Current Status of Endovascular Therapy for Intracranial Artery Stenosis from the Results of a Nationwide Survey

Toshinori Takagi,1 Yasushi Matsumoto,2 Ryo Itabashi,3 Kenichi Sato,2 and Shinichi Yoshimura1

Objective: The purpose of this study was to investigate the current status of treatment for intracranial artery stenosis (ICAS) in Japan.

Methods: A questionnaire was administered to a member of the Japanese Society for Neuroendovascular Therapy (JSNET), and data regarding the number of treatments for ICAS and the treatment strategies employed were collected via e-mail.

Results: Responses were received from 261 hospitals (25.8%) with JSNET members. From January 1 to December 31, 2017, the number of endovascular treatments for ICAS was 783. Among them, symptomatic lesions were seen in 89.8% of the cases, and 30.3% of ICAS cases were diagnosed after the reperfusion of an acute occlusion. Among the treatment strategies for ICAS detected after the reperfusion of an acute large-vessel occlusion (ALVO), antiplatelet therapy was utilized in 23.8% of cases and endovascular therapy was utilized in 70.4% of cases, in addition to antiplatelet therapy. In cases involving symptomatic severe ICAS resistant to medical treatment with cerebral blood flow (CBF) impairment, 97.8% of physicians suggested intervention. However, in cases without CBF impairment, the percentage of physicians who suggested intervention decreased to 53.1%. In contrast, for asymptomatic ICAS without CBF impairment, more than 95% of physicians selected medical treatment.

Conclusion: In cases involving symptomatic ICAS resistant to medical treatment with CBF impairment, the rate of physicians who suggested intervention was quite high in Japan. Thirty percent of ICAS cases were diagnosed after the reperfusion of an ALVO.

Keywords► intracranial artery stenosis, endovascular therapy, percutaneous transluminal angioplasty, stent, medical treatment

Introduction

Intracranial artery stenosis (ICAS) is one of the main causes of cerebral infarction and the incidence is high in Asians. In symptomatic intracranial arterial stenosis, the risk of ipsilateral ischemic stroke is high with resistant to medical treatment, and the annual risk of recurrent cerebral infarction was reported to be 23% with 70% or severer stenosis in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study.1)

Since the limitation of medical treatment for ICAS was clarified, various clinical studies to evaluate the efficacy of endovascular therapy including stent placement were performed, but the usefulness of endovascular therapy was not demonstrated in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study2) or Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT)3).

On the other hand, the safety of endovascular therapy for ICAS have recently been reported. In a multicenter registry study performed in China, the incidence of stroke, transient ischemic attack (TIA), and death within 30 days was 4.3%,4) and the incidence of stroke and death within 72 hours was 2.7% in the Wingspan Stent System Post

1Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
2Department of Neuroendovascular Therapy, Kohnan Hospital, Sendai, Miyagi, Japan
3Department of Stroke Neurology, Kohnan Hospital, Sendai, Miyagi, Japan

Received: February 6, 2019; Accepted: October 8, 2019
Corresponding author: Shinichi Yoshimura. Department of Neurosurgery, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan
Email: hyogoneuro@yahoo.co.jp

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives International License.
Furthermore, in the lead-in phase of the China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial, the incidence of stroke and death within 30 days was 2%. Based on the results of randomized studies including the SAMMPRIS study, medical treatment may be prioritized to endovascular therapy, but the treatment strategy for intracranial artery stenosis in Japan is unclear. To clarify the current status of treatment for ICAS in Japan, we performed a nationwide survey.

**Subjects and Methods**

A questionnaire was sent to the members of the Japanese Society for Neuroendovascular Therapy (JSNET) via e-mail and a reply was requested. Regarding the number of cases, the reply was requested to one person representing the institution. The questionnaire is presented in Supplement Table 1 (available online). The survey items were the numbers of endovascular treatments performed for ICAS, treated symptomatic lesions, cases with stent placement, and cases discovered after reperfusion of acute large vessel occlusion (ALVO) between January 1, 2017 and December 31, 2017. In addition, the treatment strategies for intracranial artery stenosis discovered after reperfusion of acute occlusion and those for medical treatment-resistant symptomatic and asymptomatic lesions with and without cerebral blood flow impairment were surveyed. Furthermore, the treatment strategy for low-density lipoprotein (LDL) cholesterol and target blood pressure were surveyed using a questionnaire. The value results were presented as the median and quartile and the distribution was also investigated in some items.

In this questionnaire, the definition of resistance to internal medical treatment, symptomatcity, or severe stenosis was not presented beforehand, and its judgment depended on the physicians who responded. Regarding cerebral blood flow (CBF) impairment, stage 2 on $^{123}$I-IMP SPECT, that is CBF reduction in both resting state and acetazolamide loading is considered the reduction of cerebral blood flow in general, but the judgment depended on physicians who responded to the questionnaire.

### Results

#### Number of endovascular treatments

In total, 261 institutions (25.8%) replied. Within the range of the replies, a total of 783 endovascular treatments were performed for ICAS in 2017, and a stent was placed in 313 treatments (40.0%), the lesion was symptomatic in 703 (89.8%), and stenosis was discovered after reperfusion of acute occlusion in 237 (30.3%) (Table 1). The median total number of endovascular treatments performed in the institutions was 2 (quartile: 0–4), number of stent placements was 0 (0–2), number of treatments for symptomatic lesions was 1 (0–4), and that for cases diagnosed after reperfusion of ALVO was 0 (0–1) (Table 1). The rate of the number of endovascular treatments performed in each respondent institution to the number in all institutions is shown in Fig. 1. The most frequent number of endovascular treatments among the respondent institutions was 0 (26.1%), followed by 1 (20.3%).

**Table 1** Number and details of cases treated with endovascular therapy for ICAS

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of total endovascular treatments performed for ICAS</td>
<td>313 (40.0%)</td>
<td>470 (60.0%)</td>
</tr>
<tr>
<td>Stent placement</td>
<td>703 (89.8%)</td>
<td>80 (10.2%)</td>
</tr>
<tr>
<td>Presence of symptoms</td>
<td>237 (30.3%)</td>
<td>546 (69.7%)</td>
</tr>
</tbody>
</table>

ALVO: acute large-vessel occlusion; ICAS: intracranial artery stenosis

**Fig. 1** Number and distribution of endovascular treatments performed for ICAS in respondent institutions. ICAS: intracranial artery stenosis

#### Intracranial artery stenosis discovered after reperfusion of ALVO

The content of treatment for ICAS diagnosed after reperfusion of ALVO was antiplatelet alone in 23.8%, antiplatelet and percutaneous transluminal balloon angioplasty (PTA) in 42.6%, antiplatelet and stent placement (when PTA was insufficient) in 26.0%, antiplatelet and stent placement
A National Survey of Intracranial Artery Stenosis

In the case of symptomatic severe ICAS, resistance to medical treatment, and CBF impairment

The treatment strategy was continuation of medical treatment in 3 (1.1%), PTA in 72 (25.8%), stent placement (when PTA was insufficient) in 101 (36.2%), antiplatelet with stent placement (in the premise of stenting) in 17 (6.1%), surgical treatment (bypass surgery) in 73 (26.2%), and others in 13 (4.7%) (Fig. 3A). Seventy-seven percent of the other respondents (3.6% of all) answered as PTA or bypass surgery showing that certain intervention is suggested in 97.8%.

In the case of symptomatic severe ICAS and resistance to medical treatment, and without CBF impairment

The treatment strategy was continuation of medical treatment in 118 (42.6%), PTA in 57 (20.6%), stent placement (when PTA was insufficient) in 55 (19.9%), antiplatelet with stent placement (on the premise of stenting) in 20 (7.2%), surgical treatment (bypass surgery) in 15 (5.4%), and others in 12 (4.3%) (Fig. 3A). Endovascular treatment and bypass surgery were selected in 47.7 and 5.4%, respectively, suggesting that endovascular therapy is selected for symptomatic lesions in many cases.

In the case of asymptomatic severe ICAS with CBF impairment

The treatment strategy was aggressive medical treatment in 175 (63.2%), PTA in 21 (7.6%), stent placement (when PTA was insufficient) in 21 (7.6%), antiplatelet with stent placement (on the premise of stenting) in 3 (1.1%), surgical treatment (bypass surgery) in 46 (16.6%), and others in 11 (4.0%) (Fig. 3B). Certain intervention was selected in 32.9% of cases with CBF impairment.

In the case of asymptomatic severe ICAS without CBF impairment

The treatment strategy was aggressive medical treatment in 266 (95.0%), stent placement (when PTA was insufficient) in 2 (0.7%), and others in 12 (4.3%) (Fig. 3B). Few treatment intervention was performed in most asymptomatic cases without CBF impairment.

Strategy for LDL cholesterol

In aggressive medical treatment, the target value of LDL cholesterol is controversial. Then, the current status of this treatment was surveyed. The target value of LDL cholesterol

![Fig. 2](image-url)
Takagi T, et al.

was 100 or lower in 38.7%, being the most frequent, followed by 70 or lower in 31.5%, 120 or lower in 22.6%, 140 or lower in 5.7%, and others in 1.4% (Fig. 4A). Proprotein Convertase Subtilisin/Kexin type-9 (PCSK-9) inhibitor was not used in 82.1%, used only for symptomatic cases in 9.7%, used for all cases in 0.4%, and others in 7.9% showing that it has not become a general treatment (Fig. 4B).

The target value of blood pressure
Blood pressure management in patients with ICAS was divided by the presence or absence of symptoms and surveyed in combination with CBF impairment in the questionnaire. For symptomatic cases, blood pressure was controlled at below 140/90 in the absence of CBF impairment in 62.6%, uniformly below 140/90 regardless of the CBF state in 15.8%, below 130/80 in the absence of CBF impairment in 21.8%, below 130/80 in the absence of CBF impairment in 24.6%, uniformly below 130/80 regardless of the CBF state in 5.0%, and others in 2.1% (Table 2).

Diagnosis of plaque of intracranial artery stenosis was performed in 21.7%.

Discussion
The questionnaire survey clarified the number of endovascular treatments performed for ICAS in Japan and some of its details, and important knowledge concerning the current treatment strategies for ICAS was acquired.

In 2017, 784 endovascular treatments for ICAS were performed at 262 institutions. It was also clarified that about 5% of the institutions performed the treatment 10 or more times a year. Regarding the details of cases that received endovascular treatment, about 90% were symptomatic lesions and stent placement was performed in about 40%. Based on the results of the SAMMPRIS and VISSIT studies, even for symptomatic stenosis, medical treatment is firstly selected in evidence-based treatment.
A National Survey of Intracranial Artery Stenosis

Then, in this study, the questionnaire was performed on the assumption that symptomatic stenosis is resistant to medical treatment. Accordingly, the number of endovascular treatments was not investigated in symptomatic cases without medical treatment.

As endovascular therapy for ALVO has become more common, ICAS has been increasingly diagnosed initially after reperfusion. This study clarified that intracranial artery stenosis diagnosed after reperfusion accounts for 30% of endovascular treatments performed for ICAS. Since the incidence of ICAS has been reported to be high in Asians including Japanese, the indication of reperfusion therapy for ALVO may be expanded on in the future, with which ICAS cases diagnosed after reperfusion may also increase. ICAS after acute reperfusion therapy is a hot topic and it has recently been reported one after another. Favorable outcomes of stent placement in cases refractory to thrombectomy, in which ICAS is considered closely involved, have been reported.7) However, at present, no specific guidelines for treatment strategy including appropriateness of stent placement are available. Actually, in this questionnaire, stent placement was selected in the treatment strategy for ICAS diagnosed after acute occlusion when PTA was insufficient in about 2/3 of replies, but it was treated with antiplatelet alone in about 1/4. When PTA caused dissection, stent placement was considered in more than 80%, but the course was followed with medical treatment in more than 10%.

Another problem is stents applicable for the acute phase. For the stent used in salvage therapy for severe dissection which occurred after emergency PTA for severe ICAS diagnosed after acute reperfusion therapy, Enterprise2 was most frequently used, followed by balloon-expandable stents and Neuroform. Although Wingspan has been approved as an intracranial stent, it cannot be used in many cases during emergency and a stent always prepared in a hospital may be inevitably used for salvage therapy. For ICAS after reperfusion, further study including a prospective registry study may be necessary.

Regarding the treatment for medical treatment-resistant symptomatic severe ICAS, in patients with CBF impairment, endovascular treatment and bypass surgery were selected in 68% and 26%, respectively, and surgical intervention was selected in about 98% of all cases. On the other hand, even in cases without CBF impairment, PTA/stent and bypass surgery were selected in 47% and 5.4%, respectively, indicating intervention accounted for half. For asymptomatic cases, when CBF impairment was

---

**Table 2** Antihypertensive therapy with ICAS

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 140/90 in the absence of CBF impairment</td>
<td>62.6%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Uniformly below 140/90 regardless of the CBF state</td>
<td>15.8%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Below 130/80 in the absence of CBF impairment</td>
<td>15.1%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Uniformly below 130/80 regardless of the CBF state</td>
<td>2.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Others</td>
<td>4.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

CBF: cerebral blood flow; ICAS: intracranial artery stenosis
caused, PTA/stent and bypass surgery were selected in 17.3% and 16.6%, respectively showing that intervention was performed in about one-third, and without CBF impairment, medical treatment accounted for almost all of cases. Based on the findings above, the presence or absence of CBF impairment strongly influences the treatment strategy for ICAS in Japan.

The target value of LDL cholesterol also varied among the institutions. In the medical treatment group in SAMMPRIS, lipid control targeting 70 mg/dl or lower LDL cholesterol was performed, but the most frequent target value in this survey was 100 mg/dl or lower. This may represent a hesitation to apply the lipid control value in western countries to Japanese, but the data on the cerebrovascular disease-preventing effect of lipid control in Asians including Japanese has recently been reported, so that the rights or wrongs of the direction to “The lower, the better” may be discussed in Japan in the future.

Since a randomized study on the target blood pressure involving patients with cerebrovascular disease is limited, setting a target blood pressure is difficult. Below 140/90 mmHg adopted in medical treatment in SAMMPRIS may be plausible, but the target blood pressure in primary prevention has recently been changed based on the results of the SPRINT study. In the cerebrovascular field, the results of SPS3, a randomized study on strict blood pressure lowering in the chronic phase of lacunar infarction, have been acquired. The study results about whether strict blood pressure lowering is effective for intracranial major artery stenosis are awaited.

There are some limitations of this study. Despite cooperation by many physicians of the institutions, the response rate was 25.8%, being insufficient. Moreover, since the questionnaire survey was performed in members of the JSNET, the tendency of selecting endovascular therapy may have been strong compared with selection by non-members. Therefore, it is possible that the overall treatment of ICAS in Japan was not accurately reflected. In addition, as described above, the degree to which endovascular therapy was performed for symptomatic cases not resistant to internal medical treatment could not be surveyed.

The superiority of endovascular therapy to medical treatment was not demonstrated in the SAMMPRIS or VISSIT study, but the safety of endovascular therapy for intracranial artery stenosis was reported by the registry study performed in China, WEAVE study, and the lead-in phase of the CASSISS study. To establish safe and effective endovascular therapy for ICAS in which the risk of recurrent stroke was high despite of medical treatment, it may be time to review again the content of the treatment. The results of the CASSISS study, a randomized study performed based on the results of the SAMMPRIS study, are awaited.

### Conclusion

The questionnaire results clarified the current status of endovascular therapy for ICAS and treatment strategies in Japan. Ninety percent of endovascular treatments for ICAS were performed for symptomatic lesions, and a stent was used in 40%. ICAS diagnosed after reperfusion of ALVO accounted for about 30% of endovascular treatments. For medical treatment-resistant symptomatic severe ICAS with CBF impairment, almost all institutions performed surgical treatment, but in the rate of interventions decreased to about half of cases without CBF impairment. On the other hand, asymptomatic lesions were surgically treated in one-third of cases accompanied by CBF impairment, but medical treatment was performed in cases without CBF impairment. Further study including a prospective registry study may be necessary to clarify the state of treatment and treatment outcome in Japan.

### Acknowledgments

The institutions which cooperated with this questionnaire are listed in Supplement Table 2 (available online). We are grateful to the physicians who cooperated.

### Disclosure Statement

Neither the first nor any of co-authors has conflict of interest.

### References


