Real-world Experience of Carotid Artery Stenting in Japan: Analysis of 8458 Cases from the JR-NET3 Nationwide Retrospective Multi-center Registries

Ryo TOKUDA, Shinichi YOSHIMURA, Kazutaka UCHIDA, Kiyofumi YAMADA, Tetsu SATOW, Koji IHRARA, Nobuyuki SAKAI, and the Japanese Registry of NeuroEndovascular Therapy (JR-NET) investigators

Abstract

We aimed to clarify the outcomes of carotid artery stenting (CAS) in the Japanese population. For this purpose, we reviewed data from the Japanese Registry of NeuroEndovascular Therapy 3 (JR-NET3), a retrospective, nation-wide, multi-center, observational study of neuroendovascular treatments in Japan. Of the 9207 patients who underwent CAS between January 2010 and December 2014, 8458 satisfied the inclusion criteria for our analysis. The outcome statistics of this JR-NET3 cohort were compared to those of JR-NET1 and 2 cohorts fitting the same inclusion criteria. Of the 8458 JR-NET3 patients analyzed, 8042 (95.1%) were treated by surgeons with board certification from the Japanese Society for NeuroEndovascular Therapy. Technical success was achieved in 8417 patients (99.5%), whereas 198 patients (2.3%) had clinically significant complications (CSCs). These findings mirrored those obtained for the JR-NET1 and 2 cohorts fitting the same inclusion criteria. Of the 8458 JR-NET3 patients analyzed, 8042 (95.1%) were treated by surgeons with board certification from the Japanese Society for NeuroEndovascular Therapy. Technical success was achieved in 8417 patients (99.5%), whereas 198 patients (2.3%) had clinically significant complications (CSCs). These findings mirrored those obtained for the JR-NET1 and 2 cohorts. On multivariate analysis, risk factors for CAS-associated CSC included symptomatic lesion [odds ratio (OR), 1.91; 95% confidence interval (CI), 1.23–3.00; P = 0.003] and hypoechoic lesion on carotid artery ultrasound (OR, 1.85; 95% CI, 1.21–2.84; P = 0.005), whereas use of closed-cell stents was a predictor of better outcome (OR, 0.53; 95% CI, 0.35–0.79; P = 0.002). The findings of JR-NET3 reflect good outcomes of CAS, but non-modifiable risk factors reflecting lesion characteristics remain of concern. Using closed-cell stents is advisable. Technological advances such as the introduction of new materials may help further improve CAS outcomes in Japanese patients.

Key words: carotid artery stenosis, stenting, treatment outcome, registry study

Introduction

Carotid artery stenting (CAS) is used as a potential alternative to carotid endarterectomy (CEA) for carotid artery stenosis. The SAPPHIRE\textsuperscript{1} randomized controlled trial, which enrolled patients at high risk for CEA, indicated that CAS was not inferior to CEA. On the basis of this result, in April 2008, CAS was added to the list of procedures covered by national insurance in Japan. However, subsequent studies conducted in Europe, including EVA-3S,\textsuperscript{2} SPACE,\textsuperscript{3} and ICSS,\textsuperscript{4} did not confirm that CAS was not inferior to CEA. The CREST\textsuperscript{5} study found that CAS was not inferior to CEA in normal-risk patients with asymptomatic or symptomatic lesions; however, the ACT-1\textsuperscript{6} study reported the same conclusion in a sample that excluded very elderly (>80 years) patients or patients at high risk for CEA. As not all randomized controlled trials confirmed that
CAS was not inferior to CEA, debate continues regarding the interpretation of accumulated reports and the practical use of CAS. In Japan, the number of CAS procedures far outnumber that of CEA procedures, yet the treatment outcomes of CAS remain unclear. Therefore, we reviewed the Japanese Registry of NeuroEndovascular Therapy 3 (JR-NET3), aiming to clarify the outcomes of CAS in Japanese patients.

Materials and Methods

Patient population and study design

Japanese Registry of NeuroEndovascular Therapy 3 is the third study in a series of retrospective, nation-wide, multi-center, observational studies of neuroendovascular treatments in Japan. Specifically, JR-NET3 gathered data on neuroendovascular procedures performed between January 1, 2010 and December 31, 2014. The present analysis was focused on JR-NET3 patients who underwent CAS. We evaluated the modified Rankin Scale (mRS) score 30 days after CAS, and technical success rate and the incidences of death within 30 days (related or unrelated to CAS) and adverse events (related or unrelated to CAS).

Of the 9207 patients who underwent CAS during the study period, the following were excluded: 153 with incomplete data regarding the stent; 502 treated for a disease other than carotid artery stenosis; three who received CAS as part of emergency recanalization; and 91 with inadequate data. The remaining 8458 cases were included in this retrospective analysis.

Type of data collected

The following data were analyzed: age, preoperative mRS score, gender, degree of stenosis, magnetic resonance imaging and carotid artery ultrasound findings, risk factors for CEA (as defined in the SAPPHIRE trial), symptomatic status (symptomatic or asymptomatic lesion), and type of symptoms. In this study, the stenotic lesion with transient ischemic attack (TIA) or stroke within 180 days was defined as symptomatic. We also analyzed the relationship of the incidence of complications (related or unrelated to the procedure) with preoperative usage of antiplatelet drugs, the type of embolic protection device (EPD) and stent (open-cell stent vs. closed-cell stent) utilized, and the timing of balloon dilatation (pre- vs. post-dilatation). Acute-stage CAS was defined when the procedure was done within 14 days from onset of TIA or stroke. The degree of stenosis was assessed using the protocol described in the North American Symptomatic Carotid Endarterectomy Trial. Procedure-related complications were defined as distal embolism, arterial perforation, arterial dissection, hyperperfusion, acute embolism, or myocardial infarction within 30 days post CAS. Clinically significant complications (CSCs) included clinically meaningful deteriorations occurring within 30 days following CAS. A CSC event was defined as a mRS score decline of one point (minor morbidity), a mRS score decline of two or more points (major morbidity), or death. For the purpose of this study, all CSCs will be discussed in the context of procedure-related complications.

Statistical analysis

Standard deviations and mean values were reported for normally distributed, continuous data. Median values and quartiles were reported for continuous data that were not normally distributed. We analyzed categorical variables using the chi-square test and continuous variables using the t-test or Wilcoxon signed-rank test. We used univariate and multivariate analysis to identify risk factors significantly related to treatment outcomes. Statistical significance was defined as \( P \leq 0.05 \). Odds ratios (ORs) were calculated with their 95% confidence intervals (CIs). All analyses were performed using commercially available software (Macintosh JMP13 Pro; SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

Of the 8458 patients included in the analysis, 8042 (95.1%) underwent CAS performed by a surgeon with board certification from the Japanese Society for NeuroEndovascular Therapy. Technical success was recorded in 8417 patients (99.5%). CSCs occurred in 198 patients (2.3%).

In the analyzed cohort (8458 cases; Table 1), the age was 72.8 ± 7.8 years (age range, 34–97 years) and 5888 patients (69.7%) were elders (≥70 years). The degree of stenosis was 79.7 ± 13.9%. On time-of-flight magnetic resonance angiography (TOF MRA), 2339 patients (36.9%) exhibited high-intensity signal areas indicative of intraplaque hemorrhage. On ultrasound, 2068 patients (32.0%) had hypoechoic lesions. Most patients (7942/8458, 93.9%) had good preoperative mRS scores (0–2), whereas 5925 patients (76.5%) were considered at high risk for CEA. Symptomatic lesions were noted in 5004 patients (59.2%). Specifically, 353 patients (4.2%) had amaurosis fugax, 807 (9.6%) had transient ischemic attack, 2799 (33.4%) had minor stroke, and 820 (9.8%) had major stroke. Progressive stroke was noted in 282 patients (3.4%).
Carotid Artery Stenting Outcomes in Japanese Patients

Table 1  Baseline characteristics of patients included in JR-NET3

| Variable                          | Value        |
|-----------------------------------|--------------|
| Age (years)                       | 72.8 ± 7.80  |
| Age ≥70 years                     | 5888 (69.7)  |
| mRS score 0–2 at CEA             | 7942 (93.9)  |
| Male sex                          | 7263 (85.9)  |
| Degree of stenosis (%)            | 79.7 ± 13.9  |
| High-intensity signal on TOF MRA  | 2339 (36.9)  |
| Low-echoic lesion                 | 2068 (32.0)  |
| High risk for CEA                 | 5925 (76.5)  |
| Presentation                      |              |
| Symptomatic                       | 5004 (59.2)  |
| Amaurosis fugax                   | 353 (4.2)    |
| TIA                               | 807 (9.6)    |
| Minor stroke                      | 2790 (33.4)  |
| Major stroke                      | 820 (9.8)    |
| Progressing stroke                | 282 (3.4)    |
| Asymptomatic                      | 3454 (40.8)  |

Data are shown as mean ± standard deviation or frequency (percentage), as appropriate, CEA: carotid endarterectomy, JR-NET: Japanese Registry of NeuroEndovascular Therapy, mRS: modified Rankin Scale, TOF MRA: time-of-flight magnetic resonance angiography, TIA: transient ischemic attack.

Table 2  Procedure-related complications reported in JR-NET3

| Event                                             | Value |
|---------------------------------------------------|-------|
| Postoperative mRS score 0–2                       | 7412  |
| Any death                                         | 59    |
| Any morbidity                                     | 803   |
| Any procedure-related complication                | 754   |
| Clinically significant complication               | 198   |
| Death                                             | 14    |
| Major morbidity                                   | 87    |
| Minor morbidity                                   | 97    |

Data are shown as frequency (percentage). CAS: carotid artery stenting, mRS: modified Rankin Scale, JR-NET: Japanese Registry of NeuroEndovascular Therapy.

Table 3  CAS procedural details reported in JR-NET3

| Detail                                             | Value |
|---------------------------------------------------|-------|
| Antiplatelet use                                  | 8201  |
| Single antiplatelet therapy                       | 620   |
| Dual/Triple antiplatelet therapy                  | 7581  |
| Aspirin                                           | 6862  |
| Clopidogrel                                       | 6375  |
| Cilostazol                                        | 3180  |
| Technical details                                 |       |
| Procedural success                                | 8417  |
| EPD use                                           | 8408  |
| Distal filter                                     | 3479  |
| Distal balloon                                    | 2560  |
| Proximal/combined protection                      | 1591  |
| MoMa                                              | 403   |
| Stent type                                        |       |
| Open-cell                                         | 4233  |
| Closed-cell                                       | 4051  |
| Combined                                          | 81    |

Data are shown as frequency (percentage). CAS: carotid artery stenting, EPD: embolic protection device, JR-NET: Japanese Registry of NeuroEndovascular Therapy, MoMa: Mo.Ma Ultra (Medtronic, Minneapolis, MN, USA).

Procedure-related complications

At 30 days after CAS, 7412 of the 8337 patients with complete follow-up data (88.9%) had achieved an mRS score of 0–2, indicating satisfactory outcomes in terms of disability/independence in activities of daily living (Table 2). Procedure-related complications including distal embolism, vessel dissection, hyperperfusion, acute in-stent occlusion, and myocardial infarction occurred in 754 patients (8.9%). Procedure-related CSCs occurred in 198 patients (2.3%) and included 14 deaths (0.2%), 87 instances (1.0%) of major morbidity (mRS score worsening by more than two points), and 97 instances (1.1%) of minor morbidity (mRS score worsening by one point). Complications were not related to the procedure occurred in 862 patients (1.0%), of whom 59 patients (0.7%) died.

Details of the CAS procedure

Antiplatelet therapy was administered in 8201 (98.2%) of the 8354 patients who underwent CAS perioperative management and were included in the analysis, with 620 patients (7.4%) receiving single-antiplatelet therapy, 6536 (81.7%) receiving dual-antiplatelet therapy, and 1045 (13.1%) receiving triple-antiplatelet therapy (Table 3). Among antiplatelet agents, aspirin was most commonly used (6862 cases, 85.8%), followed, in descending order, by clopidogrel.

An EPD was used in 8408 patients (99.5%), with distal filter protection used in 3479 patients (41.4%), distal balloon protection in 2560 patients (30.5%), and proximal/combined protection in 1591 patients (18.9%). The Mo.Ma Ultra proximal cerebral protection device (Medtronic, Minneapolis, MN, USA) was used in 403 patients (4.8%). Regarding the type of stent, open-cell stents were used in 4233 patients (50.0%) and closed-cell stents in 4051 patients (47.9%).
There was no difference between patients with symptomatic lesions and those with asymptomatic lesions with respect to strategy for multiple-antiplatelet therapy (Table 4); however, distal filter protection was utilized more frequently in asymptomatic patients (asymptomatic vs. symptomatic: 44.9% vs. 39.0%, \( P = 0.001 \)), whereas proximal/combined protection was used more frequently in symptomatic patients (asymptomatic vs. symptomatic: 20.7% vs. 16.7%, \( P = 0.001 \)). Closed-cell stents were used in 2561 symptomatic patients (51.2%) and 1490 asymptomatic patients (43.1%), with a significant difference in the preference for closed-cell stents according to symptomatic status (\( P = 0.0001 \)). The incidence of complications was significantly higher among symptomatic patients than among asymptomatic patients (150/5004, 3.0% vs. 48/3454, 1.4%; \( P = 0.0001 \)).

### Risk factors of CSCs

Univariate analysis showed that age (OR, 1.03/year increment; 95% CI, 1.01–1.05; \( P = 0.003 \)), symptomatic lesion (OR, 2.19; 95% CI, 1.58–3.04; \( P = 0.0001 \)), and hypoechoic lesion on carotid artery ultrasound (OR, 1.91; 95% CI, 1.38–2.66; \( P = 0.0001 \)) were significant risk factors for CSC. Use of antiplatelet therapy (OR, 0.38; 95% CI, 0.19–0.75; \( P = 0.0005 \)), use of an EPD (OR, 0.19; 95% CI, 0.07–0.48; \( P = 0.0005 \)), post-dilatation (OR, 0.47; 95% CI, 0.33–0.69; \( P = 0.0001 \)), and use of a closed-cell stent (OR, 0.66; 95% CI, 0.49–0.88; \( P = 0.005 \)) were associated with significantly reduced risk of CSC.

On multivariate analysis, symptomatic lesion (OR, 1.91; 95% CI, 1.23–3.00; \( P = 0.003 \)) and hypoechoic lesion on carotid artery ultrasound (OR, 1.85; 95% CI, 1.21–2.84; \( P = 0.005 \)) remained the only significant risk factors for CSC, whereas the use of a closed-cell stent (OR, 0.53; 95% CI, 0.35–0.79; \( P = 0.0002 \)) was the only factor associated with significantly reduced risk of CSC (Table 5).

### Risk factors of CSCs according to symptomatic status

Multivariate analysis revealed that, among symptomatic patients, age (OR, 1.03/year increment; 95% CI, 1.01–1.05; \( P = 0.016 \)) was the only independent risk factor for post-CAS CSC, whereas acute-stage CAS was associated with significantly lower risk (OR, 0.48; 95% CI, 0.35–0.67; \( P = 0.0001 \)) (Table 6). On univariate analysis, use of an EPD (OR, 0.29; 95% CI, 0.09–0.98; \( P = 0.046 \)), post-dilatation (OR, 0.51; 95% CI, 0.33–0.78; \( P = 0.002 \)), and use of a closed-cell stent (OR, 0.61; 95% CI, 0.44–0.85; \( P = 0.004 \)) were also associated with significantly lower risk of post-CAS CSC.

On multivariate analysis, use of a closed-cell stent was the only independent factor associated with reduced risk of post-CAS CSC in asymptomatic patients (OR, 0.45; 95% CI, 0.29–0.70; \( P = 0.0002 \)). No significant risk factors associated with CSC were found for asymptomatic patients (Table 7).

### Discussion

The frequency of CAS and CEA differs across the world. In the United States, CEA and CAS were performed with a frequency of 128/1,000,000 and 38/1,000,000 person-years, respectively, between 2013 and 2014.\(^9\) By contrast, CAS is more commonly performed in Japan, with 7336 CAS procedures and 4218 CEA procedures performed in 2013, reflecting a 1.7-fold higher frequency for CAS.\(^10\) Therefore, the status and therapeutic outcomes of CAS in Japan should be investigated separately. For this purpose, we conducted a retrospective analysis of CAS data obtained from the

### Table 4 Comparison of CAS procedure between symptomatic and asymptomatic lesions (JR-NET3)

| Variables                      | Asymptomatic | Symptomatic | P-value      |
|-------------------------------|--------------|-------------|--------------|
| Dual/Triple antiplatelet use, n (%) | 3155/3341 (94.4) | 4426/4656 (95.1) | 0.21         |
| Aspirin                       | 2915/3341 (87.3) | 3947/4656 (84.8) | 0.0017*      |
| Ticlopidine/Clopidogrel        | 2718/3341 (81.4) | 3799/4656 (81.6) | 0.78         |
| CiMastazol                    | 1194/3341 (35.7) | 1986/4656 (42.7) | 0.0001*      |
| Technical characteristics, n (%) |              |             |              |
| Distal filter protection      | 1542/3437 (44.9) | 1937/4969 (39.0) | 0.0001*      |
| Distal balloon protection     | 1056/3437 (30.7) | 1504/4969 (30.3) | 0.65         |
| Proximal/combined protection  | 562/3437 (16.4) | 1029/4969 (20.7) | 0.0001*      |
| Stents                        |              |             |              |
| Closed-cell type              | 1490/3454 (43.1) | 2561/5004 (51.2) | 0.0001*      |
| Clinically significant comp.  | 48/3454 (1.4)  | 150/5004 (3.0)  | 0.0001*      |

*Statistical significance. JR-NET: Japanese Registry of Neuroendovascular Therapy.
Table 5  Risk factors of clinically significant complications related to CAS

| Variable                               | Significant complications (n = 198) | Mean ± SD or n (%) | Univariate analysis | Multivariate analysis |
|----------------------------------------|------------------------------------|--------------------|--------------------|----------------------|
|                                        |                                    |                    | OR [95% CI]        | P-value              | OR [95% CI]        | P-value              |
| Age (years)                            |                                    | 74.4 ± 7.97        | 1.03 [1.01–1.05]   | 0.003*               | 1.02 [1.00–1.05]   | 0.08                 |
| Male sex                               |                                    | 167 (84.3)         | 0.86 [0.6–1.30]    | 0.52                 | 1.10 [0.61–2.00]   | 0.76                 |
| Symptomatic lesion                     |                                    | 150 (75.8)         | 2.19 [1.58–3.04]   | 0.0001*              | 1.91 [1.23–3.00]   | 0.003*               |
| Degree of stenosis (%)                 |                                    | 79.2 ± 13.9        | 1.0 [0.99–1.01]    | 0.6                  | 0.84 [0.31–2.44]   | 0.74                 |
| Low-echoic lesion                      |                                    | 69 (46.9)          | 1.91 [1.38–2.66]   | 0.0001*              | 1.85 [1.21–2.84]   | 0.005*               |
| High-intensity signal on TOF MRA      |                                    | 62 (43.7)          | 1.33 [0.95–1.87]   | 0.09                 | 1.35 [0.88–2.09]   | 0.17                 |
| Antiplatelet use                       |                                    | 188 (95.4)         | 0.38 [0.19–0.75]   | 0.005*               | –                   | –                   |
| Dual/Triple antiplatelet therapy      |                                    | 173 (94.0)         | 0.86 [0.46–1.59]   | 0.63                 | 1.05 [0.30–3.7]    | 0.94                 |
| Aspirin                                |                                    | 160 (87.0)         | 1.11 [0.72–1.71]   | 0.65                 | 1.64 [0.66–4.04]   | 0.28                 |
| Ticlopidine/Clopidogrel                |                                    | 146 (79.4)         | 0.87 [0.61–1.25]   | 0.45                 | 0.82 [0.40–1.71]   | 0.06                 |
| Cilostazol                             |                                    | 72 (39.1)          | 0.97 [0.72–1.31]   | 0.86                 | 0.88 [0.46–1.68]   | 0.69                 |
| EPD use                                |                                    | 192 (97.5)         | 0.19 [0.07–0.48]   | 0.005*               | –                   | –                   |
| Distal filter protection               |                                    | 80 (41.7)          | 1.01 [0.76–1.35]   | 0.94                 | 1.50 [0.95–2.35]   | 0.08                 |
| Proximal/Combined protection           |                                    | 43 (22.4)          | 1.24 [0.88–1.75]   | 0.22                 | 1.25 [0.72–2.18]   | 0.44                 |
| MoMa                                   |                                    | 11 (5.61)          | 1.19 [0.64–2.20]   | 0.58                 | 1.66 [0.76–3.61]   | 0.23                 |
| Pre-dilatation                         |                                    | 170 (86.3)         | 0.74 [0.49–1.12]   | 0.16                 | 0.80 [0.41–1.55]   | 0.52                 |
| Post-dilatation                        |                                    | 164 (82.8)         | 0.47 [0.33–0.69]   | 0.0001*              | 0.69 [0.38–1.26]   | 0.25                 |
| Closed-cell stent                      |                                    | 75 (37.9)          | 0.66 [0.49–0.88]   | 0.005*               | 0.53 [0.35–0.79]   | 0.002*               |

*Statistical significance. Analysis based on data from the Japanese Registry of NeuroEndovascular Therapy 3 (JR-NET3). CAS: carotid artery stenting, CI: confidence interval, OR: odds ratio, TOF MRA: time-of-flight magnetic resonance angiography, EPD: embolic protection device, MoMa: Mo.Ma Ultra (Medtronic, Minneapolis, MN, USA), SD: standard deviation.

Table 6  Risk factors of clinically significant complications in patients with symptomatic lesions

| Variable                                      | Univariate analysis | Multivariate analysis |
|-----------------------------------------------|---------------------|-----------------------|
|                                               | OR [95% CI]        | P-value               | OR [95% CI]        | P-value               |
| Age, per year increment                       | 1.03 [1.01–1.05]   | 0.016*               | 1.02 [0.99–1.05]   | 0.13                 |
| Male sex                                      | 0.81 [0.52–1.28]   | 0.37                  | 0.99 [0.55–1.81]   | 0.98                 |
| Acute intervention (within 14 days)           | 0.48 [0.35–0.67]   | 0.0001*              | 0.55 [0.36–0.86]   | 0.01*                |
| Degree of stenosis, per percentage increment  | 1.00 [0.99–1.01]   | 0.81                  | 1.00 [0.98–1.02]   | 0.79                 |
| High-intensity signal on TOF MRA              | 1.13 [0.77–1.67]   | 0.52                  | 1.34 [0.88–2.04]   | 0.17                 |
| Dual/Triple antiplatelet therapy              | 0.96 [0.45–2.09]   | 0.93                  | 0.67 [0.21–2.17]   | 0.52                 |
| Aspirin                                       | 1.28 [0.76–2.13]   | 0.35                  | 1.61 [0.73–3.55]   | 0.23                 |
| Ticlopidine/Clopidogrel                       | 0.87 [0.57–1.33]   | 0.53                  | 1.08 [0.53–2.18]   | 0.84                 |
| Cilostazol                                    | 0.96 [0.68–1.35]   | 0.8                   | 1.38 [0.75–2.56]   | 0.3                  |
| EPD use                                       | 0.29 [0.09–0.98]   | 0.046*               | –                   | –                    |
| Distal filter protection                      | 1.11 [0.80–1.55]   | 0.53                  | 1.28 [0.80–2.05]   | 0.31                 |
| Proximal/Combined protection                  | 1.07 [0.72–1.59]   | 0.75                  | 1.07 [0.60–1.91]   | 0.81                 |
| MoMa                                          | 0.58 [0.21–1.58]   | 0.28                  | 0.60 [0.18–2.00]   | 0.38                 |
| Pre-dilatation                                | 0.81 [0.50–1.31]   | 0.4                   | 0.76 [0.38–1.51]   | 0.44                 |
| Post-dilatation                               | 0.51 [0.33–0.78]   | 0.002*               | 0.78 [0.42–1.42]   | 0.43                 |
| Closed-cell stent                             | 0.61 [0.44–0.85]   | 0.004*               | 0.45 [0.29–0.70]   | 0.0002*              |

*Statistical significance. Analysis based on data from the Japanese Registry of NeuroEndovascular Therapy 3 (JR-NET3). CAS: carotid artery stenting, CI: confidence interval, OR: odds ratio, TOF MRA: time-of-flight magnetic resonance angiography, EPD: embolic protection device, MoMa: Mo.Ma Ultra (Medtronic, Minneapolis, MN, USA), SD: standard deviation.
The JR-NET3 database, covering CAS procedures performed in Japan between January 1, 2010 and December 31, 2014. Our findings showed that CAS gave satisfactory rates in terms of technical success (99.5%), with a very low incidence of CSCs (2.3%).

Japanese Registry of NeuroEndovascular Therapy 1–3 are part of a series of nation-wide, multi-center, observational studies of neuroendovascular treatments in Japan. To gauge the time-dependent trends in the management of carotid artery stenosis, we compared our present findings in the JR-NET3 cohort to those noted in the JR-NET1 and 2 cohorts, and found similar rates of post-CAS CSC (JR-NET3: 198, 2.3%; JR-NET1: 59/1943, 3.0%; JR-NET2: 166/5191, 3.2%).

On multivariate analysis, the influencing factors for CSC post-CAS were symptomatic lesion (OR, 1.91; 95% CI, 1.23–3.00; P = 0.003), hypoechoic lesion on carotid artery ultrasound (OR, 1.85; 95% CI, 1.21–2.84; P = 0.005), and use of a closed-cell stent (OR, 0.53; 95% CI, 0.35–0.79; P = 0.002) in JR-NET3, compared with age (OR, 1.04/year increment; 95% CI, 1.02–1.07; P = 0.0004), symptomatic lesion (OR, 1.87; 95% CI, 1.31–2.71; P = 0.0004), and use of a closed-cell stent (OR, 0.58; 95% CI, 0.32–1.00; P = 0.05) in JR-NET2.

The EVA3-S2 clinical trial, which was conducted in Europe, reported that low experience of the surgeon was associated with increased risk of embolism (30%) due to passing the guiding catheter through the aortic arch to the carotid artery on the affected side. Therefore, we believe that the main factor contributing to the low rate of CSCs is the fact that specialists associated with the Japanese Society for NeuroEndovascular Therapy performed nearly all procedures (8042/8458, 95.1%).

Regarding the timing of treatment in symptomatic patients, CEA was most effective if performed within 2 weeks of ischemia onset,11 whereas early CAS was considered to be high risk. In particular, for interventions performed within 7 days of symptom onset, the risk of perioperative stroke and mortality was significantly higher for CAS than for CEA.11–14 But, in JR-NET3, CAS performed within 2 weeks of ischemia onset was associated with lower risk of CSCs (Univariate analysis OR 0.48 [0.35–0.67] 0.0001, multivariate analysis OR 0.55 [0.36–0.86] 0.01).

Compared with CEA, CAS has been reported to carry a higher risk of embolism-related ischemic complications. Plaque-like formations, sometimes with a lipid core and intraplaque bleeding, are commonly observed in patients with post-CAS embolism.15,16 In this study, we found no correlation between CSC incidence and a high-intensity signal on TOF MRA. Furthermore, existence of high intensity signal in the plaque on TOF was judged in each institute. So, it was difficult to evaluate its significance. However, as reported in previous studies, we found that hypoechoic lesion on

Table 7 Risk factors of clinically significant complications in patients with asymptomatic lesions

| Variables | OR [95% CI] | P-value |
|-----------|-------------|---------|
| Age, per year increment | 1.04 [0.99–1.10] | 0.14 |
| Male sex | 0.99 [0.37–2.64] | 0.98 |
| Acute intervention (within 14 days) | 1.44 [0.55–3.74] | 0.47 |
| Degree of stenosis, per percentage increment | 0.99 [0.97–1.03] | 0.74 |
| High-intensity signal on TOF MRA | 1.51 [0.69–3.28] | 0.31 |
| Dual/Triple antiplatelet therapy | 1.74 [0.20–15.2] | 0.61 |
| Aspirin | 0.60 [0.10–3.51] | 0.57 |
| Ticlopidine/Clopidogrel | 0.34 [0.06–1.80] | 0.19 |
| Cilostazol | 0.42 [0.09–2.01] | 0.24 |
| EPD use | – | – |
| Distal filter protection | 1.60 [0.63–4.12] | 0.32 |
| Proximal/combined protection | 2.54 [0.89–7.23] | 0.08 |
| MoMa | 2.52 [0.88–7.18] | 0.1 |
| Pre-dilatation | 0.75 [0.20–2.77] | 0.68 |
| Post-dilatation | 0.71 [0.21–2.42] | 0.6 |
| Closed-cell stent | 0.63 [0.29–1.38] | 0.24 |

Analysis based on data from the Japanese Registry of NeuroEndovascular Therapy 3 (JR-NET3). CAS: carotid artery stenting, CI: confidence interval, EPD: embolic protection device, MoMa: Mo.Ma Ultra (Medtronic, Minneapolis, MN, USA), OR: odds ratio, SD: standard deviation, TOF MRA: time-of-flight magnetic resonance angiography.
carotid artery ultrasound was significantly associated with distal embolism and ischemic complications. An EPD is often utilized for preventing embolic complications. In JR-NET3, distal filter protection was the most common approach used for embolism prevention (41.4%), likely because the distal filter is relatively easy to manipulate. Nevertheless, embolic complications associated with poor adhesion of the filter to the arterial wall and abrasions caused by debris occur more often with distal filter protection than with proximal protection. Moreover, the no-flow phenomenon may occur if there is a large amount of plaque. Distal balloon protection may be indicated for curved lesions or lesions with a high degree of stenosis, as this approach is thought to allow debris to be collected more easily. Nevertheless, distal balloon protection may cause ischemic intolerance when vascular occlusion occurs, or may lead to ischemic oculopathy in interventions involving the external carotid artery.

In Japan, the Mo.Ma Ultra filter was approved in January 2013 but its frequency of use in JR-NET3 was low (only 4.8%; 403 cases), likely due to the fact that the enrollment period for JR-NET3 ended on December 31, 2014, very soon after the Mo.Ma Ultra filter was approved. Therefore, future research is warranted to clarify the risk of complications associated with proximal protection.

In JR-NET3, open- and closed-cell stents were utilized in 50.0% and 47.9% of cases, respectively. Symptomatic patients were slightly more likely to receive closed-cell stents (51.2%). Both univariate and multivariate analysis indicated that the use of closed-cell stents was associated with significantly reduced risk of CSC in symptomatic patients. Research into stent cell design has reported no effect on the rate of perioperative complications. However, Park et al. reported that the use of closed-cell stents was associated with significantly fewer complications. Similarly, Bosiers et al. reported that the rate of perioperative complications was lower for closed-cell stents than for open-cell stents (1.2% vs. 3.4%). Finally, Hart et al. reported that the use of open-cell stents in symptomatic patients increased the number of perioperative complications (OR, 4.1). Taken together, these results support the use of closed-cell stents in CAS.

Some studies have suggested that pre-dilatation is a risk factor for intraoperative embolism, whereas other studies have reported the same for post-stenotic dilatation. In this study, we found no significant effect of dilatation timing.

This study has several limitations, including its retrospective design and the non-uniform application of surgical techniques across different centers, possibly introducing bias. However, our analysis was based on real-world data and included a very large sample with nation-wide representation. Further study is warranted to clarify why some of our conclusions contradict previous findings.

To conclude, we analyzed CAS outcomes according to the devices utilized, symptomatic status, and use of antiplatelet agents. Multivariate analysis indicated that the risk factors associated with post-CAS CSC were symptomatic lesion and hypoechoic lesion on carotid artery ultrasound, whereas the use of closed-cell stents was associated with reduced risk. The findings of this study provide an overview of the current use of CAS in clinical practice and may be useful in developing improved therapeutic strategies for carotid artery stenosis in Japanese patients.

Acknowledgments

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The JR-NET3 Study Group includes the following specialists: Nobuyuki Sakai (co-principal investigator), Kobe City Medical Center General Hospital, Kobe, Japan; Koji Ihara (co-principal investigator), Kyushu University, Fukuoka, Japan; Tetsu Satow (co-principal investigator), National Cerebral and Cardiovascular Center, Suita, Japan; Yusuke Inamura (co-investigator), Sendai Medical Center, Sendai, Japan; Akio Hyodo (investigator), Dokkyo Medical University Saitama Medical Center, Koshigaya, Japan; Shigeru Miyachi (investigator), Aichi Medical University, Aichi, Japan; Susumu Miyamoto (investigator), Kyoto University, Kyoto, Japan; Yoji Nagai (investigator), Kobe University, Kobe, Japan; Kunihiro Nishimura (investigator), National Cerebral and Cardiovascular Center, Suita, Japan; Kazunori Toyoda (investigator), National Cerebral and Cardiovascular Center, Suita, Japan; Toshiyuki Fujinaka (co-investigator), Osaka Medical Center, Osaka, Japan; Toshiro Higashi (co-investigator), Fukuoka University, Fukuoka, Japan; Masaru Hirohata (co-investigator), Kurume University, Kurume, Japan; Akira Ishii (co-investigator), Kyoto University, Kyoto, Japan; Hirotoshi Iamamura (co-investigator), Kobe City Medical Center General Hospital, Kobe, Japan; Yasushi Ito (co-investigator), Shinrakuen Hospital, Niigata, Japan; Naoya Kuwayama (co-investigator), Toyama University, Toyama, Japan; Hidenori Oishi (co-investigator), Juntendo University, Tokyo, Japan; Yuji Matsumura (co-investigator), Tsukuba University, Tsukuba, Japan; Yasushi Matsumoto (co-investigator), Konan Hospital, Sendai, Japan; Ichiro Nakahara (co-investigator), Fujita Health University, Aichi, Japan; Chiaki Sakai (co-investigator), Hyogo College of Medicine, Nishinomiya, Japan; Kenji Sugiu (co-investigator), Okayama University, Okayama, Japan; Tomoaki Terada (co-investigator), Showa
University Fujigaoka Hospital, Kanagawa, Japan; Shinichi Yoshimura (co-investigator), Hyogo College of Medicine, Nishinomiya, Japan; and specialists certified by the Japanese Society of Neuro Endovascular Therapy.

Conflicts of Interest Disclosure

The authors have no competing interests to disclose.

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**Address reprint requests to:** Shinichi Yoshimura, MD, PhD, Department of Neurosurgery, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan.

**e-mail:** hyogoneuro@yahoo.co.jp