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Original Article

Reduction in High-Sensitivity C-Reactive Protein Levels in Patients with Ischemic Stroke by Statin Treatment: Hs-CRP Sub-Study in J-STARS

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***Aims*: The pleiotropic effects of statins on recurrent stroke remain unclear. We investigated the effects of pravastatin on high-sensitivity C-reactive proteins (Hs-CRP) in ischemic stroke, and explored the impact of Hs-CRP on recurrent stroke and vascular events.**

***Methods*: This randomized open-label trial was ancillary to the J-STARS trial. One thousand and ninety-five patients with non-cardiogenic ischemic stroke were assigned to the pravastatin (n=545) or control groups (n=550). The primary and secondary endpoints were serum Hs-CRP reduction and stroke recurrence, including both ischemic and hemorrhagic ones, respectively. Onset of vascular events and each stroke subtype in relation to Hs-CRP levels were also determined.**

***Results*: In the pravastatin treatment group, Hs-CRP levels (median 711 μg/L, IQR 344−1500) significantly decreased 2 months later (median 592 μg/L, IQR 301−1390), and they remained significantly lower until the end of the study. However, in the control group, baseline Hs-CRP levels were similar to those 2 months later. The reduction of Hs-CRP levels from the baseline to 2 months in the pravastatin group was statistically significant compared with the control (p=0.007). One SD increase in log-transformed Hs-CRP increased the risk of stroke recurrence (HR 1.17, 95% CI 0.97−1.40) and vascular events (HR 1.30, 95% CI 1.12−1.51). With an Hs-CRP cut-off of 1000 μg/L, higher Hs-CRP significantly increased the risk of recurrent stroke (HR 1.50, 95% CI 1.03−2.17) and vascular events (HR 1.68, 95% CI 1.23−2.29).**

***Conclusion*: In non-cardiogenic ischemic stroke, pravastatin treatment may reduce vascular inflammation as assessed by Hs-CRP, and higher Hs-CRP levels appeared to increase the risk of recurrent stroke and vascular events.**

Key words: Ischemic stroke, Statin, C-reactive protein, Inflammation

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Introduction

Vascular inflammation has attracted much attention as a crucial symptom of atherothrombosis[1]. High-sensitivity C-reactive protein (Hs-CRP) has been estab-

lished as predictive for incident myocardial infarction and ischemic stroke in meta-analysis[2]. Based on this, the measurement of Hs-CRP has been recommended as a marker of low-grade vessel inflammation in patients at high-risk for atherosclerosis in several major guidelines for primary stroke prevention[3]. Statin treatment is beneficial for the secondary prevention of an ischemic stroke[4]. In addition to lipid-lowering effects, the anti-inflammatory effects of statins, including decreased Hs-CRP levels, have been considered important for stroke prevention[5]. Several studies showed stabilization of atheromatous plaque in patients with severe carotid stenosis[6]. In the general population and patients with coronary artery disease, statin treatment was shown to decrease the level of Hs-CRP[7, 8]. Although statin treatment has been shown to decrease Hs-CRP levels in a small prospective cohort study with acute ischemic stroke[9], there is no large-scale clinical information about the effect of statins on Hs-CRP in patients with a history of ischemic stroke. Baseline Hs-CRP level was shown to predict the risk of recurrent stroke in PROGRESS[10], SPS3[11], and CHANCE trial[12], but Hs-CRP level could vary after treatment for metabolic factors, including with statins[7-9]. In fact, follow-up CRP level was shown to be more strongly associated with outcomes in acute stroke patients than in admission levels[13]. Thus, we examined median Hs-CRP levels during follow-ups in relation to stroke recurrence and incident vascular events. Furthermore, the Hs-CRP cut-off level could vary in ethnic populations, because the Hs-CRP level in Asian populations is much lower than that in Caucasian populations[14, 15]. In the US guidelines, 3000 μg/L has been used as a cut-off for vascular inflammation[3], but this value should be investigated in Asian chronic ischemic stroke patients. Thus, this study investigated the association between Hs-CRP level and vascular events in order to find a cut-off Hs-CRP value for recurrent stroke and incident vascular events in Asian populations.

Materials and Methods

Patients

The Hs-CRP sub-study was designed as an ancillary study to the J-STARS trial. This trial is registered at ClinicalTrials.gov as number NCT00361699. Details of the rationale, study design, characteristics of the participants, and principal results in J-STARS have been published elsewhere[16, 17]. Briefly, patients aged 45−80 years with a history of non-cardiogenic ischemic stroke within the preceding 1 month to 3 years, were enrolled from 123 centers between March 2004 and February 2009. All patients had been previously diagnosed with hyperlipidemia and demonstrated stable serum total cholesterol levels at 180−240 mg/dL. Major exclusion criteria included cerebral infarction of determined rare etiology, (e.g., vertebral artery dissection, fibromuscular dysplasia, or moyamoya disease), infarction associated with catheterization or surgery, and preferred use of statins for the treatment of comorbid coronary artery disease. Written informed consent was obtained from each patient. This study was conducted under the health insurance system of Japan, in accordance with the Declaration of Helsinki and the Ethical Guidelines on Clinical Studies of the Ministry of Health, Labour and Welfare of Japan.

Procedures

Patients were enrolled via a web-based registration and follow-up system provided by the data center at the Translational Research Informatics Center, Kobe, Japan. This system automatically judged patient eligibility and randomly assigned participants to the pravastatin (10 mg/day) or control group (1:1 allocation). In the randomization process, prevalence rates of stroke subtype (atherothrombotic infarction), elevated blood pressure (≥150/90 mmHg), and comorbidity of diabetes were dynamically balanced between the two groups. In the pravastatin group, pravastatin administration was initiated within 1 month after randomization, and treatment continued until the final observation. Diet and exercise therapies were reinforced when total cholesterol levels consistently exceeded 240 mg/dL at routine clinical visits. Increase of pravastatin dose or the addition of other drugs was allowed only when such reinforcements were insufficient, based on the decision of the primary physician. Use of statins other than pravastatin was prohibited. In the control group, administration of any statin was prohibited.

After randomization, patients had blood sampling at 2 and 6 months, 2 and 5 years, or at study completion. When patients underwent recurrent stroke, myocardial infarction, vascular accident, death, or hospitalization, such event information was sent to the data center and managed by dedicated data managers. Blood Hs-CRP and lipid levels were measured in the Special Reference Laboratory, Inc. (Tokyo, Japan), which was certified for major lipid measurements in accordance with the Centers for Disease Control and Prevention (Atlanta, GA, USA). Treatment compliance was monitored at every clinical visit.

The primary endpoint was the reduction of Hs-CRP. The secondary endpoint was stroke recurrence, including both ischemic and hemorrhagic ones, in relation to statin use and Hs-CRP level. We also examined the onset of all vascular events and each

Table 1. Baseline characteristics

Characteristic	J-STARS Only (N = 483)	J-STARS Hs-CRP sub-study (N = 1095)	*P* value	Pravastatin (N = 545)	Control (N = 550)
Age, years	66.0 ± 8.6	66.2 ± 8.5	0.460	66.3 ± 8.5	66.4 ± 8.4
Male, N (%)	332 (68.7)	755 (68.9)	0.933	374 (68.6)	381 (69.3)
BMI, kg/m^2	23.8 ± 3.2	23.7 ± 3.0	0.528	23.8 ± 3.1	23.6 ± 3.0
Interval between index stroke and enrolment, months	10.1 ± 10.1	9.8 ± 10.2	0.592	9.9 ± 10.3	9.7 ± 10.1
Total cholesterol, mg/dL	210.5 ± 21.9	209.9 ± 25.5	0.407	210.1 ± 25.2	209.6 ± 25.7
HDL cholesterol, mg/dL	54.5 ± 16.5	53.0 ± 15.4	0.086	53.2 ± 15.6	52.8 ± 15.3
LDL cholesterol, mg/dL	128.3 ± 23.8	129.9 ± 24.7	0.246	129.8 ± 24.7	130.0 ± 24.7
Triglyceride, mg/dL	140.7 ± 68.1	142.9 ± 76.8	0.585	141.8 ± 78.2	143.9 ± 75.5
Hypertension, N (%)	364 (75.4)	836 (76.3)	0.673	416 (76.3)	420 (76.4)
Systolic blood pressure, mmHg	138.2 ± 18.0	136.6 ± 17.7	0.094	137.1 ± 17.8	136.1 ± 17.5
Diastolic blood pressure, mmHg	79.7 ± 11.1	79.2 ± 11.4	0.471	79.4 ± 12.0	79.0 ± 10.7
Diabetes mellitus, N (%)	112 (23.2)	257 (23.5)	0.903	119 (21.8)	138 (25.1)
Fasting blood glucose, mg/dL	117.0 ± 37.1	117.9 ± 42.6	0.696	118.5 ± 44.7	117.3 ± 40.4
Coronary artery disease, N (%)	26 (5.4)	55 (5.0)	0.741	25 (4.6)	30 (5.5)
Chronic kidney disease, N (%)	107 (22.2)	271 (24.7)	0.258	142 (26.1)	129 (23.5)
Creatinine, mg/dL	0.80 ± 0.20	0.81 ± 0.21	0.671	0.81 ± 0.21	0.80 ± 0.22
Smoking habit					
Smoker, N (%)	261 (54.0)	585 (53.4)	0.716	290 (53.2)	295 (53.6)
Non-smoker, N(%)	213 (44.1)	497 (45.4)		251 (46.1)	246 (44.7)
Unknown, N (%)	9 (1.9)	13 (1.2)		4 (0.8)	9 (1.7)
Use of antiplatelet agents, N (%)	440 (91.1)	998 (91.1)	0.989	497 (91.2)	501 (91.1)
Ischemic stroke subtype					
Atherothrombotic infarction, N(%)	117 (24.2)	284 (25.9)	0.523	135 (24.8)	149 (27.1)
Lacunar infarction, N (%)	311 (64.4)	695 (63.5)		344 (63.1)	351 (63.8)
Undetermined aetiology, N (%)	55 (11.4)	116 (10.6)		66 (12.1)	50 (9.1)
Hs-CRP, Median, μg/L (IQR)	No data	691 (354-1570)		711 (344-1500)	678 (358-1640)

*: The categorical data are compared by chi-square test and the numeric data are compared by Wilcoxon two-sample test. BMI: body mass index, IQR; interquartile range

stroke subtype in relation to Hs-CRP levels in exploratory analysis. All vascular events include recurrent stroke, transient ischemic attacks (TIA), myocardial infarction, and all other vascular accidents such as aortic dissection/rupture, pulmonary embolism, cardiac failure, organ/limb infarction, carotid endarterectomy, stenting, extracranial-intracranial bypass, and coronary artery bypass graft/intervention[16].

Statistical Methods

In the protocol, expected reduction of Hs-CRP due to pravastatin was 400 μg/L, based on the PRINCE study[7]. To detect the difference, a sample size of 510 people in each group would have 89% power, assuming that the common standard deviation is 2000 μg/L, using a two group *t*-test with a 0.050 two-sided significance level. Assuming that 15% of patients would be lost during follow-up, the sample size was set at 600 in each group and 1200 for the two groups combined.

Hs-CRP levels were log-transformed to stabilize variance. Changes from the baseline were analyzed by a mixed-effects model with repeated measurements (MMRM), with the treatment group and visits defined as a fixed effect and baseline values as covariates, and Hs-CRP levels and changes were compared between pravastatin and the control groups. Multiplicity of comparison from the baseline within each group and between treatment groups in the MMRM model were adjusted using Holm's method. The Hs-CRP level

Table 2. Association between Hs-CRP at baseline and risk factors

Characteristic	Coefficient of correlation or Median (IQR)	*P* value
Age, years	0.058	0.062
Sex, men/women	768 (391-1640)/559 (274-1330)	0.006
Body mass index, kg/m^2	0.144	<0.001
Hypertension, Y/N	824 (408-1740)/633 (335-1440)	0.002
Diabetes mellitus, Y/N	745 (362-1710)/667 (349-1500)	0.108
Chronic kidney disease, Y/N	754 (351-1840)/678 (354-1480)	0.141
LDL cholesterol, mg/dL	0.024	0.435
HDL cholesterol, mg/dL	−0.241	<0.001
Triglyceride, mg/dL	0.140	<0.001
Fasting blood glucose, mg/dL	0.121	0.001
Creatinine, mg/dL	0.006	0.845
Smoking, Y/N	790 (392-1640)/583 (298-1340)	0.001
Ischemic stroke subtype		
Atherothrombotic infarction	670 (316-1530)	0.902
Lacunar infarction	706 (358-1575)	
Undermined aetiology	674 (360-1665)	

The categorical data are compared by Wilcoxon two sample test, and continuous data are calculated Spearman's coefficient of correlation and statistical test.

during follow-up was determined by the median value of multiple measurements. The cumulative incidence of time to the first events was estimated using the Kaplan-Meier method. The cumulative incidence curves for the groups were compared using a log-rank test adjusted by the subtype of stroke (atherothrombotic infarction vs. others), elevated blood pressure (≥150/90 mmHg vs. not), and diabetes mellitus (absence vs. presence). The Cox proportional hazard regression was used to estimate relative risk (hazard ratio, HR), and the 95% confidence interval (CI) for Hs-CRP with the time-to-event for recurrent stroke, each stroke subtype or all vascular events by adjusting stratification factors. Multiple Cox proportional hazards regressions were then used to estimate the adjusted hazard ratio for Hs-CRP after adjusting for age, sex, BMI, HDL-C, triglycerides (TG), fasting blood sugar (FBS), smoking, and statin use. Additional analyses used tertiles of Hs-CRP as independent variables, using those in the lowest tertile for each marker as the reference group. Because there was no consensus level to be used after a stroke in Asian populations, we tested Hs-CRP <1000 and ≥1000 μg/L as pre-specified thresholds.

All statistical analyses were predefined in the statistical analysis plan before the database lock in September 2014. All analyses were performed using SAS version 9.3 (Cary, NC, USA). The data was expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and as frequencies and percentages for discrete variables unless specifically mentioned. Significance was set at $p<0.05$ (2-tailed).

Results

A total of 1095 patients in J-STARS were enrolled in the Hs-CRP sub-study; 983 and 932 patients were followed up for 2 and 5 years, respectively. The number of follow-up patients had sufficient statistical power, over 80%. This represents about 70% of the participants in the parent J-STARS. Participants enrolled in the Hs-CRP sub-study were broadly representative of the population enrolled in J-STARS (**Table 1**). Thus, the percentages of atherothrombotic infarction, lacunar infarction, and undetermined etiology were 25.9%, 63.5%, and 10.6%, respectively. Baseline patient characteristics showed no significant difference between the pravastatin and control groups (**Table 1**). Mean time since the qualifying event was 9.8 ± 10.2 months. The median Hs-CRP level was 691 μg/L (interquartile ranges [IQR] 354−1570), which differed by sex, body mass index, history of hypertension, HDL cholesterol, triglycerides, fasting blood glucose level, and smoking use (**Table 2**). However, Hs-CRP levels in atherothrombotic infarction were similar to those in lacunar infarction and undermined etiology.

During follow-up, baseline Hs-CRP levels (median 711 μg/L, IQR 344−1500) significantly decreased 2

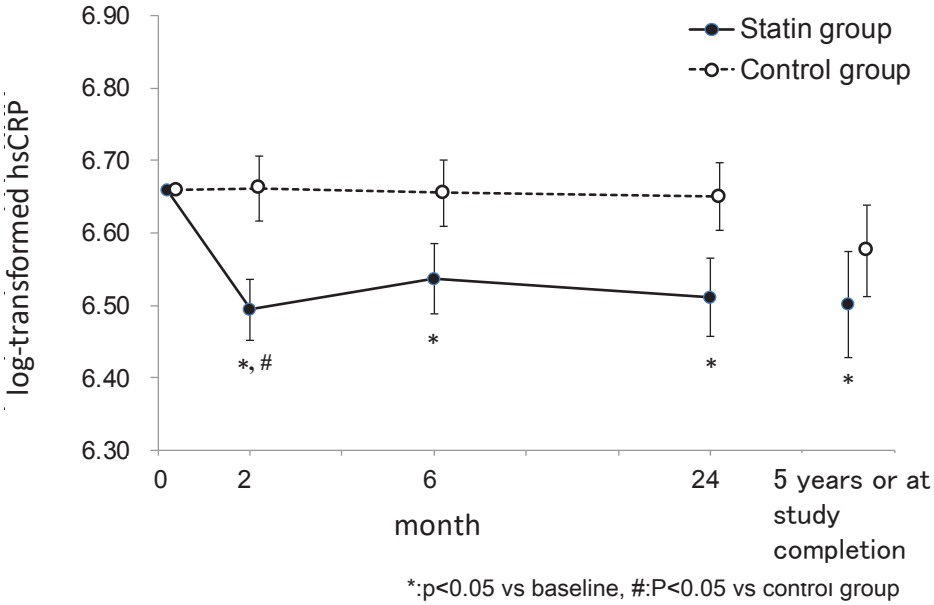

Fig. 1. High-sensitivity C-reactive protein (Hs-CRP) level by treatment group.

Open and closed circles represent mean with standard errors expressed by error bars. Statistical test was shown as the comparison from baseline within treatment group and between treatment groups in the MMRM model and multiplicity of the comparison was adjusted using Holm's method. *: $p<0.05$ vs baseline, #: $p<0.05$ vs control group.

months after the pravastatin treatment (median 592 μg/L, IQR 301−1390, $p<0.001$; **Fig. 1**). Hs-CRP levels remained significantly lower until the end of the study. However, in the control group, baseline Hs-CRP levels (median 678 μg/L, IQR 358−1640) were similar to those 2 months later (median 671 μg/L, IQR 340−1440, $p=0.955$). The reduction of Hs-CRP levels from baseline to 2 months in the pravastatin group was statistically significant compared with control ($p=0.007$). In the pravastatin group, LDL cholesterol levels also showed a significant decrease from the baseline (129.8±24.7 mg/dL) to 2 months after treatment (104.3±23.9 mg/dL, $p<0.001$). However, Hs-CRP reduction was not related to LDL cholesterol reduction (Coefficient of correlation 0.019, $p=0.546$).

As the secondary endpoint, there were 122 recurrent stroke (including 24 atherothrombotic infarctions, 54 lacunar infarctions, 5 cardioembolic infarctions, 26 infarctions of other etiology or unclassified infarctions, 12 intracerebral hemorrhage, and 1 subarachnoid hemorrhage) and 174 major vascular events (including 122 recurrent stroke, 11 TIA, 6 myocardial infarctions, and 35 vascular accidents). Recurrent stroke similarly occurred in the pravastatin and control group (2.49 vs. 2.39 %/year, $p=0.950$). Baseline Hs-CRP level in patients with recurrent stroke (median 880 μg/L, IQR, 346−1850) or all vascular events (Median 851 μg/L, IQR, 371−1960) was similar to that in those without recurrent stroke (Median 684 μg/L, IQR, 354−1500) or any vascular events (Median 670 μg/L, IQR, 349−1460). However, the median Hs-CRP level during the follow-up in patients with all vascular events (median 825 μg/L, IQR, 409−1695) was significantly higher than that in those without any vascular event (median 630 μg/L, IQR, 348−1196) ($p=0.007$). The difference between the median Hs-CRP level in patients with recurrent stroke (median 682 μg/L, IQR, 374−1530) and without (median 644 μg/L, IQR, 353−1230) was only of borderline significance. The median log-transformed Hs-CRP levels during the follow-up period, assessed as a continuous measure, were of borderline significance with a risk of recurrent stroke but significantly associated with all vascular events (**Table 3**). A one SD increase in log-transformed Hs-CRP tended to increase the risk of recurrent stroke (HR 1.17, 95% CI 0.97−1.40) and significantly increased the risk of all vascular events (HR 1.30, 95% CI 1.21−1.51) in Model 1 by adjusting stratification factors, including stroke subtype, hypertension, and diabetes. After further adjustment for age, sex, BMI, HDL-C, TG, FBS, smoking, and statin use, the association between a 1SD increase of Hs-CRP and recurrent stroke (HR 1.23, 95% CI 1.02−1.48) or all vascular events (HR 1.33, 95% CI 1.13−1.56) was significant.

Table 3. Association of Hs-CRP level during follow-up with risk of recurrent stroke and all vascular events

	Stroke				All vascular events			
	Model 1		Model 2		Model 1		Model 2	
	HR (95%CI)	*P* value	HR (95% CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
log Hs-CRP (One SD increase)	1.17 (0.97-1.40)	0.093	1.23 (1.02-1.48)	0.032	1.30 (1.12-1.51)	0.001	1.33 (1.13-1.56)	0.001
Hs-CRP (Tertile)								
Tertile 1 (reference) -440 μg/L	1		1		1		1	
Tertile 2 441-969 μg/L	1.09 (0.69-1.72)	0.712	1.17 (0.73-1.86)	0.509	1.25 (0.84-1.85)	0.276	1.28 (0.86-1.91)	0.225
Tertile 3 970- μg/L	1.46 (0.94-2.26)	0.094	1.65 (1.03-2.62)	0.036	1.78 (1.23-2.60)	0.003	1.87 (1.26-2.78)	0.002
Hs-CRP (standard clinical thresholds in Japan)								
＜1000 μg/L (reference)	1		1		1		1	
≥1000 μg/L	1.50 (1.03-2.17)	0.034	1.60 (1.09-2.36)	0.018	1.68 (1.23-2.29)	0.001	1.69 (1.22-2.33)	0.002
Hs-CRP at baseline								
＜1000 μg/L (reference)	1		1		1		1	
≥1000 μg/L	1.43 (0.99-2.16)	0.054	1.50 (1.04-2.18)	0.031	1.44 (1.06-1.95)	0.020	1.46 (1.07-1.99)	0.017

Model 1, adjusted for stroke subtypes, hypertension, and diabetes; Model 2, adjusted for model 1, age, sex, BMI, HDL-C, TG, FBS, smoking and statin use. Log Hs-CRP (One SD increase): Hs-CRP levels were log-transformed, and hazard ratio of one SD increase of log Hs-CRP for recurrent stroke and all vascular events were analysed. Hs-CRP (Tertile): Hazard ration of middle (tertile 2) and top (tertile 3) was expressed using the bottom tertile (tertile 1, reference) as the reference group.

Compared with the bottom tertile of Hs-CRP level (≤440 μg/L), those in the top tertile (≥970 μg/L) tended to have an increase risk of recurrent stroke (HR 1.46, 95% CI 0.94−2.26) and significantly increased the risk of all vascular events (HR 1.78, 95% CI 1.23−2.60) in Model 1 with adjusted stratification factors (**Fig. 2A, B, Table 3**). The increased risk for recurrent stroke and all vascular events in the top tertile remained clearly significant after additional adjustment for age, sex, BMI, HDL-C, TG, FBS, smoking, and statin use ($p=0.036$ and $p=0.002$, respectively, **Table 3**). In both statin users and non-users, the association between Hs-CRP and all vascular events was shown, but that between Hs-CRP and recurrent stroke was unclear. For recurrent stroke, in statin users HRs of middle and top tertiles of Hs-CRP were 1.65 (95% CI; 0.85−3.18) and 1.73 (95%CI; 0.89−3.39), using the bottom tertile as reference group in Model 1. In non-users, HRs of middle and top tertiles were 0,73 (95% CI; 0.38−1.39) and 1.26 (95% CI; 0.70−2.27). For all vascular events, in statin users HRs of middle and top tertiles were 1.87 (95% CI; 1.04−3.37) and 2.07 (95 % CI; 1.14−3.75) in Model 1. In non-users, HRs of middle and top tertiles were 0.86 (95% CI; 0.50−1.48) and 1.59 (95% CI; 0.98−2.60) in Model 1.

Results were similar using 1000 μg/L as a cut-off level. Patients with Hs-CRP ≥1000 μg/L had approximately 1.5-fold increase in recurrent stroke risk (HR 1.50, 95% CI 1.03−2.17) and 70% increase in the risk of all vascular events (HR 1.68, 95% CI 1.23-2.29) as a reference of those with Hs-CRP ＜1000 μg/L in Model 1 (**Fig. 2C, D, Table 3**). After further adjustment for age, sex, BMI, HDL-C, TG, FBS, smoking and statin use, association turned out more significant in both recurrent stroke risk (HR 1.60, 95% CI 1.09−2.36) and all vascular events (HR 1.69, 95% CI 1.22−2.33). In terms of stroke subtype, those with median Hs-CRP ≥1000 μg/L tended to increase risk of the onset of atherothrombotic infarction compared with those with Hs-CRP ＜1000 μg/L (HR 1.90, 95% CI 0.86−4.22) in Model 1. In contrast, the association between Hs-CRP level and lacunar infarction was no longer significant (HR 1.18, 95% CI 0.67−2.05).

The Hs-CRP during follow-up was more useful for the prediction of vascular events than it was at

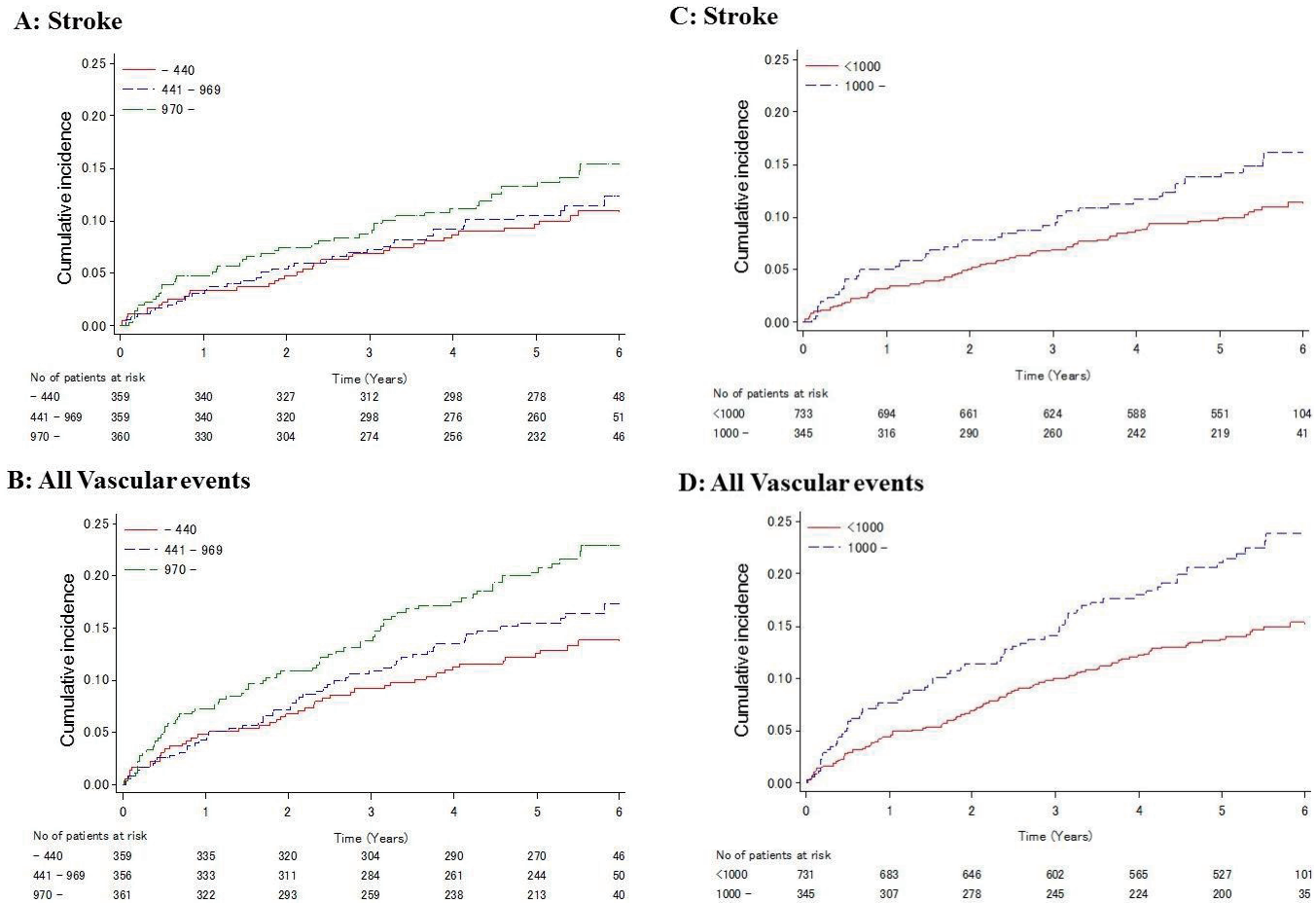

Fig. 2. Cumulative incidence of recurrent stroke and all vascular events according to high-sensitivity C-reactive protein (Hs-CRP) level during follow-up.

(A) Stroke recurrence according to the tertiles of Hs-CRP. (B) All vascular events according to the tertiles of Hs-CRP. (C) Stroke recurrence according to the cut-off value (1000 μg/L) of Hs-CRP. (D) All vascular events according to the cut-off value (1000 μg/L) of Hs-CRP.

baseline. Compared with participants with Hs-CRP <1000 μg/L at baseline, those with Hs-CRP ≥1000 μg/L only showed a tendency for increased risk of recurrent stroke and modest association with all vascular events in Model 1 (p=0.054 and p=0.020, respectively, **Table 3**).

Discussion

Statin treatments could lower Hs-CRP levels in ischemic stroke patients. Several studies with small samples have shown that statin treatment lowered the level of Hs-CRP in patients with any stroke history[9, 18], but this is the first to show anti-inflammatory effects of statins in a randomized larger-scale trial of chronic ischemic stroke patients. These findings support the recommendation in current guidelines of statin treatments for the prevention of stroke recurrence[19].

In the secondary outcome analysis, the Hs-CRP level, especially during the follow-up period, predicted incidence of all vascular events, including stroke recurrence. The baseline Hs-CRP level was associated with stroke recurrence in acute stroke patients in CHANCE trial[12], and also in chronic stroke patients the PROGRESS[10] and SPS3 trials[11]. However, Hs-CRP levels can change during follow-up. Thus, median Hs-CRP levels during follow-up are likely to be more closely related to incident vascular events than a single baseline measurement. In this study, Hs-CRP levels ≥1000 μg/L during follow-up were related to stroke recurrence, although the level at baseline was no longer predictive (**Table 3**). For better prevention management of stroke recurrence, regular measurements of Hs-CRP may be as significant as that of blood pressure, blood glucose, and lipid levels.

For management of hypertension, diabetes mellitus, and dyslipidaemia, the target levels of vascular risks, such as a blood pressure less than 140/90 mmHg,

have been established in global populations[19]. However, Hs-CRP levels significantly differ among different ethnic groups. For example, median Hs-CRP levels were 1300 μg/L in Sweden[20], but 430 μg/L in Japanese residents[14]. This is similar to the difference in the definition of metabolic syndrome between Caucasian and Asian individuals[21]. Hs-CRP levels in Asian populations are less than half of those in Caucasian populations. In guidelines published in the United States and Europe, Hs-CRP levels over 2000 or 3000 μg/L are considered to reflect low-grade vascular inflammation and an increased vascular risk[3]. However, in community cohort studies in Japan and China, Hs-CRP levels over 1000 μg/L were shown to be related to myocardial infarction[14] or ischemic stroke[22, 23]. These studies suggested that a cut-off level of 1000 μg/L is reasonable for risk stratification of stroke recurrence in Japanese patients. For clinical management, indication of target Hs-CRP levels is preferable; thus, future trials must show that this Hs-CRP cut-off level is confirmative.

There were several limitations in this study. Firstly, an aggressive reduction in LDL-cholesterol was not obtained in the J-STARS trial. This might have resulted in no reduction of recurrent stroke in the pravastatin group. Moderate, but not aggressive, reduction of LDL cholesterol would not be enough to show protective effects of statin. In the SPARCL trial, the LDL cholesterol level was 70 mg/dL in the treatment group[4], but it was 100 mg/dL in the treatment group in the J-STARS trial[17]. Additionally, we did not recruit or assign patients with regard to Hs-CRP levels. More than 60% of patients thus had Hs-CRP levels less than 1000 μg/L at baseline, as shown in **Table 1**. This background might diminish the anti-inflammatory effects of statins in arterial vessels. This is different from the patient background in the JUPITER trial[8]. In JUPITER, patients with Hs-CRP levels over 2000 μg/L were included, and treatment with rosuvastatin was shown to decrease both LDL cholesterol level and Hs-CRP levels, and reduce the occurrence of ischemic stroke by about 50%[8].

In conclusion, statin treatment decreased the Hs-CRP levels in ischemic stroke patients. The Hs-CRP levels in each patient during follow-up could predict the occurrence of all vascular events, including stroke recurrence. Although the Hs-CRP cut-off level for risk stratification in ischemic stroke patients might be over 1000 μg/L in Japanese and, potentially, Asian populations, this could differ among different ethnic populations. Finally, our results suggest that the importance of regular Hs-CRP measurements during follow-up in patients with ischemic stroke to better manage the prevention of incident vascular events.

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