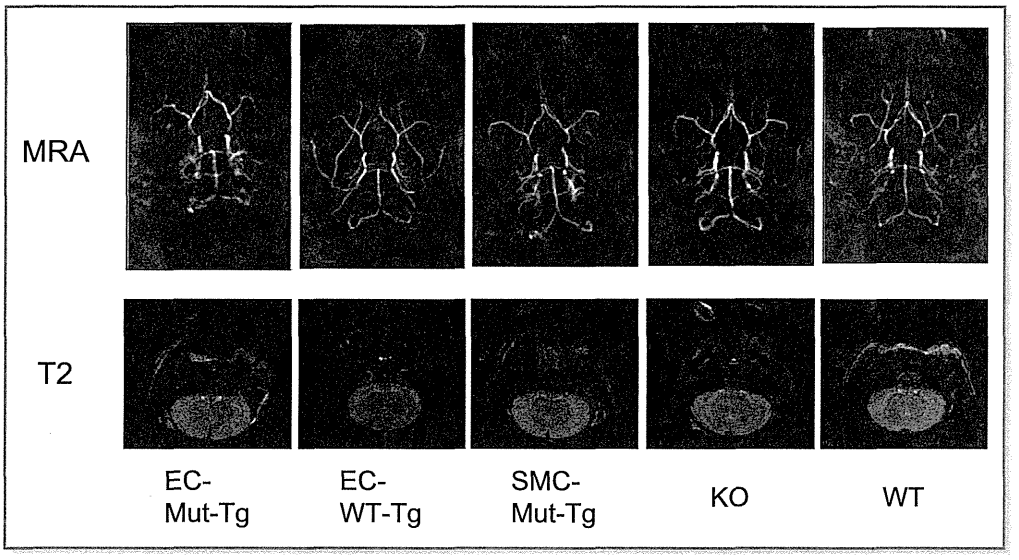

Figure 19. Representative MRI image of brain of EC-Mut Tg, EC-WT Tg, SMC-Mut Tg, KO, and WT mice with hypoxia. MRA (upper panel) represents MRA images. No stenotic lesions and moyamoya vessels were detected in brain. T2 (lower panel) represents T2-weighted images. No infarction was detected in brains. Absence of stenotic lesion, moyamoya vessel, and infarction was also confirmed in other 2 mice in each genotype. EC indicates endothelial cell; KO, knockout; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SMC, smooth muscle cells; Tg, transgenic; WT, wild type.

data provide a premature, but novel, insight into the mechanism of RNF213 R4810K mutation. AAA^+ is a class of proteins, most of which transduce phosphorus covalent bond energy of ATP into mechanical energy through conformational changes. This process is mediated by the chemical reactions of ATP binding and hydrolysis. We consider that R4810K may be trapped in the RNF213 oligomer state, thereby inhibiting conformational changes, similar to RNF213 WEQ. Rigorous 3D structure analysis is required with a focus on conformational interaction between R4810K and AAA modules.

In conclusion, the present data suggest that RNF213 R4810K carriers have lower angiogenic capacities, indicating that these carriers might be more susceptible to insults of cerebral hypoxia. The present study shows that IFNs are environmental factors. Importantly, lower angiogenic activity is causally linked with AAA^+ function of RNF213. Nevertheless, the pathological process bridging lowered angiogenesis and abnormal SMC proliferation (ie, moyamoya vessel formation or stenosis of arteries in the ring of Willis) remains unknown. This issue needs to be addressed in future studies. Studies determining the roles of RNF213 in remodeling and maintenance of the vascular system could provide comprehensive mechanisms of not only MMD, but also stenotic lesions in cerebral arteries.[32] Finally, a specific inhibitor of ATP binding to the Walker A motif in the first AAA^+ is a promising therapeutic candidate. Such a therapeutic tool could improve hypoxic tolerance of the central nervous system in R4810K carriers.

Sources of Funding

This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 25253047 to Prof. Koizumi). This work was partly supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 15K19243), a grant from the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health and Welfare of Japan (No. H26-Nanjito-Ippan-078), and by the Innovative Techno-Hub for Integrated Medical Bio-imaging of the Project for Developing Innovation Systems, from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

Disclosures

None.

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Significance of the Hemorrhagic Site for Recurrent Bleeding
Prespecified Analysis in the Japan Adult Moyamoya Trial

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Background and Purpose—The primary results of the Japan Adult Moyamoya Trial revealed the statistically marginal superiority of bypass surgery over medical treatment alone in preventing rebleeding in moyamoya disease. The purpose of this analysis is to test the prespecified subgroup hypothesis that the natural course and surgical effects vary depending on the hemorrhagic site at onset.

Methods—The hemorrhagic site, classified as either anterior or posterior, was the only stratifying variable for randomization. Statistical analyses were focused on the assessment of effect modification according to the hemorrhagic site and were based on tests of interaction.

Results—Of 42 surgically treated patients, 24 were classified as anterior hemorrhage and 18 as posterior hemorrhage; of 38 medically treated patients, 21 were classified as anterior and 17 as posterior. The hazard ratio of the primary end points (all adverse events) for the surgical group relative to the nonsurgical group was 0.07 (95% confidence interval, 0.01–0.55) for the posterior group, as compared with 1.62 (95% confidence interval, 0.39–6.79) for the anterior group (P=0.013 for interaction). Analysis within the nonsurgical group revealed that the incidence of the primary end point was significantly higher in the posterior group than in the anterior group (17.1% per year versus 3.0% per year; hazard ratio, 5.83; 95% confidence interval, 1.60–21.27).

Conclusions—Careful interpretation of the results suggests that patients with posterior hemorrhage are at higher risk of rebleeding and accrue greater benefit from surgery, subject to verification in further studies.

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

(*Stroke*. 2016;47:37-43. DOI: 10.1161/STROKEAHA.115.010819.)

Key Words: cerebral revascularization ■ confidence intervals ■ incidence ■ intracerebral hemorrhage ■ Japan ■ moyamoya disease

In adult-onset moyamoya disease, intracranial hemorrhage accounts for one half of primary manifestations. The rebleeding rate (bleeding rate after initial bleeding) is ≈7% per year, and the outcome after rebleeding is poor.[1] The Japan Adult Moyamoya (JAM) Trial, a multicenter randomized controlled trial, was conducted to determine whether direct bypass surgery reduces rebleeding in adult-onset hemorrhagic moyamoya disease. The published primary results support this hypothesis.[2]

Hemorrhage can result from the various fragile collaterals specific to moyamoya disease, including tiny collateral vessels that develop from the lenticulostriate arteries and the dilated abnormal branches from the thalamic and choroidal arteries.[3,4] This diversity of vessels contributes to the potential for hemorrhage in several regions: the basal ganglia, thalamus, intra- or periventricular region, and subarachnoid space.[5] If the benefit of bypass surgery in preventing rebleeding is explained as elimination of hemodynamic stress in fragile collaterals,[6,7] the surgical effects will vary with the bleeding site because the surgery targets a specific territory. Rebleeding risk with nonsurgical treatment might also be heterogeneous in the relation to the bleeding site. In light of these hypotheses, randomization in the JAM Trial was stratified according to

Received July 14, 2015; final revision received October 21, 2015; accepted November 3, 2015.

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*A list of all JAM Trial Investigators is given in the Appendix.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.010819/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.115.010819**

bleeding site at onset through classification as either anterior or posterior determined before randomization.

This subgroup analysis is intended to test the above prespecified hypothesis about hemorrhagic moyamoya disease: that the anterior and posterior hemorrhage groups differ in terms of the outcome of nonsurgical treatment and the effect of bypass surgery at preventing rebleeding.

Methods

The design of the JAM Trial has been described elsewhere.[2,8] In brief, participants were recruited from 22 centers specializing in moyamoya disease. Patients with moyamoya disease were eligible if they had suffered intracranial hemorrhage within the 12 months before randomization, were aged 16 to 65 years, were independent in daily life (0–2 for modified Rankin Scale score), had completed acute phase treatment at least 1 month before randomization, and had been free from ischemic/hemorrhagic attack for at least 1 month. Diagnoses of moyamoya disease were made according to the proposed criteria.[9] Participants were randomly allocated to either the surgical or the nonsurgical group. Stratified randomization according to hemorrhagic site was adopted, as described later. Those in the surgical group required direct bypass surgery, including superficial temporal artery–middle cerebral artery anastomosis, within 3 months of randomization in addition to medical treatment, and those in the nonsurgical group underwent medical treatment alone. The primary end points were defined as any of the following events: a rebleeding attack, completed stroke resulting in significant morbidity, significant morbidity or mortality from any medical cause, or requirement for bypass surgery for a nonsurgical patient as determined by a registered neurologist. The secondary end point was defined as a rebleeding attack. Both a neurologist and a neurosurgeon followed each participant in each participating institute for 5 years or until end points were reached. Although antihypertensive medication was administrated to patients with hypertension, the use of anticoagulants or antiplatelet drugs was prohibited. The patients' medical, neurological, radiological, and functional conditions were closely monitored and reported annually. The study was approved by the ethical committees of all participating centers and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, ID: C000000166, 2005).

Subgroup of Interest

Hemorrhagic site was the only stratifying variable for randomization. The study protocol allowed for analyses of the subgroup in advance. Before randomization, the study office classified the hemorrhage at onset in each participant as either anterior or posterior according to the center location of the intracerebral hemorrhage as observed in computed tomographic images (Figure 1; Figures I–IV in the online-only Data Supplement). An anterior hemorrhage was defined as one attributable to perforating arteries from the anterior or middle cerebral artery, including those located in the putamen, caudate head, frontal lobe, anterior half of the temporal lobe, subependymal area of the anterior part of the lateral ventricle, or anterior half of the corpus callosum. A posterior hemorrhage was defined as one attributable to perforating arteries from the posterior cerebral artery or choroidal arteries, including those located in the thalamus, posterior half of the temporal lobe, parietal lobe, occipital lobe, subependymal area of the posterior part of the lateral ventricle including the trigon, or posterior half of the corpus callosum. Primary intraventricular hemorrhage, defined as intraventricular hemorrhage without intraparenchymal hemorrhage, was classified as either anterior or posterior according to the distribution of hematoma (Figure 1A). Any diffusely distributed primary intraventricular hemorrhage whose origin was difficult to determine was classified as anterior. Subarachnoid hemorrhage without intracerebral hemorrhage was classified in a similar fashion (Figure 1A).

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. Kaplan–Meier survival analysis and Cox proportional hazard model were used to compare the incidence of the end points in each subgroup. The assessment of effect modification (heterogeneity of

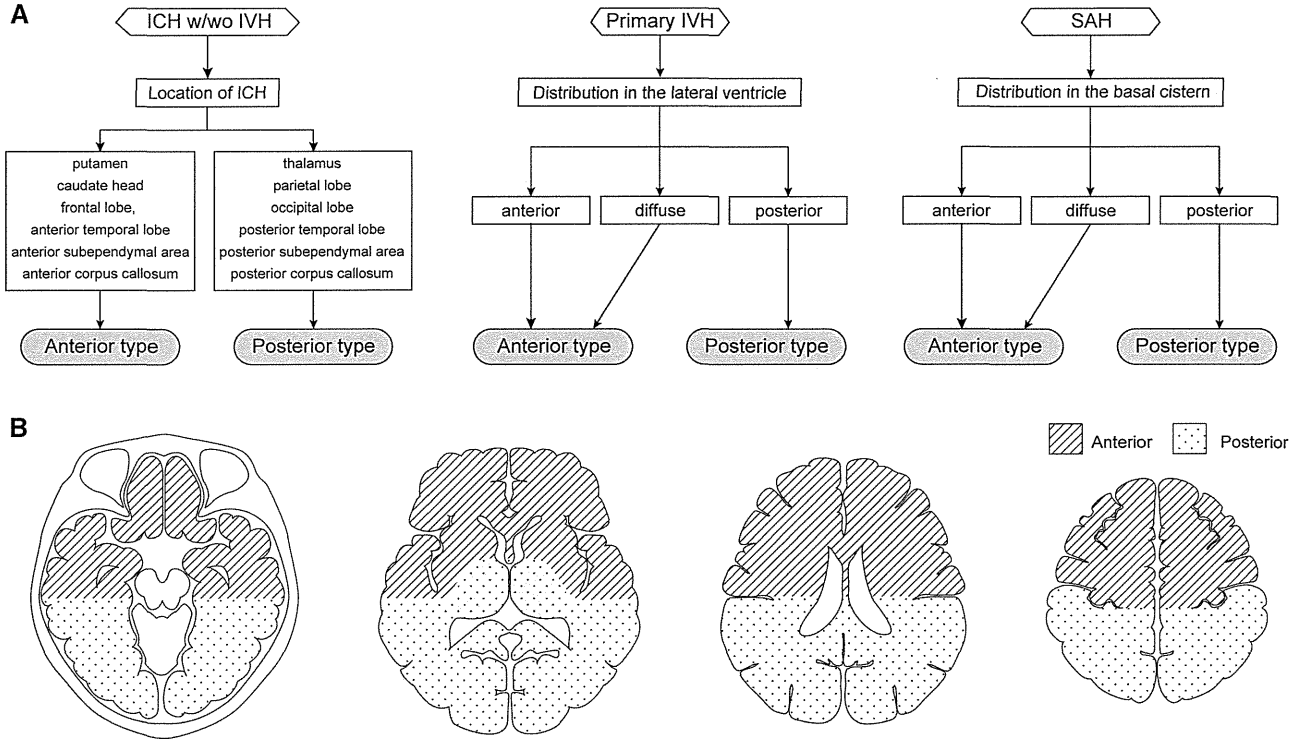

Figure 1. A, Flow diagram showing the algorithm for classifying hemorrhagic sites. **B**, Schematic illustrations showing topographical definitions of hemorrhagic sites. ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.

Table 1. Primary End Point in Subgroups

Stratification Variable	Allocation		*P* Interaction
	Nonsurgical (n=38)	Surgical (n=42)	
Hemorrhagic site			0.013
Anterior			
No. of participants	21	24	
Primary end point (no. [%])	3 (14.3)	5 (20.8)	
HR (95% CI)	1.00 (reference)	1.62 (0.39–6.79)	
Posterior			
No. of participants	17	18	
Primary end point (no. [%])	10 (58.8)	1 (5.6)	
HR (95% CI)	1.00 (reference)	0.07 (0.01–0.55)	
Age			0.705
≥42 y			
No. of participants	17	22	
Primary end point (no. [%])	6 (35.3)	4 (18.2)	
HR (95% CI)	1.00 (reference)	0.46 (0.13–1.64)	
<42 y			
No. of participants	21	20	
Primary end point (no. [%])	7 (33.3)	2 (10.0)	
HR (95% CI)	1.00 (reference)	0.30 (0.06–1.44)	
Sex			0.729
Female			
No. of participants	27	28	
Primary end point (no. [%])	10 (37.0)	4 (14.3)	
HR (95% CI)	1.00 (reference)	0.35 (0.11–1.13)	
Male			
No. of participants	11	14	
Primary end point (no. [%])	3 (27.3)	2 (14.3)	
HR (95% CI)	1.00 (reference)	0.51 (0.09–3.07)	
Hypertension			0.377
Yes			
No. of participants	8	8	
Primary end point (no. [%])	4 (50.0)	2 (25.0)	
HR (95% CI)	1.00 (reference)	0.44 (0.08–2.39)	
No			
No. of participants	30	34	
Primary end point (no. [%])	9 (30.0)	4 (11.8)	
HR (95% CI)	1.00 (reference)	0.38 (0.12–1.23)	
ICH w/o IVH			0.831
Yes			
No. of participants	8	14	
Primary end point (no. [%])	3 (37.5)	2 (14.3)	
HR (95% CI)	1.00 (reference)	0.34 (0.06–2.05)	
No			
No. of participants	30	28	
Primary end point (no. [%])	10 (33.3)	4 (14.3)	
HR (95% CI)	1.00 (reference)	0.41 (0.13–1.30)	

CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

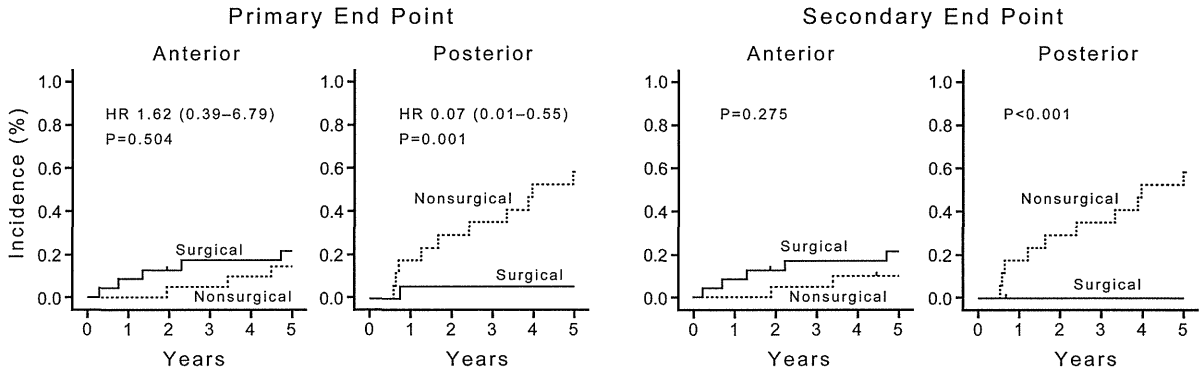

Figure 2. Kaplan–Meier estimates of the incidence of primary and secondary end points by hemorrhagic site. *P*=0.013 for interaction in the primary end point. Calculation of the hazard ratio (HR) and interaction *P* value was impossible for the secondary end point.

treatment effect) was focused on the hemorrhagic site subgroup because the sample size was insufficient to allow the assessment across all baseline subgroups. Effect modification was tested by Cox proportional hazards analyses incorporating the interaction term and was presented as a *P* value for interaction. We also analyzed effect modification for the other baseline variables: age (with the median as the cutoff point), sex, hypertension, and hemorrhage type.

Reproducibility of the classification as anterior or posterior hemorrhage was assessed by a panel assembled for this analysis, and agreement was expressed as the κ coefficient. Sensitivity analysis based on the panel classification was also performed. Two-sided values of $P<0.05$ were considered significant. All analyses were performed with IBM SPSS software, version 20 (IBM Software Group, Chicago, IL).

Results

Of the 80 patients enrolled in total, 42 were assigned to the surgical group and 38 to the nonsurgical group. Patient demographics for both the groups were comparable as described in the published article. As a result of stratified randomization, the numbers of patients with anterior or posterior hemorrhage were similar in the surgical and nonsurgical groups; the surgical group included 24 patients with anterior hemorrhage (57.1%) and 18 with posterior hemorrhage (42.9%), whereas the nonsurgical group included 21 patients with anterior hemorrhage (55.3%) and 17 with posterior hemorrhage (44.7%). The classifications of anterior and posterior hemorrhage showed almost perfect inter-rater agreement (κ=0.82; 95% confidence interval [CI], 0.70–0.95).

Surgical Effects by Hemorrhagic Site

The effect of bypass surgery on the event rate was varied by the hemorrhagic site. About the primary end point, the hazard ratio (HR) for the surgical group relative to the nonsurgical group was 0.07 (95% CI, 0.01–0.55) for the posterior group, whereas the ratio exceeded 1 in the anterior group (HR, 1.62; 95% CI, 0.39–6.79), with $P=0.013$ for interaction (Table 1; Figure 2); this indicates that significant effect modification was observed. About the secondary end point, the similar effect modification was apparent as shown in the Kaplan–Meier curves (Figure 2). Calculation of either the HR or the interaction *P* value was impossible for the secondary end point because the event rate was zero in the surgical group within the posterior hemorrhage strata. The HR was not substantially influenced by age, sex, presence of hypertension, or type of hemorrhage (Table 1). The results of the sensitivity analysis are shown in Table I in the online-only Data Supplement.

Analysis of the Nonsurgical Group

The analysis was then limited to the nonsurgical group, which comprised 38 patients (21 with anterior hemorrhage and 17

Table 2. Baseline Variables in Nonsurgical Group (n=38)

Variable	Anterior Hemorrhage (n=21)	Posterior Hemorrhage (n=17)	*P* Value*
Mean age±SD, y	41.4±11.9	41.3±13.0	0.980
Female (%)	14 (66.7)	13 (76.5)	0.508
Hypertension (%)	4 (19.0)	4 (23.5)	0.736
Diabetes mellitus (%)	2 (9.5)	0	0.191
Hyperlipidemia (%)	2 (9.5)	0	0.191
History of ischemic event (%)	6 (28.6)	4 (23.5)	0.726
History of hemorrhagic stroke (%)	1 (4.8)	3 (17.6)	0.198
Hemorrhagic type			
ICH w/o IVH	6 (28.6)	2 (11.8)	0.263
ICH w/ IVH	11 (52.4)	14 (82.4)	
Primary IVH	3 (14.3)	1 (5.9)	
SAH only	1 (4.8)	0	

ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.
*t test or χ^2 test.

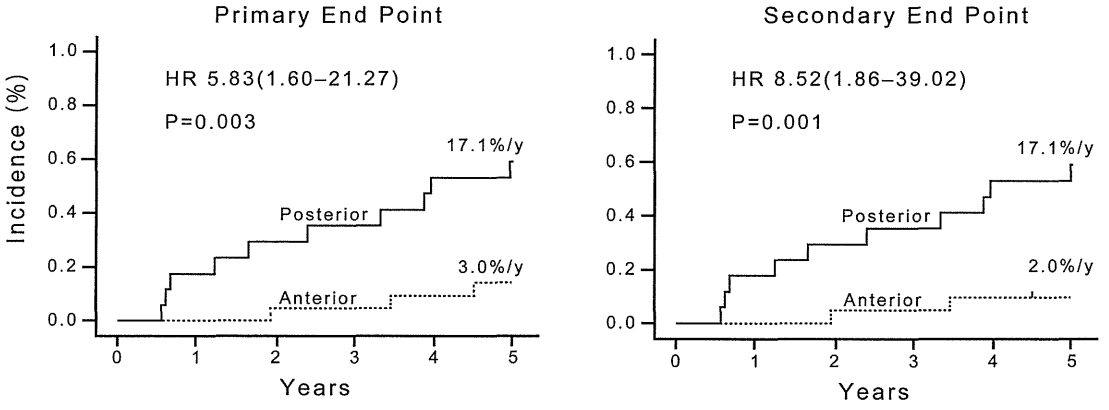

Figure 3. Kaplan–Meier estimates of incidence of primary and secondary end points within the nonsurgical group (n=38). HR indicates hazard ratio.

with posterior hemorrhage). Overall 5-year risk and annual incidence of rebleeding were 31.6% (12/38) and 7.6%, respectively. Baseline characteristics such as age, sex, coexisting disease, history of hemorrhagic or ischemic stroke, and type of hemorrhage were not significantly different between anterior and posterior groups (Table 2). The incidence rates for both the primary and secondary end points were significantly higher for the posterior group than for the anterior group (P=0.003 and 0.001 for log-rank test, respectively; Figure 3). The annual incidence rate for the primary end point was as high as 17.1% per year for the posterior group, as compared with 3.0% per year for the anterior group. The HR for posterior hemorrhage relative to anterior hemorrhage was 5.83 (95% CI, 1.60–21.27) for the primary end point and 8.52 (95% CI, 1.86–39.02) for the secondary end point. No other baseline factor was significantly associated with the incidence of end points in the univariate analysis (Table 3), and no further multivariate analysis was performed. The results of the sensitivity analysis are shown in Table II in the online-only Data Supplement.

Table 3. Univariate Analysis of Factors Associated With End Points in Nonsurgical Group (n=38)

Exposure Variable	Primary End Point HR (95% CI)	Secondary End Point HR (95% CI)
Hemorrhagic site		
Anterior	1.00 (reference)	1.00 (reference)
Posterior	5.83 (1.60–21.27)	8.52 (1.86–39.02)
Age (y; continuous variable)	1.02 (0.98–1.07)	1.03 (0.98–1.08)
Female	1.46 (0.40–5.31)	1.30 (0.35–4.80)
Hypertension	1.68 (0.52–5.47)	1.27 (0.34–4.70)
Diabetes mellitus	1.30 (0.17–9.99)	NA
Hyperlipidemia	1.30 (0.17–9.99)	NA
History of ischemic event	0.20 (0.03–1.57)	0.23 (0.03–1.76)
History of hemorrhagic stroke	0.65 (0.09–5.03)	0.71 (0.09–5.52)
Hemorrhagic type		
ICH w/o IVH	1.00 (reference)	1.00 (reference)
ICH w/ IVH	0.76 (0.20–2.88)	0.76 (0.20–2.88)
Primary IVH	0.65 (0.07–6.27)	0.66 (0.07–6.36)
SAH only	2.26 (0.23–21.91)	NA

CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NA, not applicable; and SAH, subarachnoid hemorrhage.

Analysis of the Surgical Group

The Kaplan–Meier analysis within the surgical group revealed that the incidence rate for the secondary end points was significantly higher for the anterior group than for the posterior group (P=0.045), indicating a tendency opposite to that revealed in the analysis of the nonsurgical group.

Discussion

Rebleeding Risk by Hemorrhagic Site

Our results suggest that the posterior hemorrhage group is, by its nature, at higher risk of rebleeding than the anterior group. Previous observational studies have identified only a few risk factors associated with rebleeding, including age at onset and the presence of silent cerebral microbleeds,[10,11] and have rarely addressed the bleeding site in the manner of this study. Only Kobayashi et al[1] reported a higher incidence of rebleeding in patients with thalamic hemorrhage compared with those with basal ganglia hemorrhage, although their definition of hemorrhagic site differed from ours.

The high incidence of rebleeding in the posterior hemorrhage group can be explained by the vascular morphology of moyamoya disease, which has recently received more attention. As shown in the outstanding work of Morioka et al,[4] dilated and extended choroidal or thalamic perforating arteries seem more responsible for bleeding than do the tiny vessels that proliferate from the lenticulostriate artery, which have traditionally been denoted as moyamoya vessels and suspected as source of bleeding. In moyamoya disease, the anterior choroidal artery can form abnormal anastomoses of the medullary artery around the trigon of the lateral ventricle, where bleeding can occur.[12] The dilatation and extension of the perforators from the posterior communicating artery create a risk of bleeding in the thalamus.[4] Other thalamic perforators can also proliferate, especially when the posterior cerebral artery is occluded.[13] All bleeding from these fragile collaterals could be commonly classified as posterior hemorrhage; for this reason, the rebleeding risk of the posterior group might have been elevated.

However, the causes of anterior hemorrhage might be heterogeneous because, by definition, it includes hemorrhage of

unknown origin. The lenticulostriate arteries, possible sources of anterior hemorrhage, might suffer less hemodynamic stress than the choroidal or thalamic arteries as long as the terminal portion of the internal carotid artery has narrowed. These points of speculation should be confirmed through further analysis.

Surgical Effects by Hemorrhagic Site

Our results suggest that patients with posterior hemorrhage accrue greater surgical benefit than those with anterior hemorrhage. No previous study, to the best of our knowledge, has focused on the effect modification by hemorrhagic site. Our results seem valid because biases were minimized through the prospective design of the study and the determination to analyze a prespecified (versus post hoc) subgroup.

This result might reflect the different natures of the anterior and posterior hemorrhage groups, as discussed above. The abnormal collaterals formed by the thalamic or choroidal arteries, possible sources of posterior hemorrhage, can connect to the middle cerebral artery in the cortex via the medullary artery.[3,12] Direct bypass, introduced in the territory of the middle cerebral artery, might eliminate hemorrhagic stress on the collaterals by augmenting blood flow in that very area. Kuroda et al[7] reported the elimination of peripheral aneurysms after bypass surgery, all of which had formed in the thalamic or choroidal artery. A more recent report, revealing that the dilatation and extension of the choroidal and thalamic arteries was likely to diminish after bypass surgery,[14] also supports this speculation. The degree of preoperative perfusion impairment or postoperative improvement might differ between the anterior and posterior groups and should also be analyzed in further studies.

As shown in this analysis, higher rebleeding risk and greater surgical effects in the posterior hemorrhage group might, after careful interpretation, provide valuable information on the treatment of hemorrhagic moyamoya disease. Although the efficacy of bypass surgery was confirmed in the overall comparison of the JAM Trial,[2] identification of a more beneficial subgroup is required, considering the potential invasiveness of surgery. Patients with posterior hemorrhage might comprise a more optimal target group for bypass surgery. Further studies, along with the present result, might reveal optimal indications for bypass surgery in the future.

Limitations

This study has several limitations. First, although the JAM Trial is the only randomized controlled trial for moyamoya disease, the sample size was relatively small because of the low prevalence of the disease; this resulted in the wide CIs observed in the results. Second, a type I error could have contaminated the credibility of the subgroup results, even if multiple comparisons were carefully avoided by restricting the focus on the predetermined subgroup. Third, potential misclassification of the hemorrhagic site could have affected the results, although the results of the sensitivity analysis correspond closely to those of the primary analysis and seem to support the conclusion. Further prospective studies, as well as subgroup analyses from other observational studies, should confirm whether similar results are consistently observed.

Conclusions

This analysis of the JAM Trial supports our prespecified hypothesis about hemorrhagic moyamoya disease that both the outcome of nonsurgical treatment and effect of bypass surgery at preventing rebleeding vary with the initial bleeding site. Careful interpretation of the results suggests that patients with posterior hemorrhage are, by its nature, at higher risk and accrue greater benefit from bypass surgery than do those with anterior hemorrhage. Further studies might identify the optimal target group for bypass surgery in hemorrhagic moyamoya disease.

Appendix

Study Organization: The Research Committee on Moyamoya Disease of the Japanese Ministry of Health, Labor and Welfare, Principal Investigator and Chair: 1999–2005: Takashi Yoshimoto, MD, PhD; 2005–2013: Nobuo Hashimoto, MD, PhD; 2013–: Kiyohiro Houkin, MD, PhD, Central Office and Data Management Center: Department of Neurosurgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan: Susumu Miyamoto MD, PhD; Keisuke Yamada MD, PhD; Jun C. Takahashi MD, PhD; and Takeshi Funaki MD, PhD, Statistical Center: Division of Epidemiology, Department of Health Informatics and Public Health, Tohoku University School of Public Health, 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 (Coproject Director; Neurology); Masayasu Matsumoto MD, PhD; Tsuguya Fukui MD, PhD; Ichiro Tsuji MD, PhD; Yasuo Fukuuchi MD, PhD; Takashi Ohmoto MD, PhD; Yasuo Kuwabara MD, PhD; Jyoji Nakagawara MD, PhD; and Izumi Nagata MD, PhD, Participating Centers and Researchers: Chiba University Graduate School of Medicine, Chiba, Japan: Junichi Ono, Toshio Machida; and Ryuji Sakakibara (Sakura Medical Center, Toho University), Chugoku Rousai Hospital, Kure, Japan: Kanji Yamane, Shinji Okita, and Kiyoshi Kumano, Gifu University Graduate School of Medicine, Gifu, Japan: Toru Iwama and Yasuhiko Kaku, Gunma University, Maebashi, Japan: Nobuhito Saito, Graduate School of Medicine, Kyoto University, Kyoto, Japan: Susumu Miyamoto, Keisuke Yamada, Hidenao Fukuyama, Jun C. Takahashi, and Takeshi Funaki, Hokkaido University Graduate School of Medicine, Sapporo, Japan: Kiyohiro Houkin, Satoshi Kuroda (University of Toyama), Ichiro Yabe, and Fumio Moriwaka, Iwate Medical University, Morioka, Japan: Akira Ogawa, Kuniaki Ogasawara, and Kenji Yoshida, Kitasato University School of Medicine, Sagamihara, Japan: Kiyotaka Fujii, Masaru Yamada, Kimitoshi Sato, and Tsugio Akutsu, Kurashiki Central Hospital, Kurashiki, Japan: Sen Yamagata, Nagaoka Chuo General Hospital, Nagaoka, Japan: Shigekazu Takeuchi, Nagasaki University Medical School, Nagasaki, Japan: Izumi

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Acknowledgments

We are grateful to Drs Ichiro Tsuji and Yasutake Tomata of the Department of Public Health, Tohoku University Graduate School of Medicine for performing statistical analyses.

Sources of Funding

The Japan Adult Moyamoya Trial has been funded since 1999 by a grant from the Japanese Ministry of Health, Labour and Welfare as a major project of the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease).

Disclosures

None.

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もやもや病（ウィリス動脈輪閉塞症）の診断・治療に関する研究

平成28年（2016年）5月発行

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