Present Status of Flow Diverter in the World

Satoshi Tateshima

The introduction of flow diverters induced a major paradigm shift in the treatment of intracranial aneurysms. Not just large and giant aneurysms, but also some of the aneurysms that are amenable to conventional coil embolization could be better treated with flow diverters because of the high efficacy and treatment durability. As such, there are two ongoing studies, the Flow Diversion in Aneurysms Trial study (FIAT) and Prospective Study on Embolization of Intracranial Aneurysms With Pipeline™ Embolization Device (PREMIER) study, which aim to clarify the true indication of flow diverter treatment. Simultaneously, the next generation of flow diverters is being developed by the industry. After multiple iterations of the design and improvements in the mechanical performance, industry leaders are developing a new coating technology that modifies the biocompatibility of flow diverters. Continuous improvements in the devices and compiling good quality clinical data will increase the role of the flow diverter in the treatment of intracranial aneurysms.

Keywords ► flow diverter, aneurysm, Pipeline

Introduction

The advent of flow diverters produced a major paradigm shift in the treatment of intracranial aneurysms in Western countries. In European countries where the time required for the approval of medical devices is short, many treatment results including those of on-label and off-label uses have been obtained, and various types of flow diverter such as Silk (Balt, Montmorency, France), Pipeline (Medtronic, Irvine, CA, USA), Surpass (Stryker, Fremont, CA, USA), FRED (Microvention, Irvine, CA, USA), and p64 (Phenox, Bochum, Germany) are commercially available at present.^{1–5)} In European countries, the range of indications for the use of flow diverters tends to be wide, and there have been some reports of their use for small or bifurcation aneurysms. In contrast, in the United States, since the Food and Drug Administration requires a relatively strict medical device approval process, only Pipeline can be used at present (2016). In the United

States, although many institutions actively use flow diverters, the range of indications based on the national average seems stricter and narrower than that in European countries. During a change from treatment reinforcing the aneurysm itself by endosaccular embolization to treatment that reinforces and repairs the injured parent artery as the basic cause of the disease, some studies have shown biased theories and treatment strategies. In this study, we summarize rational and highly neutral opinions in terms of clinical medicine, and mainly describe experience in the author's institution and the present status in Western countries.

Pipeline in Clinical Practice

Prior to the clinical use of flow diverters such as Pipeline, physicians should be well informed about the results of major clinical trials. The Pipeline for Uncoilable or Failed Aneurysms (PUFs) Trial is a prospective single-arm multicenter trial using patients with aneurysms of the internal carotid artery with a maximum diameter ≥ 10 mm and a neck length ≥ 4 mm and a historical control group.⁶⁾ In the PUFs trial, the historical control group was established based on an extensive literature review related to surgery or endovascular treatment for large and giant aneurysms of the internal carotid artery. The following criteria for the evaluation of effectiveness and safety were established: the rate of complete occlusion, $>50\%$; and the rate of serious

Ronald Reagan UCLA Medical Center, Interventional Neuroradiology, Los Angeles, CA, USA

Received: April 15, 2016; Accepted: August 11, 2016

Corresponding author: Satoshi Tateshima. Ronald Reagan UCLA Medical Center, Interventional Neuroradiology, 757 Westwood Plaza, Ste2129, Los Angeles, CA 90095-7437, USA

Email: stateshi@ucla.edu

©2017 The Editorial Committee of *Journal of Neuroendovascular Therapy*. All rights reserved.

adverse events (stroke showing an increase in the National Institutes of Health Stroke Scale [NIHSS] score by 4 points) or death, <20%. Among the 106 aneurysms enrolled in the trial, approximately 50% of them involved in the petrous or cavernous segment, and most of the others involved in the paraclinoid segment. Although the large averaged size of the aneurysms (mean maximum diameter, 18.2 mm), the complete aneurysm occlusion rates after 180 days and 1 year were 82% and 86%, respectively, showing high effectiveness. The rate of serious adverse events was 5.9% (six events in five patients), which was lower than the pre-determined safety criterion. Due to this success, treatment with flow diverters became widely recognized, and its indications were dramatically expanded.

In such a background, flow diverters were excessively used due to misunderstanding or broad interpretation of the results of the PUFs trial. The most frequent misunderstanding was to use the pre-determined safety criterion (5.6%) obtained in this trial as the perioperative complication rate.⁶⁾ The safety criterion in the PUFs trial was defined by narrowing further the range of generally used “serious adverse events,” and cannot be directly compared with the complication rate widely used as treatment results in retrospective studies. Indeed, during the PUFs trial performed according to a strict protocol, the rate of all complications from severe to mild ones was more than 20%. Based on the experience in our institution, the rate of serious adverse events using a definition similar to that in the PUFs trial was 6%, but the rate of all perioperative complications associated with Pipeline placement was 15%.⁷⁾

The International Retrospective Study of Pipeline Embolization Device (IntrePED) as a multicenter retrospective study after Pipeline became commercially available accurately reflects the present clinical practice with Pipeline in the United States.⁸⁾ A total of 793 patients with 906 aneurysms were registered from 17 institutions. These aneurysms included small anterior circulation aneurysms, ruptured aneurysms, and vertebrobasilar aneurysms that require off-label uses. The IntrePED showed that the complication rate associated with Pipeline placement increased in proportion to aneurysm size (4.8% for aneurysms <10 mm; 9.5% for aneurysms ≥10 mm), supporting the rationale of the expansion of its indications to small and medium aneurysms. On the other hand, the rate of serious adverse events tends to be higher for aneurysms in the posterior circulation that has more eloquent perforating arteries than the anterior circulation. In our institution, we also experienced ischemic complications related to perforating arteries from the middle cerebral artery and from

the distal internal carotid artery such as anterior choroidal artery. Therefore, in areas containing many eloquent perforating arteries, indications for the use of Pipeline should be carefully decided.^{7,9)}

The IntrePED showed a clear higher rate of adverse events when Pipeline was used for acute ruptured aneurysms than for unruptured aneurysms. Although there have been some reports of treatment with Pipeline for dissecting ruptured aneurysms with poor collateral circulation, the use of Pipeline for such aneurysms needs further discussion, including its indications and the timing of therapeutic interventions. According to the principles in our hospital, we avoid the use of Pipeline in the acute stage. Re-rupture in the acute stage is prevented by blood pressure control and partial coil embolization, and 2 weeks or more after rupture, treatment with flow diverters including Pipeline is considered.

In the IntrePED, aneurysm rupture after Pipeline placement occurred in 0.6% of the patients, and all these aneurysms had a maximum diameter ≥10 mm while no rupture after Pipeline placement occurred in aneurysms <10 mm and aneurysms treated by coil embolization. There are various theories about aneurysm rupture after flow diverter placement, and the clear mechanism remains unclear at this point. However, the result of IntrePED sheds a light on how to prevent it. In our institution, combined use of Pipeline and endosaccular coiling is strongly considered for the intradural aneurysms with high aspect ratio, contour irregularity, and large size (<15 mm). Rupture after Pipeline placement most frequently occurs during the perioperative period, and is rarely observed after more than 6 months.^{7,8)} In our institutional experience, rupture after Pipeline placement tends to frequently occur in large posterior circulation aneurysms although no statistical significance was observed.

Expanding the Indication of Pipeline: PREMIER Study

In the United States, the indications for Pipeline 2 and Pipeline Flex are unruptured internal carotid artery aneurysms with a maximum diameter ≥10 mm proximal to the posterior communicating artery. Aneurysms in the posterior circulation or those distal to the posterior communicating artery, including aneurysms of internal carotid artery-posterior communicating artery, are off-label indications. However, in clinical practice, Pipeline placement is also performed for aneurysms in the posterior circulation or those distal to the posterior communicating artery, and the rate of off-label uses is considered to be 30%–40%.

Under such circumstances, the Prospective Study on Embolization of Intracranial Aneurysms with Pipeline™ Embolization Device (PREMIER) is underway to expand clinical indications for the use of Pipeline. This is a prospective single-arm multicenter study (26 institutions in the United States and 2 institutions outside the United States) and will enroll up to 141 patients. Patients aged 22–80 years who have wide-necked (neck diameter ≥ 4 mm or dome/neck ratio ≤ 1.5) aneurysms in the anterior or posterior circulation are eligible for this study. The primary effectiveness endpoint is complete aneurysm occlusion not accompanied by parent artery stenosis ($\geq 50\%$) after 1 year. The safety endpoint is stroke within 1 year and associated death. In July 2014, the registration of patients was initiated, and the results regarding the primary effectiveness endpoint will be obtained by February 2017.

Proper Use of Flow Diverters or Coils for Treatment

The greatest advantage of treatment with flow diverters is favorable long-term angiographic outcome including the absence of recurrence of aneurysms after their complete occlusion. Concerning disadvantages, a certain period is necessary from treatment until complete aneurysm occlusion, and there are a few aneurysms not showing complete occlusion. In addition, once the flow diverter is placed, intra-aneurysmal embolization for such a residual aneurysm cannot be performed. As a perioperative problem, the incidence of adverse events is relatively high after treatment with flow diverters compared with coil embolization. The greatest advantage of coil embolization is that its preventive effects on rupture can be obtained from immediately after treatment. However, its long-term effects are not satisfactory in patients with severe parent artery injury or large aneurysms. When disadvantages are compared between treatment with flow diverters and coil embolization, it may be appropriate to use the former for fusiform aneurysms and aneurysms with a long maximum diameter and the latter for relatively small aneurysms readily treated by intra-aneurysmal embolization. However, opinion is divided on which of the two treatment methods is optimal for medium-sized paraclinoid aneurysms requiring stent-assisted coil embolization and multiple mutually adjacent small aneurysms. When either technique can be used, the optimal methodology should be finally evaluated by performing prospective randomized trials. As one of such trials, the Flow Diversion in Aneurysms Trial (FIAT),

mainly by a group in Canada, is underway.¹⁰⁾ The FIAT includes randomized and registry trials that are concurrently performed.¹⁰⁾ In the randomized trial, treatment with flow diverters is evaluated against the following interventions: 1) conservative management, 2) coil embolization, 3) parent artery occlusion, and 4) surgical clipping or bypass operation. The subjects consist of patients aged 18–75 years with aneurysms in the anterior or posterior circulation. When the operator considers that treatment with flow diverters is indicated, patients with aneurysms < 10 mm in the maximum diameter can also be registered. Registration was initiated in April 2011, and the results of the trial will be open to public viewing in April 2017.

In our hospital, 32% of patients treated with flow diverters (Pipeline 2 or Pipeline Flex) had aneurysms with a maximum diameter < 10 mm (off-label uses). Flow diverters are frequently used in patients with recanalization after coil embolization or multiple small paraclinoid aneurysms. As a principle in our hospital, flow diverters are actively considered in patients with extensive parent artery damage irrespective of the maximum diameter of aneurysms (Figs. 1A–1D).

Antiplatelet Therapy and Adverse Events

In postoperative management after the placement of flow diverters with a high surface coverage rate, antiplatelet drugs play a major role. There are opinions both for and against the necessity to optimize antiplatelet therapy based on the results of the platelet aggregation test. Clinical trials such as the PITA and PUFS showed a certain level of safety even in the absence of the platelet aggregation test. We previously evaluated the association between ischemic complications during the perioperative period after flow diverter placement (Pipeline 2 or Pipeline Flex) and the platelet aggregation test, and showed a cut-off value of the inhibition of adenosine diphosphate (ADP)-induced aggregation of 49% and a significant decrease ($p = 0.05$) in the rate of ischemic complications in the patient group showing a value of 50–75%.⁷⁾ If a certain decrease in the complication rate could be achieved practically by such a non-invasive blood examination, our position is that the platelet aggregation test should be performed.

In our institution, the administration of aspirin (325 mg/day) and clopidogrel (75 mg/day) is initiated at least 3 days before flow diverter placement. On the day of flow diverter placement, the percent inhibition of ADP-induced aggregation or P2Y₁₂ reactivity unit (PRU) is measured as the

Fig. 1 (A) Lateral angiogram of the left internal carotid artery. A patient with bilateral multiple paraclinoid aneurysms. The aneurysm on the right side had already been treated with coil embolization using a neck bridge stent. The left paraclinoid was swollen, forming a fusiform aneurysm (maximum diameter, 6.5 mm). In the posterior wall, there was a small aneurysm (1.5 cm). (B) Angiography of the left internal carotid artery, left anterior oblique position. The irregular shape of the fusiform paraclinoid aneurysm could be confirmed. During the course observation, the aneurysm grew, and was treated with Pipeline placement. (C) Lateral angiogram of the left internal carotid artery immediately after Pipeline placement. The indwelling Pipeline was observed from the paraclinoid area of the left internal carotid artery to cavernous sinus. Compared with the pre-placement state, contrast agent inflow into the fusiform aneurysm decreased, but no changes were observed in the small aneurysm in the posterior wall. (D) Lateral angiogram of the left internal carotid artery 6 months after treatment with Pipeline. Complete occlusion of both the fusiform aneurysm and small saccular aneurysm was observed.

platelet aggregation test. We increase the drug dose or change the drug to a substitute drug in low responders to clopidogrel, but have never used flow diverters in clearly low responders to aspirin. Dual-antiplatelet therapy (aspirin and clopidogrel) is continued for 6 months, and changed to therapy with aspirin alone, depending on the aneurysm occlusion status. We recommend lifelong aspirin administration with a reduction in its dose from 325 to 81 mg (baby aspirin) 1 year after flow diverter placement.

The problem in the use of antiplatelet drugs is hemorrhagic complications. Long-term dual-antiplatelet therapy can delay the process from aneurysm thrombosis to complete healing, and therefore, tailored decisions depending on each patient are necessary. In our hospital, of 113 patients who underwent flow diverter placement, two patients showed intraparenchymal hemorrhage probably associated with the use of antiplatelet agents. Hemorrhage was observed on the flow diverter placement side in one patient, and on the

opposite side in the other, and the outcome was mRS6 in one of them. We also evaluated the association between intracranial hemorrhagic complications and platelet aggregation, but observed no definite association. However, in all patients with severe intracranial hemorrhage excluding those with subarachnoid hemorrhage, certain systemic hemorrhagic adverse events such as hematoma formation at the puncture site or gastrointestinal hemorrhage also occurred ($p < 0.01$). Further evaluation in additional cases is necessary.

Next-generation Devices

With the advent of various flow diverters such as Pipeline 1, Pipeline 2, Pipeline Flex, Surpass, and FRED, the surface coverage rate gradually increased. This increases flow diversion effects, but there is a certain correlation between the surface coverage rate and thrombosis in the stent.¹¹⁾ In such a circumstance, there are attempts to reduce dependence on

antiplatelet agents by changing the biocompatibility of the metal surface using technology such as coating. One of them is the Pipeline Flex Shield. In an in vitro experiment, wire constituting the Pipeline was coated with phosphorylcholine mimicking cell membrane components (Shield technology), resulting in a decrease in thrombogenicity.¹¹⁾ The thickness of the coating using Shield technology is only 3 nm, which does not affect device placement and behavior. In March 2015, the Pipeline Flex Embolization Device with Shield Technology Clinical Study as a prospective single-arm observational trial in 50 patients was initiated in Europe, and case registration was already completed. The primary endpoint of the trial is the safety of Pipeline Shield with dual-antiplatelet therapy. The initial analysis results were reported in a scientific meeting in Europe. Compared with the existing Pipeline Flex, no harmful influences of Shield technology were reported.

Increasing the surface coverage of flow diverters while reducing thrombogenicity and dependence on antiplatelet drugs will improve both clinical and angiographic outcomes of flow diverter treatment. Such marked improvement in next-generation devices will further expand the role of flow diverter in the treatment of intracranial aneurysms.

Summary

Steady accumulation of clinical experience has allowed flow diverter treatment to acquire a certain position as a choice for treating aneurysms. In Western countries, various next-generation devices have been developed while trials such as the FIAT and PREMIER to determine real indications for treatment with flow diverters were initiated. In Japan, treatment indications for flow diverters should also be strictly observed, and in patients requiring off-label uses, evidence based on the literature or medical rationale should be clarified, and clinical data tolerable for future evaluation should be collected.

Disclosure of Personal Conflicts of Interest (2015–2016)

Consultant: Medtronic/Covidien/ev3 Neurovascular, Stryker Neurovascular, Blockade Medical, Penumbra Inc., Century Medical Inc., Reverse Medical/Medtronic, Lazarus Effect/Medtronic, Silkroad Medical

Proctor: Pipeline Flex/Pipeline2, Medtronic/Covidien/ev3 Neurovascular

Advisory board: PulsarVascular

Research instrument support: Medtronic/Covidien/ev3 Neurovascular

Disclosure of Institutional Conflicts of Interest (2015–2016)

Fellowship program support: Medtronic/Covidien/ev3 Neurovascular, Codman, Microvention/Terumo

References

- 1) Leonardi M, Cirillo L, Toni F, et al: Treatment of intracranial aneurysms using flow-diverting silk stents (BALT): a single centre experience. *Interv Neuroradiol* 2011; 17: 306–315.
- 2) Nelson PK, Lylyk P, Szikora I, et al: The pipeline embolization device for the intracranial treatment of aneurysms trial. *AJNR Am J Neuroradiol* 2011; 32: 34–40.
- 3) Briganti F, Leone G, Marseglia M, et al: p64 Flow Modulation Device in the treatment of intracranial aneurysms: initial experience and technical aspects. *J Neurointerv Surg* 2016; 8: 173–180.
- 4) Kocer N, Islak C, Kizilkilic O, et al: Flow Re-direction Endoluminal Device in treatment of cerebral aneurysms: initial experience with short-term follow-up results. *J Neurosurg* 2014; 120: 1158–1171.
- 5) De Vries J, Boogaarts J, Van Norden A, et al: New generation of Flow Diverter (surpass) for unruptured intracranial aneurysms: a prospective single-center study in 37 patients. *Stroke* 2013; 44: 1567–1577.
- 6) Becske T, Kallmes DF, Saatci I, et al: Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. *Radiology* 2013; 267: 858–868.
- 7) Raychev R, Tateshima S, Vinuela F, et al: Predictors of thrombotic complications and mass effect exacerbation after pipeline embolization: The significance of adenosine diphosphate inhibition, fluoroscopy time, and aneurysm size. *Interv Neuroradiol* 2016; 22: 34–41.
- 8) Kallmes DF, Hanel R, Lopes D, et al: International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. *AJNR Am J Neuroradiol* 2015; 36: 108–115.
- 9) Takemoto K, Tateshima S, Golshan A, et al: Endovascular treatment of pediatric intracranial aneurysms: a retrospective study of 35 aneurysms. *J Neurointerv Surg* 2014; 6: 432–438.
- 10) Raymond J, Darsaut TE, Guilbert F, et al: Flow diversion in aneurysms trial: the design of the FIAT study. *Interv Neuroradiol* 2011; 17: 147–153.
- 11) Girdhar G, Li J, Kostousov L, et al: In-vitro thrombogenicity assessment of flow diversion and aneurysm bridging devices. *J Thromb Thrombolysis* 2015; 40: 437–443.