Low-Grade Inflammation Is a Risk Factor for Clinical Stroke Events in Addition to Silent Cerebral Infarcts in Japanese Older Hypertensives

The Jichi Medical School ABPM Study, Wave 1

Joji Ishikawa, MD; Yurie Tamura, MD; Satoshi Hoshide, MD; Kazuo Eguchi, MD; Shizukiyo Ishikawa, MD; Kazuyuki Shimada, MD; Kazuomi Kario, MD

Background and Purpose—High-sensitivity C-reactive protein (hsCRP), a marker of inflammation, is associated with atherosclerosis, hypertensive target organ damage, and cardiovascular events. In the general Japanese population, the level of hsCRP is reported to be lower than that in Western countries, and the relationships among hsCRP, silent cerebral infarcts (SCIs), and clinical stroke events in older Japanese hypertensives remain unclear.

Methods—We conducted brain MRI and measured hsCRP at baseline in 514 older Japanese hypertensives (clinic blood pressure \( \geq 140/90 \) mm Hg, age \( \geq 50 \) years old) who were enrolled in the Jichi Medical School ABPM Study, wave 1. They were followed up for an average of 41 months (range: 1 to 68 months, 1751 person-years) and the incidence of subsequent clinical stroke events was evaluated.

Results—The subjects with SCIs at baseline (n = 257) had a higher hsCRP level than those without SCIs (geometric mean hsCRP \([SD\ range]\); \(0.19 [0.18 \text{ to } 0.21]\) versus \(0.14 [0.13 \text{ to } 0.16]\) mg/L, \(P = 0.007\)) after adjustment for confounding factors, and the OR for the presence of SCIs was increased with the quartile of hsCRP levels. In Cox regression analysis, the patients with above median hsCRP level (\( \geq 0.21 \) mg/L) (hazard ratio [HR]; 2.50, 95% CI: 1.24 to 5.00, \(P = 0.01\)) and those with SCIs (HR: 4.60, 95% CI: 1.91 to 11.03, \(P = 0.001\)) at baseline had independently higher risks for clinical stroke events after adjustment for age, smoking status, antihypertensive medication use, and 24-hour systolic blood pressure level. Compared with the patients with below median hsCRP level without SCIs, those with above median hsCRP level and SCIs at baseline had a higher risk for clinical stroke events (HR: 7.32, 95% CI: 2.17 to 24.76, \(P = 0.001\)), although those with below median hsCRP level and SCIs (HR: 2.46, 95% CI: 0.64 to 9.47, \(P = 0.19\)) and those with above median hsCRP level without SCIs (HR: 1.11, 95% CI: 0.22 to 5.55, \(P = 0.90\)) did not have significant risks.

Conclusion—High-sensitivity C-reactive protein is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives, indicating that the risk for clinical stroke events increases with preexisting hypertensive target organ damage in the brain and additionally with ongoing low-grade inflammation. (Stroke. 2007; 38:911-917.)

Key Words: C-reactive protein ■ hypertension ■ inflammation ■ silent cerebral infarcts ■ stroke

The incidence of stroke is higher than that of cardiovascular events in the Japanese general population, and it is reported to be related with hypertension and metabolic syndrome.1 High-sensitivity C-reactive protein (hsCRP), a marker of inflammation, is reported to be related with the pathogenesis of atherosclerosis, development of hypertension,2 metabolic syndrome,3-6 and cardiovascular events.7-9 In the guidelines of the American Heart Association,10 the following risk levels of hsCRP were reported: low risk at less than 1.0 mg/L, moderate risk at 1.0 to 3.0 mg/L, and high risk at more than 3.0 mg/L. However, Anand et al11 reported that there were ethnic differences in serum hsCRP levels among Canadian residents, and Yamada et al12 reported that the Japanese population had a much lower hsCRP level than that in Western populations.13,14 There are few data about whether hsCRP level is related to clinical stroke events at a lower hsCRP level such as that in the Japanese population.

Additionally, patients with silent cerebral infarcts (SCIs), hypertensive target organ damage in the brain, were reported to have 10.48 times higher incidence of clinical stroke events15 in Japanese subjects. Hoshi et al16 reported that hsCRP level was significantly higher in patients with SCIs.
among high-risk patients who were recently referred to a university hospital for risk assessment or primary prevention of stroke. However, there are no available data showing the interaction of SCIs (as a marker of preexisting hypertensive target organ damage) and hsCRP level (as a measure of ongoing inflammatory response) as risk factors for future clinical stroke events.

The purpose of this study was to clarify whether hsCRP is a risk factor for clinical stroke events in relation to the presence of SCIs in Japanese older hypertensive patients who have lower hsCRP levels than those in Western countries.

Methods

Patients

We initially enrolled 821 older hypertensive outpatients (clinical blood pressure \(> 140/90 \text{ mm Hg and age } \geq 50 \text{ years}\)) in the Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS-ABPM) study, wave 1,\(^{17-19}\) from 6 participating institutions (3 clinics, 2 hospitals, and 1 outpatient clinic of a medical school) between January 1, 1992, and January 1, 1998. The patients who had a history of stroke, ischemic heart disease, chronic heart failure, peripheral vascular disease, chronic renal damage, or arrhythmia at baseline were excluded from this study. Measurement of hsCRP at baseline and follow up was successfully conducted in 811 patients (99\% of the patients). Among them, analysis was performed for 514 patients after we excluded the patients who did not agree to undergo brain MRI (296 patients) or with incomplete data (one patient).

Clinic blood pressure was measured after resting for at least 5 minutes in the sitting position. Diabetes mellitus was defined as a fasting glucose level \(> 7.8 \text{ mmol/L}, a \text{ random nonfasting glucose level } > 11.1 \text{ mmol/L}, \) hemoglobin A1c \(> 6.2 \%), or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined as a total cholesterol level \(> 6.2 \text{ mmol/L or the use of an oral lipid-lowering agent. Smokers were defined as current smokers. Body mass index was calculated as weight (in kilograms)/height (in meters squared). This study was approved by the independent research ethics committee, Jichi Medical University School of Medicine, Japan, in 1998. Some of the data from the JMS-ABPM study were published previously.\(^{17-19}\) This article is a subanalysis of the study.

Blood Samples

Blood samples were drawn from the cubital vein in the fasting state within 2 months of the day of ABPM. Measurements of serum hsCRP level were conducted from 1992 to 1998 and the samples of serum were frozen at \(-80^\circ \text{C until the measurements. Serum hsCRP level was measured by nephelometry (NA Latex CRP kit; Dade Behring) in SRL, Inc.}\) When the hsCRP value was below the detectable value (0.03 mg/L), it was taken as 0.025 mg/L. Sixty-eight patients had serum hsCRP levels below the detectable value.

Brain MRI

Brain MRI was carried out using a superconducting magnet with a main strength of 1.5 T (MRT200FXII; Toshiba; SIGNA-HorizonVer.5.8; General Electric Co or Vision; SIEMENS) within 3 months of the JMS-ABPM. T1-weighted images and T2-weighted images were obtained in the transverse plane with 7.8 to 8.0-mm-thick sections. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images as described previously.\(^{17}\) Deep white matter lesions (DWLs) were also evaluated in the MRI images. Advanced DWL was defined as detection of hyperintense multiple punctuate lesions, such lesions at the early confluent stage, or those that had reached confluency in the deep white matter area on T2-weighted images. The MRI images of the subjects were randomly stored and interpreted by 2 neurologists who were blind to the subjects’ names and characteristics, and the reproducibility of the MRI reading was demonstrated previously.\(^{19}\)

Ambulatory Blood Pressure Monitoring

ABPM was measured using a validated machine: ABPM-630 (Nippon Colin),\(^{20}\) TM-2421, or TM-2425 (A&D).\(^{21}\) Patients stopped antihypertensive medication for at least 14 days before the ABPM study, and 55\% of the patients had a history of antihypertensive medication use. Measurements were performed at 30-minute intervals for 24 hours on a weekday.\(^{17,22}\)

Follow Up and Events

The collection of the follow-up data was performed once at the time of the patients’ clinics visits from 1996 to 1998 (20-month period). The patients’ medical records were reviewed after ABPM for the use of antihypertensive drugs and the occurrence of cardiovascular events. When patients failed to come to the clinic, we interviewed them by telephone. Each physician who was caring for the patient at the time of the event diagnosed stroke events. Independent neurologists reviewed the cases and confirmed the diagnosis of stroke events. The criteria for the diagnosis of stroke were sudden onset of neurologic deficit that persisted for \(\geq 24 \text{ hours in the absence of any other disease process that could explain the symptom. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurologic deficit cleared completely within 24 hours from the onset of symptoms. Statistical Analysis

Statistical analyses were conducted for 514 patients. Data are shown as the mean±SD. Serum hsCRP level had a skewed deviation and the analysis of hsCRP level was performed for the raw hsCRP value and log-transformed value. The \(x^2\) test was used to detect differences of prevalence rate among groups. Unpaired \(t\) tests and paired \(t\) tests were used for comparison of the mean values for 2 different groups. Analysis of covariation was performed to identify groups with differences of SCIs after adjustment by confounding factors and the Bonferroni test was used for pairwise comparisons of the presence of SCIs. Odds ratio and the 95\% CI of the patients with quartiles of hsCRP levels were calculated for the presence of SCIs by multiple logistic regression analysis, and the trend for the quartiles of hsCRP levels was also calculated. Cumulative incidences of clinical stroke events in 4 groups (with/without above median hsCRP level and with/without SCIs) were plotted as Kaplan-Meier curves, and the differences were assessed by the log-rank test. Hazard ratio (HR) and 95\% CI of clinical stroke events in these 4 groups (with/without above median hsCRP level and with/without SCIs) were calculated using Cox regression analyses, even after adjustments for significant covariates. Computer software (SPSS version 11.0J; SPSS Inc) was used for the analyses and a probability value \(< 0.05\) was considered statistically significant.

Results

The patients’ age (mean±SD) was 72.3±8.7 years (for 191 men and 323 women). Serum hsCRP levels in the total sample showed a highly skewed deviation. The median hsCRP level was 0.21 mg/L (75th percentile 0.43 mg/L) and the mean hsCRP level was 0.36 mg/L.

The number of patients with SCIs was 257 (50\%). The characteristics of patients who did not undergo MRI and those with or without SCI are shown in Table 1. There were no differences in age, sex, blood pressures, fasting blood glucose level, total cholesterol level, high-density lipoprotein cholesterol level, and hsCRP level at baseline between the patients who underwent MRI and those who did not; however, there were significant differences in body mass index, prevalence of diabetes, prevalence of hyperlipidemia, and percentage of antihypertensive medication use. The distribution of the number of silent infarcts had a skewed deviation.
The median number of silent infarcts was 2 per person (75th percentile 4 per person) in the patients who had SCIs. Age, percent of males and smokers, clinic systolic blood pressure (SBP), and 24-hour mean SBP (24-hour SBP) level were significantly higher in the patients with SCIs. Patients with SCIs had significantly higher hsCRP level than those without SCIs (Table 1) and the difference remained significant even after adjustments for age, smoking, diabetes, and 24-hour SBP level (Figure 1). Using multiple logistic regression analysis, the odds ratios for the presence of SCIs were estimated and are shown in Figure 2, and the trend test for the quartiles of hsCRP was significant ($P=0.010$).

Even when we classified the patients into three groups with no SCIs (257 patients), a few SCIs (1 to 2 SCIs, 155 patients), and multiple SCIs (>3 SCIs, 102 patients), the patients with multiple SCIs had significantly higher serum hsCRP level than those with a few SCIs (geometric mean hsCRP; 0.27 mg/L versus 0.17 mg/L, $P<0.05$) and than those with no SCIs (0.13 mg/L, $P<0.01$).

The patients with advanced DWL ($n=84$) had significantly higher age (75.6±7.8 versus 71.6±8.7 years, $P<0.001$), prevalence of smokers (32.1% versus 20.2%, $P=0.016$), 24-hour SBP level (144.6±17.0 versus 137.2±16.4 mm Hg, $P<0.001$), and serum hsCRP level (geometric mean hsCRP [SD range]; 0.24 [0.07 to 0.78] versus 0.16 [0.04 to 0.54] mg/L, $P=0.003$) than those without advanced DWL. However, the relationship between advanced DWL and serum hsCRP level disappeared after adjustments for age, smoking, and 24-hour SBP level (0.21 [0.18 to 0.24] versus 0.16 [0.15 to 0.17] mg/L, $P=0.071$).

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During an average duration of 41 months (range: 1 to 68 months, 1751 person-years), 43 stroke events occurred (ischemic stroke 30, cerebral hemorrhage 5, unknown 8). The characteristics of the patients who had clinical stroke events are shown in Table 2. In Cox regression analysis, patients with above median hsCRP level had a significantly higher incidence of clinical stroke events than those with below median hsCRP level independently of the presence of SCIs, even after adjustments for significant confounding factors such as age, smoking, antihypertensive medication use, and 24-hour SBP level (HR: 2.50, 95% CI: 1.24 to 5.00, $P=0.01$) (Table 3). We were unable to perform the analysis according to the subtype of stroke events such as ischemic stroke and cerebral hemorrhage because of the small number of clinical stroke events.

We divided the patients into 4 groups according to the presence or absence of SCIs and above or below median

### Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MRI (–) (n=297)</th>
<th>No SCI (n=257)</th>
<th>SCI (n=257)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.4±11.6</td>
<td>70.0±8.8</td>
<td>74.6±7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>40.4</td>
<td>31.5</td>
<td>42.8</td>
<td>0.011</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.5±3.5†</td>
<td>24.4±3.5</td>
<td>23.9±3.6</td>
<td>0.139</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>18.2</td>
<td>18.3</td>
<td>26.1</td>
<td>0.043</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>8.4*</td>
<td>11.3</td>
<td>17.5</td>
<td>0.059</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>13.1†</td>
<td>21.8</td>
<td>21.8</td>
<td>1.000</td>
</tr>
<tr>
<td>Antihypertensive mediation, %</td>
<td>45.1†</td>
<td>57.2</td>
<td>56.4</td>
<td>0.929</td>
</tr>
</tbody>
</table>

*Data are shown as mean±SD or percentage. DBP indicates diastolic blood pressure; PR, pulse rate; 24-hr SBP, 24-hour mean of SBP; 24-hr DBP, 24-hour mean of DBP; HDL, high-density lipoprotein.*

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**Table 2. Number of Clinical Stroke Events**

<table>
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<tr>
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hsCRP level. Kaplan-Meier cumulative incidences for clinical stroke events among the 4 groups are shown in Figure 3. The HRs and 95% CIs of the patients with/without above median hsCRP and with/without SCIs in Cox regression analysis after adjusting for significant covariates such as age, prevalence of current smokers, antihypertensive medication use, and 24-hour SBP are shown in Figure 4. The patients with above median hsCRP level and SCIs had a higher risk for clinical stroke events than the patients with below median hsCRP without SCIs (HR: 7.32, 95% CI: 2.17 to 24.76, \( P < 0.001 \)), than those with above median hsCRP level without SCIs (HR: 6.59, 95% CI: 2.00 to 21.79, \( P = 0.002 \)), and than those with below median hsCRP level with SCIs (HR: 2.98, 95% CI: 1.35 to 6.58, \( P = 0.007 \)) after adjustments for the significant covariates. Even after adjustment for known covariables such as age, sex, body mass index, prevalence of diabetes, prevalence of hyperlipidemia, antihypertensive medication use, and 24-hour SBP, the patients with above median hsCRP and SCIs had significantly higher risk for clinical stroke events than those with below median hsCRP without SCIs (HR: 7.58, 95% CI: 2.23 to 25.79, \( P = 0.001 \)).

The patients with advanced DWL had 2.07 times higher risk for clinical stroke events than those without advanced DWL even after adjustments for confounding factors such as age, smoking, antihypertensive medication use, and 24-hour SBP (HR: 2.07, 95% CI: 1.08 to 3.98, \( P = 0.029 \)) in Cox regression analysis. After serum hsCRP level was added to the model, the patients with above median hsCRP level had significantly higher risk for clinical stroke events than those with below median hsCRP level (HR: 2.51, 95% CI: 1.25 to

### TABLE 2. Characteristics of the Patients With or Without Clinical Stroke Events

<table>
<thead>
<tr>
<th>Stroke Event</th>
<th>(−) (n=471)</th>
<th>(+) (n=43)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71.9±8.7</td>
<td>76.9±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>36.1</td>
<td>48.8</td>
<td>0.102</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.2±3.5</td>
<td>23.4±4.1</td>
<td>0.143</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>21.0</td>
<td>34.9</td>
<td>0.053</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>14.0</td>
<td>18.6</td>
<td>0.372</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>22.1</td>
<td>18.6</td>
<td>0.702</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>58.2</td>
<td>41.9</td>
<td>0.053</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>164.1±18.6</td>
<td>171.2±18.9</td>
<td>0.016</td>
</tr>
<tr>
<td>24-hr SBP, mm Hg</td>
<td>137.6±16.6</td>
<td>147.6±15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean hsCRP, mg/L</td>
<td>0.35±0.63</td>
<td>0.43±0.35</td>
<td>0.430</td>
</tr>
<tr>
<td>Geometric mean hsCRP, mg/L</td>
<td>0.16 (0.05-0.55)</td>
<td>0.28 (0.10-0.83)</td>
<td>0.004</td>
</tr>
<tr>
<td>Median hsCRP, mg/L</td>
<td>0.20</td>
<td>0.41</td>
<td>0.041</td>
</tr>
<tr>
<td>SCIs, %</td>
<td>46.7</td>
<td>86.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Advanced DWL, %</td>
<td>14.6</td>
<td>34.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD or percentage. hsCRP level is also shown as geometric mean (SD range) and median. Overall \( P \) values for 2-group comparisons were determined for the \( \chi^2 \) test or unpaired \( t \) test. 24-hr SBP indicates 24-hour mean of SBP.
TABLE 3. Cox Regression Analysis for Clinical Stroke Events

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 1 SD (8.7) years</td>
<td>1.51</td>
<td>1.10–2.08</td>
<td>0.012</td>
</tr>
<tr>
<td>Current smoking, no=0, yes=1</td>
<td>1.32</td>
<td>0.70–2.50</td>
<td>0.398</td>
</tr>
<tr>
<td>Antihypertensive medication use, no=0, yes=1</td>
<td>0.46</td>
<td>0.24–0.87</td>
<td>0.018</td>
</tr>
<tr>
<td>24-hr SBP, 1 SD (16.7) mm Hg</td>
<td>1.84</td>
<td>1.37–2.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCI, no=0, yes=1</td>
<td>4.60</td>
<td>1.91–11.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Above the median hsCRP vs. below the median hsCRP</td>
<td>2.50</td>
<td>1.24–5.00</td>
<td>0.010</td>
</tr>
</tbody>
</table>

24-hr SBP indicates 24-hour mean systolic blood pressure.

Discussion

The patients with above median hsCRP levels and SCIs had an additional risk for clinical stroke events, whereas those with above median hsCRP level without SCIs did not have an increased risk for clinical stroke events compared with those with below median hsCRP level without SCIs. These data show that ongoing low-grade inflammation increases the risk of clinical stroke events increase in addition to the preexisting hypertensive target organ damage in the brain (such as SCIs), even in Japanese older hypertensive subjects who had a lower serum hsCRP level than that in Western populations.

In the general Japanese population, Wakugawa et al reported that male subjects with the highest quintile of serum hsCRP level (>1.57 mg/L) had 3.11 times higher risk for ischemic stroke events than those with the lowest quintile of hsCRP level. Our present data showed lower serum hsCRP levels than those in Wakugawa’s study even in the patients who had clinical stroke events. The difference of hsCRP level in our study and those data may also have been in part attributable to the increase of a Westernized lifestyle during the past approximately 10 years and to differences between urban and rural areas. In the present study of Japanese older hypertensives, median hsCRP was 0.21 mg/L (mean hsCRP was 0.36 mg/L), which was higher than the level in a general Japanese population in our previous study (median hsCRP 0.12 mg/L), in which we measured hsCRP using the same method at the same center. Additionally, hsCRP level was reported to be a risk factor for clinical stroke events in American and Japanese-American populations, although the hsCRP levels were higher than that in our subjects. These differences of hsCRP levels for predicting stroke events show the difficulty of setting cutoff levels.

The patients with SCIs had significantly higher hsCRP than those without SCIs, and the OR for predicting SCIs increased with the quartile of hsCRP levels; however, increased risk for clinical stroke events in the patients with above median hsCRP was not seen in the patients without SCIs, although it was seen in those with SCIs. This may indicate that hsCRP increased with the development of SCIs (hypertensive target organ damage in the brain), hsCRP itself was not a risk factor for clinical stroke events without SCIs, and that increased hsCRP is a risk factor in addition to the SCIs. We previously reported that dipping pattern and morning blood pressure surge in ambulatory blood pressure monitoring were strong predictors of silent cerebral infarcts. It is known that inflammation plays an important role in the pathogenesis of atherosclerosis. Inflammatory response injury is considered to be related to the initiation, growth, and complications of the atherosclerotic plaque, and elevation of the hsCRP level according to the progression of atherosclerosis has been considered to be a consequence of inflammation in the arterial wall. Recently, it was also reported that hsCRP itself, as a mediator of inflammation, may cause progression of arterial wall damage; however, the present results argue against any direct causal effects of CRP on stroke, because the relationships were similar in populations with high and very low levels. Moreover, because many inflammatory markers show the same relationships with incidence of stroke, it is unlikely that any particular property of the CRP molecule explain the relationship with stroke. On the contrary, low-grade inflammation may be a response to ischemic tissue damage. It has also been shown that chronic cerebral hypoperfusion induces microglial activation and may cause further tissue damage, and in a state of chronic low-grade inflammation, oligodendrocytes and neurons may be more susceptible to hypoperfusion and hence accelerate lesion progression. The data in the present study support the possibility that elevation of hsCRP was a consequence of SCIs; however, the patients with below median hsCRP with SCIs had a lower risk for clinical stroke events than those with above median hsCRP with SCIs.

The patients with advanced DWL had higher hsCRP level than those without advanced DWL, although the patients with...
advanced DWL had a tendency to have increased risk for clinical stroke events independently of hsCRP level. These data showed that serum hsCRP level was more strongly related with DWL than SCIs and support the conclusion of van Dijk’s report23 that the progression of DWL was more strongly related with serum hsCRP level than that of SCIs. SCIs have been considered to be lesions involving small cerebral arteries (with features such as fibrinoid necrosis or lipohyalinosis), whereas possible mechanism of DWLs include vessel occlusion, disturbed cerebral autoregulation, or increases in vascular permeability.29 Recently, Wardlaw et al30 proposed a hypothesis in which the mechanism of formation of SCIs and DWLs involves cerebral small-vessel endothelial (ie, blood–brain barrier) dysfunction with leakage of plasma components into the vessel wall and surrounding brain tissue leakage leading to neuronal damage. SCIs and DWLs may be different manifestations of the same pathophysiological condition; however, the mechanisms of the relationship between serum hsCRP levels and SCIs or DWLs were not clarified by the present study. Inzitari31 reported that DWLs share common pathophysiological mechanisms with stroke and must be regarded as an intermediate surrogate of stroke rather than a true stroke risk factor because they are likely an expression of the same disease.

Perspectives
High-sensitivity CRP is an independent risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives, indicating that the risk for clinical stroke events increase with preexisting hypertensive target organ damage in the brain and additionally with ongoing low-grade inflammation.

The relationship between SCIs and hsCRP at relatively low levels might depend in part on the size of the diseased vessel, and elevated CRP levels might reflect larger vessel atherosclerosis32,33; however, no information about the large-vessel status at baseline or the size of diseased vessels of clinical stroke events was obtained in the present study. Additionally, hsCRP and SCIs were not measured repeatedly, and the risk of clinical stroke events attributable to the progression of SCIs and hsCRP remains unclear. The low number of clinical stroke events in the present study might have affected the HRs. The diagnosis of the clinical stroke events was based on each physician’s evaluations, and we did not confirm the diagnosis by brain CT and/or brain MRI in the patients who had clinical stroke events. These were limitations of the present study.

References


Low-Grade Inflammation Is a Risk Factor for Clinical Stroke Events in Addition to Silent Cerebral Infarcts in Japanese Older Hypertensives: The Jichi Medical School ABPM Study, Wave 1
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