Vessel Wall Changes on Serial High-Resolution MRI and the Use of Cilostazol in Patients With Adult-Onset Moyamoya Disease

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Background and Purpose The natural course of adult-onset moyamoya disease (MMD) is unknown, and there is no medical treatment that halts its progression. We hypothesized that progressive shrinkage of large intracranial arteries occurs in adult-onset MMD, and that cilostazol inhibits this process.

Methods Serial high-resolution magnetic resonance imaging (HR-MRI) was performed on 66 patients with MMD: 30 patients received cilostazol, 21 received other antiplatelets, and 15 received no antiplatelets or had poor compliance to them. Serial HR-MRI was performed (interval between MRI scans: 29.67±18.02 months, mean±SD), and changes in outer diameter, luminal stenosis, and vascular enhancement were measured. Factors affecting HR-MRI changes were evaluated, including vascular risk factors and the ring finger protein 213 gene variant.

Results The progression of stenosis to occlusion, recurrent ischemic stroke, and the development of new stenotic segments were observed in seven, seven, and three patients, respectively. Serial HR-MRI indicated that the degree of stenosis increased with negative remodeling (outer diameter shrinkage). Patients who received cilostazol presented significantly larger outer diameters and lower degrees of stenosis compared with other groups (p=0.005 and p=0.031, respectively). After adjusting for clinical and genetic factors, only cilostazol use was independently associated with negative remodeling (odds ratio=0.29, 95% confidence interval=0.10–0.84, p=0.023). While vascular enhancement was observed in most patients (61 patients), the progression of enhancement or the occurrence of new vascular enhancement was rarely observed on follow-up HR-MRI (6 and 1 patients, respectively).

Conclusions Adult-onset MMD induces progressive shrinkage of large intracranial arteries, which cilostazol treatment may prevent. Further randomized clinical trials are warranted.

Trial registration ClinicalTrials.gov identifier NCT02074111.

Keywords moyamoya disease; intracranial stenosis; magnetic resonance imaging; stroke; cilostazol.

INTRODUCTION

Moyamoya disease (MMD) is a rare idiopathic progressive vasculo-occlusive disease of the large intracranial arteries, including the distal internal carotid artery (ICA). MMD is characterized by shrinkage of the involved segments, which can be observed on high-resolution magnetic resonance imaging (HR-MRI), and a hazy network of basal collaterals called moyamoya vessels. The natural course of adult-onset MMD is unclear, and no study has used serial HR-MRI to evaluate the serial changes in the vessel wall features during its course.

No medical treatment can halt MMD progression. The efficacy and safety of cilostazol, a...
phosphodiesterase 3 inhibitor, have been investigated in patients with ischemic stroke.\textsuperscript{5,7} Cilostazol has recently become the most commonly used antiplatelet agent for patients with MMD; a survey of stroke doctors in Japan found that 62.5% of physicians used cilostazol, and it was the second most commonly used antiplatelet agent for patients with MMD.\textsuperscript{8} Using a nationwide health insurance database of 25,978 South Korean patients with MMD, we recently found that cilostazol (but not other antiplatelet agents) substantially decreased the risk of death and the incidence rates of ischemic and hemorrhagic stroke in patients with MMD.\textsuperscript{9} However, no studies have investigated the efficacy of cilostazol on the vascular wall changes in patients with MMD.

The present study tested the hypothesis that progressive shrinkage of large intracranial arteries occurs in adult-onset MMD and can be inhibited by cilostazol. To this end, we serially performed HR-MRI and evaluated the effects of cilostazol and the clinical and genetic factors impacting the degree of negative remodeling progression for HR-MRI in patients with adult-onset MMD.

METHODS

Study population

We recruited patients who were diagnosed with MMD at a university medical center between January 2012 and December 2018. Potential participants were defined as patients if they were 1) older than 18 years with ≥50% unilateral or bilateral stenosis or occlusion of the distal portions of the ICA and/or the proximal middle cerebral artery (MCA) on magnetic resonance angiography (MRA), 2) diagnosed with MMD based on HR-MRI and/or conventional angiography, and 3) willing to participate in the study. We excluded patients 1) with potential proximal sources of embolism (e.g., atrial fibrillation and ≥50% stenosis of the relevant cervical carotid artery), 2) with intracranial arterial pathology other than MMD observed on HR-MRI (e.g., intracranial atherosclerosis, vasculitis, arterial dissection, or reversible cerebral vasospastic stroke), 3) with stroke that occurred in the posterior circulation territory, and 4) who underwent surgical revascularization before HR-MRI. MMD diagnosis was based on the presence of stenosis in the distal ICA/MCA and a hazy network of basal collaterals that were evaluated using conventional angiography or HR-MRI. If two or more flow-void signals were present in the basal ganglia on time-of-flight (TOF) source images of HR-MRI, it was considered to be a collateral vascular structure.\textsuperscript{10} The presence of an intimal flap/double lumen, intravascular hematoma, or aneurysmal formation was considered an indicator of arterial dissection, whereas the presence of plaque was considered an indicator of intracranial atherosclerosis. All patients underwent serial HR-MRI, in which their outer diameter, degree of stenosis, and vascular enhancement were measured based on the site with the maximum stenosis, regardless of the presence of symptoms.

Clinicoepidemiologic information, including age, sex, and vascular risk factors, was collected systematically. All patients underwent routine blood tests and echocardiography. The study participants were categorized based on 1) age and sex, 2) the presence of risk factors (e.g., hypertension, diabetes, dyslipidemia, body mass index, or current smoking), 3) family history of MMD, 4) clinical presentation (asymptomatic, transient ischemic attack [TIA], ischemic stroke, or intracerebral hemorrhage), 5) the presence of the ring finger protein 213 gene (RNF213) variant, and 6) unilateral and bilateral MMD according to the diagnostic criteria for definitive MMD by the research committee for MMD of the Japanese Ministry of Health, Labor and Welfare (2015 revision).\textsuperscript{11}

Patients were followed up for more than 6 months. Any cerebrovascular events (recurrence of ischemic/hemorrhagic stroke or TIA) were evaluated in either the same vascular territory or in that related to tandem stenotic lesions.

The Institutional Review Board of Samsung Medical Center approved this study (approval number: 2020-07-155-001). The study was conducted as part of a clinical trial (ClinicalTrials.gov identifier: NCT02074111), and all patients or their guardians provided informed consent for participation.

MRI protocol and analysis

HR-MRI images were analyzed to evaluate the vessel walls. The details of the HR-MRI parameters are described elsewhere.\textsuperscript{2,12} HR-MRI was performed using a 3-tesla MRI system (Achieva, Philips Medical Systems, Best, the Netherlands) with a 32-channel sensitivity encoding (SENSE) head coil. Neuroradiologists selected the vessel and evaluation site based on clinical presentation, three-dimensional (3D) TOF-MRA findings, and a combination of acquisition orientations (axial only or axial and sagittal).

The characteristics of the outer diameter, wall remodeling, stenotic portion enhancement, and basal collateral structure were assessed by two neurologists (J.Y.K. and E.H.C.) who were blinded to the clinical information. They independently interpreted the HR-MRI images, and one of them reassessed the images 2 weeks later to estimate the intraobserver variability. We evaluated the vessel walls of the MCA and/or distal ICA at the site of maximum stenosis or just proximal to the occlusion on 3D-TOF, and bilateral distal ICAs immediately after branching ophthalmic arteries. The outer vessel diameters and lumen areas were measured on T2- or proton-density-weighted images, and the enhancement volume was measured on contrast-enhanced T1-weighted images using the...
MIPAV (Medical Image Processing, Analysis, and Visualization) program of the National Institutes of Health. The outer vessel diameter at the sites with maximum stenosis of the symptomatic intracranial artery was measured in the analysis. When multiple stenotic lesions were detected in a symptomatic intracranial artery, the one causing the maximum stenosis was considered symptomatic and was selected for analysis. In addition, in cases of total occlusion, the neighboring proximal site of the relevant artery or the site with maximum stenosis of the contralateral intracranial artery were used. The degree of stenosis was measured only in stenosis cases (not in occlusion cases) and calculated using the following formula: [1 – (narrow lumen area)/(reference lumen area)]×100. The lumen area was defined as the entire vessel area excluding the wall area, and the reference vessel was based on the opposite normal vessel. However, if both vessels had narrowed, the midpoint of the basilar artery was selected as a reference. Enhancement was defined as an increase of at least 20% in the normalized signal intensity of the wall layer after contrast agent injection, and changes in enhancement at the involved segments were classified as follows: 1) no enhancement on both initial and follow-up images, 2) no enhancement on initial images but enhancement on follow-up images, 3) enhancement increase of larger than 50%, 4) enhancement decrease of larger than 50%, and 5) no changes in the preexisting enhancement. The inter- and intraobserver agreements of the measured HR-MRI parameters were examined, yielding intraclass correlation coefficients of 0.803 and 0.854, respectively.

Identification of RNF213 variants
Genomic DNA was extracted from peripheral blood leukocytes using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). The c.14429G>A (p.Arg4810Lys) mutation of RNF213 was amplified using primer sets designed by the authors. A polymerase chain reaction was performed using the GeneAmp 9700 PCR system thermal cycler (Applied Biosystems, Foster City, CA, USA). Direct sequencing was performed using the Big-Dye Terminator Cycle Sequencing Kit with Ready Reaction Mix (Applied Biosystems) on the 3730xl DNA Analyzer (Applied Biosystems).

Statistical analysis
Categorical and continuous variables were summarized using median (interquartile range [IQR]) or mean±SD and frequency (percentage) values, respectively. Differences in the continuous variables were examined using one-way ANOVA, the Kruskal-Wallis test, or the t-test. Differences in the distributions of the categorical variables between the two groups were examined using χ², Fisher’s exact, or Mann-Whitney U tests. The correlation between the changes in the amount of negative remodeling and the changes in the degree of stenosis on follow-up HR-MRI or the cilostazol use duration were analyzed using Spearman’s correlation coefficient. The independent factors for negative remodeling progression during the follow-up on serial HR-MRI were also evaluated using logistic regression. The adjustment variables in the multivariate regression model were selected from the potential outcome determinants with significant clinical relevance or with p<0.20 in their associations with the outcome in the univariate analysis. Before variable selection, the variance inflation factors were calculated to determine any possible multicollinearity, with 4 as the cutoff value. Significance was considered to be present when the two-tailed probability value was p<0.05. All statistical analyses were performed using a commercially available software program (SPSS Statistics version 24.0, IBM Corp., Armonk, NY, USA).

RESULTS

General characteristics
HR-MRI was performed at least twice on each of the 95 patients who were diagnosed with MMD. We excluded 29 patients, including 20 who were diagnosed with other pathologies in the follow-up HR-MRI: atherosclerosis (n=14), dissection (n=3), and vasculitis (n=3). One patient had a high-risk cardioembolic source, and one had a vertebrobasilar territory stroke. Five patients received bypass surgery during the follow-up. Follow-up HR-MRI was subsequently performed after a short duration (less than 6 months) in two patients. Finally, 66 patients were enrolled: 30, 21, and 15 were allocated to the compliance (less than 80%) groups, respectively (Fig. 1).

Baseline characteristics
The baseline characteristics of the three groups are listed in Table 1. There were no significant intergroup differences in sex, age, family history of MMD, vascular risk factors, RNF213 variant, or symptomatic cases. The outer diameter and degree of stenosis at the initial HR-MRI also did not differ significantly among the three groups (p=0.976 and p=0.839, respectively).

Serial HR-MRI findings for the involved segments
Follow-up HR-MRI was subsequently performed after an interval of 29.67±18.02 months. Negative remodeling was observed at the follow-up HR-MRI in 36.1% (13 of 36) of asymptomatic patients, 28.6% (4 of 14) of patients with TIA, 50% (7 of 14) of those with ischemic stroke, and 50% (1 of 2) of those with hemorrhagic stroke. The classification of symptomatic events did not differ significantly with the presence...
of negative remodeling ($p=0.668$).

Serial HR-MRI findings in the three groups are listed in Table 2. Outer diameters increased in the cilostazol group and decreased in both the other-antiplatelet and no-antiplatelet groups ($p=0.005$ in outer diameter changes). Similarly, the degree of stenosis decreased in the cilostazol group.

Fig. 1. Patient selection. HR-MRI, high-resolution magnetic resonance imaging; MMD, moyamoya disease; PCA, posterior cerebral artery.

Table 1. Patients’ characteristics according to the antiplatelet use

| Characteristic                     | Cilostazol group (n=30) | Other-antiplatelet group (n=21) | No-antiplatelet group (n=15) | $p$   |
|-----------------------------------|-------------------------|---------------------------------|-------------------------------|-------|
| Sex, female                       | 21 (70.0)               | 16 (76.2)                       | 13 (86.7)                     | 0.227 |
| Age at study enrollment (yr)      | 47.33±9.42              | 49.43±16.05                     | 43.87±8.59                    | 0.382 |
| Age at MMD diagnosis (yr)         | 47.10±9.43              | 50.14±16.15                     | 43.47±8.45                    | 0.090 |
| Presentation                      |                         |                                 |                               | 0.943 |
| Asymptomatic                      | 19 (63.3)               | 9 (42.9)                        | 8 (53.3)                      |       |
| TIA                               | 7 (23.3)                | 7 (33.3)                        | 1 (6.7)                       |       |
| Ischemic stroke                   | 4 (13.3)                | 5 (23.8)                        | 4 (26.7)                      |       |
| Hemorrhagic stroke                | 0 (0.0)                 | 0 (0.0)                         | 2 (13.3)                      |       |
| Family history of MMD             | 4 (13.3)                | 2 (9.5)                         | 2 (13.3)                      | 0.932 |
| RNF213 variant                    | 22 (73.3)               | 17 (85.0)*                      | 6 (40.0)                      | 0.061 |
| Bihemispheric involvement         | 13 (43.3)               | 13 (61.9)                       | 6 (40.0)                      | 0.933 |
| Risk factors                      |                         |                                 |                               |       |
| Hypertension                      | 13 (43.4)               | 8 (38.1)                        | 3 (20.0)                      | 0.146 |
| Diabetes                          | 1 (3.3)                 | 2 (9.5)                         | 0 (0.0)                       | 0.614 |
| Dyslipidemia                      | 10 (33.3)               | 10 (47.6)                       | 2 (13.3)                      | 0.327 |
| Current smoker                    | 3 (10.0)                | 2 (9.5)                         | 0 (0.0)                       | 0.278 |
| BMI (kg/m²)                       | 25.42±4.48              | 24.36±2.76                      | 24.30±3.15                    | 0.839 |
| Statin use                        | 14 (46.7)               | 16 (76.2)                       | 9 (60.0)                      | 0.227 |
| Initial HR-MRI findings           |                         |                                 |                               |       |
| Outer diameter (mm)               | 1.72±0.73               | 1.65±0.60                       | 1.73±0.73                     | 0.976 |
| Degree of stenosis (%)            | 83.12±9.66              | 84.80±8.72                      | 82.36±14.03                   | 0.839 |

Data are n (%) or mean±SD values.

*RNF213 testing was not performed in one patient.

BMI, body mass index; HR-MRI, high-resolution magnetic resonance imaging; MMD, moyamoya disease; RNF213, ring finger protein 213 gene; TIA, transient ischemic attack.
and increased in the other-antiplatelet and no-antiplatelet groups \( (p=0.031) \). There were no differences in the changes in outer diameter and degree of stenosis between the other-antiplatelet and no-antiplatelet groups \( (p=0.119 \) and \( p=0.215 \), respectively). There was also a significant correlation between the degree of stenosis and outer diameter changes, with the degree of stenosis increasing as the outer diameter decreased \( (r=-0.810, p<0.001) \).

In the cilostazol group, the duration of cilostazol use varied from 9 months to 5.83 years (median=20.5 months, IQR=15.8–42 months). Spearman’s correlation coefficient indicated that a longer cilostazol use \( (0 \) for nonusers) was associated with a larger increase in outer diameter \( (r=0.322, p=0.008) \) and less-severe stenosis \( (r=-0.310, p=0.034) \). Occlusive lesions developed within previously noninvolved segments on follow-up HR-MRI in one patient in the other-antiplatelet group and two patients in the no-antiplatelet group, but none in the cilostazol group. Recurrent ischemic stroke was observed in seven patients; stenosis and negative remodeling were observed to progress in all but one patient who exhibited occlusion of the relevant vessels on initial HR-MRI.

While vascular enhancement was observed in most \( (n=61) \) patients, the progression of enhancement and new vascular enhancement was rarely observed on follow-up HR-MRI (six and one patients, respectively). The frequencies of occurrence or the vascular enhancement changes on HR-MRI did not differ between the groups \( (p=0.914) \). Typical cases are shown in Fig. 2.

Changes in vascular remodeling, stenosis, and vascular enhancement on serial HR-MRI did not differ between statin users \( (n=39) \) and nonusers \( (n=27) \) (data not shown).

### DISCUSSION

This study observed progressive MCA shrinkage in patients with adult-onset MMD, and that cilostazol may halt or reverse negative remodeling. This was the first study that we were aware of that evaluated the effects of medical treatment using serial HR-MRI in patients with MMD. Among children and adolescents with unilateral MMD, Yeon et al.\(^\text{13}\) found that contralateral progression tended to occur in children younger than 9 years, suggesting progression

### Table 2. Serial HR-MRI findings according to antiplatelet group

|                      | Cilostazol group \((n=30)\) | Other-antiplatelet group \((n=21)\) | No-antiplatelet group \((n=15)\) | \( p \) |
|----------------------|-------------------------------|-------------------------------------|----------------------------------|------|
| Outer diameter       |                               |                                     |                                  |      |
| Change, F/U-initial (mm) | 0.17±0.09                     | -0.53±0.14                          | -1.45±0.25                       | 0.005|
| Negative remodeling  | 7 (23.3)                      | 8 (32.0)                            | 10 (40.0)                        | 0.018|
| Positive remodeling  | 10 (33.3)                     | 1 (4.8)                             | 1 (6.7)                          | 0.014|
| Degree of stenosis   |                               |                                     |                                  |      |
| Change, F/U-initial (%) | -0.97±4.47                    | 3.38±7.146                          | 6.96±12.07                       | 0.031|
| Vascular enhancement |                               |                                     |                                  |      |
| Initial \(-\), F/U \(-\) | 2 (6.7)                       | 0 (0.0)                             | 2 (5.9)                          |      |
| Initial \(+\), F/U \(+\) | 0 (0.0)                       | 1 (4.8)                             | 0 (0.0)                          |      |
| Initial \(+\), F/U decrease >50% | 14 (46.7)                   | 11 (52.4)                           | 5 (6.8)                          |      |
| Initial \(+\), F/U no change | 12 (40.0)                    | 6 (28.6)                            | 7 (46.7)                         |      |
| Initial \(+\), F/U increase >50% | 2 (6.7)                      | 3 (14.3)                            | 1 (6.7)                          |      |
| Progression of stenosis to occlusion | 2 (6.7)                     | 3 (14.3)                            | 2 (13.3)                         | 0.670|
| Development of new stenotic segments | 0 (0.0)                      | 1 (4.8)                             | 2 (13.3)                         | 0.048|
| Ischemic stroke recurrence | 2 (6.7)                      | 3 (14.3)                            | 2 (13.3)                         | 0.427|

Data are \( n \) (%), or mean±SD values. F/U, follow-up; HR-MRI, high-resolution magnetic resonance imaging; + present; −, absent.

Factors associated with negative and positive remodeling

Factors associated with negative remodeling (a decrease in the outer diameter size on follow-up HR-MRI) were evaluated. Negative remodeling was observed in 25 of 66 patients. After adjusting for other factors, including clinical and genetic factors, only cilostazol use was independently associated with negative remodeling (odds ratio \([\text{OR}]=0.29, 95\% \text{ confidence interval } \boxed{\text{CI}}]=0.10–0.84, \( p=0.023 \)) (Table 3). Similarly, positive remodeling (an increase in the outer diameter size) was observed in 12 of 66 patients, and only cilostazol use was independently associated with positive remodeling on follow-up HR-MRI \( (\text{OR}=14.08, 95\% \text{ CI}=2.19–90.41, \ p=0.005) \) (Supplementary Table 1 in the online-only Data Supplement).
in pediatric-onset MMD. The natural course of patients with adult-onset MMD might differ from that of patients with pediatric MMD. National registry data in Japan indicated that epilepsy and TIA were more frequent in pediatric cases, whereas asymptomatic cases and hemorrhagic stroke were more frequent in adults. However, the present study found that progressive shrinkage occurs in adult-onset MMD regardless of symptom occurrence, suggesting that MMD is not a stable disease in adulthood, even in asymptomatic cases. The present results are consistent with previous reports of asymptomatic adult-onset MMD disease being associated with an increased risk of stroke or TIA. While the pathogenic mechanisms of MMD remain unknown, there is an increasing amount of evidence that MMD is primarily a proliferative disease (proliferation/migration of vascular cells resulting in luminal occlusion and aberrant angiogenesis; that is, moyamoya vessels and medial thinness). Bypass surgery is the most common treatment to restore perfusion in MMD, but it is associated with the risk of complications including perioperative stroke. There is currently no available treatment to halt progressive stenosis in MMD. Whether medical treatment strategies such as using antiplatelet agents to prevent stroke are of any benefit in MMD has not yet been demonstrated. Antiplatelet agents are widely used in patients with MMD. Although a hemodynamic compromise is a major determinant of stroke in patients with MMD, our

Fig. 2. Representative case from the cilostazol group indicating a substantial improvement in vascular remodeling. A 24-year-old female presented with transient sensory changes on the right side. Genetic testing obtained the ring finger protein 213 gene (RNF213) heterozygote, and high-resolution magnetic resonance imaging (HR-MRI) indicated negative remodeling and circular enhancement. She was prescribed 100 mg of cilostazol twice daily during the study period, and underwent serial HR-MRI three times. A: Time-of-flight magnetic resonance angiography (TOF-MRA) image presenting an improvement in the bilateral stenosis of the middle cerebral arteries (MCAs) during follow-up. Baseline TOF-MRA indicated severe stenosis in bilateral MCAs, but only mild stenosis was observed in the left MCA on the last follow-up TOF-MRA. B: HR-MRI indicated left MCA shrinkage, which improved in follow-up imaging (outer diameter of MCA: 1.10 mm at baseline, 1.55 mm at the intermediate follow-up, and 1.70 mm at the last follow-up). Vascular enhancement was persistently observed in the follow-up images.
multimodal MRI study that evaluated infarct patterns and collateral statuses indicated that embolic phenomena played an important role in acute ischemic stroke in patients with MMD.21 Given the role of antiplatelet agents in preventing microembolism in patients with high degrees of intracranial stenosis, the use of appropriate antithrombotic agents could be considered for patients with MMD with recurrent embolic strokes. The results of the present study indicated that cilostazol, compared with other-antiplatelet agents, prevents or ameliorates negative remodeling with a reduction in intimal thickening, which consequently improves stenosis. The present results are consistent with those of a previous study that involved patients with symptomatic intracranial atherosclerotic stenosis, which indicated that cilostazol prevented progression and increased the regression of stenosis according to measurements by MRA and transcranial Doppler.22 Efforts to increase the outer diameter may have clinical implications from a hemodynamic perspective, although the frequency of stroke recurrence did not differ with cilostazol use, which is probably due to the small sample in the present study. In this study, patients with MMD presented constrictive/negative remodeling of the involved segments, and smaller intracranial arteries may be more vulnerable to hemodynamic compromise. Our flow dynamics study indicated that fractional flow was diminished in patients with intracranial arteries of smaller diameters with a similar degree of stenosis.12 Cilostazol, a phosphodiesterase 3 inhibitor, has antiplatelet, vasodilatory, and antithrombotic properties, and it activates bone-marrow-derived endothelial progenitor cells and inhibits the proliferation of smooth-muscle cells.23,24 Further studies are needed to identify the mechanisms underlying the beneficial effects of cilostazol in patients with MMD.

In the present study, hemorrhagic stroke risk did not increase with antiplatelet agent use, which could due to the small sample of patients with hemorrhagic stroke (only two patients had hemorrhagic stroke, and antiplatelet agents were not used in these patients). Further studies with larger samples that include more patients with hemorrhagic stroke are needed to determine the prevalence of hemorrhagic stroke after using antiplatelet agents.

In conclusion, this study suggests that MMD is a progressive disease in adults, regardless of the symptoms and the role of cilostazol in preventing the progression of vascular shrinkage in patients with MMD. However, the study had some limitations. First, luminal occlusion and aberrant angiogenesis are important pathologic findings of MMD, but this study did not consider aberrant angiogenesis and moyamoya vessels because of the limitations of using HR-MRI. In addition, more than half were diagnosed when they were older than 45 years, so many patients with quasi or probable MMD might have been included. Second, this study involved a large sample of prospective cases diagnosed by HR-MRI and RNF213 testing that can differentiate between the causes of large intracranial stenosis, such as dissection and atherosclerosis. However, it was a single-center study with a small sample and a short follow-up. Our findings therefore should be confirmed in other populations using long-term follow-up serial HR-MRI studies. Third, this was a retrospective study and the antiplate-

**Table 3.** Factors associated with negative remodeling

| Factor                          | Absent (n=41) | Present (n=25) | p     | Estimated OR (Crude 95% CI) | Adjusted (95% CI) | p     |
|---------------------------------|--------------|---------------|------|----------------------------|-------------------|------|
| Female sex                      | 30 (73.2)    | 20 (80.0)     | 0.531| 3.17 (0.69–14.63)          | 2.21 (0.35–13.82) | 0.397|
| Age at study enrollment ≥45 years| 26 (63.4)    | 13 (52.0)     | 0.362|                           |                   |      |
| Age at MMD diagnosis ≥45 years  | 26 (63.4)    | 14 (56.0)     | 0.550|                           |                   |      |
| Hypertension                    | 16 (39.0)    | 8 (32.0)      | 0.566|                           |                   |      |
| Diabetes                        | 1 (2.4)      | 2 (8.0)       | 0.320|                           |                   |      |
| Dyslipidemia                    | 12 (29.3)    | 10 (40.0)     | 0.371|                           |                   |      |
| Current smoker                  | 3 (7.3)      | 2 (8.0)       | 0.919|                           |                   |      |
| BMI ≥25 kg/m²                   | 13 (31.7)    | 9 (36.0)      | 0.720|                           |                   |      |
| Family history of MMD           | 5 (12.2)     | 3 (12.0)      | 0.981|                           |                   |      |
| RNF213 variant                  | 27 (67.5)    | 18 (72.0)     | 0.702|                           |                   |      |
| Bihemispheric involvement       | 20 (48.8)    | 12 (48.0)     | 0.951|                           |                   |      |
| Stenotic lesions on posterior cerebral artery | 3 (7.3) | 5 (20.0) | 0.140 | 3.17 (0.69–14.63) | 2.21 (0.35–13.82) | 0.397 |
| Symptomatic case                | 18 (43.9)    | 12 (48.0)     | 0.746|                           |                   |      |
| Statin use                      | 24 (58.5)    | 15 (60.0)     | 0.907|                           |                   |      |
| Cilostazol use                  | 23 (56.1)    | 7 (28.0)      | 0.029| 0.30 (0.11–0.89)          | 0.29 (0.10–0.84)  | 0.023|

Data are n (%) values.

BMI, body mass index; CI, confidence interval; MMD, moyamoya disease; OR, odds ratio; RNF213, ring finger protein 213 gene.
lets used were not controlled nor randomized. Further randomized clinical trials are warranted to evaluate the role of cilostazol in preventing stroke in patients with adult-onset MMD.

Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.6.610.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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