Soluble CD40L Is a Useful Marker to Predict Future Strokes in Patients With Minor Stroke and Transient Ischemic Attack

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D40 ligand (CD40L) plays a role in atherosclerotic plaque instability.\(^1\) Soluble CD40L (sCD40L) was released from activated platelet and shown to be a predictor of first\(^2\) and subsequent cardiovascular events.\(^3\) Recently, a genetic study indicated that CD40-1C>T polymorphisms was associated with the risk of reocclusion after successful fibrinolytic therapy in patients with stroke,\(^4\) suggesting that sCD40L might be associated with prognosis of stroke. However, the role of sCD40L in predicting recurrent stroke remained unclear.

The Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial compared efficacy of clopidogrel plus aspirin or aspirin alone.\(^5\) Serum samples were collected 24±12 hours after randomization. The primary outcome was stroke within 90-day follow-up period. The CHANCE protocol was approved by the ethics committee at each study center.

### Methods

#### Study Design

Totally 5170 patients within 24 hours after acute minor stroke or transient ischemic attack were randomized to receive either clopidogrel plus aspirin or aspirin alone.\(^5\) Serum samples were collected 24±12 hours after randomization. The primary outcome was stroke within 90-day follow-up period. The CHANCE protocol was approved by the ethics committee at each study center.

#### Measurements of Biomarkers

sCD40L levels were determined via an ELISA kit (catalogue number BMS239; eBioscience, Vienna, Austria). High-sensitive C-reactive

### Results

Patients in the top tertile of sCD40L levels had increased risk of recurrent stroke comparing with those in the bottom tertile, after adjusted for conventional confounding factors (hazard ratio, 1.49; 95% confidence interval, 1.11–2.00; \(P=0.008\)). The patients with elevated levels of both sCD40L and high-sensitive C-reactive protein also had increased risk of recurrent stroke (hazard ratio, 1.81; 95% confidence interval, 1.23–2.68; \(P=0.003\)).

### Conclusions

Elevated sCD40L levels independently predict recurrent stroke in patients with minor stroke and transient ischemic attack.

#### Clinical Trial Registration


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### Key Words

CD40 ligand ■ ischemic attack, transient ■ prognosis ■ stroke

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1990
protein (hsCRP) was measured in the clinical laboratory in Tiantan hospital. All measurements were performed by laboratory personnel blinded to the study status.

Statistical Analysis
Proportions were used for categorical variables. Medians with interquartile ranges were used for continuous variables because of skewed distribution. Categorical and continuous variables were compared with the $\chi^2$ statistics and Kruskal–Wallis test, respectively. The relationship of sCD40L and outcome was investigated with Cox proportional-hazards model. A 2-sided $P$ value of <0.05 was considered to be statistically significant.

Results

Patient Characteristics
There were 73 (64%) prespecified centers voluntarily participated in the biomarker substudy, enrolling 3044 consecutive patients.

Characteristics of patients are shown in Table I in the online-only Data Supplement. Patients in the top tertile of sCD40L levels were younger, likely had history of hypercholesterolemia, and higher baseline levels of low-density lipoprotein-cholesterol, triglycerides, hsCRP, and leukocyte count.

sCD40L and Recurrence of Stroke
Patients in the top tertile of sCD40L levels had increased risk of recurrent stroke (Figure I in the online-only Data Supplement). The increased risk remained after adjusted for other confounding factors (Table). The hazard ratios increased with rising tertiles (Table). Similar results were found when sCD40L was assessed as a continuous variable (Table). Besides sCD40L, the factors of age, history of hypertension and diabetes mellitus, baseline National Institutes of Health Stroke Scale, baseline low-density lipoprotein-cholesterol levels, and dual antiplatelet therapy also predicted subsequent strokes (Figure II in the online-only Data Supplement).

sCD40L was interacted with hsCRP in its effect on recurrent stroke ($P=0.01$). Patients were subsequently divided into 6 groups according to tertiles of sCD40L levels and concentrations of hsCRP either >3 or ≤3 mg/L. The patients with elevated levels of both sCD40L and hsCRP also had increased risk of recurrent stroke (hazard ratio, 1.81; 95% confidence interval, 1.23–2.68; $P=0.003$; Figure III in the online-only Data Supplement).

Discussion
Although the role of sCD40L in predicting cardiovascular events has been well elucidated before, the association between sCD40L and stroke was still unclear.$^6$ One potential reason for this apparent discrepancy may relate to the use of combined vascular events as the end point, which would make the individual association of sCD40L with stroke not as apparent. On the contrary, most of these researches have focused on the first stroke.

sCD40L played a role in atherosclerotic plaque instability$^1$ and platelet activation.$^8$ Our results showed sCD40L predicted recurrent stroke, which indicated that sCD40L may represent another approach other than conventional risk factors to stratify the risk of recurrent stroke. Furthermore, it has been noted well that ischemic events still occurred in some patients, despite sustained standard secondary preventive therapy, indicating other therapeutic strategies should be implemented. Our findings might suggest sCD40L as a target for studies targeting the inflammatory cascade for stroke prevention. hsCRP was another inflammatory marker associated with prognosis of stroke$^6$; however, power was limited to find an independent effect of the combination of these 2 biomarkers because of overlapped confidence intervals in the current study.

Our study had some limitations. First, only baseline levels of sCD40L were obtained and the fluctuation of sCD40L could not be completely eliminated. Second, we did not adjust statin dose because of lack of the data, which was shown to be associated with stroke risk.$^{10}$ Third, the data on stroke subtypes were absent. These should be considered in the further study.

In conclusion, this substudy of CHANCE trial suggested that baseline sCD40L could serve as a prognostic factor of future recurrent stroke in patients with acute minor ischemic

Table. Risk of Recurrent Stroke According to Levels of sCD40L

<table>
<thead>
<tr>
<th>sCD40L levels†</th>
<th>Model 1*</th>
<th></th>
<th>Model 2*</th>
<th></th>
<th>Model 3*</th>
<th></th>
<th>Model 4*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events (%)</td>
<td>HR (95% CI)</td>
<td>$P$ Value</td>
<td>HR (95% CI)</td>
<td>$P$ Value</td>
<td>HR (95% CI)</td>
<td>$P$ Value</td>
<td>HR (95% CI)</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>78 (7.7%)</td>
<td>1 (reference)</td>
<td>...</td>
<td>1 (reference)</td>
<td>...</td>
<td>1 (reference)</td>
<td>...</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>107 (10.5%)</td>
<td>1.38 (1.03–1.85)</td>
<td>0.029</td>
<td>1.43 (1.07–1.92)</td>
<td>0.016</td>
<td>1.42 (1.06–1.90)</td>
<td>0.020</td>
<td>1.44 (1.08–1.94)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>114 (11.2%)</td>
<td>1.49 (1.11–1.98)</td>
<td>0.007</td>
<td>1.49 (1.11–2.00)</td>
<td>0.008</td>
<td>1.45 (1.08–1.95)</td>
<td>0.013</td>
<td>1.56 (1.16–2.08)</td>
</tr>
<tr>
<td>Continuous model‡</td>
<td>1.04 (1.01–1.07)</td>
<td>0.007</td>
<td>1.03 (1.01–1.06)</td>
<td>0.012</td>
<td>1.03 (1.00–1.06)</td>
<td>0.022</td>
<td>1.04 (1.01–1.07)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and sCD40L, soluble CD40 ligand.

*Model 1, unadjusted; model 2, adjusted for age, sex, body mass index, current or previous smoking, medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, transient ischemic attack, myocardial infarction, angina, known atrial fibrillation or flutter and valvular heart disease, randomized treatment of aspirin monotherapy or dual antiplatelet therapy, National Institutes of Health Stroke Scale score at 1 day after randomization, qualifying event and baseline levels of serum lipids (low-density lipoprotein-cholesterol, high-density lipoprotein, and triglycerides); model 3, adjusted for all factors in model 2, baseline high-sensitive C-reactive protein levels and baseline leukocyte count; model 4, adjusted for all factors in model 2 and the use of lipid-lowering agents, hypoglycemic agents or antihypertension agents during 90-day follow-up period.

†sCD40L level was divided by tertiles: tertile 1, sCD40L <6.21 ng/mL; tertile 2, sCD40L 6.21 to 9.32 ng/mL; and tertile 3, sCD40L ≥9.32 ng/mL.

‡Hazard ratios correspond to per unit increment of sCD40L value (ng/mL).
stroke and transient ischemic attack. Analysis of this biomarker may represent another approach to stratify the risk of recurrent stroke.

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**Disclosures**

None.

**References**

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### Table I. Baseline Characteristics and Medication within 90-day Follow-up Period According to Tertiles of sCD40L

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;6.21)</td>
<td>(6.21 to 9.32)</td>
<td>(≥9.32)</td>
<td></td>
</tr>
<tr>
<td>n=1014</td>
<td>n=1016</td>
<td>n=1014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>63 (56 to 72)</td>
<td>63 (55 to 71)</td>
<td>61 (53 to 70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>24 (23 to 26)</td>
<td>24 (23 to 26)</td>
<td>25 (23 to 27)</td>
<td>0.074</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>321 (31.7)</td>
<td>346 (34.1)</td>
<td>350 (34.5)</td>
<td>0.341</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>184(18.1)</td>
<td>206(20.3)</td>
<td>192(18.9)</td>
<td>0.467</td>
</tr>
<tr>
<td>TIA</td>
<td>32(3.2)</td>
<td>29(2.9)</td>
<td>34(3.4)</td>
<td>0.809</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22(2.2)</td>
<td>17(1.7)</td>
<td>16(1.6)</td>
<td>0.562</td>
</tr>
<tr>
<td>Angina</td>
<td>30(3.0)</td>
<td>33(3.2)</td>
<td>32(3.2)</td>
<td>0.929</td>
</tr>
<tr>
<td>Known atrial fibrillation or flutter</td>
<td>16(1.6)</td>
<td>22(2.2)</td>
<td>19(1.9)</td>
<td>0.621</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>87(8.6)</td>
<td>108(10.6)</td>
<td>123(12.1)</td>
<td>0.032</td>
</tr>
<tr>
<td>Hypertension</td>
<td>680(67.1)</td>
<td>638(62.8)</td>
<td>666(65.7)</td>
<td>0.120</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>211(20.8)</td>
<td>198(19.5)</td>
<td>204(20.1)</td>
<td>0.759</td>
</tr>
<tr>
<td>Current or previous smoking, No. (%)</td>
<td>450(44.4)</td>
<td>423(41.6)</td>
<td>432(42.6)</td>
<td>0.448</td>
</tr>
<tr>
<td>NIHSS, median (IQR) *</td>
<td>2 (0 to 2)</td>
<td>2 (0 to 2)</td>
<td>2 (0 to 2)</td>
<td>0.809</td>
</tr>
<tr>
<td>Baseline biomarkers, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.0(2.4 to 3.7)</td>
<td>3.1(2.5 to 3.8)</td>
<td>3.2(2.6 to 4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2 (1.0 to 1.5)</td>
<td>1.2(1.0 to 1.4)</td>
<td>1.2(1.0 to 1.5)</td>
<td>0.259</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.4 (1.0 to 1.9)</td>
<td>1.4(1.0 to 2.0)</td>
<td>1.5(1.1 to 2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.6(0.8 to 3.7)</td>
<td>1.7(0.8 to 3.9)</td>
<td>2 (0.9 to 4.8)</td>
<td>&lt;0.001</td>
</tr>
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<td></td>
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<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Leukocyte count, (10^9/L)</strong></td>
<td>6.4(5.4 to 7.7)</td>
<td>6.4(5.4 to 7.7)</td>
<td>6.9(5.8 to 8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Medication within 3 months, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensive agent</td>
<td>357(35.3%)</td>
<td>375(37.1%)</td>
<td>393(39.1%)</td>
<td>0.217</td>
</tr>
<tr>
<td>Hypoglycemic agents</td>
<td>129(12.8%)</td>
<td>126(12.5%)</td>
<td>120(11.9%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>431(42.7%)</td>
<td>408(40.3%)</td>
<td>428(42.6%)</td>
<td>0.476</td>
</tr>
</tbody>
</table>

sCD40L indicates soluble CD40 ligand; IQR, interquartile range; BMI, body-mass index; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; LDL-C, LDL cholesterol; HDL, HDL cholesterol; and hsCRP, high sensitivity C reactive protein.
Figure I. Kaplan–Meier curves showing the probability of survival free of stroke during 90-day follow-up according to tertiles of sCD40L levels. sCD40L level was divided by tertiles: tertile 1, sCD40L < 6.21 ng/ml; tertile 2, sCD40L 6.21 to 9.32 ng/ml; tertile 3, sCD40L ≥ 9.32 ng/ml. The inset shows the same data on an enlarged segment of the y axis.
Figure II. Factors associated with recurrent stroke during 90-day follow-up. sCD40L tertiles, age, sex, body-mass index (BMI), current or previous smoking, medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, TIA, myocardial infarction, angina, known atrial fibrillation or flutter and valvular heart disease, randomized treatment of aspirin monotherapy or dual antiplatelet therapy, NIHSS score at 1 day after randomization, qualifying event, baseline levels of serum lipids (LDL-c, HDL and triglycerides), baseline hsCRP levels and baseline leukocyte count were included in the Cox proportional-hazards model with time-to-event for stroke as the dependent variable.
Figure III. Combination of sCD40L with hsCRP predicted outcomes. Patients were divided into 6 groups according to tertiles of sCD40L levels and concentrations of hsCRP either > 3 or ≤ 3 mg/L, the cut point recommended by the Centers for Disease Control and the American Heart Association for high risk category to develop cardiovascular events (low risk, <1.0 mg/L; average risk, 1 to 3 mg/L; and high risk, >3 mg/L) and associated with increased risk of recurrent stroke: group 1: sCD40L<6.21 ng/mL and hsCPR ≤ 3 mg/L; group 2: sCD40L 6.21 to 9.32 ng/mL and hsCPR ≤ 3 mg/L; group 3: sCD40L ≥ 9.32 ng/mL and hsCPR ≤ 3 mg/L; group 4: sCD40L<6.21 ng/mL and hsCPR > 3 mg/L; group 5: sCD40L 6.21 to 9.32 ng/mL and hsCPR > 3 mg/L; group 6: sCD40L ≥ 9.32 ng/mL and hsCPR > 3 mg/L. Group 1 was assigned as a reference category with a relative risk of 1. The Cox proportional-hazards model was adjusted for age, sex, BMI, current or previous smoking, medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, TIA, myocardial infarction, angina, known atrial fibrillation or flutter and valvular heart disease, randomized treatment of aspirin monotherapy or dual antiplatelet therapy, NIHSS score at 1 day after randomization, qualifying event and baseline levels of serum lipids (LDL-c, HDL and triglycerides). * p<0.05 vs patients in group 1.

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