Atorvastatin augments collateral formation and functional recovery after indirect revascularization in adult ischemic moyamoya disease: A randomized trial

DAWEI WANG[1], JINGYA DAI[2], SHUMEI LI[3], YAPING LIU[4], XIAOFENG XING[5], LEI HUANG[1] and QIJUN PANG[1]

[1]Department of Neurosurgical Trauma I, Cangzhou Central Hospital, Cangzhou, Hebei 061000, P.R. China; [2]Administration Office, Cangzhou Central Hospital, Cangzhou, Hebei 061000, P.R. China; [3]Department of Gynecological Oncology Surgery III, Cangzhou Central Hospital, Cangzhou, Hebei 061000, P.R. China; [4]Anesthesia Medicine Center, Cangzhou Central Hospital, Cangzhou, Hebei 061000, P.R. China; [5]Department of Cerebrovascular Surgery IV, Cangzhou Central Hospital, Cangzhou, Hebei 061000, P.R. China

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Abstract. The present study aimed to assess whether atorvastatin enhances indirect revascularization outcomes in adult ischemic moyamoya disease (MMD). In a randomized trial, 80 adults received postoperative atorvastatin (20 mg/day, n=40) or standard care (n=40); the primary outcome was good neovascularization (Matsushima grade, Good) at 6 months. The results revealed that good neovascularization was higher with atorvastatin (65.0 vs. 37.5%; risk ratio, 1.73; P=0.014). In addition, the atorvastatin group exhibited greater improvement in cerebral blood flow (mean difference, 4.3 ml/100 g/min; P<0.001) and functional outcome (72.5 vs. 50.0% with modified Rankin Scale improvement; P=0.039). Ischemic event recurrence was also lower in the atorvastatin group (2.5 vs. 12.5%; P=0.201), whereas safety profiles were similar. In conclusion, the present single-center randomized trial provides preliminary evidence that adjunctive atorvastatin may improve collateral formation, cerebral perfusion and functional status after indirect revascularization in adult ischemic MMD. Large-scale multi-center studies are warranted to validate these findings. This trial was registered in the Chinese Clinical Trial Registry as trail no. ChiCTR1800016363, on June 3, 2018.

Correspondence to: Dr Dawei Wang, Department of Neurosurgical Trauma I, Cangzhou Central Hospital, 16 Xinhua West Road, Yunhe, Cangzhou, Hebei 061000, P.R. China
E-mail: wangdw_120@163.com

Abbreviations: MMD, moyamoya disease; DSA, digital subtraction angiography; CTP, computed tomography perfusion; CBF, cerebral blood flow; MTT, mean transit time; mRS, modified Rankin Scale; TIA, transient ischemic attack; RR, risk ratio; CI, confidence interval; aOR, adjusted odds ratio; EDAS, encephaloduroarteriosynangiosis

Key words: MMD, atorvastatin, indirect revascularization, neovascularization, cerebral ischemia

Introduction

Moyamoya disease (MMD) is a rare, chronic and progressive cerebrovascular occlusive disorder of unknown etiology. MMD is characterized by bilateral stenosis or occlusion of the terminal portions of the internal carotid arteries and the proximal anterior and middle cerebral arteries, accompanied by the formation of a fragile collateral network at the base of the brain, the so-called 'moyamoya' (meaning 'puff of smoke' in Japanese) vessels (1,2). The disease has a bimodal age distribution, with peaks in childhood and in adults in their fourth decade, and exhibits a notable predominance in East Asian populations (3,4). Clinically, MMD manifests primarily as cerebral ischemia in children and adults <40 years old, whereas intracranial hemorrhage becomes more common in older adults (5). In adult patients with the ischemic phenotype, the persistent hypoperfusion leads to transient ischemic attacks (TIAs) or cerebral infarctions, resulting in the accumulation of neurological deficits, cognitive decline and a notable deterioration in quality of life, posing a substantial burden on individuals, families and society (6,7). Currently, there are no effective pharmacological treatments to halt or reverse the underlying pathological progression of MMD. The mainstay of management is revascularization surgery, which aims to augment cerebral blood flow by establishing collateral pathways from the external carotid circulation (8,9). Indirect revascularization techniques, such as encephaloduroarteriosynangiosis (EDAS), are widely employed, particularly for pediatric patients and in cases where direct anastomosis is technically challenging (10). This procedure involves placing vascularized tissues from the scalp or dura onto the ischemic brain surface, inducing a natural and gradual neovascularization response over weeks to months. Compared with direct bypass, indirect revascularization offers advantages including relative technical simplicity, shorter operative time, lower risk of perioperative hyperperfusion syndrome, and a more tempered, self-regulating blood supply restoration (11,12).

Nevertheless, the therapeutic efficacy of indirect revascularization is entirely dependent on postoperative *de novo* collateral formation, as this procedure provides no immediate blood

flow restoration unlike direct bypass. A substantial number of adult patients fail to develop adequate collateral circulation, which perpetuates the risk of ischemic events (13,14). This limitation highlights the urgent need for adjuvant strategies to enhance surgical neovascularization, the core determinant of indirect revascularization efficacy. The pathogenesis of MMD, which involves inflammatory dysregulation and impaired vascular remodeling, provides a compelling rationale for the use of atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) conventionally indicated for hypercholesterolemia and atherosclerotic cardio-cerebrovascular disease prevention (15,16). Beyond its lipid-lowering properties, atorvastatin exhibits pleiotropic effects, including endothelial protection, anti-inflammatory action and the promotion of functional angiogenesis, which are theoretically synergistic with indirect revascularization (17-20). Large-scale clinical studies have confirmed that good neovascularization (Matsushima grade, Good) after indirect revascularization is an independent predictor of reduced long-term ischemic event risk in adult MMD (12,14). Although some evidence has suggested that statins may improve collateral circulation in ischemic cerebrovascular disease (21,22), robust prospective evidence for its specific use in adult patients with MMD undergoing indirect revascularization is lacking (23). The current prospective, randomized study selected 6-month angiographic neovascularization grade as the primary endpoint, with the aim of directly assessing the effects of atorvastatin on the core determinant of indirect revascularization efficacy.

Materials and methods

Study design and patient population. The present single-center, prospective, randomized, open-label, blinded endpoint study was conducted at the Department of Neurosurgical Trauma I, Cangzhou Central Hospital (Cangzhou, China). Consecutive adult patients (aged 18-65 years) who were diagnosed with ischemic-type MMD and scheduled to undergo indirect revascularization surgery between March 2023 and August 2024 were assessed for eligibility.

Inclusion criteria. The diagnosis of MMD was confirmed using digital subtraction angiography (DSA) based on the diagnostic criteria established by the Japanese Ministry of Health and Welfare (24). The inclusion criteria were as follows: i) Aged between 18 and 65 years. ii) Radiologically confirmed ischemic-type MMD (presence of TIAs and/or cerebral infarction). iii) Planned treatment with indirect revascularization surgery. iv) Ability to provide written informed consent.

Exclusion criteria. Patients were excluded from the present study based on the following criteria: i) Hemorrhagic-onset MMD or a history of intracranial hemorrhage. ii) Presence of notable comorbidities, including severe cardiac, hepatic or renal insufficiency (defined as alanine aminotransferase or aspartate aminotransferase levels >3 times the upper limit of normal, or an estimated glomerular filtration rate <30 ml/min/1.73 m^2). iii) Known allergy or contraindication to statin therapy. iv) Pregnancy or lactation. v) Preoperative modified Rankin Scale (mRS) score >3 (25), indicating severe disability. vi) Concurrent conditions requiring long-term anticoagulation therapy. vii) History of statin use within 3 months prior to enrollment. viii) MMD associated with other conditions such as atherosclerosis, autoimmune diseases or cranial radiotherapy.

A total of 80 patients who met the inclusion criteria were finally enrolled and randomly assigned in a 1:1 ratio to either the control group or the atorvastatin group.

Randomization, blinding and intervention. Randomization: Eligible patients were randomly assigned in a 1:1 ratio to either the control group or the atorvastatin group. The random allocation sequence was generated by an independent statistician using computer-generated random numbers. The sequence was concealed using sequentially numbered, opaque, sealed envelopes. After a patient provided written informed consent and prior to surgery, the attending neurosurgeon opened the next envelope in the sequence to reveal the group assignment. Blinding: Given the nature of the pharmacological intervention, this was an open-label study for the patients and treating physicians to ensure practical feasibility and patient safety. However, a blinded endpoint assessment was strictly implemented to minimize bias. The neuroradiologists who evaluated the postoperative DSA results and the clinicians who performed the mRS assessments at follow-up were completely unaware of the group assignments of the patients. All imaging data were anonymized before being presented to the evaluators. Intervention: All patients underwent indirect revascularization surgery (EDAS) performed by senior neurosurgeons with extensive experience in cerebrovascular surgery.

The patients in the control group (n=40) received standard postoperative medical therapy. This included a single antiplatelet agent [either aspirin (100 mg, daily) or clopidogrel (75 mg, daily)] and management of vascular risk factors (for example, antihypertensive drugs) as clinically indicated.

The patients in the atorvastatin group (n=40) received identical standard postoperative medical therapy to the control group, but also received oral atorvastatin calcium tablets (20 mg, once daily). This dose was selected based on its well-established safety profile in Chinese patients with adult cerebrovascular disease, its consistency with domestic clinical practice guidelines, and due to prior prospective evidence supporting its pro-angiogenic effect in MMD (26,27). The atorvastatin administration was initiated on postoperative day 1, provided the condition of the patient was stable, and was continued for ≥6 months. No dose-escalation regimen, higher-dose (40 mg/day) group or predefined management protocol for concomitant potent CYP3A4 inhibitors was included in this trial design, as enrolled patients excluded those requiring long-term use of such medications.

Outcome measures and data collection. The primary outcome of the present study was the rate of good neovascularization at the 6-month follow-up, assessed by DSA. Angiographic collateral formation was evaluated according to the Matsushima grading system (28), which classifies the extent of revascularization into three categories: Poor, Fair and Good. For the purpose of the current study, a Matsushima grade of 'Good' was defined as a good outcome, whereas 'Fair' and 'Poor' were defined as poor outcomes.

The secondary outcomes were assessed at 6 months postoperatively and included: i) Functional outcome: An improvement of ≥1 point on the mRS compared with the preoperative baseline. ii) Ischemic event recurrence: The recurrence of any ischemic event, defined as a composite of TIA or new cerebral infarction, confirmed by clinical assessment and neuroimaging (MRI). Prespecified root cause analysis was performed for all recorded ischemic events to explore the association between event occurrence and postoperative neovascularization grade. iii) Hemodynamic improvement: Changes in cerebral hemodynamics were evaluated using computed tomography perfusion (CTP). Parameters of interest included cerebral blood flow (CBF) and mean transit time (MTT) in the middle cerebral artery territory of the operated hemisphere. iv) Safety outcomes: The incidence of all adverse events, with specific attention paid to statin-related adverse events, such as liver enzyme elevation, myalgia and creatine kinase (CK) elevation. No patient-reported Health-Related Quality of Life (HRQoL) data (29), blood-based biomarkers, or full-cycle medical cost data for cost-effectiveness analysis were collected as prespecified outcomes in the trial.

Regarding data collection and follow-up, baseline demographic data, clinical presentation, vascular risk factors, Suzuki angiographic stage (30) and preoperative mRS scores were recorded for all patients upon enrollment. Follow-up assessments were conducted at 6 weeks (via telephone) and 6 months (via outpatient visit). The 6-week follow-up primarily documented adherence to medication, adverse events and the occurrence of TIA. No routine 1-3 month imaging [including transcranial Doppler (TCD) or interim CTP] was prescheduled in the trial design. The 6-month follow-up served as the primary efficacy endpoint, with all patients completing clinical assessment (mRS), cerebral perfusion imaging (CTP) and DSA (the reference standard for neovascularization grading). Routine follow-up reminders were provided for all patients, but no specific adherence-boosting interventions for asymptomatic/minimally symptomatic patients were prespecified in this trial.

Regarding endpoint adjudication, to ensure objectivity, all DSA and CTP images were analyzed by two independent, experienced neuroradiologists who were blinded to the clinical data and group assignments. Any discrepancies in the assessment were resolved by consensus or by a third senior neuroradiologist. Clinical mRS scores at follow-up were assessed by a trained neurologist who was also blinded to the treatment allocation.

Statistical analysis. All statistical analyses were performed using SPSS (version 26.0; IBM Corp.), with two-sided P<0.05 considered to indicate a statistically significant difference. Baseline characteristics were compared using independent samples t-test, Mann-Whitney U tests or χ^2/Fisher's exact tests, as appropriate. Efficacy analyses followed the intention-to-treat principle. For binary outcomes (for example, good neovascularization rate), the risk ratio (RR) with 95% confidence interval (CI) was calculated and groups were compared using the χ^2 test. For continuous outcomes (such as CBF), the mean difference (MD) with 95% CI was calculated, and intergroup comparisons were performed using independent samples t-tests. A multivariate logistic regression model was used to identify independent predictors, reporting adjusted odds ratio (aOR) with 95% CI. The consistency of the treatment effect across prespecified subgroups was explored via subgroup analysis, with formal interaction tests performed by adding a treatment-by-subgroup interaction term to the multivariate logistic regression model, with significance assessed via the Wald test.

Results

Patient characteristics. Between March 2023 and August 2024, a total of 80 eligible adult patients with ischemic-type MMD were enrolled and randomly allocated to the control group (n=40) or the atorvastatin group (n=40). All patients received their assigned treatment and were included in the final analysis. The baseline demographic and clinical characteristics were well-balanced between the two groups, as detailed in Table I

Primary efficacy outcomes. The impact of atorvastatin on the primary efficacy endpoints at the 6-month follow-up is summarized in Table II. A significantly higher proportion of patients in the atorvastatin group achieved good neovascularization, as defined by a Matsushima grade of 'Good', compared with the control group [65.0% (26/40) vs. 37.5% (15/40)]. This difference was statistically significant, with an RR of 1.73 (95% CI, 1.10-2.74; P=0.014). This corresponded to an absolute risk reduction (ARR) of 27.5% for the primary endpoint of good neovascularization, with a number needed to treat (NNT) of 4 (calculated as the reciprocal of the ARR: 1/0.275=3.64). Analysis of the full distribution of Matsushima grades revealed a significant shift toward better angiographic outcomes in the atorvastatin group (P=0.031 for trend). Specifically, the atorvastatin group had nearly double the number of 'Good' responses and fewer 'Poor' responses [5.0% (2/40)] compared with in the control group [17.5% (7/40)]. Notably, all 6 postoperative ischemic events in the cohort occurred in patients with Poor or Fair neovascularization, providing risk-based evidence for treatment escalation decisions in non-responders.

Consistent with the angiographic findings, postoperative hemodynamic improvements were significantly greater in the atorvastatin group. The mean improvement in CBF was 12.8±5.1 ml/100 g/min in the atorvastatin group, compared with 8.5±4.2 ml/100 g/min in the control group, resulting in a MD of 4.3 ml/100 g/min (95% CI: 2.2-6.4; P<0.001). Similarly, the reduction in MTT was more pronounced in the atorvastatin group (-1.9±0.7 seco) than in the control group (-1.2±0.6 sec), with a MD of -0.7 sec (95% CI: -0.9 to -0.5; P<0.001).

Secondary clinical and safety outcomes. Outcomes related to clinical function and event recurrence are presented in Table III. An improvement of ≥1 point on the mRS scale was observed in 29 patients (72.5%) in the atorvastatin group, compared with 20 patients (50.0%) in the control group (RR: 1.45; 95% CI: 1.03-2.04; P=0.039). The composite endpoint of TIA or stroke recurrence occurred in 1 patient (2.5%) in the atorvastatin group and 5 patients (12.5%) in the control group; this difference was not statistically significant (P=0.201). Root cause analysis confirmed all 6 events occurred in patients with

Table I. Baseline characteristics of the patients (n=80).

Characteristic	Control group (n=40)	Atorvastatin group (n=40)	Test statistic	P-value
Age, years, mean ± SD	44.8±11.2	46.1±10.5	t=-0.552	0.584
Sex, n (%)			χ^2=0.205	0.651
Male	24 (60.0)	22 (55.0)		
Female	16 (40.0)	18 (45.0)		
Body mass index, kg/m^2, mean ± SD	24.5±3.0	24.3±2.9	t=0.473	0.642
Clinical presentation/qualifying event, n (%)			χ^2=0.503	0.478
Cerebral infarction	25 (62.5)	28 (70.0)		
TIA only	15 (37.5)	12 (30.0)		
Preoperative mRS score, median (IQR)	2 (1-2)	2 (1-2)	Z=-0.114	0.915
Suzuki stage, n (%)			χ^2=0.063	0.969
Stage III	14 (35.0)	13 (32.5)		
Stage IV	19 (47.5)	20 (50.0)		
Stage V	7 (17.5)	7 (17.5)		
Involved side, n (%)			χ^2=0.313	0.576
Unilateral	7 (17.5)	9 (22.5)		
Bilateral	33 (82.5)	31 (77.5)		
Operated side, n (%)			χ^2=0.201	0.654
Left		18 (45.0)	20 (50.0)	
Right	22 (55.0)	20 (50.0)		
Comorbidities, n (%)				
Hypertension	19 (47.5)	18 (45.0)	χ^2=0.050	0.823
Diabetes mellitus	11 (27.5)	9 (22.5)	χ^2=0.052	0.819
Hyperlipidemia	26 (65.0)	23 (57.5)	χ^2=0.474	0.491
Laboratory values, mean ± SD				
Total cholesterol, mmol/l	4.6±0.9	4.5±0.8	t=0.537	0.598
LDL-C, mmol/l	2.8±0.7	2.7±0.6	t=0.706	0.485

For continuous variables with normal distribution, data are presented as the mean ± SD and were analyzed by independent samples t-test (t-value reported). For non-normally distributed continuous variables, data are presented as the median (IQR]) and were analyzed by Mann-Whitney U test (Z-value reported). Categorical variables are presented as n (%) and were analyzed by χ^2 test (χ^2-value reported). IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; SD, standard deviation; TIA, transient ischemic attack.

poor neovascularization on 6-month DSA, with statistical analysis limited by the small number of events.

The frequency of adverse events is also detailed in Table III. The proportion of patients experiencing any adverse event was 55.0% in the atorvastatin group and 42.5% in the control group (P=0.263). Liver enzyme elevation was observed in 3 patients (7.5%) in the atorvastatin group and in none of the control group patients (0.0%); this difference was not statistically significant (P=0.241). The incidence of myalgia was similar between groups (5.0 vs. 2.5%, P=1.000).

Multivariate analysis of predictors for good neovascularization. To determine whether atorvastatin treatment was an independent predictor of good neovascularization after adjusting for potential confounding variables, a multivariate logistic regression analysis was performed. The model included treatment group, age, sex, Suzuki stage and qualifying event type as covariates (Table IV). After adjustment for these baseline characteristics, treatment with atorvastatin remained significantly associated with a higher likelihood of achieving good neovascularization (aOR: 3.125; 95% CI: 1.281-7.624; P=0.012). None of the other variables included in the model, age, sex, Suzuki stage or qualifying event type, demonstrated a statistically significant association with the primary outcome (all P>0.05).

Subgroup analysis. An exploratory subgroup analysis was conducted to evaluate the consistency of the treatment effect of atorvastatin on the primary outcome of good neovascularization across key baseline patient characteristics. The results are presented in Fig. 1. The beneficial effect of atorvastatin was consistently observed across all predefined subgroups, including sex, age, Suzuki stage and qualifying event type. As shown in Fig. 1, all point estimates of the RR favored the atorvastatin group, with all values >1 and falling to the right of the line of no effect (RR=1) in the forest plot. Formal Wald tests for interaction were not statistically significant for any subgroup (all P-values for interaction >0.05), indicating that

Table II. Primary efficacy outcomes at 6-month follow-up.

Outcome measure	Control group (n=40)	Atorvastatin group (n=40)	Effect size (95% CI)	P-value
Angiographic outcomes				
Good neovascularization[a], n (%)	15 (37.5)	26 (65.0)	RR: 1.73 (1.10-2.74)	0.014
Matsushima grade distribution, n (%)			-	0.031
Good	15 (37.5)	26 (65.0)		
Fair	18 (45.0)	12 (30.0)		
Poor	7 (17.5)	2 (5.0)		
Hemodynamic outcomes				
Improvement in CBF, ml/100 g/min, mean ± SD	8.5±4.2	12.8±5.1	MD: 4.3 (2.2-6.4)	0.001
Reduction in MTT, sec, mean ± SD	-1.2±0.6	-1.9±0.7	MD: -0.7 (-0.9 to -0.5)	0.001

The primary outcome was the rate of good neovascularization ([a]Matsushima grade 'Good') assessed by digital subtraction angiography. Hemodynamic parameters were evaluated using computed tomography perfusion. Statistical tests: Pearson's χ^2 test was used for the between-group comparison of good neovascularization rate; Mann-Whitney U test was used for the between-group comparison of Matsushima grade distribution; independent samples Student's t-test was used for the between-group comparisons of CBF improvement and MTT reduction. CBF, cerebral blood flow; CI, confidence interval; MD, mean difference; MTT, mean transit time; RR, risk ratio.

Table III. Secondary clinical and safety outcomes at 6-month follow-up.

Outcome measure	Control group (n=40)	Atorvastatin group (n=40)	Effect size (95% CI)	P-value
Secondary clinical outcomes				
mRS improvement ≥1, n (%)	20 (50.0)	29 (72.5)	RR: 1.45 (1.03-2.04)	0.039
TIA/stroke recurrence, n (%)	5 (12.5)	1 (2.5)	-	0.201[a]
Safety outcomes				
Any adverse event, n (%)	17 (42.5)	22 (55.0)	-	0.263
Liver enzyme elevation, n (%)	0 (0.0)	3 (7.5)	-	0.241[a]
Myalgia, n (%)	1 (2.5)	2 (5.0)	-	1.000[a]

[a]P-value calculated using Fisher's exact test. All other P-values were calculated using Pearson's χ^2 test. mRS, modified Rankin Scale; RR, risk ratio; TIA, transient ischemic attack.

the treatment effect did not significantly differ based on these baseline characteristics.

Discussion

The present prospective, randomized trial demonstrates that adjunctive low-dose atorvastatin significantly enhances the core efficacy determinant of indirect revascularization in adult patients with ischemic MMD. The principal finding was a markedly higher rate of good neovascularization (Matsushima grade, Good) in the atorvastatin group, which is an established independent predictor of reduced long-term ischemic event risk, supported by improved cerebral hemodynamics and functional recovery. The 27.5% absolute increase in good neovascularization (65.0 vs. 37.5%) and the aOR of 3.125 underscored a substantial treatment effect. The favorable outcomes observed with atorvastatin may be explained by three evidence-based mechanisms aligned with ischemic MMD pathogenesis: i) Endothelial-protective effects to rescue the endothelial dysfunction driving MMD progression; ii) anti-inflammatory actions to mitigate the chronic inflammatory dysregulation that inhibits physiological angiogenesis in MMD; iii) direct pro-angiogenic effects, including endothelial nitric oxide synthase upregulation and endothelial progenitor cell mobilization, which augment collateral formation induced by indirect revascularization (31,32). The present results are consistent with those of Wang *et al* (27), whose prospective study also identified atorvastatin as an independent predictor of good collateral formation post-EDAS. However, the current study advances this evidence by employing a randomized design, which minimizes confounding bias and provides a higher level of evidence than the previous observational cohort.

The hemodynamic improvements observed in the present study, namely, greater increases in CBF and greater reductions

Table IV. Multivariate logistic regression analysis of predictors for good neovascularization.

Variable	Adjusted odds ratio	95% CI	P-value
Treatment group			
Control	1.000 (Reference)		
Atorvastatin	3.125	1.281-7.624	0.012
Age			
≤45 years	1.000 (Reference)		
>45 years	0.812	0.334-2.007	0.652
Sex			
Female	1.000 (Reference)		
Male	1.291	0.522-3.188	0.583
Suzuki stage			
III-IV	1.000 (Reference)		
V	0.615	0.186-2.109	0.436
Qualifying event			
TIA only	1.000 (Reference)		
Cerebral infarction	0.702	0.285-1.763	0.448

The model was adjusted for treatment group, age, sex, Suzuki stage and qualifying event type. CI, confidence interval; TIA, transient ischemic attack.

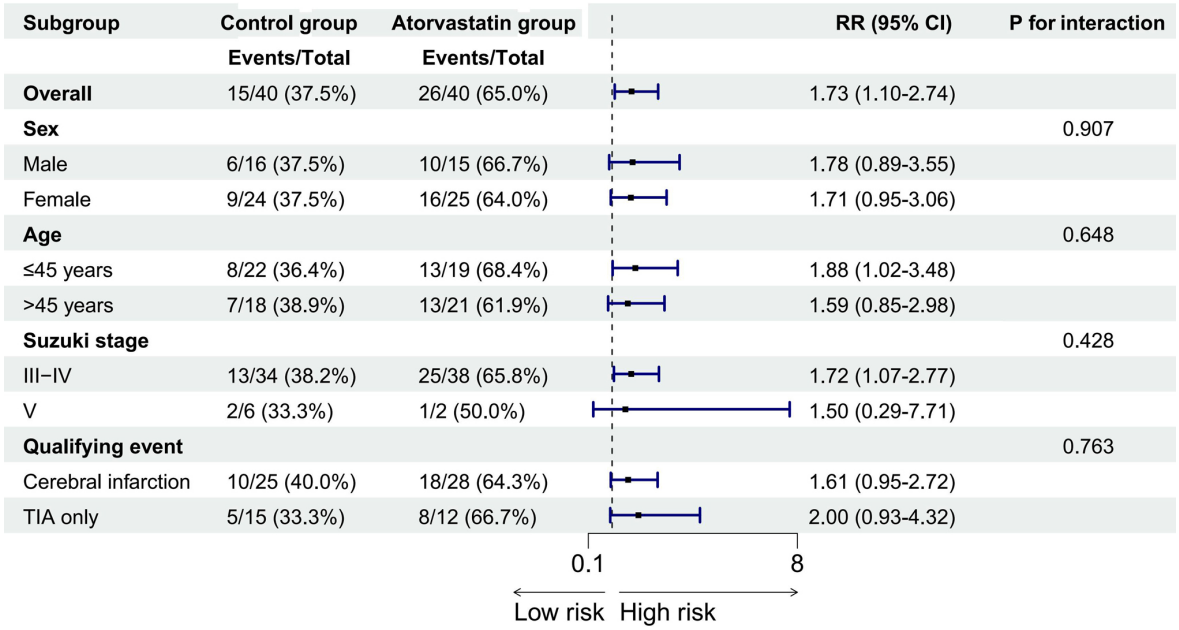

Figure 1. Subgroup analysis of the primary outcome. Forest plot showing the effects of atorvastatin on the rate of good neovascularization (Matsushima grade, 'Good') across various patient subgroups. The primary outcome was assessed at 6 months by digital subtraction angiography. The RR and 95% CI for each subgroup are displayed. The overall treatment effect from the primary analysis is presented at the top. The P-value for interaction indicates whether the treatment effect differs significantly between the subgroups. The vertical line represents the line of no effect. CI, confidence interval; RR, risk ratio.

in MTT, provide direct functional physiological evidence corresponding to the superior angiographic neovascularization in the atorvastatin group, indicating that the newly formed collaterals are functionally competent. This functional benefit translated into a significantly higher proportion of patients achieving functional independence (mRS improvement ≥1: 72.5 vs. 50.0%). While the reduction in TIA/stroke recurrence (2.5 vs. 12.5%) was not statistically significant, likely due to sample size constraints, the direction of effect is clinically encouraging and warrants further investigation in larger trials. A notable strength of the study is its randomized design, which addresses a key limitation of the earlier prospective trial by Wang *et al* (27) where treatment allocation was non-random. Furthermore, the present findings provide key preliminary clinical evidence supporting the core scientific hypothesis of the ongoing large-scale, double-blind randomized controlled

trial [whose formal trial protocol was published by Gao *et al* in 2023 (33)], which aims to definitively confirm the efficacy of atorvastatin in this patient population. The positive results of the present study provide preliminary support for the hypothesis being tested in that larger trial. The multivariate and subgroup analyses strengthen the conclusions, confirming atorvastatin as an independent predictor of good neovascularization and demonstrating a consistent treatment effect across key patient subgroups. Regarding safety, adjunctive atorvastatin was well-tolerated. The incidence of transient liver enzyme elevation (7.5%) was consistent with the known safety profile of low-dose statins and similar to that reported in previous studies (27,34,35), with no serious adverse events leading to drug discontinuation.

For clinical decision-making, this effect size, combined with a favorable safety profile, supports postoperative atorvastatin as a recommended adjuvant option for eligible patients; however, current single-center data are insufficient to establish it as a universal standard of care. For patients with Poor or Fair neovascularization (non-responders) at 6 months, we recommend comprehensive re-evaluation of cerebral hemodynamics and ischemic risk. Complementary direct bypass surgery may be considered for those with persistent hypoperfusion or recurrent ischemic symptoms, although the efficacy of this escalated strategy was not formally evaluated in the present study. Given the exclusion of patients with concurrent atherosclerosis or other cerebrovascular comorbidities in this trial, the current conclusions cannot be directly extrapolated to patients with mixed pathologies. For this population, more intensive safety monitoring (including regular lipid, liver enzyme and CK testing) is recommended, and further targeted studies are required to confirm treatment efficacy. For patients achieving Good neovascularization at 6 months, statin discontinuation may be considered for those without atherosclerotic risk factors and stable cerebral perfusion, while long-term maintenance therapy is recommended for patients with underlying vascular risk factors to sustain endothelial protection and anti-inflammatory benefits. This recommendation is based on the established pleiotropic effects of statins, as the current study did not collect long-term data to compare outcomes between maintenance and discontinuation. In line with global statin clinical guidelines, for patients requiring short-term concomitant use of potent CYP3A4 inhibitors (for example, clarithromycin and amiodarone), temporary suspension of atorvastatin for the full duration of inhibitor use is recommended; for those requiring long-term use, switching to a statin not metabolized by the CYP3A4 pathway may be considered. This recommendation is based on established drug interaction specifications (36), as the present trial did not enroll patients requiring such concomitant medications.

Preclinical and clinical studies have confirmed that VEGF and inflammatory cytokines are key mediators of neovascularization after indirect revascularization, with potential value for guiding personalized statin use (37-39); however, the present trial did not prospectively explore such blood-based biomarkers. Biomarker-guided treatment stratification will be a core focus of our subsequent prospective studies. For primary care settings without routine DSA access, a guideline-aligned alternative monitoring pathway combining regular clinical assessment for new ischemic events or neurological decline, and serial TCD is recommended for preliminary efficacy and safety screening. Prompt referral is recommended for definitive angiographic evaluation for patients with abnormal findings; however, this non-invasive strategy cannot fully replace DSA as the reference standard for neovascularization grading. For asymptomatic or minimally symptomatic patients on long-term statin therapy, guideline-aligned adherence-improving measures are recommended, including standardized patient education on treatment benefits, regular follow-up reminders and simplified medication regimens, although the efficacy of these measures was not formally evaluated in the current trial. Given the 6-month short-term follow-up and lack of prespecified full medical cost collection in this single-center small-sample trial, a robust decision-tree model and formal Incremental Cost-Effectiveness Ratio estimation cannot be reliably constructed with the current data. A formal cost-effectiveness analysis will be conducted as a core secondary analysis in our upcoming large-scale multi-center confirmatory trial.

No formal guideline revision recommendations are proposed at this stage, as the findings of the present single-center small-sample trial require further validation in large-scale multi-center prospective studies. The prespecified primary endpoint of the present trial was 6-month postoperative efficacy; we aim to initiate 2- to 5-year extended follow-up of this cohort to assess long-term stroke recurrence and cognitive outcomes. Mechanistically, preclinical evidence suggests potential synergistic pro-angiogenic effects between atorvastatin and collateral-promoting drugs such as cilostazol (40); the current single-agent trial provides a preliminary clinical basis for subsequent combination therapy trials. The findings of the present study on the pro-neovascularization efficacy of statins provide preliminary human clinical evidence from a treatment response perspective, supporting the core role of vascular endothelial dysfunction and inflammation in the pathogenesis of MMD. For the upcoming multi-center confirmatory trial, we aim to involve patient representatives in the study design process, to optimize patient-centric outcome measures. and improve recruitment and implementation efficiency.

The present study has several limitations that should be considered. First, as a single-center trial, the patient population and surgical expertise may reflect a specific institutional context, which could affect the generalizability of the results. Second, although the sample size was adequate to detect a significant difference in the primary angiographic endpoint, it was relatively modest, which limited statistical power for subgroup analyses and precludes definitive conclusions regarding the clinical efficacy of atorvastatin, especially for less frequent endpoints such as ischemic event recurrence, as reflected by the wide CIs in some subgroup analyses. Third, clinical or imaging data were not collected at 1-3 months postoperatively, which prevented the identification of early predictors of final neovascularization outcomes; such data are critical for dynamic, individualized treatment adjustment and will be a core focus of subsequent research. Fourth, the 6-month follow-up period was sufficient to evaluate angiographic maturation as the primary outcome, but is too short to assess the long-term stability of newly formed collateral vessels or the sustained impact on preventing lifelong disability

or fatal stroke. Fifth, while randomization ensured baseline comparability and multivariate regression adjusted for known confounders, residual confounding from unmeasured factors, such as subtle differences in intrinsic angiogenic potential, cannot be entirely excluded. Sixth, the strict exclusion of patients with MMD related to atherosclerosis or other concurrent cerebrovascular diseases restricts the generalizability of the findings to patients with mixed pathological mechanisms. Seventh, functional recovery was evaluated only using the physician-assessed mRS, without collection of patient-reported HRQoL data, limiting the comprehensive assessment of the overall clinical value of the treatment. HRQoL assessment will be included as a core secondary endpoint in our future large-scale confirmatory trials. Eighth, the present trial only investigated the efficacy and safety of a fixed 20 mg/day atorvastatin regimen, with no prespecified dose-escalation design or exploration of higher-dose (40 mg/day) therapy. The preplanned subgroup analyses only evaluated the consistency of the 20 mg/day effect across baseline subgroups and cannot support a potential greater benefit of 40 mg/day in specific populations (for example, younger patients without liver disease); dose optimization across subgroups will be a key focus of our future prospective studies. Ninth, the study was designed with only a 6-month treatment course and follow-up endpoint, without predefined long-term evaluation of statin maintenance versus discontinuation after achieving good neovascularization. Long-term follow-up to clarify optimal treatment duration and sustained clinical benefits will be a central aim of our subsequent research.

In conclusion, the present single-center prospective randomized trial provides preliminary evidence that adjunctive atorvastatin 20 mg/day is associated with higher good neovascularization rate, improved cerebral hemodynamics and better functional recovery at 6 months after indirect revascularization in adult ischemic MMD, with a manageable safety profile. Further large-scale multi-center studies are warranted to validate these findings and to determine the definitive clinical role of atorvastatin for this patient population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DW conceptualized and designed the study, developed the study methodology, including the randomization and endpoint assessment protocols, performed the clinical investigation, led data curation, including prospective data collection and quality control, drafted the original manuscript and administered the project. JD performed the formal statistical analysis, created all data visualizations, and critically reviewed and edited the manuscript. SL participated in the clinical investigation and patient follow-up, and provided essential study resources, including clinical site and operating platform support. YL participated in the clinical investigation and patient recruitment, and provided essential study resources, including neuroimaging data acquisition and technical support. XX contributed to the study methodology, including the statistical analysis plan, and performed validation of all endpoint data and statistical results via independent blinded review. LH participated in the clinical investigation, and assisted with data curation, including standardized data entry and source verification against original medical records. QP made substantial contributions to the conception and design of the study, led the interpretation of core study results, secured funding for the research, provided critical supervision for all study procedures, critically revised the manuscript for important intellectual content, and oversaw final approval of the manuscript for publication. DW and QP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work in full accordance with ICMJE authorship guidelines.

Ethics approval and consent to participate

The current study was performed in accordance with The Declaration of Helsinki and was approved by the local ethics committee of the Cangzhou Central Hospital [approval no. 2023-235-01(z); Cangzhou, China]. Each patient provided written informed consent for participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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