Protection by Physical Activity Against Deleterious Effect of Smoking on Carotid Intima-media Thickness in Young Japanese

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Background: The hazardous effects of smoking and the favorable influence of physical activity on the progression of atherosclerosis have been well studied, but little is known about the interactions of these 2 factors. *Methods:* A total of 1090 subjects who were screened for brain disease (at annual medical checkups) between April 2007 and March 2008 were studied to clarify the effects of smoking on maximum carotid intima-media thickness (IMT) in patients with different grades of physical activity. Univariate and multivariate analyses were performed to investigate relationships between maximum IMT and independent variables, such as smoking status, age, gender, coexisting disease, physical activity, alcohol drinking, family history, subjective symptoms, body mass index, systolic blood pressure, diastolic blood pressure, blood sugar, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. *Results:* Univariate analysis revealed only the low physical activity group to have a significant relationship between smoking and maximum IMT. When the subjects were divided into 3 age groups (≤49, 50-59, and ≤60 years of age, respectively), the same association was noted for high and moderate physical activity groups ≤49 years of age. Multivariate analysis further revealed smoking status to be a significant predictor of maximum IMT in the young low and moderate activity groups. *Conclusions:* In physically inactive young people, smoking might have detrimental effects on maximum IMT, while high physical activity may be protective. **Key Words:** Carotid artery—intima-media thickness—physical activity—smoking.

Smoking has hazardous effects on health. Cigarette smoking increases the risk of cerebrovascular and cardiovascular events and is well documented to be a risk factor for ischemic stroke in general, with relative risks of 1.5 to 5.7.[1] It has also been reported that smoking increases carotid intima-media thickness (IMT),[2] which is a well-known surrogate marker for atherosclerosis.[3]

In contrast, appropriate physical activity may promote health, reducing cardiovascular and cerebrovascular events, while inactivity may increase risk of stroke,[4] although the issue is still controversial.[5-7] Concerning physical activity and IMT, most reports have revealed a reverse association, but the data are inconclusive.[8-10]

Few investigators, however, have analyzed the relationship between the effects of smoking and physical activity in detail.[4,5,11] We investigated a series of Japanese patients undergoing a brain dock, an annual physical check for cerebral disease, to clarify the effects of smoking on people with different grades of physical activity. We used maximum IMT of the carotid artery on carotid ultrasonography as the end point.

Methods

Subjects

A total of 2012 subjects (1369 men and 643 women 54.3 ± 9.6 years of age) visited the Health Management

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Center at Chunichi Hospital (Nagoya, Japan) between April 2007 and March 2008 for a medical checkup of the brain at their annual physical examination. A self-administered questionnaire, including questions about smoking status, physical activity, coexisting disease, alcohol intake, family medical history, and subjective symptoms was applied. The examination included carotid ultrasonography, blood pressure measurement, and routine blood tests.

A clerk randomly picked 20 records once or twice a week for a total of 58 weeks, for a total sample of 1160 patients. Among these, 30 had had no data for blood because of sampling option, 28 ceased smoking within 3 years, and 7 wrote the period of the cessation of smoking as 0, with no description of a smoking history. One subject had no description of smoking history and 4 filled out the interview sheets incompletely. One thousand ninety patients were enrolled in the present study. The study design was approved by the local ethical committee and strictly followed the ethics guidelines for clinical studies by the Japanese Health Labor and Welfare Ministry (2007), including informed consent.

Carotid Ultrasonography

Carotid IMT was evaluated using high-resolution sonography, with a linear transducer at 7.5 MHz in the B mode (EUB-7000HV; Hitachi, Tokyo, Japan), by 3 trained investigators blinded to the background of the patients. The IMT of each common and internal carotid artery was manually measured on a frozen frame in the longitudinal plane of the region 1 cm to 3 cm proximal and distal to the carotid bifurcation at 3 levels of lateral and medial walls, respectively. The maximum IMT was defined as the thickest wall of the lateral and medial walls of the common and internal carotid arteries on both sides. Plaques are included when maximum IMT is measured.

Analysis and Definitions

Self-reported physical activity was classified into 3 levels: (1) high, which included weekly exercising or sports (jogging, swimming, training at a gym, tennis, golf, etc.) for at least 30 minutes twice a week; (2) moderate, which included daily walking at least for 1 hour or compatible activity; and (3) low, which included not meeting the criteria for either high or moderate physical activity.

Smoking status was classified into 3 categories: (1) never smoker, a person who never smoked in his or her lifetime; (2) former smoker, a person smoking at least 1 cigarette per day at some period, but not smoking for the preceding 3 years or more; and (3) current smoker, a person smoking at least 1 cigarette per day for the preceding 3 years or more. They were scored 0, 1, and 2, respectively.

Alcohol drinking was categorized into 0, 1, or 2, corresponding to 0 or <1 unit per day (where 1 unit = 20 g of pure alcohol), 1 to 3 units per day, and ≥3 units per day.

Numbers of coexisting diseases were covered, including hypertension, diabetes mellitus, hyperlipidemia, cerebral infarction, and ischemic heart disease, all known as risk factors for atherosclerosis, and were categorized into 0, 1, 2, 3, and more. A family medical history was included if the patient's parents or siblings had one of the same diseases, and this was similarly counted and categorized.

Body mass index (BMI) was calculated as kg/m^2.

Numbers of subjective symptoms that patients described were counted and categorized into 0, 1, 2, 3, and more, including headache, numbness of limbs, tinnitus, floating feelings, dizziness, memory loss, and speech problems.

Among routine blood parameters, blood sugar, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were chosen for analysis. Because low-density lipoprotein (LDL) cholesterol was only an option for testing so that values were not available in all cases, LDL cholesterol was excluded from the present analysis.

Statistical Analysis

All statistical evaluations were performed with statistical software (JMP version 5 and Statview version 4.5 [SAS, Inc, Cary, NC]) and the results are mean ± standard deviation. To test for differences between 2 or more groups, Kruskal–Wallis and Chi-square tests were used, with multiple test procedure (Bonferroni correction). $P < .05$ was considered statistically significant. An initial univariate selection of candidate predictor variables for IMT was conducted. Correlations between 2 continuous variables were quantified using Spearman rank order correlation coefficients (ρ values) with a zero correlation, except for the categorical variable (sex) using the Mann–Whitney *U* test. We applied maximum IMT as a dependent variable and independent variables as candidate predictors were as follows: age, sex, coexisting disease, physical activity, alcohol intake, family medical history, symptoms, BMI, systolic blood pressure, diastolic blood pressure, blood sugar, total cholesterol, HDL cholesterol, and triglycerides. All subjects were divided into 3 age groups (≤49, 50-59, and ≤60 years old) and univariate analysis was performed for each. Before multiple linear regression analysis was performed, 9 dependent variables were selected by cluster analysis (the Ward method was applied to calculate the distance) to avoid multicolinearity among the dependent variables. Sex was included in the model as a variable coded as 1 (male) or 0 (female). Multivariate regression analysis with the least squares method for the selected 9 dependent valuables was performed for each age group with each grade of physical activity. Dependent valuables with $P < .05$ for the F statistics in the analysis with $R^2 \geq 0.2$ were considered significant predictors for the independent variable.

Results

The 1090 patients included 756 males and 334 females. Their clinical characteristics are summarized in Table 1. Average ages of the high physical activity group were rather higher than with the moderate and low physical activity groups ($P = .0002$ and $P < .0001$, respectively). This may be because of greater numbers of health conscious people in the middle- and high-age groups. Systolic blood pressure was higher in the high physical activity group ($P = .026$ and $P = .095$, respectively). No significant differences were detected for other continuous variables. Mean values for maximum IMT were higher in the high physical activity group than in the moderate and low physical activity groups (both $P < .0001$). The relatively high average age of patients in the high physical activity group described above may have the relation to it.

Differences in maximum IMT among 3 groups of smoking status in each physical activity group were analyzed by multigroup analyses (Table 2). In high and moderate physical activity groups, no significant differences in maximum IMT were found among 3 smoking status groups, whereas with low physical activity, significant differences were found between current and never smokers ($P = .003$) and former and never smokers ($P = .025$).

Univariate analysis also revealed a significant association between smoking status and maximum IMT for the low physical activity group ($\rho = 0.182$; $P < .0001$; Table 3).

Given the age-dependence observed, univariate analysis was reconducted with division into 3 age subgroups (≤49, 50-59, and ≤60 years old; Table 4). With low physical activity, smoking had significant associations with maximum IMT in all 3 groups ($\rho = 0.159$ and $P = .026$, $\rho = 0.169$ and $P = .006$, and $\rho = 0.169$ and $P = .050$, respectively). This was also the case for high and moderate physical activity groups ≤49 years of age ($\rho = 0.293$ and $P = .031$; $\rho = 0.268$ and $P = .041$, respectively).

Results of multivariate analysis for different physical activity in each age group for the 9 independent variables are summarized in Table 5. With R^2 analyses, smoking status was a significant predictor for maximum IMT in young moderate and low physical activity groups ($F = 7.343$ and $P = .009$; $F = 3.929$ and $P = .049$, respectively). Smoking status in patients ≥60 years of age high and low physical activity groups had P values for F statistics <.05, but the R^2 values were low.

Discussion

The present study provides evidence of smoking and physical activity interactions with regard to the maximum IMT endpoint in the youngest age group. In the group ≤49 years of age amelioration of the detrimental effects of smoking may be observed with high levels of exercise. Regarding smoking alone, our results are in line with the literature. Love et al[12] inspected young adults

Table 1. *Mean values for factor with reference to intensity of physical activity*

	Total (n = 1090)	P value*	High physical activity (n = 303)	Moderate physical activity (n = 191)	P value† (versus high)	Low physical activity (n = 596)	P value† (versus high)
Current smoker (%)	252	—	48 (15.8)	40 (20.9)	—	164 (27.5)	—
Former smoker (%)	245	—	92 (30.4)	42 (22.0)	—	111 (18.6)	—
Never smoker (%)	593	—	163 (53.8)	109 (57.1)	—	321 (53.9)	—
Male (%)	756 (69.4)	.077	225 (74.3)	125 (65.4)	—	407 (68.3)	—
Age, y	54.1 ± 9.9	<.0001*	57.7 ± 9.7	54.5 ± 8.5	.0002	53.3 ± 9.2	<.0001
Body mass index, kg/m^2	23.5 ± 9.1	.071	24.3 ± 16.5	22.7 ± 3.4	—	23.3 ± 3.3	—
Systolic blood pressure, mm Hg	114.4 ± 37.6	.023*	118.2 ± 65.6	110.4 ± 16.4	.026	113.8 ± 17.7	.095
Diastolic blood pressure, mm Hg	69.6 ± 13.1	.185	69.9 ± 13.0	68.5 ± 13.2	—	69.7 ± 13.1	—
Blood sugar, mg/dL	102.3 ± 18.4	.499	102.8 ± 19.4	101.2 ± 13.1	—	102.4 ± 19.3	—
Total cholesterol, mg/dL	206.4 ± 35.0	.521	208.4 ± 32.6	207.3 ± 36.1	—	205.2 ± 35.9	—
HDL cholesterol, mg/dL	60.2 ± 15.2	.094	62.0 ± 16.1	60.4 ± 15.1	—	59.3 ± 14.7	—
Triglycerides, mg/dL	120.1 ± 84.3	.084	116.1 ± 73.9	113.7 ± 90.1	—	124.2 ± 87.3	—
Maximum IMT, mm	1.04 ± 0.72	<.0001*	1.18 ± 0.78	1.11 ± 0.83	<.0001	1.02 ± 0.77	<.0001

Abbreviations: HDL, high-density lipoprotein; IMT, intima-media thickness.
Plus/minus values are means ± standard deviation or number of subjects (for gender).
*Kruskal–Wallis test.
†Bonferonni/Dunn post hoc test (versus high physical activity).

Table 2. *Multigroup analysis of maximum intima-media thickness with reference to smoking status and intensity of physical activity*

	Level of physical activity		
	High	Moderate	Low
P*	0.354	0.279	<.0001
P† (current versus former smoker groups)	—	—	.740
P† (former versus never smoker groups)	—	—	.025
P† (current versus never smoker groups)	—	—	.003

*Kruskal–Wallis test.
†Bonferonni/Dunn post hoc test.

(15-45 years of age) and reported that a smoker was 1.6 times more likely to have a cerebral infarction than a nonsmoker and that there was a cumulative dose effect with each additional pack-year. Robbins et al[13] noted a dose-dependent increased risk of ischemic stroke in male physicians, with a relative risk of 2.0 when smoking 1 to 19 cigarettes per day and 2.7 with >20 cigarettes per day. Bhat et al[14] analyzed data from the Stroke Prevention in Young Women Study and reported a strong dose–response relationship between cigarette smoking and ischemic stroke risk in young women. Mast et al[15] collected data from 2 prospective studies and revealed smoking to be significantly associated with high-grade carotid artery stenosis (>60%), especially in white smokers and patients smoking 20 pack-years or more, this effect being independent of other risk factors. Nakashima et al[16] reported a positive correlation between maximum IMT and smoking in hemodialysis patients. They considered that mean IMT was merely related to arterial wall thickening, influenced by age, hypertension, and dyslipidemia, while the maximum IMT was related to atheroma formation, with age, diabetes, and smoking as risk factors. Adachi et al[17] also found smoking status to not impact mean IMT, despite positive associations between mean IMT and blood pressure and low HDL cholesterol. Bots et al[18] recommended the use of mean maximum IMT rather than mean common IMT as a primary outcome measure in random controlled trials, and their reasoning was followed in this study.

Physical activity is a plausible factor to decrease cardiovascular and cerebrovascular event risk, but epidemiologic studies have been inconclusive. In their analysis of the Northern Manhattan Stroke Study, Sacco et al[4] reported leisure time physical activity to be significantly protective for stroke, with a dose–response relationship for both intensity and duration of physical activity. Hu et al[19] prospectively followed 47,721 subjects and found that a high level of leisure time physical activity reduced the risk of all subtypes of stroke, and that daily active commuting also protected against ischemic stroke. Lee et al[20] reported highly active individuals to have a 27% lower risk of stroke incidence or mortality (relative risk 0.73) than their low-activity counterparts through a meta-analysis of 23 studies (18 cohort and 5 case control). Wendel-Vos et al[21] drew similar conclusions from a meta-analysis of observational data from 31 publications, while Gillum et al[11] described nonrecreational

Table 3. *Univariate analysis of maximum intima-media thickness with each factor for 3 intensities of physical activity*

	Level of physical activity					
	High		Moderate		Low	
	ρ	P	ρ	P	ρ	P
Smoking status	0.083	.150	0.116	.110	0.182*	<.0001
Age	0.348	<.0001	0.483	<.0001	0.435	<.0001
Coexisting disease	0.195	.001	0.265	.0003	0.293	<.0001
Alcohol drinking	−0.002	.978	−0.069	.339	0.118	.004
Family history	0.017	.764	−0.018	.808	−0.016	.693
Subjective symptom	−0.047	.417	0.064	.378	−0.042	.304
Body mass index	0.043	.453	0.121	.096	0.111	.007
Systolic blood pressure	0.166	.004	0.315	<.0001	0.248	<.0001
Diastolic blood pressure	0.099	.087	0.240	.001	0.195	<.0001
Blood sugar	0.115	.045	0.171	.018	0.206	<.0001
Total cholesterol	−0.017	.770	0.178	.014	0.071	.085
HDL cholesterol	−0.134	.020	−0.054	.456	−0.147	.0004
Triglyceride	0.099	.086	0.092	.203	0.186	<.0001
Male sex†	—	.001	—	.046	—	<.0001

Abbreviation: HDL, high-density lipoprotein.
*Spearman correlation test.
†Mann–Whitney analysis.

Table 4. *Age-specific univariate analysis of maximum intima-media thickness with each factor for 3 intensities of physical activity*

	≤49		50-59		≤60	
Age, y	ρ	P	ρ	P	ρ	P
High physical activity	n = 55		n = 125		n = 123	
Smoking status	0.293*	.031	−0.027	.767	0.112	.215
Age	0.119	.382	0.194	.031	0.240	.008
Coexisting disease	0.410	.003	0.022	.809	0.246	.007
Alcohol drinking	−0.006	.965	0.226	.012	−0.126	.164
Family history	0.276	.043	0.007	.940	−0.012	.896
Subjective symptom	−0.044	.747	−0.113	.208	−0.096	.290
Body mass index	0.255	.061	0.014	.879	−0.057	.531
Systolic blood pressure	0.173	.205	0.171	.058	0.010	.909
Diastolic blood pressure	0.319	.019	0.095	.290	−0.152	.093
Blood sugar	0.316	.020	0.029	.745	0.075	.679
Total cholesterol	−0.064	.638	−0.001	.993	0.037	.278
HDL cholesterol	−0.327	.016	−0.096	.283	−0.098	.818
Triglycerides	0.267	.050	0.120	.183	−0.021	.717
Male sex†	—	.039	—	.006	−0.033	.390
Moderate physical activity	n = 59		n = 73		n = 59	
Smoking status	0.268*	.041	−0.145	.219	0.124	.345
Age	0.372	.005	0.141	.230	0.231	.079
Coexisting disease	0.104	.430	0.289	.014	0.156	.235
Alcohol drinking	0.072	.585	−0.116	.323	−0.086	.512
Family history	−0.050	.702	−0.093	.400	0.170	.196
Subjective symptom	0.139	.291	−0.032	.430	−0.067	.610
Body mass index	0.354	.007	−0.027	.818	0.054	.682
Systolic blood pressure	0.271	.039	0.178	.131	0.274	.037
Diastolic blood pressure	0.223	.090	0.217	.066	0.141	.285
Blood sugar	0.195	.137	0.042	.721	0.006	.963
Total cholesterol	0.444	.001	0.026	.826	−0.034	.794
HDL cholesterol	−0.130	.324	−0.080	.500	0.053	.688
Triglycerides	0.389	.003	−0.092	.434	−0.083	.525
Male sex†	—	.236	—	.169	—	.405
Low physical activity	n = 198		n = 262		n = 136	
Smoking status	0.159*	.026	0.169*	.006	0.169*	.050
Age	0.264	.000	0.165	.008	0.162	.060
Coexisting disease	0.148	.038	0.230	.000	0.206	.017
Alcohol drinking	0.116	.105	0.127	.040	0.107	.214
Family history	0.298	.766	0.022	.719	−0.019	.825
Subjective symptom	−0.056	.429	−0.094	.130	0.062	.469
Body mass index	0.161	.024	0.143	.021	−0.025	.768
Systolic blood pressure	0.144	.043	0.238	.000	0.069	.720
Diastolic blood pressure	0.218	.002	0.179	.004	−0.028	.745
Blood sugar	0.205	.004	0.117	.059	0.093	.279
Total cholesterol	0.173	.015	−0.044	.474	−0.059	.491
HDL cholesterol	−0.227	.002	−0.225	.000	0.029	.737
Triglycerides	0.286	<.0001	0.170	.006	0.070	.944
Male sex†	—	.000	—	.006	—	.002

Abbreviation: HDL, high-density lipoprotein.
*Spearman correlation test.
†Mann–Whitney analysis.

activity in women and men to be associated with an increased risk of stroke (relative risk 1.83%).

On the other hand, Evenson et al[5] investigated 14,575 individuals followed for an average of 7.2 years and showed that physical activity was only weakly associated with ischemic stroke risk. In the Framingham study, among an older cohort, the strongest protective effect was detected in the medium tertile physical activity subgroup, with no additional benefit gained from higher levels of physical activity. Lee et al[6] reported the results

Table 5. *Age-specific multiple regression analysis of maximum intima-media thickness with each factor for 3 intensities of physical activity*

Age, y									
≤49				50-59				≤60			
Variables	F	*P* value	R^2	Variables	F	*P* value	R^2	Variables	F	*P* value	R^2
High physical activity											
Smoking status	3.501	.068		Smoking status	1.626	0.205		Smoking status	5.383	0.022	
Age	0.411	.525		Age	3.218	0.076		Age	4.827	0.030	
Coexisting disease	8.550	.005		Coexisting disease	0.269	0.605		Coexisting disease	8.327	0.005	
Family history	0.119	.732		Subjective symptom	0.291	0.591		Subjective symptom	0.505	0.479	
Subjective symptom	0.057	.812		Systolic blood pressure	0.151	0.698		Body mass index	0.022	0.883	
Body mass index	0.117	.734		Blood sugar	0.1080	0.743		Systolic blood pressure	0.107	0.744	
Systolic blood pressure	0.290	.593		HDL cholesterol	0.480	0.490		Total cholesterol	1.141	0.288	
Total cholesterol	0.933	.339		Triglycerides	0.659	0.419		Blood sugar	1.436	0.233	
Male sex	0.721	.400		Male sex	3.846	0.052		HDL cholesterol	3.021	0.085	
			0.324				0.096				0.178
Moderate physical activity											
Smoking status	7.343*	.009		Smoking status	0.539	0.466		Smoking status	0.262	0.609	
Age	1.490	.228		Age	0.062	0.805		Age	4.283	0.040	
Coexisting disease	0.106	.746		Coexisting disease	1.083	0.302		Coexisting disease	0.773	0.380	
Alcohol drinking	0.040	.842		Family history	0.931	0.338		Family history	0.011	0.918	
Family history	0.019	.891		Subjective symptom	0.729	0.397		Subjective symptom	1.080	0.300	
Subjective symptom	8.252	.006		Body mass index	2.617	0.111		Body mass index	1.822	0.178	
Body mass index	0.121	.730		Systolic blood pressure	4.015	0.049		Systolic blood pressure	2.706	0.101	
Blood sugar	2.077	.156		Total cholesterol	0.226	0.636		Blood sugar	0.601	0.439	
HDL cholesterol	0.378	.541		HDL cholesterol	0.009	0.926		HDL cholesterol	6.775	0.010	
			0.343				0.117				0.075
Low physical activity											
Smoking status	3.929*	.049		Smoking status	0.262	0.609		Smoking status	6.136	0.015	
Age	5.298	.022		Age	4.283	0.040		Age	3.078	0.082	
Coexisting disease	11.360	.001		Coexisting disease	1.080	0.300		Coexisting disease	4.377	0.039	
Family history	0.015	.904		Family history	0.011	0.918		Family history	0.010	0.921	
Subjective symptom	0.065	.799		Subjective symptom	0.773	0.380		Body mass index	0.018	0.893	
Diastolic blood pressure	2.686	.103		Body mass index	1.822	0.178		Systolic blood pressure	0.175	0.676	
Blood sugar	8.054	.005		Systolic blood pressure	2.706	0.101		Total cholesterol	0.020	0.888	
Total cholesterol	7.426	.007		Blood sugar	0.601	0.439		HDL cholesterol	0.971	0.326	
HDL cholesterol	4.207	.042		HDL cholesterol	6.775	0.010		Triglycerides	0.017	0.898	
			0.200				0.075				0.106

Abbreviation: HDL, high-density lipoprotein.
Listed dependent variables were selected by cluster analysis.

of a prospective cohort study of 11,130 Harvard University alumni, revealing that with higher levels of energy expenditure (up to 3000 kcal/week), risk declined steadily, but beyond this the association weakened. Walking >20 km per week was associated with significantly lower risk, while light intensity activities (<4.5 metabolic equivalent tasks) were unrelated. Wannamethee and Shaper[7] pointed out that the benefit of vigorous physical activity for stroke was offset by an increased risk of heart attack.

In most previous studies, interactions between physical activity and smoking were not of major concern.[5] Sacco et al[4] stated briefly that the protective effects of physical activity did not differ by smoking status, unlike other risk factors, such as hypertension, diabetes, and cardiac disease. Gillum et al[11] speculated that high nonrecreational physical activity was less protective in white male smokers than in nonsmokers, but did not provide detailed data to this end. The Honolulu Heart Program, covering only older middle-aged men of Japanese ancestry, revealed a protective effect of habitual physical activity against thromboembolic stroke that was limited to their nonsmoking group.[22]

Here, we found smoking status to be a significant prediction was noted of maximum IMT in all age groups with low physical activity. Even with high and moderate physical activity, significant prediction was noted in patients ≤49 years of age.

Concerning people in the same age group with high physical activity, however, smoking status was not selected as a predictor of maximum IMT with multivariate analysis ($F = 3.501$; $P = .068$). There are 2 plausible interpretations for these results. One is the attenuation of hazardous effects of smoking by the beneficial effects of physical activity, and the other is that other independent factors are more influential determinants. With older age groups, the fact that thickening of intima and atherosclerosis occur because of many factors as people age[23] may result in attenuation of the malicious effects of smoking as a whole.

There are limitations to the present study. First, although the subjects were randomly selected independent of the present study purpose during each week of the study period, there is still a possibility of selection bias. Second, because carotid IMT measurement was made using ultrasonographic methods, inter- and intraobserver variability is conceivable, although all 3 examiners were experienced. Third, physical activities were classified into 3 groups according to the intensity of activity but were not quantitatively determined—for example, using a minimum equivalent task score or the International Physical Activity Questionnaire.[24,25] Fourth, medications such as statins,[26] antihypertensives,[27] and antiplatelets,[28] which are reported to decrease IMT (mostly mean IMT), were not considered. Finally, we did not control for environmental smoke exposure in nonsmokers, which has been reported to increase the risk of cardiovascular and cerebrovascular events.[29-31]

The present study shows that at least in young people (≤49 years of age), physically inactive smokers tend to have a higher maximum IMT. There is a possibility that in this age group, the detrimental effects of smoking on maximum IMT may be alleviated by physical activity.

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

Recent Trends in Neuroendovascular Therapy in Japan: Analysis of a Nationwide Survey—Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

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Abstract

The present study retrospectively analyzed the database of the Japanese Registry of Neuroendovascular Therapy 1 and 2 (JR-NET1&2) to determine annual trends, including adverse events and clinical outcomes at 30 days after undergoing neuroendovascular therapy. JR-NET1&2 are surveys that targeted all patients in Japan who underwent neuroendovascular therapy delivered by physicians certified by the Japanese Society of Neuroendovascular Therapy (JSNET) between 2005 and 2009. Medical information about the patients was anonymized and retrospectively registered via a website. Data from 32,608 patients were analyzed. The number of treated patients constantly increased from 5,040 in 2005 to 7,406 in 2009 and the rate of octogenarians increased from 7.0% in 2005 to 10.4% in 2009. The proportion of procedures remained relatively constant, but ratios of angioplasty slightly increased from 32.8% in 2005 to 33.7% in 2009. Procedural complications were associated more frequently with acute stroke (9.6%), ruptured aneurysms (7.4%), intracranial artery disease (ICAD) (5.4%), and arteriovenous malformation (AVM, 5.2%). The number of patients requiring neuroendovascular treatment in Japan is increasing and the outcomes of such therapy are clinically acceptable. Details of each type of treatment will be investigated in sub-analyses of the database.

Key words: nationwide survey, endovascular treatment, cerebral aneurysm, angioplasty, clinical outcome

Introduction

Neuroendovascular therapy is a less invasive method of treating various cerebrovascular diseases such as cerebral aneurysm, supra-aortic artery stenosis/occlusion, arteriovenous shunts, and acute stroke[1–8] that has become increasingly popular. However, the current status of this therapy including numbers of procedures, clinical outcomes, and adverse events remain unknown.[9,10]

The Japanese Society of Neuroendovascular Therapy (JSNET) established a board certification system in 2000 that certified physicians with ≥200 primary operator experiences, ≥10 presentations at medical meetings, and ≥3 publications as primary author as senior trainers and specialists through a board examination. The JSNET produced an expert consensus document in 2009 when a systematic review revealed a scarcity of high-quality clinical evidence in this field, especially in Japan. Thus, the society implemented retrospective studies (Japanese Registry of Neuroendovascular Therapy 1 and 2; JR-NET1&2) to clarify the general status of neuroendovascular therapy delivered by JSNET-certified physicians. Clinical and procedural data were retrospectively collected from January 2005 through December 2007 (JR-NET1) and from January 2008 through December 2009 (JR-NET2).

These studies aimed to determine annual changes in neuroendovascular treatment modalities and in major adverse events within 30 days thereafter.

Methods

I. Study design

JR-NET1 (2005–2006): This was the first nationwide survey of neuroendovascular treatments in Japan. The registry targeted all patients treated by JSNET board-certified physicians between January 2005 and December 2006, except for those whom their physicians judged unsuitable for this registry. Medical information about the patients was anonymized and retrospectively registered via a website (https://jr-net.tri-kobe.net/jr-net/).

JR-NET2 (2007–2009): This second nationwide survey of neuroendovascular treatment in Japan targeted all patients treated by JSNET board-certified physicians between January 2007 and December 2009. Medical information of the patients was anonymized and registered as described above.

Data were collected at the Translational Research Informatics Center (TRI, http://www.tri-kobe.org/). The study protocol, which is summarized briefly here, is available on line with the full text of this article (https://jr-net.tri-kobe.net/jr-net/). All members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study with regard to the protocol.

II. Patients

All patients treated by neuroendovascular treatment at participating centers during the study period were basically enrolled in the study. The local institutional review boards at each institution approved the study protocol before the investigators proceeded with the study.

III. Primary and secondary endpoints

The primary endpoint was activities of daily life (ADL) determined according to modified Rankin scale (mRS) scores. The secondary endpoints comprised the technical success of procedures and major adverse events (MAEs) that occurred within and at 30 days after procedures.

A score of 0 on the mRS indicates no disability, whereas scores of 1 or 2 indicate slight disability (some help required with ADL but basically independent), scores of 3 to 5 indicate moderate disability (some help required with ADL) to severe disability (bedridden or constant specific care required), and a score of 6 indicates death.

Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥2 points, respectively.

IV. Statistical analysis

Data were statistically analyzed using JMP 7 software (SAS Institute, Cary, North Carolina, USA). The statistical significance of intergroup differences was assessed using the *t*-test for quantitative scales, Pearson's χ^2 test; $p < 0.05$ was considered significant.

Results

I. Backgrounds and characteristics of patients

A total of 32,068 patients (mean age, 63.5 ± 13.9

Table 1 Annual trends of JR-NET data

	2005	2006	2007	2008	2009	Total
Total number	n = 5,040	n = 6,174	n = 6,690	n = 6,758	n = 7,406	n = 32,068
Age	64.0+/–13.8	63.4+/–12.9	64.1+/–13.7	64.6+/–13.3	64.4+/–13.8	63.5+/–13.9
Female	2,341 (46.4%)	2,921 (47.3%)	3,109 (46.5%)	3,131 (46.3%)	3,495 (47.2%)	14,997 (46.8%)
mRS before treatment	0.7	0.7	0.7	0.6	0.6	0.7
Procedures	n = 4,500	n = 5,457	n = 6,466	n = 6,503	n = 7,232	n = 30,158
Aneurysm treatment	1,777 (39.5%)	2,396 (43.9%)	2,725 (42.1%)	2,668 (41.0%)	3,112 (43.0%)	12,678 (40.5%)
Dome embolization, ruptured	751 (16.7%)	963 (17.7%)	1,073 (16.6%)	1,091 (16.8%)	1,254 (17.3%)	5,132 (17.0%)
Dome embolization, unruptured	883 (19.6%)	1,105 (20.3%)	1,373 (21.2%)	1,302 (20.0%)	1,597 (22.1%)	6,260 (20.8%)
Dissection/parent artery occlusion	143 (3.2%)	328 (6.0%)	279 (4.3%)	275 (4.2%)	261 (3.6%)	1,439 (4.8%)
Angioplasty/stenting	1,476 (32.8%)	1,734 (31.2%)	2,275 (35.2%)	2,363 (36.3%)	2,438 (33.7%)	10,286 (34.1%)
Carotid artery	1,042 (23.2%)	1,281 (23.5%)	1,717 (26.6%)	1,855 (28.5%)	1,926 (26.6%)	7,821 (25.9%)
Vertebral/subclavian artery	203 (4.5%)	230 (4.2%)	281 (4.4%)	282 (4.3%)	254 (3.5%)	1,250 (4.1%)
Intracranial artery	231 (5.1%)	223 (4.1%)	277 (4.3%)	226 (3.5%)	258 (3.6%)	1,215 (4.0%)
Brain & spinal AVM embolization	217 (4.8%)	281 (5.1%)	204 (3.2%)	213 (3.3%)	259 (3.6%)	1,174 (3.9%)
DAVF embolization	317 (7.0%)	424 (7.8%)	468 (7.2%)	464 (7.1%)	525 (7.3%)	2,198 (7.3%)
Tumor embolization	347 (7.7%)	373 (6.8%)	317 (4.9%)	319 (4.9%)	382 (5.3%)	1,738 (5.8%)
Acute stroke treatment	366 (8.1%)	249 (4.6%)	277 (4.3%)	266 (4.1%)	281 (3.9%)	1,439 (4.8%)
Physicians in charge	n = 4,935	n = 5,988	n = 6,690	n = 6,758	n = 7,406	n = 31,777
Senior trainer, board certified	3,139 (63.6%)	3,573 (59.7%)	3,097 (46.3%)	3,277 (48.5%)	3,624 (48.9%)	16,710 (52.6%)
Specialist, board certified	1,355 (27.5%)	1,801 (30.1%)	3,103 (46.4%)	3,044 (45.0%)	3,358 (45.3%)	12,661 (39.8%)
Non-specialist	438 (8.9%)	617 (10.3%)	462 (6.9%)	375 (5.5%)	405 (5.5%)	2,297 (7.2%)

AVM: arteriovenous malformation, DAVF: dural arteriovenous fistula, mRS: modified Rankin Scale.

years; female, 46.8%) were registered in this study (Table 1), which involved 200 and 256 board-certified physicians at 122 and 150 centers in JR-NET[11] and in JR-NET2, respectively (Appendix). Figure 1 shows the proportions of treated patients within various age groups. Although patients aged between 40 years and 70 years were the main recipients of treatment, the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$). In contrast, the ratio of younger patients (< 40 years) remained constant ($p = 0.361$; Fig. 1).

II. Procedures

Among a total of 32,068 neuroendovascular procedures implemented between 2005 and 2009, angioplasty and treatment for aneurysms accounted for 34.1% and 40.5%, respectively. Embolization of brain and spinal arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF), tumors, and treatment for acute stroke accounted for 3.9%, 7.3%, 5.8%, and 4.8% of procedures, respectively. Carotid artery stenting (CAS) accounted for 25.9% of all procedures (Table 1). The proportions of treatments remained relatively constant, except for CAS, which slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$; Fig. 2).

Elective or emergency procedures: The total numbers of elective and emergency procedures increased annually, but the rate of emergency treatment remained relatively constant between 28% and 30% throughout the study period (Fig. 3).

Physicians in charge: Senior trainers certified by JSNET were in charge of 63.6% and 48.9% of procedures during 2005 and in 2009 (Table 1), respectively. The total number of treatment procedures with JSNET senior trainers and specialists in charge increased annually, but the rate of procedures supervised by JSNET senior trainers gradually decreased, although the difference did not reach significance. However, treatment delivered with JSNET non-specialist in charge decreased from 8.9% in 2005 to 5.5% in 2009 ($p = 0.029$).

mRS scores before and after treatment: Figure 4A and 4B shows the overall proportions of mRS scores before and after treatment. Before treatment, ≥90% of patients were in relatively good condition, with mRS scores of 0–2 (Fig. 4A). At 30 days after undergoing procedures, >80% of patients maintained mRS scores of 0–2 (Fig. 4B).

mRS scores after each type of procedure: Figure 5 shows the outcomes of each type of treatment

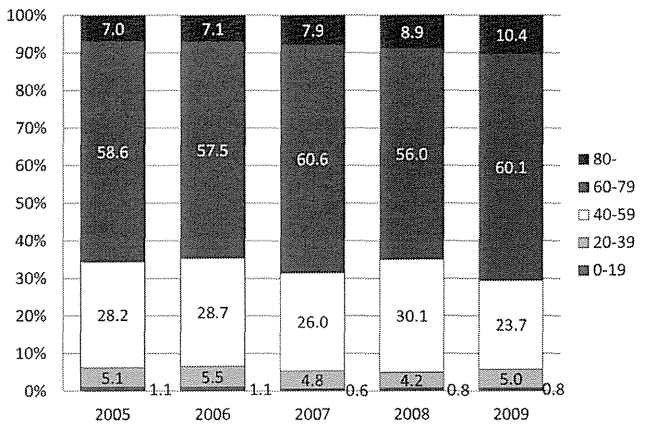

Fig. 1 Annual changes in patients' age during JR-NET1&2. Rates of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$), whereas the ratio of younger patients (< 40 years) remained constant ($p = 0.361$). JR-NET1&2: Japanese Registry of Neuroendovascular Therapy 1 and 2.

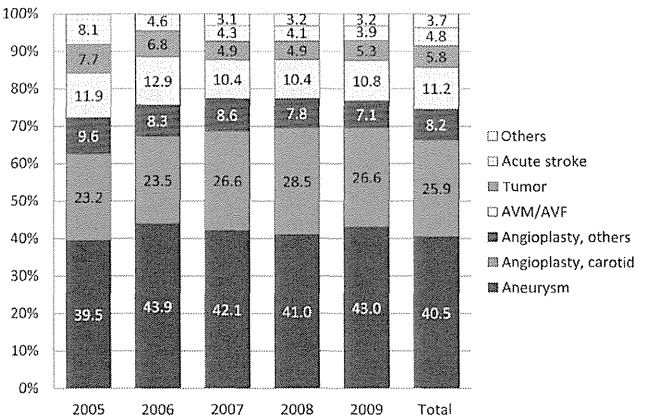

Fig. 2 Annual changes in the types of procedures. The proportion of treatments remained relatively constant, but carotid artery stenting (CAS) slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$).

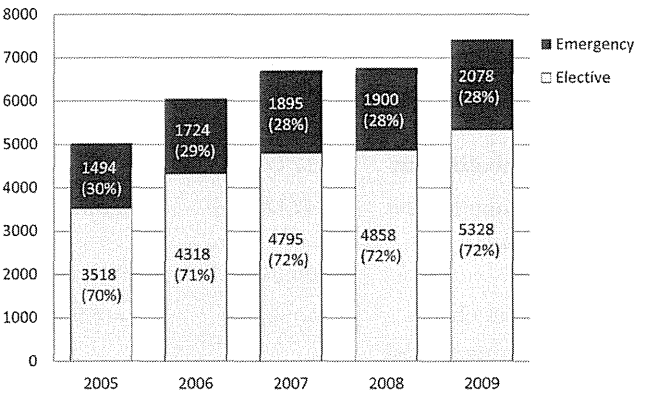

Fig. 3 Number of elective and emergency procedures. The total numbers of elective and emergency procedures increased annually, although the overall rate of emergency treatment remained between 28% and 30% throughout the period.

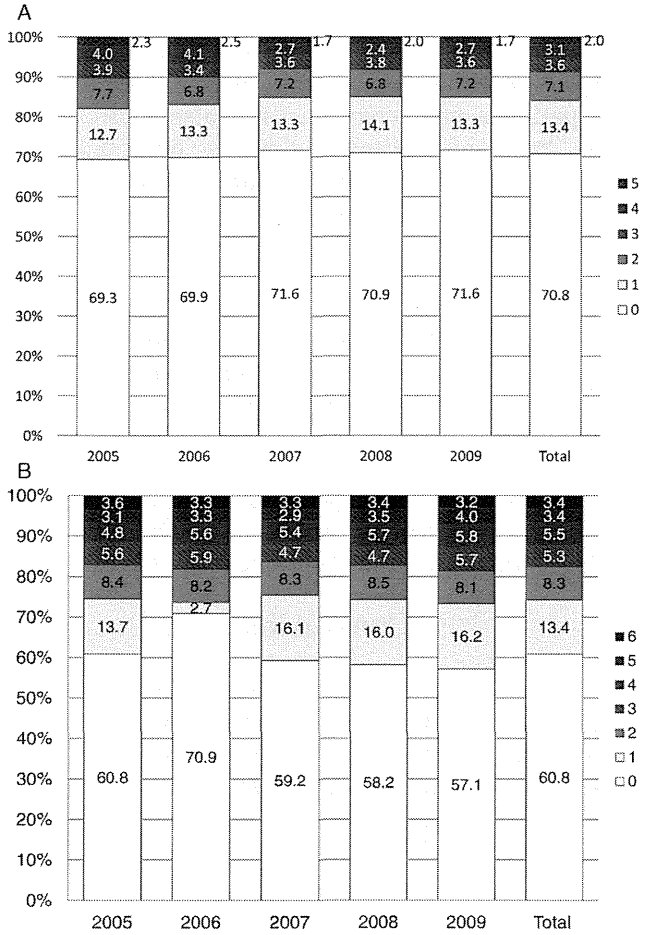

Fig. 4 Proportions of modified Rankin scale (mRS) scores before and after procedures. Ratio of patients with mRS 0–2 was ≥90% before therapeutic procedures (A), decreased at 30 days thereafter (B), but remained >80%.

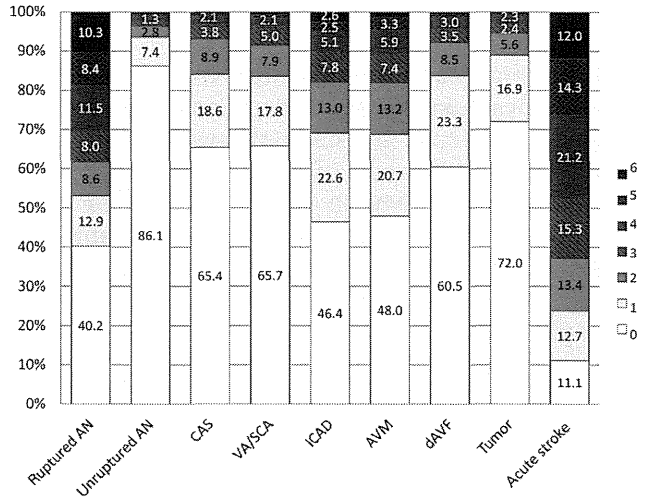

Fig. 5 Proportions of modified Rankin scale (mRS) scores at 30 days after various procedures. Outcomes were favorable (mRS 0–2) for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms respectively. Ratios of favorable outcomes of carotid artery stenting (CAS), vertebral artery (VA)/SCA (subclavian artery), dural arteriovenous fistula (dAVF), and tumor embolization were >90%. On the other hand, the ratios of favorable outcomes were 82.0%, 81.9%, and only 37.2% in intracranial artery disease (ICAD), arteriovenous malformation (AVM) and acute stroke, respectively.

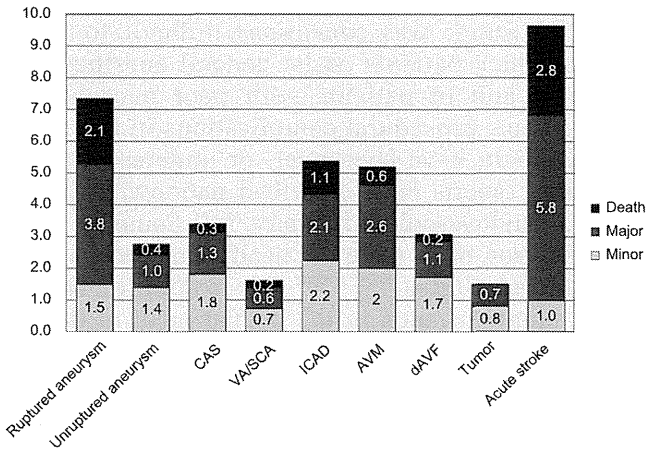

Fig. 6 Complications associated with each procedure. Complication rates were higher after procedures for ruptured aneurysm (7.4%) and acute stroke (9.5%), but less frequent for those that treated unruptured aneurysms (2.8%), VA/SCA (1.5%), and tumor embolization (1.5%).

according to mRS scores. Outcomes were favorable for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms, respectively, (mRS 0–2) and for ≥90% those after CAS, VA/SCA, dAVF, and tumors. On the other hand, 82.0%, 81.9%, and 37.2% of those treated for intracranial artery disease (ICAD), in AVM, and acute stroke had favorable outcomes.

Procedural complications of each treatment: Figure 6 shows the frequency of procedural complications after each type of treatment. Death, major and minor procedural complications occurred in 7.4% and 2.8% of patients treated for ruptured and unruptured aneurysms, respectively. Among angioplasties, procedural complications occurred in 3.4%, 1.5%, and 5.4% in the carotid artery, the VA/SCA and in ICAD, respectively. Among arteriovenous shunt diseases, complications developed in 5.2% and 3.0% of those treated for AVM and dAVF, respectively. The rate of complications of tumor embolization was 1.5%, and none of the patients died of procedure-related complications. On the other hand, complications developed at a rate of 9.6% in patients treated for acute stroke, including 2.8% who died.

Discussion

The present study investigated recent trends in neuroendovascular therapy through analyses of 32,608 patients registered in the nationwide JR-NET1&2 surveys. The number of procedures constantly increased from 5,040 in 2005 to 7,406 in 2009, and the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009. The proportion of treatments remained relatively constant, but angioplasty/stenting for carotid diseases slightly increased from 23.2% in 2005 to 26.6% in 2009. More procedural complications were associated with acute stroke (9.5%), ruptured aneurysm (7.4%), ICAD (5.4%), and AVM (5.2%).

The number of annual neuroendovascular procedures increased by 46.9% (from 5,040 to 7,406). The annual numbers of procedures required to treat intracranial aneurysms and angioplasty/stenting for atherosclerotic disease between 2005 and 2009 increased by 75.1% (from 1,777 to 3,112) and 65.2% (1,476 to 2,438), respectively. The mRS scores after procedures remained favorable in >80% of the patients each year. Clinical outcomes and complication rates significantly differed among procedures. Rates of favorable outcomes of procedures to treat ruptured aneurysms and acute stroke were around 60% and < 40%, respectively, and more procedural complications were also associated with these conditions. However, whether complications were major or minor was sometimes difficult to judge in emergency patients under general anesthesia or sedation, and in patients with poor neurological status. Thus, procedural complications in these two groups might have been over- or underestimated.

Several reports have described nationwide trends in neuroendovascular therapies.[12–19] Some of them are analyses of a national healthcare database in the United States.[12–15,17,20] For example, Huang et al. reported trends in the management of unruptured cerebral aneurysms in the United States.[15] They analyzed the length of hospital stay, in-hospital mortality rates, the number of hospitalizations, and total national charges related to inpatient treatment. Their findings provide valuable information regarding trends, but obtaining clinical data about neurological status, neuroendovascular procedures, and follow-up results might be difficult. Detailed evaluations and analyses could be achieved if areas or centers were selected. Higashida et al. described endovascular treatment for unruptured intracranial aneurysms in 18 of 47 states in the United Staes during 2007.[21] Qureshi et al. described how class I evidence (ISAT) from a nationwide impact survey impacted clinical practice. Their database was derived from stratified sampling at 20% of US hospitals.[20] In that regard, data from the nationwide JR-NET1&2 surveys are valuable because the study collected precise information regarding not only patient's characteristics, but also neurological status, types of treatment, devices, complications, and follow-up at 30 days after procedures.

This study has some limitations. Although JR-NET 1&2 provided a robust amount of patient information including clinical details, particularly information related to neuroendovascular therapies, it covered only about 35% of all procedures performed in Japan, which was calculated according to annual reports of training facilities of the Japan neurosurgical society (unpublished). This was a significant drawback in terms of avoiding selection bias. This shortcoming might be improved in a new nationwide survey (JR-NET 3), which is collecting information between 2010 and 2013 in a similar setting to that of JR-NET 1&2.

Conclusion

Data from this study suggest an increasing trend towards neuroendovascular treatment in Japan. The rate of neuroendovascular intervention is increasing annually and clinical outcomes seem acceptable. Details about each treatment or disease will be assessed in sub-analyses of this database.

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Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS members.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal.

Appendix

Participants, their hospitals, and the number of registered patients in JR-NET2 are listed when >100 patients were registered; names of investigators are listed when < 100 patients were registered. This information has already been reported for JR-NET1.[11]

Y Matsumoto, R Kondo, E Kondo, Y Matsumori, Kohnan Hp., 913; N Sakai, H Adachi, Y Ueno, H Imamura, H Yamagami, Y Kuramoto, Kobe City Med. Ctr General Hp., 809; I Nakahara, Y Watanabe, Kokura Memorial Hp., 586; T Abe, M Hirohata, Kurume Univ., 535; K Sugiu, K Tokunaga, Okayama Univ., 485; M Ezura, S Nishimura, N Kimura, I Suzuki, Sendai Med. Ctr, 471; M Nakamura, Hyogo Brain and Heart Ctr at Himeji, 448; T Suyama, M Nagashima, Tominaga Hp., 427; K Goto, S Ota, Brain Attack Ctr Ota Memorial Hp., 409; S Yamazaki, Tsuchiura Kyodo Hp., 348; T Nakazawa, Shiga Med. Univ., 347; Y Matsumaru, W Tsuruta, M Hayakawa, Toranomon Hp., 344; K Kazekawa, M Tsutsumi, H Aikawa, T Kodama, Fukuoka Univ. Chikushi Hp., 334; W Taki, H Sakaida, N Toma, F Asakura, Mie Univ. 324; E Kobayashi, N Hayasaka, Chiba Univ., 322; S Yoshimura, Y Enomoto, Gifu Univ., 290; K Iihara, T Satow, N Nakajima, Y Takenobu, National Cardiovascular Ctr, 289; M Kawanishi, A Shindo, K Kawakita, T Yano, Kagawa Univ., 276; H Shibuya, Sagamihara Kyodo Hp., 262; C Sakai, N Sakai, Institute of BioMed. Research and Innovation, 258; N Fukui, Kochi Med. Ctr, 258; T Hyogo, T Kataoka, Nakamura Memorial Hp., 230; I Naito, T Iwai, M Takatama, N Miyamoto, Geriatrics Research Institute and Hp., 228; T Ueda, T Takada, Y Otsuka, St. Marianna Univ. Toyoko Hp., 222; N Kuwayama, N Eiraku, N Akioka, Toyama Univ., 217; H Ishihara, Yamaguchi Univ., 214; T Nonaka, A Takahashi, Shiroishi Neurosurgical Hp., 213; T Hatano, M Murakami, Kyoto Med. Ctr, 205; T Hashimoto, Tokyo Med. Univ., 201; D Sato, Aizawa Hp, 200; A Nakahara, R Ogami, M Hp., 200; T Ichihashi, Fukuroi Municipal Hp., 196; T Fujinaka, M Hirata, M Sakaguchi, T Nishida, Osaka Univ., 196; M Komiyama, T Ishiguro, Osaka City General Hp., 193; Y Kiura, T Okazaki, S Sakamoto, Hiroshima Univ., 193; Y Akiyama, Tenri Hp., 186; H Sato, Tokyo Police Hp.,185; A Ishii, A Morizane, Kyoto Univ., 182; K Takayama, Ishinkai Yao Hp., 181; M Imaoka, Aso General Hp., 177; J Hamada, N Uchiyama, M Mori, Kanazawa Univ., 173; H Abe, Tachikawa General Hp., 170; A Nishio, Y Mitsuhashi, T Kawakami, Osaka City Univ., 170; S Iwabuchi, M Hayashi, Toho Med. Univ. Ohashi Hp., 162; M Nagahata, N Shimamura, Hirosaki Univ., 159; T Kubota, Hakodate Neurosurgical Hp., 158; K Imai, T Takeshita, Kyoto First Red Cross Hp., 153; H Sakai, Toyohashi Med. Ctr, 150; K Fujimoto, Osaka General Med. Ctr, 150; T Higa, Tokyo Women's Med. Univ., 147; K Harada, Fukuoka Wajiro Hp., 145; S Kobayashi, N Koguchi, T Yamauchi, Chiba Emergency Med. Center, 144; N Ikeda, Ube Kosan Central Hp.; H Hiramatsu, Hamamatsu Med. Univ., 142; J Satomi, Tokushima Univ.,139; H Ota, I Ikushima, Miyakonojo Med. Association Hp., 138; H Tenjin, Y Kosaka, Kyoto Second Red Cross Hp.,134; K Akaji, Mihara Memorial Hp., 128; S Aketa, Osaka Police Hp., 124; K Hayashi, M Morikawa, N Horie, K Hiu, Nagasaki Univ., 121; H Morishima, St. Marianna Univ. School of Medicine, 111; F Oya, Nagano Municipal Hp., 111; A Hyodo, K Suzuki, Dokkyo Med. Univ. Koshigaya Hp., 109; Y Arai, Fukui Univ., 106; M Sakamoto, Tottori Univ., 103; J-H Son, Shinmatsudo Chuo General Hp., 101; K Hayasaki, Saiseikai Ibaraki Hp., 101; S Tamatani, S Yamamoto, Dokkyo Med. Univ., 100; M Yasuda, Y Fumoto, Kano Hp., 100.

K Haraguchi, H Manabe, M Hayashi, O Kikuchi, S Iihoshi, K Miyata, J Sakurai, S Yamauchi, A Takahashi, N Tamagawa, J Moroi, A Shimada, K Asakura, H Shimaguchi, O Miyagi, M Matsumoto, A Kojima, T Takahashi, S Ishihara, S Kohyama, F Yamane, T Dembo, R Kanazawa, K Nakai, M Katayama, S Kittipong, M Tanaka, Y Numaguchi, M Fujimoto, A Uemura, T Saguchi, O Tone, Y Sato, K Shigeta, Y Yoshida, T Ohashi, K Amari, Y Sakata, S Tateshima, Y Ito, T Sorimachi, S Inagawa, K Morita, K Kitazawa, M Arai, N Minamide, Y Hirota, Y Takabatake, K Kanemaru, J Yamada, H Kitajima, S Fukazawa, T Okamoto, T Nakano, A Tsurumi, T Kojima, M Negoro, A Sadato, M Hayakawa, T Watanabe, K Irie, T Tanaka, T Hattori, N Kobayashi, A Tsuji, M Kawanishi, M Yamada, M Hirai, K Owada, M Ohashi, T Ota, K Maeno, S Sakamoto, T Kuroiwa, K Murao, K Nakazawa, J Kobayashi, N Nakagawa, T Fukawa, A Fujita, K Matsumoto, Y Yoshida, I Yamaura, A Masuda, H Minami, K Uchida, M Shirakawa, H Nakagawa, I Nakagawa, H Takeuchi, S Kawada, A Handa, M Koyanagi, K Yoshida, S Matsubara, T Mizogami, K Migita, H Yasuda, S Kato, K Satoh, M Hanaoka, N Hayashi, K Yoshino, A Nishida, T Shiraishi, O Nishizaki, M Iwanaga, T Higashi, M Iwaasa, M Okawa, K Nakahara, T Yoshioka, M Kaji, Y Hori, T Asano, M Okahara, A Kashiwagi, H Kiyosue, S Tanoue, T Kubo, and H Yonaha.

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Original Contribution

Endovascular Therapy for Asymptomatic Unruptured Intracranial Aneurysms

JR-NET and JR-NET2 Findings

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Background and Purpose—National registration studies (the Japanese Registry of Neuroendovascular Therapy [JR-NET] and JR-NET2) have determined the current status and outcomes of neuroendovascular therapy (neuro-EVT). We analyzed short-term outcomes of EVT for asymptomatic unruptured intracranial aneurysms (UIAs).

Methods—We extracted periprocedural information about EVT for 4767 asymptomatic UIAs from 31 968 registered procedural records of all EVT in the JR-NET and JR-NET2 databases. We assessed the features of the aneurysms and procedures, immediate radiographic findings, procedure-related complications, and clinical outcomes at 30 days after the procedures.

Results—We located 80.0% of UIAs in the anterior circulation, and the most frequent were paraclinoid. The diameter of 2.5%, 32.9%, 51.9%, 12.0%, and 0.7% of the UIAs was <3, 3 to 4, 5 to 9, 10 to 19, and >20 mm, respectively. EVT failed in only 2.1%. Adjunctive techniques were applied in 54.8% of procedures. Pre- and postprocedural antiplatelet agents were prescribed in 85.6% and 84.0%, respectively, of the procedures. The immediate radiographic outcomes of 57.7%, 31.9%, and 10.0% of the UIAs comprised complete occlusion, residual necks, and residual aneurysms, respectively. Complications that were associated with 9.1% of procedures comprised 2.0% hemorrhagic and 4.6% ischemic, and the 30-day morbidity and mortality rates were 2.12% and 0.31%, respectively.

Conclusions—The radiographic results of EVT for asymptomatic UIAs in Japan were acceptable, with low mortality and morbidity rates. **(*Stroke*. 2013;44:00-00.)**

Key Words: complications ■ embolization ■ endovascular procedures ■ intracranial aneurysm ■ treatment outcome ■ unruptured aneurysm

The management of incidental unruptured intracranial aneurysms (UIAs) remains undefined. After the International Study of Unruptured Intracranial Aneurysms (ISUIAs)[1,2] prospectively showed very low rupture rates of small aneurysms of the anterior circulation, others described the natural course of UIAs.[3–6] Although the reported rupture rate of small UIAs is low, when they do rupture, they lead to life-threatening subarachnoid hemorrhage (SAH).[7]

To determine how to manage patients with UIAs, the risks of various treatments with respect to the natural history and other risk factors should be assessed. The outcomes of clipping have been systematically described.[8] Some retrospective single-center outcomes of endovascular therapy (EVT) have been excellent,[9,10] and prospective data from France and Canada have been published,[11] but the actual risks of EVT remain poorly understood.

The Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2 are surveys that the Japanese Society for Neuroendovascular Therapy conducted in 2007 and 2010, respectively, to determine the status of EVT in Japan, and to standardize endovascular procedures and plan education for Japanese neurointerventionists on the basis of outcomes. The primary end point was the 30-day clinical outcome (modified Rankin Scale [mRS]) and secondary end points comprised technical success, adverse events arising within 30 days, and procedure-related complications arising after 30 days.

We collected a considerable amount of clinical data about EVT for UIAs through the JR-NET and JR-NET2 investigations. Here, we evaluated the outcomes of EVT for asymptomatic UIAs in Japan.

Methods

JR-NET and JR-NET2 Protocols

All EVT specialists certified by Japanese Society for Neuroendovascular Therapy were invited to register consecutive procedures on the JR-NET 2007 and JR-NET2 2010 databases. Patients

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in the JR-NET study were registered from 122 Japanese neurointerventional centers with 200 EVT specialists. The inclusion criteria comprised all patients who underwent EVT performed by EVT specialists between January 2005 and December 2006. Overall, 10715 patients who underwent 11114 EVT procedures were registered. Similarly, included in JR-NET2 were patients who underwent EVT at 150 neurointerventional centers with 255 EVT specialists between January 2007 and December 2009. Overall, 20272 patients who underwent 20854 EVT procedures were registered. The participants in these studies are listed in Appendix in the online-only Data Supplement.

Clinical and procedural data were entered through a Web site constructed by the Translation Research Informatics Center (Kobe, Japan) and anonymously reviewed by the principal investigators. Each JR-NET and JR-NET2 data set of cerebral aneurysms included the following parameters: demographics (sex, age, date of treatment), clinical data (mRS before and 30 days after EVT), complication data (procedure-related complications, adverse events), treatment parameters (aneurysmal location, size, shape, associated or not with SAH, symptomatic or asymptomatic), and procedural data (number of cerebral aneurysms treated in a single procedure, endovascular techniques, immediate radiographic outcomes, antithrombotic regimen). Table 1 shows the 16 locations of cerebral aneurysms listed in the registration studies. The aneurysms were classified according to maximal diameters of 3, 5, 10, and 20 mm. Aneurysms <10 mm were also classified as having favorable (neck, ≤4 mm; dome-to-neck ratio, ≥1.5) or wide (neck, >4 mm or dome-to-neck ratio, <1.5) necks. The degree of aneurysm occlusion was defined on the basis of 3-point Raymond classification scale.[12] That is, CO (class I) for complete occlusion, RN (class II) for residual neck, and RA (class III) for residual aneurysm. We also defined incident obstructive aneurysms causing parent artery occlusion as unpredicted parent artery occlusion that differed from parent artery aneurysms that were scheduled for treatment.

Clinical status was defined using the mRS. Morbidity and mortality were defined as deterioration of >0 on the mRS and death related to treatment at 30 days thereafter. Any such changes within 30 days of EVT were considered treatment related.

Data Extraction

All data sets registered as aneurysmal treatment and initially extracted from the JR-NET and JR-NET2 databases were screened in a single session to collect only information about treatment of asymptomatic UIAs. In other words, ruptured aneurysms, dissecting aneurysms, symptomatic UIAs, extracranial aneurysms, aneurysms associated with ruptured or symptomatic aneurysms, and treated UIAs concomitant with other diseases were excluded. We also screened procedures for eligibility criteria comprising pre- (sex, age, date of treatment, preprocedural mRS, aneurysm characteristics), intra- (techniques), and postprocedural status (radiographic outcomes, procedure-related adverse events, and mRS at 30 days). Treatment for intentional parent artery occlusion and nonsaccular aneurysms was also excluded. We thus isolated 1506 (1571 UIAs) and 3067 (3,196 UIAs) procedures from JR-NET and JR-NET2, respectively, with complete data for almost all variables on which this analysis was based (Figure). Combining these data from 4573 (4767 UIAs) procedures, 1262 (27.6%) and 3311 (72.4%) men and women, respectively, ranging in age from 6 to 93 (mean, 60.6±11.1) years underwent procedures. The numbers of treated UIAs were 1 (96.1%) of 4395, 2 of 164, 3 of 12, and 4 of 2 procedures (Table 2).

Statistical Analysis

Mean and frequency data were compared using Student *t* test and the χ^2 test or Fisher exact test, respectively. Trends were analyzed using the Cochran–Armitage test. All data were statistically analyzed using JMP version 10.0 software (SAS Institute, Cary, NC). The significance threshold was established at $P<0.05$.

Table 1. Treated Aneurysms

	n (%)
Location	
Anterior circulation	3814 (80.0)
ICA-cav	201 (4.2)
ICA-para	1575 (33.0)
ICA-Pcom	682 (14.3)
ICA-ACHOA	157 (3.3)
ICA-bif	142 (3.0)
MCA	301 (6.3)
ACRBA	39 (0.8)
Acom	588 (12.3)
DACA	101 (2.1)
Other (AC)	28 (0.6)
Posterior circulation	953 (20.0)
VA	132 (2.8)
BA-trunk	44 (0.9)
BA-SCA	188 (3.9)
BA-bif	520 (10.9)
PCA	42 (0.9)
Other (PC)	27 (0.6)
Size (*r*, mm)*	
<3	119 (2.5)
3 to <5	1569 (32.9)
5 to <10	2476 (51.9)
10 to <20	570 (12.0)
≥20	33 (0.7)
Appearance (% of UIA<10 mm)	
Narrow neck†	1816 (43.6)
Wide neck‡	2348 (56.4)

Acom indicates anterior communicating artery; ACRBA, anterior cerebral artery proximal to anterior communicating artery; BA, basilar artery; BA-bif, bifurcation of BA; BA-SCA, superior cerebellar artery of basilar artery; BA-trunk, trunk of basilar artery; DACA, anterior cerebral artery distal to anterior communicating artery; ICA-ACHOA, anterior choroidal artery; ICA-bif, bifurcation of internal carotid artery; ICA-cav, cavernous segment of ICA; ICA-para, paraclinoid segment of ICA; ICA-Pcom, posterior communicating artery; MCA, middle cerebral artery; Other (AC), other locations in anterior circulation; Other (PC), other locations in posterior circulation; PCA, posterior cerebral artery; and VA, vertebral artery.

**r*, maximal diameter.

†Neck, ≤4 mm and Dome-to-neck (D/N) ratio ≥1.5.

‡Neck >4 mm or D/N ratio <1.5.

Results

Aneurysm Characteristics

We analyzed periprocedural data from 4767 asymptomatic UIAs. Table 1 shows the features of the aneurysms, 3814 (80.0%) and 953 (20.0%) of which were located in the anterior and posterior circulation, respectively. One third was located in the internal carotid artery-paraclinoid, followed by the internal carotid artery-posterior communicating artery (14.3%), anterior communicating artery (12.3%), bifurcation of basilar artery (10.9%), and middle cerebral artery (6.3%). The maximal diameters of 2476 (51.9%) and 1569 (32.9%) aneurysms were 5 to 9 and 3 to 4 mm,

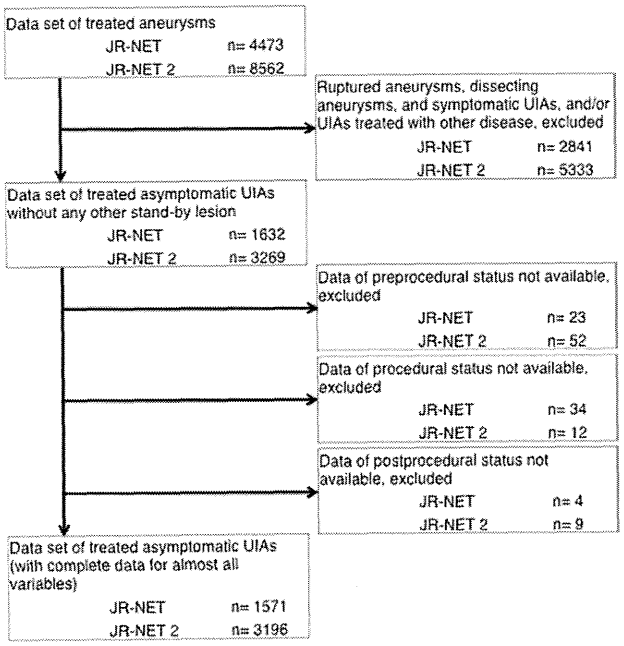

Figure. Included and excluded data sets. Preprocedural status: sex, age, date of treatment, preprocedural modified Rankin Scale (mRS) and aneurysm characteristics. Intraprocedural status: techniques. Postprocedural status: radiographic outcome, procedure-related adverse events and mRS 30 days after EVT. JR-NET indicates the Japanese Registry of Neuroendovascular Therapy; and UIA, unruptured intracranial aneurysm.

respectively. The maximal diameters of 570 (12.0%), 33 (0.7%), and 119 (2.5%) aneurysms were 10 to 19, >20, and <3 (very small) mm, respectively. Among UIAs <10 mm, 1816 (43.6%) and 2348 (53.4%) had narrow and wide necks, respectively.

Modalities of EVT for UIAs

Of 2155 (45.2%) aneurysms that were scheduled for intraaneurysmal embolization, all were treated by intrasaccular coil embolization using a single microcatheter and coils, and the remaining 2612 (54.8%) underwent adjunctive therapies, including balloon remodeling,[13] double catheters,[14] and intracranial stenting. Intracranial stents were applied to only 51 (1.1%) aneurysms because they were not approved in Japan until 2010. Systemic heparinization was included in 4488 (98.1%) procedures. Continuous anticoagulation therapy and post- and preprocedural antiplatelet medications were applied in 3108 (68.0%), 3841 (84.0%), and 3914 (85.6%) procedures, respectively. Preferences for adjunctive techniques increased annually (P<0.001), and the rates of post- and preprocedural antiplatelet therapy also statistically increased annually (P<0.001, each; Table I in the online-only Data Supplement).

EVT Feasibility and Immediate Radiographic Outcomes

EVT for 102 (2.1%) aneurysms failed (Table 3) at rates of 4.2%, 2.9%, 1.7%, 1.4%, and 3.0% for aneurysms with diameters of <3, 3 to 4, 5 to 9, 10 to 19, and >20 mm, respectively. The failure rate statistically decreased along with

Table 2. Characteristics of Patients and Procedures

UIAs (n)	4767
Procedures (n)	4573
Age (y, range)	60.6±11.1 (6–93)
Female, n (%)	3311 (72.4)
Male, n (%)	1262 (27.6)
Preprocedural mRS (n %)	
0	4262 (93.2)
1	182 (4.0)
2	75 (1.6)
3	24 (0.5)
4	26 (0.6)
5	4 (0.1)
Aneurysms/procedure, n (%)	
1	4395 (96.1)
2	164 (3.4)
3	12 (0.3)
4	2 (0.0)

mRS indicates modified Rankin scale; and UIA, unruptured intracranial aneurysm.

increasing aneurysmal size (P=0.003; Table II in the online-only Data Supplement). Failure rates did not significantly differ between aneurysms of the anterior and posterior circulation (2.2% versus 1.9%; Table III in the online-only Data Supplement). The immediate radiographic outcomes of 4665 successfully treated aneurysms (Table 3) showed that 2690 (57.7%) were completely occluded, 1490 (31.9%) had residual necks, 468 (10.0%) had residual aneurysmal domes, and 17 (0.4%) ended in unpredicted parent artery occlusion. The rate of residual aneurysm tended to increase annually (P=0.03; Table 4).

Adverse Events Related to EVT

Procedure-related adverse events occurred in 417 (9.1%) patients and 23.0% of those (n=96; 2.1% of total) had a reduced 30-day mRS (Table 3). Intracranial hemorrhagic and ischemic complications developed after 90 (2.0%) and 210 (4.6%) procedures, respectively, and 65 aneurysms ruptured intraprocedurally (1.4% per each aneurysm and procedure). We also found 5 aneurysms that had ruptured during the post-treatment period. Ischemic complications significantly decreased annually (P=0.01), but the total complication rates had no significant trend (Table 4). Analysis according to aneurysm size revealed that total complication rates were higher in aneurysms with very small (<3 mm) and large (≥10 mm) diameters than in those with diameters between 3 and 9 mm (Table II in the online-only Data Supplement). Rates of ischemic and hemorrhagic complications were significantly higher in larger (P<0.001) and smaller aneurysms (P<0.001), respectively. The complication rates were significantly lower for aneurysms in the anterior than in the posterior circulation: 8.3% (316/3,814) versus 11.2% (113/953), P=0.005 (Table III in the online-only Data Supplement). Furthermore, among UIAs <10 mm in diameter, complication rates were lower in those with

Table 3. Summary of Overall Outcomes of EVTs

	n	%
Technique (pa)		
Simple	2155	45.2
Adjunctive	2612	54.8
Antithrombotic regimen (pp)		
PRE antiplatelet therapy	3914	85.6
INTRA systemic heparinization	4488	98.1
CONT anticoagulation	3108	68.0
POST antiplatelet therapy	3841	84.0
Feasibility (pa)		
Success	4665	97.9
Failure	102	2.1
Anatomic outcome (per successfully treated UIA)		
CO	2690	57.7
RN	1490	31.9
RA	468	10.0
uPAO	17	0.4
Adverse events (pp)*		
Procedure-related complications	417 (96)	9.1 (2.1)
Hemorrhagic	90 (29)	2.0 (0.7)
Intraprocedural aneurysmal rupture	65 (18)	1.4 (0.3)
Aneurysmal rupture in post-treatment period	5 (5)	0.1 (0.1)
Ischemic	210 (59)	4.6 (1.3)
Puncture site	33	0.7
Other	84	1.8
mRS 30 days after EVT		
0	4193	91.7
1	207	4.5
2	81	1.8
3	31	0.7
4	37	0.8
5	10	0.2
6	14	0.3
Clinical outcome (pp)		
30-day morbidity	97	2.12
30-day mortality	14	0.31

CO indicates complete occlusion; CONT, continuous; EVT, endovascular therapy; INTRA, intraprocedural; pa, per aneurysm; mRA, modified Rankin Scale; POST, postprocedural; pp, per procedure; PRE, preprocedural; RA, residual aneurysm; RN, residual neck; and uPAO, unpredicted parent artery occlusion.

*With mRS deterioration.

favorable than in those with wide necks (Table IV in the online-only Data Supplement).

Clinical Outcomes at 30 Days

The 30-day morbidity and mortality rates were 97 (2.12%) and 14 (0.31%) of 4573 procedures, respectively (Table 3). All deaths were accompanied by hemorrhagic complications (aneurysmal ruptures, n=10; arterial dissections, n=2; arterial perforation, n=1) except one with ischemic complications caused by branch occlusion. No death was associated with other systemic conditions, such as coronary disease, pneumonia, or cancer.

Discussion

The incidence of detecting incidental asymptomatic UIAs has recently increased together with increasing opportunities for radiological assessments and developments in neuroimaging devices. However, consensus has not been reached on UIA management, which requires understanding of the natural history balanced against risks of treatment and long-term protection.

The largest study of the natural course of UIAs was compiled in 1998 by ISUIA investigators who first reported 0.5% annual rates of SAH for aneurysms <10 mm and 0.05% annual rates in patients with and without a history of SAH. On the basis of reports thereafter about the natural history, especially of small UIAs, risk factors for aneurysmal rupture and SAH resulting from small aneurysms, the Japan Stroke Society released statements for the management of UIAs within guidelines for the management of stroke,[15] and relatively clear recommendations for UIA management have also been reported.[16] Morita et al[6] (Unruptured Cerebral Aneurysm Study [UCAS] Japan Investigators) documented 111 patients with a 0.95% annual rate of rupture during a follow-up comprising 11 660 aneurysm-years. However, the results of clipping UIAs and coiling are difficult to compare. Although some prospective randomized studies, such as the ISAT[17] or Barrow Trial,[18] have compared coiled with clipped ruptured aneurysms, the results for UIAs were determined from aggregate analyses[19] or analyses of recent databases[20,21] because designing randomized controlled trials is difficult.

We aimed to clarify the current risks and short-term outcomes of EVT for UIAs in Japan, considering individual UIA management. We analyzed the outcomes of EVT for asymptomatic UIAs between 2005 and 2009 on the basis of information accumulated from the JR-NET and JR-NET2 databases created from information provided by >100 institutions throughout Japan. Most EVT for asymptomatic UIAs was performed by Japanese Society for Neuroendovascular Therapy–certified EVT specialists. Thus, this study is the first large cohort investigation of the nationwide results of EVT for asymptomatic UIAs.

In the present study, most of the patients were women and anterior circulation aneurysms were the most prevalent, which reflected the findings of the ISUIA[1] and Analysis of Treatment by Endovascular approach of Non ruptured Aneurysms (ATENA)[11] studies. However, the patients were a mean of 10 years, and most aneurysms (87.3%) were <10 mm. Although the Japanese guidelines recommend treating UIAs ≥5 mm in maximal diameter,[15] UIAs <5 mm account for 35.4% of the total; Oishi et al[10] reported that 223 (44.6%) of 500 small (<10 mm in diameter) treated UIAs were <5 mm. As part of the annual health checks characteristic of the unique Japanese healthcare system, complete physical examinations and whole brain screenings are widespread, and more small UIAs have been discovered through these routine procedures than elsewhere. Moreover, the Japanese insurance system covers treatment for such UIAs if the patient elects to proceed. Thus, small UIAs have abundant opportunities for treatment in Japan.

Some retrospective single-center results of EVT for UIAs have been reported. Although Im et al[9] and Oishi et al[10] have recently reported comparatively large-volume series, most