Effect of Statin on Stroke Recurrence Prevention at Different Infarction Locations: A Post Hoc Analysis of The J-STARS Study

Tomohisa Nezu1, Naohisa Hosomi1, Kazuo Kitagawa2, Yoji Nagai3, Yoko Nakagawa4, Shiro Aoki1, Tatsuo Kagimura4, Hirofumi Maruyama1, Hideki Origasa5, Kazuo Minematsu6, Shinichiro Uchiyama7 and Masayasu Matsumoto1,8; J-STARS collaborators

1 Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
2 Department of Neurology, Tokyo Women’s Medical University School of Medicine, Tokyo, Japan
3 Center for Clinical Research, Kobe University Hospital, Kobe, Japan
4 Division of Medical Statistics, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan
5 Division of Biostatistics and Clinical Epidemiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan
6 National Cerebral and Cardiovascular Center, Suita, Japan
7 Clinical Research Center for Medicine, International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Hospital and Sanno Medical Center, Tokyo, Japan
8 Sakai City Medical Center, Sakai City Hospital Organization, Sakai, Japan

Aim: Posterior circulation stroke (PCS) has different clinical features and prognosis compared with anterior circulation stroke (ACS), and whether the effect of statin therapy on stroke prevention differs according to infarction location remains unclear. This post hoc analysis of the J-STARS study aimed to compare the usefulness of statin at different infarction locations (i.e., ACS and PCS).

Methods: In the J-STARS study, 1578 patients were randomly assigned to the pravastatin or control group. The subjects were divided into two subgroups (ACS and PCS groups) based on the arteries responsible for the infarction. Cox proportional hazards models were used to investigate whether the all stroke recurrence rate was different between the ACS and PCS groups.

Results: The PCS group (n=499) had a significantly higher prevalence of diabetes than the ACS group (n=1022) (30.7% vs. 19.8%, P<0.001). During the follow-up (4.9 ± 1.4 years), the incidence of all stroke was significantly lower in the pravastatin group than in the control group among patients with PCS (adjusted hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.25–0.83, P=0.009); however, the stroke recurrence rates were not significantly different between both groups among patients with ACS (adjusted HR 1.32, 95% CI 0.93–1.88, P=0.123). A significant interaction between the ACS and PCS groups in terms of pravastatin effects was noted (P=0.003 for interaction).

Conclusions: Pravastatin significantly reduced the recurrence rate of all stroke among patients with PCS. Thus, the effect of statin on the recurrence of stroke may differ according to infarction location.

Key words: Statin, Stroke prevention, Anterior circulation stroke, Posterior circulation stroke

Introduction

Statins have been shown to reduce the risk of stroke in 174,000 participants enrolled in 27 randomized clinical trials (RCTs)1). However, RCTs of statins in patients with a history of stroke or transient ischemic attack (TIA) are limited. A previous meta-analysis found that the estimated statin’s efficacy in preventing recurrent stroke is marginal2). We have recently conducted the Japan Statin Treatment Against Recurrent Stroke (J-STARS) study to examine whether pravastatin (10 mg/day) reduces stroke recurrence in patients with non-cardioembolic ischemic stroke3). The J-STARS study showed that the incidence of ath-
The use of statins. Major exclusion criteria included ischemic stroke of rare etiology, ischemic stroke associated with catheterization or surgery, and use of statins for the treatment of comorbid coronary artery disease.

**Procedures**

A total of 1578 patients were randomly assigned to the pravastatin group (10 mg/day; n = 793) or the control group (n = 785). In the randomization process, the prevalence rates of stroke subtype at baseline (atherothrombotic stroke vs. others), high blood pressure (≥150/90 mmHg), and diabetes mellitus (presence vs. absence) were dynamically balanced between the groups. Total cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were measured as previously described. Treatment compliance was monitored at every clinical visit. The primary endpoint was the onset of stroke or TIA. Secondary endpoints included the onset of a stroke subtype, myocardial infarction, other vascular events, death, or hospitalization.

In the J-STARS study, the infarction locations at baseline were classified as cortical lesions, perforating lesions, and both. In addition, the arteries responsible for the infarction were classified as ACA, MCA, PCA, VB, and border zone (BZ). In this post hoc analysis, subjects with ACA, MCA, and BZ territory infarctions were assigned to the ACS group and those with PCA and VB territory infarctions were assigned to the PCS group.

**Statistical Analysis**

In accordance with the intention-to-treat (ITT) principle, the analysis set was defined as the ITT population, including all randomized patients. The distribution of the baseline characteristics between the ACS and PCS groups was compared using analysis of variance (for continuous variables) or χ² tests (for discrete variables). Data were expressed as mean ± standard deviation for continuous variables and as frequencies and percentages for discrete variables. In this post hoc analysis, the cumulative incidences of time to the first event were estimated by the Kaplan–Meier method. The cumulative incidence curves were compared by the log-rank test after adjustment for the stratification factors at randomization, i.e., stroke subtype at baseline (atherothrombotic stroke vs. others), high blood pressure (≥150/90 vs. <150/90 mmHg), and diabetes mellitus (presence vs. absence) were dynamically balanced between the groups. Total cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were measured as previously described. Treatment compliance was monitored at every clinical visit. The primary endpoint was the onset of stroke or TIA. Secondary endpoints included the onset of a stroke subtype, myocardial infarction, other vascular events, death, or hospitalization.

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characteristics according to infarction patterns are shown in Table 1. The PCS group had a significantly higher prevalence of diabetes mellitus than the ACS group (30.7% vs. 19.8%, \(P<0.001\)). In addition, the PCS group had a higher frequency of antiplatelet agent use (94.4% vs. 90.2%, \(P=0.006\)) and lower HDL cholesterol levels (1.3 ± 0.4 vs. 1.4 ± 0.4 mmol/L, \(P=0.014\)) than the ACS group. No significant differences in baseline characteristics between the pravastatin and control groups among patients with ACS or PCS were observed (Supplemental Table 1).

Effects of Pravastatin on the Outcomes between the ACS and PCS Groups

The incidence of all stroke and that of each stroke subtype (lacunar stroke, atherothrombotic stroke, and cerebral hemorrhage) during the follow-up (4.9 ± 1.4 years) are shown in Table 2. No significant difference in the incidence of stroke between the pravastatin and control groups among patients with ACS or PCS was noted (adjusted HR 1.32, 95% CI 0.93–

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**Table 1. Baseline characteristics of the participants**

|                      | ACS group \((n = 1022)\) | PCS group \((n = 499)\) | \(p\) |
|----------------------|--------------------------|-------------------------|------|
| **Age, years**       | 66.4 ± 8.5               | 65.8 ± 8.5              | 0.23 |
| **Male, n (%)**      | 694 (67.9)               | 360 (72.1)              | 0.09 |
| **BMI, kg/m\(^2\)**  | 23.7 ± 3.1               | 23.9 ± 3.0              | 0.09 |
| **Hypertension, n (%)** | 778 (76.1)         | 388 (77.8)              | 0.48 |
| **Diabetes mellitus, n (%)** | 202 (19.8)     | 153 (30.7)              | <0.001 |
| **Chronic kidney disease, n (%)** | 238 (23.3)        | 124 (24.8)              | 0.50 |
| **History of coronary disease, n (%)** | 54 (5.3)          | 22 (4.4)                | 0.45 |
| **Current and past smoking habit, n (%)** | 556 (54.4)      | 266 (53.3)              | 0.58 |
| **Duration after stroke onset, months** | 9.8 ± 10.2            | 8.9 ± 9.7               | 0.09 |
| **Initial NIHSS score, median (range)** | 1.0 (0–17)          | 1.0 (0–19)              | 0.78 |
| **Use of antiplatelet agents, n (%)** | 922 (90.2)        | 471 (94.4)              | 0.006 |
| **Use of antihypertensive agents, n (%)** | 612 (59.9)         | 313 (62.7)              | 0.19 |
| **Stroke subtype**   |                          |                         |      |
| Atherothrombotic stroke, n (%) | 258 (25.2)      | 137 (27.5)              | 0.12 |
| Lacunar stroke, n (%) | 680 (66.5)         | 297 (59.5)              |      |
| Undetermined, n (%)  | 84 (8.2)                | 65 (13.0)               |      |
| **Location of infarction** |                       |                         |      |
| Cortical, n (%)      | 191 (18.7)              | 101 (20.2)              | 0.49 |
| Perforating, n (%)   | 780 (76.3)              | 379 (76.0)              |      |
| Both, n (%)          | 51 (5.0)                | 19 (3.8)                |      |
| **Laboratory data**  |                          |                         |      |
| Total cholesterol, mmol/L | 5.4 ± 0.6             | 5.4 ± 0.6               | 0.45 |
| LDL cholesterol, mmol/L | 3.3 ± 0.6            | 3.4 ± 0.6               | 0.51 |
| Triglycerides, mmol/L | 1.6 ± 0.8            | 1.6 ± 0.9               | 0.29 |
| HDL cholesterol, mmol/L | 1.4 ± 0.4             | 1.3 ± 0.4               | 0.014 |
| Systolic blood pressure, mmHg | 136.7 ± 17.7        | 138.1 ± 18.1           | 0.14 |
| Diastolic blood pressure, mmHg | 79.3 ± 11.1         | 79.7 ± 11.6            | 0.47 |

ACS: anterior circulation stroke, PCS: posterior circulation stroke, BMI: body mass index, NIHSS: National Institutes of Health Stroke scale, LDL: low-density lipoprotein, HDL: high-density lipoprotein.
There were no significant differences in other stroke subtypes between the ACS and PCS groups among patients assigned to either pravastatin or control.

**Discussion**

In this post hoc analysis of the J-STARS study, pravastatin treatment significantly reduced stroke recurrence among patients with PCS but not among those with ACS. The interaction in the reduction of recurrent stroke risk by pravastatin was significant between the ACS and PCS groups.

In the present study, patients in the PCS group had a significantly higher prevalence of diabetes mellitus than those in the ACS group. Several studies have shown that diabetes mellitus is associated with brain stem infarction or posterior circulation infarction among patients with acute ischemic stroke, which is consistent with our findings for patients with non-cardioembolic stroke. Kim et al. showed that diabetes...
mellitus is related to intracranial or extracranial atherosclerotic lesions in the posterior circulation). In addition, Qiao et al. reported that posterior circulation arteries had a greater capacity to remodel in response to plaque formation than anterior circulation arteries. Hence, patients with PCS, who have a higher risk of systemic or intra-/extracranial atherothrombosis, would benefit from statin therapy. We also found that patients with PCS had lower HDL cholesterol levels than those with ACS. A previous study has also shown that HDL cholesterol levels in patients with acute ischemic stroke with posterior circulation infarction are decreased compared with the levels in patients with anterior circulation infarction. Decreased HDL cholesterol levels were assumed to be associated with atherosclerosis or endothelial dysfunction. Therefore, lower HDL cholesterol levels and diabetes may indicate that patients with PCS possibly have more severe systematic atherosclerosis than those with ACS. We speculated that the different baseline characteristics between the ACS and PCS groups may influence the decision of attending physicians on the frequency of antiplatelet agent use, especially in patients with PCS.

Furthermore, pravastatin significantly reduced stroke recurrence, especially atherothrombotic stroke, among patients with PCS. We initially speculated that several different baseline characteristics influence the effect of pravastatin. However, we could not find the indicators related to the effect of pravastatin on stroke prevention among patients with PCS. Although the reason for the different effects of pravastatin between the ACS and PCS groups remains unclear, the difference could be attributed to the possibly higher risk of systematic atherosclerosis in patients with PCS. Moreover, a high-sensitivity C-reactive protein (hs-CRP) sub-study in J-STARS found a significant reduction in CRP levels in the pravastatin group and showed that increased hs-CRP levels at baseline are associated with lower HDL levels and higher blood glucose levels. The J-STARS echo study, which evaluated the intima–media complex thickness (IMT) of the carotid artery, found that the presence of diabetes mellitus and decreased HDL cholesterol levels are independently associated with increased mean and max IMT. These sub-studies may support the hypothesis that patients with PCS have a higher risk of systematic atherosclerosis than those with ACS. However, Tan et al. reported that there were no differences in the statin effect on progression of atherosclerosis between anterior circulation and posterior circulation. In the present study, the reduction of atherothrombotic infarction recurrence showed similar trends among patients with ACS and patients with PCS, although it was not statistically significant among patients with ACS. In addition, we could not evaluate the recurrent infarction patterns according to responsible arteries. Therefore, it was not conclusive as to whether statin treatment more effectively reduces atherosclerosis progression for posterior circulation than for anterior circulation. Although the statin effect might contribute to secondary stroke prevention more among patients with PCS, our findings do not mean that one should refrain from the use of statin for secondary prevention among patients with ACS.

This study has several limitations. First, the study was a post hoc analysis of a prospective randomized open, blinded-endpoint design study. Subjects in the pravastatin and control groups were not randomized for the ACS and PCS groups. Hence, a definitive conclusion is difficult. Second, the small sample size may not provide sufficient statistical power to adequately assess the effects of pravastatin. Moreover, the number of events in each stroke subtype was limited. Statistical tests for the events in each stroke subtype also had limited power. Third, baseline infarction patterns according to responsible arteries could not be evaluated in all patients, thereby resulting in possible selection bias. Fourth, 43 patients with BZ infarction were classified into the ACS group; however, detailed information on infarction locations involving the ACA, MCA, and PCA could not be obtained. Nevertheless, a reduction in recurrent stroke risk by pravastatin was still significantly different between the ACS and PCS groups after excluding patients with BZ infarction ($P=0.002$ for interaction).

Conclusions

Pravastatin significantly reduced stroke recurrence among Japanese non-cardioembolic stroke patients with PCS. The reduction in recurrent stroke risk by pravastatin was significantly different between patients with ACS and those with PCS. Physicians should keep in mind that the statin effect may vary according to baseline infarction lesions. Further studies on whether the reduction in recurrent stroke risk by a high-dose or strong statin is different between patients with ACS and those with PCS may be necessary.

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Disclosures

Dr. Kitagawa reports personal fees from Daiichi Sankyo, during the conduct of the study; personal fees from Bayer Inc., Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Astellas Pharma, and Sanofi, outside the submitted work; and grants from Daiichi Sankyo during the conduct of the study; grants from Bayer Inc., Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Astellas Pharma, and Sanofi, outside the submitted work.

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The other authors declare that they have no conflicts of interest.

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Supplemental Table 1. Baseline characteristics of the participants

|                  | ACS group (n=1022) | PCS group (n=499) |
|------------------|--------------------|-------------------|
|                  | Pravastatin (n=494) | Control (n=528)   | Pravastatin (n=275) | Control (n=224) |
| Age, years       | 66.1 ± 8.5         | 66.7 ± 8.6        | 66.0 ± 8.3          | 65.6 ± 8.7      |
| Male, n (%)      | 331 (67.0)         | 363 (68.8)        | 198 (72.0)          | 162 (72.3)      |
| BMI, kg/m²       | 23.7 ± 3.2         | 23.6 ± 3.0        | 24.0 ± 2.9          | 23.8 ± 3.0      |
| Hypertension, n (%) | 367 (74.3)       | 411 (77.8)        | 215 (78.2)          | 173 (77.2)      |
| Diabetes mellitus, n (%) | 97 (19.6)     | 105 (19.9)        | 81 (29.5)           | 72 (32.1)       |
| Chronic kidney disease, n (%) | 117 (23.7)    | 121 (22.9)        | 69 (25.1)           | 55 (24.6)       |
| History of coronary disease, n (%) | 23 (4.7)       | 31 (5.9)          | 12 (4.4)            | 10 (4.5)        |
| Current and past smoking habit, n (%) | 263 (53.2)    | 293 (55.5)        | 149 (54.2)          | 117 (52.2)      |
| Duration after stroke onset, months | 9.8 ± 10.2    | 9.9 ± 10.0        | 9.3 ± 10.2          | 8.4 ± 9.1       |
| Initial NIHSS score, median (range) | 1.0 (0-17)    | 1.0 (0-14)        | 1.0 (0-19)          | 1.0 (0-17)      |
| Use of antiplatelet agents, n (%) | 444 (89.9)    | 478 (90.5)        | 259 (94.2)          | 212 (94.6)      |
| Use of antihypertensive agents, n (%) | 287 (58.1)    | 325 (61.6)        | 177 (64.4)          | 136 (60.7)      |
| Stroke subtype   |                   |                   |                   |                 |
| Atherothrombotic stroke, n (%) | 102 (25.3)    | 133 (25.2)        | 67 (24.4)           | 70 (31.3)       |
| Lacunar stroke, n (%) | 325 (65.8)    | 355 (67.2)        | 168 (61.1)          | 129 (57.6)      |
| Undetermined, n (%) | 44 (8.9)       | 40 (7.6)          | 40 (14.5)           | 25 (11.2)       |
| Location of infarction |                 |                   |                   |                 |
| Cortical, n (%)  | 94 (19.0)         | 97 (18.4)         | 50 (18.2)           | 51 (22.8)       |
| Perforating, n (%) | 376 (76.1)     | 404 (76.5)        | 216 (78.5)          | 163 (72.8)      |
| Both, n (%)      | 24 (4.9)          | 27 (5.1)          | 9 (3.3)             | 10 (4.5)        |
| Laboratory data  |                   |                   |                   |                 |
| Total cholesterol, mmol/L | 5.5 ± 0.6     | 5.4 ± 0.7         | 5.5 ± 0.6           | 5.4 ± 0.6       |
| LDL cholesterol, mmol/L | 3.3 ± 0.7     | 3.4 ± 0.4         | 3.4 ± 0.6           | 3.3 ± 0.6       |
| Triglycerides, mmol/L  | 1.6 ± 0.8     | 1.6 ± 0.8         | 1.7 ± 0.6           | 1.6 ± 0.6       |
| HDL cholesterol, mmol/L | 1.4 ± 0.4     | 1.4 ± 0.4         | 1.3 ± 0.4           | 1.4 ± 0.4       |
| Systolic blood pressure, mmHg | 136.9 ± 17.6 | 136.5 ± 17.9     | 138.4 ± 17.8        | 137.8 ± 18.4    |
| Diastolic blood pressure, mmHg | 79.4 ± 11.2  | 79.2 ± 11.0       | 79.5 ± 12.3         | 80.0 ± 10.8     |

ACS: anterior circulation stroke, PCS: posterior circulation stroke, BMI: body mass index, NIHSS: National Institutes of Health Stroke scale, LDL: low-density lipoprotein, HDL: high-density lipoprotein
Supplemental Fig. 1. Exploratory analyses of the effects of pravastatin on all stroke recurrence in patients with anterior circulation stroke.
Supplemental Fig. 2. Exploratory analyses of the effects of pravastatin on all stroke recurrence in patients with posterior circulation stroke