Table 7. Effects of Consciousness Level at Admission on Primary Outcomes (mRS=5 to 6) Among Acute Stroke Patients Determined Using Model 2

		Total Population		IS		SAH		ICH	
Admission Time	Japan Coma Scale	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Off-hour	0	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	1 digit	3.53 (3.18 to 3.90)	<0.001	4.08 (3.60 to 4.62)	<0.001	1.72 (1.22 to 2.44)	0.002	2.87 (2.32 to 3.56)	<0.001
	2 digit	12.31 (11.00 to 13.78)	<0.001	16.70 (14.41 to 19.35)	<0.001	2.68 (1.88 to 3.81)	<0.001	10.33 (8.25 to 12.92)	<0.001
	3 digit	72.27 (64.01 to 81.59)	<0.001	45.98 (38.17 to 55.39)	<0.001	24.79 (17.93 to 34.28)	<0.001	90.05 (71.19 to 113.91)	<0.001
Nighttime	0	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	1 digit	3.10 (2.72 to 3.53)	<0.001	3.66 (3.10 to 4.31)	<0.001	1.73 (1.13 to 2.64)	0.011	2.28 (1.75 to 2.97)	<0.001
	2 digit	10.89 (9.42 to 12.58)	<0.001	15.89 (13.08 to 19.31)	<0.001	2.96 (1.90 to 4.59)	<0.001	7.79 (5.91 to 10.26)	<0.001
	3 digit	69.17 (59.18 to 80.85)	<0.001	51.80 (40.27 to 66.64)	<0.001	24.79 (16.49 to 37.28)	<0.001	68.28 (51.33 to 90.82)	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.

Two sensitivity analyses that used different outcomes showed almost the same trend observed in the original analysis, except for ICH patients in sensitivity analysis 2 (Figure 4). Here, the effect of admission time was observed in ICH patients even when adjusted for consciousness level at admission (adjusted OR, 1.17; 95% CI 1.06 to 1.30; P=0.003 for off-hour compared to working-hour). Additional sensitivity analyses performed using mRS at admission as a confounder instead of JCS revealed a trend similar to that observed in the original analysis (Figure 5). Here, the effects of admission time were no longer significant even when stratified to each stroke subtype.

Discussion

Using nationwide population data on acute stroke patients, we found that outcome varied with admission time. Patients admitted outside of regular working hours were about 1.2 times more likely to have a poor outcome than those admitted during working hours. The effect of admission time remained significant for almost all stroke subtypes without adjusting for consciousness level at admission, which is similar to what has been reported previously. However, once we adjusted for consciousness level, the effects of admission time were dramatically attenuated; comatose patients were approximately 70 times more likely to suffer severe disabilities or death than lucid patients. Therefore, the different outcomes observed depending upon admission times were because of differences in stroke severity.

This study has several strengths. First, we included a large number of subjects from hospitals certified for training by the Japan Neurosurgical Society, the Societas Neurologica Japonica, and/or the Japan Stroke Society. Therefore, our results accurately reflect current practice in acute stroke care and are not influenced by changes in therapeutic strategy. The second strength is that we highlighted risks associated with nighttime admission. During the nighttime shift, hospital functions are reduced, and we observed a higher percentage of poorer outcomes for nighttime admitted patients. This finding is in accordance with a Dutch study that did not adjust for case severity, but did describe risk among IS patients admitted during the night.[27] Third, we adjusted for case severity at admission by using consciousness level. Case severity is a major confounding factor because it is one of the most important prognosis factors and is related to healthcare-seeking behaviors in stroke patients.[10–13] However, only 5 previous studies adjusted for case severity and they reported inconsistent results.[14–18] Among these, the Canadian study was the only one including a large number of subjects and reported a positive relationship between weekend hospital admission and stroke mortality among 20 000 acute stroke

Table 8. Crude Primary Outcome Comparisons Between Each Admission Time by Stroke Subtype and Japan Coma Scale

Japan Coma Scale	Admission Time	Total Population		IS		SAH		ICH	
		Admission (n)	Severe Disability/ Death at Discharge, n (%)	Admission (n)	Severe Disability/ Death at Discharge, n (%)	Admission (n)	Severe Disability/ Death at Discharge, n (%)	Admission (n)	Severe Disability/ Death at Discharge, n (%)
0	Working-hours	5793	286 (4.9)	4388	193 (4.4)	345	37 (10.7)	1069	56 (5.2)
	Off-hour	5420	293 (5.4)	4051	203 (5.0)	337	29 (8.6)	1042	62 (6.0)
	Nighttime	1079	78 (7.2)	781	46 (5.9)	100	8 (8.0)	199	25 (12.6)
1-digit	Working-hours	5679	991 (17.5)	3546	664 (18.7)	344	57 (16.6)	1799	276 (15.3)
	Off-hour	6354	1243 (19.6)	3869	831 (21.5)	431	65 (15.1)	2075	355 (17.1)
	Nighttime	1250	202 (16.2)	713	120 (16.8)	142	25 (17.6)	398	57 (14.3)
2-digit	Working-hours	1867	774 (41.5)	894	451 (50.5)	250	55 (22.0)	727	271 (37.3)
	Off-hour	2469	1034 (41.9)	1108	576 (52.0)	340	74 (21.8)	1026	387 (37.7)
	Nighttime	579	195 (33.7)	217	94 (43.3)	110	29 (26.4)	253	73 (28.9)
3-digit	Working-hours	1745	1383 (79.3)	447	351 (78.5)	468	350 (74.8)	841	690 (82.1)
	Off-hour	2665	2027 (76.1)	602	429 (71.3)	778	565 (72.6)	1291	1038 (80.4)
	Nighttime	785	567 (72.2)	142	95 (66.9)	254	178 (70.1)	391	294 (75.2)

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

Table 9. Effects of Admission Time on Primary Outcomes (mRS=5 to 6) Among Acute Stroke Patients by Japan Coma Scale

Japan Coma Scale	Admission Time	Total Population		IS		SAH		ICH	
		Adjusted OR† (95% CI)	*P* Value*	Adjusted OR† (95% CI)	*P* Value*	Adjusted OR† (95% CI)	*P* Value*	Adjusted OR† (95% CI)	*P* Value*
0	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.45 (1.33 to 1.58)	<0.001	1.07 (0.87 to 1.33)	0.515	0.87 (0.48 to 1.56)	0.633	1.29 (0.86 to 1.93)	0.220
	Nighttime	1.45 (1.33 to 1.58)	<0.001	1.59 (1.11 to 2.29)	0.011	0.83 (0.34 to 1.99)	0.672	2.87 (1.66 to 4.98)	<0.001
1-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.20 (1.09 to 1.33)	<0.001	1.20 (1.07 to 1.36)	0.003	1.00 (0.64 to 1.55)	0.998	1.21 (1.00 to 1.45)	0.044
	Nighttime	1.06 (0.89 to 1.26)	0.536	0.98 (0.78 to 1.23)	0.856	1.28 (0.71 to 2.31)	0.416	1.01 (0.73 to 1.41)	0.941
2-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.08 (0.94 to 1.24)	0.295	1.03 (0.85 to 1.25)	0.770	0.93 (0.60 to 1.44)	0.751	1.18 (0.93 to 1.48)	0.170
	Nighttime	0.91 (0.73 to 1.14)	0.406	0.89 (0.63 to 1.25)	0.498	1.56 (0.84 to 2.88)	0.160	0.81 (0.57 to 1.16)	0.250
3-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	0.81 (0.69 to 0.95)	0.008	0.65 (0.48 to 0.88)	0.006	0.81 (0.60 to 1.10)	0.169	0.89 (0.70 to 1.13)	0.325
	Nighttime	0.70 (0.57 to 0.86)	0.001	0.50 (0.31 to 0.81)	0.005	0.77 (0.51 to 1.15)	0.196	0.67 (0.49 to 0.90)	0.009

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.
*Off-hour and nighttime were compared with working-hours.
†Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and hospital volume.

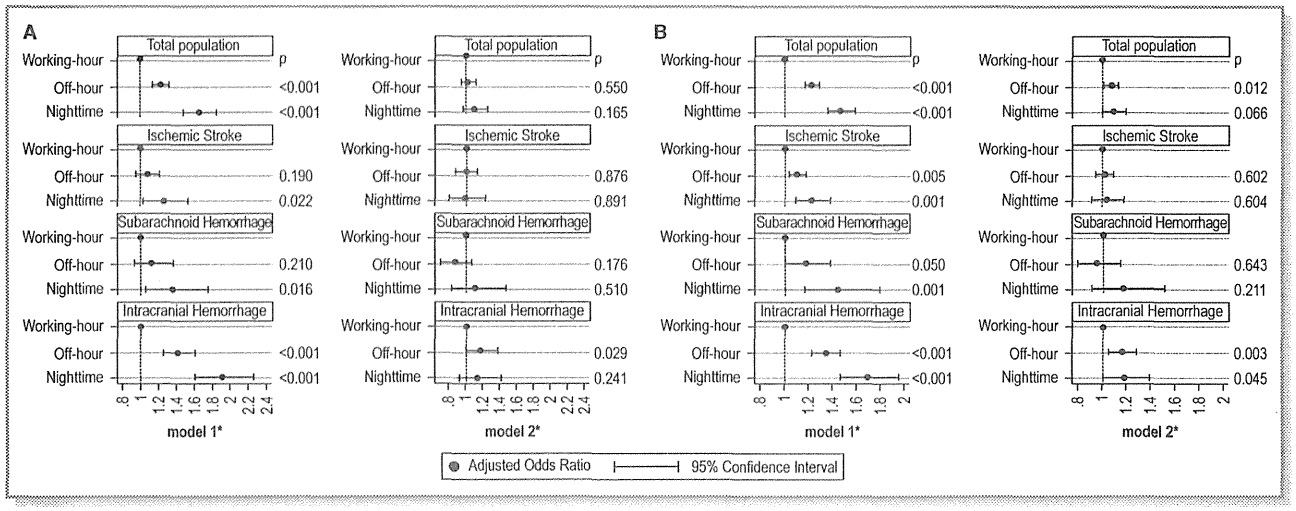

Figure 4. Sensitivity analyses for effects of admission time on modified Rankin Scale (mRS)=6 (A) and mRS=4 to 6 (B) among acute stroke patients with 2 different models. *Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and number of beds. Model 2 further adjusted for Japan Coma Scale.

or TIA patients at 11 hospitals.[14] The major differences of this study and the Canadian study are the number of participating hospitals and the definition of stroke subtypes. The Canadian study did not perform subtype-specific analyses, whereas we evaluated both total population and stroke subtype outcomes. Therapeutic strategies and responses vary with stroke subtypes. Therefore, we considered that stratified analysis by subtype was more appropriate.

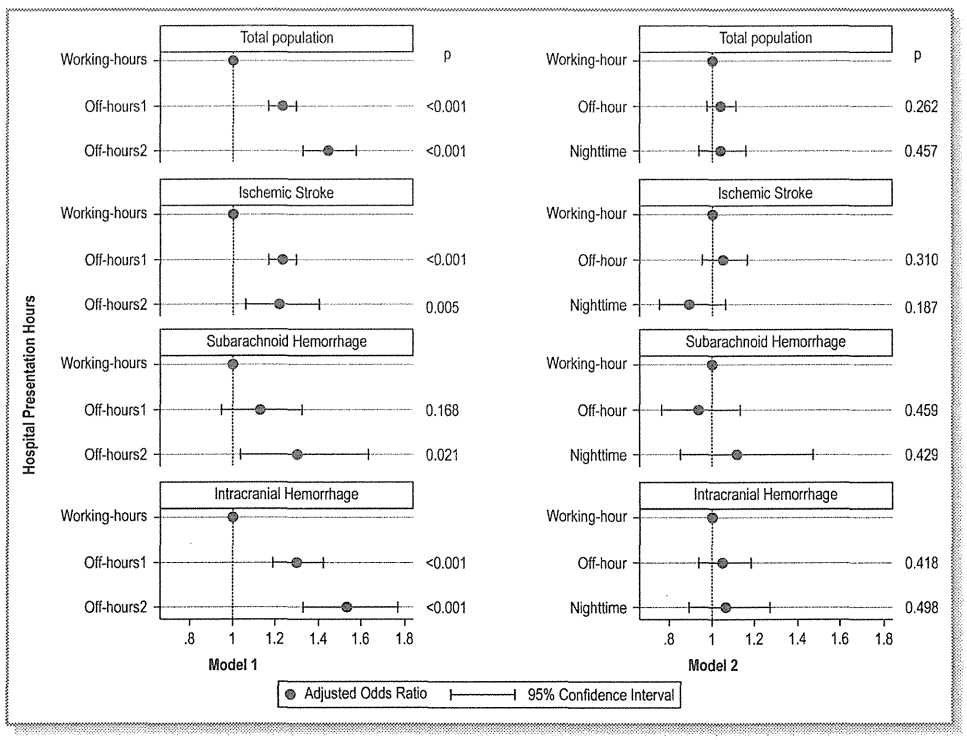

Figure 5. Sensitivity analysis for effects of admission time on primary outcomes (modified Rankin Scale [mRS]=5 to 6) among acute stroke patients with 2 different models using mRS at admission as a confounder instead of JCS. *Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and hospital volume. Model 2 further adjusted for modified Rankin Scale at admission instead of Japan Coma Scale.

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The reason why admission outside of working hours is related to case severity remains unknown. A circadian rhythm of stroke has been reported in large studies and may partially explain this phenomenon. Stroke is more frequent in the morning and evening,[28–31] and a surge in blood pressure and altered heart rate may be responsible for diurnal variation in stroke incidence.[32,33] However, the exact effect of circadian rhythm on stroke severity is unclear. Other factors such as limited access, minor symptoms, and age are known to be reasons that patients delay coming to the hospital.[10–12] Larger percentages of patients are admitted at off hours because baseline consciousness levels decrease during nighttime. Delayed perception of stroke symptoms or postponement of hospital consultation until regular working hours by patients with minor symptoms might have caused the perceived diurnal variation in stroke admission, though we could not confirm this from our data. Interestingly, in the subgroup analysis by baseline consciousness level, effects of admission time were reversed to a favorable outcome, as baseline consciousness levels got poorer in IS and ICH patients. These results may be inconsistent with the true values as a result of over stratification. Compared with patients with good consciousness level, patients with poor consciousness level could have been transferred to skilled hospitals by emergency medical services personnel and this may have led to this reverse effect of admission time, although we could not verify whether selective transfers existed in our dataset. Thus, health service managers must ensure that adequate stroke care is provided during off hours to promptly identify and treat severe stroke cases. Moreover, it is important to increase awareness among the general population about the appropriate facilities at Japanese hospitals for receiving stroke treatment in the acute phase.

In the sensitivity analyses, ICH patients admitted outside of working hours did not show robust results, but the effects of admission outside of working hours remained significant even when adjusted for baseline consciousness level among ICH patients. This is an important point because the numbers of hemorrhagic patients who are admitted outside of working hours are increasing. Although we could not measure any metrics of acute stroke care, our results suggest that the quality of acute stroke care provided by hospitals in Japan for hemorrhagic patients during the day are inconsistent. The results of a study published by the Get With The Guidelines-Stroke Program may support these findings; appropriate care and prevention were less frequently provided for ICH and SAH patients than for IS patients.[34] Systematic care processes for ICH and SAH may be poor during off-hours because of impaired healthcare systems, such as differential response times by night-shift workers and the presence of less skilled neurosurgeons, general physicians, residents, and paramedics.

We could not detect outcome differences for SAH patients probably because of the poor clinical prognosis associated with this stroke subtype. However, further studies that measure acute stroke care quality, such as prompt examination or available procedures during working hours and off hours, are necessary to verify this hypothesis.

This study has some limitations. Because the Japanese DPC/PDPS data were used, JCS scores were used to adjust for severity instead of the National Institute of Health Stroke Scale (NIHSS) or GCS.[25,26] However, our findings did not change even when data were adjusted by mRS at admission. Second, we used information on the occurrence of additional billings from the DPC/PDPS data to classify admission time; therefore, some data on the occurrence of additional billings were missing. We excluded subjects with missing values from analysis, and this may have biased our results. However, we believe that this exclusion does not alter our findings because severities of consciousness levels at admission and outcomes at discharge were not significantly different between subjects who were excluded and those who were included. Third, as for the classification of hospital admission time, we could not split the times in a more detailed manner because of data restriction, ie, daytime admissions during weekends and on national holidays were considered to be off-hour admissions. However, if patients admitted during this time exhibited less severe stroke symptoms or if hospitals during this time indeed provided better stroke care than at other off-hour times among off-hour, it could underestimate the effects of differences in severity on relationships between admission time and outcome at discharge. Fourth, although we collected nationwide data, we may have underestimated the relationship between admission time and outcomes because participating hospitals were certified training hospitals, which are considered to offer similar qualities of care. If hospitals that provide fewer resources and less professional stroke care were included in the analysis, stronger relationships may have been identified. Furthermore, we could not follow-up on post-discharge outcomes and we were unable to include multiple metrics representing acute stroke care quality, such as promptness or execution of specific procedures and protocols. Most studies have dealt with the inequality of care between working hours and off hours, such as reduced availability of highly skilled personnel and less access to urgent procedures, as the main reason for outcome disparity.[2,3] Further studies that focus on acute stroke care metrics are needed to better identify variability in care quality between admission times.

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Disclosures

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Consciousness Level and Off–Hour Admission Affect Discharge Outcome of Acute Stroke Patients: A J–ASPECT Study

Satoru Kamitani, Kunihiro Nishimura, Fumiaki Nakamura, Akiko Kada, Jyoji Nakagawara, Kazunori Toyoda, Kuniaki Ogasawara, Junichi Ono, Yoshiaki Shiokawa, Toru Aruga, Shigeru Miyachi, Izumi Nagata, Shinya Matsuda, Yoshihiro Miyamoto, Michiaki Iwata, Akifumi Suzuki, Koichi B. Ishikawa, Hiroharu Kataoka, Kenichi Morita, Yasuki Kobayashi and Koji Iihara

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Effects of Extracranial–Intracranial Bypass for Patients With Hemorrhagic Moyamoya Disease

Results of the Japan Adult Moyamoya Trial

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Background and Purpose—About one half of those who develop adult-onset moyamoya disease experience intracranial hemorrhage. Despite the extremely high frequency of rebleeding attacks and poor prognosis, measures to prevent rebleeding have not been established. The purpose of this study is to determine whether extracranial–intracranial bypass can reduce incidence of rebleeding and improve patient prognosis.

Methods—This study was a multicentered, prospective, randomized, controlled trial conducted by 22 institutes in Japan. Adult patients with moyamoya disease who had experienced intracranial hemorrhage within the preceding year were given either conservative care or bilateral extracranial–intracranial direct bypass and were observed for 5 years. Primary and secondary end points were defined as all adverse events and rebleeding attacks, respectively.

Results—Eighty patients were enrolled (surgical, 42; nonsurgical, 38). Adverse events causing significant morbidity were observed in 6 patients in the surgical group (14.3%) and 13 patients in the nonsurgical group (34.2%). Kaplan–Meier survival analysis revealed significant differences between the 2 groups (3.2%/y versus 8.2%/y; P=0.048). The hazard ratio of the surgical group calculated by Cox regression analysis was 0.391 (95% confidence interval, 0.148–1.029). Rebleeding attacks were observed in 5 patients in the surgical group (11.9%) and 12 in the nonsurgical group (31.6%), significantly different in the Kaplan–Meier survival analysis (2.7%/y versus 7.6%/y; P=0.042). The hazard ratio of the surgical group was 0.355 (95% confidence interval, 0.125–1.009).

Conclusions—Although statistically marginal, Kaplan–Meier analysis revealed the significant difference between surgical and nonsurgical group, suggesting the preventive effect of direct bypass against rebleeding.

Clinical Trial Registration—URL: http://www.umin.ac.jp/ctr/index.htm. Unique identifier: C000000166.

(*Stroke*. 2014;45:1415-1421.)

Key Words: cerebral revascularization ■ hemorrhage ■ moyamoya disease

See related article, p 1245.

Moyamoya disease is a unique cerebrovascular disease characterized by progressive occlusion of the bilateral internal carotid arteries at their terminal portions and unusual secondarily formed vascular networks (moyamoya vessels) that act as collateral pathways.[1,2] Unlike pediatric patients, who usually present with transient ischemic attacks (TIAs) or cerebral infarction, about one half of adult patients have intracranial hemorrhage that seriously affects their prognosis.[1–3] Long-term hemodynamic stress to the collateral vessels is thought to induce vascular pathologies leading to hemorrhage.[1,2] Although the rate of recurrent bleeding is known to be extremely high, no therapeutic method of preventing rebleeding attacks has yet been established. Extracranial–intracranial bypass surgery is often used for ischemic moyamoya disease, and angiographic diminishment of moyamoya vessels can be observed after surgery, which is regarded as decreased hemodynamic stress to these vessels.[4] A hypothesis has therefore emerged that bypass surgery can also reduce this stress, even in hemorrhagic moyamoya disease, and prevent rebleeding attacks. In fact, many cases of bypass surgery for hemorrhagic moyamoya disease have been reported, but all are retrospective studies and the benefit of bypass surgery has not yet been scientifically clarified. To resolve this, the Japan Adult Moyamoya (JAM) Trial was

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planned in 1999.[5] The study started in 2001, and follow-up of all enrolled patients was completed in 2013.

Methods

Patient Eligibility

This study is a multicentered, prospective, randomized, controlled trial to clarify the effect of bypass surgery on moyamoya disease with hemorrhagic onset. Twenty-two institutes with sufficient surgical experience with moyamoya disease participated in the study. The target was adult patients who had experienced episodes of intracranial bleeding within the preceding year and could be observed for 5 years after enrollment. The diagnosis of moyamoya disease was made according to the diagnostic guidelines proposed by the Ministry of Health and Welfare of Japan.[3] Table 1 lists all the inclusion and exclusion criteria. The study office carefully checked the radiological data and determined eligibility for the trial in each case.

Table 1. Patient Eligibility for the JAM Trial

Clinical requirements
Age: between 16 and 65 years at the time of the initial bleeding episode
Independent in daily life (modified Rankin disability scale score of 0–2)
Intracerebral hemorrhage, intraventricular hemorrhage, or subarachnoid hemorrhage occurring within the preceding 12 months
At least 1 month since the last stroke episode, either ischemic or hemorrhagic
At least 1 month since the completion of acute phase treatment for hemorrhage and for related secondary pathophysiology (eg, hydrocephalus)
Radiological requirements
CT/MRI
Lack of large infarction spread widely over the territory of a main arterial trunk
Lack of contrast enhancement in the infarcted area
Angiography
Angiographic findings should satisfy the diagnostic criteria of the spontaneous occlusion of the circle of Willis (moyamoya disease) published by the Ministry of Health, Labor and Welfare of Japan:
Occlusive lesions should exist in the terminal portion of the intracranial internal carotid artery or in the proximal portion of the anterior or middle cerebral arteries
An abnormal vascular network in the region of basal ganglia and thalamus (moyamoya vessels) is demonstrated in the arterial phase of angiography
These findings should be demonstrated on both sides
Exclusion criteria
Not independent in daily life (modified Rankin disability scale score of 3–5)
Atherosclerotic carotid disease or cardiac arrhythmia that may cause thromboembolic complications
Malignant tumors or organ failure of the heart, liver, kidney, or lung
Unstable angina or myocardial infarction within the past 6 months
Hematologic abnormality showing bleeding diathesis
Uncontrolled diabetes mellitus showing a serum fasting blood glucose level >300 mg/dL, or requires insulin
Hypertension with a diastolic blood pressure of >110 mm Hg
Treated with extracranial–intracranial bypass surgery before enrollment
Pregnancy

CT indicates computed tomography; and JAM, Japan Adult Moyamoya.

Sample Size

At the beginning of the study, the optimal sample size was calculated on the assumption that the incidence of adverse neurological events would be 8%/y in the nonsurgical group and 4%/y in the surgical group. The follow-up period was 5 years, and the sample size of 160 (80 patients per group) was expected to have 80% of the statistical validity required to detect a difference between the 2 groups with a significance level of 0.05. However, this number was reduced to 80 in January 2006 because the number of patients eligible for the study was revealed to be far smaller than expected. The number of new registration was 13.2/y at that time point, which meant that the completion of the study would be later than 2018. Then, the JAM Trial Executive and Steering Committee determined that the original sample size would be impossible to attain within the adequate study period. The calculation of 80% statistical power told us that the number of 80 patients would be able to detect the statistical significance if the event rate of the surgical group was <2.8%/y when that of the nonsurgical group was set to be 8%/y.

Randomization

According to computed tomography and digital subtraction angiography performed at the onset of intracranial hemorrhage, the study office estimated the bleeding point in each case as type A (bleeding from collateral vessels in the anterior circulation) or type B (bleeding from those in the posterior circulation). After informed consent was obtained, a computer-generated randomization scheme was applied, and the patient was assigned to receive either conservative medical care alone (nonsurgical group) or medical care plus extracranial–intracranial bypass (surgical group). To ensure a balance between these groups with respect to the bleeding point, a randomization scheme was performed separately within type A and type B (stratified randomization). This was required because the outcome could differ between hemorrhages of the basal ganglia (type A) and those of the thalamus (type B), although such a difference had not been proven. To avoid inclusion bias and ensure the quality of the trial, all ineligible patients and patients who were eligible but did not participate in this study for whatever reason were reported and checked by the study office. Bypass surgery for these nonparticipants was prohibited unless a legitimate reason compelled it, such as frequent TIAs or progressive ischemic stroke.

Surgical Treatment

Extracranial–intracranial bypass, if assigned to the surgical group, was performed on both sides (each side at some interval within 3 months after enrollment) by a registered neurosurgeon at each institute. As the operative maneuver, a direct anastomotic procedure such as superficial temporal artery–middle cerebral artery anastomosis was required. Indirect bypass procedures can be added to direct bypass; however, indirect bypass alone was not permitted, nor was high-flow bypass such as venous graft or radial artery graft.

Patient Follow-Up

Table 2 shows the follow-up protocol. Each patient was observed for 5 years after enrollment by a pair of neurosurgeons and a neurologist in each participating institute. Postprocedure inpatient events were also handled by this pair. Blood pressure medication was given to patients with hypertension to control it. The use of anticoagulants or antiplatelet drugs was not allowed unless the patient was having significant cerebral ischemic attacks. The patients' medical, neurological, radiological, and functional status was checked and reported every year. Both bleeding time and coagulation time were also monitored.

End Points

The following items constitute primary end points: (1) recurrent bleeding; (2) completed stroke causing significant morbidity; (3) significant morbidity or mortality from other medical cause; or (4) requirement for extracranial–intracranial bypass for a nonsurgical

Table 2. Follow-Up Protocol of the JAM Trial

	Registration	6 mo	1 y	Each Anniversary	Recurrent Bleeding or Other End Point
Neurological examination	●	●	●	●	●
CT/MRI	●	●	●	●	●
MR angiography			●	●	
SPECT	●	●			●
Angiography	●	● (surgical group only)			●
Bleeding time, PT, and APTT	●	●	●	●	●

●indicates examination required; APTT, activated partial thrombin time; CT, computed tomography; JAM, Japan Adult Moyamoya; MR, magnetic resonance; PT, prothrombin time; and SPECT, single-photon emission computed tomography.

patient because of progressive ischemic stroke or crescendo TIAs, as determined by a registered neurologist. Significant morbidity was defined as having a modified Rankin disability scale[6] score of ≥3. The following items constitute a secondary end point: (1) recurrent bleeding occurring later than 3 months after enrollment or (2) related death or significant morbidity. This was because surgical operations were to be performed on each side at some interval within 3 months after enrollment. Asymptomatic bleeding incidentally detected by MRI in the routine follow-up examination was not regarded as an end point. All the adverse events were reported to the central office of the trial, and end points were finally adjudicated in the executive and steering committee consisted of neurologists and neurosurgeons who were not blinded to the allocation.

Statistical Analysis

All statistical analyses were executed by 2 statisticians in the statistical center of the trial (listed in the Appendix). Statistical analysis with a Kaplan–Meier survival analysis and a Cox proportional hazard model was used to compare the length of time without an adverse event for each group. The unpaired 2-group t test, χ^2 for independence test, and Fisher exact probability test were used to compare baseline characteristics of the 2 groups. All analyses were performed with IBM SPSS software, version 20 (IBM Software Group, Chicago, IL).

Ethical Considerations

All institutes participating in the JAM Trial received the approval of the committee of bioethics at each center. The JAM Trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, ID: C000000166, 2005), which was approved by the International Committee of Medical Journal Editors.

Results

Randomization, Treatment, and Follow-Up

Figure 1 demonstrates the flow diagram of the JAM Trial. During the period of January 2001 to June 2008, 213 patients were assessed for eligibility. After 133 patients were excluded for the reasons listed in Figure 1, 80 patients were enrolled in the JAM Trial and randomized: 42 to the surgical group and 38 to the nonsurgical group. Table 3 summarizes the baseline characteristics of the patients.

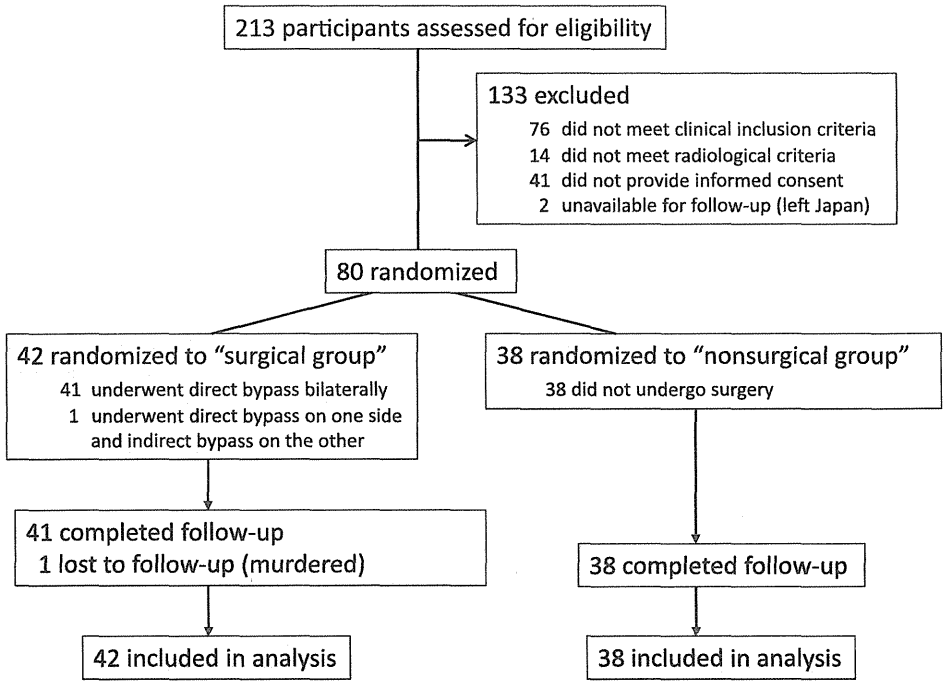

Figure 1. Flow diagram of the Japan Adult Moyamoya (JAM) Trial.

Table 3. Baseline Characteristics of Patients

	Surgical Group (n=42)	Nonsurgical Group (n=38)	*P* Value
Mean age±SD, y	42.5±11.3	41.4±12.2	0.34
Female ratio	66.7%	73.7%	0.49
Hypertension (%)	7 (16.7)	9 (23.7)	0.43
Diabetes mellitus (%)	1 (2.4)	2 (5.3)	0.46
Hyperlipidemia (%)	2 (4.8)	2 (5.3)	0.65
Valvular heart disease (%)	0 (0.0)	0 (0.0)	
Atrial fibrillation (%)	0 (0.0)	0 (0.0)	
Moyamoya disease in relatives (%)	6 (14.3)	1 (2.6)	0.07
History of hemorrhagic stroke (%)	4 (9.5)	4 (10.5)	0.59
History of ischemic events (%)	12 (28.6)	10 (26.3)	0.82
Hemorrhagic types			
Intraparenchymal (ICH)	14	8	0.22
Extraparenchymal extension			
ICH+IVH	26	29	
SAH only	2	1	
Site of hemorrhage			
Anterior (type A)*	24	21	0.87
Posterior (type B)†	18	17	

ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.

*Hemorrhage attributed to rupture of the anterior collateral vessels (eg, caudate nucleus or putamen).

†Hemorrhage attributed to rupture of the posterior collateral vessels (eg, thalamus or trigone of the lateral ventricle).

In the surgical group, all patients but 1 underwent bilateral direct anastomotic bypass. One patient received direct bypass on one side and indirect bypass on the other side because no cortical artery feasible for direct anastomosis could be identified in the operative field. In the nonsurgical group, all patients were treated conservatively with no protocol violation. All patients but 1 were observed until the occurrence of adverse events compatible with end points or until 5 years had elapsed after enrollment. The murder of 1 patient in the surgical group at the point of 1.95 years after enrollment ended that patient's follow-up. The event-free period of this case was included in the statistical analysis. However, this event was dealt with as a dropout and not as an end point because it had no relation to the patient's medical issues. The mean follow-up period was 4.32 years (4.46 years in the surgical group and 4.17 in the nonsurgical group).

Study Outcomes

The last patient completed the 5-year follow-up in June 2013. Table 4 shows the outcomes of the patients. The primary end point was observed in 6 (14.3%) in the surgical group and 13 (34.2%) in the nonsurgical group. In the surgical group, 5 patients experienced rebleeding attacks and 1 patient had a completed ischemic stroke during the follow-up period. In the nonsurgical group, 12 patients experienced rebleeding attacks and 1 patient had crescendo TIAs requiring emergent bypass surgery as determined by the attendant neurologist. Accordingly, the secondary end point was observed in 5 (11.9%) in the surgical group and 12 (31.6%) in the nonsurgical group. Cox regression analysis revealed that the hazard ratios of the surgical group compared with the nonsurgical group were 0.391 (95% confidence interval, 0.148–1.029) as to the primary end point and 0.355 (95% confidence interval, 0.125–1.009) as to the secondary end point. Figure 2 shows the Kaplan–Meier cumulative curves for the analysis of the primary and secondary end points. The log-rank test revealed that the surgical group was at significantly lower risk than the nonsurgical group for both the primary end point (3.2%/y versus 8.2%/y; P=0.048) and the secondary end point (2.7%/y versus 7.6%/y; P=0.042).

Perioperative Complications

Among the 84 surgical procedures for the 42 patients in the surgical group, perioperative complications were observed in 8 cases (9.5%). Symptoms of local hyperperfusion around the anastomotic sites were the most frequent (3 cases). Other perioperative events consisted of TIA, seizure, local vasogenic edema, scalp bedsore, and tear of a subcutaneous drainage tube. Seven of the 8 events were clinically transient, and no sequelae remained. One patient with local hyperperfusion syndrome showed a deterioration in modified Rankin disability scale score. This event, however, was not severe enough to fulfill the criteria of the end point.

Discussion

It is known that about one half of the adult patients with moyamoya disease have intracranial hemorrhage, whereas most pediatric cases present with cerebral ischemia.[1–3] Typically, the hemorrhage involves the thalamus and basal ganglia with

Table 4. Details of Outcomes and Cox Regression Analysis

	Surgical Group (n=42)		Nonsurgical Group (n=38)			
	n	Rate, %	n	Rate, %	Hazard Ratio (95% CI)	*P* Value
Primary end point	6	14.3	13	34.2	0.391 (0.148–1.029)	0.057
Recurrent bleeding	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052
Completed stroke	1	2.4	0	0.0	...	...
Crescendo TIA (bypass required)	0	0.0	1	2.6	...	...
Secondary end point (recurrent bleeding or related death/severe disability)	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052

CI indicates confidence interval; and TIA transient ischemic attack.

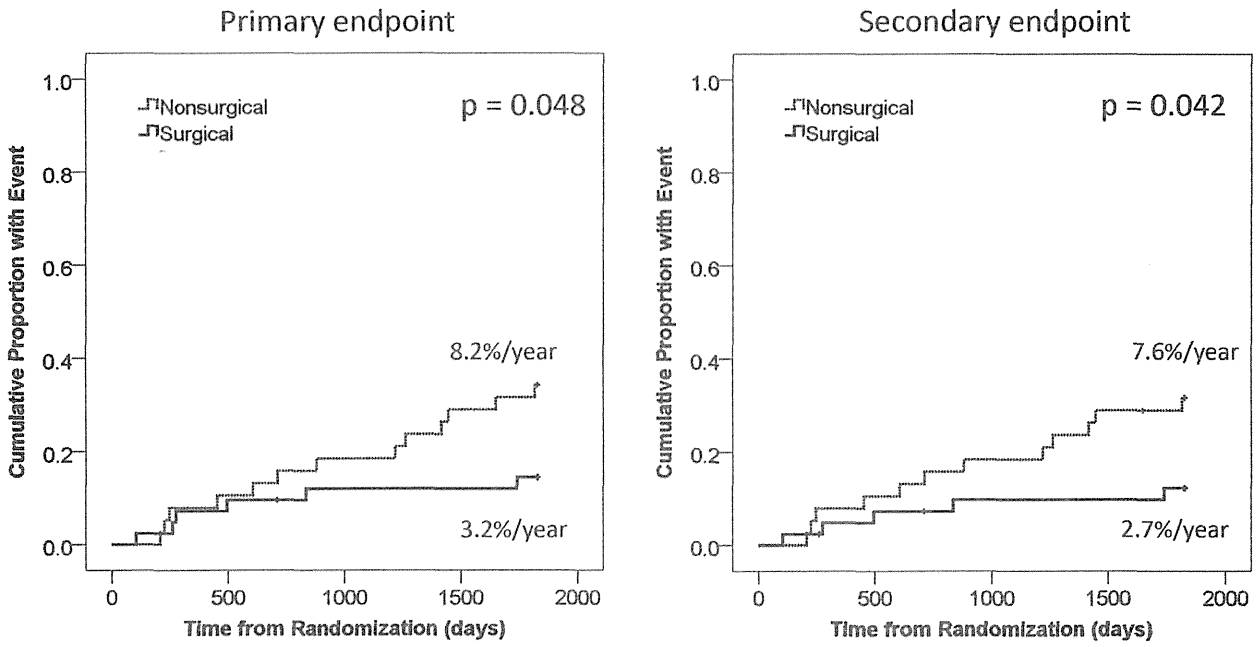

Figure 2. Kaplan–Meier cumulative curves for end points.

frequent perforation to the ventricles. It is speculated that long-term hemodynamic overstress can induce pathological change in the dilated collateral vessels such as lenticulostriate arteries, choroidal arteries, and other basal moyamoya vessels, which leads to the bleeding.[1,2] The rupture of microaneurysms formed in the collateral vessels has also been recognized.[7] Such bleeding attacks, which are potentially fatal, seriously affect the patient's prognosis.[8]

The natural history of hemorrhagic moyamoya disease is extremely poor because of the high rate of recurrent bleeding attacks. Kobayashi et al[9] reported that 33.3% of the patients who were conservatively treated had rebleeding attacks during the follow-up period of mean 6.7 years and estimated the annual rebleeding rate to be 7.09%/y. Because the majority of the patients were in their 30s to 50s at the onset of hemorrhage,[3,10] this annual rate indicates that, over a long period, rebleeding attacks seriously threaten their lives. No therapeutic method for preventing rebleeding attacks, however, has been established. No evidence exists that treatment of hypertension reduces the rebleeding rate. Even the relationship between hypertension and intracranial hemorrhage in moyamoya disease has not been proven.

At present, the only promising strategy is extracranial–intracranial bypass. In ischemic moyamoya disease, angiography often demonstrates that moyamoya vessels can diminish after bypass surgery.[4] It is likely that the dominant bypass flow reduces the burden on moyamoya vessels to maintain the cerebral blood flow, which results in relief of hemodynamic stress. Microaneurysms in collateral vessels that disappear after surgery have also been reported.[11,12] Consequently, a hypothesis has emerged that bypass surgery can also reduce the long-term hemodynamic stress in hemorrhagic moyamoya disease and prevent rebleeding attacks. In fact, some authors have reported the effectiveness of bypass for hemorrhagic moyamoya disease. Kawaguchi et al[13] revealed that superficial temporal artery–middle cerebral artery bypass reduced the rate of hemorrhagic and ischemic stroke. Karasawa et al[14] reported that patients who had undergone bypass surgery experienced rebleeding attacks less frequently than those treated conservatively. Several authors, on the contrary, failed to reveal the effectiveness of bypass.[8,15] A multicenter retrospective questionnaire study conducted by Fujii et al[15] revealed that rebleeding attacks were less frequent in patients who had undergone bypass surgery than in the nonsurgical cases, but the difference was not statistically significant. All previous reports, however, were retrospective studies that potentially contain various biases. Consequently, the effectiveness of bypass surgery on hemorrhagic moyamoya disease has remained unclear.

The JAM Trial, which is the first prospective, randomized, controlled trial focused on moyamoya disease, has demonstrated how bypass surgery affects patients' prognosis and the rebleeding rate in hemorrhagic moyamoya disease. Kaplan–Meier survival analysis revealed that direct bypass surgery significantly decreased the rate of both all adverse events (primary end point) and rebleeding attacks (secondary end point) during the following 5 years. These results strongly suggest that the newly established bypass flow can influence the hemodynamic state of the collateral vessels and lessen their overstress. This study required direct anastomotic bypass because indirect bypass alone can fail to establish sufficient extracranial–intracranial collateral flow in adult patients.[3,4] To ensure the quality of the trial, every institute was requested to report all patients who were assessed for eligibility but were not enrolled in the study, and bypass surgery for these cases was prohibited. In addition, no protocol violation was observed regarding the enrolled patients.

Care must be taken when interpreting the results of the JAM Trial. First, the result was statistically marginal. Kaplan–Meier survival analysis revealed the significant benefits of bypass surgery, but the *P* values of the primary and secondary

end points were 0.048 and 0.042, respectively, which are close to 0.05. In the Cox regression analysis, the upper limit of the 95% confidence interval of the hazard ratio was 1.029 for the primary end point and 1.009 for the secondary end point, both of which slightly exceed 1.0. Therefore, the authors cannot declare with assurance that bypass surgery is absolutely superior to conservative therapy. This difference can be attributed to the small sample size. As mentioned earlier, the optimal sample size initially calculated was larger. Hemorrhagic moyamoya disease, however, is not common, and recruitment of patients with good modified Rankin disability scale scores was far more difficult than expected. Considering that an excessively long registration period would degrade the quality of this trial, the number of the cases was reduced.

Second, some limitations apply to the JAM Trial regarding generalization. All institutes participating in the trial had sufficient experience with direct bypass surgery for moyamoya disease, and only registered surgeons were allowed to operate on patients. Consequently, the rate of perioperative complications, including transient events, turned out to be 9.5%, and permanent severe disability was not observed. The authors think that ensuring the quality of surgeons is indispensable to this kind of randomized trial involving surgery. As for interpretation of the results, however, it should be emphasized that the results do not necessarily apply to all neurosurgical institutes.

Third, and perhaps most important, the JAM Trial has only revealed the effect of bypass surgery within 5 years and does not suggest an improved prognosis for the surgical group thereafter. It is well known that recurrent bleeding can take place >10 years after the initial attack.[9] Therefore, patients enrolled in the JAM Trial should be observed for longer periods in the future. The JAM Trial Executive and Steering Committee has already decided to continue with patient follow-up and report the 10-year results. Subanalyses regarding the site of initial and recurrent hemorrhage, hemodynamic impairment evaluated by single-photon emission computed tomography, and angiographic reduction of moyamoya vessels after bypass surgery should also be performed, and the results should be reported.

Conclusions

Although statistically marginal, the JAM Trial revealed that direct bypass surgery for adult patients with hemorrhagic moyamoya disease reduces the rebleeding rate and improves a patient's prognosis during the 5 years after enrollment. To determine the long-term benefits of surgery, further follow-up is required.

Appendix: Study Organization

The Research Committee on Moyamoya Disease of the Japanese Ministry of Health, Labour and Welfare

Principal Investigator and Chair

1999 to 2005: Takashi Yoshimoto, MD, PhD
2005 to 2013: Nobuo Hashimoto, MD, PhDJAM Trial Group

Central Office and Data Management Center

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Statistical Center

Department of Public Health, Tohoku University Graduate School of Medicine, Sendai, Japan: Ichiro Tsuji, MD, PhD; and Yasutake Tomata PhD.

Randomization and Quality Control Center

Department of General Internal Medicine, St. Luke's International Hospital, Tokyo, Japan: Tsuguya Fukui, MD, PhD.

Executive and Steering Committee

Takashi Yoshimoto, MD, PhD (principal investigator); Susumu Miyamoto, MD, PhD (project director; neurosurgery); Yasushi Okada, MD, PhD (co-project director; neurology), Tsuguya Fukui, MD, PhD; Ichiro Tsuji, MD, PhD; Yasuo Fukuuchi, MD, PhD; Takashi Ohmoto, MD, PhD; Yasuo Kuwabara, MD, PhD; Jyoji Nakagawara, MD; and Izumi Nagata MD, PhD.

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Disclosures

None.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Intracranial Hemorrhage During Dabigatran Treatment

– Case Series of Eight Patients –

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Background: The incidence of intracranial bleeding during dabigatran treatment is lower than that during warfarin treatment. The characteristics of intracranial hemorrhage during dabigatran therapy, however, remain unclear.

Methods and Results: The clinical data and treatment summaries of 9 intracranial bleeds that developed during dabigatran treatment in 8 patients with non-valvular atrial fibrillation were retrospectively reviewed. Five patients had small–moderate subdural hematomas, 2 had intracerebral hemorrhage and 1 had traumatic subarachnoid and parenchymal hemorrhage associated with cerebral contusion. Activated partial thromboplastin time upon admission ranged from 31.6 to 72.4 s. After admission, systolic blood pressure in the 2 patients with intracerebral hemorrhage was maintained below 140 mmHg, and the subdural hematomas in 4 patients were surgically treated. None of the hematomas became enlarged and outcome was good in most cases.

Conclusions: Hematomas that arise due to acute intracranial bleeding during dabigatran treatment seem to remain small to moderate, hard to expand, and manageable. (*Circ J* 2014; **78:** 1335–1341)

Key Words: Blood pressure; Dabigatran; Intracranial hemorrhage; Novel oral anticoagulant

The RELY phase III trial of dabigatran found a significantly lower incidence of intracranial bleeding in patients treated with dabigatran (150 and 110 mg b.i.d.) than with warfarin.[1] The incidence of intracranial bleeding during dabigatran treatment is lower not only in patients younger, but also in those older than 75 years of age.[2,3] Patients treated with warfarin sometimes develop intracranial hemorrhage and the outcome of such patients is poor due to the development of large hematomas and their subsequent expansion.[4,5] The characteristics of intracranial hemorrhage during dabigatran therapy, however, remain unclear. Therefore, we analyzed data from 9 intracranial hemorrhages that developed in 8 patients treated with dabigatran.

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Methods

We retrospectively investigated the clinical data and treatment summaries of 9 intracranial bleeds that developed in 8 patients during treatment with dabigatran for prevention of stroke associated with non-valvular atrial fibrillation (NVAF) between March 2011 and February 2013 at 5 hospitals. We investigated data including age, gender, period from onset of symptoms to arrival at consulting hospital, dose of dabigatran, period after dabigatran started, activated partial thromboplastin time (APTT) on admission,[6] treatment with prothrombin com-

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Table. Case Series

Case No.	1	2	3	4	5
Age (years)	79	87	80	86	74
Gender	M	F	F	M	M
Time from onset to first CT	Asymptomatic	1 month	19 days	On the day of symptom	4 days
Type of intracranial bleeding	CSDH	CSDH	CSDH	CSDH	CSDH
Recent head injury	No	Yes	Yes	Yes	Yes
Dose of dabigatran	110 b.i.d.	110 b.i.d.	110 b.i.d.	110 b.i.d.	110 b.i.d.
Period since dabigatran commenced	1 month	6 months	3 months	1 month	8 days
APTT					
(s) at admission	31.6	47.2	46.9	37.5	38.2
Prothrombin complex concentrate	No	No	1,500 IU	No	No
Size of hematoma	Small, 9 mm thick	Medium, 15 mm thick	Medium, 14 mm thick	Medium Left, 8 mm thick; right, 11 mm thick	Medium 19 mm thick
Expansion of hematoma	No	No	No	No	No
Surgical treatment	None	Burr-hole evacuation	Burr-hole evacuation	Bilateral burr-hole evacuation	Burr-hole evacuation
mRS before and after	0, 0 after 7 days	0, 0 after 3 months	0, 0 after 2 weeks	0, 0 after 21 days	0, 0 after 28 days
Hypertension history	Yes	No	No	Yes	No
Anti-hypertensive medicine	Yes	No	No	Yes	No
BP at admission	100/75	120/60	156/89	123/69	130/79
BP before admission	126/70	104/60	112/81	129/72	124/82
BP control after admission	Yes	No	No	Yes	No
Diabetes mellitus	No	No	No	No	No
Creatin clearance (ml/min)	72.9	46	32	43	53
Renal dysfunction, creatinin >2.26 mg/dl	No	No	No	No	No
Liver disease	No	No	No	Yes	No
Stroke history	No	Yes	No	No	No
Prior major bleeding or predisposing to bleeding	No	No	No	No	No
Elderly ≥65 years old	Yes	Yes	Yes	Yes	Yes
Antiplatelet	No	No	No	No	No
NSAIDS	No	No	No	No	No
Alcohol	No	No	No	No	No
Smoking	No	No	unknown	Ex smoker	No

(Table continued the next page.)

plex concentrate, head computed tomography (CT) findings, hematoma size, hematoma expansion, surgical treatment, blood pressure control, diabetes mellitus, smoking habit and modified Rankin Scale (mRS) score before onset and at discharge. We also studied data regarding hypertension, renal dysfunction, liver disease, past history of stroke, major bleeding history, predisposition to bleeding, concomitant therapy such as antiplatelet and non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol (consuming ≥8 alcoholic drinks per week) according to HAS-BLED score criteria for evaluating risk of major bleeding.[7] Chronic subdural hematoma (CSDH) was defined as follows: thickness <10 mm, small; 10–19 mm, medium; and >20 mm, large. We defined other intracranial hematomas according to diameters <15, 15–29 and >30 mm as small, medium and large, respectively.

Case Reports

Case 1 A 79-year-old man with NVAF treated with dabigatran (110 mg b.i.d.) underwent brain magnetic resonance imaging (MRI) to evaluate an unruptured intracranial aneurysm at the left anterior communicating artery. The size and shape of the aneurysm had remained constant and the patient had an asymptomatic 9-mm thick CSDH at the left frontal area (Table). Three days later, APTT was 31.4 s and follow-up brain CT indicated no change in the size of the hematoma. Dabigatran was switched to warfarin and the hematoma disappeared after 3 months without any symptoms.

Case 2 Brain CT confirmed CSDH at the left frontal and temporal areas of an 87-year-old woman with atrial fibrillation treated with dabigatran (110 mg b.i.d.) who presented with headache and gait disturbance (Figure 1; Table). The physician in charge continued the dabigatran to avoid brain infarction, but the symptoms did not improve over the next 6 days

Case No.	6	7	8
Age (years)	87	92	82
Gender	F	F	M
Time from onset to first CT	1 h	1 h	1 h and 20 min	5 h and 30 min
Type of intracranial bleeding	Traumatic subarachnoid hemorrhage	Hemorrhage in the contusion lesion	Thalamic hemorrhage	Putaminal hemorrhage
Recent head injury	Yes	Yes	No	No
Dose of dabigatran	110 b.i.d.	110 b.i.d.	110 b.i.d.	110 b.i.d.
Period since dabigatran commenced	10 months	–	9 months	3 months
APTT (s) at admission	45.8	–	44.7	72.4
Prothrombin complex concentrate	No	No	500 IU	No
Size of hematoma	Small, diameter <15 mm	Medium, diameter <30 mm	Medium, 5 ml, diameter <30 mm	Small, 1 ml, diameter <15 mm
Expansion of hematoma	No	No	No	No
Surgical treatment	None	None	None	None
mRS before and after	0, 0 after 14 days	0, 2 after 14 days	3, 4 after 1 month	0, 1 after 8 days
Hypertension history	No	–	Yes	Yes
Anti-hypertensive medicine	No	–	Yes	Yes
BP at admission	149/84	–	164/85	154/90
BP before admission	128/61	–	NA	140/86
BP control after admission	No	–	Yes <140 mmHg	Yes <140 mmHg
Diabetes mellitus	No	–	No	No
Creatin clearance (ml/min)	35	–	38	55
Renal dysfunction, creatinin >2.26 mg/dl	No	–	No	No
Liver disease	No	–	No	No
Stroke history	Yes	–	Yes	No
Prior major bleeding or predisposing to bleeding	No	–	No	No
Elderly ≥65 years old	Yes	–	Yes	Yes
Antiplatelet	No	–	No	Yes, aspirin
NSAIDS	No	–	No	No
Alcohol	No	–	No	No
Smoking	No	–	No	Ex smoker

Alcohol usage history, ≥8 drinks/week; CSDH, chronic subdural hematoma (thickness: <10 mm, small; 10–19 mm, medium; ≥20 mm, large); hypertension history, uncontrolled, systolic blood pressure >160 mmHg; liver disease, cirrhosis, bilirubin >2× normal, AST/ALT/ALP >3× normal; other intracranial hematoma: diameter <15 mm, small; 15–29 mm, medium; ≥30 mm, large; renal dysfunction, creatinin >2.26 mg/dl. ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; mRS, modified Rankin Scale; NSAID, non-steroidal anti-inflammatory drug.

and the patient was referred to National Hospital Organization Kyushu Medical Center. Upon admission, APTT was 47.2 s and CT confirmed that the hematoma had not expanded. Dabigatran was stopped for 24 h, the hematoma was evacuated through a burr-hole and then dabigatran was started again 48 h later. The patient fully recovered.

Case 3 A head contusion was followed by a gait disturbance 1 month later in an 80-year-old woman on dabigatran (110 mg b.i.d.) with NVAF. Head CT 19 days after symptom onset showed a 14-mm-thick CSDH on the left side (Table). APTT on admission was 46.3 s. Dabigatran was stopped and prothrombin complex concentrate 1,500 IU was given. APTT was 47.7 s at 10 min later and 41.6 s on the following day. The size of the hematoma remained constant. The hematoma was treated by burr-hole evacuation, from which she fully recovered. Dabigatran 110 mg b.i.d. was restarted 2 days after the surgery and rebleeding did not occur.

Case 4 An 86-year-old man given dabigatran (110 mg b.i.d.) for prevention of stroke associated with paroxysmal atrial fibrillation developed walking difficulties and started to fall easily (Table). Head CT showed bilateral CSDH, and APTT on admission was 37.5 s. Dabigatran was stopped and the hematoma was treated by burr-hole evacuation from which the patient fully recovered. Anticoagulant therapy was not restarted due to the patient and family's concern about the risk of recurrent hemorrhage.

Case 5 A 74-year-old man treated with dabigatran (110 mg b.i.d.) fell and hit his head after consuming alcohol. He presented at a hospital 6 weeks later with gait disturbance, right hemiparesis and incontinence. Head MRI showed CSDH on the left side (Table), and APTT was 38.2 s. Burr-hole evacuation was done and he recovered uneventfully. Anticoagulation with dabigatran 110 mg b.i.d. was resumed.

Case 6 An 87-year-old woman on dabigatran (110 mg

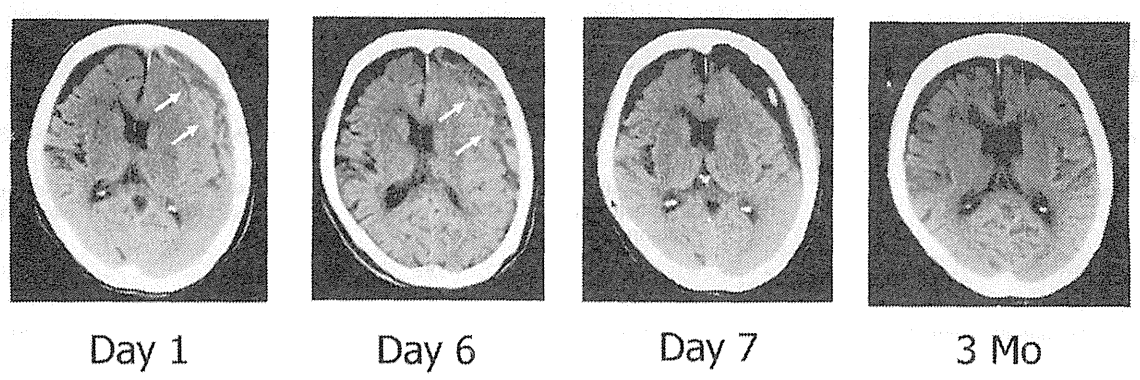

Figure 1. Head computed tomography of an 87-year-old woman (case 2) on days 1, 6, 7 and 3 months thereafter. The arrows show that subdural hematoma on day 1 has not expanded by day 6. The patient fully recovered at 3 months after burr-hole evacuation on day 7.

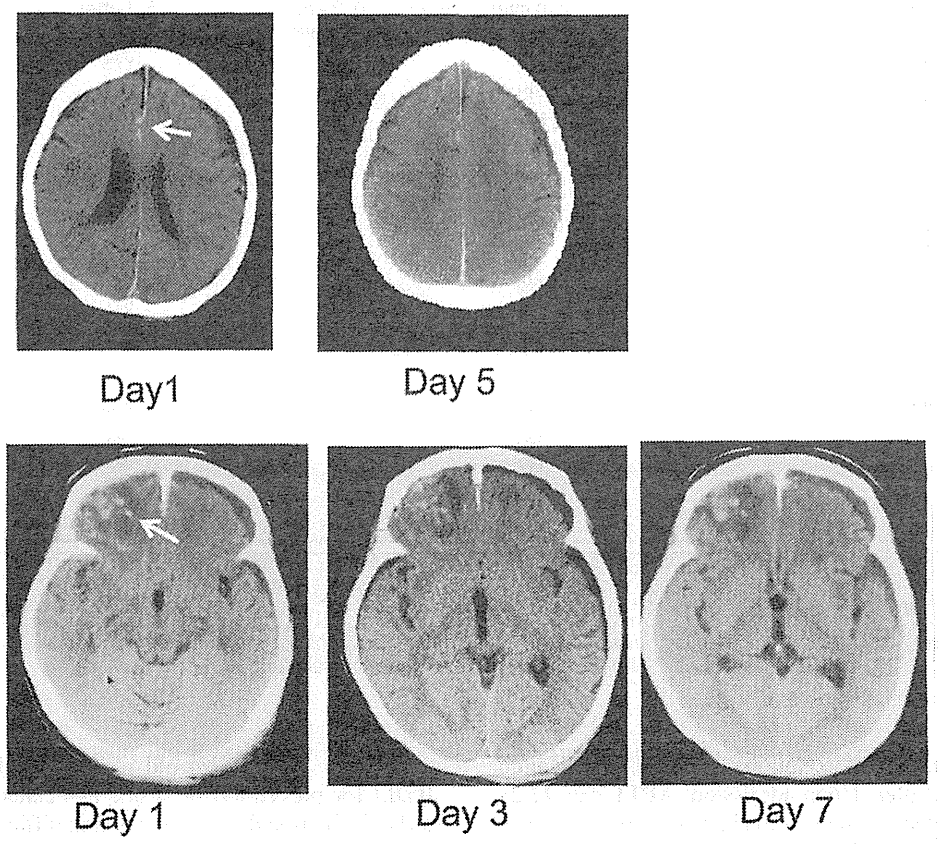

Figure 2. Head computed tomography of an 87-year-old woman (case 6): (**Upper**) traumatic subarachnoid hemorrhage on days 1 (arrow) and 5; (**Lower**) head contusion on days 1 (arrow), 3 and 7.

b.i.d.) to prevent recurrent cardioembolic stroke associated with NVAF fell and hit her head. She developed headache and presented at hospital, where head CT confirmed traumatic subarachnoid hemorrhage (**Figure 2**; **Table**). APTT was 45.8 s. Dabigatran was stopped for 4 days and resumed. One week later, she fell and hit her head again. Head CT showed a contusion on the right frontal lobe. Dabigatran was stopped for 7 days and the hematoma in the area of contusion was monitored. The hematoma did not expand and she recovered. Dabigatran (110 mg b.i.d.) was started once again.

Case 7 A 92-year woman given dabigatran 110 mg b.i.d. with mRS 4 due to a previous stroke suddenly became unconscious and developed right hemiparesis. She was transferred to hospital 1 h 20 min later. Head CT showed a left thalamic

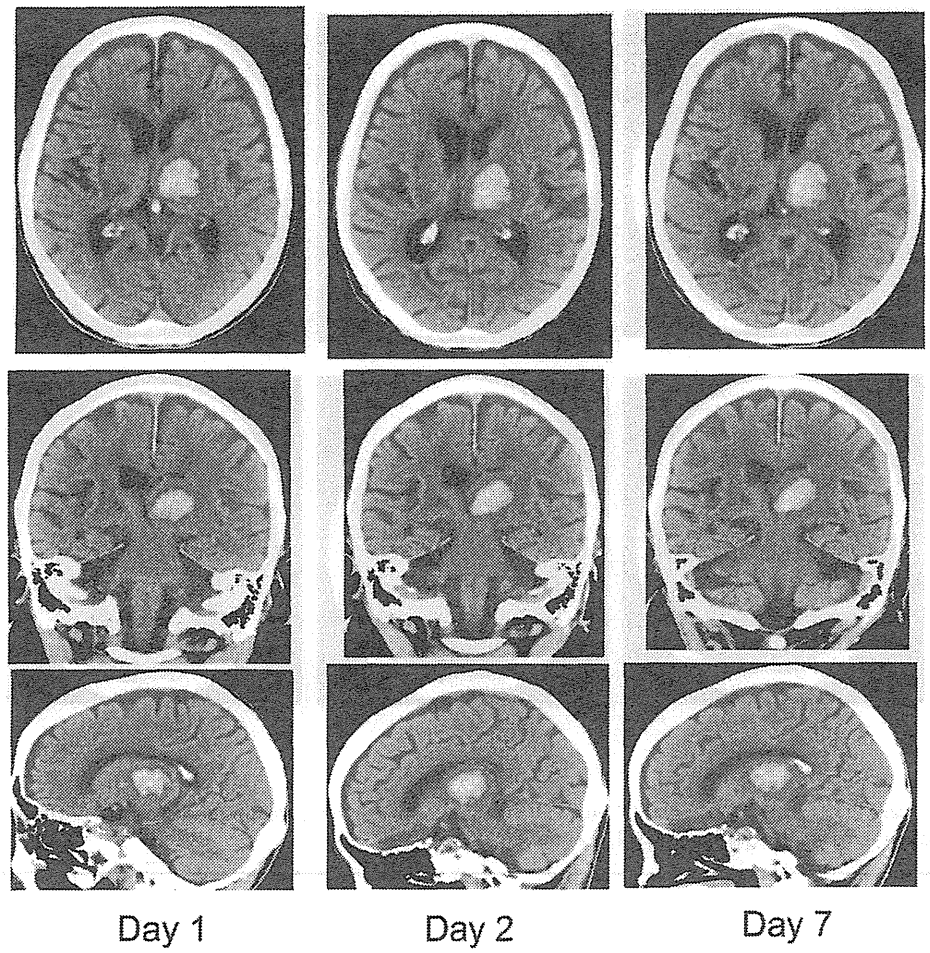

Figure 3. Head computed tomography of a 97-year-old woman with left thalamic hemorrhage (case 7): (Upper) axial, (Middle) coronal and (Lower) sagittal imaging on days 1, 2, and 7.

hemorrhage of approximately 5 ml (Figure 3; Table). Blood pressure was 164/85 mmHg and thus the systolic pressure was lowered and maintained below 140 mmHg thereafter. APTT on admission was 44.7 s and prothrombin complex concentrate (500 IU) was given. Two hours later, APTT was 50.1 s. The hematoma remained unchanged on days 2 and 7. Warfarin therapy was started and she was discharged with mRS 4.

Case 8 An 82-year-old man with atrial fibrillation treated with dabigatran (110 mg b.i.d.) who developed a right putaminal hemorrhage with headache and left hemiparesis was admitted to hospital (Figure 4; Table). APTT was 72.4 s; blood pressure, 154/90 mmHg and NIH stroke scale, 4. Head CT indicated a small right putaminal hemorrhage. Dabigatran was stopped and systolic blood pressure was controlled at <140 mmHg. The symptoms improved and mRS was 1 when he was discharged 8 days later. Anticoagulation was restarted on day 3 with rivaroxaban (10 mg q.d.). Brain CT on days 2 and 5 showed that the hematoma had not expanded.

Discussion

That all 9 of the hematomas associated with CSDH as well as traumatic subarachnoid and intracerebral hemorrhages were small to moderate, remained unchanged during the observation period and resulted in good outcome, is remarkable. Seven of the 9 episodes resulted in mRS scores of 0 or 1. The acute hematoma at the putamen was particularly small and did not expand, with good outcome of mRS 1 at discharge irrespective of advanced APTT of 72.4 s on admission. This phenomenon might have been due to not only strict blood pressure control in the 2 patients with intracerebral hemorrhage but also the characteristics of novel oral anticoagulants including dabigatran, which do not affect plasma concentration of factor VII or of complexes of tissue factor and factor VIIa that are essential for the first reaction in the coagulation cascade. Warfarin suppresses factor VII production even within the therapeutic range of prothrombin time, which is a reason why the incidence of intracranial hemorrhage and major bleeding are higher on warfarin than novel oral anticoagulants including dabigatran, and why acute intracranial hematoma developing during warfarin therapy easily expands.[1,4,5,8–13]

Another explanation might be that dabigatran interacts selectively and reversibly with the active site of the thrombin molecule but does not inhibit thrombin activatable fibrinolysis inhibitor generation, leading to downregulation of fibrinolysis and has a short half-life of 12–17 h, leading to early excretion from the body.[1,14,15] It seems that recent findings of experimental studies are consistent with the present case series analy-

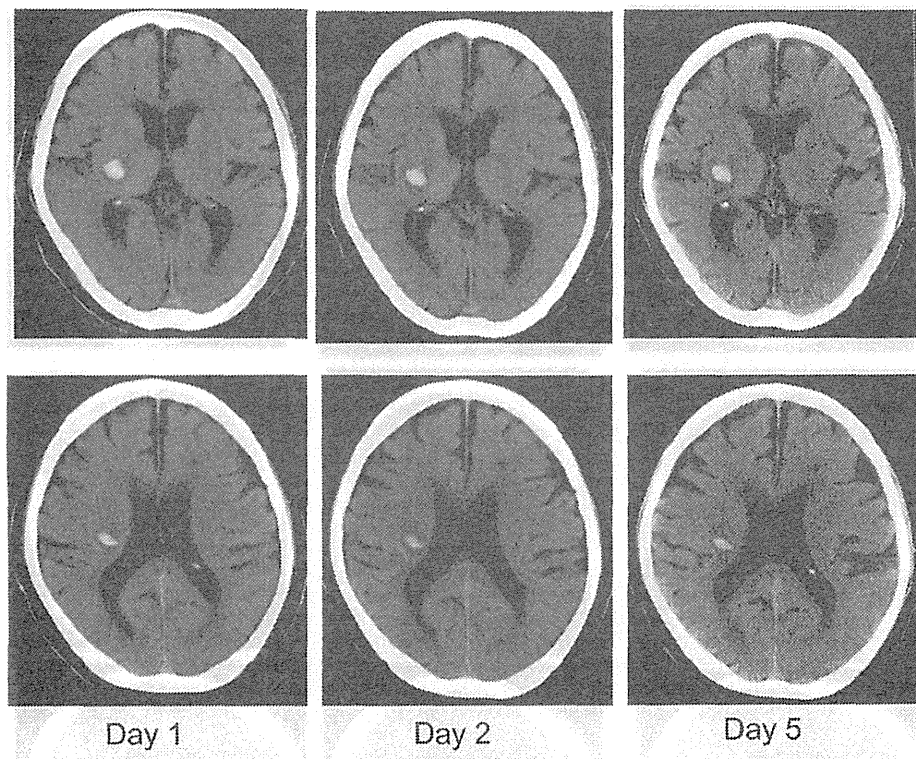

Figure 4. Head computed tomography of an 82-year-old man with right putaminal hemorrhage (case 7): (**Upper**) axial, (**Middle**) coronal, and (**Lower**) sagittal imaging on days 1, 2 and 7.

sis.[14,15] Won et al measured contrast medium extravasation using dual-energy CT in experimental intracerebral hemorrhage mice models treated with dabigatran or warfarin and found that dabigatran induced less contrast medium extravasation, a marker of ongoing bleeding, than warfarin.[14] Lauer et al found that, in contrast with warfarin, pretreatment with dabigatran did not increase hematoma volume in experimental mice models of intracerebral hemorrhage.[15]

The reported incidence of intracranial hemorrhage is higher among Asian than non-Asian individuals.[16,17] Therefore, the present findings and those of reports describing the value of dabigatran for treating Asian patients[17] indicate that dabigatran is useful for treating Asian patients including Japanese patients.

The HAS-BLED score before onset in the 8 subjects was 1 or 2, and none had a HAS-BLED score ≥3, which may also be related to the small–moderate size of the hematomas and good prognosis.[7]

With regard to HAS-BLED score, "elderly ≥65 years old" was seen in all subjects. Hart et al noted that age was a predisposing factor for intracranial hemorrhage during anticoagulation with dabigatran in the RE-LY trial.[18] Seven of the 9 episodes described herein were CSDH, traumatic subarachnoid hemorrhage and brain contusion related to head injury in the elderly. Thus, such elderly patients treated with dabigatran should be advised to walk carefully to avoid falls.

Prothrombin complex concentrate was given to 2 patients. Rapid reversal of APTT was not evident but none of the present hematomas expanded. These results are consistent with previous findings showing that prothrombin complex concentrate prevents excess hematoma expansion after dabigatran treatment.[19] Because dabigatran treatment does not rule out hematoma expansion,[20] guidelines on how to reverse dabigatran activity in major hemorrhage need to be established. Reviews and experiments suggest that this can be rapidly achieved using 4-factor prothrombin complex concentrate, activated prothrombin complex concentrate and antibodies.[19,21–23]

Hematomas that arise due to acute intracranial bleeding during dabigatran treatment seem to remain small to moderate, are unlikely to expand, and are manageable.

Disclosures

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