**Table 5A Risk factors for clinically significant complications in symptomatic lesions (JR-NET 2)**

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR [95% CI] | P value | OR [95% CI] | P value |
| Age, years | 1.05 [1.02–1.08] | 0.0002* | 1.04 [1.02–1.08] | 0.0008* |
| Male gender | 0.90 [0.55–1.11] | 0.69 | 1.02 [0.56–1.73] | 0.95 |
| Acute intervention (within 14 days) | 1.63 [1.02–2.51] | 0.04* | 1.69 [1.02–2.70] | 0.04* |
| Degree of stenosis, % | 1.00 [0.99–1.01] | 0.95 | 0.99 [0.97–1.00] | 0.13 |
| Dual/Triple antiplatelet | 0.77 [0.42–1.69] | 0.46 | 1.58 [0.54–5.13] | 0.42 |
| Aspirin | 0.81 [0.48–1.46] | 0.46 | 0.72 [0.30–1.81] | 0.47 |
| Ticropidine/Clopidogrel | 0.86 [0.59–1.17] | 0.41 | 0.73 [0.34–1.43] | 0.37 |
| Cilostazol | 1.05 [0.72–1.55] | 0.79 | 0.85 [0.40–1.74] | 0.67 |
| EPD use | 0.15 [0.04–1.00] | 0.05 | – | |
| Distal filter protection | 1.14 [0.79–1.65] | 0.49 | 0.97 [0.63–1.53] | 0.91 |
| Proximal/combined protection | 0.90 [0.47–1.56] | 0.73 | 0.64 [0.29–1.29] | 0.22 |
| Predilatation | 1.47 [0.85–2.76] | 0.17 | 2.41 [1.22–5.34] | 0.01* |
| Postdilatation | 1.02 [0.57–2.03] | 0.95 | 1.69 [0.74–4.85] | 0.23 |
| Closed-cell stent | 0.68 [0.37–1.16] | 0.16 | 0.66 [0.33–1.22] | 0.19 |

*indicates statistical significance. EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio, CI: confidence interval.

complication (Table 4).

### V. Risk factors for clinically significant complications in asymptomatic and symptomatic lesions

Table 5A demonstrates the risk factors for clinically significant complications in symptomatic lesions. Age (OR, 1.05 per year; 95% CI, 1.02–1.08; p = 0.0002) and acute intervention (within 14 days after symptom onset) (OR, 1.63; 95% CI, 1.02–2.51; p = 0.04) were determined as risk factors for clinically significant complications by univariate logstic analysis. In multivariate analysis, age (OR, 1.04 per year; 95% CI, 1.02–1.08; p = 0.0008), acute intervention (OR, 1.69; 95% CI, 1.02–2.70; p = 0.04), and performing predilatation (OR, 2.41; 95% CI, 1.22–3.54; p = 0.01) were determined as independent risk factors for clinically significant complication. On the other hand, in asymptomatic lesions, any variables were not estimated as the significant risk factors for clinically significant complication (Table 5B).

**Table 5B Risk factors for clinically significant complications in asymptomatic lesions (JR-NET2)**

| Variables | OR [95% CI] | P value |
|---|---|---|
| Age, years | 1.02 [0.98–1.08] | 0.23 |
| Male gender | 0.48 [0.11–1.35] | 0.18 |
| Degree of stenosis, % | 0.99 [0.96–1.01] | 0.35 |
| Dual antiplatelet | 0.66 [0.26–5.42] | 0.46 |
| Aspirin | 1.30 [0.47–1.49] | 0.65 |
| Ticropidine/Clopidogrel | 0.96 [0.51–1.77] | 0.88 |
| Cilostazol | 0.91 [0.49–1.72] | 0.76 |
| EPD use | – | 0.5 |
| Distal filter protection | 1.31 [0.70–2.53] | 0.4 |
| Proximal/combined protection | 0.36 [0.02–1.67] | 0.23 |
| Predilatation | 0.56 [0.29–1.15] | 0.11 |
| Postdilatation | 0.97 [0.34–4.06] | 0.96 |
| Closed-cell stent | 0.46 [0.11–1.29] | 0.16 |

CI: confidence interval, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio.

## Discussion

In the present study, we demonstrated the current strategy and the treatment results of CAS in Japan. From these results, it was considered that almost all procedures were conducted in accordance with current recommendation guidelines, and that the rates of technical success (99.99%) and clinically significant complication (approximately 3%) were good ones. We thought that there were several reasons leading to these favorable results of CAS in Japan.

First, it was proved that almost all cases of CAS (5,008/5,191; 96.5%) were performed by board-certified surgeons of JSNT. There is no doubt that adequate training and experience of surgeons is an important factor to maintain the quality and the treatment results of CAS, and this issue has been discussed in many reports following the results of the European randomized controlled trials (RCTs).[7] In Japan, the training and experiences of CAS is strictly regulated by the concerned societies, and sectional seminars and society-oriented continuing education are frequently held to educate surgeons not only about technical aspects, but also about periorerative management.[5] These systems would certainly contribute to improve the rate of technical success without perioperarive complications.

Second, it was suggested that Japanese CAS surgeons selected optimal strategy for each case, especially in protection methods, in accordance with preoperative risk evaluation. One of the major concerns associated with CAS is the potential of embolic infarction during the procedure. Plaque components of stenotic site, especially lipid core and intraplaque hemorrhage is associated with an increasing number of embolic infarction after CAS.[8] In most Japanese institutions, the patients who elected CAS routinely underwent plaque imaging by magnetic resonance imaging (MRI) and/or carotid ultrasound to predict the potential of embolic infarction.[9–11] In JR-NET2 registry, distal filter protection device were most widely used (52.1%) because distal filter protection device (Angioguard XP; Cordis/Johnson & Johnson, Miami, Florida, USA) was the only EPD which was officially approved for carotid use in the latter half of JR-NET2 surveillance period (between April 2008 and December 2009). However, distal filter protection systems have some limitations owing to its structure.[5] It has been considered that distal balloon protection is more effective for debris collection without leakage through the occlusion site.[12] Moreover, it was reported that proximal protection resulted in a significant reduction in the incidence and volume of new ischemic lesion during CAS compared to distal filter protection.[13] Based on these data and risk evaluation, Japanese CAS surgeons more frequently used proximal or combined protection system in symptomatic lesions than in asymptomatic lesions (11.8% vs. 6.3%, $p < 0.001$) in spite of limitation of available devices. In the present study, it was demonstrated that use of closed-cell type stent significantly reduced the rate of clinically significant complications. Recently, similar results were reported by Park, et al.; ischemic lesions detected by diffusion-weighted MR imaging were more frequent in the open-cell stent than in the closed-cell stent.[14] These results also indicated the importance of optimal therapeutic strategy in order to reduce the rate of perioperative complication. After this surveillance periods, several different EPDs (distal balloon protection and proximal protection devices) or stents were approved in succession. It is expected that the introduction of new devices would lead to further improvement of the clinical results of CAS.

The rate of clinically significant complication (approximately 3%) in this study period was comparable to another Japanese large study,[5] and this rate was considered as a good one. Similar to the above-mentioned report, the rate of clinically significant complications was significantly higher in symptomatic lesions than those of asymptomatic lesions (4.2% vs. 2.0%, $p < 0.0001$). In the symptomatic lesions, age and acute intervention (within 2 weeks after symptom onset) were determined as the significant risk factors for clinically significant complications. It has been reported that the timing of intervention influences the benefit in patients with symptomatic carotid stenosis, and CEA surgery was most effective when performed within the first 2 weeks after symptom onset.[15] On the other hand, the ideal timing of CAS in the symptomatic lesions still remains unclear. Recent study showed that the patients with symptomatic carotid stenosis treated with CAS within 7 days after onset had remarkably higher risk of periprocedural stroke or death compared to the similar patients treated with CEA (9.4% vs. 2.8%, respectively).[16] Our results also demonstrated the risk of early CAS within 2 weeks after symptoms (OR, 1.69; 95% CI, 1.02–2.70; $p = 0.04$). Interestingly, performing predilatation was determined as one of the independent risk factor for clinically significant complication in symptomatic lesions (OR, 2.41; 95% CI, 1.22–3.54; $p = 0.01$). Although cerebral embolism may occur throughout the procedure, it has been still controversial as to which part of procedure most frequently causes the embolism. One previous study reported that the highest embolic loads occurred during predilatation.[17] However, another study indicated that most embolsm were produced by postdilatation.[18] Further investigations would be necessary to determine the optimal timing and the procedural strategy in patients with symptomatic carotid stenosis.

In contrast, in asymptomatic lesions, the rate of clinically significant complications was low (2.0%), and no significant risk factors for clinically significant complications were identified. These data confirmed that CAS is a beneficial therapeutic alternative to CEA in patients with asymptomatic carotid stenosis, as previously described.[5,19]

This study includes several limitations. This study was conducted in a retrospective way. The treatment strategy, the determination of complications, and the outcome measurements were independently made by each interventional team. Further investigation with standardized treatment protocol and clinical evaluation are required to clarify the optimal treatment strategy and therapeutic efficacy of CAS.

## Conclusion

We demonstrated the current strategy and the therapeutic results of CAS in Japan. Relatively favorable clinical results were obtained because of tailor-made strategy based on perioperative risk evaluation. It is expected that the evolution of devices and increasing experiences of surgeons would lead to further improvement of the clinical results, and further investigation would be required to clarify the optimal treatment strategy and therapeutic efficacy of CAS, especially in symptomatic lesions.

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## Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part I

# Angioplasty and Stenting for Intracranial Stenosis

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## Abstract

**Of the patients enrolled in the Japanese Registry of Neuroendovascular Therapy (JR-NET), a surveillance study in Japanese, 1133 patients who underwent intracranial percutaneous transluminal angioplasty (PTA)/stenting for intracranial stenosis during the period from 2005 to 2009 were investigated. A technical success was achieved in 98.3% of the patients, and 70.5% and 7.5% had a residual stenosis of < 30% and ≥ 50%, respectively. The incidence of ischemic complications and hemorrhagic complications was as low as 7.7% and 2.5%, respectively, but tended to increase in patients who underwent stenting. While a significant correlation with ischemic complications was observed in previously untreated patients and patients who underwent stenting followed by post-dilatation, a significant correlation with hemorrhagic complications was observed in patients who received emergency treatment and those treated between 24 hours and 14 days of the onset. Flexible intracranial stents are expected to contribute to improvement in the treatment outcome.**

Key words: intracranial stenosis, angioplasty, stenting

## Introduction

Angioplasty has traditionally been used for the treatment of intracranial stenosis, primarily for intracranial stenosis refractory to medical therapy. However, since no stent is specifically designed for intracranial arteries, treatment is usually completed with balloon angioplasty alone, and stenting using a coronary stent is applied only in unavoidable circumstances. While more flexible intracranial stents that are compatible with the characteristics of more tortuous intracranial arteries have been awaited for a long time, the Wingspan (Stryker, Kalamazoo, Michigan, USA) was approved in the United States in 2005, and an investigator-initiated clinical trial is under way in Japan with the aim of gaining coverage by the Japanese National Health Insurance system. In advance of introduction of intracranial stents in Japan, review of previous treatment results in Japan may be essential for the development of endovascular therapy for intracranial stenosis. The Japanese Registry of Neuroendovascular Therapy (JR-NET) was a retrospective registration survey on all neuroendovascular procedures performed in Japan. Procedures performed from 2005 to 2006 were included in JR-NET1, and those from 2007 to 2009 were included in JR-NET2. We report the results of the JR-NET, including analysis and discussion.

## Materials

All patients enrolled in JR-NET1 or JR-NET2 who were treated with intracranial percutaneous transluminal angioplasty (PTA)/stenting for intracranial stenosis were included in the present study. Data from a total of 1133 patients who underwent angioplasty/stenting for intracranial stenosis were analyzed: 438 patients in JR-NET1 (2005 to 2006) and 695 patients in JR-NET2 (2007 to 2009).

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## Methods

Data files from JR-NET 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. Data were analyzed for each factor, except for "unknown" data and missing data. For the factors asked about in JR-NET2 but not in JR-NET1 (presence or absence of pre-dilatation and post-dilatation, type of stent, timing of treatment, and presence or absence ofgeneral anesthesia), only data from JR-NET2 were used. Statistical analysis was performed by 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 66.7 (19 to 94) years, and the proportion of male subjects was as high as 76.5%. At baseline, the mean modified Rankin scale (mRS) was 0.86, and patients with an mRS of 0 to 2 accounted for 89.1%. Of all patients, 25.0% received treatment under general anesthesia, and 17.0% received emergency treatment. Stenting was performed in 60.6% patients. The most common preoperative antiplatelet treatment was treatment with two agents in 71.6%, followed by treatment with one agent in 14.1%. While the most common postoperative antithrombotic agents

**Table 1 Characteristics of 1,133 patients**

| Patient characteristics | | |
|---|---|---|
| Baseline characteristics of patients | Age | Mean 66.8 (19–94) years |
| | Sex | Male 76.5% |
| | mRS at baseline | Mean 0.86 |
| | mRS 0 to 2 | 89.1% |
| | Previously untreated | 92.7% |
| Lesion profile | Region | IC (intracranial epidural): 36.0%, IC (intradural): 84.7%, MCA: 22.2%, VA: 16.6%, BA: 14.4%, other: 2.4% |
| | Symptom at diagnosis | Asymptomatic: 19.9%, amaurosis: 1.4%, TIA (cerebrum): 22.1%, minor stroke: 36.5%, major stroke: 8.7%, progressing: 11.3% |
| | Timing of treatment (JR-NET2) | Within 24 hr: 13.5%, within 14 days: 20%, after at least 15 days: 66.5% |
| | Percent diameter stenosis | < 50%: 2.4%, 50% to 60%: 4.5%, 60% to 70%: 9.9%, 70% to 80%: 32.0%, 80% to 90%: 26.7%, 90% to 100%: 22.2%, 100%: 2.3% |
| | Lesion length | < 5 mm: 25.0%, 5–10 mm: 53.2%, 10–15 mm: 16.3%, ≥ 15 mm: 5.5% |
| | Normal vascular diameter | < 2 mm: 1.9%, 2–2.5 mm: 16.0%, 2.5–3 mm: 24.1%, 3–3.5 mm: 25.1%, 3.5–4 mm: 19.7%, ≥ 4 mm: 13.2% |
| | Pathology | Arteriosclerosis: 93%, traumatic dissection 0.3%, iatrogenic dissection 0.7%, idiopathic dissection 1.1%, others 4.7% |
| | Refractory to medical therapy | 44.9% |
| Treatment situation | Diagnostic cerebral angiography | 39.6% |
| | Emergency treatment | 17.0% |
| | Treatment at another hospital | 10.6% |
| | Investigator | Supervisory physician: 55.0%, specialist: 37.4%, nonspecialist: 7.5% |
| | Scrub-in of supervisory physician | 62.5% |
| | No. of scrub-in supervisory physicians and specialists | 1: 58.0%, 2: 33.0%, ≥ 3: 9.0% |
| | General anesthesia (JR-NET2) | 25.0% |

(*Continued*)

**Table 1 (Continued)**

| | | |
|---|---|---|
| Treatment | Stenting | Yes: 60.6% |
| | Presence or absence of pre-dilatation (JR-NET2) | Yes: 72.0% |
| | Use of coronary stent (JR-NET2) | 97.9% |
| | Presence or absence of post-dilatation (JR-NET2) | 28.8% |
| | Preoperative antiplatelet treatment | No: 5.4%, 1 agent: 14.1%, 2 agents: 71.6%, 3 agents: 8.9% |
| | Postoperative antiplatelet treatment | No: 6.0%, 1 agent: 12.7%, 2 agents: 71.7%, 3 agents: 9.6% |
| | Postoperative antithrombotic treatment | No: 26.4%, heparin: 25.9%, argatroban: 38.9%, ozagrel: 3.1%, combination: 5.6% |
| | Other concurrent treatment | 12.8% |
| Treatment outcome | Technical success | 98.3% |
| | Residual stenosis immediately after treatment | < 30%: 70.5%, 30% to 50%: 22.1%, ≥ 50%: 7.5% |
| | Hemorrhagic complication | 2.5% |
| | Ischemic complication | 7.7% |
| | mRS at 30 days postoperatively | Mean 1.02 |
| | Postoperative increase in mRS ≥ 2 points | 8.6% |
| | Mortality | 1.9% |

BA: basilar artery, IC: internal cerebral artery, JR-NET: Japanese Registry of Neuroendovascular Therapy, MCA: middle cerebral artery, mRS: modified Rankin scale, TIA: transient ischemic attack, VA: vertebral artery.

**Table 2 Details of ischemic complications and hemorrhagic complications**

| | Total | Incidence(%) |
|---|---|---|
| Ischemic complication | | |
| Distal embolization | 39 | 3.4 |
| Vascular dissection | 21 | 1.9 |
| Acute obstruction | 15 | 1.3 |
| Other | 4 | 0.4 |
| Unknown | 8 | 0.8 |
| Total | 87 | 7.7 |
| Hemorrhagic complication | | |
| Vascular rupture | 7 | 0.6 |
| Hyperperfusion | 5 | 0.4 |
| Vascular dissection | 3 | 0.3 |
| Vessel perforation | 2 | 0.2 |
| Other | 5 | 0.4 |
| Unknown | 6 | 0.5 |
| Total | 28 | 2.5 |

were argatroban in 38.9% and heparin in 25.9%, no postoperative antithrombotic treatment was performed in 26.4%. Technical success was achieved in 98.3%, and 70.5% and 7.5% had a residual stenosis of < 30% and ≥ 50%, respectively. The incidence of ischemic complications and hemorrhagic complications was 7.7% (87 patients) and 2.5% (28 patients), respectively, and 1 patient had both ischemic and hemorrhagic complications. As a result, the incidence of hemorrhagic and ischemic complications within 30 days postoperatively was 10.1%. At 30 days postoperatively, the mean mRS was 1.02, and the mRS increased from baseline by 2 points or more in 8.6%. The mortality was 1.9%.

Ischemic and hemorrhagic complications are listed in Table 2. The most common ischemic complication was distal embolization in 3.4%, followed by vascular dissection in 1.9%. The most common hemorrhagic complications were vascular rupture in 0.6% and hyperperfusion-related hemorrhage in 0.4% of patients.

Correlation between each factor tested and ischemic complications are shown in Table 3. The following factors were significantly correlated with ischemic complications: no previous treatment; not refractory to medical therapy; stenting followed by post-dilatation; postoperative antithrombotic treatment; and supervisory physician who served as the investigator. The incidence of ischemic complications was significantly lower in patients who received

**Table 3 Correlation between each factor and ischemic complications**

| | | |
|---|---|---|
| Baseline characteristics of patients | Age | ≤ 49 years: 7.0%, 50 to 59 years: 6.9%, 60 to 69 years: 7.1%, 70 to 79 years: 6.7%, ≥ 80 years: 2.7% |
| | Sex | Male: 6.6%, female: 6.6% |
| | mRS at baseline | 0 to 2: 6.9%, 3 to 5: 5.2% |
| | Previous treatment | Previously untreated: 8.4%, previously treated: 2.2% ($p < 0.05$) |
| Lesion profile | Region | IC (intracranial epidural): 6.2%, IC (intradural): 5.5%, MCA: 7.5%, VA: 9.6%, BA: 11.0% |
| | Symptom at diagnosis | Asymptomatic: 8.0%, symptomatic: 7.8% |
| | | Nonprogressively symptomatic: 8.1%, progressively symptomatic: 5.8% |
| | Timing of treatment (only symptomatic patients) | Within 24 hr: 8.8%, between 24 hr and 14 days: 5.9%, after at least 15 days: 7.7% |
| | Percent diameter stenosis | < 50%: 8.0%, 50% to 60%: 8.7%, 60% to 70%: 8.9%, 70% to 80%: 7.3%, 80% to 90%: 7.3%, 90% to 100%: 8.4%, 100%: 8.7% |
| | Lesion length | < 5 mm: 8.3%, 5–10 mm: 6.4%, 10–15 mm: 12.2%, ≥ 15 mm: 5.4% |
| | Normal vascular diameter | < 2 mm: 0%, 2–2.5 mm: 10.4%, 2.5–3 mm: 10.2%, 3–3.5 mm: 5.9%, 3.5–4 mm: 6.5%, ≥ 4 mm: 6.7% |
| | Pathology | Arteriosclerosis: 7.2%, traumatic dissection 0%, iatrogenic dissection 0%, idiopathic dissection 12.5%, others 3.1% |
| | Refractory to medical therapy | No: 8.8%, yes: 5.0% ($p < 0.05$) |
| Treatment | Stenting | No: 6.6%, yes: 9.7% |
| | Presence or absence of pre-dilatation (JR-NET2) | No: 10.1%, yes: 6.0% |
| | Presence or absence of post-dilatation (JR-NET2) | No: 5.7%, yes: 9.8% |
| | Stent + presence or absence of post-dilatation (JR-NET2) | No: 5.6%, yes: 14.0% ($p < 0.05$) |
| | Preoperative antiplatelet treatment | No: 8.9%, 1 agent: 6.2%, 2 agents: 8.2%, 3 agents: 7.6% |
| | Postoperative antiplatelet treatment | No: 11.2%, 1 agent: 8.3%, 2 agents: 7.0%, 3 agents: 12.0% |
| | Postoperative antithrombotic treatment | No: 4.9%, heparin: 3.5%, argatroban: 9.7%, ozagrel: 12.9%, combination: 30.3% ($p < 0.000000001$*) |
| | Other concurrent treatment | No: 7.3%, yes: 11.0% |
| Treatment situation | Diagnostic cerebral angiography | No: 8.0%, yes: 7.4% |
| | Emergency treatment | Planned: 7.2%, emergency: 10.4% |
| | Treatment facility | Hospital at work: 8.2%, another hospital: 3.3% |
| | Investigator | Supervisory physician: 10.1%, specialist: 4.5%, nonspecialist: 5.8% ($p < 0.01$**) |
| | Scrub-in of supervisory physician | No: 2.7%, yes: 10.0% ($p < 0.001$) |
| | No. of scrub-in supervisory physicians and specialists | 1: 7.1%, 2: 8.8%, ≥ 3: 3.3% |
| | General anesthesia | Local anesthesia: 7.7%, general anesthesia: 5.7% |
| Treatment outcome | Residual stenosis immediately after treatment | < 30%: 7.4%, 30% to 50%: 7.0%, ≥ 50%: 11.7% |

*: Each p-value is shown in Table 4. **: Supervisory physician vs. specialist ($p < 0.001$). mRS: modified Rankin scale.

**Table 4 Correlation between postoperative antithrombotic treatment and ischemic complications**

| | Ischemic complication (–) | Ischemic complication (+) | Total | Incidence | p value | | | |
|---|---|---|---|---|---|---|---|---|
| No postoperative antithrombotic treatment | 253 | 13 | 266 | 4.9% | $p < 0.000000001$ | n.s. | $p < 0.05$ | $p < 0.01$ |
| Heparin | 251 | 9 | 260 | 3.5% | $p < 0.00000001$ | n.s. | $p < 0.05$ | * |
| Argatroban | 353 | 38 | 391 | 9.7% | $p < 0.001$ | n.s. | * | |
| Ozagrel | 27 | 4 | 31 | 12.9% | n.s. | * | | |
| Combination | 39 | 17 | 56 | 30.3% | * | | | |

*: control. n.s.: no significant.

**Table 5 Correlation between each factor and hemorrhagic complications**

| | | |
|---|---|---|
| Baseline characteristics of patients | Age | ≤ 49 yrs: 4.2%, 50–59 yrs: 2.8%, 60–69 yrs: 1.6%, 70–79 yrs: 2.2%, ≥ 80 yrs: 4.1% |
| | Sex | Male: 2.1%, female: 3.1% |
| | mRS at baseline | 0% to 2: 2.2%, 3% to 5: 3.2% |
| | Previous treatment | Previously untreated: 2.8%, previously treated: 2.2% |
| Lesion profile | Region | IC (intracranial epidural): 1.8%, IC (intradural): 4.4%, MCA: 2.5%, VA: 3.4%, BA: 4.0% |
| | Symptom at diagnosis | Asymptomatic: 1.9%, symptomatic: 2.9% |
| | | Nonprogressively symptomatic: 2.2%, progressively symptomatic: 6.6% ($p < 0.05$) |
| | Timing of treatment (only symptomatic patients) | Within 24 hr: 2.9%, between 24 hr and 14 days: 5.9%, after at least 15 days: 1.5% ($p < 0.05$*) |
| | Percent diameter stenosis | < 50%: 0%, 50% to 60%: 0%, 60% to 70%: 3.0%, 70% to 80%: 1.5%, 80% to 90%: 4.0%, 90% to 100%: 3.5%, 100%: 0% |
| | Lesion length | < 5 mm: 1.6%, 5–10 mm: 3.0%, 10–15 mm: 3.0%, ≥ 15 mm: 3.6% |
| | Normal vascular diameter | < 2 mm: 4.8%, 2–2.5 mm: 1.8%, 2.5–3 mm: 2.0%, 3–3.5 mm: 2.3%, 3.5–4 mm: 3.0%, ≥ 4 mm: 5.2% |
| | Pathology | Arteriosclerosis: 1.9%, traumatic dissection 0%, iatrogenic dissection 20%, idiopathic dissection 0%, others 0% |
| | Refractory to medical therapy | No: 2.7%, yes: 2.5% |
| Treatment | Stenting | No: 2.4%, yes: 3.2% |
| | Presence or absence of pre-dilatation (JR-NET2) | No: 1.6%, yes: 2.5% |
| | Presence or absence of post-dilatation (JR-NET2) | No: 2.3%, yes: 2.1% |
| | Stent + presence or absence of post-dilatation (JR-NET2) | No: 3.7%, yes: 5.0% |
| | Preoperative antiplatelet treatment | No: 5.4%, 1 agent: 4.8%, 2 agents: 2.0%, 3 agents: 3.2% |
| | Postoperative antiplatelet treatment | No: 10.0%, 1 agent: 6.0%, 2 agents: 1.3%, 3 agents: 1.0% ($p < 0.000000001$**) |
| | Postoperative antithrombotic treatment | No: 7.1%, heparin: 1.9%, argatroban: 0.8%, ozagrel: 0%, combination: 1.8% ($p < 0.0001$***) |

(*Continued*)

**Table 5 (Continued)**

| | | |
|---|---|---|
| | Other concurrent treatment | No: 3.0%, yes: 0.7% |
| Treatment situation | Diagnostic cerebral angiography | No: 3.1%, yes: 2.2% |
| | Emergency treatment | Planned: 2.1%, emergency: 5.7% ($p < 0.01$) |
| | Treatment facility | Hospital at work: 2.7%, another hospital: 3.3% |
| | Investigator | Supervisory physician: 3.4%, specialist: 2.4%, nonspecialist: 0% |
| | Scrub-in of supervisory physician | No: 2.3%, yes: 2.1% |
| | No. of scrub-in supervisory physicians and specialists | 1: 2.0%, 2: 3.1%, ≥ 3: 0.0% |
| | General anesthesia | Local anesthesia: 1.7%, general anesthesia: 4.0% |
| Treatment outcome | Residual stenosis immediately after treatment | < 30%: 2.6%, 30% to 50%: 3.1%, ≥ 50%: 0% |

*: Within 24 hr vs. between 24 hr and 14 days: $p < 0.05$. **: Each p-value is not shown. ***: Each p-value is not shown. JR-NET: Japanese Registry of Neuroendovascular Therapy.

**Table 6 Correlation between complications and mortality**

| | Mortality | | |
|---|---|---|---|
| | No | Yes | |
| Hemorrhagic complication | 1.3% | 23.3% | ($p < 0.0000001$) |
| Ischemic complication | 1.8% | 2.3% | n.s. |

n.s.: no significant.

postoperative antithrombotic treatment with heparin alone than in those who received no postoperative antithrombotic treatment (Table 4).

Correlation between each factor tested and hemorrhagic complications are shown in Table 5. The following factors were significantly correlated with hemorrhagic complications: progressively symptomatic; treatment between 24 hours and 14 days of the onset; no postoperative antiplatelet treatment; no postoperative antithrombotic treatment; and emergency treatment. In patients with hemorrhagic complications, the mortality was very high at 23.3% (Table 6).

## Discussion

In this study, the incidence of ischemic complications and hemorrhagic complications was 7.7% and 2.5% in 1,133 patients who underwent angioplasty/stenting, respectively, resulting in an overall incidence of approximately 10%. Nguyen et al. reported that of 74 patients, 5% of patients who underwent angioplasty for symptomatic intracranial stenosis experienced major stroke within 30 days postoperatively.[1] In the present study, the incidence of ischemic complications and hemorrhagic complications was 6.6% and 2.4%, respectively, in patients who underwent PTA alone. The higher incidence of complications in this study may be because the complications included minor stroke, unlike in Nguyen's study.

When limited to patients who underwent stenting, on the other hand, the incidence of ischemic complications and hemorrhagic complications was relatively high at 9.7% and 3.2%, respectively, in Japan. This outcome was worse compared even with a 30-day stroke rate of 5.7% reported with Wingspan, an intracranial stent approved in the United States, at the time of approval.[2] This may have been due to the use of inflexible coronary stents in the present study, which was more likely to result in vascular injury at the time of access or stent deployment. In addition, since the incidence of complications was greatly different with or without stenting in this study, it is likely that there may have been problems with the device. On the other hand, the proportion of patients who had a residual stenosis of ≥ 50% postoperatively was significantly lower in the stenting group, showing the usefulness of stenting in maintaining cerebral artery patency and thus warranting quick approval of flexible intracranial stents.

In this study, which had a large sample size (1,133 patients), several factors were found to be correlated with complications, and even multifactorial analysis could have been performed. However, since the data were retrospectively collected and analyzed, it is not doubtful that various biases existed. For instance, hemorrhagic complications may substantially restrict subsequent antithrombotic therapy. For significantly

biased data, it may be more important to analyze individual factors correlated with complications carefully, rather than to perform a multifactorial analysis.

In the analysis, first, several factors were correlated with ischemic complications. The incidence of complications was significantly lower in previously treated patients. Patients who experienced complications at the initial treatment often preclude retreatment for medical or social reasons, thus more patients who experienced no complications at the initial treatment might have been included in the previously treated group. In many previously treated patients, angioplasty may have been more suitable in terms of plaque characteristics or position of penetrating branches in the lesion. In addition, the intima formed after the initial treatment may have been histopathologically stable. In this study, an unexpected negative correlation was observed in patients unresponsive to medical therapy, although such patients generally have an increased risk of ischemic complications. Many of the patients enrolled with the disease refractory to medical therapy may have received not only adequate antiplatelet treatment, but also medical therapy such as statins or intensive antidiabetic treatment that can contribute to plaque stabilization. It may be hypothesized that medical therapy contributing to plaque stabilization reduced ischemic complications and is thus useful in enhancing the safety of angioplasty although this is a matter of speculation since non-antithrombotic drugs were not investigated. Additional post-dilatation following placement of balloon-expandable coronary stent was also significantly correlated with ischemic complications. Plaques excluded by repeated PTA may have impaired blood flow in the penetrating branches. As for postoperative antithrombotic therapy, the incidence of ischemic complications was significantly lower in heparin-treated patients than in untreated patients, indicating the usefulness of heparin. On the other hand, treatment with multiple antithrombotics was also positively correlated with ischemic complications. This may be because ischemic complications occurred in many of the patients who received multiple antithrombotics for the treatment of intraoperative ischemic symptoms.

In addition, some factors were found to be correlated with hemorrhagic complications. Progressively symptomatic disease, which is complicated by so-called misery perfusion, may have resulted in cerebral hemorrhage due to hyperperfusion syndrome. The higher incidence of hemorrhagic complications in patients treated between 24 hours and 14 days of the onset may be explained by the assumption that hemorrhagic changes were caused by reperfusion of brain tissue that had just undergone irreversible ischemic changes, although there was no data on cerebral blood flow, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), in our study. Likewise, postoperative hemorrhagic complications were more likely to occur in patients who received emergency treatment, because such patients often develop acute cerebral infarction. In addition, inadequate preoperative assessment or equipment may have resulted in vascular injury during catheter manipulation or PTA in patients who received emergency treatment. A positive correlation with hemorrhagic complications was observed in patients who received no postoperative antiplatelet or antithrombotic treatment, but this may be explained by the fact that hemorrhagic complications precluded the use of these drugs.

As mentioned above, the data were retrospectively collected and analyzed in this study, requiring prospective confirmatory studies to determine whether each factor found to be correlated with complications is actually a risk factor for complications. This procedure is associated with more complications than other neuroendovascular procedures, and unfortunately the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, a randomized controlled study in the United States, failed to show the effectiveness of stenting and abandoned.[3] The final result of this study also showed that the early benefit of aggressive medical management over aggressive medical management plus stenting with the Wingspan stent persists during a median follow-up of 32.4 months.[4] It may be important to not only use intracranial stents, which are expected to be introduced in Japan in the near future, but also to seek to improve the treatment outcome in a multidimensional manner based on the findings of the present study.

## Conclusion

Angioplasty for intracranial stenosis in Japan is almost as safe as that in the West. On the other hand, stenting using a coronary stent is associated with a higher incidence of complications, warranting quick introduction of intracranial stents.

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## Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS members.

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# 脳卒中高リスク群の診断及び治療による循環器疾患制圧に関する研究

平成２４年度～平成２６年度総合研究報告書

別冊3　研究成果の刊行物・別刷り

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# Guidelines for Management of Patients with Transient Ischemic Attack

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**Abstract**

A transient ischemic attack (TIA) is a medical emergency that is associated with a high risk of early ischemic stroke and other vascular events. Several evidence-based guidelines have been published to provide recommendations for the evaluation and treatment of patients with TIA. These guidelines underline the need for the urgent referral of patients with TIA so that they can access expert evaluation and immediate treatment. The distinction between TIA and ischemic stroke has recently become less important because these two conditions share pathophysiological mechanisms and many of the preventive approaches are applicable to both. Therefore, current guidelines are often described without a distinction between TIA and ischemic stroke. However, the applicability of recommendations for applying treatment for ischemic stroke to TIA has not been proven. Further studies are required to determine the effects of urgent intervention or treatment early after TIA.

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A transient ischemic attack (TIA) is a medical emergency that is associated with a high risk of early ischemic stroke and other vascular events. Among patients with TIA, 10–15% develop stroke within 90 days, with about half occurring within 48 h [1–4]. Urgent assessment and management of patients in a dedicated TIA clinic has decreased the 90-day stroke risk by almost 80% [5, 6]. Patients with TIA are also at high risk of cardiovascular events [1]. A previous study found that 2.6% of patients were hospitalized for major cardiovascular events including myocardial infarction, unstable angina, or ventricular arrhythmia within 90 days of TIA [7]. These findings underline the need for the urgent referral of patients with TIA so that they can access expert evaluations and immediate treatment. Several evidenced-based guidelines have provided recommendations for the evaluation and treatment of patients with TIA [8–24].

T.U. and K.M. contributed equally to this chapter.

The classical definition of TIA is the presence of focal neurological symptoms ascribable to a vascular etiology lasting <24 h irrespective of imaging findings [25]. The advent of brain imaging techniques has led to the understanding that up to one third of patients with symptoms lasting <24 h actually has an infarction [1]. This has led to a new tissue-based definition of TIA, that is 'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction' [1], which is different from the traditional time-based definition. According to this definition, the diagnostic certainty of TIA would depend on the extent of evaluations that a patient undergoes. A brain imaging procedure is prerequisite for concluding a diagnosis of TIA or ischemic stroke.

In contrast, the distinction between TIA and ischemic stroke has become less important because these two conditions share the same pathophysiological mechanisms, and many of the preventive approaches are applicable to both [1]. Acute ischemic stroke and TIA in the acute setting are considered to span the same spectrum, and a new clinical concept termed acute cerebrovascular syndrome has been proposed [26]. Current guidelines are usually presented without a distinction between TIA and ischemic stroke.

We present representative guidelines for the management of patients with TIA [8–24].

## Representative Guidelines for the Management of Transient Ischemic Attack

A panel of the American Heart Association (AHA) Stroke Council published 'Guidelines for the management of transient ischemic attacks' in 1994 and a supplement in 1999, and both were separate from the guidelines for the management of stroke [8, 9]. The AHA/American Stroke Association (ASA) issued a scientific statement for the definition and evaluation of TIA in 2009 [1]. The National Stroke Association (NSA) published guidelines for the management of TIA in 2006, and recommendations for systems of care for TIA in 2011 [10, 11]. Guidelines for the assessment and management of people with recent TIA were published in New Zealand in 2008 [12]. A chapter for TIA management was newly added in the second edition of the guidelines for management of stroke in Japan in 2009. The English version of the Japanese guidelines was published recently [13]. A separate chapter for the management of TIA was similarly described in guidelines for management of stroke in the UK [14, 15] and Australia [16]. The AHA/ASA published a scientific statement for 'Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke' in 2003 [17], and 'Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack' in 2006, 2008 and 2011 [18–20], without a distinction between stroke and TIA. 'Guidelines for management of ischaemic stroke and transient ischaemic attack' published in 2008 by the European Stroke Organization (ESO) [21] is an update of the European Stroke Initiative (EUSI) Recommendations for Stroke Management pub-

lished in 2000. The American College of Chest Physicians evidence-based clinical practice guidelines for antithrombotic and thrombolytic therapy for ischemic stroke [22], a Science Advisory of AHA/ASA for oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation (AF) [23], and an update of the 2010 ESC guidelines for the management of AF [24] covered both ischemic stroke and TIA.

## Risk Stratification for Referral to a Specialized Hospital

Patients with suspected TIA require a differential diagnosis from TIA mimics, an assessment of vascular risk factors, and investigations to determine the potential causes of TIA. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) sequences should be the preferred diagnostic test for patients with suspected TIA. An additional diagnostic workup, including vessel imaging, cardiac evaluation and laboratory testing, should be completed as soon as possible, preferably within hours or a day or two.

To determine the short-term risk of stroke facing the individual patient is important. Patients at high risk of subsequent stroke would benefit more by urgent referral to a specialized stroke center, timely identification of the underlying etiology, and preventive measures such as antiplatelet agents, anticoagulants, and carotid endarterectomy (CEA). Admitting high-risk patients to specialized stroke centers might also provide opportunities to administer acute timely treatments in the event of a subsequent stroke [27].

Simple stratification scores are used to estimate the individual risk for patients with TIA. The most popular tool is the $ABCD^2$ score [28]. The $ABCD^2$ score is recommended to identify patients at high risk of stroke in several guidelines [1, 10, 12, 14–16], and it can be used in primary care to select patients for referral to specialized stroke centers. The presence of ischemic lesions on DWI and TIA etiology, such as large artery atherosclerosis and AF, could improve stroke risk prediction after TIA. However, clinical plus imaging scores, such as the $ABCD^2$-I [29], require additional estimations, and are more difficult to apply. Although these scores could be used in specialized stroke centers to individualize TIA management, they cannot be applied in primary care.

## Initial Management and Estimations

*Guidelines of the ESO* [21]

The ESO guidelines recommend that patients with suspected TIA be referred without delay to a TIA clinic or to a medical center with a stroke unit that can provide expert evaluation and immediate treatment. An immediate diagnostic workup, including urgent vascular imaging (ultrasound, CT or MR angiography), is recommended for patients with TIA, minor stroke or early spontaneous recovery.

*National Clinical Guidelines of the National Institute for Clinical Excellence* [14]
The National Institute for Clinical Excellence (NICE) guidelines recommend that all patients with TIA should be given immediate antiplatelet therapy with 300 mg/day of aspirin and then referred for urgent specialist assessment. The NICE guidelines recommend that individuals with suspected TIA and at high risk for stroke (for example, $ABCD^2$ score ≥4 or with crescendo TIA) in whom the vascular territory or pathology is uncertain should undergo urgent (within 24 h) brain imaging studies (preferably DWI). Those with suspected TIA at low risk for stroke (for example, $ABCD^2$ <4) in whom the vascular territory or pathology is uncertain should undergo brain imaging studies (preferably DWI) within 7 days. Individuals with suspected TIA who require brain imaging due to uncertain vascular territory or pathology should undergo DWI except where contraindicated, in which case CT scanning should be used (fig. 1a).

*National Stroke Strategy of the Department of Health (UK) in 2007* [15]
This strategy recommends immediate referral for appropriately urgent specialist assessment and an assessment of all patients presenting with recent TIA or minor stroke. All higher-risk patients with TIA and minor stroke (e.g. $ABCD^2$ score ≥4) need to be assessed by a specialist and treated within 24 h. Immediate hospital admission might be justified for those at highest risk. High-risk patients who are not considered to require immediate hospital admission have better outcomes if they are assessed, investigated and treated within 24 h of referral. Lower-risk patients with TIA or minor stroke are best assessed within 7 days of the event. Non-urgent referral for TIA or minor stroke is appropriate only for very low-risk patients, such as those presenting with events that occurred several weeks or months previously (fig. 1b).

*Clinical Guidelines by National Stroke Foundation (Australia) in 2010* [16]
These guidelines recommend that all patients with suspected TIA should have a full assessment including a detailed history and clinical, prognostic (e.g. $ABCD^2$ score) and investigative tests (e.g. blood tests, brain and carotid imaging and electrocardiography, ECG) at the initial point of healthcare contact, regardless of whether it is in primary or secondary care. Patients identified as being at high risk (e.g. $ABCD^2$ score ≥4 and/or any one of AF, carotid territory symptoms or crescendo TIA) should undergo urgent brain assessment preferably MRI with DWI and carotid imaging within 24 h. In settings with limited access to such modalities, patients should be referred within 24 h to the nearest center where such assessments can be quickly conducted. Patients classified as low risk (e.g. $ABCD^2$ score <4 without AF or carotid territory symptoms or who present more than one week after the last symptoms) should be assessed by brain and carotid imaging as soon as possible, preferably within 48 h (fig. 1c).

*Guidelines of Stroke Foundation of New Zealand* [12]
The New Zealand guidelines recommend an assessment of stroke risk for all patients with suspected TIA using the $ABCD^2$ tool at the initial point of health care contact

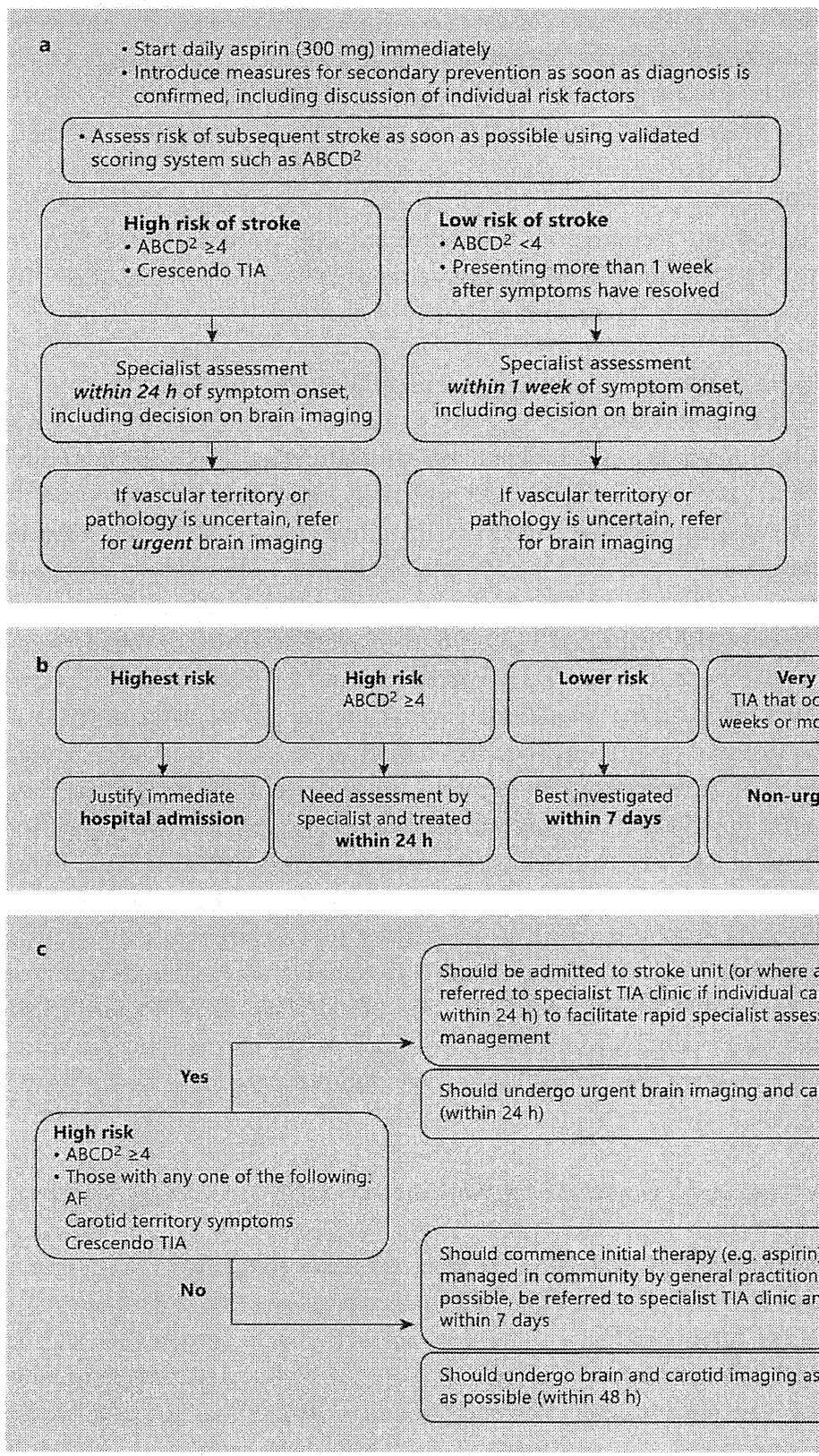


**Fig. 1.** Algorithms for initial management and estimations. **a** Guidelines of NICE [14]. **b** National Stroke Strategy (UK) [15]. **c** Guidelines of National Stroke Foundation (Australia) [16].

regardless of whether in primary or secondary care. High risk is indicated by any of the following: presence of symptoms at first contact; $ABCD^2$ score ≥4; crescendo TIAs, AF or already receiving anticoagulation therapy. Low risk is indicated by any of the following: $ABCD^2$ score <4 and late presentation (one week after symptoms appear).

*Guidelines in Japan* [13]
The Japanese guidelines recommend evaluating patients with suspected TIA to identify the onset mechanism and initiating treatment as soon as possible after TIA onset to prevent subsequent cerebral infarction.

*Scientific Statement for Definition and Evaluation of Transient Ischemic Attack Published by AHA/ASA in 2009* [1]
This statement recommends evaluating patients with suspected TIA as soon as possible after an event. Patients with TIA should preferably undergo neuroimaging evaluation within 24 h of symptom onset, and MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed. The cervicocephalic vessels should be imaged noninvasively as part of the routine evaluation of patients with suspected TIAs. Noninvasive assessment of the intracranial vasculature reliably excludes intracranial stenosis, and the likelihood of intracranial steno-occlusive disease that would alter management can be determined. Patients should be assessed by ECG as soon as possible after TIA. Prolonged cardiac monitoring (inpatient telemetry or Holter monitoring) is useful for patients with an unclear origin after initial brain imaging and electrocardiography. At least transthoracic echocardiography is reasonable when evaluating patients with suspected TIAs, especially when no cause has been identified by other elements of the workup. Transesophageal echocardiography is useful in identifying patent foramen ovale, aortic arch atherosclerosis and valvular disease, and is reasonable when identification of these conditions will alter management. Routine blood tests, including complete blood count, chemistry panel, prothrombin time and partial thromboplastin time, and fasting lipid panel, are reasonable in the evaluation of patients with suspected TIAs.

*National Stroke Association Guidelines for the Management of Transient Ischemic Attacks* [10]
These guidelines recommend establishing specialized clinics for the rapid assessment of TIA within 24–48 h of diagnosis. Physicians and institutions that provide care for patients with recent TIA should have same-day access to imaging modalities such as CT/CTA, MR/MR angiography and ultrasound for patients who need it. Patients with suspected TIA who are not admitted to hospital should have rapid (within 12 h) access for urgent assessment and investigation by CT or MRI brain scanning, ECG and carotid Doppler ultrasonography. Patients should be initially assessed within 24–48 h if they are not already assessed by cross-sectional imaging, ECG, or carotid ultrasound