Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke  
ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient)

Shinichi Yoshimura, MD, PhD; Kazutaka Uchida, MD; Takashi Daimon, PhD; Ryuzu Takashima, BA; Kazuhiro Kimura, PhD; Takeshi Morimoto, MD, PhD, MPH; on behalf of ASSORT Trial Investigator*

**Background and Purpose**—Several studies suggested that statins during hospitalization were associated with better disability outcomes in patients with acute ischemic stroke, but only 1 small randomized trial is available.

**Methods**—We conducted a multicenter, open-label, randomized controlled trial in patients with acute ischemic strokes in 11 hospitals in Japan. Patients with acute ischemic stroke and dyslipidemia randomly received statins within 24 hours after admission in the early group or on the seventh day in the delayed group, in a 1:1 ratio. Statins were administered for 12 weeks. The primary outcome was patient disability assessed by modified Rankin Scale at 90 days.

**Results**—A total of 257 patients were randomized and analyzed (early 131, delayed 126). At 90 days, modified Rankin Scale score distribution did not differ between groups (P=0.68), and the adjusted common odds ratio of the early statin group was 0.84 (95% confidence interval, 0.53–1.3; P=0.46) compared with the delayed statin group. There were 3 deaths at 90 days (2 in the early group, 1 in the delayed group) because of malignancy. Ischemic stroke recurred in 9 patients (6.9%) in the early group and 5 patients (4.0%) in the delayed group. The safety profile was similar between groups.

**Conclusions**—Our randomized trial involving patients with acute ischemic stroke and dyslipidemia did not show any superiority of early statin therapy within 24 hours of admission compared with delayed statin therapy 7 days after admission to alleviate the degree of disability at 90 days after onset.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02549846. (Stroke. 2017;48:3057-3063. DOI: 10.1161/STROKEAHA.117.017623.)

**Key Words:** cholesterol, LDL ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ prognosis ■ randomized controlled trial ■ stroke

See related article, p 2922

To improve survival and ameliorate disability after ischemic stroke, many treatment modalities have been used in the acute stage of stroke. Among them, intravenous tPA (tissue-type plasminogen activator) therapy and immediate endovascular thrombectomy have improved clinical outcomes, especially in patients with severe acute ischemic stroke.

Several observational studies showed that the administration of statins before ischemic stroke onset was associated with less physical disability and that statin administration during hospitalization was associated with better survival and disability outcomes. However, 1 small randomized controlled trial (RCT) failed to show the benefit of statin use at the acute phase of ischemic stroke for significantly decreased disability. A recent meta-analysis proposed the necessity of an RCT to determine the usefulness of statin therapy for acute ischemic stroke.

Thus, we conducted a multicenter RCT to determine the relative efficacy of early versus delayed statin treatment in patients with acute ischemic stroke. We hypothesized that early statin treatment would be associated with significantly improved physical disability at 90 days after acute ischemic stroke.
Methods

Trial Design

We conducted a multicenter, randomized, open-label, parallel-group trial to determine the efficacy of early versus delayed statin treatment in patients with acute ischemic stroke.

Inclusion criteria were ≥20 years old, history of dyslipidemia or low-density lipoprotein cholesterol (LDL-C) ≥2.6 mmol/L (100 mg/dL) on admission, able to take oral medications within 24 hours after admission, and hospitalized within 24 hours after acute ischemic stroke onset, confirmed by high signals with fluid-attenuated inversion-recovery imaging and diffusion-weighted imaging on magnetic resonance imaging.

Exclusion criteria were diagnosis of transient ischemic attack or cardioembolic stroke; surgical or endovascular therapy performed within 24 hours after onset; statin allergy; liver dysfunction; renal dysfunction; on cyclosporine or telaprevir; pregnant; acute coronary syndrome history within 6 months; valvular heart disease history, atrial fibrillation, or atrial thrombus; familial hypercholesterolemia; premorbid modified Rankin Scale (mRS) score of ≥3; and National Institute of Health Stroke Scale (NIHSS) on admission ≥20.11 The mRS ranged from 0 to 6, which assessed the degree of disability or dependence in daily activities, with scores ranging from 0 (no symptoms) to 6 (death). The NIHSS ranged from 0 to 42, with higher scores indicating more severe stroke.

Randomization was performed centrally through the electronic data capture system with a stochastic minimization algorithm to balance treatment assignment within and across hospitals, age (<70 vs ≥70 years), NIHSS at hospitalization (<8 vs ≥8), tPA use, and dyslipidemia treatment assignment within each participating hospital.

Analytical Methods

The primary outcome was patient disability expressed by mRS at 90 days. The mRS at 90 days was evaluated by a physical therapist or research doctor who was unaware of treatment allocation. If mRS could not be assessed, patients or their legally authorized representatives provided written informed consent before randomization. If mRS at 90 days was not assessed, patients diagnosed as cardioembolic after enrollment were included in the analyses. Follow-up was done at the hospital outpatient clinic, rehabilitation facilities, and nursing homes, and transfer facilities provided patient information to us.

Figure 1. Trial profile. FAS indicates full analyses set; mRS, modified Rankin Scale; and SAS, safety analyses set.
Secondary outcomes were changes in NIHSS from admission through day 7, changes in LDL-C from admission until 21 days or discharge, whichever came first, and major adverse cardiovascular or cerebrovascular events until 90 days. Major adverse cardiovascular or cerebrovascular events were defined as acute myocardial infarction, unstable angina, new acute ischemic stroke, nontraumatic cerebral bleeding, nontraumatic subarachnoid hemorrhage, or major/peripheral arterial diseases needing treatment.

Safety outcomes were death and any adverse events systematically reported until 90 days after randomization, including symptom progression, new cerebral infarction region, musculoskeletal adverse events, and liver dysfunction. We included symptoms requiring hospital admission, according to Japanese Ethical Guidelines. We also assessed elevated creatine kinase, aspartate transaminase, and alanine aminotransferase (≥3× upper limit of normal) during follow-up. The locations of stroke classified by Alberta Stroke Program Early CT Score on diffusion-weighted imaging were also measured at baseline and 21 days after onset or discharge.

Statistical Analysis

The primary hypothesis was that early statin treatment would be associated with lower mRS 90 days after acute ischemic stroke. We anticipated that mRS score distribution in the delayed group would be similar to a previous report where patients were twice as likely to have a lower mRS score with early statin treatment than with delayed statin treatment.7

On the basis of Whitehead method,15 for a 2-sided test size of 0.05 and score with early statin treatment than with delayed statin treatment.7

Statistical Analysis

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On the basis of Whitehead method,15 for a 2-sided test size of 0.05 and power of 0.8, the sample size was calculated as 228. Considering a dropout rate of 15%, we set 270 as the sample size. Because of short enrollment and follow-up periods, we planned no interim analyses.

Categorical variables are expressed as frequencies with percentages, and continuous variables are expressed as means with SDs or medians with interquartile ranges. Prespecified primary analysis was conducted under the intention-to-treat principle. The full analysis set included patients who received allocated treatment and provided assessable outcome data, excluding patients with protocol violation. Safety analysis set included patients who received allocated treatment at least once. We used full analysis set for primary and secondary outcomes and safety analysis set for safety outcomes. The primary outcome between groups was compared across the whole distribution of scores with the generalized Cochran–Mantel–Haenszel test with adjustment for a prespecified prognostic factor of history of stroke and balancing factors at randomization of age (≥ or <70 years), NIHSS at hospitalization (≥ or <8), tPA use, and admission dyslipidemia treatment status. Treatment effect was estimated with the proportional odds model as a common odds ratio (OR) for a shift toward better or worse mRS outcomes at 90 days, adjusted for the aforementioned prognostic and balancing factors. The adjusted common OR measured the likelihood that early statin treatment would result in lower mRS at 90 days compared with delayed statin treatment and is presented with 95% confidence intervals (CIs). The proportional odds model shift analysis relies on the assumption of proportionality of odds, which has been shown to be robust to minor deviations.18 Thus, the proportional odds assumption was checked and verified by plotting the logits of cumulative mRS score probabilities being greater than or equal to its cutoff value at all levels of the prognostic and balancing factors. An assumption-free ordinal analysis based on the Wilcoxon–Mann–Whitney generalized OR with its corresponding 95% confidence interval (CI) was performed to assess robustness. We dichotomized the mRS into excellent outcome (0, 1) and other (2–6) and performed the logistic regression analysis for excellent outcome, adjusting the aforementioned prognostic and balancing factors. Secondary outcomes were compared between groups with the Student t test, Wilcoxon–Mann–Whitney test, or Fisher exact test, as appropriate.

Primary outcome subgroup analyses were determined before fixing the statistical analysis plan. The adjusted common ORs of early versus delayed administration were estimated in the same way as primary analysis in prespecified subgroups of patients including age (≥ or <70 years), LDL-C (≥ or <2.8 mmol/L [110 mg/dL]), NIHSS at hospitalization (≥ or <8), tPA use, treatment of dyslipidemia on admission, history of stroke, and stroke classification. Thresholds were determined by clinical meaning or reports. Statistical significance of possible treatment effect heterogeneity between subgroups was assessed with interaction terms in the proportional odds model. Because of the exploratory nature of these analyses, no correction for multiplicity was made.

All statistical analyses were performed with the R statistical package, version 3.2.3 (R Development Core Team) based on the statistical analysis plan. All P values were 2-sided, and P<0.05 was considered statistically significant. Missing data were not imputed, and data with missing data were analyzed as they were.

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early Statin Group (n=131)</th>
<th>Delayed Statin Group (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>70 (13)</td>
<td>70 (11)</td>
</tr>
<tr>
<td>Age ≥70 y, n (%)</td>
<td>76 (58)</td>
<td>68 (54)</td>
</tr>
<tr>
<td>Sex male, n (%)</td>
<td>86 (66)</td>
<td>81 (64)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>69 (53)</td>
<td>70 (56)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>103 (79)</td>
<td>93 (74)</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>38 (29)</td>
<td>44 (35)</td>
</tr>
<tr>
<td>History of dyslipidemia, n (%)</td>
<td>64 (49)</td>
<td>59 (47)</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>41 (31)</td>
<td>48 (38)</td>
</tr>
<tr>
<td>Statin use before admission, n (%)</td>
<td>23 (18)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean (SD)</td>
<td>160 (24)</td>
<td>160 (26)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg, mean (SD)</td>
<td>87 (15)</td>
<td>89 (16)</td>
</tr>
<tr>
<td>Body weight, kg, mean (SD)</td>
<td>64 (14)</td>
<td>63 (13)</td>
</tr>
<tr>
<td>NIHSS on admission, median (IQR)</td>
<td>3 (1–5)</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td>Stroke classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar, n (%)</td>
<td>56 (43)</td>
<td>56 (44)</td>
</tr>
<tr>
<td>Atherothrombotic, n (%)</td>
<td>55 (42)</td>
<td>54 (43)</td>
</tr>
<tr>
<td>Cardioembolic, n (%)</td>
<td>5 (4)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Others*, n (%)</td>
<td>15 (11)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Intravenous thrombolysis, n (%)</td>
<td>11 (8.4)</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>ASPECTS, median (IQR)</td>
<td>9 (8–10)</td>
<td>9 (9–10)</td>
</tr>
<tr>
<td>ASPECTS on DWI, median (IQR)</td>
<td>9 (8–9)</td>
<td>9 (9–9)</td>
</tr>
<tr>
<td>pc-ASPECTS on DWI, median (IQR)</td>
<td>8 (8–9)</td>
<td>8 (8–9)</td>
</tr>
<tr>
<td>Laboratories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L, mean (SD)</td>
<td>3.52 (0.78); [136 (30)]</td>
<td>3.52 (0.85); [136 (33)]</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L, mean (SD)</td>
<td>1.37 (0.36); [53 (14)]</td>
<td>1.32 (0.44); [51 (17)]</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean (SD)</td>
<td>5.54 (0.91); [214 (35)]</td>
<td>5.44 (0.93); [210 (36)]</td>
</tr>
<tr>
<td>Triglycerides, mmol/L, median (IQR)</td>
<td>3.16 (2.07–4.09); [122 (80–158)]</td>
<td>3.11 (2.23–4.56); [120 (86–176)]</td>
</tr>
<tr>
<td>HbA1c, % (NGSP), median (IQR)</td>
<td>6.0 (5.6–6.6)</td>
<td>6.0 (5.6–7.0)</td>
</tr>
<tr>
<td>CRP, mg/dl, median (IQR)</td>
<td>0.11 (0.05–0.28)</td>
<td>0.11 (0.05–0.29)</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; CRP, C-reactive protein; DWI, diffusion-weighted imaging; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; NIHSS, National Institute of Health Stroke Scale; and pc-ASPECTS, posterior circulation-Alberta Stroke Program Early CT Score.

*Abnormality of coagulation, arterial dissection, vasculitis, or undetermined.
Results

Patient Population
Two hundred seventy patients were enrolled from 11 Japanese hospitals from September 2015 until August 2016: 135 were assigned to the early statin group and 135 to the delayed statin group (Figure 1). The patients’ mean age (SD) was 70.0 years (11.9 years), and 65% were men. Thirty percent had an ischemic stroke history, and 15% received statins before admission. Lacunar stroke (44%) and atherothrombotic infarction (42%) were the most common. There were 14 (5%) cardioembolic infarctions in patients not diagnosed as cardioembolic at enrollment. Demographic and clinical characteristics were similar in both groups (Table 1). The median (interquartile ranges) length of hospital stay in early and delayed statin group were 18 (13–30) and 15 (12–21), respectively. The poor compliance rates (taking statins <75% of prescribed) at 90th day were 6% (7/123) and 1% (1/118) in the early and delayed statin groups, respectively.

Primary and Secondary Outcomes
Ninety days after stroke, the mRS score distribution did not differ between groups (P=0.7), and adjusted common OR of the early statin group was 0.84 (95% CI, 0.53–1.3) compared with the delayed statin group. The results were confirmed by the Wilcoxon–Mann–Whitney generalized OR of 1.1 (95% CI, 0.79–1.4). About 70% of all patients had improved mRS disability status ranging from 0 to 2 (Figure 2). The OR of the early statin group for excellent outcome (mRS score of 0 or 1) was 1.59 (95% CI, 0.90–2.85) compared with the delayed statin group.

Prespecified subgroup analyses indicated no significant effect of early statin treatment on mRS at 90 days in any subgroups (Figure 3). The interaction P values were not significant for any subgroup factors.

Secondary outcomes also did not differ between groups except for the change in LDL-C (Table 2). There were only small changes in NIHSS (median −1) in both groups (P=0.4), but the change in LDL-C in the early statin group was significantly larger than that in the delayed statin group (−65.0 versus −51.0; P=0.001). Major adverse cardiovascular or cerebrovascular events were infrequent, except that new acute ischemic stroke occurred in 6.9% and 4.0% of the early and delayed statin patients, respectively.

Safety
The 90-day safety profile was similar between groups (Table 3). There were 92 deaths from malignancy in the early statin group and 1 in the delayed group. Including minor symptoms, there were 32 (23.9%) adverse events in the early statin group and 22 (17.1%) in the delayed statin group, and half were symptom progression necessitating hospital admission. Infrequent musculoskeletal adverse events (myalgia or orthostatic symptoms but no rhabdomyolysis or myositis) were observed in both groups. Creatine kinase, aspartate transaminase, and alanine aminotransferase laboratory changes were also similar between groups. There were 11 (9.5%) and 20 (17.5%) patients with creatine kinase elevated to ≥3× the upper normal limit in the early and delayed statin groups, respectively. The locations of stroke regressed until 21 days after onset or discharge in both groups (Table in the online-only Data Supplement).

Discussion
Early statin administration did not have favorable effects on mRS disability at 90 days compared with delayed administration in patients with acute ischemic stroke and dyslipidemia. Early versus delayed statin administration did not affect major
adverse cardiovascular or cerebrovascular events or safety outcomes. This neutral effect was similar across subgroups including age, baseline LDL-C or high-sensitivity C-reactive protein values, imaging classification, neurological symptoms at onset, intravenous tPA or statin use, stroke history, and stroke classification.

Immediate statin administration after ischemic stroke was reported to decrease infarct size and improve physical function in animal models.17–20 The neuroprotective effects of statin on acute ischemic stroke has been reported as antioxidation, anti-inflammation, vasodilation, antithrombosis, angiogenesis, synaptogenesis, and neural progenitor cell migration to the injury site.20–24 The clinical effects of statin on recurrence of ischemic stroke or survival in patients with acute ischemic stroke were reported. The SPARCL trial (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) showed that statin administration at 2 to 3 months after onset was associated with more event-free patients with ischemic stroke or transient ischemic attack.25 A retrospective observational study reported that 1-year survival rates among patients with ischemic stroke who were administered statins before or during admission were higher than the counterparts.6 About disability outcomes, the subanalysis of SPARCL Trial also showed that statin administration at nonacute phase was associated with reduced disability measured by mRS.26 Another non-RCT found that statin withdrawal for 3 days after ischemic stroke onset in patients previously on statins was associated with significantly worse disability status after 90 days compared with patients receiving statins immediately after onset.4 Thus, statin withdrawal at acute phase or nonadministration at nonacute phase should be associated with worse outcomes in patients with acute ischemic stroke, but the clinical significance of early administration to naive patients should be evaluated.

Table 2. Secondary Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Early Statin Group (n=131)</th>
<th>Delayed Statin Group (n=126)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in NIHSS from baseline through seventh day, median (IQR)</td>
<td>−1 (−2 to 0)</td>
<td>−1 (−2 to 0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Change in LDL-C from baseline through 21st day or discharge, mmol/L, mean (SD); [mg/dL, mean (SD)]</td>
<td>−1.68 (0.79); [−63.0 (30.6)]</td>
<td>−1.32 (0.76); [−51.0 (29.2)]</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute myocardial infarction, n (%)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>New acute ischemic stroke, n (%)</td>
<td>9 (6.9)</td>
<td>5 (4.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Nontraumatic cerebral hemorrhage, n (%)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Nontraumatic subarachnoid hemorrhage, n (%)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Large vessel or peripheral artery disease requiring treatment, n (%)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; LDL-C, low-density lipoprotein cholesterol; and NIHSS, National Institutes of Health Stroke Scale.
The median NIHSS on admission was 3, and the almost half of prevalent cause of ischemic stroke in our study was lacunar, whereas in the previous study the median NIHSS was 12, and athrothrombosis was the major cause and lacunar was only 18%. Although the enrolled patients were similar to the epidemiology of Japanese patients, such differences in stroke severity or cause might be associated with the attenuated results. Statin administration in patients with transient ischemic attack or mild stroke had failed to show beneficial effects on stroke recurrence within 90 days. Thus, neuroprotective effect of statin may be more apparent in patients with moderate severity and warrants further study. Thus, the clinical significance of statin administration for acute phase ischemic stroke is still uncertain, especially in patients with more severe disability or other causes, and use of intravenous tPA or endovascular thrombectomy. These area of uncertain should be confirmed with well-conducted randomized trials.

This study had some limitations. First, the enrolled patients had relatively less severe stroke. In addition, we used mRS as primary outcome measure because mRS was most frequently used in stroke trials. Because mRS was not sensitive to evaluate the mild disability, statin administration in patients with acute ischemic stroke might be beneficial if patients with severe disability were enrolled or more sensitive outcome measurements such as Fugl-Meyer or grip strength were used. Second, this was an open-label randomized trial. Although individuals performing primary outcome assessments were blinded to treatment allocation, concomitant therapies such as rehabilitation might differ between hospitals. However, the effect of such differences on results should be small because hospital was included in the stratification variable at randomization and all patients received the statin at discharge. Third, we enrolled patients with preexisting dyslipidemia, and the doses of statins were relatively lower than the regular doses in the Western countries. However, the THRAS study (The Thrombolysis and Statins) reported that atorvastatin 10 to 20 mg/d had similar effect to 40 to 80 mg/d on neurological outcomes, and the type of statin also did not matter. Indeed, Asian cohorts was reported to be more sensitive to statin than the Western cohorts so that lower doses provided similar LDL-lowering effect compared with the higher dose in Western cohorts.

Therefore, the doses and types of statin were rational in our study, but the higher dose should be attested in the future studies. Final, the sample size was based on the common OR of 2 calculated from the distribution of mRS at 90 days in the previous observational study. However, the observed OR of our study was 1.1 for 1 decrement of mRS. The resultant effect size was smaller than expected, and effect size in observational study was generally larger because of prescribing bias and others. The animal studies also showed positive effect of statins for recovery from stroke. The injection of statin in these animal studies might enhance the effect on the recovery from stroke in addition to the maximum doses used. In addition, accumulation of milder disability (mRS score of 0–2) decreases the power of detection of efficacy in the neuroprotective trial. However, OR of 1.59 for excellent outcome in our study was clinically important, and further study with appropriate sample size should be conducted to attest the role of early statin administration for acute ischemic stroke.

Conclusions

Our RCT involving patients with acute ischemic stroke and dyslipidemia did not show any superiority of early statin therapy administered within 24 hours of admission versus delayed administration until the seventh day of admission to alleviate the degree of disability at 90 days after admission.

Appendix


Acknowledgments

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solely conducted by the academic authors (Drs Yoshimura, Uchida,
Daimon, and Morimoto).

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Randomized controlled trial of early versus delayed statin therapy in patients with acute ischemic stroke - ASSORT Trial

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Supplemental Table. Change in Location of Stroke on MRI-DWI

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<td>Baseline (n=101)</td>
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<tr>
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<td>M1, n (%)</td>
<td>3 (3.0)</td>
<td>1 (1.2)</td>
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<tr>
<td>M2, n (%)</td>
<td>6 (5.9)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>M3, n (%)</td>
<td>6 (5.9)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>M4, n (%)</td>
<td>8 (7.9)</td>
<td>8 (9.5)</td>
</tr>
<tr>
<td>M5, n (%)</td>
<td>26 (25.7)</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>M6, n (%)</td>
<td>11 (10.9)</td>
<td>7 (8.3)</td>
</tr>
</tbody>
</table>

M1: Anterior MCA cortex
M2: MCA cortex lateral to insular ribbon
M3: Posterior MCA cortex
M4: Anterior MCA territory immediately superior to M1
M5: Lateral MCA territory immediately superior to M2
M6: Posterior MCA territory immediately superior to M3
Study Organization

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