Table 4. Annual Outcomes of EVT for Asymptomatic UIAs

	2005	2006	2007	2008	2009	*P* Value	Overall (2005–2009)
Feasibility (pa)							
Success	98.0	97.5	97.7	97.1	98.8	NS	97.9
Failure	2.0	2.5	2.3	2.9	1.2		2.1
Anatomic outcome (per successfully treated UIA)							
CO	55.3	60.0	58.1	58.1	56.6	NS	57.7
RN	33.2	31.6	32.7	29.8	32.5	NS	31.9
RA	10.7	7.4	9.2	11.7	10.9	0.03	10.0
uPAO	0.9	0.9	0	0.3	0	...	0.4
Adverse events (pp)							
Procedure-related complications	9.5	8.7	10.0	9.2	8.4	NS	9.1
Hemorrhagic	2.4	1.3	2.2	1.9	2.1	NS	2.0
Aneurysmal rupture	1.9	0.8	1.7	1.1	1.4	NS	1.4
Ischemic	5.7	5.6	4.23	4.1	3.9	0.01	4.6
Puncture site	0.8	0.6	0.4	1.2	0.7	NS	0.7
Other	0.6	1.2	3.1	2.1	1.8	...	1.8
Clinical outcome							
30-Day morbidity	2.70	2.14	2.09	1.77	2.09	NS	2.12
30-Day mortality	0.75	0.12	0.42	0.31	0.09	NS	0.31

All values except *P* values area shown as ratios (%). CO indicates complete occlusion; EVT, endovascular therapy; ns, not significant; pa, per aneurysm; pp, per procedure; RA, residual aneurysm; RN, residual neck; UIA, unruptured intracranial aneurysms; and uPAO, unpredicted parent artery occlusion.

others describe small patient cohorts. The ATENA study[11] prospectively studied EVT outcomes at several neuroradiological centers in France and Canada during 2005 and 2006. Table V in the online-only Data Supplement lists the case series of EVT for UIAs reported after the 1998 ISUIA study and Table 5 summarizes them and compares the ATENA and present studies.

Feasibility and Clinical Outcomes of EVT

The 2.1% failure rate in the present study was lower than those in the ATENA (4.3%) and other (3.8% to 10%) studies. The failure rates were significantly higher and lower for small aneurysms with wide and narrow necks, respectively, and tended to increase as aneurysms decreased. Failure rates did not significantly differ between aneurysms of the anterior and aneurysms of the posterior circulation.

The ATENA study that defined morbidity at 1 month after treatment as mRS 2 to 5 and a preoperative mRS>1 as any increase in the mRS, reported morbidity and mortality rates of 2.6% and 1.1%, respectively. These rates in retrospective case series range from 0% to 7.7% and from 0% to 1.7%, respectively. One systematic review found that at 1 month, 1.8% of patients had died in addition to 4.7% with unfavorable outcome rates, including death.[22] In addition, Brinjikji et al[21] found from the 2001 to 2008 Nationwide Inpatient Sample hospital discharge database that 4.9% patients were discharged to long-term facilities and 0.6% died after undergoing EVT for UIAs. Recent randomized controlled trials of bioactive coils have also shown risks of EVTs. The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS)[23] found mRS 3 to 6 at 18 months in 10.3% of patients with target aneurysms that had not ruptured recently. Besides, 2.3% of the patients treated for a UIA in the Cerecyte trial[24] had mRS 2 to 5 at discharge, and no deaths were determined. We defined morbidity and mortality as any deterioration >0 on the mRS and any death related to treatment, respectively, which were similar to Oishi's definitions.[10] We determined 2.1% and 0.3% morbidity and mortality rates from JR-NET and JR-NET2 data, respectively, which we think are justified. We could not evaluate cognitive status as in the ISUIA study, and because neurologists did not always perform independent neurological examinations, we might have underestimated morbidity.

Radiographic Outcomes

The other case series used various classifications. To compare rates of insufficient radiographic outcomes of coil embolization among studies, we determined how many were defined as incomplete occlusion (<90%) or residual aneurysm. The radiographic outcomes of coil embolization were insufficient in 19.3% of aneurysms in the ATENA study, 1.2% to 20.8% in other studies, and 10.0% in the present study. We also determined the initial radiographic outcomes of the HELPS[23] and the Cerecyte trial[24]; 14.5% were insufficient in the former and 11.7% were insufficient in the latter,[24] which used bare platinum coils. The radiographic outcomes herein usually depended on the judgment of the treating physicians, and thus poor outcomes might have been underestimated, which the second report of the ATENA study also considers.[25]

Adverse Events

The rate of procedure-related complications is 15.4% in the ATENA study (including 2.6% and 7.1% hemorrhagic and ischemic complications, respectively) and 2.5% to 28% in

Table 5. Case Series After ISUIA (1–9), Including ATENA and Present Study

Study	Case Series Summary*	ATENA Study (Pierot et al[11])	Present Study
Study period	1991–2011	2005.6–2006.10	2005.1–2009.12
NOP	39–457	649	4573
UIAs	42–500	739	4767
F, %	51–89	72	72
Age, y	48–73	51	61
UAC, %	53–91	92	80
PMORB, %	0–7.7	2.6	2.1
MORT, %	0–1.7	1.1	0.3
IAO†, %	1.2–20.8	19.3	10.0
FAIL, %	0–10.0	4.3	2.1
PRC†, %	2.5–28.0	15.4	9.1
Ischemic complications, %	0.8–18.0	7.1	4.6
Hemorrhagic complications‡, %	0–2.6	2.9	2.0

EVT indicates endovascular therapy; F, female; FAIL, failure; IAO, insufficient anatomic outcome; ISUIA, International Study of Unruptured Intracranial Aneurysms; LIM, limitation; MORT, mortality; NOP, number of patients or procedures; PMORB, permanent morbidity; PRC, procedure-related complications; RA, residual aneurysms; and UAC, UIAs in anterior circulation.

*Summary of data from case series of EVT for UIAs reported after ISUIA study (1998). Details are shown in online supplement.

†Total number of incomplete occlusions (<90%) or RA in each report.

‡Complications manually determined when complications were not specified.

other studies. This variation might be associated with studies defining complications differently. We found that intra- or postprocedural complications were associated with 417 (9.1%) of 4573 procedures within 30 days and comprised intracranial hemorrhagic and ischemic complications in 2.0% and 4.6% of those, respectively. About 75% of these were asymptomatic or transiently symptomatic and did not result in mRS deterioration. Systemic heparinization is recommended before placing guiding catheters to maintain activated coagulation times within 250 to 300 seconds and to avoid thromboembolic or ischemic complications of UIAs.[26] Antiplatelet therapy has also been recommended to prevent thromboembolic complications.[27,28] Here, intraprocedural systemic heparinization was applied in 98.1% of procedures, and pre- and postprocedural oral antiplatelet agents were applied significantly more often every year. Continuous intravenous anticoagulation therapy with not only heparin but also antithrombin agents (Argatroban)[29] has also been added. Ischemic complications decreased annually, and the frequency of thrombogenic adjunctive techniques has increased. We could not identify the efficacy of antiplatelet medication against ischemic complications, and thus prospective studies are required. We found significantly higher complication rates, especially ischemic, for aneurysms of the posterior as compared with the anterior circulation, which contradicted the findings of a recent systematic review.[22] Recently, UCAS Japan found similar rupture rates of aneurysms in the posterior and anterior circulation, but those of aneurysms in the internal carotid artery-posterior communicating artery and anterior communicating artery were higher.[6] The lower complication rate associated with aneurysms of the posterior circulation should be further investigated. Notably, larger and smaller aneurysms were associated with higher ischemic and hemorrhagic complication rates, respectively, and the risks of hemorrhagic complications and insufficient radiographic results were significantly higher in tiny aneurysms <3 mm than in those of UIAs 5 to 9 mm (odds ratios, 2.8 [P=0.04] and 2.1 [P=0.09], respectively). In contrast, risks of failure or total complications were not significantly increased in tiny aneurysms <3 mm. These findings should be considered in the management of small UIAs. Intraprocedural aneurysmal rupture occurred at a rate of 2.6% per procedure in the ATENA study,[11] 1.4% per aneurysm in the series of Oishi et al,[10] and 1.9% per patient treated for a UIA in the Cerecyte trial.[24] We found similar rates of 1.4%. Because 10 of 65 aneurysmal ruptures led to mortality, intraprocedural aneurysmal rupture must be scrupulously avoided. We found 5 (0.1%) post-treatment aneurysmal ruptures, although such events in the HELPS or the Cerecyte trial were not reported. Of these 5 ruptures, only 1 was associated with intraprocedural rupture. All of them led to poor clinical outcomes (mRS, 4–6). On the basis of our findings of complication rates, physicians should reconsider treatment indications for smaller aneurysms, such as those that were treated in the Japanese system and which we determined before comparing the risk of complications with the low risk of rupture (ISUIA2 or UCAS Japan).

Limitations

We extracted information about the outcomes of EVT for asymptomatic UIAs from those of all EVTs that were retrospectively registered by physicians at several neurointerventional centers but they do not represent the nationwide total. The Japan Neurosurgical Society found that 3053 EVTs were performed to treat unruptured cerebral aneurysms during 2006. Our database included 1103 unruptured cerebral aneurysms for the same period, which was 36.1% of the total. Furthermore, aneurysms that were treated more than once could not be excluded from the present study. Our results could be inherently biased because the treating physicians assessed radiographic and clinical outcomes and procedure-related complications. Decisions on treatment indications might have also introduced inclusion bias. To understand the full outcomes of EVTs for UIAs in Japan, Japanese Society for Neuroendovascular Therapy will continue to collect data from all certified neurointerventionists throughout Japan. In addition, a prospective study, especially of EVT for unruptured aneurysms, might be warranted. Intracranial stent-assisted techniques and bioactive coil usage were not assessed because these devices were not fully approved in Japan during the study period. This report simply describes the outcomes of EVT for asymptomatic UIAs, which did not include surgically treated or untreated UIAs, and the population of patients with asymptomatic UIAs was not representative of the total.

Conclusions

This is the largest nationwide study of the outcomes of EVT for UIAs in Japan in which the immediate radiographic

results, short-term outcomes, and actual status were retrospectively analyzed. We found that EVT for UIAs was feasible (98.4%), with low morbidity and mortality rates (2.12% and 0.31%, respectively), although the total complication rate was relatively high (9.1%). Nevertheless, because complication rates tended to be higher for very small UIAs, treatment indications should be reconsidered, considering their low risk of rupture. These results could be used as a reference for deciding strategies to manage asymptomatic UIAs in routine clinical practice.

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Disclosures

The JR-NET Study Group: Principle Investigator, Dr N. Sakai; 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); Dr C. Sakai (17C-1, 20C-2), Tetsu Satow, 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, Dr Fujinaka, 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, Tokyo, 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.

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ONLINE SUPPLEMENT

Endovascular therapy for asymptomatic unruptured intracranial aneurysms: JR-NET and JR-NET2 findings

Supplementary Table I. Annual endovascular techniques and antithrombotic regimens.

	2005	2006	2007	2008	2009	p	Overall (2005-2009)
Technique (pa)							
Simple	57.2	49.8	45.9	39.9	38.6	<0.001	45.2
Adjunctive	42.8	50.2	54.1	60.1	61.4		54.8
Antithrombotic regimen (pp)							
PRE antiplatelet therapy	71.6	80.6	86.5	93.5	89.9	<0.001	85.6
INTRA systemic heparinization	98.5	98.7	97.9	98.3	97.6	NS	98.1
CONT anticoagulation	63.1	66.7	72.7	72.8	63.8	NS	68.0
POST antiplatelet therapy	76.0	76.8	86.1	87.9	88.9	<0.001	84.0

All values except p values are shown as ratios (%). CONT, continuous; INTRA, intra-procedural; NS, not significant; pa, per aneurysm; POST, post-procedural; pp, per procedure; PRE, pre-procedural.

Supplementary Table II. Insufficient anatomic outcome, failure rate and complication rates in each size subgroups.

	Maximal radius (mm %)					p	Overall (%)
	<3	3–<5	5–<10	10–<20	≥20		
Failure rate	4.2	2.9	1.7	1.4	3.0	0.003	2.1
RA	16.7	10.2	8.7	13.5	18.8	NS	10.0
Procedure-related complications	8.4	7.9	8.5	12.8	18.2	<0.001	8.9
Hemorrhagic	5.0	2.5	1.9	0.7	0	<0.001	2.0
Ischemic	2.5	3.6	4.4	7.7	18.2	<0.001	4.6

NS, not significant; RA, residual aneurysm.

Supplementary Table III. Feasibility and complication rates of anterior and posterior circulation.

	Anterior circulation (%)	Posterior circulation (%)	p	Overall (%)
Failure rate	2.2	1.9	NS	2.1
RA	10.0	10.2	NS	10.0
Procedure-related complications	8.3	11.2	0.005	8.9
Hemorrhagic	1.9	2.3	NS	2.0
Aneurysmal rupture	1.3	1.5	NS	1.4
Ischemic	4.0	6.9	<0.001	4.6

All values except p values area shown as ratios (%).NS, not significant; RA, residual aneurysm.

Supplementary Table IV. Results of coil embolization for aneurysms < 10 mm with wide and favorable necks.

	Favorable neck* (%)	Wide-neck† (%)	p	Total (%)
Failure rate	1.4	2.9	0.002	2.2
RA	7.0	11.4	<0.001	9.5
Procedure-related complications	6.4	9.7	<0.001	8.3
Hemorrhagic	1.5	2.7	0.01	2.2
Aneurysmal rupture	1.3	1.7	NS	1.5
Ischemic	2.9	5.0	<0.001	4.1

RA, residual aneurysm; *Favorable neck: neck, ≤4 mm and dome-to-neck (D/N) ratio ≥1.5; NS, not significant; †Wide neck: neck >4 mm or D/N ratio <1.5.

Supplementary Table V. Case series of EVT for UIAs reported after ISUIA study (1998).

Authors	LIM UIAs	Study period	NOP	UIAs	F	Age (y)	UAC	PMORB	MORT	IAO*	FAIL	PRC†	Ischemic complications	Hemorrhagic complications†
Murayama et al., 1999	-	1991.8-1998.1	115	120	79	51	73	3.4	0	4.2	5.0	6.7	5.0	0.9
Roy et al., 2001	r ≥ 3 mm	1992.8-1999.6	116	125	78	51	78	4.3	0	4.8	5.6	10.3	7.8	2.6
Wanke et al., 2002	-	1997.7-2000.12	39	42	59	48	74	4.8	0	10.5	10.0	2.5	2.5	0
Gonzalez et al., 2004	-	1991.8-2000.6	217	247	77	54	76	5.5	0.9	1.2	5.7	6.9	3.7	1.4
Terada et al., 2005	-	1999.7-2004.5	76	78	68	59	53	3.7	0	20.3	-	7.3	6.1	1.2
van Rooij et al., 2006	-	1995.1-2005.7	149	176	89	52	72	2.6	1.3	4.6	-	3.4	2.8	0.6
Gallas et al., 2008	-	1998.1-2005.1	290	321	63	49	-	7.7	1.7	3.7	6.0	14.4	9.0	2.6
Standhardt et al., 2008	-	1992.2-2004.8	173	202	73	52	79	3.5	0.5	8.5	-	19.3	10.9	2.0
Im et al., 2009	r ≤ 7 mm	2002.5-2006.12	370	435	75	58	90	0.3	0	5.1	-	10.1	5.5	0.9
Benes et al., 2010	-	1996.12-2005.9	131	151	71	51	87	0.8	0.8	6.0	4.0	10.5	7.0	0.7
Hwang et al., 2011	age ≥ 70 y	2003.5-2010.2	96	122	83	73	91	0	0	12.2	0.0	4.1	0.8	0.8
Yue, 2011	-	2008.1-2011.1	74	80	51	49	64	1.3	1.3	13.8	-	4.1	-	-
Khosla et al., 2012	-	2000.1-2010.1	355	394	76	57	73	3.3	0.5	12.2	6.3	28.0	≤18.0	2.0
Oishi et al., 2012	r < 10 mm	2001.6-2009.12	457	500	73	60	90	0.8	0.2	20.8	3.8	7.6	3.8	2.2

All values except NOP, UIAs and Age area shown as ratios (%). *Total number of incomplete occlusions (<90%), residual aneurysms (RA) or body filling (BF), in each report. †Complications manually determined when unspecified. IAO, Insufficient anatomic outcome; F, female; FAIL, failure; LIM, limitation; MORT, mortality; NOP, Number of patients or procedures; PRC, procedure-related complications; UAC, UIAs in anterior circulation

Online Appendix

The JR-NET Study Group (on Apr. 2005)

Chief Researcher

N. Sakai, Kobe City Medical Center General Hospital.

Chief Researcher

N. Sakai, Kobe City Medical Center General Hospital.

Steering Committee

W. Taki, and S. Matsushima, Mie University Graduate School of Medicine; K. Murao, and T. Sato, National Cerebral and Cardiovascular Center; A. Hyodo, University of the Ryukyus; T. Terada, Wakayama Rosai Hospital; S. Miyachi, Nagoya University Graduate School of Medicine; M. Ezura, Tohoku University Graduate School of Medicine; K. Sato, The University of Tokushima Graduate School; I. Hattori, National Hospital Organization Himeji Medical Center; and T. Hyogo, Nakamura Memorial Hospital.

Registration Committee

S. Nemoto, Jichi Medical University School of Medicine; N. Kuwayama, University of Toyama; M. Komiyama, Osaka City General Hospital; Y. Murayama, The Jikei University School of Medicine; I. Nakahara, Kokura Memorial Hospital; Y. Matsumaru, Toranomon Hospital; S. Yoshimura, Gifu University Graduate School of Medicine; K. Sugiu, Okayama University School of Medicine; T. Fujinaka, Osaka University Graduate School of Medicine; Y. Ito, Niigata University; S. Kobayashi, Chiba Emergency Medical Center; T. Abe, Kurume University; M. Nakamura, Kobe University Graduate School of Medicine; H. Nagashima, Aizawa Hospital; H. Kiyosue, Oita University Graduate School of Medicine; and Y. Matsumoto, Hohnan Hospital.

Administration Committee

M. Negoro, Fujita Health University; A. Takahashi, Tohoku University Graduate School of Medicine; M. Sonobe, Mito Medical Center; and T. Koike, Niigata City General Hospital.

Independent Monitoring Committee

I. Nagata, Nagasaki University; N. Hashimoto, Kyoto University Graduate School of Medicine; A. Ogawa, Iwate Medical University; S. Miyamoto and K. Minematsu, National Cerebral and Cardiovascular Center; S. Uchiyama, Tokyo Women's Medical University; Y. Okada, National Hospital Organization Kyushu Medical Center.

Protocol Committee

N. Sakai, Kobe City Medical Center General Hospital; Y. Nagai and K. Kuronaka, Translational Research Informatics Center; and the members from registration and administration committee.

Analysis Committee

H. Imamura, Kobe City Medical Center General Hospital; Y. Matsumaru, Toranomon Hospital; and S. Yoshimura, Gifu University Graduate School of Medicine.

JR-NET Investigators

Each neuroendovascular therapy specialist, certified by the Japanese Society for Neuroendovascular Therapy as of September 2006, was asked to accompany the registration survey. Data were registered by; T. Hyogo, T. Kataoka, and K. Hayase, Nakamura Memorial Hospital; S. Ushigoe, Teine Keijinkai Hospital; M. Nonaka, T. Baba, and Y. Yonemasu, Sapporo Medical University; T. Kubota, Hakodate Neurosurgical Hospital; S. Nishi, Sapporo Higashi Tokushukai Hospital; M. Hayashi, Ohkawahara Neurosurgical Hospital; M. Nagahata, Hirosaki University; H. Konno, Hanamaki-Kosei Hospital; A. Takahashi, and M. Ezura, Tohoku University Graduate School of Medicine; Y. Matsumoto, and M. Nishimura, Kohnan Hospital; S. Araki, Ohta Nishinouchi Hospital; A. Shimada, Shirakawa Hospital; M. Sonobe, Y. Nakai, and N. Kato, Mito Medical Center; S. Yamasaki, Tsuchiura Kyodo General Hospital; K. Suzuki, and W. Tsuruta, University of Tsukuba; S. Nemoto, and M. Shojima, Jichi Medical University; S. Tamatani, and K. Asakuno, Dokkyo Medical University; O. Miyagi, M. Matsumoto, Tatebayashi Kosei Hospital; K. Akaji, Mihara Memorial Hospital; O. Noguchi, National Hospital Organization Takasaki General Medical Center; S. Ishihara, S. Kamiyama, and F. Yamane, Saitama Medical University; K. Yasutani, Dokkyo Medical University Koshigaya Hospital; S. Kobayashi, H. Oishi, and Y. Koguchi, Chiba Emergency Medical Center; M. Tanaka, Kameda Medical Center; Y. Matsumaru, T. Kubo, Toranomon Hospital; Y. Murayama, T. Ishibashi, and M. Ebara, Jikei university School of Medicine; S. Iwabuchi, and T. Yokouchi, Toho University Ohashi medical Center; T. Ueda, Tokyo Saiseikai Central hospital; Y. Yoshida, and R. Kanazawa, Nippon Medical University; T. Ueno, Teikyo University; H. Shibutani, and T. Suma, Sagamihara Kyodo Hospital; M. Imaoka, Yokohama Shintoshi Neurosurgical Hospital; K. Tsumura, Kawasaki Saiwai Hospital; H. Morishima, St. Marianna University School of Medicine; H. Ozawa, Ushioda General Hospital; T. Koike, and S. Nakazato, Niigata City General Hospital; H. Abe, Tachikawa General Hospital; Y. Ito, and K. Nishino, Niigata University; K. Morita, Niigata Rosai Hospital; N. Kuwayama, and M. Kubo, University of Toyama; J. Hamada, and H. Uchiyama, Kanazawa University; N. Minamide, Ishikawa Prefectural Central Hospital; Y. Takahata, Fukui Ken Saiseikai Hospital; Y. Arai, University of Fukui; H. Nagashima, Aizawa Hospital; Y. Kaku, J. Ishizawa, and T. Tanaka, Murakami Memorial Hospital; S. Yoshimura, and J. Yamada, Gifu University Graduate School of Medicine; Y. Sugiura, Seirei Mikatahara General Hospital; K. Murata, Shimada

Municipal Hospital; S. Fukazawa, Shizuoka Hospital; M. Fujii, IUHW Atami Hospital; M. Negoro, A. Sadato, and M. Hayakawa, Fujita Health University; S. Miyachi, and K. Hattori, Nagoya University Graduate School of Medicine; T. Okamoto, Japanese Red Cross Nagoya Daiichi Hospital; H. Sakai, National Hospital Organization Toyohashi Medical Center; K. Fukui, Toyohashi Municipal Hospital; M. Matsumoto, and N. Aihara, Nagoya City University Graduate School of Medical Sciences; K. Watanabe, and T. Takagi, Okazaki City Hospital; Y. Kawamura, Ookuma Hospital; N. Kobayashi, Aichi Koseiren Kainan Hospital; T. Hattori, Ichinomiya Municipal Hospital; W. Taki, H. Sakaida, K. Kawaguchi, N. Toma, and F. Asakura, Mie University Graduate School of Medicine; T. Nakazawa, Japanese Red Cross Otsu Hospital; M. Ohashi, Shiga University of Medical Science; H. Owaki, Kyoto-Katsura Hospital; H. Tenjin, and Y. Osaka, Japanese Red Cross Kyoto Daini Hospital; Y. Inoue, and K. Owada, Kyoto Prefectural University of Medicine; M. Komiyama, Osaka City General Hospital; T, Ota, Kitano Hospital; K. Murao, Shiroyama Hospital; A. Kinoshita, Kawachi General Hospital; K. Takayama, Ishinkai Yao Hospital; J. Deguchi, and M. Yamada, Osaka medical College; A. Nishio, and Y. Mitsuhashi, Osaka City University Graduate School of Medicine; K. Yamanaka, National Hospital Organization Osaka Medical Center; T. Sato, K. Iihara, and N. Nakajima, National Cerebral and Cardiovascular Center; T. Harakuni, and T. Suyama, Tominaga hospital; M. Yasuda, Kano General Hospital; K. Matsumoto, Iseikai Hospital; N. Sakai, H. Adachi, and Y. Ueno, Kobe City Medical Center General Hospital; M. Nakamura, and T. Shimizu, Kobe University Graduate School of Medicine; S. Katayama, Nishikobe Medical Center; Y. Hara, Japanese Red Cross Kobe Hospital; S. Yamaura, Kobe Tokushukai Hospital; I. Hattori, National Hospital Organization Himeji Medical Center; H. Nakagawa, Nara Medical University; Y. Akiyama, Tenri Hospital; T. Terada, Wakayama Rosai Hospital; H. Matsumoto, O. Masuo, T. Tsumoto, H. Yamaga, and Y. Ohura, Wakayama Medical University; M. Sakamoto, Tottori University; K. Sugiu, K. Tokunaga, and A. Nishida, Okayama University School of Medicine; K. Goto, S. Ota, Brain Attack Center Ota Memorial Hospital; K. Migita, National Hospital Organization Higashi Hiroshima Medical Center; S. Kato, and H. Ishihara, Yamaguchi University School of Medicine; K. Sato, S. Matsubara, The University of Tokushima Graduate School; M. Kawanishi, and A. Shindo, Kagawa University; Y. Terai, and K. Yoshino, Kagawa Rosai Hospital; A. Takechi, Ehime Prefectural Central Hospital; Y. Nojima, Hata Kenmin Hospital; N. Fukui, Kochi Health Science Center; T. Abe, M. Hirohata, and K. Nakahara, Kurume University; I. Nakahara, T. Azuma, and Y. Iwamuro, Kokura Memorial Hospital; N. Fujimura, Saiseikai Yahata General Hospital; O. Ito, Shin-Koga Hospital; K. Uda, and K. Yasumori, National Hospital

Organization Kyushu Medical Center; N. Kitagawa, M. Morikawa, and K. Hayashi, Nagasaki University; H. Takahata, and H. Ishimaru, National Hospital Organization Nagasaki Medical Center; T. Yoshioka, Nagasaki Rosai Hospital; Y. Kai, and M. Watanabe, Kumamoto University; K. Kiyosue, S. Tanoue, Y. Sagara, and T. Kubo, Oita University; Y. Hori, T. Asano, and J. Kashiwagi, Nagatomi Neurosurgical Hospital; M. Okahara, Shin Beppu Hospital; I. Ikushima, and H. Ota, Miyakonojo Regional Medical Center; T. Shimozuru, Ichiki Kushikino City Medical Association Neurosurgical Center; K. Ishimaru, M. Kaji, and T. Nagayama, Kagoshima University; A. Hyodo, University of the Ryukyus; J. Momoji, Naha City Hospital; S. Tateshima, UCLA Medical Center.

The JR-NET2 Study Group (on Jan. 2010)

Chief Researcher

N. Sakai, Kobe City Medical Center General Hospital.

Steering Committee

T. Sato, National Cerebral and Cardiovascular Center; W. Taki, Mie University Graduate School of Medicine; T. Terada, Wakayama Rosai Hospital; K. Hayashi, Nagasaki University; A. Hyodo, Dokkyo Medical University Koshigaya Hospital; S. Matsushima, Mie University Graduate School of Medicine; and S. Miyachi, Nagoya University Graduate School of Medicine.

Registration Committee

T. Abe, Kurume University; Y. Ito, Niigata University; M. Ezudra, Sendai Medical Center; H. Kiyosue, Oita University Graduate School of Medicine; N. Kuwayama, University of Toyama; S. Kobayashi, Chiba Emergency Medical Center; M. Komiyama, Osaka City General Hospital; K. Sugiu, Okayama University School of Medicine; H. Nagashima, Aizawa Hospital; I. Nakahara, Kokura Memorial Hospital; M. Nakamura, Hyogo Brain and Heart Center; S. Nemoto, Jichi Medical University School of Medicine; T. Hyogo, Nakamura Memorial Hospital; T. Fujinaka, Osaka University Graduate School of Medicine; Y. Matsumaru, Toranomon Hospital; Y. Matsumoto, Hohnan Hospital; Y. Murayama, The Jikei University School of Medicine; and S. Yoshimura, Gifu University Graduate School of Medicine.

Administration Committee

M. Negoro, Fujita Health University; A. Takahashi, Tohoku University Graduate School of Medicine; M. Sonobe, Mito Medical Center; and T. Koike, Niigata City General Hospital.

Independent Monitoring Committee

K. Iihara, National Cerebral and Cardiovascular Center; S. Uchiyama, Tokyo Women's

Medical University; K. Ogasawara, Iwate Medical University; Y. Okada, National Hospital Organization Kyushu Medical Center; I. Nagata, Nagasaki University; K. Minematsu, National Cerebral and Cardiovascular Center; and S. Miyamoto, Kyoto University Graduate School of Medicine.

Protocol Committee

N. Sakai, Kobe City Medical Center General Hospital; C. Sakai, Institute of Biomedical Research and Innovation Hospital; Y. Nagai and K. Kuronaka, Translational Research Informatics Center; and the members from registration and administration committee.

Analysis Committee

H. Imamura, Kobe City Medical Center General Hospital; Y. Matsumaru, Toranomon Hospital; Y. Matsumoto, Kohnan Hospital; and S. Yoshimura, Gifu University Graduate School of Medicine.

JR-NET2 Investigators

Each neuroendovascular therapy specialist certified by the Japanese Society for Neuroendovascular Therapy, as of September 2009. Data were registered by; T. Nonaka, A. Takahashi, Shiroishi Neurosurgical Hospital; T. Kubota, Hakodate Neurosurgical Hospital; K. Haraguchi, and H. Manabe, Hakodate Shintoshi Hospital; M. Hayashi, Ohkawahara Neurosurgical Hospital; T. Kikuchi, Tomakomai Nisshou Hospital; S. Iiboshi, and K. Miyata, Sapporo Medical University; T. Hyogo, and T. Kataoka, Nakamura Memorial Hospital; T. Sakurai, Genseikai Moriyama Hospital; S. Yamauchi, Hokuto Hospital; M. Nagahata, and N. Shimamura, Hirosaki University; A. Takahashi, Tohoku University Graduate School of Medicine; Y. Matsumoto, R. Kondo, E. Furui, and Y. Matsumori, Kohnan Hospital; M. Ezura, M. Nishimura, N. Kimura, and I. Suzuki, Sendai Medical Center; N. Tamagawa, J. Moroi, Research Institute for Brain and Blood Vessels Akita; A. Shimada, Shirakawa Hospital; S. Yamasaki, Tsuchiura Kyodo General Hospital; S. Tamatani, and S. Yamamoto, Dokkyo Medical University; K. Asakura, and H. Shimaguchi, Maebashi Red Cross Hospital; I. Naito, F. Iwai, M. Takatama, and N. Miyamoto, Geriatrics Research Institute and Hospital; O. Miyagi, M. Matsumoto, Tatebayashi Kosei Hospital; K. Akaji, Mihara Memorial Hospital; A. Kojima, Saitama Municipal Hospital; T. Takahashi, Saitama Red cross Hospital; S. Ishihara, S. Kamiyama, F. Yamane, and T. Dembo, Saitama Medical University International Medical Center; A. Hyodo, and K. Suzuki, Dokkyo Medical University Koshigaya Hospital; K. Nakai, National Defense Medical Collage; E. Kobayashi, and N. Hayasaka, Chiba University Graduate School of Medicine; S. Kobayashi, Y. Koguchi, and T. Yamauchi, Chiba Emergency Medical Center; JH. Son Shin Matsudo Central General Hospital; M. Katayama, Tokyo Dental College Ichikawa General Hospital;

S. Kittipong, General hospital National Health Insurance Asahi central hospital; M. Tanaka, Kameda Medical Center; Y. Numaguchi, M. Fujii, and A. Uemura, St. Luke's International Hospital; Y. Matsumaru, K. Tsuruta, and M. Hayakawa, Toranomon Hospital; T. Saguchi, Japanese Red Cross Medical Center; S. Iwabuchi, and M. Hayashi, Toho University Ohashi medical Center; T. Hashimoto, Tokyo Medical University; T. Higa, Tokyo Women's Medical University; H. Sato, Tokyo Metropolitan Police Hospital; O. Tone, and Y. Sato, Japanese Red Cross Musashino Hospital; K. Shigeta, National Disaster Medical Center; Y. Yoshida, Ebara Hospital; T. Ohashi, Tokyo Medical University Ibaraki Medical Center; T. Ueda, T. Takada, and Y. Otsuka, St. Marianna University School of Medicine Toyoko Hospital; H. Morishima, St. Marianna University School of Medicine; H. Shibutani, and T. Suma, Sagamihara Kyodo Hospital; K. Amari, Yokohama Strake & Brain Center; Y. Sakata, Seirei Yokohama Hospital; S. Tateshima, Atsugi City Hospital; M. Imaoka, Asao General Hospital; H. Abe, Yachikawa General Hospital; Y. Ito, T. Sorimachi, S. Inagawa, and K. Morita, Niigata University; K. Kitazawa, Murakami General Hospital; N. Kuwayama, N. Eiraku, and N. Akioka, University of Toyama; M. Arai, Kouseiren Takaoka Hospital; N. Minamide, Ishikawa Prefectural Central Hospital; J. Hamada, H. Uchiyama, and M. Mori Kanazawa University; Y. Hirota, Kanazawa Municipal Hospital; Y. Arai, University of Fukui; Y. Takahata, Fukui Ken Saiseikai Hospital; K. Kanemaru, University of Yamanashi; F. Oya, Nagano Municipal Hospital; D. Sato, Aizawa Hospital; S. Yoshimura, and Y. Enomoto, Gifu University Graduate School of Medicine; J. Yamada, Hashima Municipal Hospital; H. Kitajima, Toki General Hospital; S. Fukazawa, Shizuoka Hospital; H. Hiramatsu, Hamamatsu University School of Medicine; E. Ichihashi, Fukuroi Municipal Hospital; H. Sakai, National Hospital Organization Toyohashi Medical Center; T. Okamoto, and T. Nakano, Japanese Red Cross Nagoya Daiichi Hospital; A. Tsurumi, National Hospital Organization Nagoya Medical Center; T. Kojima, Japanese Red Cross Nagoya Danichi Hospital; M. Negoro, A. Sadato, M. Hayakawa, T. Watabe, K. Irie, and T. Tanaka, Fujita Health University; N. Kobayashi, Aichi Koseiren Kainan Hospital; T. Hattori, Ichinomiya Municipal Hospital; W. Taki, Mie University Graduate School of Medicine; T. Nakazawa, Shiga University of Medical Science; A. Tsuji, Kusatsu General Hospital; M. Kawanishi, and M. Yamada, Ijinkai Takeda General Hospital; M. Hirai, Kyoto Kujo Hospital; H. Tenjin, and Y. Osaka, Japanese Red Cross Kyoto Daini Hospital; K. Owada, Kyoto Prefectural University of Medicine; K. Imai, and T. Takegami, Japanese Red Cross Kyoto Daiichi Hospital; S. Ishii, Kyoto University Graduate School of Medicine; A. Morizane, Kyoto University; T. Hatano, and M. Murakami, National Hospital Organization Kyoto Medical Center; M. Ohashi, Soseikai General Hospital; T, Ota, Kitano Hospital; Y.

Fumoto, and M. Yasuda, Kano General Hospital; M. Komiyama, and T. Ishiguro, Osaka City General Hospital; S. Aketa, Osaka Police Hospital; A. Nishio, Y. Mitsuhashi, and T. Kawakami, Osaka City University Graduate School of Medicine; T. Suyama, and M. Nagashima, Tominaga hospital; K. Fujimoto, Osaka General Medical Center; K. Maeno, and D. Sakamoto, Yuaikai Hospital; T. Fujinaka, M. Hirata, M. Sakaguchi, and T. Nishida, Osaka University Graduate School of Medicine; T. Sato, K. Iihara, N. Nakajima, and Y. Takenobu, National Cerebral and Cardiovascular Center; K. Hayasaki, Osakafu Saiseikai Ibaraki Hospital; T. Kuroiwa, Osaka medical College; K. Takayama, Ishinkai Yao Hospital; K. Murao, and K. Nakazawa, Shiroyama Hospital; J. Kobayashi, National Hospital Organization Osaka Minami Medical Center; N. Nakagawa, and N. Fukawa, Kinki University; A. Fujita, Kobe University Graduate School of Medicine; N. Sakai, H. Adachi, Y. Ueno, H. Yamagami, H. Imamura, and Y. Kuramoto, Kobe City Medical Center General Hospital; C. Sakai, Institute of Biomedical Research and Innovation Hospital; K. Matsumoto, Shakaihoken Kobe Central Hospital; Y. Yoshida, I. Yamaura, A. Masuda, and H. Minami, Yoshida Hospital; K. Uchida, and M. Shirakawa, Hyogo Collage of Medicine; M. Nakamura, Hyogo Brain and Heart Center; Y. Akiyama, Tenri Hospital; H. Nakagawa, and I. Nakagawa, Nara Medical University; H. Takeuchi, Nojima Hospital; M. Sakamoto, Tottori University; K. Sugiu, and K. Tokunaga, Okayama University School of Medicine; S. Kawata, Okayama Kyokuto Hospital; A. Handa, M. Koyanagi, and K. Yoshida, Kurashiki Central Hospital; S. Matsubara, Kawasaki Medical School Hospital; K. Goto, S. Ota, Brain Attack Center Ota Memorial Hospital; T. Mizogami, Hiroshima Prefectural Hospital; Y. Kiura, T. Okazaki, and S. Sakamoto, Hiroshima University; T. Nakahara, and R. Ogami, Mazda Hospital; K. Migita, National Hospital Organization Higashi Hiroshima Medical Center; H. Yasuda, Yamaguchi Grand Medical Center; N. Ikeda, Ube Industries Central Hospital; H. Ishihara, Yamaguchi University School of Medicine; S. Kato, Saiseikai Yamaguchi Hospital; J. Satomi, The University of Tokushima Graduate School; K. Sato, and M. Hanaoka, Tokushima Red Cross Hospital; M. Kawanishi, A. Shindo, K. Kawakita, and T. Yano, Kagawa University; N. Hayashi, Osaka Neurosurgical Hospital; K. Yoshino, and A. Nishida, Kagawa Rosai Hospital; T. Shiraishi, and, O. Nishizaki, Saiseikai Imabari Hospital; N. Fukui, Kochi Health Science Center; I. Nakahara, and Y. Watanabe, Kokura Memorial Hospital; M. Iwanaga, Yahata Hospital; S. Yamaguchi, Hamanomachi Hospital; T. Azuma, M. Iwaasa, and, M. Okawa, Fukuoka University; K. Kazekawa, M. Tsutsumi, H. Aikawa, and T. Kodama, Fukuoka University Chikushi Hospital; T. Abe, and M. Hirohata, Kurume University; K. Nakahara, Takagi Hospital; K. Harada, Fukuoka Wajiro Hospital; M. Morikawa, K. Hayashi, N. Horie, and T. Hiu, Nagasaki University; T. Yoshioka, Nagasaki

Rosai Hospital; M. Kaji, Saiseikai Kumamoto Hospital; Y. Hori, and T. Asano, Nagatomi Neurosurgical Hospital; M. Okahara, and J. Kashiwagi, Shin Beppu Hospital; K. Kiyosue, S. Tanoue, and T. Kubo, Oita University; I. Ikushima, and H. Ota, Miyakonojo Regional Medical Center; Y. Hirokatsu, Okinawa Red Cross Hospital.

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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

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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.