



**AALBORG UNIVERSITY**  
DENMARK

**Aalborg Universitet**

## **Long-term stroke risk in moyamoya disease**

Birkeland, Peter; Hansen, Victoria; Tharmabalan, Vinosha; Lauritsen, Jens; Nielsen, Troels; Truelsen, Thomas; Rosenbaum, Sverre; von Weitzel-Mudersbach, Paul

*Published in:*  
International Journal of Stroke

*DOI (link to publication from Publisher):*  
[10.1177/17474930231216037](https://doi.org/10.1177/17474930231216037)

*Creative Commons License*  
CC BY-NC-ND 4.0

*Publication date:*  
2023

*Document Version*  
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*  
Birkeland, P., Hansen, V., Tharmabalan, V., Lauritsen, J., Nielsen, T., Truelsen, T., Rosenbaum, S., & von Weitzel-Mudersbach, P. (2023). Long-term stroke risk in moyamoya disease. *International Journal of Stroke*. Advance online publication. <https://doi.org/10.1177/17474930231216037>

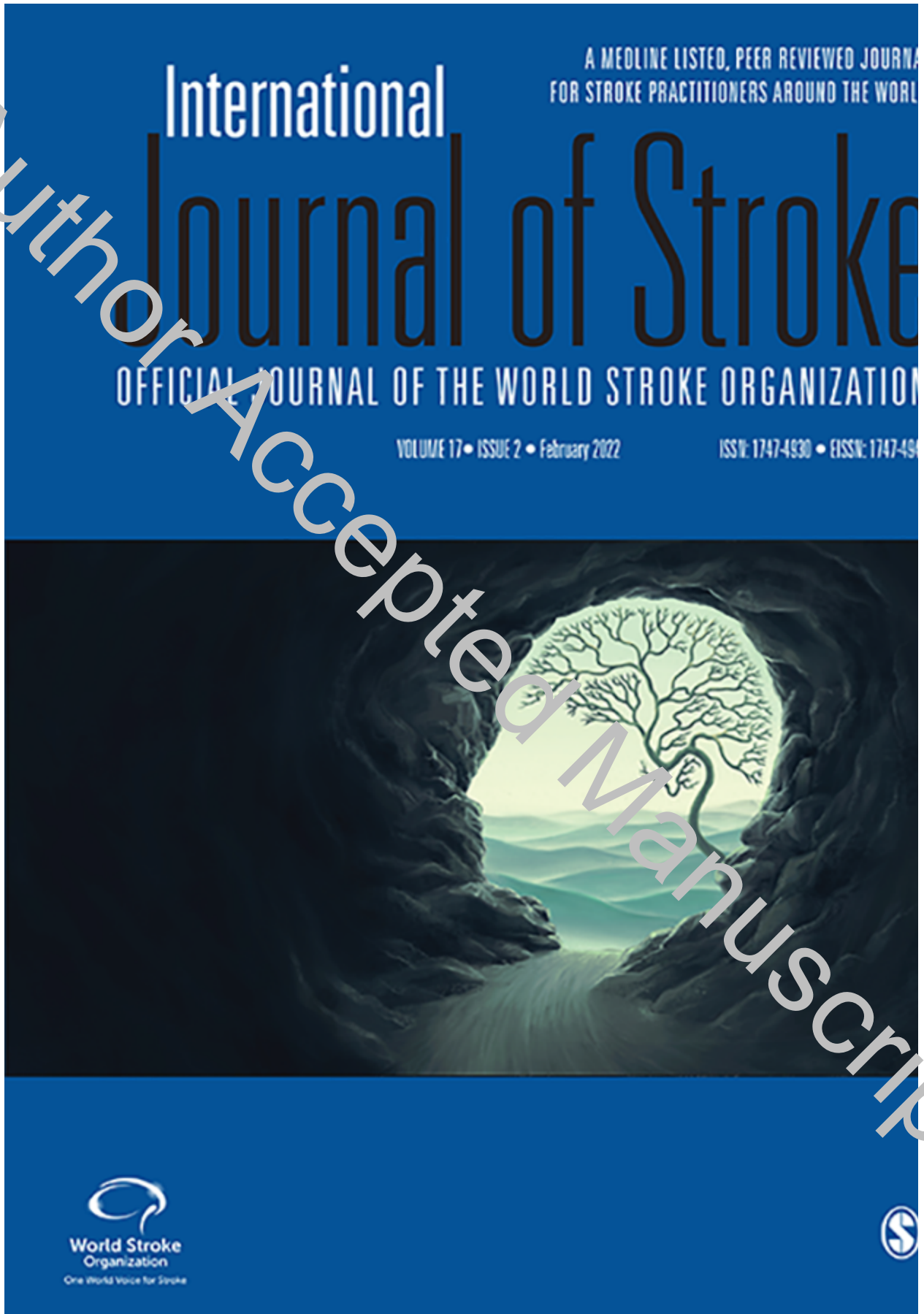
### **General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

### **Take down policy**

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.



### Long-term stroke risk in moyamoya disease

Journal:	<i>International Journal of Stroke</i>
Manuscript ID	IJS-10-23-11453
Manuscript Type:	Research
Date Submitted by the Author:	15-Oct-2023
Complete List of Authors:	Birkeland, Peter; Rigshospitalet, Department of Neurosurgery Hansen, Victoria; Aalborg University Hospital, Department of Neurology Tharmabalan, Vinosha; Rigshospitalet, Department of Neurosurgery Lauritsen, Jens; University of Southern Denmark, Department of Orthopaedic Surgery Nielsen, Troels; University of Southern Denmark, Department of Neurosurgery Truelsen, Thomas; University Hospital of Copenhagen Rigshospitalet, Stroke Center Rigshospitalet; University of Copenhagen Faculty of Health Sciences Rosenkum, Sverre; Bispebjerg Hospital, Department of Neurology von Weitzel, Mundersbach, Paul ; Aarhus University Hospital, Department of Neurology
Keywords:	Cerebral hemorrhage, Cerebral Infarction, Stroke, Chronic disease, Epidemiology, Vascular events

SCHOLARONE™  
Manuscripts

## LONG-TERM STROKE RISK IN MOYAMOYA DISEASE

Peter Birkeland MD<sup>1\*</sup>, Victoria Hansen MD<sup>2</sup>, Vinosha Tharmabalan MD<sup>1</sup>, Jens Lauritsen MD, PhD<sup>3,4</sup>, Troels Nielsen MD, PhD<sup>5</sup>, Thomas Truelsén MD, PhD<sup>6</sup>, Sverre Rosenbaum MD<sup>7</sup>, Paul von Weitzel-Mudersbach MD, PhD<sup>8</sup>

<sup>1</sup>Department of Neurosurgery, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 København Ø, Denmark. E-mail: Peter@Birkeland.dk (*corresponding author*)

<sup>2</sup>Department of Neurology, Aalborg University Hospital, Hobrovej 18 - 22, DK-9100 Aalborg, Denmark

<sup>3</sup>Department of Orthopaedic Surgery, Odense University Hospital, Sdr. Boulevard 29. DK-5000 Odense, Denmark

<sup>4</sup>Department of Clinical Research, University of Southern Denmark, Denmark

<sup>5</sup>Department of Neurosurgery, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark

<sup>6</sup>Department of Neurology, Copenhagen University Hospital, Blegdamsvej 9. DK-2100 København Ø, Denmark

<sup>7</sup>Department of Neurology, Bispebjerg Hospital, Bispebjerg Bakke 23, DK- 2400 København, Denmark

<sup>8</sup>Department of Neurology, The Danish Stroke Center, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark

Keywords: moyamoya disease, long-term, stroke risk

Word count: 4,175

This manuscript includes two tables and four figures

## ABSTRACT

### Background

Moyamoya disease is considered a progressive disease with an ongoing risk of recurrent stroke. However, there is a lack of long-term observational data to quantify the extent of the stroke risk.

### Methods

This study aimed to provide insight into the long-term stroke risk in MMD and explore possible risk factors for stroke. Records from all patients diagnosed with MMD in 13 clinical departments from six different Danish hospitals between 1994 and 2017 were retrospectively reviewed until 2021.

### Results

The cohort comprised 50 patients (33 females and 17 males). Patients were followed up for a median of 9.4 years, with more than 10 years of follow-up for 24 patients. Ten patients had 11 new stroke events - 6 ischemic strokes and 5 brain hemorrhages. Events occurred at a median of 7 years and up to 25 years after diagnosis. The overall Kaplan-Meier 5-year stroke risk was 10%. Patients with bypass performed had significantly fewer events than conservatively treated patients (HR 0.25, 95% CI 0.07 - 0.91,  $p < 0.05$ ). All but one event occurred in females, a difference that reached statistical significance.

### Conclusions

The study provides data on the extent of the risk of recurrent stroke in MMD. Bypass surgery patients had fewer stroke events than those treated conservatively. There was a trend toward a higher stroke risk in females.

### Data access statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

## INTRODUCTION

Moyamoya disease (MMD) is a rare idiopathic steno occlusive cerebrovascular disease affecting the distal intracranial internal carotid artery or its proximal branches with a network of basal collaterals [1]. The disease was formerly almost exclusively associated with East Asia but is now known to occur worldwide. The highest incidence is in Japan, i.e., 0.94 per 100,000 person-years [2,3]. Characteristically, the disease either presents in childhood or young middle age [3]. It is almost twice as common in females as in males; a few studies have suggested a more aggressive disease course in females [4,5].

Clinical events include ischemic stroke caused by narrowed vessels and hemorrhage from rupture of fragile collaterals. MMD is considered a progressive disease with a continued significant risk of recurrent stroke. However, there is a lack of observational data on long-term natural history to support this [6, 7], presumably because such data are hard to collect.

Bypass surgery is performed to prevent stroke and alter the disease course [1], although its long-term durability and overall impact in preventing ischemic stroke have never been demonstrated [8]. Neither can we predict the prognosis for an individual patient and, on this basis, balance the natural risk with the risk of bypass surgery [7]. A working group under the European Stroke Organisation (ESO) recently published guidelines for managing MMD, addressing many of these open clinical issues [9]. A particular case we have encountered is a patient referred for surgical evaluation years after a single event. If, contrary to current thinking, MMD was to enter a stable phase, secondary prevention should be initiated early to be effective, and consequently, this patient might not benefit from surgery.

In a previous study, we identified a cohort of patients with MMD diagnosed between 1994 and 2017 [10]. During this time, understanding of MMD and indications for surgery markedly improved with the establishment of collaborations between interested clinicians [11]. Consequently, our cohort is a case mix of operated and conservatively treated patients with an extended follow-up - of which most patients would likely have been offered surgery by today's standard. This gives a unique opportunity to look into the natural history of the disease, investigate the long-term course after bypass surgery, and identify clinical risk factors for subsequent stroke.

## METHODS

### The cohort population

The cohort was established as previously described [10]. Briefly, all patients diagnosed with MMD (n=675) between 1994 and 2017 were identified in the Danish National Patient Register, which covers all hospital discharges and visits to outpatient clinics in Denmark [12]. Clinical notes, clinic letters, and radiology reports from 13 clinical departments from six different Danish hospitals were reviewed. The diagnosis was validated according to the definition of MMD stated by the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya disease) in Japan [13]. We did a pooled analysis of patients with probable (pMMD) and definite MMD (dMMD). We reviewed all collected data up to 15 March 2021 to ensure that the previous diagnosis of MMD could be maintained. The following features were recorded: age at diagnosis, sex, race, MMD type (pMMD or dMMD), and initial clinical presentation (TIA, ischemic stroke, brain hemorrhage, seizures, headache, other presentation, asymptomatic). TIA, i.e., transient ischemic attack, was defined as neurological deficits of presumed vascular origin resolving within 24 hours.

### Study timeline

This was a retrospective cohort study. Subjects were included at the date of the first angiography fulfilling the diagnostic criteria for MMD and were followed up to 15 March 2021 or death.

### Medical management and revascularisation surgery

We recorded the date, type (direct or indirect), and side of the surgical revascularisation procedure if applicable. We also noted if patients were on antiplatelet medication.

### Perioperative complications

Perioperative complications, i.e., events occurring within 30 days of surgery, were recorded separately and not included in events due to MMD per se.

### Events

Stroke events (neurological deficits lasting 24 hours or longer or sudden onset headache) were recorded from the clinical notes and categorized as ischemic stroke or brain hemorrhage based on the results of brain imaging (computed tomography or magnetic resonance imaging). Brain hemorrhage included intracerebral hemorrhage, subarachnoid hemorrhage, and intraventricular

hemorrhage. Patients with stroke during follow-up were assigned a modified Rankin score (mRS) based on a structured phone interview [14].

### **Statistical analysis**

Data were collected on data sheets using the EpiData Entry Software (www.epidata.dk; The EpiData Association). The chi-square test was used to test for association between baseline characteristics. Follow-up was defined as the time from angiographic diagnosis to the time of the first event or until 15 March 2021. Multiple events were not included. Kaplan–Meier survival analysis was performed using EpiData Analysis software (www.epidata.dk). Differences in hazard are shown as hazard rate (HR) and 95% confidence interval (CI) with a p-value for the log-rank test of homogeneity among groups. A level of 5% was considered statistically significant.

### **Standard Protocol Approvals, Registration, and Patient Consents**

The Danish Patient Safety Authority (ref. no. 3-3013-1699/1 and ref. no. 3-3013-1699/2) and The Capital Region of Denmark (ref. no. P-1016187) approved the study. Patient consent was not required.

### **Data Availability Statement**

The data supporting this study's findings are available from the corresponding author upon reasonable request.

### **Conflicts of Interest Statement**

The authors have nothing to disclose.

### **Funding Statement**

This research received no external funding.



## RESULTS

### Characteristics of the cohort

One patient from the original cohort was eventually diagnosed with ACTA 2 gene mutation, and another with neurofibromatosis type 1. Both patients were excluded from further analysis. That left us with 50 patients for retrospective follow-up. The baseline characteristics of the cohort are summarized in Table 1.

### Medical and surgical management

Sixteen patients were treated conservatively, while thirty-four underwent bypass surgery. Sex and clinical presentation were not significantly different between groups, but there were more pediatric patients and patients of East Asian origin in the bypass group (table 1). Among those conservatively treated, bypass surgery was not found to be indicated in six patients due to a lack of ongoing symptoms and, in one case, after the vascular neurosurgeon reviewed the angiogram and in another case because of a normal positron emission tomography with acetazolamide challenge. For four other patients, we did not find clinical notes indicating that bypass surgery was even considered. Four patients declined surgery. The decision to proceed to bypass surgery was determined jointly between the referring neurologist and the vascular neurosurgeon. The most common indication for surgery was a previous cerebrovascular event (table 1). In one of thirty-four patients having bypass surgery, a bypass was only considered after a second stroke. Most surgical procedures were performed in international centers, i.e., outside Denmark. The median time from diagnosis to first bypass was 116 days (range 5 - 8401 days). The preoperative radiological studies were not available for review in two cases; however, postoperative angiography could ascertain the diagnoses in both cases. Patients were first operated on in the symptomatic hemisphere. Twenty-six (76%) were direct or combined bypasses, and eight (24%) were indirect. There were no reports of bypass occlusion. In two cases, perioperative complications to surgery were recorded, i.e., a subdural hematoma and an ischemic stroke in one patient and an intracerebral hemorrhage in another patient. 25 patients had additional bypass(es) performed. Twenty-six patients were on aspirin, five on clopidogrel, and six on both. Among surgically treated patients, twenty-two patients were on aspirin, three on clopidogrel, and three on both. Aspirin and clopidogrel were generally administered at a dose of 75 mg o.d.

## Events

During a follow-up of 507 person-years (median: 9 years; range: 0.10 to 29.0 years), 11 events - 6 ischemic strokes and 5 brain hemorrhages - occurred in 10 adult patients (Table 2 and Figure 1). One patient had two ischemic strokes. Subsequent events occurred at a median of 7 years and up to 25 years after diagnosis. Three patients in the bypass group had new events. One patient - diagnosed as an infant and had bilateral combined bypasses performed - had an ischemic stroke in the territory of the left middle cerebral artery almost 25 years later. Another patient was diagnosed with MMD and had a direct bypass after presenting with a headache. Two and a half years later, the patient had a fatal hemorrhage a few days after stenting of a contralateral stenotic extracranial internal carotid artery. The third patient had recurrent bleeding 2.5 years after diagnosis of MMD and an indirect bypass at the exact location. Seven patients in the conservatively-treated group had a new stroke. Three patients had a brain hemorrhage 1 y, 17 y, and 18 years after diagnosis. The first crossed over to have bypasses performed after recurrent bleeding, and the second was on dual platelets. Four patients had ischemic strokes one month, 1.5 y, 11.5 y, and 14.5 y after diagnosis. 11 patients initially presented with a brain hemorrhage. Of these, 4 (36%) developed a new stroke event during observation (3 brain hemorrhages and one ischemic stroke). The overall Kaplan-Meier 5-year stroke risk was 10%.

## Subgroup analyses

We performed subgroup analyses based on race (figure 2), sex (figure 3), and bypass status (figure 4). Two patients of East Asian origin had a stroke during follow-up, accounting for two of three events in the bypass group, but the difference did not reach a statistical significance. Noteworthy, 7 of 8 East Asian patients had bypass performed, pointing at bypass status as a confounder. Patients with bypass performed had significantly fewer events than conservatively treated patients (HR 0.25, 95% CI 0.07 - 0.91,  $p < 0.05$ ). There was a significant difference between the sexes; all but one subsequent event occurred in females (HR 4.02, 95% CI 1.11 - 14.49,  $p < 0.05$ ). The Kaplan-Meier 5-year stroke risks were 6% and 18% in operated and conservatively treated patients, respectively, while the risks were 6% and 12% in males and females, respectively.

## DISCUSSION

In this retrospective cohort study, we have used a real-world case mix of operated and conservatively treated patients to provide insight into the long-term stroke risk in MMD and explore possible risk factors.

### Stroke risk in conservatively treated patients

In an oft-cited German study [15], the 2.75-year Kaplan–Meier risk of stroke after angiographic diagnosis was 32.5% among ten conservatively treated patients. In a North American study [16], the 5-year Kaplan–Meier risk of ipsilateral stroke was 27% among 20 conservatively treated patients. In a French study, Hervé et al. [17] followed 90 initially conservatively treated patients with moyamoya vasculopathy (54 had MMD) for a median of 42.8 months and observed 10 strokes in 8 patients. The Kaplan–Meier 5-year stroke risk in our conservatively treated patients was 18%. The differences in stroke risk may be due to differences in cohort composition and selection criteria for surgery. Little is known about the longer-term natural history of MMD, as few investigators have followed untreated patients with MMD. Among our 16 conservatively treated patients, 4 of 7 events occurred more than ten years after the MMD diagnosis. This result indicates that patients remain at increased stroke risk and that the disease cannot be expected to change to a more benign phase.

### Long-term stroke risk after bypass surgery

Bypass surgery has long been recommended to prevent stroke in symptomatic ischemic MMD, even though no randomized trial has proven its efficacy [18]. On the other hand, a randomized trial from 2014 [19] showed a marginally significant effect of bypass surgery in hemorrhagic MMD with a follow-up of 5 years. Concern has been expressed about whether bypass provides long-term protection against stroke, particularly intracerebral hemorrhage - the most dreaded manifestation of the disease. Kuroda et al. followed up on 93 pediatric and adult patients for over ten years after combined bypass surgery. They observed only one event, a recurrent hemorrhage 9.5 years after surgery [20]. Our cohort's 5-year Kaplan–Meier risk of recurrent stroke after bypass surgery was 6%. Only one event, an ischemic stroke, occurred beyond five years (i.e., after 25 years), suggesting bypass surgery reduces but does not eliminate the risk of stroke in the long term.

### **Risk factors for stroke**

Identifying patients at risk for stroke at an early stage is essential. In our study, 36% of patients presenting with hemorrhage had a recurrent stroke, consistent with previous reports of increased stroke risk in patients with an initial presentation with hemorrhage [19]. Although it has long been known that MMD is more common in females [2,10], it is somewhat surprising that the stroke risk in females was higher than in males. The overall stroke incidence is higher for males, but since females live longer, there is a slight excess in absolute numbers [21]. The difference was only marginally significant, and the finding should be interpreted cautiously. However, two previous studies [4,5] have also reported an increased stroke risk in females.

### **Correlation between clinical presentation, subsequent event, and use of antiplatelets**

Prescription of platelet inhibitors in MMD rests on the assumption that the risk of hemorrhage is negligible without a hemorrhagic presentation. In our study, two patients who did not present with bleeding and were put on antiplatelets had a later hemorrhagic event. In Europe, administering platelet inhibitors in patients without bleeding has long been a clinical practice. At the same time, there has been hesitancy in Asia, partly due to a fear of hemorrhage [22]. However, a recent study from South Korea [23] showing the survival benefit of platelet inhibitors in MMD has paved the way for a practice change in Asia.

### **Can the findings be extrapolated to other populations?**

It remains to be seen whether the findings in our predominantly non-Asian cohort from Denmark can be extrapolated to other non-Asian populations and to what extent the disease course in non-Asian populations differs from that of Asians. In the French study, Hervé et al. suggested that Asian origin was associated with an increased risk of stroke or new brain lesions [17]. A distinct European phenotype has previously been proposed, vaguely characterized by a lower propensity for a hemorrhagic presentation [24, 25]. So far, we have not been able to confirm this [10]. A difference is sought to be caused by genetic factors such as RNF213, but if environmental factors also play a role, the disease course of Asians in Europe will approach that of other Europeans. Two of our East Asian patients were diagnosed with mutations in the RNF213 gene. 7 of 8 East Asian patients in our cohort underwent bypass surgery, and due to confounding, no conclusion can be reached based on our data.

### Strengths and limitations

The strength of this study rests on providing complete long-term follow-up in a nationwide cohort of 50 MMD patients with strict inclusion criteria, including 16 patients treated conservatively. Twenty-four of the patients were followed up for more than 10 years. Currently, the approach to treating MMD is more proactive, so a long-term cohort study with almost 1/3 of conservatively-treated patients is unlikely to be repeated.

There are also some limitations. First, our cohort is a real-world case mix of operated and conservatively treated patients. This introduces a selection bias as the selection for surgery may be confounded by severity. The reasons for choosing a conservative approach may point to lesser disease severity, or, interestingly, all but one conservatively treated patient had been symptomatic, and 62.5% had had a previous stroke. The study period was a transitional phase from MMD being relatively unknown in Denmark to an increased understanding of indications for surgery. Many conservatively treated patients would likely have been referred for surgery by today's standards. Also, the groups were comparable except for more East Asians and pediatric patients among those who had bypass surgery. This arguably reduces but does not eliminate the selection bias. Ultimately, the conservatively treated patients had a significantly higher stroke risk than the bypass group. However, the study did not aim to prove bypass surgery's efficacy. Second, observational studies in conservatively treated patients can only be a substitute for natural history studies. They are subjected to the same selection bias as above, as disease severity may distinguish conservatively treated patients from those referred for surgery. However, long-term natural history studies are not feasible as some patients will invariably be referred for surgery. Third, retrospective data have inherent limitations, but comparable prospective data over so many years will not likely be collated. Fourth, the cohort size is limited to 50 patients, but it is difficult to assemble a large cohort in a primarily non-Asian population. In particular, the subgroup analyses should be interpreted cautiously. Fifth, we may also have underestimated the risk of stroke as some patients may have had events before angiographic diagnosis. Some authors alternatively report stroke risk after the clinical presentation, but this will often be retrospectively confirmed and not easily translated into clinical practice.

**Conclusions**

The study provides evidence for the hitherto assumption of a continued risk of recurrent stroke in MMD. Bypass surgery patients had fewer stroke events than those treated conservatively. There was a trend toward a higher stroke risk in females.

Author Peer Review Accepted Manuscript

## REFERENCES

1. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med* 2009; 360: 1226–1237.
2. Kleinloog R, Regli L, Rinkel GJE et al. Regional differences in incidence and patient characteristics of moyamoya disease: a systematic review. *J Neurol Neurosurg Psychiatry* 2012; 83:521–536.
3. Taba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. *J Neurol Neurosurg Psychiatry* 2008; 79: 900–904.
4. Kuroda S, Uchikawa T, Houkin K et al. Incidence and clinical features of disease progression in adult moyamoya disease. *Stroke* 2005;36:2148–2153.
5. Gross BA, Du R. The natural history of moyamoya in a North American adult cohort. *J Clin Neurosci* 2013;20:44–48.
6. Ahmed SU, Steinberg GK. Long Term Outcomes in the USA. In: Kuroda S (ed). *Moyamoya Disease: Current Knowledge and Future Perspectives*. Singapore: Springer Nature, 2021, pp. 253-264.
7. Ganesan V, Smith ER. Moyamoya: defining current knowledge gaps. *Dev Med Child Neurol* 2015; 57(9):786-7.
8. Kuroda S, Houkin K. Moyamoya disease: current concepts and future perspectives. *Lancet Neurol* 2008;7(11):1056-66.
9. Bersano A, Khan N, Fuentes B et al. European Stroke Organisation (ESO) Guidelines on Moyamoya angiopathy. *Eur Stroke J* 2023;8: 55–84.
10. Birkeland P, Tharmabalan V, Lauritsen J et al. Moyamoya disease in a European setting: A Danish population-based study. *Eur J Neurol* 2020;12:2446-2452.
11. Birkeland P, Lauritsen J. Incidence of moyamoya disease in Denmark: A population-based register study. *Acta Neurochir Suppl* 2018;129:91-93.
12. Schmidt M, Schmidt SA, Sandegaard JL et al. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; 7: 449–490.
13. Hashimoto N, Tominaga T, Miyamoto S et al. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)* 2012; 52: 245–266.

14. Bruno A, Akinwuntan AE, Lin C et al. Simplified Modified Rankin Scale Questionnaire Reproducibility Over the Telephone and Validation With Quality of Life. *Stroke* 2011;42:2276–2279.
15. Kraemer M, Heienbrok W, Berlitz P. Moyamoya disease in Europeans. *Stroke* 2008 39(12):3193–200.
16. Hallemeier CL, Rich KM, Grubb RL et al. Clinical features and outcome in North American adults with moyamoya phenomenon. *Stroke* 2006;37(6):1490–6.
17. Hervy D, Ibos-Augé N, Calvière L et al. Predictors of clinical or cerebral lesion progression in adult moyamoya angiopathy. *Neurology* 2019;93:e388-e397.
18. Fujimura M, Tamura T, Kuroda S et al. 2021 Japanese Guidelines for the Management of Moyamoya Disease: Guidelines from the Research Committee on Moyamoya Disease and Japan Stroke Society. *Neurol Med Chir (Tokyo)* 2022;62:165-170.
19. Miyamoto S, Yoshimoto T, Hashimoto N et al. Effects of Extracranial–Intracranial Bypass for Patients With Hemorrhagic Moyamoya Disease. *Stroke* 2014;45:1415-1421.
20. Kuroda S, Nakayama N, Yamamoto S et al. Late (5-20 years) outcomes after STA-MCA anastomosis and encephalo-duro-myoarterio-pericranial synangiosis in patients with moyamoya disease. *J Neurosurg* 2020:1–8.
21. Rexrode KM, Madsen TE, Yu A YX et al. The Impact of Sex and Gender on Stroke. *Circ Res* 2022;130:512–528.
22. Kraemer, M, Berlitz, P, Diesner et al. What is the experts' opinion on antiplatelet therapy in moyamoya disease? Results of a worldwide Survey. *Eur J Neurol* 2012; 19:163–167.
23. Seo WK, Kim JY, Choi EH et al. Association of Antiplatelet Therapy Including Cilostazol, With Improved Survival in Patients With Moyamoya Disease in a Nationwide Study. *J Am Heart Assoc* 2021;10:e017701.
24. Hever P, Alamri A, Tolias C. Moyamoya angiopathy - is there a western phenotype? *Br J Neurosurg* 2015; 29:765–771.
25. Acker G, Goerdes S, Schneider UC et al. Distinct clinical and radiographic characteristics of moyamoya disease amongst European Caucasians. *Eur J Neurol* 2015; 22: 1012–1017.



TABLE 1

## Baseline characteristics of the cohort

	bypass patients (n=34)	conservatively treated patients (n=16)	p value
<b>Age at diagnosis (years)</b>			
<b>0 -18</b>	14	2	
<b>≥18</b>	20	14	p=0.04
<b>Sex</b>			
<b>Female</b>	22	11	
<b>Male</b>	12	5	p>0.05
<b>Race</b>			
<b>Caucasian</b>	27	15	
<b>East Asian</b>	7	1	p>0.05
<b>Initial presentation</b>			
<b>TIA</b>	6	1	
<b>Ischemic stroke</b>	13	4	
<b>Brain hemorrhage</b>	5	6	
<b>Seizures</b>	2	0	
<b>Headache</b>	6	2	
<b>Other</b>	2	2	
<b>Asymptomatic</b>	0	1	p>0.05*
<b>MMD type</b>			
<b>pMMD</b>	13	11	
<b>dMMD</b>	21	5	p>0.05

\* stroke vs. other presentation

TABLE 2

## Characteristics of patients with stroke during follow-up

	Sex	Age at presentation (years)	Type of presentation	Platelet inhibitor	Bypass status	Type of stroke during f/u	Age at stroke during f/u (years)	mRS at latest f/u
patient 1	F	30	seizures	aspirin	yes	ischemic	25	3
patient 2	F	47	incidental finding	aspirin, CLO	no	SAH	64	0
patient 3	F	32	headache	no	no	ischaemic	43	6
patient 4	F	47	hemorrhage	no	no	hemorrhage	64	4
patient 5	F	32	other	CLO	no	ischemic	33	UK
patient 6*	F	65	TIA	aspirin, CLO	no	ischemic ischemic	65 69	3
patient 7	M	41	headache**	aspirin, CLO	yes	hemorrhage	43	6
patient 8	F	49	hemorrhage	aspirin	no***	hemorrhage	50	5
patient 9	F	37	hemorrhage	no	yes	hemorrhage	40	1
patient 10	F	38	hemorrhage	no	no	ischaemic	52	6****

## Abbreviations

f/u: follow-up, mRS: modified Rankin score, CLO: clopidogrel, SAH: subarachnoid hemorrhage, UK: unknown

## Notes

- \* Patient 6 had two strokes during follow-up
- \*\* Computed tomography was consistent with recent infarction
- \*\*\* This patient had bypass surgery after the second stroke
- \*\*\*\* Died of another cause

## FIGURE LEGENDS

Figure 1: Kaplan-Meier plot of the overall time to first stroke after diagnosis in the cohort

Figure 2: Kaplan-Meier plot of time to first stroke after diagnosis according to sex (females - blue, males - red)

Figure 3: Kaplan-Meier plot of time to first stroke after diagnosis according to bypass status (bypass - blue, no bypass - red)

Figure 4: Kaplan-Meier plot of time to first stroke after diagnosis according to race (Asians blue, non-Asian - red)

Figure 1

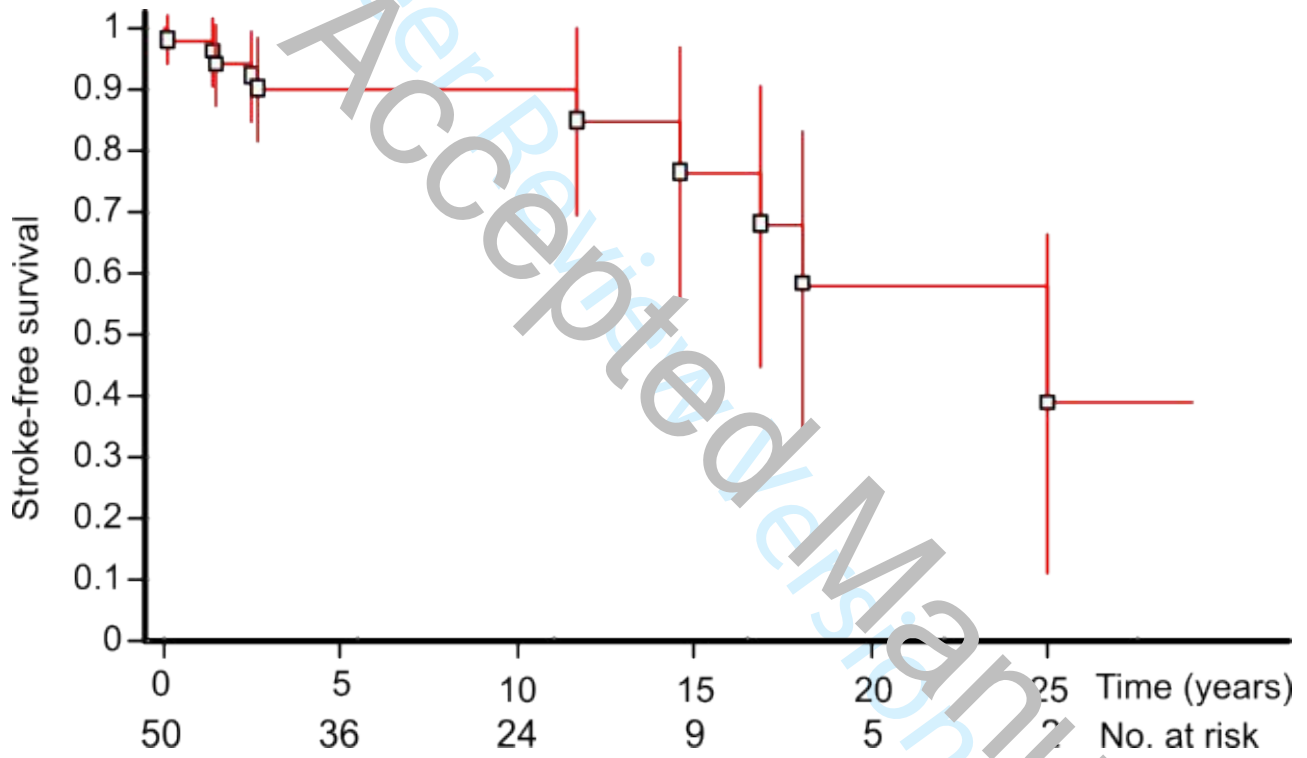


Figure 2

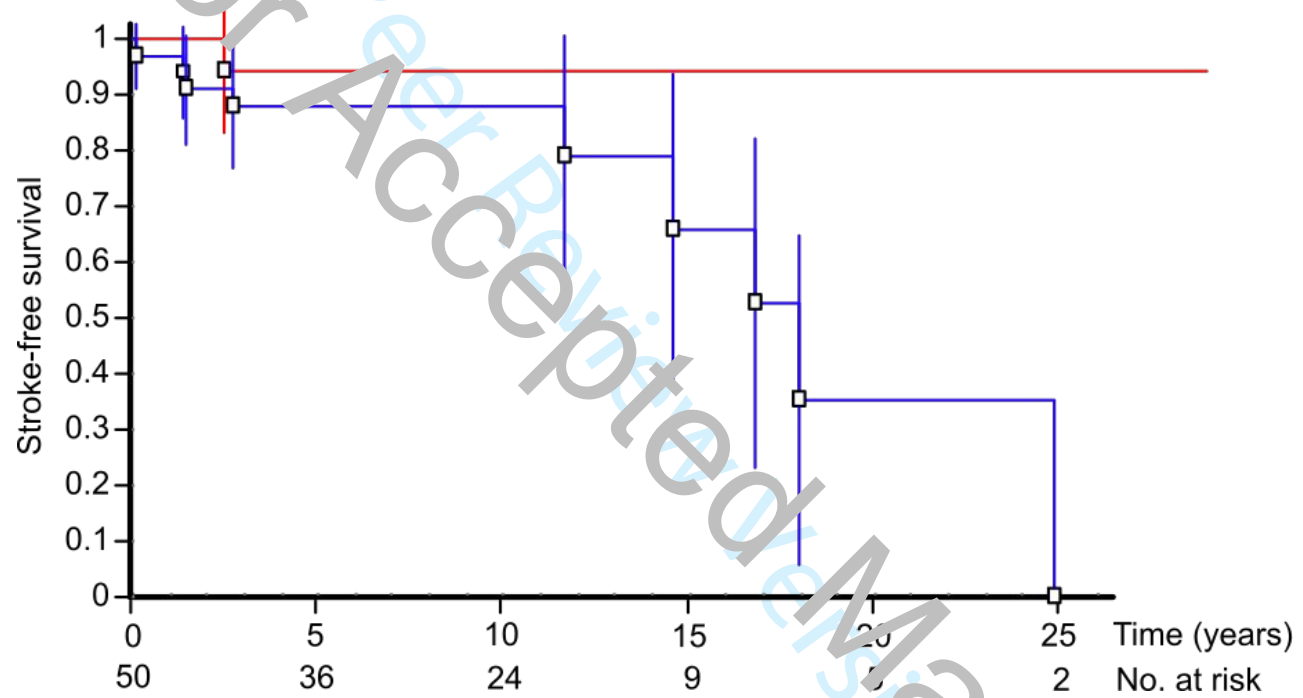


Figure 3

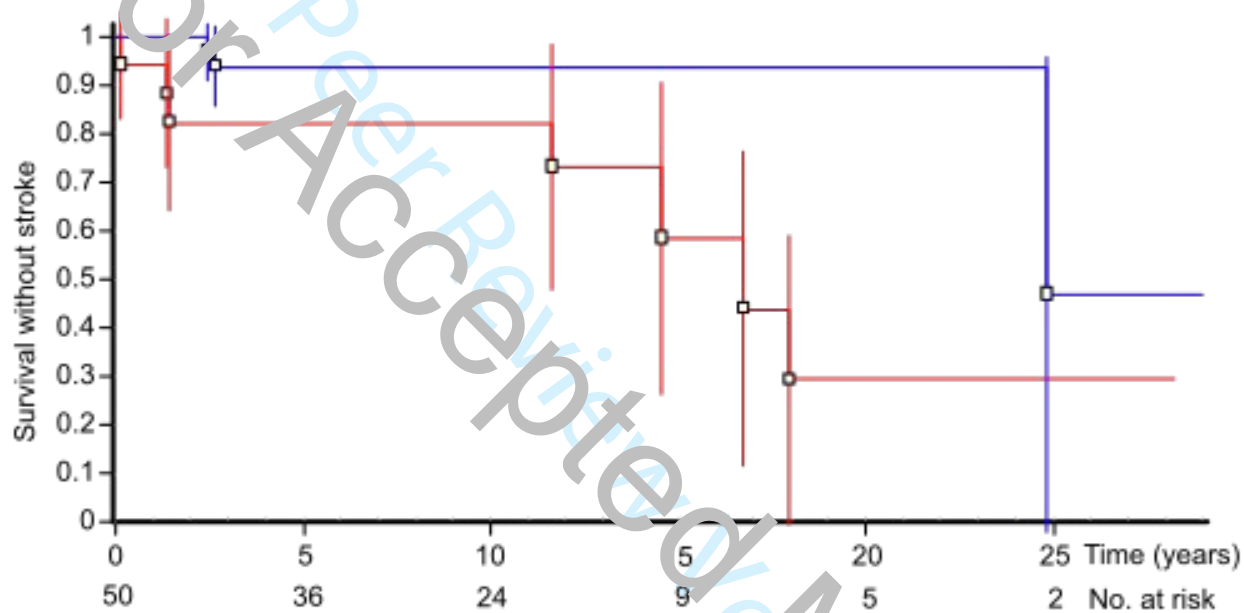


Figure 4

