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

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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-analy-

sis 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-

erothrombotic stroke was lower in the pravastatin group than in the control group, although the total stroke or TIA incidence was similar between both the groups⁴. Moreover, in the subgroup analysis, baseline arteries responsible for stroke (e.g., anterior cerebral artery [ACA], middle cerebral artery [MCA], posterior cerebral artery [PCA], and vertebrobasilar artery [VB]) influenced the effect of statin on the prevention of stroke or TIA (the *P* value for the interaction test of statin heterogeneity across the subgroup of stroke responsible arteries was 0.01)⁴. To date, few studies on whether the benefits of statins differ, depending on the site of baseline infarction, have been conducted.

Stroke is a heterogeneous disease with different etiologies. Hence, physicians should consider stroke subtypes or infarction sites in stroke management. Infarction locations are generally classified as anterior or posterior circulation lesions^{5, 6}. Posterior circulation stroke (PCS) accounts for 20%–25% of all ischemic stroke cases and has different clinical features, baseline characteristics, etiologies, and prognosis compared with anterior circulation stroke (ACS)⁵. The aim of this post hoc analysis of the J-STARS study was to evaluate the difference in clinical characteristics and compare the benefit of statin for ACS and PCS.

Materials and Methods

Details of the rationale, study design, characteristics of the participants, and principal results in J-STARS have been published elsewhere^{3, 4, 7}. This study was conducted as a post hoc analysis of J-STARS under the health insurance system of Japan and in accordance with the Declaration of Helsinki and Ethical Guidelines on Clinical Studies of the Ministry of Health, Labor, and Welfare of Japan. The study was also approved by the Institutional Review Board of each participating center, and written informed consent was obtained from all the patients. This trial is registered at ClinicalTrials.gov under number NCT00221104.

Subjects

Subjects aged 45–80 years with a history of non-cardioembolic ischemic stroke within the preceding 1 month to 3 years from 123 centers between March 2004 and February 2009 were enrolled. At enrollment, all patients had a total cholesterol level between 180 and 240 mg/dL (4.65 and 6.21 mmol/L) without

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 ($\geq 150/90$ 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^{3, 4}. 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 χ^2 tests (for discrete variables). Data were expressed as mean \pm 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 ($\geq 150/90$ vs. $< 150/90$ mmHg), and diabe-

Table 1. Baseline characteristics of the participants

| | ACS group (<i>n</i> = 1022) | PCS group (<i>n</i> = 499) | <i>p</i> |
|--|------------------------------|-----------------------------|----------|
| Age, years | 66.4 ± 8.5 | 65.8 ± 8.5 | 0.23 |
| Male, <i>n</i> (%) | 694 (67.9) | 360 (72.1) | 0.09 |
| BMI, kg/m ² | 23.7 ± 3.1 | 23.9 ± 3.0 | 0.09 |
| Hypertension, <i>n</i> (%) | 778 (76.1) | 388 (77.8) | 0.48 |
| Diabetes mellitus, <i>n</i> (%) | 202 (19.8) | 153 (30.7) | < 0.001 |
| Chronic kidney disease, <i>n</i> (%) | 238 (23.3) | 124 (24.8) | 0.50 |
| History of coronary disease, <i>n</i> (%) | 54 (5.3) | 22 (4.4) | 0.45 |
| Current and past smoking habit, <i>n</i> (%) | 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, <i>n</i> (%) | 922 (90.2) | 471 (94.4) | 0.006 |
| Use of antihypertensive agents, <i>n</i> (%) | 612 (59.9) | 313 (62.7) | 0.19 |
| Stroke subtype | | | |
| Atherothrombotic stroke, <i>n</i> (%) | 258 (25.2) | 137 (27.5) | 0.12 |
| Lacunar stroke, <i>n</i> (%) | 680 (66.5) | 297 (59.5) | |
| Undetermined, <i>n</i> (%) | 84 (8.2) | 65 (13.0) | |
| Location of infarction | | | |
| Cortical, <i>n</i> (%) | 191 (18.7) | 101 (20.2) | 0.49 |
| Perforating, <i>n</i> (%) | 780 (76.3) | 379 (76.0) | |
| Both, <i>n</i> (%) | 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

tes mellitus (presence vs. absence), between the ACS and PCS groups. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and the 95% confidence interval (CI) by adjusting the stratification factors. To compare the pravastatin effects between the ACS and PCS groups, a test of interaction was performed in the stratified Cox proportional hazards model. All analyses were conducted using SAS version 9.3 (Cary, NC). The level of significance was set at $P < 0.05$ (two-tailed).

Results

Baseline Characteristics between the ACS and PCS Groups

Of the 1578 patients in the J-STARS study, 1521 (96.4%) were evaluated for baseline infarction patterns according to responsible arteries: 1022 were included in the ACS group (ACA, $n=32$; MCA, $n=947$; BZ, $n=43$) and 499 were included in the PCS group (PCA, $n=120$; VB, $n=379$). The baseline

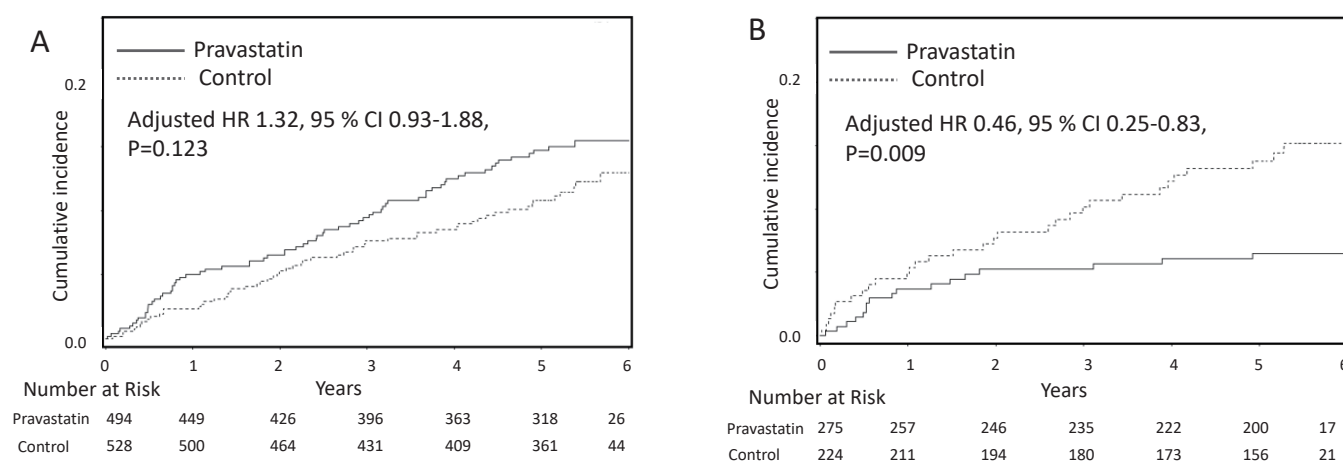
characteristics according to infarction patterns are shown in **Table 1**. The PCS group had a significantly higher prevalence of diabetes mellitus than the ACS group (30.7% vs. 19.8%, $P < 0.001$). In addition, the PCS group had a higher frequency of antiplatelet agent use (94.4% vs. 90.2%, $P=0.006$) 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 was noted (adjusted HR 1.32, 95% CI 0.93–

Table 2. Incidence of stroke and stroke subtypes

| | ACS group (<i>n</i> = 1022) | | PCS group (<i>n</i> = 499) | |
|--|----------------------------------|------------------------------|----------------------------------|------------------------------|
| | Pravastatin (<i>n</i> = 494) | Control (<i>n</i> = 528) | Pravastatin (<i>n</i> = 275) | Control (<i>n</i> = 224) |
| Stroke, <i>n</i> (100 person-years) | 68 (3.08) | 57 (2.32) | 17 (1.30) | 31 (2.98) |
| Stroke subtypes, <i>n</i> (100 person-years) | | | | |
| Atherothrombotic stroke | 6 (0.25) | 16 (0.62) | 2 (0.15) | 9 (0.81) |
| Lacunar stroke | 34 (1.48) | 23 (0.91) | 13 (0.98) | 15 (1.38) |
| Cerebral hemorrhage | 7 (0.29) | 6 (0.23) | 3 (0.22) | 4 (0.36) |

**Fig. 1.** Kaplan–Meier curves for patients with anterior circulation stroke (A) and patients with posterior circulation stroke (B) from both the pravastatin and control groups

The Cox proportional hazards model was applied by adjusting for stroke subtype (atherothrombotic stroke vs. others), high blood pressure ($\geq 150/90$ vs. $< 150/90$ mmHg), and diabetes mellitus (presence vs. absence). HR, hazard ratio; CI, confidence interval.

1.88, $P=0.123$; **Fig. 1A**). In contrast, the event rates of all stroke were significantly lower in the pravastatin group than in the control group among patients with PCS (adjusted HR 0.46, 95% CI 0.25–0.83, $P=0.009$; **Fig. 1B**). A significant interaction between the ACS and PCS groups in terms of pravastatin effects was noted ($P=0.003$ for interaction). There were no significant interactions between the other subgroups except for lower body mass index and pravastatin effect in patients with ACS (**Supplemental Fig. 1**). Similarly, no significant interactions between any subgroups and the pravastatin effect in patients with PCS were found (**Supplemental Fig. 2**). Furthermore, the pravastatin group had a significant reduction in atherothrombotic infarction recurrence compared with the controls among patients with PCS (adjusted HR 0.21, 95% CI 0.05–0.99, $P=0.030$). For patients with ACS, the pravastatin effect of reduction for the atherothrombotic infarction recurrence showed similar trends, but it was not statistically significant (adjusted HR 0.42, 95% CI 0.16–1.07,

$P=0.059$). 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^{8, 9}, 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 circulation¹⁰). In addition, Qiao *et al.* reported that posterior circulation arteries had a greater capacity to remodel in response to plaque formation than anterior circulation arteries¹¹). 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 infarction¹²). Decreased HDL cholesterol levels were assumed to be associated with atherosclerosis or endothelial dysfunction^{13, 14}). 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 levels¹⁵). 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 IMT¹⁶). 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 circulation¹⁷). 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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Ms. Nakagawa and Mr. Kagimura are employed at the Translational Research Informatics Center, which contracted with the J-STARS office as a data center and received a data center fee.

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

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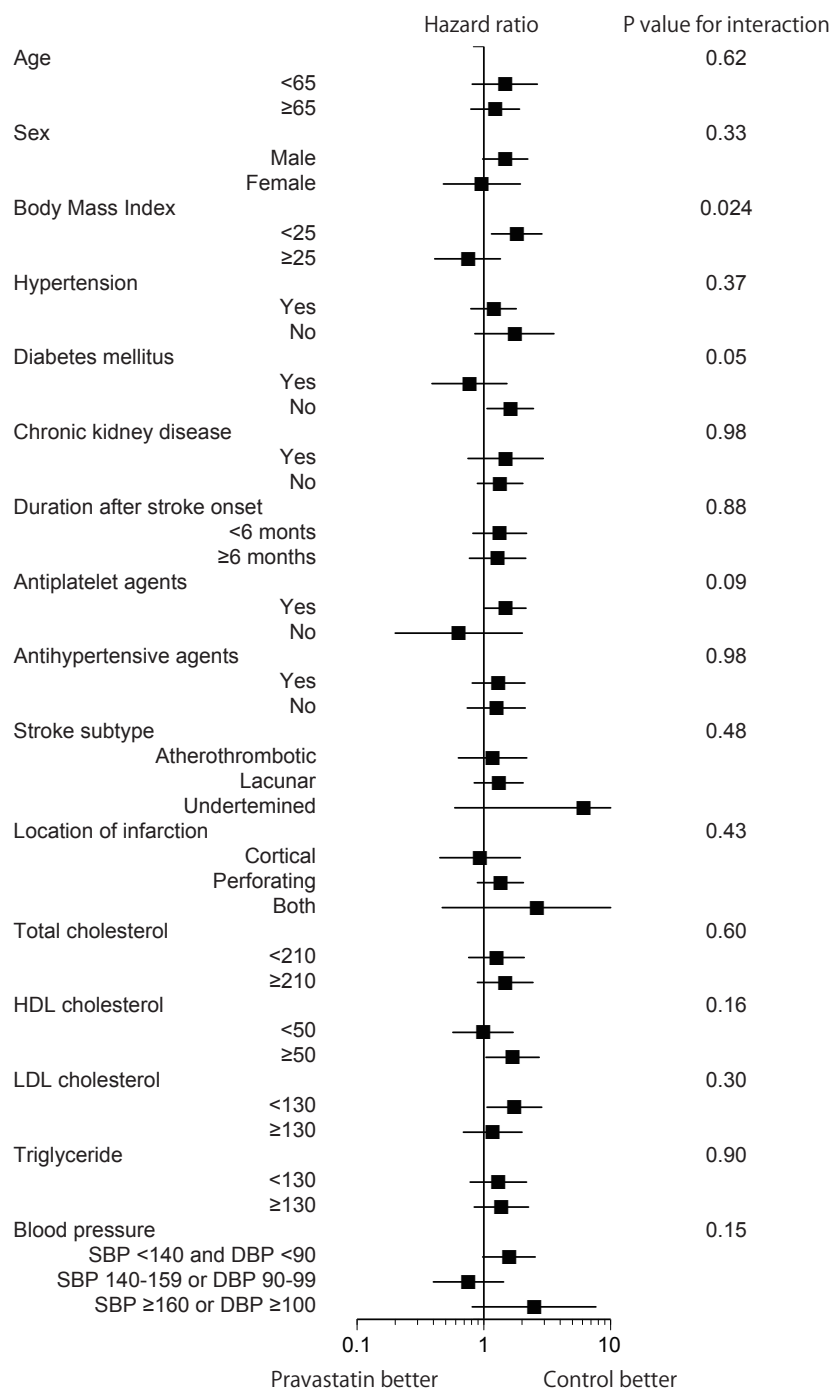
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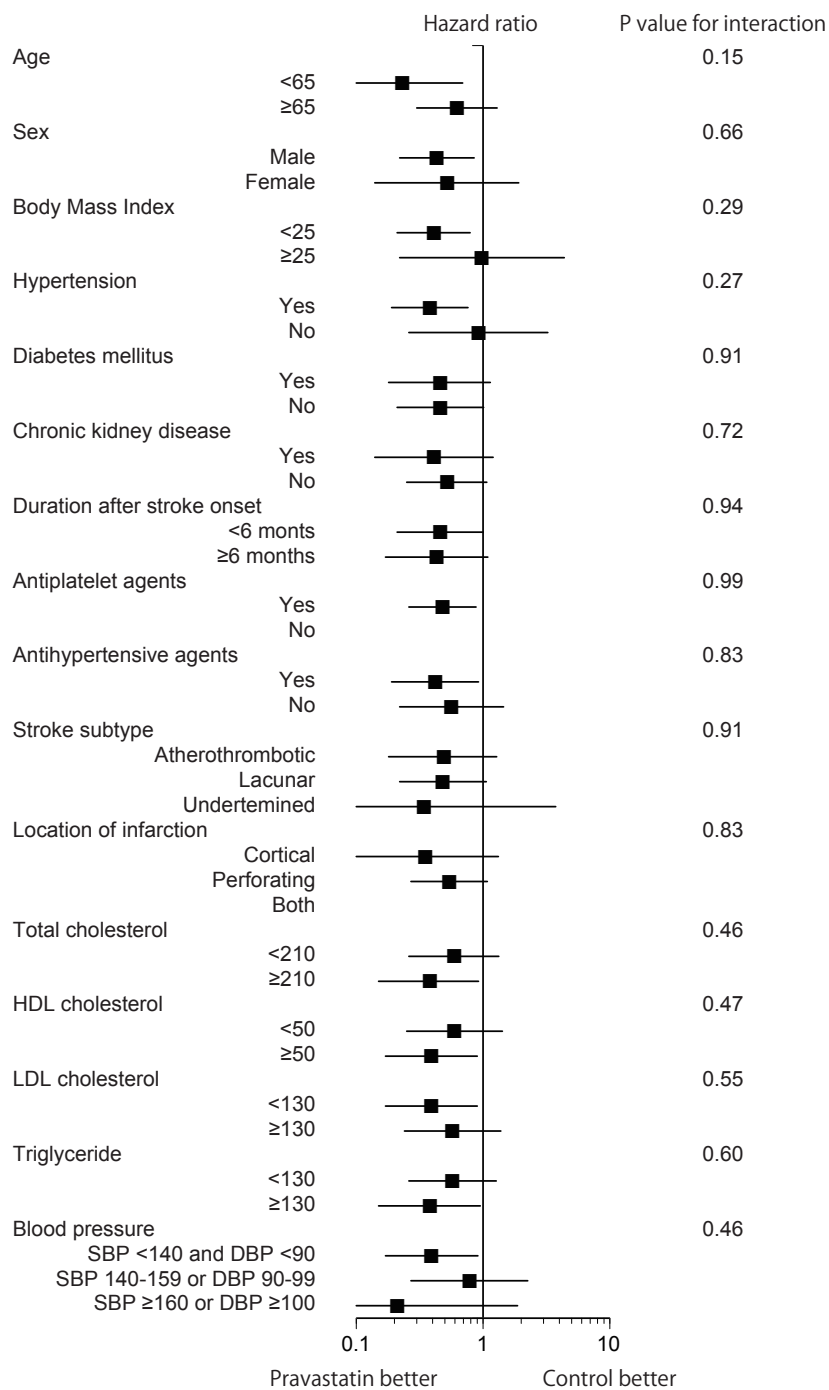
Supplemental Table 1. Baseline characteristics of the participants

| | ACS group (<i>n</i> =1022) | | PCS group (<i>n</i> =499) | |
|--|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| | Pravastatin (<i>n</i> =494) | Control (<i>n</i> =528) | Pravastatin (<i>n</i> =275) | Control (<i>n</i> =224) |
| Age, years | 66.1 ± 8.5 | 66.7 ± 8.6 | 66.0 ± 8.3 | 65.6 ± 8.7 |
| Male, <i>n</i> (%) | 331 (67.0) | 363 (68.8) | 198 (72.0) | 162 (72.3) |
| BMI, kg/m ² | 23.7 ± 3.2 | 23.6 ± 3.0 | 24.0 ± 2.9 | 23.8 ± 3.0 |
| Hypertension, <i>n</i> (%) | 367 (74.3) | 411 (77.8) | 215 (78.2) | 173 (77.2) |
| Diabetes mellitus, <i>n</i> (%) | 97 (19.6) | 105 (19.9) | 81 (29.5) | 72 (32.1) |
| Chronic kidney disease, <i>n</i> (%) | 117 (23.7) | 121 (22.9) | 69 (25.1) | 55 (24.6) |
| History of coronary disease, <i>n</i> (%) | 23 (4.7) | 31 (5.9) | 12 (4.4) | 10 (4.5) |
| Current and past smoking habit, <i>n</i> (%) | 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, <i>n</i> (%) | 444 (89.9) | 478 (90.5) | 259 (94.2) | 212 (94.6) |
| Use of antihypertensive agents, <i>n</i> (%) | 287 (58.1) | 325 (61.6) | 177 (64.4) | 136 (60.7) |
| Stroke subtype | | | | |
| Atherothrombotic stroke, <i>n</i> (%) | 102 (25.3) | 133 (25.2) | 67 (24.4) | 70 (31.3) |
| Lacunar stroke, <i>n</i> (%) | 325 (65.8) | 355 (67.2) | 168 (61.1) | 129 (57.6) |
| Undetermined, <i>n</i> (%) | 44 (8.9) | 40 (7.6) | 40 (14.5) | 25 (11.2) |
| Location of infarction | | | | |
| Cortical, <i>n</i> (%) | 94 (19.0) | 97 (18.4) | 50 (18.2) | 51 (22.8) |
| Perforating, <i>n</i> (%) | 376 (76.1) | 404 (76.5) | 216 (78.5) | 163 (72.8) |
| Both, <i>n</i> (%) | 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