The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2020; 27: 524-533. http://doi.org/10.5551/jat.51391

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

Tomohisa Nezu[1], Naohisa Hosomi[1], Kazuo Kitagawa[2], Yoji Nagai[3], Yoko Nakagawa[4], Shiro Aoki[1], Tatsuo Kagimura[4], Hirofumi Maruyama[1], Hideki Origasa[5], Kazuo Minematsu[6], Shinichiro Uchiyama[7] and Masayasu Matsumoto[1, 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 marginal[2]. 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 stroke[3]. 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 groups[4]. 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 noncardioembolic 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 (≥ 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 ± 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 diabe-

Address for correspondence: Naohisa Hosomi, Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan E-mail: nhosomi@hiroshima-u.ac.jp

Received: July 24, 2019 Accepted for publication: August 22, 2019

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

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 (n = 1022)		PCS group (n = 499)	
	Pravastatin (n = 494)	Control (n = 528)	Pravastatin (n = 275)	Control (n = 224)
Stroke, n (100 person-years)	68 (3.08)	57 (2.32)	17 (1.30)	31 (2.98)
Stroke subtypes, n (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)

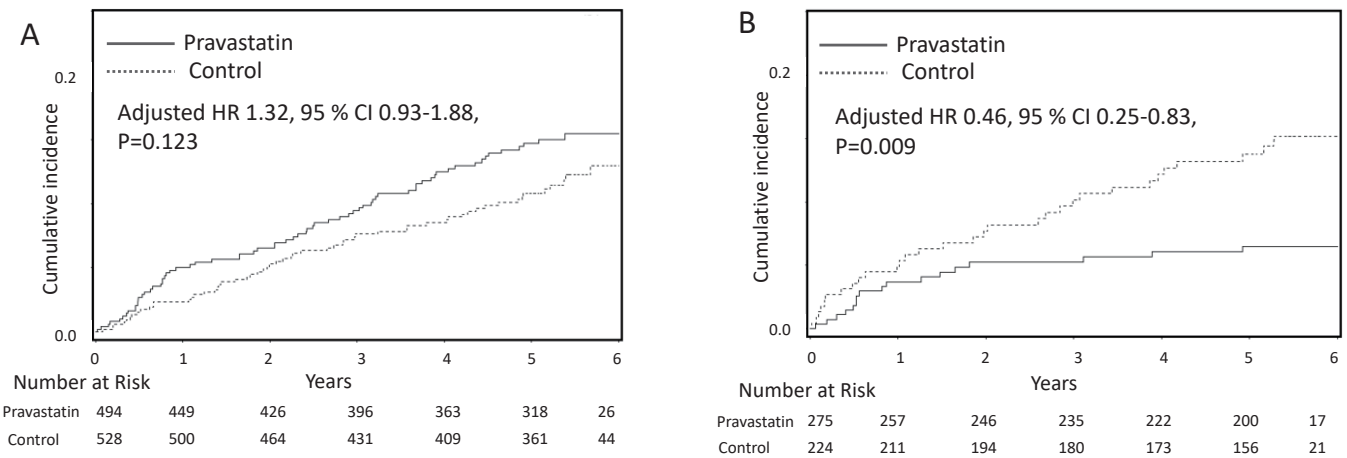


Fig. 1. Kaplan–Meier curves for patients with anterior circulation stroke (A) and patients with posterior circulation stroke (B) from both the pravastatin and control groups

The Cox proportional hazards model was applied by adjusting for stroke subtype (atherothrombotic stroke vs. others), high blood pressure (≥ 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 circulation[10]. 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[11]. 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[12]. 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 levels[15]. 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[16]. 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[17]. 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.

Acknowledgments

The authors would like to thank the patients and their families, the physicians and medical staff, and their co-workers for their assistance in the preparation and execution of this study.

Sources of Funding

This study was initially supported by a grant from the Ministry of Health, Labor, and Welfare of Japan. After the governmental support expired, the study was conducted in collaboration with Hiroshima University Graduate School of Biomedical and Health Sciences and the Foundation for Biomedical Research and Innovation. The latter organization received unconditional research grants from several pharmaceutical companies, including Daiichi Sankyo Co., Ltd., which commercializes pravastatin. However, the company was not involved in the design or execution of this study. In addition, the company did not provide pravastatin for this study and has not reviewed the manuscript.

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.

Dr. Maruyama reports grants from Grants-in-Aid for Scientific Research, Eisai, Pfizer, Otsuka Pharmaceutical, Shionogi, Sumitomo Dainippon Pharma, Nihon Medi-Physics, Bayer, MSD, Daiichi Sankyo, Sanofi, and Astellas Pharma, outside the submitted work.

Dr. Minematsu reports personal fees from Bayer Yakuhin, Otsuka Pharmaceutical, Boehringer-Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma Corporation, Japan Stryker, Daiichi Sankyo, Astellas Pharma, Nippon Chemiphar, Fuji Film RI Pharma, CSL Behring, Medicos Hirata, EPS Corporation, HEALIOS K.K., and T-PEC Corporation, outside the submitted work.

Dr. Uchiyama reports personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, Daiichi Sankyo, Dainippon Sumitomo, Astellas Pharma, AstraZeneca, Sannwa Kagaku, Shionogi, Mitsubishi Tanabe, and Pfizer, outside the submitted work.

Dr. Matsumoto reports personal fees from Kowa Pharmaceutical Co Ltd, Takeda Pharmaceutical Co Ltd, Bayer Yakuhin, Ltd, Sanofi KK, Daiichi Sankyo Co Ltd, Otsuka Pharmaceutical Co Ltd, Astellas Pharma Inc, Astra Zeneca KK, Mochida Pharmaceutical Co Ltd, Sumitomo Dainippon Pharma Co Ltd, Amgen Astellas BioPharma KK, Eisai Co Ltd, and Pfizer Japan Inc, outside the submitted work.

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.

References

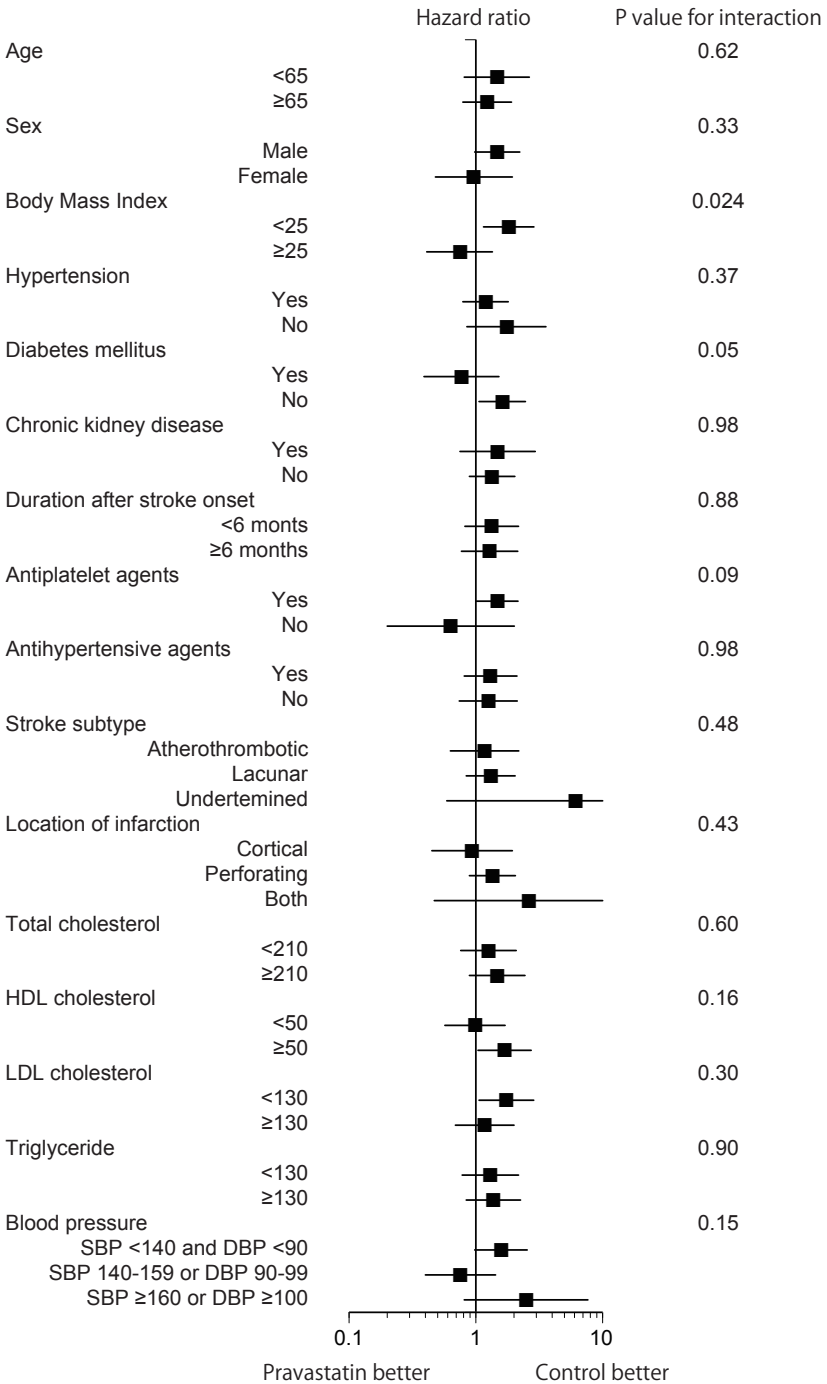
1) Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of ldl-lowering therapy among men and women: Meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet, 2015; 385: 1397-1405
2) Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev, 2009: CD002091
3) Nagai Y, Kohriyama T, Origasa H, Minematsu K, Yokota C, Uchiyama S, et al. Rationale, design, and baseline features of a randomized controlled trial to assess the effects of statin for the secondary prevention of stroke: The Japan Statin Treatment Against Recurrent Stroke (J-STARS). Int J Stroke, 2014; 9: 232-239
4) Hosomi N, Nagai Y, Kohriyama T, Ohtsuki T, Aoki S, Nezu T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): A multicenter, randomized, open-label, parallel-group study. EBioMedicine, 2015; 2: 1071-1078
5) Merwick Á, Werring D. Posterior circulation ischaemic stroke. BMJ, 2014; 348: g3175
6) Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: Diagnosis, investigation, and secondary prevention. Lancet Neurol, 2013; 12: 989-998
7) Hosomi N, Kitagawa K, Nagai Y, Nakagawa Y, Aoki S, Nezu T, et al. Desirable low-density lipoprotein cholesterol levels for preventing stroke recurrence: A post hoc analysis of the J-STARS study (Japan Statin Treatment Against Recurrent Stroke). Stroke, 2018; 49: 865-871
8) Ichikawa H, Kuriki A, Kinno R, Katoh H, Mukai M, Kawamura M. Occurrence and clinicotopographical correlates of brainstem infarction in patients with diabetes mellitus. J Stroke Cerebrovasc Dis, 2012; 21: 890-897
9) Zeng Q, Tao W, Lei C, Dong W, Liu M. Etiology and risk factors of posterior circulation infarction compared with anterior circulation infarction. J Stroke Cerebrovasc Dis, 2015; 24: 1614-1620
10) Kim JS, Nah HW, Park SM, Kim SK, Cho KH, Lee J, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: Intracranial compared with extracranial and anterior compared with posterior circulation disease. Stroke, 2012; 43: 3313-3318
11) Qiao Y, Anwar Z, Intrapiromkul J, Liu L, Zeiler SR, Leigh R, et al. Patterns and implications of intracranial arterial remodeling in stroke patients. Stroke, 2016; 47:

434-440
12) Luo Y, Li Z, Zhang J, Li J, Lu Z. Dyslipidaemia was correlated to the posterior circulation infarction in non-diabetic populations. Lipids Health Dis, 2018; 17: 150
13) Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 2009; 302: 1993-2000
14) Kratzer A, Giral H, Landmesser U. High-density lipoproteins as modulators of endothelial cell functions: Alterations in patients with coronary artery disease. Cardiovasc Res, 2014; 103: 350-361
15) Kitagawa K, Hosomi N, Nagai Y, Kagimura T, Ohtsuki T, Origasa H, et al. Reduction in High-Sensitivity C-Reactive Protein Levels in Patients with Ischemic Stroke by Statin Treatment: Hs-CRP Sub-Study in J-STARS. J Atheroscler Thromb, 2017; 24: 1039-1047
16) Wada S, Koga M, Toyoda K, Minematsu K, Yasaka M, Nagai Y, et al. Factors Associated with Intima-Media Complex Thickness of the Common Carotid Artery in Japanese Noncardioembolic Stroke Patients with Hyperlipidemia: The J-STARS Echo Study. J Atheroscler Thromb, 2018; 25: 359-373
17) Tan TY, Kuo YL, Lin WC, Chen TY. Effect of lipid-lowering therapy on the progression of intracranial arterial stenosis. J Neurol, 2009; 256: 187-193

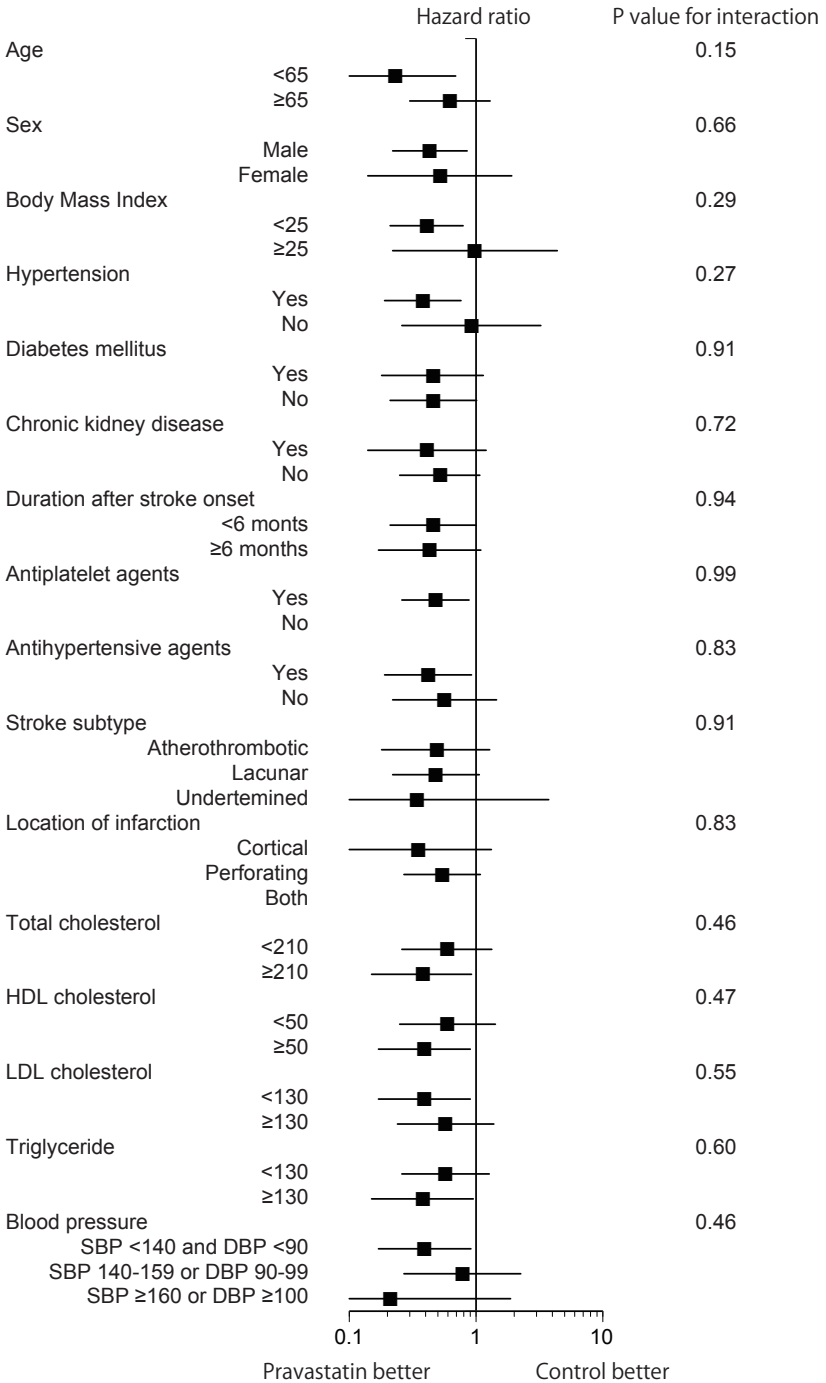
Supplemental Table 1. Baseline characteristics of the participants

	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/m^2	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