The Current Status of Endovascular Treatment for Extracranial Steno-occlusive Diseases in Japan: Analysis Using the Japanese Registry of Neuroendovascular Therapy 3 (JR-NET3)

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Abstract

Endovascular treatment of extracranial steno-occlusive lesions is an alternative to direct surgery. There is no consensus regarding the natural course and standard treatment of these lesions. The aim of this study was to identify the current status of endovascular treatment for extracranial steno-occlusive lesions. A total of 1154 procedures for extracranial steno-occlusive lesions, except for internal carotid artery stenosis, were collected from the Japanese Registry of Neuroendovascular Therapy 3 (JR-NET3). Atherosclerotic lesions were most frequent (1021 patients, 88.5%). Endovascular treatment was performed for 456 (39.5%) patients with subclavian artery, 349 (30.2%) with extracranial vertebral artery, 172 (14.9%) with the origin of common carotid artery, and 38 (3.3%) with innominate artery stenosis; the overall technical success rate was 98.0%. Percutaneous transluminal angioplasty was performed in 307 patients (26.6%) and stenting in 838 (72.6%). An embolic protection device (EPD) was used in 571 patients (49.5%), and procedure under general anesthesia was performed in 168 (14.6%). Preoperative antiplatelet therapy was administered in 1091 procedures (94.5%). A good outcome was obtained for 962 patients (83.4%). Complications were observed in 89 patients (7.7%). The procedure under general anesthesia was statistically significant factors (P <0.01), and also after multivariable adjustment (odds ratio 2.29; 95% confidence interval 1.25–4.17; P <0.01). Comparisons between JR-NET3 and previous cohorts (JR-NET1&2), the utilization of EPD and complications increased significantly, and the type of antiplatelet therapy changed markedly. Based on the results of this study, endovascular treatment for extracranial steno-occlusive lesions is relatively safe. Further prospective studies are necessary to validate the beneficial effects.

Key words: subclavian artery stenosis, vertebral artery stenosis, embolic protection device, antiplatelet therapy

Introduction

Stenosis and occlusion of the extracranial arteries has been frequently identified as a result of progress in neuroimaging, such as magnetic resonance imaging. Previous reports have demonstrated that these lesions can cause stroke events.[1,2] However, the ideal treatment of these lesions has not yet been established. There have been no randomized, controlled trials of antiplatelet or anticoagulant drugs in patients with stenosis or occlusion of the extracranial arteries, such as the vertebral and subclavian arteries. Direct surgery at these sites, such as endarterectomy and vessel

reconstruction, is technically challenging because of the difficulty involved in accessing the lesions; in addition, the rate of complications is considerable.[3] In contrast, because of the advancement of endovascular devices, endovascular treatment [e.g., percutaneous transluminal balloon angioplasty (PTA) and stenting] is an increasingly important treatment option for the management of extracranial steno-occlusive lesions.[4–7]

We recently reported the results of endovascular treatment for extracranial steno-occlusive lesions, using data collected from two Japanese Registry of Neuroendovascular Therapy (JR-NET) studies.[8] To evaluate current endovascular treatment, this investigation retrospectively analyzed patient data from the JR-NET3 study.

Materials and Methods

Data collection

The data in this study were collected from JR-NET3. JR-NET3 comprises the registration of therapeutic procedures and outcomes from certified members of the Japanese Society for Neuroendovascular Therapy (JSNET) from January 2010 to December 2014. Medical information about the patients was anonymized and retrospectively registered through a website (https://jr-net.tri-kobe.net/jr-net/). Data were collected at the Translational Research Informatics Center (TRI, http://www.tri-kobe.org/).[9] The Institutional Review Boards at the participating centers approved the use of retrospective data.

Patients who had extracranial steno-occlusive diseases were extracted from these registries and analyzed retrospectively. Datasets included the following parameters: patient demographics, procedure, clinical data (status at 30 days post-procedure), complication data (procedure-related, adverse events, and outcomes), disease data (symptoms, stenosis, and location), and antithrombotic regimen (antiplatelet and anticoagulant therapy). Procedure-related complications were documented along with the information regarding clinical outcome. Pre- and post-procedural clinical status was assessed by the modified Rankin Scale (mRS) score. Morbidity and mortality were defined as deterioration of 2 or more points on the mRS and as any death at 30 days after the procedure, respectively. Good outcome was defined as a mRS score of 0–1 at 30 days after the procedure.

We also compared the data from JR-NET3 with those from JR-NET1&2 (registries from January 2005 to December 2006 and from January 2007 to December 2009, respectively), which have been reported elsewhere.[8]

Patient demographics

A total of 1380 patients with PTA or stenting procedures for extracranial steno-occlusive lesions, except for internal carotid artery stenosis, were selected from JR-NET3 data. Among these patients, 226 patients with incomplete data were excluded, and detailed information was available for 1154 patients. Thus, data from these 1154 patients was subjected to further analysis.

Statistical analysis

The chi-squared test was used to compare categorical variables between groups; the Mann–Whitney U test or Wilcoxon test was used to compare continuous variables. To investigate the association with complications, the pretreatment variables were first analyzed using univariate analysis, and then were entered into a multiple logistic regression analysis. P-values <0.05 were judged to indicate statistical significance. All statistical analyses were performed with JMP software (version 14, SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and lesions

In the JR-NET3 cohort, mean age was 68.7 ± 10.3 years old. Males comprised 920 patients (79.7%). Pre-procedural mRS was 0 in 822 patients (71.2%), 1 in 196 patients (17.0%), 2 in 73 patients (6.3%), 3 in 31 patients (2.7%), 4 in 17 patients (1.5%), 5 in 1 patients (0.1%). Regarding lesions, 1021 patients (88.5%) had atherosclerotic lesions. Seventy-seven patients (6.7%) were treated for dissections related to iatrogenic, traumatic, or idiopathic causes. Nineteen patients (1.6%) were treated for lesions associated with aortitis.

Among 407 patients (35.3%) who were resistant to antithrombotic therapy, 164 patients (14.2%) were asymptomatic, while 225 (19.5%) had symptomatic presentation. Twenty patients (1.7%) had major stroke, 102 (8.8%) had minor stroke, 52 (4.5%) had progressing stroke, and 42 (3.6%) had transient ischemic attack including amaurosis fugax. In this cohort, preoperative symptoms in patients without resistance to antithrombotic therapy were not available.

In this cohort, 456 patients (39.5%) had subclavian artery stenosis, 349 (30.2%) had extracranial vertebral artery (VA) stenosis, 172 (14.9%) had the stenosis of the orifice of the common carotid artery (CCA), and 38 (3.3%) had innominate artery stenosis.

The degree of stenosis was documented as 100% (occluded) in 89 patients (7.7%), 70–99% in 849 (73.6%), 50–69% in 134 (11.6%), and <50% in 57 (4.9%).

Details are shown in Table 1.

Table 1 Patient demographics

	Patients (*n* = 1154)
Mean age (years old ± SD)	68.7 ± 10.3
Male	920 (79.7)
mRS 0–2 (before procedure)	1091 (94.5)
Lesion	
Atherosclerosis	1021 (88.5)
Dissection	77 (6.7)
Aortitis	19 (1.6)
Others	28 (2.4)
Resistance to antithrombotic therapy	407 (35.3)
Asymptomatic	164 (14.2)
Symptomatic presentation	225 (19.5)
Major stroke	20 (1.7)
Minor stroke	102 (8.8)
Progressive stroke	52 (4.5)
TIA/Amaurosis fugax	42 (3.6)
Others	9 (0.8)
Location	
Subclavian artery	456 (39.5)
Vertebral artery	349 (30.2)
Orifice of CCA	172 (14.9)
Innominate artery	38 (3.3)
Others	21 (1.8)
Degree of stenosis (%)	
<50	57 (4.9)
50–69	134 (11.6)
70–99	849 (73.6)
100	89 (7.7)

CCA: common carotid artery, SD: standard deviation, TIA: transient ischemic attack.

Procedures

Technical success was achieved in treatment of 1131 patients (98.0%). Scheduled procedure was performed in 1056 patients (91.5%). Stenting was performed in 838 patients (72.6%), while PTA alone was used in 307 procedures (26.6%). A balloon expandable stent was used in 485 patients (42.0%), a self-expandable/open cell stent in 233 (20.2%), and a self-expandable/closed cell stent in 63 (5.5%). An embolic protection device (EPD) was used in 571 patients (49.5%). Among EPD, distal balloon protection was used in 305 patients (26.4%), distal filter protection in 115 (10.0%), proximal protection in 90 (7.8%), and both distal and proximal balloon protection in 25 (2.2%). Post-stenting dilatation was performed in 493 patients (42.7%). More detailed information regarding balloon or stent was not available from this registry.

Procedure under general anesthesia was performed in 168 patients (14.6%), and in 983 patients (85.2%) under local anesthesia and/or sedation. Treatment in 1054 patients (91.3%) was mainly performed by certified specialists of JSNET, and in 99 patients (8.6%) by non-specialists. Details of procedure are shown in Table 2.

Antithrombotic therapy

Antiplatelet therapy was administered preoperatively for 1091 patients (94.5%) and postoperatively for 1118 patients (96.9%). In the preoperative state, single antiplatelet therapy was administered for 103 patients (8.9%), dual antiplatelet therapy for 849 patients (73.6%), and triple antiplatelet therapy for 122 patients (10.6%). In the postoperative state, single antiplatelet therapy was administered for 108 patients (9.4%), dual antiplatelet therapy for 903 patients (78.2%), and triple antiplatelet therapy for 95 patients (8.2%). For preoperative treatment, the single antiplatelet regimen most frequently employed was aspirin (45 patients, 3.9%), followed by thienopyridine (40 patients, 3.5%) and cilostazol (18 patients, 1.6%); the most frequent

Table 2 Details of procedure

	Patients (*n* = 1154)
Procedural success	1131 (98.0)
Scheduled procedure	1056 (91.5)
Procedure	
PTA	307 (26.6)
Stenting	838 (72.6)
Balloon expandable stent	485 (42.0)
Self-expandable/open-cell stent	233 (20.2)
Self-expandable/close-cell stent	63 (5.5)
Others	46 (4.0)
EPD use	571 (49.5)
Distal balloon	305 (26.4)
Distal filter	115 (10.0)
Proximal balloon	90 (7.8)
Proximal and distal balloon	25 (2.2)
Others	32 (2.8)
Anesthesia	
General	168 (14.6)
Local	983 (85.2)
Main surgeon	
Specialist	1054 (91.3)
Non-specialist	99 (8.6)

EPD: embolic protection device, PTA: percutaneous transluminal angioplasty.

dual antiplatelet regimen comprised aspirin and thienopyridine (590 patients, 51.1%), followed by aspirin and cilostazol (145 patients, 12.6%), and thienopyridine and cilostazol (113 patients, 9.8%). For postoperative treatment, the single antiplatelet regimen most frequently employed was thienopyridine (54 patients, 4.7%), followed by aspirin (42 patients, 3.6%) and cilostazol (12 patients, 1.0%); the most frequent dual antiplatelet regimen comprised aspirin and thienopyridine (602 patients, 52.2%), followed by aspirin and cilostazol (152 patients, 13.2%), and thienopyridine and cilostazol (147 patients, 12.7%).

Anticoagulants were administered postoperatively for 614 patients (53.2%). Argatroban was used most frequently (406 patients, 35.2%), followed by heparin (141 patients, 12.2%). Details are shown in Table 3.

Outcomes and procedure-related complications

The mRS of 1154 patients at 30 days after treatment was 0 in 784 patients (67.9%), 1 in 178 patients (15.4%), 2 in 68 patients (5.9%), 3 in 52 patients (4.5%), 4 in 39 patients (3.4%), 5 in 7 patients (0.6%), and 6 in 6 patients (0.5%). The good outcome (mRS 0–1) was obtained in 962 patients (83.4%). Morbidity and mortality were observed in 18 (1.6%) and 6 patients (0.5%), respectively.

A total of 89 complications in 89 patients (7.7%) were documented. The most common complication was distal embolism (31 patients, 2.7%), followed

by vessel dissection (26 patients, 2.3%), hyperperfusion (6 patients, 0.5%), and perforation (5 patients, 0.4%). Hemorrhagic complication occurred in 3 patients (0.3%). Complications occurred during the procedure in 45 patients (3.9%), within 24 h postoperatively in 33 patients (2.9%), and within 7 days in 8 patients (0.7%). Although most patients (62 patients, 5.4%) experiencing complications were treated conservatively, endovascular treatment was needed in 20 patients (1.7%), whereas direct surgery was needed in 4 patients (0.3%). More detailed information regarding therapy for complication was not available from this registry. Details are shown in Table 4.

The results for factors of the development of complications are shown in Table 5. From the univariate analysis, procedure under general anesthesia was significantly associated with the development of complications (P <0.01). There was no significant association with other variables, including EPD use. The multivariate analysis also showed procedure under general anesthesia was significantly associated with the development of complications (odds ratio 2.29; 95% confidence interval 1.25–4.17; P <0.01).

Differences between the lesion locations

Comparisons between groups of lesions (subclavian artery, vertebral artery, the orifice of the CCA, and innominate artery) revealed a significant effect of lesion location on several survey items. Dissection as a cause of steno-occlusive lesion was observed more frequently in the orifice of the CCA (18.0% in the orifice of the CCA, 4.3% in VA, 2.6% in innominate artery, and 1.1% in subclavian artery stenosis, P <0.01). Among patients who were resistant to antithrombotic therapy, 66 patients (14.5%) in subclavian artery had symptomatic presentation, 81 patients (23.2%) in VA, 32 patients (18.6%) in

Table 3   Antithrombotic therapy before and after procedure

	Patients (n = 1154)	
	Before procedure	After procedure
Antiplatelet therapy	1091 (94.5)	1118 (96.9)
Single	103 (8.9)	108 (9.4)
Aspirin	45 (3.9)	42 (3.6)
Thienopyridine	40 (3.5)	54 (4.7)
Cilostazol	18 (1.6)	12 (1.0)
Dual	849 (73.6)	903 (78.2)
Aspirin + Thienopyridine	590 (51.1)	602 (52.2)
Aspirin + Cilostazol	145 (12.6)	152 (13.2)
Thienopyridine + Cilostazol	113 (9.8)	147 (12.7)
Triple	122 (10.6)	95 (8.2)
Anticoagulant therapy*	–	614 (53.2)
Argatroban	–	406 (35.2)
Heparin	–	141 (12.2)
Others	–	55 (4.8)

*Data of anticoagulants before procedure were not available.

Table 4   Outcomes and procedure-related complications

	Patients (n = 1154)
Good outcome (mRS 0–1)	962 (83.4)
Mortality	18 (1.6)
Morbidity	6 (0.5)
Complication	89 (7.7)
Distal embolism	31 (2.7)
Vessel dissection	26 (2.3)
Hyperperfusion	6 (0.5)
Perforation	5 (0.4)
Hemorrhage	3 (0.3)

mRS: modified Rankin Scale.

Table 5   Factors related to the development of complications

	Complication		Univariate analysis *P*-value	Multiple logistic regression	
	Yes	No		OR (95% CI)	*P*-value
	n = 89	*n* = 1064			
Age	70.4 ± 1.1	68.6 ± 0.3	0.10	0.25 (0.04–1.48)	0.12
Male	68 (76.4)	852 (80.1)	0.42	1.27 (0.70–2.31)	0.44
Location	–	–	0.54	–	0.64
Procedure (PTA)	27 (30.3)	280 (26.3)	0.44	0.99 (0.51–1.92)	0.98
EPD use	46 (51.7)	525 (49.3)	0.72	0.99 (0.58–1.71)	0.98
Non-specialist	6 (6.7)	93 (8.7)	0.52	1.74 (0.61–5.00)	0.27
Preoperative mRS (0–2)	87 (97.8)	1004 (94.4)	0.28	0.75 (0.17–3.30)	0.70
Scheduled Procedure	81 (91.0)	975 (91.6)	0.77	1.27 (0.44–3.62)	0.66
General anesthesia	23 (25.8)	145 (13.6)	<0.01	2.29 (1.25–4.17)	<0.01
Degree of stenosis (70–100%)	68 (76.4)	870 (81.8)	0.31	1.53 (0.83–2.84)	0.19
Antiplatelet drugs before procedure (0–3)	–	–	0.48	–	0.65

EPD: embolic protection device, PTA: percutaneous transluminal angioplasty.

the orifice of the CCA, and 8 patients (21.1%) in innominate artery (*P* = 0.06).

Endovascular treatment for total occlusion was performed more frequently in patients with innominate artery and subclavian artery lesions (15.8% in innominate artery, 15.1% in subclavian artery, 2.3% in VA, and 0.6% in the orifice of the CCA, *P* <0.01). EPD was performed most frequently in patients with lesions in the orifice of the CCA (84.9% in the orifice of the CCA, 45.6% in VA, 42.1% in innominate artery, and 32.0% in subclavian artery, *P* <0.01). PTA alone was performed more frequently in patients with lesions in the orifice of the CCA, while stenting was performed more frequently in patients with lesions in VA, innominate artery, and subclavian artery (*P* <0.01).

There was no apparent effect of the location on other survey items, including antiplatelet therapy or complication. Details are shown in Table 6.

Comparison between JR-NET3 and two previous cohorts (JR-NET1&2)

The number of patients with extracranial PTA or stenting in JR-NET3 (1154 patients) was higher than in JR-NET1 (442 patients) and JR-NET2 (817 patients). Technical success was obtained at a similarly high rate similarly in both registries (98.0% in JR-NET3 and 97.2% in JR-NET1&2, *P* = 0.22).

Antiplatelet therapy was administered preoperatively in 1091 patients (94.5%) in JR-NET3 and in 921 patients (96.0%) in JR-NET1&2. Single antiplatelet therapy was administered in 8.9% of patients in JR-NET3, whereas it was administered in 14.5% in JR-NET1&2. Dual antiplatelet therapy was administered in 73.6% of patients in JR-NET3, whereas it was administered in 74.2% in JR-NET1&2. Triple antiplatelet therapy was administered in 10.6% of patients in JRNET3, whereas it was administered in 3.9% in JRNET1 and 2. The type of antiplatelet therapy was significantly different when comparing registries (*P* <0.01, Fig. 1). The combination of thienopyridine and aspirin was primarily administered as dual antiplatelet therapy in both registries; the combination of thienopyridine, aspirin, and cilostazol was primarily administered as triple antiplatelet therapy in both registries.

The rate of utilization of EPD was significantly different between the two registries (49.8% in JR-NET3 and 34.8% in JR-NET1&2, *P* <0.01). Distal balloon protection was the most popular embolic protection method in both registries. PTA alone was performed more frequently in JR-NET3, while stenting was performed more frequently in JR-NET1&2 (*P* <0.01). Treatment was performed under general anesthesia more frequently in JR-NET3 (*P* <0.01).

The complication rate was significantly higher in JR-NET3 (7.7%) than in JR-NET1&2 (4.2%, *P* <0.01). Embolic complication was the most frequent complication in both registries. Variation in the incidence of complications was not significantly different between the registries. Hemorrhagic complication was low in both registries (0.3% in JR-NET3 and 0.1% in JR-NET1&2). A favorable outcome (mRS 0–1 at 30 days) occurred at a similarly high rate

Table 6 Differences between locations of lesion

	Subclavian artery	Vertebral artery	Orifice of CCA	Innominate artery	P-value
	(n = 456)	(n = 349)	(n = 172)	(n = 38)	
Lesion					<0.01
Atherosclerosis	437 (95.8)	333 (95.4)	124 (72.1)	34 (89.5)	
Dissection	5 (1.1)	15 (4.3)	31 (18.0)	1 (2.6)	
Others	10 (2.2)	1 (0.3)	16 (9.3)	3 (7.9)	
Resistance to antithrombotic therapy	153 (33.6)	126 (36.1)	54 (31.4)	15 (39.5)	0.64
Asymptomatic	71 (15.6)	44 (12.6)	22 (12.8)	6 (15.8)	0.06
Symptomatic	66 (14.5)	81 (23.2)	32 (18.6)	8 (21.1)	
Degree of stenosis (%)					<0.01
<50	16 (3.5)	17 (4.9)	14 (8.1)	1 (2.6)	
50–69	34 (7.5)	54 (15.5)	21 (12.2)	5 (13.2)	
70–99	331 (72.6)	262 (75.1)	132 (76.7)	23 (60.5)	
100	69 (15.1)	8 (2.3)	1 (0.6)	6 (15.8)	
EPD use	146 (32.0)	159 (45.6)	146 (84.9)	16 (42.1)	<0.01
Procedure					<0.01
PTA	45 (9.9)	74 (21.2)	99 (57.6)	6 (15.8)	
Stenting	409 (89.7)	273 (78.2)	71 (41.3)	31 (81.6)	
Antiplatelet therapy (before procedure)	435 (95.4)	331 (94.8)	160 (93.0)	36 (94.7)	0.78
Single	40 (8.8)	27 (7.7)	22 (12.8)	5 (13.2)	0.16
Dual	346 (75.9)	271 (77.7)	112 (65.1)	28 (73.7)	
Triple	42 (9.2)	29 (8.3)	23 (13.4)	3 (7.9)	
Complication	31 (6.8)	24 (6.9)	16 (9.3)	4 (10.5)	0.63

CCA: common carotid artery, EPD: embolic protection device, PTA: percutaneous transluminal angioplasty.
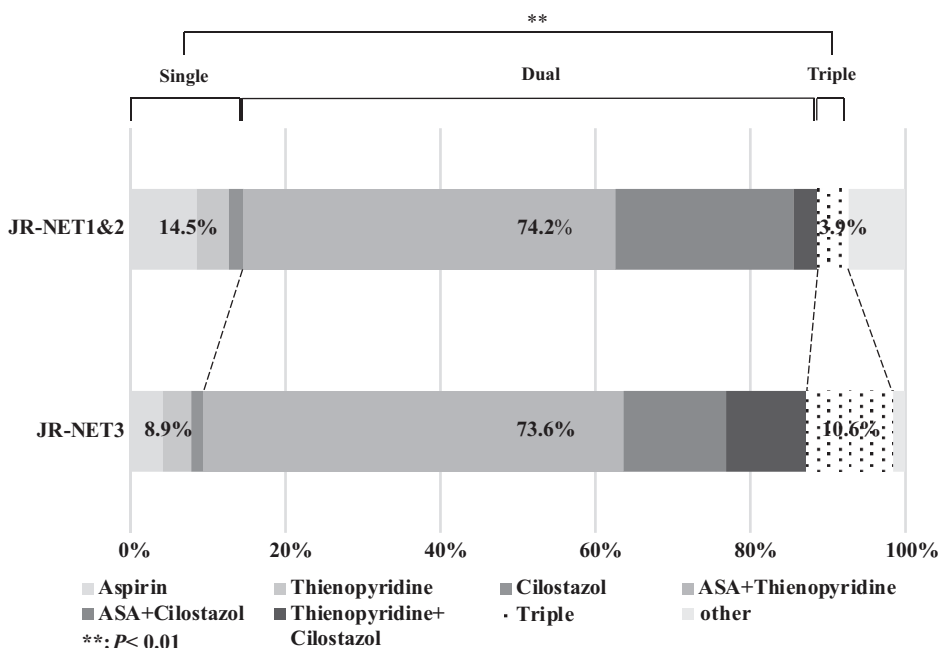

Fig. 1 Numbers and types of preoperative antiplatelet treatments administered between JR-NET3 and JR-NET1&2. Single: single antiplatelet therapy, Dual: dual antiplatelet therapy, Triple: triple antiplatelet therapy.

in both JR-NET3 and JR-NET1&2 (83.4% vs 85.4%, P = 0.20), and the morbidity and mortality rates were similarly low in both JR-NET3 and JR-NET1&2 (morbidity: 1.6% vs 2.3%, P = 0.22; mortality: 0.5% vs 0.3%, P = 0.46). Details are shown in Table 7.

Discussion

Endovascular techniques have been progressively used in the treatment for extracranial steno-occlusive lesions. The reported postoperative 30-day stroke and/or death rate after endovascular treatment ranged from 1.1% to 5.4%.[10–13] To evaluate current status of endovascular treatment in Japan, we conducted a retrospective analysis of data obtained from the JR-NET3 database. The overall results of JR-NET3 suggest that endovascular treatment, i.e., stenting and PTA, for extracranial steno-occlusive lesions is relatively safe. Technical success was obtained in the satisfactory rates (98.0%). Post-procedural 30-day morbidity and mortality rates were low (1.6% and 0.5%, respectively). The rates in JR-NET3 was equal to or lower than other previous reports.

The complication rate was significantly higher in JR-NET3 than in JR-NET1&2. However, the rate of good outcomes (mRS 0–1) in JR-NET3 was similar to that in JR-NET1&2, and the morbidity and mortality was also similarly low. Distal embolism was most frequent in both registries. Considering

Table 7   Differences between JR-NET3 and JR-NET1&2

	JR-NET3 (n = 1154)	JR-NET1&2 (n = 959)	P value
Procedural success	1131 (98.0)	932 (97.2)	0.22
EPD use	571 (49.5)	334 (34.8)	<0.01
PTA	307 (26.6)	183 (19.1)	<0.01
Stenting	838 (72.6)	775 (80.8)	
Postoperative anticoagulant therapy	614 (53.2)	468 (48.8)	0.04
Good outcome (mRS 0–1 at 30 days)	962 (83.4)	819 (85.4)	0.20
General anesthesia	168 (14.6)	60 (9.5)*	<0.01
Complication	89 (7.7)	40 (4.2)	<0.01
Distal embolism	31 (2.7)	12 (1.3)	
Vessel dissection	26 (2.3)	10 (1.0)	
Hemorrhage	3 (0.3)	1 (0.1)	
Morbidity	18 (1.6)	22 (2.3)	0.22
Mortality	6 (0.5)	3 (0.3)	0.46

*The data was available only in JR-NET2 (n = 632). EPD: embolic protection device, PTA: percutaneous transluminal angioplasty.

the detailed information was not available from the registry, asymptomatic ischemic change, detected as small hyper-intensity spots on diffusion-weighted imaging, might be counted in the most recent study as ischemic complications, as mentioned in another JR-NET study.[14]

From univariate and multivariate analysis, the procedure under general anesthesia was significantly associated with the development of complications. There is little information regarding perioperative stroke in the endovascular treatment for extracranial steno-occlusive lesions under general anesthesia, but complications or poor outcome associated with general anesthesia were reported in other lesions. Contralateral internal carotid occlusion increased the perioperative stroke risk of carotid artery endarterectomy,[15] and the treatment for vertebrobasilar stenosis under general anesthesia highly caused the perioperative stroke mainly due to hypotension.[3] In other JR-NET studies, in endovascular treatment of vasospasm following subarachnoid hemorrhage, general anesthesia was significantly associated with unfavorable outcome, probably affected to blood pressure and cerebral ischemia. In addition, in ruptured vertebral artery dissecting aneurysms, general anesthesia was significantly associated with unfavorable outcome and highly with ischemic complications. In this registry, the rate of procedure under general anesthesia was significantly higher in JR-NET3 than in JR-NET2. This suggests that endovascular treatment might have been performed in more difficult cases in JR-NET3, in which procedure under general anesthesia was necessary. Unfortunately, detailed information, e.g. stenosis or occlusion of other intracranial arteries, or blood pressure during procedure, was not available. We should not recommend avoiding procedure under general anesthesia, but to identify the appropriate cases for procedure under general anesthesia will be necessary.

The rate of utilization of EPD was significantly higher in JR-NET3, although the effectiveness of such devices in transfemoral stenting remains controversial.[6] Regarding antiplatelet therapy, dual antiplatelet therapy was administered most frequently in both JR-NET3 and JR-NET1&2, and considerable rates of triple antiplatelet therapy were administered in JR-NET3. No protocol has been established for management of antiplatelet therapy in patients undergoing endovascular therapy for extracranial steno-occlusive diseases, especially as for triple antiplatelet therapy. For coronary intervention, the safety and efficacy of triple antiplatelet therapy compared with dual antiplatelet therapy have been reported.[16,17] For neurointervention, the safety of triple antiplatelet therapy has been reported only

for stent-assisted coil embolization of an unruptured intracranial aneurysm.[18] However, a prospective, multicenter, observational study revealed that multiple antithrombotic therapy for stroke and cardiovascular diseases leads to bleeding events.[19] In the present cohort, the rate of hemorrhagic complications was not different between JR-NET3 and JR-NET1&2, but the rate of distal embolism in JR-NET3 was not lower than that in JR-NET1&2. Further studies are warranted to determine the optimal utilization of EPD and antiplatelet therapy.

This study has several limitations. It was conducted retrospectively, and strategy of treatment was determined independently at each facility. In addition, preoperative symptoms only in patients with resistance to antithrombotic therapy were available, and the extent of experience of the operators was not determined. These factors might have influenced the findings, especially with regard to rates of complications. In particular, endovascular treatment approaches for stenosis at the orifice of the CCA and in the innominate artery include an anterograde approach via the femoral artery[20,21] and a retrograde approach via carotid artery reduction.[22,23] A transfemoral anterograde approach is technically difficult because of the poor stability of the guiding catheter[6] and may lead to an increased rate of complications. Endovascular treatment to prevent ischemic events is an important clinical goal, but the follow-up period in JR-NET3 (30 days after procedures) was too short to clearly evaluate the benefits of endovascular treatment.

In conclusion, from the results of this study, endovascular treatment in steno-occlusive lesions of the extracranial arteries was relatively safe; however, current endovascular treatment did not necessarily reduce the rates of complications or improve patient prognoses, compared with previous registries. Further prospective studies are necessary to establish the beneficial effects and strategies of endovascular treatment for stenosis and occlusion of the extracranial arteries.

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Conflicts of Interest Disclosure

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