Original Article doi: 10.2176/nmc.oa.2019-0271

Neurol Med Chir (Tokyo) 60, 256–263, 2020 Online April 15, 2020

Endovascular Therapy for Intracranial Artery Stenosis: Results from the Japanese Registry of Neuroendovascular Therapy (JR-NET)3

Takashi Izumi,[1] Masahiro Nishibori,[1] Hirotoshi Imamura,[2] Koji Iihara,[3] Nobuyuki Sakai,[2] and JR-NET investigators

[1]*Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan;*
[2]*Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan;*
[3]*Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan*

Abstract

A total of 907 patients enrolled in the Japanese Registry of Neuroendovascular Therapy (JR-NET)3, a surveillance study in Japan, who underwent intracranial percutaneous transluminal angioplasty (PTA)/stenting for intracranial stenosis during the period from 2010 to 2014 were investigated. Technical success was achieved in 97.5% of the patients, and 6.8% had a residual stenosis of ≥50%. The incidence rates of ischemic and hemorrhagic complications were as low as 5.3% and 3.1%, respectively, and the mortality rate was 1.9%. However, the mortality rate of cases with either complications was higher at 10.7%. About half of the treatment cases were performed between 24 h and 14 days after onset, and the incidence of perioperative complications was similar to that after at least 15 days. Although it is necessary to verify the effectiveness of PTA/stenting within 14 days, the results of this treatment were stable regardless of the intervention period.

Key words: intracranial stenosis, angioplasty, stenting

Introduction

In Asian countries, patients who often presented with frequent or crescendo transient ischemic attacks (TIAs) constituted a high proportion of symptomatic intracranial artery stenosis (ICAS), which is one of the significant pathological causes of ischemic cerebrovascular disorders. Particularly, 28% of atherothrombotic cerebral infarctions have severe intracranial artery stenosis or occlusion in Japan.[1)] In a WASID trial for patients with symptomatic stenosis of 50–99% in the cerebral large vessels, medical management reveals that 22% of composite endpoints, including cerebral infarction, occurred.[2)] In Japan, angioplasty has been used for intracranial stenosis treatment, primarily for intracranial stenosis refractory to medical therapy. Since no stent was specifically designed for the intracranial arteries before, treatment is often completed with balloon angioplasty alone, and stenting using a coronary stent is applied only in limited situations such as dissection after balloon angioplasty or restenosis. The Wingspan stent developed for the intracranial artery was approved in the US in 2005.

The SAMMPRIS study, a randomized trial published in 2011, was discontinued because the stenting group was clearly inferior to the aggressive medical management group.[3)] Because of that, when the Wingspan stent was approved in Japan in 2013, the purpose of use was set as rescue treatment for vascular dissociation, acute occlusion, and imminent occlusion after angioplasty and re-treatment after angioplasty. The Japan Stroke Guidelines 2015 considers percutaneous transluminal angioplasty (PTA) and stent placement as insufficient scientific basis.[4)] The Japanese Registry of Neuroendovascular Therapy (JR-NET)/JR-NET2 study was conducted from 2005 to 2009

Received December 9, 2019; Accepted February 25, 2020

for all intracranial therapies conducted in Japan, and the ischemic and hemorrhagic complication rates within 30 days after PTA/stenting for ICAS were 6.6% and 2.4%, respectively.[5] The JR-NET3 is a retrospective registration survey conducted in Japan from 2010 to 2014. In this study, we report on the results of the JR-NET3 with analysis and consideration.

Materials and Methods

Of the 1047 cases that were registered as intracranial PTA/stenting in the JR-NET3 from January 2010 to December 2014, 909 were designated as the target disease, i.e., ICAS. Two cases that were treated simultaneously for acute cerebral artery occlusion were excluded, and the remaining were included in the analysis.

Data files from the JR-NET3 were used to determine correlations between differences in the baseline characteristics of patients, procedures, or perioperative management and the occurrence of hemorrhagic or ischemic complications in a retrospective manner. Items that were not entered were treated as unknown and analyzed. Statistical analysis was performed by the Chi-square test using Excel Statistics.

Results

The baseline characteristics of patients, lesion profile, treatment situation, treatment, treatment outcome, and complications are shown in Table 1.

The mean age was 66.8 (17–93) years, and the proportion of male participants was as high as 77.4%. At baseline, the mean modified Rankin scale (mRS) was 0.65, and patients with a mRS of 0–2 accounted for 91.2%. Of all patients, 25.1% received treatment under general anesthesia. The treatment timing was highest in 54.2% within 14 days after 24 h and 26.1% within 24 h. A stent was used during the procedure in 43.9% of cases. The most common preoperative antiplatelet treatment was treatment with two agents in 72.7%, followed by that with three agents in 16.0%. While the most common postoperative antithrombotic agents were argatroban and heparin in 37.8% and 11.6%, respectively, no postoperative antithrombotic treatment was performed in 38.3%. Technical success was achieved in 97.5%, and 67.6% and 6.8% had a residual stenosis of <30% and ≥50%, respectively. The incidence rates of ischemic and hemorrhagic complications were 5.3% and 3.1%, respectively, and no complication of both was noted. Therefore, within 30 days after surgery, the incidence

Table 1 Characteristics of 907 patients

Patient characteristics	
Baseline characteristics of patients	
Age	Mean, 68.3 (17–93) years
Sex	Male, 77.4
mRS	Mean, 0.65
mRS 0–2	91.2%
Lesion profile	
Region	IC (intracranial epidural), 37.0%; IC (intradural), 9.4; MCA, 22.5%; VA, 13.8; BA, 12.6%; multiple, 3.7%; other, 0.6%; unknown, 0.6%
Symptom at diagnosis	Asymptomatic, 18.2%; amaurosis, 1.4%; TIA (cerebrum), 15.1%; minor stroke, 40.8%; major stroke, 13.1%; others, 0.1%; unknown, 1.1%
	Nonprogressively symptomatic, 85.9%; progressively symptomatic, 14.1%
Timing of treatment (only symptomatic patients)	Within 24 h, 26.1%; within 14 days after 24 h, 54.2%; after at least 15 days, 19.8%
Percent diameter stenosis	<50%, 1.8%; 50–60%, 5.6%; 60–70%, 10.0%; 70–80%, 27.5%
Lesion length	<5 mm, 16.9%; 5–10 mm, 51.4%; 10–15 mm, 20.8%; ≥15 mm, 6.0%; unknown, 5.0%
Normal vascular diameter	<2 mm, 4.3%; 2–2.5 mm, 17.0%; 2.5–3 mm, 21.7%; 3–3.5 mm, 23.5%
Pathology	Arteriosclerosis, 93.5%; traumatic dissection, 0%; iatrogenic dissection, 0.4%
Refractory to medical therapy	43.3%

(*Continued*)

Table 1 (Continued)

Patient characteristics	
Treatment situation	
Assessment of cerebral blood flow	55.3%
Emergency treatment	22.1%
Treatment at another hospital	2.8%
Investigator	Supervisory physician, 50.3%; specialist, 43.4%; nonspecialist, 6.3%
Scrub-in of supervisory physician	64.5%
No. of scrub-in supervisory physicians and specialists	1, 36.4%; 2, 39.0%; ≥3, 24.4%
General anesthesia	25.1%
Treatment	
Stenting	Yes, 43.9%
Stent type	Coronary, 74.6%; self-expandable, 15.8%; combination, 3.0%; other, 0.6%; unknown, 0.8%
Presence of post-dilatation	27.8%
Stent + presence of post-dilatation	32.7%
Preoperative antiplatelet treatment	No, 3.9%; one agent, 8.8; two agents, 70.0%; three agents, 15.7% unknown, 1.2%
Postoperative antiplatelet treatment	No, 1.8%; one agent, 6.7%; two agents, 72.7%; three agents, 16.0%
Postoperative antiplatelet treatment	No, 38.3%; heparin, 11.6%; argatroban, 37.8%; ozagrel, 4.4%; combination, 3.2%; unknown, 0.2%
Other concurrent treatment	8.7%
Treatment outcome	
Technical success	97.5%
Residual stenosis immediately after treatment	<30%, 67.6%; 30–50%, 22.4%; ≥50%, 6.8%
Hemorrhagic complication	3.1%
Ischemic complication	5.3%
mRS at 30 days postoperatively	Mean, 1.35
Mortality	1.9%

BA: basilar artery, IC: internal cerebral artery, MCA: middle cerebral artery, mRS: modified Rankin scale, TIA: transient ischemic attack, VA: vertebral artery.

rate of hemorrhagic and ischemic complications was 8.4%. Furthermore, the incidence rate of hyperperfusion syndrome was 1.2%, and most occurred during treatment and within 24 h. The treatment timing for patients with hyperperfusion syndrome was as low as one case within 24 h after onset, six cases within 14 days after 24 h, and one case after 15 days. At 30 days postoperatively, the mean mRS and mortality were 1.35% and 1.9%, respectively.

Ischemic and hemorrhagic complications are listed in Table 2. The most common ischemic complication was distal embolization (2.1%), followed by vascular dissection (0.7%). On the other hand, vessel perforation (0.9%) and vascular rupture and dissection (0.8%), retrospectively, were the most common hemorrhagic complications.

The correlation between each factor tested and ischemic complications is shown in Table 3. The following factors were significantly correlated with ischemic complications: mRS 3 or more at baseline, VA or BA stenosis, stenosis of 80–90%, idiopathic stenosis, postoperative antithrombotic treatment with ozagrel, no assessment of the cerebral blood flow, general anesthesia, and residual stenosis of 30–50% (Table 4).

The correlation between each factor tested and hemorrhagic complications is shown in Table 5. The following factors were significantly correlated with hemorrhagic complications: progressively symptomatic, stenosis of 70–80%, 10–15-mm lesion length, stent use, preoperative antiplatelet treatment with three agents, no postoperative antiplatelet treatment, and

Table 2 Details of ischemic and hemorrhagic complications

Ischemic complication	Total	Incidence (%)
Distal embolization	19	2.1
Vascular dissection	6	0.7
Acute obstruction	5	0.6
Other	9	1.0
Unknown	9	1.0
Total	48	5.3
Hemorrhagic complication	Total	Incidence (%)
Vessel perforation	8*	0.9
Vascular rupture	7	0.8
Vascular dissection	7	0.8
Hyperperfusion	2*	0.2
Other	4	0.4
Unknown	1	0.4
Total	28	3.1

*One case has both vessel parforation and hyperperfusion.

residual stenosis of ≥50%. The mortality rates of patients with ischemic and hemorrhagic complications were 6.3% and 10.7%, respectively, which were significantly higher than those without complications (1.6% and 1.6%, P <0.05 and P <0.001).

Discussion

Similar to the previous study (JR-NET/JR-NET2), the survey period of this study was 5 years, but the number of cases decreased considerably from 1103 to 907.

The fact that the SAMMPRIS trial was reported in 2011, which resulted in denying the effectiveness of stenting for symptomatic intracranial stenosis, was thought to have had a significant impact on this decline. The stent usage rate also decreased from 60.6% in the previous study to 43.9%. The fact that Wingspan's indication was limited to cases of dissection or acute occlusion due to balloon dilatation may also be a factor responsible for the decrease in the usage ratio. On the other hand, the percentage

Table 3 Correlation between each factor and ischemic complications

Baseline characteristics of patients	
Age	≤49 years, 5.1%; 50–59 years, 6.3%; 60–69 years, 5.0%; 70–79 years, 5.2%; ≥80 years, 5.8%
Sex	Male, 5.0%; female, 6.4%
mRS	0–2, 4.8%; 3–5, 11.1% (P <0.05)
Lesion profile	
Region	IC (intracranial epidural), 2.7%; IC (intradural), 1.2%; MCA, 4.4%; VA, 9.6%; BA, 12.3%; multiple, 8.8% (*P <0.001)
Symptom at diagnosis	Asymptomatic, 3.0%; symptomatic, 5.7%
	Nonprogressively symptomatic, 5.7%; progressively symptomatic, 5.8%
Timing of treatment (only symptomatic patients)	Within 24 h, 7.5%; within 14 days after 24 h, 5.1%; after at least 15 days, 4.6%
Percent diameter stenosis	<50%, 12.5%; 50–60%, 2.0%; 60–70%, 7.7%; 70–80%, 5.2%; 80–90%, 7.3%; 90–100%, 2.4%; 100%, 8.8% (**P <0.05)
Lesion length	<5 mm, 3.9%; 5–10 mm, 5.6%; 10–15 mm, 6.9%; ≥15 mm, 5.6%
Normal vascular diameter	<2 mm, 2.6%; 2–2.5 mm, 7.1%; 2.5–3 mm, 5.6%; 3–3.5 mm, 7.0%; 3.5–4 mm, 4.0%; ≥4 mm, 3.4%
Pathology	Arteriosclerosis, 4.9%; iatrogenic dissection, 0%; idiopathic dissection, 13.8%; others, 0% (***P <0.05)
Refractory to medical therapy	No, 3.9%; yes, 6.1%
Treatment	
Stenting	No, 5.0%; yes, 5.8%
Stent type	Coronary, 5.4%; self-expandable, 7.9%; other, 9.1%; combination, 0%
Presence or absence of post-dilatation	No, 4.5%; yes, 7.5%
Stent + presence or absence of post-dilatation	No, 5.3%; yes, 6.9%

(*Continued*)

Table 3 (Continued)

Preoperative antiplatelet treatment	No, 11.4%; one agent, 4.3%; two agents, 5.7%; 3 agents, 2.8%
Postoperative antiplatelet treatment	No, 6.3%; one agent, 4.9%; two agents, 5.5%; three agents, 4.8%
Postoperative antithrombotic treatment	No, 3.5%; heparin, 4.8%; argatroban, 5.2%; ozagrel, 25.0%; combination, 6.9% (P <0.00001)
Other concurrent treatment	No, 5.3%; yes, 5.1%
Treatment situation	
Assessment of cerebral blood flow	No, 7.5%; yes, 3.8% (P <0.05)
Emergency treatment	Planned, 5.2%; emergency, 5.5%
Treatment facility	Hospital at work, 5.3%; another hospital, 4.0%
Investigator	Supervisory physician, 5.5%; specialist, 5.1%; nonspecialist, 5.3%
Scrub-in of supervisory physician	No, 4.0%; yes, 6.0%
No. of scrub-in supervisory physicians and specialists	1, 4.2%; 2, 5.6%; ≥3, 6.3%
General anesthesia	Local anesthesia, 4.4%; general anesthesia, 7.9% (P <0.05)
Treatment outcome	
Residual stenosis immediately after treatment	<30%, 4.6%; 30%–50%, 8.9%; ≥50%, 3.2% (***P <0.05)

*Each P-value is shown in Table 4. **80–90% vs. 90–100%, P <0.05; Arteriosclerosis vs. idiopathic dissection, P <0.05. ***<30% vs. 30–50%, P <0.05.

Table 4 Correlation between the region of stenosis and ischemic complications

	Ischemic complication		Total	Incidence (%)	P-value				
	(–)	(+)							
IC (intracranial epidural)	326	9	335	2.7%	n.s.	<0.0001	<0.01	n.s.	n.s.
IC (intradural)	84	1	85	1.2%	n.s.	<0.01	<0.05	n.s.	*
MCA	195	9	204	4.4%	n.s.	<0.01	n.s.	*	
VA	113	12	125	9.6%	n.s.	n.s.	*		
BA	100	14	114	12.3%	n.s.	*			
Multiple	31	3	34	8.8%	*				

*Control. n.s.: no significant.

Table 5 Correlation between each factor and hemorrhagic complications

Baseline characteristics of patients	
Age	≤49 years, 0%; 50–59 years, 3.1%; 60–69 years, 4.3%; 70–79 years, 2.4%; ≥80 years, 3.8%
Sex	Male, 3.1%; female, 3.0%
mRS	0–2, 2.9%; 3–5, 5.6%
Lesion profile	
Region	IC (intracranial epidural), 2.7%; IC (intradural), 0%; MCA, 3.9%; VA, 4.8%; BA, 4.4%; multiple, 0%
Symptom at diagnosis	Asymptomatic, 1.8%; symptomatic, 3.4%
	Nonprogressively symptomatic, 2.9%; progressively symptomatic, 6.8% (P <0.05)
Timing of treatment (only symptomatic patients)	Within 24 h, 4.0%; within 14 days after 24 h, 3.6%; after at least 15 days, 1.3%

(*Continued*)

Table 5 (Continued)

Percent diameter stenosis	<50%, 0%; 50–60%, 2.0%; 60–70%, 1.1%; 70–80%, 6.0%; 80–90%, 2.1%; 90–100%, 2.0%; 100%, 5.9% ($^{*}P$ <0.05)
Lesion length	<5 mm, 1.3%; 5–10 mm, 2.4%; 10–15 mm, 5.8%; ≥15 mm, 3.7% ($^{**}P$ <0.05)
Normal vascular diameter	<2 mm, 2.6%; 2–2.5 mm, 2.6%; 2.5–3 mm, 3.0%; 3–3.5 mm, 4.2%; 3.5–4 mm, 2.7%; ≥4 mm, 2.6%
Pathology	Arteriosclerosis, 3.3%; iatrogenic dissection, 0%; idiopathic dissection, 0%; others, 0%
Refractory to medical therapy	No, 2.5%; yes, 4.1%
Treatment	
Stenting	No, 1.2%; yes, 5.5% (P <0.001)
Stent type	Coronary, 5.4%; self-expandable, 6.3%; combination, 16.7%; other, 0%
Presence or absence of post-dilatation	No, 3.5%; yes, 2.4%
Stent + presence or absence of post-dilatation	No, 6.0%; yes, 4.6%
Preoperative antiplatelet treatment	No, 2.9%; one agent, 0%; two agents, 2.7%; three agents, 5.6% ($^{***}P$ <0.05)
Postoperative antiplatelet treatment	No, 31.2%; one agent, 4.9%; two agents, 1.8%; three agents, 4.1% ($^{****}P$ <0.000000001)
Postoperative antithrombotic treatment	No, 4.6%; heparin, 2.9%; argatroban, 2.3%; ozagrel, 0%; combination, 0%
Other concurrent treatment	No, 3.3%; yes, 1.3%
Treatment situation	
Assessment of cerebral blood flow	No, 2.3%; yes, 3.4%
Emergency treatment	Planned, 3.5%; emergency, 1.5%
Treatment facility	Hospital at work, 3.1%; another hospital, 4.0%
Investigator	Supervisory physician, 3.7%; specialist, 2.8%; nonspecialist, 0%
Scrub-in of supervisory physician	No, 2.8%; yes, 3.2%
No. of scrub-in supervisory physicians and specialists	1, 3.0%; 2, 2.5%; ≥3, 4.1%
General anesthesia	Local anesthesia, 2.8%; general anesthesia, 3.9%
Treatment outcome	
Residual stenosis immediately after treatment	<30%, 3.1%; 30%–50%, 1.0%; ≥50%, 6.4% ($^{*****}P$ <0.05)

*70%–80% vs. 80%–90%, P <0.05; 70%–80% vs. 90%–100%, P <0.05. **<5 vs. 10–15 mm, P <0.05; 5–10 vs. 10–15 mm, P <0.05. ***One vs. three agents, P <0.05. ****No agent vs. one agent, P <0.01; no agent vs. two agents; P <0.000000001; no agent vs. three agents, P <0.0001. *****30–50% vs. ≥50%, P <0.05. BA: basilar artery, IC: internal cerebral artery, MCA: middle cerebral artery, mRS: modified Rankin scale, TIA: transient ischemic attack, VA: vertebral artery.

of treatments within 14 days after onset was as high as 80.3%, a significant increase from 33.5% in the previous study. The reason for this is thought to be the background that mechanical thrombectomy for cerebral infarction associated with main artery occlusion has gradually spread, and doctors have wanted more early intervention to prevent cerebral infarction recurrence. The use of Wingspan for lesions within 14 days of onset is not recommended in Japan and may be a cause for the reduced use of stents.

The incidence rates of ischemic and hemorrhagic complications in 907 angioplasty cases for ICAS in Japan were 5.3% and 3.1%, respectively. It is a major issue to reduce the incidence of complication. The complication rates for JR-NET/JR-NET2 were 7.7% and 2.5%, indicating a decrease in ischemic complications.

The following reasons can be considered for the decrease in the incidence of ischemic complications: the proportion of high-risk posterior circulation decreased from 31% to 26%,[6,7] the administration

rate of two or more antiplatelet drugs increased, and the complication rate of internal carotid artery stenosis decreased significantly. Since the internal carotid artery has no perforators to the brain parenchyma, the risk associated with PTA is assumed to be low. In previous studies, the incidence of cerebral infarction was not low, and it is presumed that the position of ICA contributed to a decrease in the complication rate. Several other items were correlated with ischemic complications in this study. However, all of them showed the opposite trend in the previous study. It is necessary to accumulate further data to know whether those items are true risk factors.

The ratio from onset to treatment within 24 h to 14 days increased rapidly to 54%, but the incidence rate of ischemic complications during this period was 5.1%, almost the same as in the chronic phase. Although early intervention may be able to suppress cerebral infarction recurrence, a report also described that the incidence of restenosis is higher in the group treated within 14 days of onset[8] to determine the optimal treatment intervention time. Therefore, it is considered necessary to analyze both short- and long-term results.

Among the bleeding complications, most were caused by obvious manipulations such as vascular perforation and rupture, and bleeding by other factors such as hyperperfusion syndrome was as low as 0.2%.

In the SAMMPRIS trial using the Wingspan stent, vascular perforation and rupture were reported to occur in 1.3% and 0.5%, respectively, and the cause was reported to be device replacement with a long guidewire and penetration with a guidewire in cases of complete occlusion.[9] Considering that hemorrhagic complications can be fatal, it seemed to be necessary to respond flexibly by discontinuing the procedure and switching to medical treatment for lesions that are difficult to pass by devices or lesions with strong calcification.

No difference was noted in the incidence of hemorrhagic complications with or without the scrubbing of the supervisory physician, but there are also reports of learning curves due to accumulated experience.[10,11] Given the several complications resulting from the manipulation of the procedure, all physicians performing this treatment should particularly pay attention. Stent placement for ICAS was inferior to the medical treatment group in the SAMMPRIS and VISITIT trials, but from Asia, where the prevalence of atherosclerotic cerebral artery stenosis is high, better results have been reported.[12–14] Although the effectiveness of angioplasty for this disease is not yet clear, the most significant point is to select appropriate patients and reduce complications to enhance the therapeutic effect. Patients with hypoperfusion stroke secondary to ICAS who continue to have symptoms despite double antiplatelet therapy, statins, and tight control of hypertension and diabetes mellitus will be a good indication for angioplasty or stenting.[15] In this study, the proportion of patients without ischemic symptoms was 18%, and the effectiveness of this treatment has not been scientifically clarified. When treating patients with asymptomatic stenosis, sufficient consideration should be given to the physicians who are not practicing. To summarize, treatment can be performed relatively safely in cases where the lesion is located in the internal carotid artery stenosis or when the lesion length is less than 10 mm. Patients with pre-onset mRS of 3 or more have a higher complication rate and should be carefully judged for treatment indication. General anesthesia resulted in poor results. Although this study has the limitation that data were collected retrospectively, it is considered to be an important basic data for clinical practice.

Conclusion

In Japan, treatment for angioplasty/stenting for ICAS was safely performed. The number of treatment cases within 14 days after the onset of ischemic symptoms has increased rapidly, and it is considered necessary to verify the effectiveness and safety in the future.

Acknowledgments

We would like to thank Nancy Schatken, BS, MT (ASCP) from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

JR-NET3 Study Group: Co-principal investigators: Nobuyuki Sakai, Kobe City Medical Center General Hospital, Kobe, Japan; Koji Iihara, Kyushu University, Fukuoka, Japan; Tetsu Satow, National Cerebral and Cardiovascular Center, Suita, Japan. Investigators: Masayuki Ezura, Sendai Medical Center, Sendai, Japan; Akio Hyodo, Dokkyo Medical University Saitama Medical Center, Koshigaya, Japan; Shigeru Miyachi, Aichi Medical University, Aichi, Japan; Susumu Miyamoto, Kyoto University, Kyoto, Japan; Yoji Nagai, Kobe University, Kobe, Japan; Kunihiro Nishimura, National Cerebral and Cardiovascular Center, Suita, Japan; Kazunori Toyoda, National Cerebral and Cardiovascular Center, Suita, Japan. Co-investigators: Toshiyuki Fujinaka, Osaka Medical Center, Osaka, Japan; Toshio Higashi, Fukuoka University, Fukuoka, Japan; Masaru Hirohata, Kurume University, Kurume, Japan; Akira Ishii, Kyoto University, Kyoto, Japan; Hirotoshi Imamura, Kobe City Medical Center General

Hospital, Kobe, Japan; Yasushi Ito, Shinrakuen Hospital, Niigata, Japan; Naoya Kuwayama, Toyama University, Toyama, Japan; Hidenori Oishi, Juntendo University, Tokyo, Japan; Yuji Matsumaru, Tsukuba University, Tsukuba, Japan; Yasushi Matsumoto, Konan Hospital, Sendai, Japan; Ichiro Nakahara, Fujita Medical University, Aichi, Japan; Chiaki Sakai, Hyogo College of Medicine, Nishinomiya, Japan; Kenji Sugiu, Okayama University, Okayama, Japan; Tomoaki Terada, Showa University Fujigaoka Hospital, Kanagawa, Japan; Shinichi Yoshimura, Hyogo College of Medicine, Nishinomiya, Japan; and Certified Specialists of Japanese Society of Neuroendovascular Therapy.

Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest except for T. Izumi and N. Sakai. T. Izumi reports nonrelated research grants from Kaneka. N. Sakai reports nonrelated research grants from Terumo and Daiichi-Sankyo, lecturer's fees from Jimro, Otsuka, Johnson & Johnson, Medtronic, Stryker, and Terumo and Medico's Hirata; membership on the advisory boards for Medtronic and Jimro.

All the authors who are members of the Japan Neurosurgical Society (JNS) have registered self-reported conflict of interest disclosure statement forms online through the website for JNS members.

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Address reprint requests to: Takashi Izumi, MD, Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumaicho, Syowa-ku, Nagoya, Aichi 466-0065, Japan.
e-mail: panda_aichi@yahoo.co.jp