

Association between statin therapy and the risk of stroke in patients with moyamoya disease: a nationwide cohort study

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ABSTRACT

Background and objective Knowledge regarding the pharmacological treatment for moyamoya disease (MMD), a chronic and progressive cerebrovascular disease conferring greater stroke risk, is limited. In the present study, whether statin therapy is associated with a reduced risk of stroke in patients with MMD was investigated.

Methods This was a retrospective cohort study in which the occurrence of stroke in patients with newly diagnosed MMD was investigated using the nationwide health insurance database in Korea from January 2007 to March 2021. A multivariable Cox proportional hazards regression model was constructed for stroke, in which statin therapy after MMD diagnosis was treated as a time-dependent variable. Adjustment was done for sex, age, presence of comorbidities, concurrent stroke, revascularisation surgery and treatment with antiplatelets.

Results The present study included 13 373 newly diagnosed patients with MMD; 40.8% had a concurrent stroke at the time of MMD diagnosis. During the mean follow-up of 5.1±3.3 years, 631 patients (4.7%) suffered a stroke event (haemorrhagic stroke: 458 patients, ischaemic stroke: 173 patients). Statin therapy after MMD diagnosis was significantly associated with a reduced risk of stroke (adjusted HR 0.74; 95% CI 0.60 to 0.91, p=0.004). In the secondary outcome analysis, the risk of haemorrhagic stroke (adjusted HR 0.74; 95% CI 0.58 to 0.95, p=0.018) and ischaemic stroke (adjusted HR 0.75; 95% CI 0.52 to 1.08, p=0.124) were reduced with the statin treatment. Taking statins was also associated with a lower risk of all-cause mortality (adjusted HR 0.47; 95% CI 0.33 to 0.67, p<0.001).

Conclusion In patients with MMD, statin therapy was associated with a reduced risk of subsequent stroke. The findings indicate statin treatment may be beneficial for patients with MMD, however the results should be confirmed in randomised controlled trials.

INTRODUCTION

Moyamoya disease (MMD) is a rare cerebrovascular disease characterised by progressive non-atherosclerotic steno-occlusive changes in the terminal portion of the bilateral internal carotid artery (ICA) and formation of abnormal vascular networks.^{1–3}

As the disease progresses, patients with MMD are at increased risk of experiencing

cerebrovascular complications of ischaemic and haemorrhagic stroke. For patients with MMD with severe haemodynamic impairment and repeated ischaemic symptoms, surgical revascularisation is considered the standard treatment to prevent future stroke but is not applicable to all patients.^{4 5} Currently, an established effective pharmacological strategy for the delay of disease progression or the prevention of stroke in patients with MMD, except control of coexisting conventional risk factors such as hypertension and diabetes mellitus, does not exist.^{6–8}

Statins are widely prescribed lipid-lowering drugs shown to reduce the risk for cardiovascular disease, particularly due to atherosclerosis, such as ischaemic stroke or myocardial infarction. Based on extensive evidence, statin therapy is highly recommended as primary and secondary prevention for individuals with established atherosclerotic cardiovascular disease or subjects at high risk of developing atherosclerotic cardiovascular disease.⁹ Although MMD is a non-atherosclerotic vasculopathy, statins have multiple pleiotropic and vasculoprotective activities including endothelial protection, vascular remodelling, antithrombotic, anti-inflammatory, immunomodulatory and lipid-lowering effects.¹⁰ Inflammation and immune responses play an important role in the development and progression of MMD.^{11 12} Therefore, statins are considered potential candidates for medical treatment in MMD. Because the cardiovascular preventive role of statins has been demonstrated in various disease populations considered at high risk, statin therapy may also be beneficial in reducing stroke in patients with MMD. However, evidence supporting statin therapy in patients with MMD is lacking and current guidelines do not mention the role of statins in the treatment of MMD.⁷ In the present study, whether statin therapy in patients with MMD was associated

with a reduced risk of stroke was investigated using a nationwide population-based health insurance database.

METHODS

Study design and data source

This was a retrospective population-based cohort study in which a nationwide health insurance claims database in Korea was used. Korea has a single public insurance system for the entire Korean population (approximately 50 million people). The Health Insurance Review and Assessment Service (HIRA) is an organisation responsible for reviewing medical claims from healthcare providers and quality of care. The HIRA database consists of information on healthcare services including medical diagnosis, prescriptions, procedures and surgery whenever a patient visits a medical institution.¹³ Each time a patient visits a hospital, diagnoses are recorded according to the 10th edition of the International Statistical Classification of Diseases (ICD-10) code. The HIRA database has become publicly available for health researchers who have completed the proper application process (<http://opendata.hira.or.kr/>). The HIRA database is provided only for academic or public research purposes and is completely anonymised and does not contain any identifying information.

Study participants

From the HIRA database, patients with a diagnosis of MMD between January 2007 and March 2021 were selected (figure 1). The ICD-10 code I67.5 and the special code V128 were used to identify patients with MMD.^{14 15}

Korea maintains a registry to provide financial support to patients with rare and incurable diseases; the special code V128 has been used for patients with MMD since 2006.¹⁶

In the present cohort study, the index date was defined as the date of initial diagnosis of MMD. To include only newly diagnosed patients with MMD, subjects diagnosed with MMD during the washout period (2007–2008) were excluded. Patients who received surgical revascularisation (direct or indirect bypass surgery) more than 3 months before MMD diagnosis were also excluded. To exclude patients who had an established indication of statin therapy, patients with a prior diagnosis of ischaemic heart disease (ICD 10-codes I21, I22) or patients who underwent cardiovascular procedures (carotid artery stent, carotid endarterectomy, percutaneous coronary artery intervention, coronary artery bypass graft), were excluded. In addition, patients who had a history of stroke (ICD 10-codes I60–64, I69) were excluded. However, patients with MMD with a diagnosis of stroke (ICD 10-codes I60–63) within 3 months before and after the index date were included

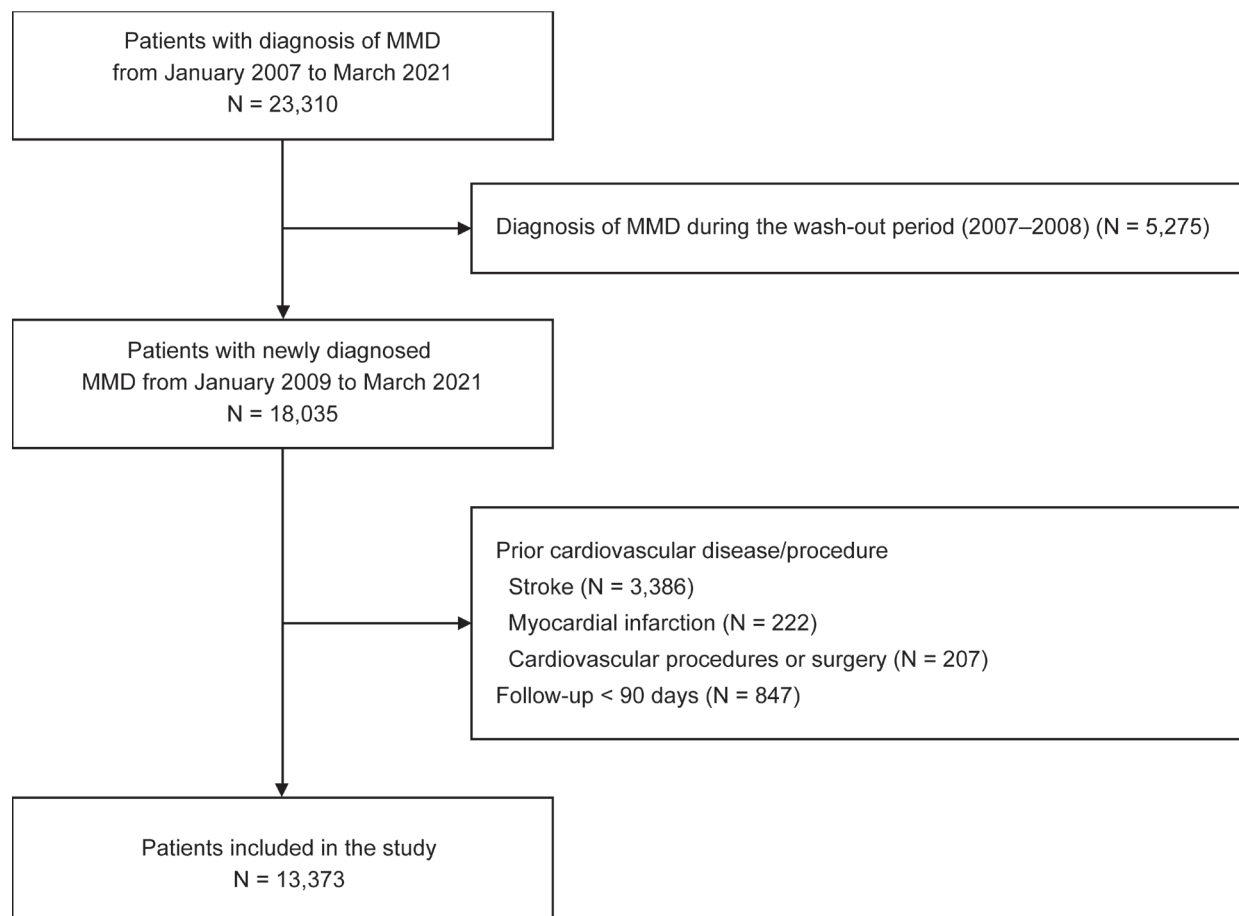


Figure 1 Flow chart of study participants. MMD, moyamoya disease.

and separately classified as patients with MMD presenting with concurrent stroke because MMD is often diagnosed simultaneously with stroke or during the stroke evaluation period. Patients with <3 months of follow-up were excluded.

Study outcomes

The study patients with newly diagnosed MMD were followed up to the occurrence of the primary outcome, censoring, or until 31 March 2021, the study end date. The primary outcome was defined as the development of stroke after 3 months from the index date of MMD diagnosis. Patients were diagnosed with stroke if they admitted with a primary diagnosis of I60–63 and underwent brain CT or MRI during admission.¹⁷ Diagnostic accuracies for stroke based on the health claims data in Korea were reported sufficient in previous validation studies.^{18,19} Secondary outcomes were the development of haemorrhagic stroke (I60–62), ischaemic stroke (I63) and all-cause death. In the secondary outcome analysis, the development of competing events was treated as censored at that time (the first event was considered an outcome).

Covariates and statin treatment

Information on the demographics and comorbidities of study patients was collected from the HIRA database. Identified comorbidities were hypertension, diabetes mellitus, atrial fibrillation, renal disease and malignancy and determined based on whether they were present until 3 months after the index date of MMD diagnosis.

Whether the patient received revascularisation surgery within ± 3 months of MMD diagnosis was investigated. Concurrent stroke was determined based on whether the patient experienced a stroke event ± 3 months from the index date of MMD diagnosis.

Drug administration during the longitudinal period is dynamic in each patient and typically has time-varying characteristics. In Korea, statins should be prescribed by physicians. Thus, HIRA contains all prescription data for statins; type (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin), dosage, date and duration. The intensity of statin was determined according to the 2013 American College of Cardiology/American Heart Association guideline,²⁰ and it was divided into two groups: low-intensity and high-intensity statin group. The statin intensity higher than the low-intensity group was classified as the high-intensity group. On each day of the follow-up period, the use of statins was determined based on exposure to the medication within the last 7 days (figure 2). The follow-up period was divided into ‘time period covered by statin’ and ‘time period not covered by statin’, which were included as time-dependent variable in the analysis. For the time-dependent covariate, data for use of oral antiplatelets (aspirin, clopidogrel, ticlopidine, ticagrelor, prasugrel, triflusal and cilostazol) on each follow-up day were also collected in the same manner as for statins. Use of antiplatelet is subdivided into single antiplatelet and dual antiplatelet (taking combination of two or more antiplatelet agents).

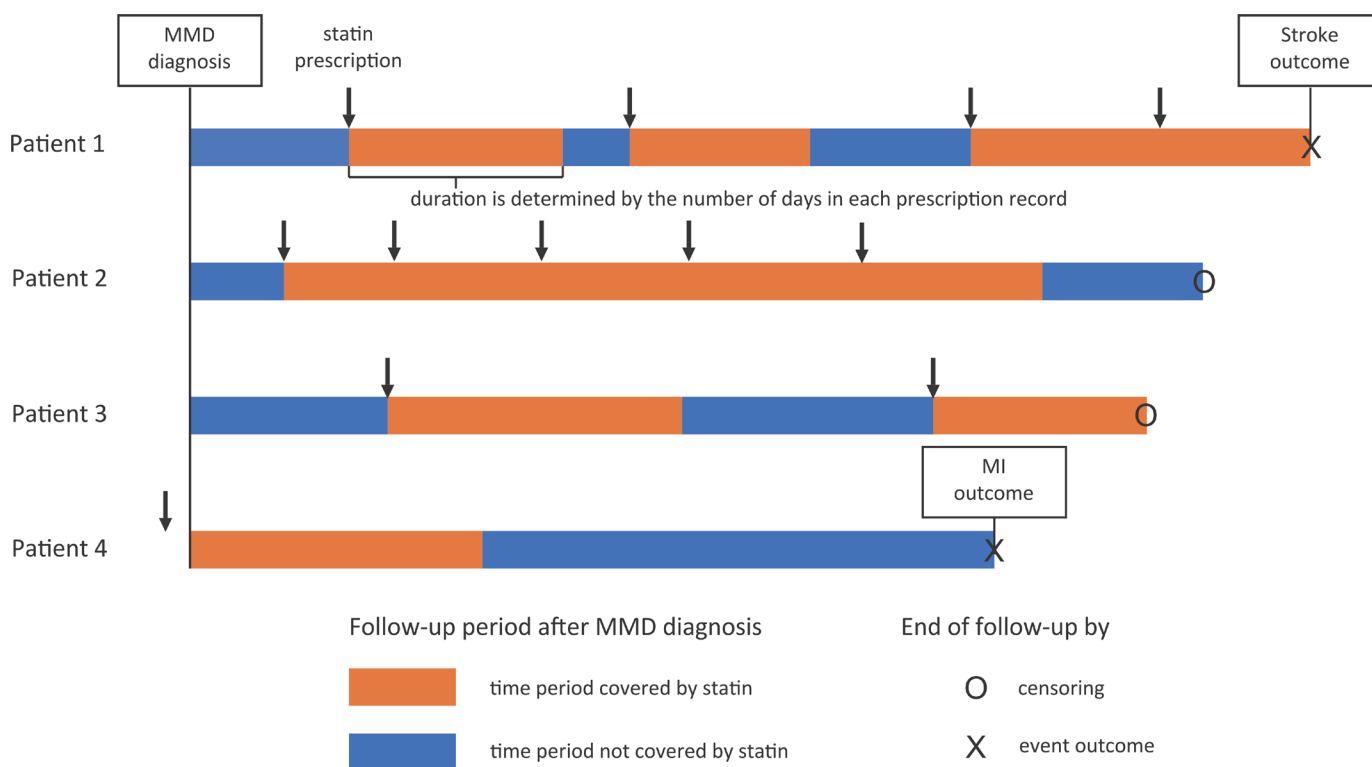


Figure 2 Example of determining the follow-up period as a time-dependent variable according to the statin treatment. MI, myocardial infarction; MMD, moyamoya disease.

Data availability statement

The dataset used in this study is accessible from HIRA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data are only available on reasonable request of investigators for academic or political purposes and permission from the inquiry committee of research support in HIRA (<https://opendata.hira.or.kr/or/orb/useGdInfo.do>).

Statistical analysis

Because medication intake varies over time, treatments with medications were considered time-dependent variables. A time-dependent Cox proportional hazards regression model was constructed to assess the risk of stroke based on statin treatment after MMD diagnosis. Adjustments were made for sex, age, presence of comorbidities (hypertension, diabetes mellitus, atrial fibrillation, renal disease and malignancy), concurrent stroke, revascularisation surgery and treatment with antiplatelets. Subgroup analyses were performed based on sex, age (MMD diagnosis <30 years and ≥30 years of age), the presence of a concurrent stroke and revascularisation surgery. All statistical analyses were performed using SAS (V.9.4, SAS Institute) and R (V.3.5.1, R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Characteristics of the included patients

In this nationwide cohort study, 23 310 patients had a diagnosis of MMD from January 2007 to 31 March 2021. After excluding 9937 patients with prediagnosed MMD, prior cardiovascular disease/procedure or less than 3 months of follow-up, the study included 13 373 patients newly diagnosed with MMD (figure 1). Excluded patients were older and had more vascular risk factors than included patients (online supplemental table S1). The mean age of the included patients was 38.7 ± 18.2 years at MMD diagnosis and 4657 patients (34.8%) were male (table 1). Among the subjects, 5454 patients (40.8%) had a diagnosis of stroke within ±3 months of MMD diagnosis and were classified as patients with concurrent stroke. There were 3877 patients (29.0%) who received revascularisation surgery within ±3 months of MMD diagnosis. When the longitudinal data on the proportion of patients who received statin therapy were evaluated, the number of patients taking statins increased to approximately 30% immediately after MMD diagnosis and then remained in the mid-20% range (online supplemental figure S1). There were 3585 patients (26.8%) taking statins on day 90 from the index date. Detailed information on types and daily doses of statins at that time are described in online supplemental table S2. Patients taking statins were older, experienced more concurrent strokes and had more vascular risk factors than those who were not taking

Table 1 Baseline characteristics of the patients included in the study

Variable	Total (N=13373)
Sex, male	4657 (34.8)
Age, year	38.7 ± 18.2
Age <30	3776 (28.2)
Age ≥30	9597 (71.8)
Concurrent stroke	5454 (40.8)
Revascularisation surgery	3877 (29.0)
Comorbidity	
Hypertension	4800 (35.9)
Diabetes mellitus	1377 (10.3)
Atrial fibrillation	340 (2.5)
Renal disease	439 (3.3)
Malignancy	372 (2.8)

The data are represented as numbers (%) or mean ± SD.

statins at 90 days from the index date (online supplemental table S3).

Outcomes after MMD diagnosis

The mean ± SD of the follow-up period after MMD diagnosis was 5.1 ± 3.3 years. During the follow-up period, 631 patients (4.7%) had a stroke; 458 patients experienced haemorrhagic stroke and 173 patients experienced ischaemic stroke. In addition, all-cause mortality occurred in 237 patients. In the multivariable time-dependent Cox analysis, statin treatment was significantly associated with a lower risk of stroke (adjusted HR 0.74; 95% CI 0.60 to 0.91; table 2) (online supplemental figure S2). The use of antiplatelet was not related to the primary outcome (table 2). We performed further analysis regarding the statin intensity (low and high). Compared with no statin, treatment with low-intensity statin showed a tendency to decrease in the primary outcome, but there was no statistical significance (adjusted HR 0.63; 95% CI 0.28 to 1.41). Treatment with high-intensity statin showed a significant decrease in the primary outcome compared no statin treatment (adjusted HR 0.75; 95% CI 0.61 to 0.92) (online supplemental table S4).

When we performed secondary outcome analyses (table 3), statin treatment was effective in reducing both haemorrhagic stroke (adjusted HR 0.74; 95% CI 0.58 to 0.95) and ischaemic stroke (adjusted HR 0.75; 95% CI 0.52 to 1.08), but there was no statistical significance in ischaemic stroke. Taking statins was also associated with a lower risk of all-cause mortality (adjusted HR 0.47; 95% CI 0.33 to 0.67).

Subgroup analysis

Subgroup analysis was performed based on sex, age, presence of concurrent stroke and revascularisation surgery. Significant interaction was not observed in any subgroup analyses (figure 3). A reduced risk of stroke was observed

Table 2 Association factors for the primary outcome after diagnosis of MMD

Variable	Adjusted HR (95% CI)*	P value
Sex, male	0.90 (0.75 to 1.06)	0.209
Age, year	1.02 (1.02 to 1.03)	<0.001
Concurrent stroke†	1.28 (1.09 to 1.51)	0.003
Revascularisation surgery	0.67 (0.54 to 0.84)	<0.001
Comorbidities		
Hypertension	0.85 (0.71 to 1.02)	0.772
Diabetes mellitus	1.04 (0.80 to 1.35)	0.772
Atrial fibrillation	0.79 (0.45 to 1.41)	0.426
Renal disease	1.32 (0.91 to 1.94)	0.147
Malignancy	1.24 (0.81 to 1.91)	0.318
Medication		
Statin	0.74 (0.60 to 0.91)	0.004
Antiplatelet		
No antiplatelet	1 (ref)	–
Single antiplatelet	1.00 (0.84 to 1.20)	0.986
Dual antiplatelet	1.27 (0.94 to 1.73)	0.123

Data were obtained from multivariable time-dependent Cox proportional hazards regression model for the development of stroke.
*Adjusted for the covariates listed in this table.
†Stroke within 3 months before or after the diagnosis of MMD. MMD, moyamoya disease.

with statin therapy in both females and males, but statistical significance was identified only in female. When the cut-off age for MMD diagnosis was set at 30, stroke occurred in 76 cases (2.0%) under the age of 30 and 555 cases (5.8%) in those over 30 years of age. Statin therapy had a low incidence of stroke in both age groups, however, the finding did not reach statistical significance in patients <30 years of age. In subgroup analyses according to the presence or absence of concurrent stroke or revascularisation surgery, statin treatment was associated with lower stroke incidence in all groups, but the effects were marginal in all groups.

DISCUSSION

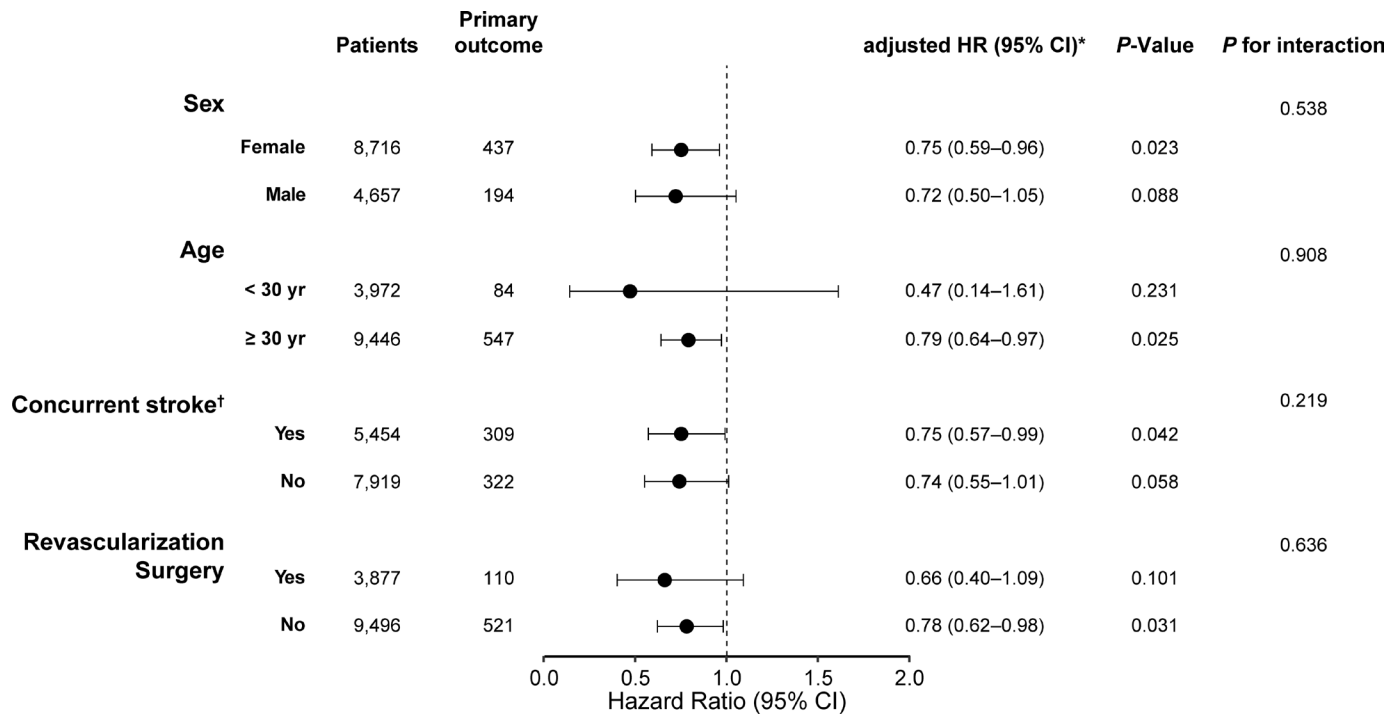
In this nationwide population-based cohort study conducted with 13 373 newly diagnosed patients with MMD followed up for 5.1 ± 3.3 years, statin treatment was associated with a lower incidence of stroke. Patients with MMD who received statin treatment were also at lower risk of all-cause mortality. Regardless of a concurrent stroke at the time of MMD diagnosis and revascularisation surgery, statins tend to be associated with a decreased risk of stroke. Although the proportion of patients who received statin prescriptions increased after diagnosis of MMD, further increase over the mid-20% range was not observed throughout the study period.

The exact pathomechanism of MMD has not yet been fully elucidated but MMD may occur as a consequence of complex interactions of multiple genetic and environmental influences, and statins may play a role in these processes. Patients with MMD have a risk of ischaemic stroke due to the progressive steno-occlusion of the blood vessel and a risk of cerebral haemorrhage caused by the rupture of abnormal collaterals known as ‘moyamoya vessels’.² The observed pathological abnormality in the stenotic segment of the intracranial cerebral artery is primarily fibrocellular thickening of the intima of the endothelium.¹¹ Recently, the Ring finger protein 213 gene (*RNF213*) has been suggested a strong susceptibility gene of MMD.^{21–22} Although the function of the *RNF213* has not been clearly elucidated, the *RNF213* was shown involved in lipotoxicity, inflammation, angiogenesis, nitric oxide-mediated vascular protection and regulation of endothelial integrity.²³ In recent functional studies, the emerging role of *RNF213* in lipid metabolism by mediating lipid droplet formation, fat storage and lipotoxicity, which may be a link between the pathogenesis of MMD and lipid metabolism, was emphasised.^{24–25} Statins are involved in lipid metabolism through several molecular pathways and effectively reduce low-density lipoprotein cholesterol (LDL-C). In a case-control study of 138 patients with MMD, dyslipidaemia was identified a modifiable risk factor, indicating the role of *RNF213* mutation in fat metabolism may contribute to pathogenesis of MMD.²⁴ In a study including patients with asymptomatic MMD, dyslipidaemia was reported a major risk factor for stroke.²⁶ The Japanese guidelines for MMD suggest

Table 3 Risk of all-cause mortality, ischaemic and haemorrhagic stroke according to the statin treatment after diagnosis of MMD

Outcome	Haemorrhagic stroke	Ischaemic stroke	Death
No of events	458	173	237
Adjusted HR (95% CI)* for statin treatment, p value	0.74 (0.58 to 0.95), 0.018	0.75 (0.52 to 1.08), 0.124	0.47 (0.33 to 0.67), <0.001

Data were obtained from multivariable time-dependent Cox proportional hazard regression models for each outcome. When a competing event occurred, the subject was censored at that time.
*Adjusted for the covariates listed in table 2.
MMD, moyamoya disease.



*Adjusted for sex, age, comorbidities, stroke, revascularization, and antiplatelets except variables of interest

†Stroke within 3 months before or after the diagnosis of MMD

Figure 3 Subgroup analyses for the primary outcome based on the statin treatment after diagnosis of MMD. MMD, moyamoya disease.

that treatment with lipid-lowering agents is reasonable in patients with MMD with concurrent dyslipidaemia.²⁷

In patients with MMD, various circulating proinflammatory molecules and angiogenic factors are involved in the formation of moyamoya vessels by causing endothelial proliferation, intimal thickening, smooth muscle cell migration and matrix accumulation.²⁸ Therefore, controlling the inflammatory and pathogenic cascade could be a possible target in the treatment of MMD.²⁹ Experimental and clinical evidence has shown that statins exert various vasculoprotective effects on immunomodulatory, anti-inflammatory and antioxidant properties independent of their LDL-C-lowering effects.³⁰ Statins increase the bioavailability of nitric oxide, promote re-endothelialisation, reduce oxidative stress and suppress CD40 expression and nuclear factor (NF)- κ B activation, which inhibit the inflammatory response.³¹ Statins also modulate hypoxia-induced endothelial proliferation, formation of reactive oxygen species and the angiogenesis signalling pathway.³² We hypothesised that a wide range of the vasculoprotective functions of statins, many of which are associated with attenuation of chronic vascular inflammation, could be effective in the prevention of future stroke and treatment of MMD. In addition, in a recent study of 106 patients with MMD, statin was effective in collateral formation after revascularisation surgery.³³ In a recent study, cilostazol was reportedly associated with improved survival in patients with MMD.¹⁴ In addition, cilostazol has been reported effective in

improving cerebral perfusion in patients with MMD.³⁴ A main beneficial mechanism of cilostazol is the pleiotropic effect involved in endothelial nitric oxide synthase,³⁵ an effect exerted by statins.

In the present study, statins were associated with a lower incidence of haemorrhagic stroke in patients with MMD who are at high risk of haemorrhagic stroke due to their vulnerable moyamoya vessels. In addition, haemorrhagic stroke occurred more frequently than ischaemic stroke in the present study. When rebleeding occurs in patients with MMD with prior haemorrhagic stroke, the prognosis is very poor.³⁶ In patients with MMD, increased proinflammatory molecules, such as vascular endothelial growth factor and matrix metalloproteinase-9, play essential roles in vascular fragility, leakage of the blood–brain barrier and abnormal vasculogenesis, which are involved in the development of haemorrhagic stroke.^{21 28 37} Statin therapy can inhibit the expression of the proinflammatory molecules,³⁸ which may contribute to the reduction of haemorrhagic stroke, a critical complication in patients with MMD. A major reason for the reluctance of statin therapy in clinical practice is the concern that statins may increase the risk of cerebral haemorrhage. However, conclusive evidence that statins increase the risk of haemorrhagic stroke does not exist.³⁹ The results of the present study indicate statins may protect against haemorrhagic stroke in patients with MMD, and statins can at least be used relatively safely in patients with MMD at increased risk of haemorrhagic stroke. On the other hand, in the



case of ischaemic stroke, the use of statin had no statistical significance in the reduction of ischaemic stroke. This may be somewhat surprising given the well-known effects of statins on ischaemic stroke. The finding may be due to the lack of statistical power with not enough outcomes compared with haemorrhagic stroke in patients with MMD, but additional research is needed in the future.

In the subgroup analyses, the effects of statins tended to be associated with lower primary outcomes in all subgroups, but it showed marginal tendency without statistical significance in several subgroups. We think that this is because the number of outcomes that occurred in each subgroup is insufficient to be displayed as a meaningful number when divided into subgroups. In the group over 30 years of age, the occurrence of primary outcome was more frequent, and the effect of statin was also statistically significant. In older age groups, more prevalent vascular risk factors may be associated with more outcomes,⁴⁰ which may have made the effect of statins more pronounced. The relationship between statin and the lower primary outcome showed a similar trend regardless of the presence or absence of concurrent stroke or revascularisation surgery. Because the interaction between each group was not observed, these results suggest that the use of statins would have a similar effect in most patients with MMD.

The present study had several strengths and limitations. Because a nationwide cohort was used, the relationship between statin therapy and the long-term prognosis could be investigated in a relatively large number of patients with MMD (>10 000), a rare disease. The dataset of the National Health Insurance Service provides high-quality longitudinal data on statin prescription and clinical outcomes of patients with MMD. However, this was a retrospective analysis of prospectively enrolled data, and biases may have existed with uncollected confounders. Genetic factors have been proposed as major aetiologic factors of MMD, and only Korean subjects were included in the present study. Therefore, caution is needed in generalising the results of this study. Due to the limitation of claims-based study, detailed clinical information of individual patients and the indications of why patients received statins were not available. In addition, because it was not possible to collect the lipid profile of an individual patient due to a lack of data in the healthcare claims database, we could not analyse the difference in the effect of statins according to the lipid profile. It should be taken into account that underlying dyslipidaemia, common indication of statins, could be acted as a confounding factor. On the other hand, regarding that those with dyslipidaemia have a higher cardiovascular risk, the protective effect of statins might be greater than that reported in this study. We selected patients with MMD based on health claims data. Clinically, a case of bilateral distal ICA stenosis due to severe atherosclerosis may be confused with MMD. To reduce the possibility of misclassification/inclusion of non-MMD patients, the rare disease code was used and patients with a previous cardiovascular history were excluded. Several previous studies have been published

in which the same criteria have been used with the ICD-10 codes for MMD and the special code based on the health claims data in Korea.^{14–16} There was no significant interaction between statins and surgical revascularisation, a procedure generally not recommended for intracranial cerebral atherosclerosis and selectively performed for patients with MMD. However, despite the strengths of this study, there are fundamental limitations as a retrospective observational study, so the results of this study should be reconfirmed through a randomised controlled trial in the future.

CONCLUSIONS

In this nationwide cohort study, statin therapy was associated with lower incidence of stroke in newly diagnosed patients with MMD. Although statins are not commonly used in patients with MMD, statins may be a useful treatment option for the prevention of stroke in patients with MMD. The potential effects of statins demonstrated in this study should be further confirmed in prospective studies.

Contributors JY and JK: conception and design. JJ and JK: acquisition of data. JY, JJ, MB, and JK: analysis and interpretation of data. JY: drafting the article. All authors critically revising the article and approved the final version of the manuscript. JK: study supervision and is responsible for the overall content as guarantor.

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Competing interests JY and JK report research grants from Chong Kun Dang pharmaceutical.

Patient consent for publication Not applicable.

Ethics approval The Institutional Review Board of Yongin Severance Hospital, Yonsei University College of Medicine (9-2021-0120) approved this study. Because retrospective analyses were performed using fully anonymized data in the present study, the requirement for informed consent was waived.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The dataset used in this study is accessible from HIRA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data are only available on reasonable request of investigators for academic or political purposes and permission from the inquiry committee of research support in HIRA (<https://opendata.hira.or.kr/orb/useGdInfo.do>).

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