Objective: The objective of this study was to clarify the current status of endovascular thrombectomy for acute ischemic stroke due to large vessel occlusion in Japan.

Methods: A questionnaire was sent to members of the Japanese Society for Neuroendovascular Therapy (JSNET) by email, and the answers were collected.

Results: A questionnaire was sent to 1324 facilities, and answers were obtained from 159 (response rate: 12%). There were areas in which endovascular treatment (EVT) was impossible in almost all the prefectures. The mean number of endovascular thrombectomy procedures per facility was 14.1 ± 12.2 per year, and the initial imaging examination was CT at 81% and MRI at 91% of the facilities. Concerning the patients for whom EVT is recommended by the American Heart Association (AHA) guidelines, 119 facilities (76%) answered that all patients were treated by EVT. The baseline Alberta Stroke Program Early CT score (ASPECTS) of ≥6 was considered as an indication for EVT at 45%, and ≥5 at 22% of the facilities. The mean time from hospital arrival (door) to reperfusion was 174.3 ± 63.2 min, and that from arterial puncture to reperfusion was 71.8 ± 26.3 min. The successful reperfusion rate was 75% ± 14% (Thrombolysis in cerebral infarction [TICI] ≥2b) and 45% ± 15% (TICI = 3).

Conclusion: In acute stroke treatment for large vessel occlusion in Japan, MRI was performed as the initial imaging examination at about 90% of the facilities, the number of patients treated per facility was relatively small, and the time to reperfusion, particularly that from arterial puncture to reperfusion, was long. For the future, development of the diagnosis and treatment system for endovascular thrombectomy and approaches to shorten the time to reperfusion are necessary to improve neurologic outcome in EVT.

Keywords: endovascular thrombectomy, clot retrieval, large vessel occlusion, nationwide survey, acute ischemic stroke

Introduction

In 2015, endovascular thrombectomy was first shown to be effective for the treatment of acute ischemic stroke due to large vessel occlusion of the anterior circulation by a randomized controlled trial (RCT) called Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN). Based on the results, interim analysis was performed in four RCTs that were conducted simultaneously (ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT), and the effectiveness of endovascular thrombectomy was demonstrated in all studies. The HERMES study, which was a meta-analysis of these five studies, showed that patients with a favorable outcome (modified Rankin scale [mRS] score: 0–2 after 90 days) increased by about 20% by the addition of endovascular treatment (EVT) to medical therapy including intravenous thrombolysis using recombinant tissue-type plasminogen activator (rt-PA). In addition, the American Heart Association (AHA) guidelines strongly recommend EVT for large vessel occlusion of the anterior circulation that fulfill certain conditions as an evidence level of IA.

Although the efficacy of endovascular thrombectomy has been sufficiently established, the current status in
Japan remained unclear. In this study, a nationwide questionnaire survey was carried out in members of the Japanese Society for Neuroendovascular Therapy (JSNET) to clarify the current status of endovascular thrombectomy for acute ischemic stroke due to large vessel occlusion in Japan.

### Subjects and Methods

A questionnaire was sent to members of the JSNET by email, requesting one member representing each facility to answer. The investigation items were the diagnosis and treatment system of the facility, number of cases treated between January 2014 and September 2016, preoperative imaging examinations, times related to treatment, indication criteria for endovascular thrombectomy, treatment principles for occlusion of distal anterior circulation and posterior circulation, reperfusion rate, and postprocedural antithrombotic therapy. The numerical data are expressed as the mean ± standard deviation, and the distribution of the answers was also examined in part of the items.

### Results

Answers were obtained from 159 of the 1324 facilities to which members of the JSNET belonged (as of October 24, 2016) (response rate: 12%).

### Diagnosis and treatment system for acute stroke

The number of physicians involved in the stroke diagnosis and treatment was 10.6 ± 7.3, the number of physicians involved in endovascular treatment was 4.1 ± 2.8, the number of JSNET members was 5.3 ± 4.0, the number of JSNET specialists was 2.4 ± 1.9, and the number of JSNET instructors was 0.8 ± 0.76. The treatment system was available 24 hours a day, 7 days a week at 96.8% of the facilities. A few days a week was available at 1.3% of the facilities, and daytime office hours alone were available at 1.9% of the facilities. Transfer from other hospital (including drip-and-ship treatment) was available at 89.3% of the facilities, and 10.7% of the facilities did not provide such services. Dispatch service (including mobile stroke treatment) was available at 21.4% of the facilities, and 78.6% of the facilities did not provide such services. The annual number of cases was 19.0 ± 16.2 for intravenous thrombolysis with rt-PA therapy and 14.1 ± 12.2 for endovascular thrombectomy. The preprocedural imaging examinations included CT with plain CT alone at 71.7%, 3D-CTA at 6.3%, perfusion CT at 3.1%, and not performed at 18.9%. MRI with plain MRI alone was performed at 83.5%, perfusion MRI at 7.0%, and not performed at 9.5%.

The treatment times were as follows: door to image at 30.0 ± 18.7 min, door to puncture at 103.0 ± 41.7 min, puncture to reperfusion at 71.8 ± 26.3 min, and door to reperfusion at 174.3 ± 63.2 min. The numerical data are presented as the mean ± standard deviation. JSNET: Japanese Society for Neuroendovascular Therapy; rt-PA: recombinant tissue-type plasminogen activator.

### Table 1: Diagnosis and treatment system, imaging examinations, and treatment-related times at the facilities

<table>
<thead>
<tr>
<th>Diagnosis and treatment system for stroke at the facilities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of physicians involved in the diagnosis and treatment of stroke</td>
<td>10.6 ± 7.3</td>
</tr>
<tr>
<td>Number of physicians involved in endovascular treatment</td>
<td>4.1 ± 2.8</td>
</tr>
<tr>
<td>Number of JSNET members</td>
<td>5.3 ± 4.0</td>
</tr>
<tr>
<td>Number of JSNET specialists</td>
<td>2.4 ± 1.9</td>
</tr>
<tr>
<td>Number of JSNET instructors</td>
<td>0.8 ± 0.76</td>
</tr>
</tbody>
</table>

The time when endovascular treatment is available:

- 24 hours a day, 7 days a week: 96.8% |
- A few days a week: 1.3% |
- Daytime office hours alone: 1.9%

Transfer from other hospital (including drip-and-ship treatment):

- Yes: 89.3% |
- No: 10.7%

Dispatch service (including mobile stroke treatment):

- Yes: 21.4% |
- No: 78.6%

Annual number of cases:

- Intravenous thrombolysis with rt-PA therapy: 19.0 ± 16.2 |
- Endovascular thrombectomy: 14.1 ± 12.2

Preprocedural imaging examinations:

- CT:
  - Plain CT alone: 71.7% |
  - 3D-CTA: 6.3% |
  - Perfusion CT: 3.1% |
  - Not performed: 18.9%

- MRI:
  - Plain MRI alone: 83.5% |
  - Perfusion MRI: 7.0% |
  - Not performed: 9.5%

Treatment time:

- Door to image: 30.0 ± 18.7 min |
- Door to puncture: 103.0 ± 41.7 min |
- Puncture to reperfusion: 71.8 ± 26.3 min |
- Door to reperfusion: 174.3 ± 63.2 min

The numerical data are presented as the mean ± standard deviation.
puncture time was 103.0 ± 41.7 min, puncture to reperfusion time was 71.8 ± 26.3 min, and door to reperfusion time was 174.3 ± 63.2 min (Table 1). The door to image time within 20 min was at 41% of the facilities but exceeded 40 min at 19% (Fig. 2C). Although the door to puncture time within 75 min was at 30%, it exceeded 120 min at 28% of all facilities (Fig. 2D). The puncture to reperfusion time was within 35 min at only 7% of the facilities (Fig. 2E), and the door to reperfusion time within 110 min was at only 11% (Fig. 2F).

Indications for endovascular thrombectomy
All cases for which the AHA guidelines recommend EVT were treated at 76% of the facilities, and 24% answered that they could not be treated when physicians capable for the treatment were absent (Table 2). To the question, “How many percent of patients for whom EVT is recommended by the AHA guidelines are actually treated?”, the answer was 87% ± 26.3%. Concerning the indication for endovascular thrombectomy based on the Alberta Stroke Programme Early CT Score (ASPECTS) in initial imaging examination, the criterion was ≥ 6 at 45% of the facilities, followed by ≥ 5 at 22%, but 17% of the facilities disregarded the ASPECTS.

The indication criteria for endovascular thrombectomy in patients with internal carotid artery (ICA)/M1 segment middle cerebral artery (M1) occlusion 6–8 hours after the onset were based on mismatch between neurologic symptoms and imaging findings at 66% of the facilities and the ASPECTS in initial image at 29%. Intervention was made by establishing indication criteria at 95% of all facilities (Table 2). However, in patients with ICA/M1 occlusion more than 8 hours after the onset, the indications were evaluated according to mismatch between neurologic symptoms and imaging findings at 51% of the facilities and according to the ASPECTS in initial image at 10% (Table 3).

Distal lesions
Concerning the areas of distal occlusion of the middle cerebral artery (MCA) that are indications for treatment, 83% of the facilities answered up to the M2, and 12% answered up to the M3, and the remaining 5% answered that there were no restrictions (Table 2). Concerning distal occlusions of the anterior cerebral artery (ACA), those up to A2 were regarded as indications by 83% of the facilities, those up to A3 by 6%, there were no restrictions at 16% of the facilities, and 1% answered that distal occlusion of the ACA was not an indication (Table 2). The first-line device...
used for endovascular thrombectomy was the stent retriever at 41%, Penumbra at 16%, and selected on a case-by-case basis at 43%. Concerning distal lesions, endovascular thrombectomy was indicated for those without a large cerebral infarction at 81% of the facilities and for those with no hyperintensities on fluid attenuated inversion recovery (FLAIR) even when diffusion-weighted imaging (DWI) was positive on MRI (Table 2). The pc-ASPECTS was evaluated at only 20% of the facilities.

**Reperfusion rate**

According to the Thrombolysis in cerebral infarction (TICI) grading system, the mean reperfusion rate was 75% ± 14% for TICI 2b or 3, and 45% ± 15% for TICI 3 (Fig. 3).

**Postprocedural antithrombotic therapy**

Concerning the time of the beginning of postprocedural antithrombotic therapy in patients with cardiogenic embolism who previously underwent intravenous thrombolysis, antithrombotic drugs were not used within 24 hours after the procedure at 85% of the facilities, and they were used from immediately after the procedure if there was no postoperative hemorrhage at 14%. On the other hand, in patients who had not undergone intravenous thrombolysis, antithrombotic drugs were not used within 24 hours after the

---

**Fig. 2 Initial imaging examination and treatment-related times. (A) CT. (B) MRI. (C) Distribution of the door to image time. (D) Distribution of the puncture to reperfusion time. (E) Distribution of the puncture to reperfusion time.**
<table>
<thead>
<tr>
<th>Treatment indications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients recommended by the AHA guidelines to receive EVT</td>
<td>75.8%</td>
</tr>
<tr>
<td>All patients are treated</td>
<td>23.6%</td>
</tr>
<tr>
<td>Treated when the qualified physician can be contacted</td>
<td>0.6%</td>
</tr>
<tr>
<td>Percentage of patients treated among those recommended by the AHA guidelines to receive EVT</td>
<td>87 ± 26.3%</td>
</tr>
<tr>
<td>Minimum ASPECTS as a treatment indication</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.2%</td>
</tr>
<tr>
<td>5</td>
<td>22.1%</td>
</tr>
<tr>
<td>6</td>
<td>45.5%</td>
</tr>
<tr>
<td>7</td>
<td>10.4%</td>
</tr>
<tr>
<td>8</td>
<td>1.9%</td>
</tr>
<tr>
<td>Not considered</td>
<td>16.9%</td>
</tr>
<tr>
<td>Indications in patients with ICA/M1 occlusion 6–8 hours after the onset</td>
<td></td>
</tr>
<tr>
<td>Mismatch between neurologic symptoms and images</td>
<td>66.5%</td>
</tr>
<tr>
<td>Judged according to the ASPECTS in initial image</td>
<td>29.1%</td>
</tr>
<tr>
<td>All patients are treated</td>
<td>0.6%</td>
</tr>
<tr>
<td>Not treated, in principle</td>
<td>3.8%</td>
</tr>
<tr>
<td>Indications in patients with ICA/M1 occlusion ≥8 hours after the onset</td>
<td></td>
</tr>
<tr>
<td>Mismatch between neurologic symptoms and images</td>
<td>10.1%</td>
</tr>
<tr>
<td>Judged according to the ASPECTS in initial image</td>
<td>51.3%</td>
</tr>
<tr>
<td>All patients are treated</td>
<td>0.0%</td>
</tr>
<tr>
<td>Not treated, in principle</td>
<td>38.6%</td>
</tr>
<tr>
<td>Distal lesions</td>
<td></td>
</tr>
<tr>
<td>Treatment indications of distal MCA lesions</td>
<td></td>
</tr>
<tr>
<td>Up to M2</td>
<td>82.9%</td>
</tr>
<tr>
<td>Up to M3</td>
<td>12.0%</td>
</tr>
<tr>
<td>No restrictions</td>
<td>5.1%</td>
</tr>
<tr>
<td>Treatment indications of distal ACA lesions</td>
<td></td>
</tr>
<tr>
<td>Up to A2</td>
<td>83.0%</td>
</tr>
<tr>
<td>Up to A3</td>
<td>6.1%</td>
</tr>
<tr>
<td>No restrictions</td>
<td>15.6%</td>
</tr>
<tr>
<td>No indication</td>
<td>0.7%</td>
</tr>
<tr>
<td>First-line device</td>
<td></td>
</tr>
<tr>
<td>Stent retriever</td>
<td>40.8%</td>
</tr>
<tr>
<td>Penumbra</td>
<td>15.9%</td>
</tr>
<tr>
<td>Case-by-case selection</td>
<td>43.3%</td>
</tr>
<tr>
<td>Indications according to images</td>
<td></td>
</tr>
<tr>
<td>Performed if there is no large infarction</td>
<td>80.8%</td>
</tr>
<tr>
<td>Performed even if there is a large DWI hyperintense area unless the FLAIR signal is high</td>
<td>19.2%</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td></td>
</tr>
<tr>
<td>Time-related indications</td>
<td></td>
</tr>
<tr>
<td>Performed within 8 hours after the onset</td>
<td>17.7%</td>
</tr>
<tr>
<td>Performed even 8 or more hours after the onset depending on imaging findings</td>
<td>58.2%</td>
</tr>
<tr>
<td>There are no time restrictions</td>
<td>23.4%</td>
</tr>
<tr>
<td>Not treated, in principle</td>
<td>0.6%</td>
</tr>
<tr>
<td>Indications according to imaging findings</td>
<td></td>
</tr>
<tr>
<td>Performed if there is no large infarction in the brainstem</td>
<td>82.8%</td>
</tr>
<tr>
<td>Performed even if there is a large DWI-positive area in the brainstem unless the FLAIR signal is high</td>
<td>14.6%</td>
</tr>
<tr>
<td>Performed regardless of imaging findings</td>
<td>1.9%</td>
</tr>
<tr>
<td>Not performed regardless of imaging findings</td>
<td>0.6%</td>
</tr>
<tr>
<td>Use of pc-ASPECTS</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19.6%</td>
</tr>
<tr>
<td>No</td>
<td>80.4%</td>
</tr>
</tbody>
</table>

Numerical data are shown as the mean ± standard deviation. ASPECTS: Alberta Stroke Program Early CT Score; EVT: endovascular therapy; ACA: anterior cerebral artery; AHA: American Heart Association; DWI: diffusion-weighted magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery; ICA: internal carotid artery; MCA: middle cerebral artery.
In patients with embolic stroke of undetermined source (ESUS), the antithrombotic agents used were unfractionated heparin at 48% and DOACs at 25% of the facilities (Table 3).

### Discussion

Our questionnaire survey revealed the current status of EVT for acute ischemic stroke in Japan.

First, the numbers of physicians and neuro-interventionist involved in the diagnosis and treatment of stroke patients and the diagnosis and treatment system for stroke are discussed. Requirements for a comprehensive stroke center first reported in 2005, and while they are also described in the AHA guidelines, there was no mention about the number of physicians. However, it is impossible for a neuro-interventionist to treat all patients with indications for reperfusion therapy for 24 hours a day, 365 days a year. This is complemented by patient transfer including the drip-and-ship approach and dispatch treatment by a mobile stroke team, and it is considered necessary to formulate a treatment system by combining these services.

Concerning the annual number of patients per facility is 14 on average, development of the diagnosis and treatment
system with endovascular therapy is necessary for the future.

Regarding the target times related to EVT, the HERMES study recommended an image to puncture time of 50 min, a door to puncture time of 75 min, and a door to reperfusion time of 110 min as appropriate. Also, the AHA/American Society of Anesthesiologists (ASA) guidelines for the management of acute-stage cerebral infarction published in 2013 mentioned 25 min or less as a recommendable door to image time in intravenous thrombolysis with rt-PA. In our present survey, however, the mean door to image time was ≤25 min at 53% of the facilities, the mean door to puncture time was ≤75 min at 30%, and the mean door to reperfusion time was ≤110 min at only 11%. In addition, the puncture to reperfusion time was longer than the door to puncture time in our survey. In Japan, further shortening of the time from the onset to reperfusion is an issue.

Concerning imaging examinations of patients with acute ischemic stroke, CT was not performed at 19% of the facilities, and MRI was not performed at 9%. Although MRI was performed at many facilities in Japan, the door to image time was relatively short. However, the mean door to image time was less than 25 min at about half the facilities. In addition, an estimated 70% of the facilities performed both CT and MRI, and the evaluation of indications based on the findings of either modality alone is considered to be a possible option.

According to the present survey, EVT was always possible at 97% of the facilities, and patient transfer including drip-and-ship treatment was accepted at 90%, but only 76% of the facilities treated all patients who fulfilled the criteria recommended by the AHA guidelines. Thus, a pressing issue is to reduce the situations in which patients recommended to undergo EVT by the guidelines cannot be treated due to the absence of a qualified physician. It is also necessary to establish a cooperation system with facilities in the neighborhood for transfers by drip-and-ship and mobile stroke treatment if the patient cannot be treated by the first facility.

Although the AHA guidelines recommend EVT for acute ischemic stroke within 6 hours after the onset, stent retrievers and thrombus aspiration devices are indicated within 8 hours after the onset, in principle, in Japan. Therefore, 95% of the facilities evaluated the indications of patients 6–8 hours after the onset in consideration also of neurologic symptoms and imaging findings. However, it was found that about 40% of the facilities did not perform EVT in patients more than 8 hours after the onset. The results of ongoing RCTs (POSITIVE Stroke Clinical Trial, Clinical Trials.gov Identifier: NCT01852201, DAWN Trial: NCT02142283, DEFUSE 3: NCT02586415) will be useful as references in the evaluation of indications for EVT of acute ischemic stroke more than a certain time after the onset. Concerning distal occlusion of the anterior circulation and occlusion of the major arteries of the posterior circulation, indications for EVT must also be clarified by registry studies and RCTs.

Postprocedural antithrombotic therapy is not recommended within 24 hours after intravenous thrombolysis with rt-PA, and many facilities are considered to follow this guideline. When intravenous thrombolysis was not performed, antithrombotic therapy was initiated immediately after the end of EVT at many facilities (Table 3). Many facilities used unfractionated heparin or DOAC for cardio-embolic embolism and argatroban or antiplatelet agents for atherothrombotic stroke, and original antithrombotic treatments were widely adopted in Japan. There are no clear guidelines concerning the time of initiation of antithrombotic therapy when postoperative hemorrhage is observed. According to the present survey, antithrombotic treatment was initiated after 1 day at about 10% of the responder facilities, after 2 days at about 10%, after 3–6 days at about 40%, and after 1 week at about 20%. Antithrombotic therapy was initiated with some delay at many facilities. Further research is necessary concerning the optimal timing of initiation of antithrombotic therapy.

Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism (RESCUE)-Japan Registry 2, which is a prospective registry study, is in progress, and the publication of its results is awaited as they are expected to reveal the current status of EVT for acute ischemic stroke in Japan.

## Limitations

The present study has some limitations. First, this study was based on a questionnaire survey, and detailed data concerning individual patients were not obtained. Second, the response rate was low at 12%, and completeness of the survey was insufficient. For the future, prospective registry studies with higher completeness are considered necessary to more precisely clarify the status of reperfusion therapy in Japan.

## Conclusion

The current status of reperfusion therapy for acute ischemic stroke was investigated by a questionnaire survey. MRI was performed as the initial imaging modality at about 90% of the facilities, the number of patients treated...
per facility was small, and the time to reperfusion, particularly puncture to reperfusion time, was long.

For the future, development of the diagnosis and treatment system for endovascular thrombectomy and approaches to shorten the time to reperfusion are considered necessary to improve neurologic outcome in EVT.

## Acknowledgments

The facilities that kindly cooperated with the present questionnaire survey are listed in the supplement file. The authors are deeply grateful to the physicians who took the trouble of answering the questionnaire.

## Disclosure Statement

In the publication of this paper, the author Shinichi Yoshimura was granted a research fund from Terumo Corporation. Neither the first author nor any other coauthors have any conflicts of interest.

## References


