**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

**Introduction**

Vascular inflammation has attracted much attention as a crucial symptom of atherothrombosis1). High-sensitivity C-reactive protein (Hs-CRP) has been estab-
lished as predictive for incident myocardial infarction and ischemic stroke in meta-analysis. 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. Statin treatment is beneficial for the secondary prevention of an ischemic stroke. In addition to lipid-lowering effects, the anti-inflammatory effects of statins, including decreased Hs-CRP levels, have been considered important for stroke prevention. Several studies showed stabilization of atheromatous plaque in patients with severe carotid stenosis. In the general population and patients with coronary artery disease, statin treatment was shown to decrease the level of Hs-CRP. Although statin treatment has been shown to decrease Hs-CRP levels in a small prospective cohort study with acute ischemic stroke, 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, SPS3, and CHANCE trial, but Hs-CRP level could vary after treatment for metabolic factors, including with statins. In fact, follow-up CRP level was shown to be more strongly associated with outcomes in acute stroke patients than in admission levels. 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. In the US guidelines, 3000 µg/L has been used as a cut-off for vascular inflammation, 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. 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.

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
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. 

| 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/m² | 23.8 ± 3.2 | 23.7 ± 3.0 | 0.528 | 23.8 ± 3.1 | 23.6 ± 3.0 |
| Interval between index stroke 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 (24.7) | 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) | 0.028 | 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) | 0.749 | 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) | 0.654 | 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.

Using a two group *t*-test with a 0.05 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.

**Statistical Methods**

In the protocol, expected reduction of Hs-CRP due to pravastatin was 400 µg/L, based on the PRINCE study. 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
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 range [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 undetermined etiology. 

During follow-up, baseline Hs-CRP levels (median 711 µg/L, IQR 344–1500) significantly decreased 2
months after the pravastatin treatment (median 592 µg/L, IQR 301–1390, \( p \leq 0.001 \); 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 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, 409–1695) (\( p = 0.007 \)). 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.

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.
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 baseline. 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 0.86 (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 baseline.
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 \(\geq 1000\) 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\(^9\). 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\(^11\). 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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