Angioplasty and Stenting for Intracranial Atherosclerosis with the Wingspan System: Long-term Clinical and Radiological Outcome

Yoshitaka Suda,1 Kouki Iwaya,1 Kenji Kikuchi,1 Kouhei Kokubun,2 and Hiroaki Shimizu2

Objective: We examined the long-term incidence of in-stent restenosis (ISR) on angiographic follow-up and ipsilateral ischemic events after Wingspan stenting for intracranial arterial stenosis.

Methods: Between July 2014 and September 2015, patients who underwent Wingspan treatment at our institution and have been followed for more than 1 year were retrospectively analyzed.

Results: In all, 13 lesions of 12 patients (average age, 67.1 years; 9 men) were enrolled. Target lesions involved nine internal carotid, three middle cerebral, and one vertebral artery. Wingspan was successfully placed in all 13 lesions. Pretreatment stenosis was 79.7 ± 9.3% (mean ± SD), which improved to 20.8 ± 9.6% after stent placement (p < 0.001). There was one temporary periprocedural neurological complication and no ischemic stroke in follow-up (mean follow-up: 20.4 months). At 3–6 months, aggravation of the stenosis occurred in seven patients; however, all lesions improved 1 year later. As a result, ISR was demonstrated in one patient (8.3%).

Conclusion: One-year clinical and angiographic outcomes of Wingspan stenting were promising for intracranial atherosclerotic diseases.

Keywords ▶ intracranial atherosclerotic disease, percutaneous transluminal angioplasty/angioplasty, Wingspan stent, in-stent restenosis

Introduction

Symptomatic intracranial atherosclerotic arterial stenosis is associated with a high stroke recurrence rate of 12%–15% per year even under recent advancement of medical management1–3) and is still refractory to treatment. Scientific evidence of endovascular treatment for stenotic lesions is considered insufficient in the Japanese guidelines for the management of stroke 2015 (grade C1).4) but percutaneous transluminal angioplasty (PTA) has been performed in some patients to relieve intracranial arterial stenosis. Because of the frequent occurrence of elastic recoil and restenosis after the PTA, coronary stents, which are balloon-dilating types, have been used in an off-label fashion. Their navigation into intracranial vessels, however, was difficult due to rigidity of the shaft.

The Wingspan stent system (Stryker, Kalamazoo, MI, USA) is a self-expandable intracranial arterial stent for arteriosclerosis. Although it initially showed favorable treatment results5,6) the subsequent SAMMPRIS study2,3) reported a significantly higher complication rate in the stent group compared to the best medical treatment group. Therefore, in Japan, its application became possible in July 2014 with restriction of its indications to a rescue stenting for post-PTA vascular dissection and acute occlusion and post-PTA restenosis.7) In this study, we evaluated the long-term efficacy and safety of Wingspan stent placement following such indications.
Subjects and Methods

In all, 13 consecutive patients with 14 lesions underwent Wingspan stent placement in our department between July 2014 and October 2016. Among them, 12 patients with 13 lesions who had been followed up more than 1 year were enrolled in this study.

Indications of PTA and stenting

The basic policy concerning PTA for atherosclerotic intracranial arterial stenosis in our department is as follows. PTA was indicated for ≥70% stenosis by the Warfarin–aspirin symptomatic intracranial disease (WASID) method when ischemic symptoms remained to occur under optimal medical treatments or when the resting cerebral blood flow in the areas peripheral to the stenotic lesion measured by 123I-IMP single photon emission computed tomography (SPECT) was 34 mL/100 g/min or less, and the cerebrovascular reserve capacity measured by acetazolamide loading was +10% or less (a state called misery perfusion or hemodynamic compromise).8)

The Wingspan was used as a rescue stenting in cases of vascular dissection or acute/impending occlusion caused by PTA, or acute restenosis after PTA judged to have no other effective treatment. The decision was made by consulting to a stroke specialist who was not in charge of the endovascular treatment. These policies were in accordance with the Guidelines for the proper use of intracranial arterial stents (for arteriosclerosis) by three relevant Japanese societies (Japan Stroke Society, Japan Neurosurgical Society, and Japanese Society for Neuroendovascular Therapy).7)

Wingspan stent placement protocol

The angiographic systems used were Allura Xper FD 20 (Philips Medical Systems, the Netherlands) with a precise angiometric function and, after December 2015, Allura Clarity FD20/15 Biplane. The approach was via the femoral artery, but if access by this route was difficult, transbrachial artery approach or direct puncture of the common carotid artery was selected, and PTA was performed after prolonging the ACT 2–3 times compared with the preprocedural level. Following the approval of the Wingspan, PTA was performed using a coaxial system consisting of SHUTTLE 6 Fr (Cook Medical, Bloomington, IN, USA) or CELLO 9 Fr (Fuji Systems Corporation, Tokyo, Japan) and Asahi Fubuki 6 Fr (Asahi Intecc, Aichi, Japan). After Excelsior SL-10 (Striker, Kalamazoo, MI, USA) and Asahi Chikai 0.014” (Asahi Intecc) were advanced across the lesion, the microcatheter was guided as distally as possible and replaced with a 300-cm guidewire to increase the support force. The Gateway PTA balloon catheter (Stryker) had a diameter of 80% of the normal blood vessel or less and a size sufficient to cover the entire length of the lesion.5,9) The lesions were slowly compressed at a pressure of 6 atmospheres or less in the intradural arteries. If rescue was necessary, the Gateway was withdrawn, and the Wingspan was guided along the guidewire. A device that had a diameter 0.3–0.9 mm greater than the normal blood vessel and could cover 3 mm or more of the normal parts on both sides of the lesion5) was selected. Post-dilatation was not performed, in principle.

Although an antiplatelet agent had already been administered, dual-antiplatelet therapy (DAPT) with 100 mg aspirin and 75 mg clopidogrel was performed for 7 days or longer before treatment, continued for 6 months after treatment, and, then, replaced with clopidogrel alone. In patients under anticoagulant therapy or oral clostazol therapy, this therapy was also continued for 1 month after treatment, and continuous intravenous injection of argatroban (60 mg/24 hours) was performed for 48 hours after treatment. The efficacy evaluation of antiplatelets was not performed. Noninvasive continuous monitoring of cerebral oxygen saturation was performed in all patients, and general anesthesia was employed as much as possible for safe respiratory and circulatory management, but local anesthesia was also permitted for intracranial extradural lesions with no reduction in the cerebral circulation reserve.

Postprocedural follow-up

The presence or absence of cerebral infarction was checked by MRI diffusion-weighted imaging (DWI) within 48 hours after the procedure. Neurological evaluation and CT or MRI were carried out 3 months, 6 months, and 1 year after the procedure with angiography as much as possible. In-stent restenosis (ISR) was defined as the concurrence of WASID 50% or severer stenosis compared with the normal vascular diameter and 20% or severer luminal loss compared with the state immediately after the procedure.10) The morphology of ISR was evaluated using a modified Mehran classification.11,12)

Evaluation items

The study design was retrospective, and the evaluation items were the periprocedural results (procedure, all strokes, outcome) and results after the periprocedural period (recurrence rate of cerebral infarction in the territory of the treated lesion, the microcatheter was guided as distally as possible and replaced with a 300-cm guidewire to increase the support force. The Gateway PTA balloon catheter (Stryker) had a diameter of 80% of the normal blood vessel or less and a size sufficient to cover the entire length of the lesion.5,9) The lesions were slowly compressed at a pressure of 6 atmospheres or less in the intradural arteries. If rescue was necessary, the Gateway was withdrawn, and the Wingspan was guided along the guidewire. A device that had a diameter 0.3–0.9 mm greater than the normal blood vessel and could cover 3 mm or more of the normal parts on both sides of the lesion5) was selected. Post-dilatation was not performed, in principle.

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vessel, change in percent stenosis and incidence of restenosis, activity of daily living (ADL). The percentages of stenosis before and after treatment and during follow-up were compared using the paired Student’s t-test, and p < 0.05 was regarded as statistically significant. The ADL was evaluated using the modified Rankin Scale (mRS).

### Results

The results are summarized in Tables 1 and 2.

#### Patient background

The patients were aged 51–84 years with a mean of 67.1 years and consisted of nine males and three females. The follow-up period was 12–25 months with a mean of 20.4 ± 3.7 months (mean ± standard deviation [SD]). The site of stenosis was the middle cerebral artery (M1) in three patients, intracranial internal carotid artery in eight patients (nine lesions including two in the intradural C2), and vertebral artery (V4) in one patient.

All patients had hypertension, diabetes, or dyslipidemia and were receiving drug therapy, and 11 patients (92%) had two or more of these underlying disorders. Eight patients (67%) had stenotic lesions in the head and neck region and intracranial vessels other than the lesions treated with the Wingspan and exhibited symptoms of cerebral ischemia, and three of them had previously undergone carotid artery stenting or intracranial stenting (coronary stent). In Case 4, the hemodynamic compromise was difficult to demonstrate, but PTA was performed to avoid the risk of cerebral ischemia associated with open-heart surgery due to the occlusion of the contralateral vertebral artery (VA). With the above background, the preprocedural mRS score was 0 in seven patients and 1 in five patients.

Wingspan stent placement was performed for four lesions of dissection, three lesions of impending occlusion, and six lesions for re-treatment after PTA. Only Case 12 underwent Wingspan stent placement with a percent stenosis of ≤70%, but the treatment was selected due to exacerbation of the percent stenosis from 19% to 58% in 1 month.

#### Periprocedural results

The stents could be placed successfully in all patients. The mean percent stenosis improved significantly from 79.7 ± 9.3% before treatment to 20.8 ± 9.6% immediately after treatment (t-test, p < 0.001) (Fig. 1). No complicating hemorrhagic or permanent ischemic cerebral vascular disorder was noted. Postprocedural DWI showed acute period...
<table>
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<tr>
<th>Case no</th>
<th>Lesion location/Length</th>
<th>Lesion characteristics</th>
<th>Wingspan indication</th>
<th>Wingspan size (mm)</th>
<th>DWI (&lt; 72 hour) high signal</th>
<th>Percentage stenosis (WASID)</th>
<th>mRS (month)</th>
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Average: 79.7, 20.8, 33.6, 31.4, 27.3

Standard deviation: 9.3, 9.6, 21.7, 19.6, 18.4

DWI: diffusion-weighted imaging; mRS: modified Rankin Scale; WASID: Warfarin–aspirin symptomatic intracranial disease; IC: internal carotid artery
Wingspan Stenting for Intracranial Atherosclerosis

After a mean follow-up period of 20.4 ± 3.7 months, none showed recurrence of cerebral infarction or transient ischemic attack (TIA) or exacerbation of the mRS score. Restenosis (Fig. 1) Angiography was performed in 11 patients with 12 lesions except for one patient who rejected the examination due to old age (Case 2). It was performed at 3 months for 6 lesions, at 6 months for 10 lesions (at both 3 and 6 months for 6 lesions), and at 1 year for 12 lesions.

The percent stenosis increased at 3 months (33.6 ± 21.7%, p = 0.20) and at 6 months (31.4 ± 19.6%, p = 0.15) compared with the value immediately after stenting (neither difference was significant). Exacerbation of stenosis was seen in seven lesions (7/11, 64%) temporarily at 3–6 months; however, all these improved at 1 year. The vascular lumen was dilated at 1 year compared with the state immediately after the procedure in six lesions (6/12, 50%). At all points of measurement, the vascular lumen was dilated significantly compared with the state before stenting (p < 0.004 at 3 months, p < 0.001 at 6 months, and 1 year). ISR at 3 months was observed in diffuse hyperintensities in five patients (42%). All hyperintensities were spots of 3 mm or less in diameter, and they were asymptomatic in four patients. In one patient (Case 5), who showed 10 hyperintensity spots after the Wingspan stenting through a direct puncture with post-dilatation, impairment of skilled movements of the right fingers appeared and disappeared on the next day. In this patient, the risk of embolization may have been increased because the above procedure was carried out simultaneously with the placement of two Carotid Wallstents (Boston Scientific, Natick, MA, USA) under filter protection for complicating ipsilateral cervical internal carotid artery stenoses.

In the six patients with hemodynamic compromise, no abnormal elevation of the regional saturation of brain oxygen was noted immediately after stenting, suggesting no evidence of hyperperfusion. None of the patients developed de novo neurological symptoms, and the mRS score at discharge was the same as the preprocedural score.

Long-term results

Medication was reduced to clopidogrel alone 6 months after stenting in 11 patients, but DAPT was continued until after 1 year in one patient who suffered ISR (Case 11). After a mean follow-up period of 20.4 ± 3.7 months, none showed recurrence of cerebral infarction or transient ischemic attack (TIA) or exacerbation of the mRS score.

Restenosis (Fig. 1)

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However, while the SAMMPRIS Study\textsuperscript{2,3} was conducted with the aim to expand indications of Wingspan, the intention was betrayed by the rejection of the usefulness of PTA and stenting (PTAS). The frequency of stroke or death during 1 year was significantly higher in the PTAS group, and this difference was ascribed primarily to the significant difference during the periprocedural period (5.7% in the internal group and 14.7% in the PTAS group). In this study, however, about three-fourths of the patients in both groups had no history of cerebral infarction, the percentage of patients who were administered antiplatelet agents at the onset was 65% or less, and resistance to drug therapy was not a requirement for enrollment, constituting striking differences of the study population compared with the clinical situation. In addition, the mean period from the onset to PTAS was 7 days, which was markedly shorter than in previous studies,\textsuperscript{5,6} and the results of PTAS performed within 7 days from the onset were extremely poor.\textsuperscript{14} Nevertheless, this study exerted a strong impact, leading to the recommendation in the United States to perform Wingspan stent placement for 70% or severer stenosis more than 7 days after the onset with ischemic stroke not including TIA during internal

Discussion

The Wingspan, a stent system specifically for intracranial use, was originally indicated for severe intracranial atherosclerotic stenotic lesions resisting drug therapy, and favorable results were reported in Western countries.\textsuperscript{5,6} The percent stenosis improved from 74.9% to 31.9%, and the mortality due to ipsilateral stroke was reported to be 4.5% within 30 days and 9.7% within 6 months after the procedure,\textsuperscript{9} which was better than the results in the group treated with coronary stents at a Japanese facility (12.9%).\textsuperscript{13} These results are considered to be due to the high trackability of the Wingspan with a consequent decrease in the risk of complications, and its early approval was also requested in Japan.

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![Image](https://example.com/image1.png)

**Fig. 2** Case 1. (A) A flair image MR showing hyperintensity lesions on the bilateral fronto-parietal deep white matter. (B) MRA showing bilateral M1 stenosis. (C) CBF study reveals hemodynamic compromise on left MCA area. (D) Digital subtraction angiography showing 82.5% stenosis on left MCA: M1 at presenting baseline. (E) Angiogram immediately post-stenting showing favorable dilation (residual stenosis of 13%). (F) Residual focal stenosis of 51.3% that is classified into ISR at 3 months. (G) Residual focal stenosis of 53.8% at 6 months showing no exacerbation. (H) 1-year improvement of residual stenosis (44.3%) showing out of ISR classification. (I) 3-month CBF reveals no hemodynamic compromise. The ends of the stent are indicated by arrowheads. CBF: cerebral blood flow; ISR: in-stent restenosis; MCA: middle cerebral artery; MR: mitral valve regurgitation.
Fig. 3  Case 3. (A) A flair image MR showing hyperintensity lesions on the right prefrontal lobe. (B) CBF study reveals stage II hemodynamic ischemia on right MCA area. (C) Digital subtraction angiography showing 80% stenosis on right MCA: M1 at presenting baseline. (D) Angiogram immediately post-stenting showing favorable dilatation (residual stenosis of 5%). (E) Residual stenosis of 11.1% at 3 months. (F) Residual stenosis of 3.3% at 6 months showing further improvement. (G) There is no residual stenosis, indicating luminal gain 1 year after stenting. (H) 3-month CBF study reveals no hemodynamic compromise. CBF: cerebral blood flow; ISR: in-stent restenosis; MCA: middle cerebral artery; MR: mitral valve regurgitation.

Fig. 4  Case 9. (A) Angiogram after initial PTA for symptomatic left M1 severe stenosis. (B) 13-month follow-up angiogram showing severer restenosis than the pre-PTA baseline. (C) Angiogram immediately post-stenting showing favorable dilatation (residual stenosis of 34.8%). (D) Residual stenosis of 30% at 6 months. (E) There is no exacerbation at 1 year. PTA: percutaneous transluminal angioplasty.
In Japan, the use of Wingspan began in July 2014 under strict guidelines restricting the use of the device for rescue stenting in the event of vascular dissection and acute or impending occlusion occurring during PTA and retreatment after PTA without other treatment options and requiring consultation with specialists not in charge of treatment. The significance of reporting long-term results of Wingspan stent placement performed for indications in Japan after the SAMMPRIS study is considered great.

Occlusion of adjacent penetrating branches by plaque fragmented during PTA and mechanical obstruction by the stent struts are known as ischemic complications of PTAS in the territory of the penetrating branches, but no reliable preventive measures against them are available at present. Therefore, only 36.6% of the stenoses of the middle cerebral artery (MCA) and basilar artery (BA) involving the penetrating branches are treated in Japan. We also treated only three such lesions (23.1%) in the present study. However, in the SAMMPRIS study, the lesions in the MCA and BA accounted for 63% unlike previous reports. This may have caused the high frequency of penetrating branch occlusion among the surgical complications.

The narrowness of the struts is an advantage of the Wingspan compared with coronary stents, but careful application remains necessary in relation to such penetrating branches. Intracranial stenotic lesions showing hemodynamic compromise are reported to be resistant to drug therapy resulting in stroke recurrence rate of 30% per year. Therefore, they may be considered a good candidate for PTA. In the present study, three patients with MCA stenosis demonstrated hemodynamic compromise by SPECT.

The SAMMPRIS study suggested that stenting should be avoided during the acute period, in which the drug effect is still insufficient, or if vulnerable plaque is suspected.

According to previous reports, ISR was observed in 24%–35% of the patients but the mean follow-up period was 8 months in many of these reports and 2–3 months in some. In our study, on serial evaluations until 1 year after the procedure, the percent stenosis increased at 3–6 months compared with the state immediately after the procedure in seven lesions (7/11, 64%) but decreased at 1 year (3M vs. 1Y: p = 0.080, 6M vs. 1Y: p = 0.085), and the luminal diameter was increased at 1 year compared with the state immediately after the procedure in six lesions (6/12, 50%). As a result, ISR was observed in two lesions at 3–6 months but only one lesion (8.3%) at 1 year.

Concerning the intimal repair after bare metal stent placement in the coronary artery, the stent surface was reportedly stabilized as it was covered by smooth muscles and proliferating endothelial cells at 3 months. However, such intimal proliferation regressed in the subsequent course of 6 months. There is also a report that in-stent stenosis of a nitinol stent, which was similar to the Wingspan, placed in an intracranial vessel regressed spontaneously after 9 months.

The results of our study suggest that intimal thickening, which is a major cause of ISR, was also stabilized in intracranial arteries at around 3–6 months and regressed spontaneously thereafter. Therefore, 1 year is considered to be an appropriate timing for the final and long-term diagnosis of ISR.

Yu et al., who also evaluated ISR after 1 year, recently reported that ISR was observed in 16.7% and that the vascular lumen was dilated compared with the state immediately after stenting in 48% of the patients, supporting our findings. Also, in their report, the percentage of patients with MCA and BA stenosis involving the penetrating branches was very high at 66.6%, but no cerebral infarction was observed for 1 year after the periprocedural period with 3-month DAPT followed by the administration of aspirin alone. Wang et al. also reported that the frequency of ipsilateral cerebral infarction in 168 patients with MCA stenosis was very low at 4.8% on a long-term follow-up with a mean duration of 30 months. We performed DAPT for 6 months and noted no cerebral infarction or asymptomatic cerebral infarction on imaging studies during a mean follow-up period of 20.4 months. Therefore, the possibility of cerebral infarction during the chronic period including penetrating branch occlusion is considered extremely low.

Characteristics of ISR are reported to be a high frequency of localized stenosis in the stent and risk factors such as a patient age of under 55 years, anterior circulation (suprasellar region, in particular), small vascular diameter, and diabetes. In our study, the patient who suffered ISR after 1 year was aged 51 years, had a lesion in the C1-2 of the internal carotid artery, and was diabetic, showing features consistent with previous reports, but poor control of the blood sugar level for 1 year after treatment with a hemoglobin A1c (HbA1c) level of about 8% may have further increased the risk of ISR.

Limitations of this study include a retrospective investigation at a single institution and the statistical power might be insufficient due to the small number of patients. Comparative evaluation between patients treated with a coronary and by the Wingspan stents by the same surgeon may better highlight clinical characteristics of the Wingspan.
**Conclusion**

The early and long-term results of Wingspan stent placement according to indications in Japan were satisfactory. While in-stent stenosis was temporarily noted after 3–6 months, it was resolved spontaneously thereafter.

**Disclosure Statement**

Neither the first author nor any of the coauthors have any conflicts of interest to disclose.

**References**


