	Total (n=459)	P value
Unsatisfiable Device Deployment	11 (2.8%)	5 (7.2%)	16 (3.5%)	0.136
Balloon angioplasty	68 (17.4%)	21 (30.4%)	89 (19.4%)	0.012
PED associated with coiling	146 (37.4%)	29 (42.0%)	175 (38.1%)	0.469
Used PED>1	46 (11.8%)	9 (13.0%)	55 (12.0%)	0.769
Aneurysm Neck	6.69 (4.45—11.1 0)	10.10 (6.52—15.7 5)	7.04 (4.50—11.6 0)	P<0.001
Maximum Diameter	10.40 (6.29—16.7 0)	13.30 (9.07—22.2 0)	10.90 (6.40—17.1 0)	0.003
Aneurysm Height	7.37 (4.76—11.8 0)	7.87 (6.57—14.4 5)	7.43 (4.95—12.1 0)	0.025
Aneurysm Width	8.48 (4.81—14.6 3)	12.9 (6.80—20.9 5)	9.02 (5.07—15.3 0)	P<0.001
Aneurysm Perpendicular Height	6.96 (4.50—11.2 3)	7.87 (5.83—14.2 5)	7.18 (4.68—11.6 0)	0.017
Parental Artery Diameter	3.64 (3.16—4.17)	3.82 (3.30—4.36)	3.66 (3.17—4.19)	0.304
Proximal Artery Diameter	3.91 (3.45—4.49)	4.00 (3.15—4.79)	3.92 (3.42—4.53)	0.890
Distal Artery Diameter	3.43	3.49	3.44	0.327

	(3.04—3.86)	(2.82—4.22)	(2.98—3.88)	
Mean Artery Diameter	3.68	3.80	3.68	0.702
	(3.21—4.08)	(3.19—4.36)	(3.21—4.09)	
Difference between Proximal and Distal Artery	0.45	0.49	0.46	0.882
	(0.09—1.01)	(0.06—1.08)	(0.09—1.01)	
Proximal/Distal Ratio	1.13	1.12	1.13	0.900
	(1.03—1.30)	(1.02—1.34)	(1.03—1.31)	
Aspect Ratio	1.07	0.94	1.04	0.141
	(0.74—1.59)	(0.66—1.50)	(0.73—1.59)	
Height/Width Ratio	0.89	0.81	0.87	0.012
	(0.74—1.02)	(0.64—0.95)	(0.72—1.01)	
Bottle Neck Factor	0.94	1.00	0.95	0.865
	(0.69—1.00)	(0.68—1.00)	(0.69—1.00)	
Size Ratio	2.87	3.56	3.00	0.007
	(1.64—4.73)	(2.18—6.32)	(1.73—4.81)	
Neck Ratio	1.91	2.93	1.99	P<0.001
	(1.15—3.02)	(1.56—4.40)	(1.19—3.40)	1

PED: Pipeline Embolization Device

Supplementary Figure 1 Flow Chart

