Neurol Med Chir (Tokyo) 54, 32–39, 2014
doi: 10.2176/nmc.oa2013-0187
Online December 5, 2013

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

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

Yusuke EGASHIRA,[1] Shinichi YOSHIMURA,[1,2] Nobuyuki SAKAI,[3] Yukiko ENOMOTO,[1] and the Japanese Registry of Neuroendovascular Therapy (JR-NET) investigators

[1]*Department of Neurosurgery, Gifu University Graduate School of Medicine, Gifu, GIfu;*
[2]*Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Hyogo;*
[3]*Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Hyogo*

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% CT, 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.[1)] However, the succeeding randomized controlled trials, Symptomatic Severe Carotid Stenosis trial (EVA-3S),[2)] Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial,[3)] and International Carotid Stenting Study (ICSS)[4)] 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

Received May 28, 2013; Accepted October 16, 2013

worldwide. On the other hand, CAS was officially approved in Japan in April 2008, and the number of patients undergoing CAS has been increasing because of its less-invasiveness. Carotid revascularization was performed in approximately 7,500–8,500 cases per year in 2007–2009, and CAS is performed nearly 1.5–2 times more often than CEA in Japan.[5] The present study aimed to demonstrate the "real-world" experiences of CAS in Japan using the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2 retrospective nationwide surveillances.

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. The reasons of exclusion from this study were as follows: 66 procedures had undergone CAS not for atherosclerotic carotid stenosis, 261 procedures simultaneously performed other disorders, and the details of 360 procedures were not available. In the present study, we mainly focused and analyzed the data from JR-NET2 because CAS has been officially approved since April 2008 in Japan, and JR-NET2 registry mainly covered this period.

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,[1] 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.[6] "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

Table 1 Patient and lesion characteristics (JR-NET2)

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 (%)	
Symptomatic	3,075 (59.3)
Amaurosis fugax	226 (4.4)
TIA	679 (13.1)
Minor completed stroke	1,617 (31.2)
Major stroke	371 (7.1)
Progressing 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.

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 5,191 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 (Ticropidine or Clopidogrel) were combined in most cases in this study. Procedural success was achieved in

Table 2 Results of CAS and procedure-related complications (JR-NET1 & 2)

	JR-NET1 (n = 1,943)	JR-NET2 (n = 5,191)
mRS 0–2	1,815 (93.4)	4,770 (93.0)
Any death, n (%)	13 (0.7)	14 (0.3)
Any morbidity, n (%)	106 (5.5)	397 (7.8)
Any procedure related complication, n (%)	174 (9.0)	508 (9.8)
Clinically significant complication, n (%)	58 (3.0)	166 (3.2)
Death	8 (0.4)	7 (0.1)
Major morbidity	32 (1.7)	81 (1.6)
Minor morbidity	18 (0.9)	78 (1.5)

CAS: carotid artery stenting, mRS: modified Rankin Scale, JR-NET: Japanese Registry of Neuroendovascular Therapy.

Table 3A Details of current CAS procedure in Japan (JR-NET2)

Antiplatelet use, n (%)	5,093 (99.3)
Dual/Triple antiplatelet	4,504 (93.4)
Aspirin	4,349 (90.2)
Ticropidine/Clopidogrel	2,315 (48.0)
Cilostazol	3,046 (63.2)
Technical characteristics, n (%)	
Procedural success	5,186 (99.99)
EPD use	5,161 (99.6)
Distal filter	2,683 (52.1)
Distal balloon	1,972 (38.3)
Proximal/combined protection	492 (9.5)
Stents	
Open-cell type	4,373 (84.5)
Closed-cell type	762 (14.7)
Combined	14 (0.3)

CAS: carotid artery stenting, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy.

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

Table 3B Comparison of technical characteristics between symptomatic and asymptomatic lesions (JR-NET2)

Variables	Asymptomatic (n = 2,114)	Symptomatic (n = 3,075)	p value
Dual/Triple antiplatelet use, n (%)	1,840 (93.4)	2,664 (93.4)	0.95
Aspirin	1,792 (90.1)	2,557 (86.7)	0.15
Ticlopidine/ Clopidogrel	960 (48.7)	1,355 (47.5)	0.41
Cilostazol	1,217 (61.8)	1,829 (64.2)	0.09
Technical characteristics, n (%)			
Distal filter protection	1,220 (58.2)	1,462 (47.9)	< 0.0001
Distal balloon protection	743 (35.4)	1,229 (40.2)	< 0.001
Proximal/ combined protection	132 (6.3)	360 (11.8)	< 0.0001
Stents			
Closed-cell type	295 (14.0)	482 (15.8)	0.08
Clinically significant complication	42 (2.0)	124 (4.1)	< 0.0001

JR-NET: Japanese Registry of Neuroendovascular Therapy.

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 asymptomartic 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

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
Ticropidine/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.

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.

Acknowledgments

The authors would like to express their sincere thanks to the participants who devoted their time to this investigation.

The JR-NET Study Group: Principle Investigator; Nobuyuki Sakai, Kobe City Medical Center General Hospital, Kobe, Japan: Investigators; Akio Hyodo, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan (17C-1, 20C-2), Shigeru Miyachi, Nagoya University, Nagoya, Japan (17C-1, 20C-2), Yoji Nagai, Translational Research Informatics Center, Kobe, Japan (17C-1, 20C-2), Chiaki Sakai, Institute of Biomedical Research and Innovation, Kobe, Japan (17C-1, 20C-2), Tetsu Satoh, National Cerebral and Cardiovascular Center, Suita, Japan (17C-1, 20C-2), Waro Taki, Mie University, Tsu, Japan (17C-1, 20C-2), Tomoaki Terada, Wakayama Rosai Hospital, Wakayama, Japan (17C-1, 20C-2), Masayuki Ezura, Sendai Medical Center, Sendai, Japan (17C-1), Toshio Hyogo, Nakamura Memorial Hospital, Sapporo, Japan (17C-1), Shunji Matsubara, Tokushima University, Tokushima, Japan (17C-1), Kentaro Hayashi, Nagasaki University, Nagasaki Japan (20C-2); Co-Investigators; Toshiyuki Fujinaka, Osaka University, Suita, Japan, Yasushi Ito, Niigata University, Niigata, Japan, Shigeki Kobayashi, Chiba Emergency Medical Center, Chiba, Japan, Masaki Komiyama, Osaka City General Hospital, Osaka, Japan, Naoya Kuwayama, Toyama University, Toyama, Japan, Yuji Matsumaru, Toranomon Hospital, Japan, Yasushi Matsumoto, Konan Hospital, Sendai, Japan, Yuichi Murayama, Jikei Medical University, Tokyo, Japan, Ichiro Nakahara, Kokura Memorial Hospital, Kokura, Japan, Shigeru Nemoto, Jichi Medical University, Shimotsuke, Japan, Koichi Sato, Tokushima Red Cross Hospital, Tokushima, Japan, Kenji Sugiu, Okayama University, Okayama, Japan, Shinichi Yoshimura, Gifu University, Gifu, Japan, and certified specialist of Japanese Society of Neuroendovascular Therapy.

This study was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan.

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.

S. Yoshimura and N. Sakai received Speakers' Bureau/Honoraria from Sanofi and Otsuka Pharmaceutical Co.

References

1) Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators: Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 351: 1493–1501, 2004
2) Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, Bossavy JP, Denis B, Piquet P, Garnier P, Viader F, Touzé E, Julia P, Giroud M, Krause D, Hosseini H, Becquemin JP, Hinzelin G, Houdart E, Hénon H, Neau JP, Bracard S, Onnient Y, Padovani R, Chatellier G; EVA-3S investigators: Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 7: 885–892, 2008
3) SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368: 1239–1247, 2006
4) International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM: Carotid artery stenting compared with endarterectomy in

patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 375: 985–997, 2010
5) Miyachi S, Taki W, Sakai N, Nakahara I; Japanese CAS Survey Investigators: Historical perspective of carotid artery stenting in Japan: analysis of 8,092 cases in The Japanese CAS survey. *Acta Neurochir (Wien)* 154: 2127–2137, 2012
6) North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 325: 445–453, 1991
7) Fiehler J, Bakke SJ, Clifton A, Houdart E, Jansen O, Rüfenacht D, Söderman M, Cognard C: Plea of the defence-critical comments on the interpretation of EVA3S, SPACE and ICSS. *Neuroradiology* 52: 601–610, 2010
8) Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, Nicolaides AN, Griffin M, Raithel D, Reid DB, Valsecchi MG: Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation* 110: 756–762, 2004
9) Yamada K, Kawasaki M, Yoshimura S, Enomoto Y, Asano T, Minatoguchi S, Iwama T: Prediction of silent ischemic lesions after carotid artery stenting using integrated backscatter ultrasound and magnetic resonance imaging. *Atherosclerosis* 208: 161–166, 2010
10) Yoshida K, Narumi O, Chin M, Inoue K, Tabuchi T, Oda K, Nagayama M, Egawa N, Hojo M, Goto Y, Watanabe Y, Yamagata S: Characterization of carotid atherosclerosis and detection of soft plaque with use of black-blood MR imaging. *AJNR Am J Neuroradiol* 29: 868–874, 2008
11) Yoshimura S, Yamada K, Kawasaki M, Asano T, Kanematsu M, Takamatsu M, Hara A, Iwama T: High-intensity signal on time-of-flight magnetic resonance angiography indicates carotid plaques at high risk for cerebral embolism during stenting. *Stroke* 42: 3132–3137, 2011
12) Hamner JW, Tan CO, Lee K, Cohen MA, Taylor JA: Sympathetic control of the cerebral vasculature in humans. *Stroke* 41: 102–109, 2010
13) Bijuklic K, Wandler A, Hazizi F, Schofer J: The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. *J Am Coll Cardiol* 59: 1383–1389, 2012
14) Park KY, Kim DI, Kim BM, Nam HS, Kim YD, Heo JH, Kim DJ: Incidence of embolism associated with carotid artery stenting: open-cell versus closed-cell stents. *J Neurosurg* 119: 642–647, 2013
15) Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration: Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 363: 915–924, 2004
16) Rantner B, Goebel G, Bonati LH, Ringleb PA, Mas JL, Fraedrich G; Carotid Stenting Trialists' Collaboration: The risk of carotid artery stenting compared with CEA is greatest in patients treated within 7 days of symptoms. *J Vasc Surg* 57: 619–626.e2; discussion 625–626, 2013
17) Orlandi G, Fanucchi S, Fioretti C, Acerbi G, Puglioli M, Padolecchia R, Sartucci F, Murri L: Characteristics of cerebral microembolism during carotid stenting and angioplasty alone. *Arch Neurol* 58: 1410–1413, 2001
18) Martin JB, Pache JC, Treggiari-Venzi M, Murphy KJ, Gailloud P, Puget E, Pizzolato G, Sugiu K, Guimaraens L, Théron J, Rüfenacht DA: Role of the distal balloon protection technique in the prevention of cerebral embolic events during carotid stent placement. *Stroke* 32: 479–484, 2001
19) Giacovelli JK, Egorova N, Dayal R, Gelijns A, McKinsey J, Kent KC: Outcomes of carotid stenting compared with endarterectomy are equivalent in asymptomatic patients and inferior in symptomatic patients. *J Vasc Surg* 52: 906–913, 913.e1–4, 2010

Address reprint requests to: Shinichi Yoshimura, MD, PhD, Department of Neurosurgery, Hyogo College of Medicine, Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
e-mail: shinichiyoshimura@hotmail.com