High-Sensitive C-Reactive Protein Predicts Recurrent Stroke and Poor Functional Outcome

Subanalysis of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events Trial

Jiejie Li, MD, PhD; Xingquan Zhao, MD, PhD; Xia Meng, MD, PhD; Jinxin Lin, MD, PhD; Liping Liu, MD, PhD; Chunxue Wang, MD, PhD; Anxin Wang, MD, PhD; Yilong Wang, MD, PhD; Yongjun Wang, MD; on behalf of the CHANCE Investigators*

Background and Purpose—Minor stroke and transient ischemic attack are common disorders with high rate of subsequent disabling stroke. We aim to investigate the role of high-sensitive C-reactive protein (hsCRP) in predicting recurrent stroke and poor functional outcome.

Methods—In the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial, 3044 (59%) consecutive patients from 73 (64%) prespecified centers had hsCRP levels measured. The primary outcome was any stroke within 90 days. The secondary outcome included combined vascular events and dependence or death defined as modified Rankin Scale score of 2 to 6 at 90 days and a new vascular event during 1-year follow-up. The associations of hsCRP with recurrent stroke and functional outcome were analyzed by using Cox proportional hazards and logistic regression models.

Results—Elevated hsCRP (>3.0 mg/L) was observed in 32% of the study population. Patients with hsCRP >3 mg/L had an increased risk of recurrent stroke (adjusted hazard ratio, 1.46; 95% confidence interval, 1.08–1.98; \( P = 0.039 \)), ischemic stroke and combined vascular events, and poor functional outcome (adjusted odds ratio, 1.68; 95% confidence interval, 1.22–2.32; \( P = 0.002 \)) compared with those with hsCRP <1 mg/L within 90-day follow-up period. High hsCRP levels also independently predicted recurrent stroke during 1-year follow-up. There was no interaction of hsCRP levels with randomized antiplatelet therapy.

Conclusions—High hsCRP levels predict recurrent stroke and poor functional outcome in acute patients with minor stroke or transient ischemic attack.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00979589.

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Key Words: C-reactive protein ▪ prognosis ▪ risk factor ▪ stroke ▪ transient ischemic attack

Acute minor ischemic stroke and transient ischemic attack (TIA) are common, and patients with recent stroke or TIA are at high risk for subsequent stroke. It is estimated that 10% to 20% of these patients have a stroke within 3 months after the index event, most of which even occur within the first 2 days.¹⁴ Though several clinical risk factors have been reported to be associated with recurrent stroke, these characteristics do not fully explain the risk of recurrence of stroke.⁵

Inflammation is increasingly recognized as playing a central role in atherosclerosis and cardiovascular disease.⁶ High-sensitive C-reactive protein (hsCRP), one of the most investigated inflammatory makers in cardiovascular research, has been independently associated with increased risk of recurrent cardiovascular events.⁷ However, the association between hsCRP and recurrent stroke is less established.⁸–¹⁰ On the contrary, disability from stroke has brought huge personal and societal burden. Though the predictive value of hsCRP in mortality has been proved,¹¹,¹² its association with functional disability in the patients with stroke is still undefined.¹³,¹⁴

The CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) trial showed that the combination of clopidogrel and aspirin was superior to aspirin alone in reducing recurrent stroke in patients with acute minor stroke or high-risk TIA during 90-day and 1-year follow-up.
follow-up. Furthermore, it was recently suggested that the 90-day functional outcome was also improved.17 In this subgroup analysis, we aimed to assess the relationship of hsCRP with recurrent stroke and functional outcome.

Materials and Methods

Study Design
The design and major results of the CHANCE trial have been described in detail previously. In brief, CHANCE trial was a randomized, double-blind, placebo-controlled clinical trial that randomized 5170 patients with acute minor stroke or high-risk TIA to antiplatelet therapy of clopidogrel and aspirin or aspirin alone. Acute minor stroke was defined by a score of 3 or less at the time of randomization on the National Institutes of Health Stroke Scale. High-risk TIA was defined as an episode of focal cerebral dysfunction lasting <24 hours, followed by a return to normality, and with a score of ≥4 on the ABCD2 assessing the risk of stroke according to age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes when randomized, indicating great short-term recurrent risk. All participants or their legal proxies provided written informed consent. The CHANCE trial was approved by the ethics committee at each study center.

Study Populations
Among 114 clinical centers included in CHANCE trial, 73 (64%) prespecified centers voluntarily participate in the blood substudy and totally enrolled 3044 consecutive patients and samples. Seventeen patients were lost within 90 days (follow-up rate 99.4%).

Follow-Up and Efficacy Outcomes
Patients were followed up for 90 days in the original plan of the CHANCE trial. Another visit to follow patients for 1 year after enrollment was performed between October 2010 and July 2013. All follow-up visits were in person by a trained site coordinator, collecting information of any end point events, assessment of the patient’s modified Rankin Scale score ranging from 0 (no symptoms) to 6 (death), and medications used during follow-up period. All patients’ medical records for any reported events were reviewed and confirmed by a central adjudication committee that was blinded to the study-group assignments.

The primary efficacy outcome was a new stroke event (ischemic or hemorrhagic) within 90 days. Secondary efficacy outcomes included combined vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death) and dependence or death defined as modified Rankin Scale score of 2 to 6 at 90 days and a new vascular event during 1-year follow-up period.

Measurement of hsCRP
Venous blood was drawn from fasting patients 24±12 hours after randomization. Frozen serum samples were collected and stored at −80°C. No freezing and thawing circle occurred before test. hsCRP was centrally measured on a Roche Modular P800 analyzer (Ji’en Technique Co Ltd, Shanghai, China) in the clinical laboratory in Tiantan hospital. The intra-assay and interassay coefficients of variation were 2.5% and 2.0%, respectively. All measurements were performed by laboratory personnel blinded to the study samples regarding treatment assignment and outcomes.

Statistical Methods
In the univariate analysis, Kruskal–Wallis test was used for comparisons of skewed continuous variables and ordinal variable. Categorical variables were compared with the χ² statistics or Fisher exact test as appropriate.

The associations of hsCRP with recurrence of stroke, ischemic stroke, and combined vascular events were investigated with the use of Cox proportional hazards models. Logistic regression model was used to explore the association of hsCRP with poor functional outcome. The potential confounders were demographic factors, prior published traditional or clinical risk factors, index event, study intervention, and medications used during follow-up period. Variable was included into the multivariate model if associated with outcomes in univariate analysis, with a P value of <0.20. hsCRP level was analyzed by relative risk category recommended by the Centers for Disease Control and American Heart Association (low risk, <1.0 mg/L; average risk, 1–3 mg/L; and high risk, >3 mg/L), originally recommended for the risk assessment of cardiovascular disease. This cut point was also associated with increased risk of recurrent stroke. A 2-sided P value of <0.05 was considered to indicate statistical significance. SAS software, version 9.3 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

Results

Patient Characteristics
The baseline characteristics of patients included and not included in this substudy were well balanced, except that the patients enrolled had a slightly lower proportion of history of diabetes mellitus, qualifying TIA, and lower baseline National Institutes of Health Stroke Scale score and were more likely to receive antihypertensive treatment during follow-up (Table I in the online-only Data Supplement). Elevated hsCRP (≥3.0 mg/L) was observed in 32% of the study population. The median hsCRP was 1.70 mg/L. This distribution of hsCRP was almost identical with that of other stroke studies. Characteristics of patients after stratification by relative risk of hsCRP are shown in Table 1. The patients with high hsCRP levels were significantly older, had higher body mass index and baseline National Institutes of Health Stroke Scale score, had histories of ischemic stroke and hypertension, had minor stroke, and received hypoglycemic treatment (Table 1).

hsCRP and Recurrent Vascular Events
There were 299 (9.8%) patients with recurrent stroke within 90 days. These patients had higher hsCRP levels compared with those without recurrent stroke (4.02 mg/L versus 3.38 mg/L; P=0.010).

At 90 days, in crude models, higher hsCRP level was associated with increased risk of stroke, ischemic stroke, and combined vascular events (Table 2). After adjustment for age, body mass index, sex, histories of myocardial infarction, hypertension and diabetes mellitus, baseline National Institutes of Health Stroke Scale score, baseline leukocyte count, study intervention, and use of antihypertension agents, lipid-lowering agents, and hypoglycemic agents during follow-up period, such associations were maintained (Table 2). High hsCRP levels also independently predicted recurrence of stroke, ischemic stroke, and combined vascular events during 1-year follow-up (Table 2).

Similar results were seen when hsCRP level was divided into 4 levels by quartiles (Table 2). The association was partially attenuated in the adjusted model when hsCRP was assessed as a continuous variable (Table 2).

No interactions of hsCRP with randomized antiplatelet treatment (P=0.58) or use of lipid-lowering agents (P=0.42), hypoglycemic agents (P=0.18), or antihypertension agents (P=0.10) were found.
hsCRP and Functional Outcome

Totally, 321 (10.5%) patients had poor functional outcome at 90 days. These patients had higher hsCRP levels compared with those with good functional outcome (4.20 mg/L versus 3.34 mg/L; \( P < 0.001 \)). The rate of recurrent stroke within 90-day follow-up period was higher in the patients with poor functional outcome (68.8% versus 2.9%; \( P < 0.001 \)).

As shown in Table 3, patients with high levels of hsCRP had poor functional outcome at 90 days in the crude and multivariate model.

Discussion

The major finding of this study is that higher levels of hsCRP are independent predictors of stroke and vascular events as well as unfavorable functional outcome in patients with minor stroke or high-risk TIA. Elevated hsCRP level has been consistently associated with cardiovascular disease and thus is recommended for risk assessment in patients with intermediate risk according to guidelines.\(^{19-21}\) However, previous researches on the association between hsCRP and first stroke yielded conflicting results.\(^{12,22,23}\) A large meta-analysis with a
total of 160,309 participants then proved that CRP was associated with risk of initial stroke.24 On the contrary, most8,9,25 but not all11 prior studies indicated that hsCRP played a critical role in stroke recurrence. One of the reasons for these discrepancies might be the difference of study population. In LIMITS (Levels of Inflammatory Markers in the Treatment of Stroke) study, hsCRP predicted recurrent stroke among patients with lacunar stroke;6 hsCRP also predicted further ischemic events in the first-ever TIA or stroke patients with intracranial large-artery occlusive disease.8 However, the predictive effect of hsCRP on recurrent stroke was markedly attenuated in the research including patients with all etiologic subtypes of stroke.11 Some genetic data suggested that CRP is not a causal factor but merely a marker of stroke.26 Most of its association...
CRP and Prognosis in Minor Stroke and TIA

Table 3. Associations of hsCRP Levels With Poor Functional Outcome at 90 Days

<table>
<thead>
<tr>
<th>hsCRP, mg/L*</th>
<th>Unadjusted Model</th>
<th>Adjusted Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>&lt;1</td>
<td>1 (Reference)</td>
<td>...</td>
</tr>
<tr>
<td>1–3</td>
<td>1.77 (1.30–2.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2.13 (1.57–2.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; hsCRP, high-sensitive C-reactive protein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*hsCRP values were divided into 3 levels (low risk, <1.0 mg/L; average risk, 1–3 mg/L; and high risk, >3 mg/L) by recommendation from the Centers for Disease Control and American Heart Association for primary prevention of cardiac disease.
†Adjusted for variables of which association with poor functional outcome achieved a P value of <.20 in univariate analysis, including age, sex, medical histories of hypertension, diabetes mellitus and ischemic stroke, baseline NIHSS score, baseline mRS score, baseline leukocyte count, qualifying event, randomized treatment of aspirin or dual antiplatelet therapy, and use of hypoglycemic agents and anti-hypertension agents during 90 days follow-up period.

with recurrent stroke and functional outcome depends on conventional risk factors, indicating that the discordance of included pertinent confounding factors might also affect the predictive value of hsCRP. Therefore, full adjustment for predictors of recurrent stroke and functional outcome is necessary. It was suggested previously that stroke severity was associated with recurrent stroke and functional outcome. It was also suggested that elevated leukocyte count indicated an increased risk of recurrent stroke. On the contrary, the JUPITER (Justification for the Use of statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) study indicated that statin significantly reduced the incidence of major cardiovascular events in healthy persons with elevated hsCRP levels. In our study, the usage of lipid-lowering medications, hypoglycemic agents, and antihypertension agents was adjusted in addition to stroke severity and baseline leukocyte count, which was rarely considered in other studies. We found that hsCRP independently correlated with recurrent stroke, which to some extent suggested that hsCRP might be a target for secondary prevention for stroke. Development of specific human hsCRP inhibitors would further help elaborate the contribution of hsCRP to recurrent stroke.

Consistent with prior studies, we found no interaction between hsCRP and antiplatelet therapy. Moreover, no interaction was found between lipid-lowering medication usage and hsCRP either. One reason might be that the use of lipid-lowering medication was not under control in our study. Another explanation might be that the predictive role of hsCRP in patients’ response to secondary prevention was not as overt as that in primary prevention shown by JUPITER trial, especially when all patients received antiplatelet treatment of aspirin or more powerful aspirin plus clopidogrel combination. Further researches are needed to confirm our results.

The patients included in CHANCE trial had nondisabling cerebrovascular events. However, some patients had functional disability at 90 days. We found that the rate of recurrent stroke was remarkably higher in the patients with poor functional outcome. Because prognosis of recurrent stroke was unfavorable, it is possible that subsequent stroke instead of minor stroke or TIA per se led to functional disability in our study. Our study had some limitations. First, only one-point measurement of hsCRP was available. Though we strictly controlled the time window of sampling, fluctuation of hsCRP could not be completely excluded because of its intrinsic nature of reflecting system inflammatory response. However, the magnitude of fluctuation is likely to be low because the level of hsCRP was stable after stroke when repeated annually measurement. Second, we collected venous blood after an overnight fast when patients had already taken the first dosage of antiplatelet drug. Several studies have investigated the effect of clopidogrel or aspirin on hsCRP. One recent large trial randomly assigning patients either to clopidogrel plus aspirin or placebo plus aspirin, in line with our study intervention, found that clopidogrel had no effect on hsCRP compared with placebo. This finding was consistent with other previous studies. Therefore, we suppose that the administration of first dosage of antiplatelet drug might rarely affect the predictive role of hsCRP in our study, given all patients received antiplatelet therapy. This speculation was affirmed by the similar distribution of hsCRP levels between our and other stroke studies.

Conclusions

This substudy of CHANCE trial suggested that hsCRP levels played a role in predicting recurrent stroke and functional outcome in acute patients with minor ischemic stroke or high-risk TIA.

Sources of Funding

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/06/21/STROKEAHA.116.012901.DC1.html
**Online-Only Data Supplement**

**Supplemental Tables**

Table I. Baseline characteristics of patients included versus not included in biomarker substudy of CHANCE trial

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients included (n=3044)</th>
<th>All other patients (n=2126)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>62 (55 to 71)</td>
<td>62 (55 to 71)</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>24 (23 to 27)</td>
<td>24 (23 to 26)</td>
<td>0.26</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>1017 (33.4)</td>
<td>733 (34.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>582 (19.1)</td>
<td>451 (21.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>TIA</td>
<td>95 (3.1)</td>
<td>79 (3.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>55 (1.8)</td>
<td>41 (1.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>54 (1.8)</td>
<td>26 (1.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Known atrial fibrillation or flutter</td>
<td>57 (1.9)</td>
<td>39 (1.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>10 (0.3)</td>
<td>4 (0.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>318 (10.4)</td>
<td>255 (12.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1984 (65.2)</td>
<td>1415 (66.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>613 (20.1)</td>
<td>480 (22.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current or previous smoking, No. (%)</td>
<td>1305 (42.9)</td>
<td>916 (43.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>TIA</td>
<td>817 (26.8)</td>
<td>628 (29.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>2227 (73.2)</td>
<td>1498 (70.5)</td>
<td></td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>2 (0-2)</td>
<td>1 (0-2)</td>
<td>0.04</td>
</tr>
<tr>
<td>mRS score before the onset of index event, NO. (%)</td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>0</td>
<td>2523 (82.9)</td>
<td>1740 (81.8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>445 (14.6)</td>
<td>321 (15.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>76 (2.5)</td>
<td>65 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Aspirin alone, NO. (%)</td>
<td>1526 (50.1)</td>
<td>1060 (49.9)</td>
<td>0.85</td>
</tr>
<tr>
<td>Clopidogrel plus aspirin, NO. (%)</td>
<td>1518 (49.9)</td>
<td>1066 (50.1)</td>
<td></td>
</tr>
<tr>
<td>Medication within 90-day follow-up period, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensive agents</td>
<td>1125 (37.0)</td>
<td>689 (32.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypoglycemic agents</td>
<td>375 (12.3)</td>
<td>281 (13.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>1267 (41.6)</td>
<td>904 (42.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Stroke within 90 days</td>
<td>299(9.8)</td>
<td>216(10.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>mRS score of 2-6 at 90 days</td>
<td>321(10.5)</td>
<td>232(10.9)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; BMI, body-mass index (the weight in kilograms divided by the square of the height in meters); TIA, transient ischemic attack; mRS, modified Rankin Scale.
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