Association Between Interleukin-6 Levels and First-Ever Cerebrovascular Events in Patients With Vascular Risk Factors

Kaori Miwa, Makiko Tanaka, Shuhei Okazaki, Shigetaka Furukado, Manabu Sakaguchi, Hideki Mochizuki, Kazuo Kitagawa

Objective—The objective of this study was to examine the association of inflammatory markers with risk of first-ever cerebrovascular events (CVEs), while simultaneously evaluating subclinical vascular disease.

Methods and Results—We enrolled 464 outpatients who had vascular risk factors without any preexisting cardiovascular disease. We examined the presence of silent lacunar infarction (SLI) by magnetic resonance imaging; carotid intima-media thickness by ultrasound; and measured high-sensitivity C-reactive protein, interleukin (IL)-6, and IL-18 at baseline, and assessed their associations with CVEs using Cox proportional hazards models of 4.8±2.6 years follow-up. We further calculated measures of reclassification and discrimination. In age- and sex-adjusted analysis, IL-6, but neither high-sensitivity C-reactive protein nor IL-18, was associated with CVEs. The association remained significant after adjustment for conventional risk factors, intima-media thickness, and SLI (hazard ratios: 1.80, per 1-SD increase in log IL-6, P=0.03). Compared with the patients with below median IL-6 without SLI, those with above median IL-6 and SLI had a higher risk of CVEs (hazard ratios: 4.14, P=0.0014). The combination of IL-6 and SLI resulted in the net reclassification improvement of 14.3% (P=0.04), and the integrated discrimination improvement gain of 2.1% (P=0.05).

Conclusion—IL-6 levels were independently associated with CVEs and could improve reclassification in those with SLI.

Key Words: cerebrovascular disease prevention ■ epidemiology ■ inflammation ■ interleukin (IL)-6 ■ risk factors

Low-grade chronic inflammation has been widely recognized as playing an important role in the process of atherogenesis,1 and levels of inflammatory markers (eg, high-sensitivity C-reactive protein [hsCRP], interleukin [IL]-6, and IL-18) are associated with risk of cardiovascular disease (CVD).2–4 However, investigation of inflammatory markers for cerebrovascular events (CVEs) as a principal outcome measure is limited.

With the growing interest in CVD-risk stratification by combining vascular imaging with conventional risk factors, established surrogate markers of subclinical CVD, such as carotid intima-media thickness (IMT),5 and asymptomatic cerebral small-vessel disease on brain magnetic resonance imaging (MRI), such as silent lacunar infarction (SLI),6 might more accurately predict risk assessment for clinical CVEs. Such findings make sense because the greater the progression of subclinical atherosclerotic disease, the closer an asymptomatic patient should be to a clinical outcome. Indeed, inflammatory markers are associated with both the severity of IMT5 and presence of small-vessel disease.8 Thus, the association between inflammatory markers and CVE risk could be modified by IMT5 and SLI.10 Consequently, to help evaluate complementary information as risk predictors and stratification of more high-risk patients, studies of different sets of markers might be informative, as inflammatory marker measurement alone could provide little improvement in prediction compared with conventional risk factors, as evaluated by C-statistic.11–13

Therefore, the objective of this study was to clarify the values of 3 inflammatory markers (hsCRP, IL-6, and IL-18) for predicting CVEs in a cohort of patients with cardiovascular risk factors without prior CVD, while simultaneously evaluating IMT and the presence of SLI.

Materials and Methods

The participants originated from the Osaka Follow-up Study for Carotid Atherosclerosis, Part 2—a prospective cohort study in which physicians control risk factors in high-risk patients for primary and secondary prevention of CVD.14 Outpatients aged ≥40 years with ≥1 cardiovascular risk factor, including hypertension, diabetes mellitus, hyperlipidemia, history of smoking, established arteriosclerosis documented as transient ischemic attack (TIA), stroke, coronary heart disease, or peripheral artery disease, were enrolled. Between January 2001 and December 2009, 811 outpatients who visited the Department of Neurology and Stroke Center at Osaka University Hospital were enrolled. All participants underwent a baseline clinical assessment that included medical history, inquiry into medications and smoking habits, physical and neurological examination, blood

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sampling, carotid ultrasound, and brain MRI. MRI was mostly performed to examine lesions in cases of stroke history or suspicious neurological symptoms (eg, headache, vertigo, dizziness, numbness, syncope, or subjective memory impairment). After we excluded participants who did not revisit our hospital because of a refusal of further participation, a change of address, or physical inability, as well as those who had incomplete baseline examinations (n=20), 791 subjects were identified as candidates. Then, individuals with clinical history of CVD and patients with evidence of nonvascular inflammatory disease were excluded. Thus, patients with a history of stroke or TIA (n=251), carotid revascularization (n=15), ischemic heart disease (n=27), peripheral vascular disease (n=6), collagen disease (n=5), or cancer (n=16) were excluded. Patients with a history of acute infections, and those with obvious signs and clinical evidence of acquired infection, were also excluded (n=7). Finally, all analyses were based on 464 patients (Figure 1). This study was approved by the local ethical review board; all patients gave written informed consent.

**Risk Factors**

Hypertension was defined as blood pressure ≥140/90 mm Hg on measurements taken at least twice, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose level ≥126 mg/dL, HbA1c level ≥6.5%, or the use of antidiabetic therapy. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥140 mg/dL, total cholesterol level ≥220 mg/dL, or triglyceride level ≥150 mg/dL, or the use of cholesterol-lowering therapy. Smoking was classified as current smoking. Habitual alcohol intake was defined as alcohol drinking of ≥20 g/day.

**Inflammatory Marker Measurement**

After MRI examination, blood was drawn with minimally traumatic venipuncture to measure serum inflammatory markers. Blood was centrifuged at 3000 rpm at 4°C for 15 minutes; aliquots were stored at −80°C. Circulating hsCRP was measured by latex turbidimetric immunoassay with a sensitivity of 0.01 mg/L (Shionogi Biomedical Laboratory Inc). Serum IL-6 and IL-18 levels were measured by ELISA (High-sensitivity Quantikine Kit, R&D System; Human IL-18 ELISA Kit, MBL Co Ltd, respectively). The detection limits for IL-6 and IL-18 were 0.10 and 12.5 pg/mL, respectively. The intraassay variations for IL-6 and IL-18 were 7.8% and 5.6%, respectively; the corresponding interassay coefficients were 7.2% and 7.6%, respectively.

**MRI Protocol and Assessment**

MRI protocol scans has been described.13 MRI assessment was performed by 2 trained observers blinded to the clinical information. SLI was defined as a focal lesion >3 mm and <15 mm with a hypointense lesion and hyperintense rim on FLAIR images when located supratentorially, according to the corresponding hyperintensity and hypointensity on T2- and T1-weighted images, respectively, without stroke history. Briefly, SLI was defined as lacunar infarction on MRI without any history of clinically evident CVD. The degree of white-matter hyperintensities was visually rated on FLAIR using the Fazekas scale.16 The interrater reliability for the presence of SLI expressed as Cohen κ was 0.80.

We evaluated the degree of intracranial artery stenosis according to MRA, as previously reported.17 Briefly, assessment of stenosis on MRA was based on comprehensive images, and on the least change of vessel column width in those images. Stenosis was categorized by degree into 5 grades depending on the narrowing of the arteries (normal, mild, moderate, severe, and occluded).17 We assigned patients with at least 1 stenotic segment with more than moderate stenosis to the intracranial large-artery atherosclerosis group.

**Carotid Atherosclerosis Evaluation**

We calculated the mean IMT by averaging the thickness at 12 sites: the near and far walls of the right and left distal common carotid arteries, bifurcation, and internal carotid artery.18

**Follow-Up**

Subjects visited outpatient clinic settings to control risk factors (eg, hypertension and hyperlipidemia) every 3 months, 6 months, or 1 year. Follow-up data were collected in June 2011. If subjects did not undergo regular examinations, their health status was checked by telephone annually, and a questionnaire about clinical events was completed upon hospitalization. If a cardiovascular event was reported, original medical records were reviewed to determine the occurrence of CVD. All possible events were audited independently by 3 physicians. Follow-up was terminated when patients withdrew from the study because of death (n=23) or personal reasons (n=18). The outcomes used in Osaka Follow-up Study for Carotid Atherosclerosis, Part 2 were death as a result of vascular or nonvascular mortality, CVEs, coronary heart disease, and peripheral artery disease.19 However, in this study, the primary end point was fatal or nonfatal CVEs. CVEs included stroke, which was defined as an acute disturbance of focal neurological dysfunction with symptoms lasting >24 hours (or resulting in earlier death) and thought to be a result of either cerebral infarction or hemorrhage. We also included surgical or endovascular treatment resulting from of TIA as CVEs. However, we excluded TIA in which the neurologic deficit cleared completely within 24 hours from the onset of symptoms, without imaging evidence of stroke.

**Statistical Analysis**

Patients were followed from the date of MRI scan until death, loss to follow-up, or the end of follow-up. Baseline characteristics were compared using Student t test or χ² test, as appropriate. Where necessary, continuous variables were transformed logarithmically to give near-normal distributions of data for parametric analysis. The hazard ratio (HR) from Cox proportional hazards model with a stepwise multivariable regression (ie, backward elimination) was used to estimate the risk associated with a 1-SD increase in 3 inflammatory marker levels (hsCRP, IL-6, and IL-18) for CVEs, adjusted for age and sex (Model 1); hypertension, diabetes mellitus, smoking, hyperlipidemia, and variables showing P<0.10 on univariate testing (Model 2); and the white-matter hyperintensities -grade, a 1-SD increase in IMT, and the presence of SLI (Model 3). Additionally, we used a global measure of model-fit (the likelihood-ratio test), calibration (Hosmer-Lemeshow χ²), and discrimination (C-statistics) after addition of the identified marker, individually and in combination, to the base model, including conventional cardiovascular risk factors (age, sex, hypertension, hyperlipidemia, diabetes mellitus, and smoking) and IMT. We further assessed the incremental utility of the identified individual markers in predicting CVEs by calculating the net reclassification improvement (NRI)19 and the integrated discrimination index (IDI).19 All analyses were performed with SAS-9.2, with statistical significance inferred as 2-sided values <0.05.

**Results**

**Patient Characteristics**

The baseline characteristics are summarized in Table 1. The mean age at the time of the MRI was 68.8±8.6 years. Vascular
risk factors were more prevalent. The correlations between inflammatory markers and conventional risk factors are summarized in Table I in the online-only Data Supplement.

**Outcome**

During an average duration of 4.8±2.6 years, 25 patients experienced a new onset of CVEs, including 16 ischemic, 5 hemorrhagic, and 4 surgical or endovascular treatments after TIA. We classified 16 patients with ischemic stroke, 5 with large-artery atherosclerosis, 4 with cardioembolism, 2 with lacunar infarction, and 5 with undefined type of infarction.

**Stroke Risk**

Table 1 shows the clinical characteristics with respect to CVE outcomes. Patients who had development of CVEs showed significantly higher rates of male, SLI, higher IL-6 levels, and IMT. Distributions of conventional risk factors, levels of blood pressure, cholesterol, fasting glucose, HbA1c, white blood cell counts, hsCRP and IL-18, rates of intracranial large-artery atherosclerosis, and the grade of white-matter hyperintensity were not statistically different between CVEs-group and non–CVEs-group. Also, for the association between inflammatory markers and atherothrombotic CVEs (n=11), IL-6 levels showed borderline significance (P=0.054), whereas neither hsCRP (P=0.53) nor IL-18 levels (P=0.196) did. CVEs-free rate curves created using the Kaplan–Meier method, with respect to the presence of SLI and median IL-6 levels are shown in Figure 2A and 2B.

In the stepwise Cox regression model (Table 2), IL-6, but neither hsCRP nor IL-18, was positively associated with risk of CVEs in Model 1. The adjusted HR for IL-6 was virtually unchanged, after adjusting for conventional risk factors in Model 2 (HR: 2.06 [1.18–3.83], P=0.01). After additional adjustment for white-matter hyperintensities grade, IMT, and SLI in Model 3, IL-6 levels remained significant (HR: 1.80 [1.06–3.08], P=0.03).

To test the hypothesis that the proportional risk of CVEs might differ according to above-median IL-6 levels (1.4 pg/mL), and the presence of SLI, both, or neither, patients were categorized into 4 groups on the basis of the median IL-6 level with SLI. Relative to those with low IL-6/SLI (–), there was no significant heterogeneity in the proportional predictive value in low–IL-6/SLI (+) or high–IL-6/SLI (–) groups. However, those with high IL-6/SLI (+) had a significantly increased risk of CVEs (HR: 4.14 [1.31–15.73], P=0.014; Figure 2C).

Table 3 shows that incorporation of the set of markers individually or in combination (ie, SLI, IL-6, SLI+IL-6) into the base model with conventional risk factors and IMT significantly improved the goodness of fit. All models were well calibrated with Hosmer-Lemeshow P values >0.05, suggesting neither model had a significant lack of fit (data not shown). A base model had a C-statistics of 0.673 (95%
CI, 0.637–0.724), and the addition of individual markers resulted in increases in the C-statistics (all changes >0.05), but made less statistically significant (Table 3). When the risk was reclassified into risk categories of <5%, 5% to 15%, or >15% risk of CVEs, reclassification tables of the estimated risk using the models with and without SLI+IL-6 are shown in Table II in the online-only Data Supplement. We observed significant reclassification improvement with NRI of 0.149 (P=0.04) in the base model with SLI+IL-6, and the NRI of 0.259 (P=0.03) in the base model with IL-6, whereas the NRI was nonsignificant for SLI (P=0.44). The IDI was borderline significant improvement for SLI+IL-6 (0.021, P=0.05), IL-6 (0.012, P=0.06), whereas the IDI was nonsignificant for SLI (0.009, P=0.74). We performed additional analyses restricted to intermediate-risk groups (5% to 15% risk of CVEs). The NRI in the base model with SLI+IL-6 was significant (0.423, P=0.01), whereas the NRI was nonsignificant for both IL-6 (0.286, P=0.17) and SLI (0.05, P=0.74; Table 3).

Discussion

Among the 3 inflammatory markers, IL-6 levels is of potential, clinical value to predict future CVEs and to add marginally to the information obtained from determination of conventional risk factors and surrogate markers (ie, IMT, SLI) in individuals without prior CVD, as measured by significant reclassification in both the overall cohorts and in patients categorized as intermediate-risk group.

We confirmed that IL-6 levels are investigated with composite CVD incidence, stroke incidence and recurrence, mortality, or prognosis after stroke. However, the results of only a few clinical studies on initial stroke incidence remain controversial. The Health ABC Study demonstrated that IL-6, but not hsCRP or tumor necrosis factor-α, predict stroke incidence in elderly populations without prior CVD.23 In contrast, both the PROSPER24 and Caerphilly22 studies confirmed that no inflammatory markers, including IL-6, hsCRP, and IL-18, showed independent associations and discrimination of stroke risk. The significance of inflammation marker in these previous studies has not been consistently shown in terms of discriminatory ability, judged from the C-statistic. Furthermore, prospective data on the combination of inflammatory markers and SLI for stroke are also limited. Only 1 prospective study reported the predictive value of hsCRP with stroke-risk incorporating SLI; meanwhile, higher hsCRP was no longer a significant predictor without SLI.10 To our knowledge, this is the first study to examine not only the association of IL-6 with first CVEs, but also the potential predictive ability at the individual levels in calculating the NRI in contrast with previous studies. Folsom et al12 showed IL-6 measurement added only a small increment in the C-statistics in the CVD-risk prediction. They had not applied NRI in statistical approaches. However,

Table 2. Stepwise Cox Proportional Hazards Regression Analysis of Baseline Inflammatory Markers for the Risk of CVEs

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>1.95 (1.15–3.31) P=0.01</td>
<td>2.06 (1.18–3.83) P=0.01</td>
<td>1.80 (1.06–3.08) P=0.03</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1.31 (0.91–1.84) P=0.15</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IL-18</td>
<td>1.47 (0.62–3.55) P=0.38</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

IL indicates interleukin; hsCRP, high-sensitivity C-reactive protein; and CVEs, cerebrovascular events. Hazards ratios are for a 1-SD increase in log inflammatory markers. Model 1: adjusted age and sex. Model 2: Model 1+ hypertension, hyperlipidemia, diabetes, smoking, and variables showing P<0.10 on univariate testing. Model 3: Model 2+ white-matter hyperintensity grade, IMT, or SLI.
Table 3. Measures of Model-Fit, Discrimination, and Reclassification of Risk Models Without and With IL-6 in the Prediction of CVEs

<table>
<thead>
<tr>
<th></th>
<th>Likelihood-Ratio Test (P*)</th>
<th>C-Statistics (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td>0.681 (0.637–0.724)</td>
<td>0.723 (0.680–0.764)</td>
<td>0.59</td>
</tr>
<tr>
<td>+SLI</td>
<td>0.09</td>
<td>0.746 (0.695–0.795)</td>
<td>0.26</td>
</tr>
<tr>
<td>+IL-6</td>
<td>0.02</td>
<td>0.748 (0.706–0.787)</td>
<td>0.38</td>
</tr>
<tr>
<td>+SLI+IL-6</td>
<td>0.01</td>
<td>0.766 (0.725–0.804)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

SLI indicates silent lacunar infarction; IL, interleukin; and CVEs, cerebrovascular events.

<table>
<thead>
<tr>
<th></th>
<th>P*</th>
<th>IDI Value</th>
<th>P*</th>
<th>NRI (Intermediate-Risk Group) Value</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+SLI</td>
<td>0.07</td>
<td>0.44</td>
<td>0.09</td>
<td>0.74</td>
<td>0.05</td>
</tr>
<tr>
<td>+IL-6</td>
<td>0.259</td>
<td>0.03</td>
<td>0.012</td>
<td>0.06</td>
<td>0.286</td>
</tr>
<tr>
<td>+SLI+IL-6</td>
<td>0.149</td>
<td>0.04</td>
<td>0.021</td>
<td>0.05</td>
<td>0.423</td>
</tr>
</tbody>
</table>

SLI indicates silent lacunar infarction; IL, interleukin; NRI, net reclassification improvement; and IDI, integrated discrimination index. P* value compared with the base model (cardiovascular risk factors [age, sex, hypertension, hyperlipidemia, diabetes mellitus, and smoking]) and IMT.

Recent epidemiologic statistics has proposed that C-statistic should not be the sole determinant of clinical utility. Briefly, when examining the usefulness of a marker in improving the overall risk prediction, important parameters to consider include improvement in the C-statistic, as well as the model performance and the calibration. Reclassification is also a practical approach to gauging the effects of adding new risk factors to the conventional risk factors, when differences in the C-statistic are marginal. Therefore, it is important to note that our results show a consistent pattern for IL-6 levels across statistical methods.

Neither hsCRP nor IL-18 was predictive of stroke incidence in this study. However, a recent meta-analysis suggests hsCRP is associated with the prediction for ischemic stroke, but not with hemorrhagic stroke. In this study, the lack of association between hsCRP and CVEs is possible because the end point—any CVEs including hemorrhagic stroke—could underestimate the strength of their association. Furthermore, a small number of end points precluded a separate analysis for CVEs subtype. Several prospective studies have similarly failed to confirm an association between hsCRP and stroke risk in elderly populations, or those with more vascular risk factors. However, Mendelian randomization studies have reported a lack of concordance between the associations among CRP genotypes, CRP concentrations, and CVD, which has been interpreted as an argument against causality. However, 2 recent genetic meta-analyses lend support for the causality of a lifelong genetic predisposition to high levels of IL-6 pathway (ie, upstream of CRP) in determining a proportionally increased risk of CVD, raising expectations for anti-inflammatory strategies for risk reduction.

IL-18, specific alternative pathways as the interferon-γ-dependent atherogenesis, predicts CVD, because both clinical and experimental studies have supported its role in atherosclerotic plaque progression and destabilization, as well as predominantly coronary endpoints. However, significance of IL-18 for risk of stroke remains unclear. The lack of association between IL-18 and stroke in our study is concordant with recent studies that IL-18 was not associated with an increased risk of stroke incidence or recurrence.

Furthermore, hsCRP, IL-6, and IL-18 levels have all been in positive correlation with IMT, body mass index, and triglycerides, but only IL-6 had predictive value for CVEs (Table I in the online-only Data Supplement). Recent genetic analysis, as discussed above, shows that IL-6-receptor genotype is associated with the risk of CVD, but it is not related to conventional risk factors. The effect of Asp358Ala on IL-6-receptor for CVD-risk is unlikely to be mediated by conventional risk factors. Taken together, elevated IL-6 level may reflect a response to atherosclerosis and genetic causality, so IL-6 might be of potential clinical value.

We acknowledge several limitations. First, it includes the low incidence of CVEs in this cohort. Thus, although we can speculate that inflammation marker levels are related to atherothrombotic CVEs, we cannot draw any conclusion about the value of inflammatory markers in each stroke subtype from this study. The prevalence of vascular risk factors was relatively high at baseline, but our participants in the ambulatory setting of cardiovascular prevention clinics may have had more intensive risk factor modification in lifestyle and by drug therapy during follow-up, thereby reducing the number of events and decreasing the statistical power. Nonetheless, the association between only IL-6 levels and atherothrombotic CVEs has shown borderline significance. Second, the blood sampling by a single measure could not be corrected for within-person variability. Third, the present study is limited to the cohort of Japanese elderly individuals with vascular risk factors, without known CVD. Consequently, the predictive values of IL-6 may be specific to this population, not generalizable to other races and cohorts. Fourth, we observed a significant improvement in model prediction using the likelihood-ratio test and calibration; however, the improvement in C-statistics was not statistically significant, although this highlights the deficiencies of C-statistics, which are insensitive to small changes in predictive accuracy. We assessed the incremental prognostic value of IL-6 and SLI in combination in using the NRI and IDI, but we recognize that changing the boundaries used to define risk categories would influence the NRI computed, and there is no widely agreed on definition of clinically important boundaries for the prediction of CVEs. Furthermore, direct comparisons with studies evaluating the NRI with other markers should be made with caution because the number of risk categories used, definition of the outcome, and length of follow-up often differ between studies. The lack of consensus in this particular area needs to be addressed. Furthermore, we also calculated the IDI, a newer method for evaluating improvement in risk discrimination, which was marginally significant but was of small magnitude. Therefore, despite a consistent pattern for IL-6 levels across statistical methods, our study does not seem to bring major advances in risk stratification. Thus, given the characteristics of our cohort, our results suggest IL-6 measurement should not routinely be performed in the general population because the overall added value may be small and unlikely to be a clinical importance at the moment. We concluded that determining a patient’s stroke risk on the basis of IL-6 level may be clinically challenging, if IL-6 is used in low-risk populations. We assume that further studies are needed to better define the target population.
In conclusion, IL-6 level was independently associated with the incidence of CVEs in patients with vascular risk factors, but without prior CVD. However, whether to use screening based on IL-6 levels as a more routine test for risk prediction requires full consideration. Further, large investigation or randomized controlled trial will be needed to assess whether risk refinements measuring IL-6 levels lead to a meaningful change in clinical outcome.

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Disclosures

None.

References

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Supplemental Material

Title
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Short title
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Table I
Correlation coefficients between conventional risk factors and hsCRP, IL-6, and IL-18 in the whole population

<table>
<thead>
<tr>
<th></th>
<th>hsCRP</th>
<th>IL-6</th>
<th>IL-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.012</td>
<td>0.261**</td>
<td>0.151**</td>
</tr>
<tr>
<td>BMI</td>
<td>0.177**</td>
<td>0.120*</td>
<td>0.138*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.024</td>
<td>0.046</td>
<td>0.091</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.044</td>
<td>-0.086</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>0.119*</td>
<td>0.053</td>
<td>0.088</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.156**</td>
<td>0.164*</td>
<td>0.051</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>-0.01</td>
<td>0.015</td>
<td>-0.133*</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>-0.228**</td>
<td>-0.214**</td>
<td>-0.250**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.226**</td>
<td>0.146*</td>
<td>0.178**</td>
</tr>
<tr>
<td>White blood cell</td>
<td>0.204**</td>
<td>0.223**</td>
<td>0.139**</td>
</tr>
<tr>
<td>IMT</td>
<td>0.110*</td>
<td>0.133*</td>
<td>0.190**</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1</td>
<td>0.329**</td>
<td>0.197**</td>
</tr>
<tr>
<td>IL-6</td>
<td>—</td>
<td>1</td>
<td>0.196**</td>
</tr>
</tbody>
</table>

**p<0.001; *p<0.05

Hs-CRP, IL-6, and IL-18 were all positively correlated with BMI, IMT, and triglycerides and negatively correlated with HDL. There was a mutual correlation between inflammatory markers.
Table II
Reclassification tables:

<table>
<thead>
<tr>
<th>CVEs risk in base model</th>
<th>low (≤5%)</th>
<th>intermediate (5% to &lt;15%)</th>
<th>high (≥15%)</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>242</td>
<td>29</td>
<td>0</td>
<td>271</td>
</tr>
<tr>
<td>intermediate</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>5% to &lt;15%</td>
<td>52</td>
<td>88</td>
<td>17</td>
<td>157</td>
</tr>
<tr>
<td>high</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>≥15%</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>overall</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>294</td>
<td>121</td>
<td>24</td>
<td>439</td>
</tr>
</tbody>
</table>

Table II shows number of patients in risk categories calculated using established risk factors who are reclassified into new risk categories calculated using both established risk factors, SLI and IL-6; stratified by whether or not they had a development of cerebrovascular events (CVEs).