Real-world Experience of Carotid Artery Stenting in Japan: Analysis of 7,134 Cases from JR-NET1 and 2 Nationwide Retrospective Multi-center Registries

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Abstract

The present study aimed to demonstrate the “real-world” experiences of carotid artery stenting (CAS) in Japan using Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2, retrospective nationwide multi-center surveillances. JR-NET1 and 2 registries are retrospective surveillances conducted between January 2005 and December 2007 and January 2008 and December 2009, respectively, in Japan regarding neuroendovascular therapy. A total of 7,134 procedures (1,943 for JR-NET1 and 5,191 for JR-NET2) were included in this study and retrieved data were analyzed retrospectively. Treatment results of two surveillance periods were similar. In JR-NET2 registry, total of 5,191 lesions were treated by CAS and 5,008 of 5,191 procedures (96.5%) were performed by the board-certified surgeons of Japanese Society of Neuroendovascular Therapy. The rate of technical success was extremely high (99.99%), and the rate of clinically significant complication was low (3.2%). These results were comparable to a previous large study in Japan. Multivariate logistic analysis revealed that age [odds ratio (OR), 1.04 per year; 95% confidence interval (CI), 1.02–1.07; p = 0.0004], symptomatic lesion (OR, 1.87; 95% CI; p = 0.0004), and the use of closed-cell type stent (OR, 0.58; 95% CI, 0.32–1.00; p = 0.05) were independently associated with clinically significant complications. It was revealed that good clinical results were achieved in patients who underwent CAS in Japan. 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.

Keywords: carotid artery stenosis, nationwide surveillance, stenting, treatment results

Introduction

Carotid artery stenting (CAS) has been widely accepted as a valuable therapeutic alternative to carotid endarterectomy (CEA) for the treatment of atherosclerotic stenosis of cervical internal carotid artery. In 2005, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial demonstrated that CAS carried a better outcome than CEA in patients with CEA high-risk characteristics. However, the succeeding randomized controlled trials, Symptomatic Severe Carotid Stenosis trial (EVA-3S), Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and International Carotid Stenting Study (ICSS) failed to prove the non-inferiority of CAS compared to CEA. Together with these results, the safety and efficacy of CAS compared to CEA still remains questioned, and CEA has been considered to the first-line treatment of carotid stenosis in
Materials and Methods

I. Patient population

JR-NEt1 and 2 registries are retrospective surveillances conducted between January 2005 and December 2007 and January 2008 and December 2009, respectively, in Japan regarding neuroendovascular therapy. A total of 7,821 procedures of CAS in Japan were registered with JR-NEt1 and JR-NEt2 registries (2,323 for JR-NEt1 and 5,498 for JR-NEt2). Among these 7,821 procedures, 687 were excluded, and the remaining 7,134 procedures (1,943 for JR-NEt1 and 5,191 for JR-NEt2) were included in this study and retrieved data were analyzed retrospectively.

II. Analysis of characteristics of patients and CAS procedures

First, to determine the characteristics and background of patients who underwent CAS, age, gender, CEA high-risk characteristics according to SAPPHIRE trial, presentation of symptoms, and degree of stenosis were analyzed. Next, procedural success, periprocedural antiplatelet use, embolic protection device (EPD) use, the type of stent strut (open-cell or closed-cell), the execution of pre- or post balloon dilatation, and procedure-related complications were analyzed to clarify the current strategy and the treatment results of CAS. Degree of stenosis was measured in accordance with North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. “Procedural success” was defined as the achievement of sufficient dilatation of stenotic site by stent placement. Procedure-related complications were defined as distal embolism, vascular perforation, arterial dissection, hyperperfusion, acute thrombosis, myocardial infarction, and any other complications occurred within 30 days after procedure that related to the CAS procedure.

III. Clinical evaluation

The modified Rankin Scale (mRS) score of disability was used to evaluate the pre- and postprocedural neurological conditions of the patients. “Morbidity” was defined as worsening of mRS score between onset and at 30 days after CAS procedure, and “clinically significant complication” was defined as any morbidity related to the CAS procedure. “Minor morbidity” was defined as 1 point worsening of mRS score, and “major morbidity” was defined as 2 or more points worsening of mRS score.

IV. Statistical analysis

All quantitative variables are expressed as mean ± standard deviation (SD). The statistical significance of intergroup differences was assessed using the Chi-square test for categorical variables and the Student’s t-test for quantitative variables. The retrieved clinical variables were interrogated using univariate and multivariate logistic analysis to identify risk factors for clinically significant complications. P-values less than 0.05 were considered statistically significant. The odds ratio (OR) and 95% confidential interval (CI) were also determined. Commercially available software (JMP 7 for Macintosh; SAS Institute Inc., Cary, North Carolina, USA) was used for all statistical analysis.

Results

I. Baseline characteristics of patients and lesions (JR-NEt2)

Among a total of 5,191 CAS procedures included in JRNET-2 registry, 5,008 (96.5%) were performed by the board-certified surgeon of Japanese Society of Neuroendovascular Therapy (JSNT). Characteristics of patients are shown in Table 1. Total of 5,191 lesions with a mean age of 71.6 ± 7.6 years (range 16–95 years) and a mean degree of stenosis of 78.1 ± 12.5% according to NASCET method were treated by CAS in JR-NEt2 surveillance. Among these 5,191 procedures, 4,871 (93.9%) were performed for the patients who scored as good clinical status (mRS 0 to 2 at CAS procedure), and 4,262 (84.4%) were performed for the patients who had CEA high-risk characteristics. Symptomatic lesions were 3,075 (59.3%) and asymptomatic lesions were 2,114 (40.7%). Detailed presentations of treated lesions were as follows: 226 (4.4%) were amaurosis...
fugax, 679 (13.1%) were transient ischemic attack (TIA), 1,617 (31.2%) were minor completed stroke, 371 (7.1%) were major stroke, and 100 (1.9%) were progressing stroke.

II. Results of CAS and procedure-related complications (JR-NET1 and 2)

The clinical results of CAS in each surveillance period are presented in Table 2. At 30 days after CAS procedure, 1,815 of 1,943 (93.4%) and 4,770 (93.0%) of treated patients scored as mRS 0–2, and 13 (0.7%) and 14 (0.3%) patients died in JR-NEt1 and 2, respectively. Procedure-related complications occurred in 174 (9.0%) and 508 (9.8) procedures, and in 58 (3.0%) and 166 (3.2%) the complications were clinically significant. Major morbidity occurred in 32 (1.7%) and 81 (1.6%), and minor morbidity occurred in 18 (0.9%) and 78 (1.5%) after CAS procedure in JR-NEt1 and 2, respectively.

III. Details of current CAS procedure in Japan

Table 3A shows the details of current strategy of CAS determined by JR-NEt2. Antiplatelet agents were used in 5,093 (99.3%) procedures; dual or triple antiplatelet agents were employed in 4,504 procedures (93.4%). Aspirin was most widely used and Cilostazol or Thienopyridine derivatives (Ticlopidine or Clopidogrel) were combined in most cases in this study. Procedural success was achieved in 5,186 (99.99%) procedures. Most procedures (5,161 procedures, 99.6%) were performed using EPDs, and used EPDs were as follows: 2,683 (52.1%) with distal filter protection device; 1,972 (38.3%) with distal balloon protection; and 492 (9.5%) with proximal or combined protection. Open-cell type stent was used in 4,373 (84.5%) procedures, and closed-cell type stent was used in 762 (14.7%) procedures.

Table 3B shows the comparison of technical characteristics between asymptomatic and symptomatic

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Table 1 Patient and lesion characteristics (JR-NEt2)

| Characteristic                        | Value     |
|---------------------------------------|-----------|
| Age, mean ± SD                        | 71.6 ± 7.6|
| Range                                 | 16–95     |
| Age ≥ 70 years, n (%)                 | 3,358 (64.7)% |
| mRS 0–2 at procedure                  | 4,871 (93.9)% |
| Male gender, n (%)                    | 4,496 (86.6)% |
| Degree of stenosis, %, mean ± SD      | 78.1 ± 12.5 |
| CEA high risk characteristics, n (%)  | 4,262 (84.4)% |
| Presentation, n (%)                   | 3,075 (59.3)% |
| Symptomatic                           | 226 (4.4)% |
| Amaurosis fugax                       | 679 (13.1)% |
| TIA                                   | 1,617 (31.2)% |
| Minor completed stroke                | 371 (7.1)% |
| Major stroke                          | 100 (1.9)% |
| Asymptomatic                          | 2,114 (40.7)% |

CEA: carotid endarterectomy, JR-NEt: Japanese Registry of Neuroendovascular Therapy, mRS: modified Rankin Scale, TIA: transient ischemic attack.
lesions. Distal filter protection was less frequently used in symptomatic lesions than asymptomatic lesions (47.9% vs. 58.2%, p < 0.0001). Instead, distal balloon protection was more frequently used in symptomatic lesions than asymptomatic lesions (40.2% vs. 35.4%, p < 0.001). Furthermore, proximal/combined protection was used about two times frequency in symptomatic lesions (11.8% vs. 6.3%, p < 0.0001). The rate of clinically significant complication was significantly higher in symptomatic lesions than those of asymptomatic lesions (4.1% vs. 2.0%, p < 0.0001).

**IV. Risk factors for clinically significant complications following CAS**

Clinically significant complication related to CAS occurred in 166 (3.2%) procedures in JR-NET2. Age (OR, 1.05 per year; 95% CI, 1.02–1.07; p < 0.0001) and symptomatic lesion (OR, 2.05; 95% CI, 1.45–2.90; p < 0.0001) were determined as risk factors for clinically significant complications by univariate logistic analysis. Multivariate analysis showed that age (OR, 1.04 per year; 95% CI, 1.02–1.07; p = 0.0004), symptomatic lesion (OR, 1.87; 95% CI, 1.31–2.71; p = 0.0004), and the use of closed-cell stent (OR, 0.58; 95% CI, 0.32–1.00; p = 0.05) were independently associated with clinically significant complications.

### Table 4 Risk factors for clinically significant complication related to CAS procedure (JR-NET2)

| Variables                          | Significant complication (n = 166) | Univariate analysis | Multivariate analysis |
|-----------------------------------|-----------------------------------|---------------------|----------------------|
|                                   | mean ± SD or n (%)                | OR [95% CI]         | P value              | OR [95% CI] | P value |
| Age, years                        | 73.8 ± 6.2                        | 1.05 [1.02–1.07]    | < 0.0001*            | 1.04 [1.02–1.07] | 0.0004* |
| Male gender                       | 145 (87.4)                        | 0.93 [0.57–1.45]    | 0.77                 | 0.86 [0.51–1.39] | 0.56    |
| Symptomatic lesion                | 124 (74.7)                        | 2.05 [1.45–2.90]    | < 0.0001*            | 1.87 [1.31–2.71] | 0.0004* |
| Degree of stenosis, %             | 77.6 ± 13.0                       | 1.00 [0.98–1.01]    | 0.64                 | 0.99 [0.98–1.01] | 0.46    |
| Antiplatelet use                  | 165 (100)                         | –                   | 0.63                 | –           | –       |
| Dual/triple antiplatelet          | 149 (91.4)                        | 0.74 [0.44–1.36]    | 0.31                 | 0.86 [0.36–2.17] | 0.75    |
| Aspirin                           | 145 (89.0)                        | 0.87 [0.54–1.49]    | 0.60                 | 0.98 [0.46–2.14] | 0.96    |
| Ticlopidine/Clopidogrel           | 73 (44.8)                         | 0.88 [0.64–1.20]    | 0.41                 | 0.85 [0.46–1.49] | 0.59    |
| Cilostazol                        | 104 (63.8)                        | 1.02 [0.75–1.43]    | 0.86                 | 1.01 [0.54–1.81] | 0.98    |
| EPD use                           | 164 (98.8)                        | 0.32 [0.09–1.21]    | 0.14                 | –           | –       |
| Distal filter protection          | 88 (54.3)                         | 1.10 [0.81–1.51]    | 0.54                 | 0.97 [0.67–1.41] | 0.85    |
| Proximal/combined protection      | 14 (8.6)                          | 0.89 [0.49–1.50]    | 0.68                 | 0.58 [0.27–1.10] | 0.10    |
| Predilatation                     | 140 (84.9)                        | 1.08 [0.71–1.65]    | 0.83                 | 1.12 [0.70–1.89] | 0.64    |
| Postdilatation                    | 151 (91.5)                        | 0.97 [0.56–1.66]    | 0.89                 | 1.15 [0.62–2.37] | 0.68    |
| Closed-cell stent                 | 17 (10.4)                         | 0.64 [0.37–1.04]    | 0.07                 | 0.58 [0.32–1.00] | 0.05*   |

*indicates statistical significance. CAS: carotid artery stenting. CI: confidence interval, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio, SD: standard deviation.
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 logistic 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).

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 perioperative management.\(^5\) These systems would certainly contribute to improve the rate of technical success without perioperative 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 embolism 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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