ORIGINAL RESEARCH

Joint High Level of Oxidized Low-Density Lipoprotein and High-Sensitivity C-Reactive Protein are Associated With Recurrent Stroke and Poor Functional Outcome in Minor Stroke or Transient Ischemic Attack

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BACKGROUND: Oxidized low-density lipoprotein (oxLDL) and hs-CRP (high-sensitivity C-reactive protein) plays an important role in cardiovascular diseases though inflammation and oxidative stress, etc. However, evidence on their combined effects on stroke prognosis is still limited. We aimed to explore the joint association of oxLDL and hs-CRP with outcomes of minor stroke or transient ischemic attack.

METHODS AND RESULTS: A subgroup of 3019 patients from the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) were analyzed. Baseline oxLDL and hs-CRP levels were measured. The primary outcome was any stroke within 90 days. The secondary outcomes included any stroke within 1 year, and ischemic stroke, combined vascular events, and poor functional outcomes (modified Rankin Scale 2–6) at 90 days and 1 year. Vascular events outcomes were analyzed with Cox proportional hazards and poor functional outcomes with logistic models. Elevated oxLDL (>28.81 μg/dL) and hs-CRP (>4.20 mg/L) was observed in 624 (20.67%) of the 3019 patients. Patients with oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L had a higher risk of recurrent stroke within 90 days (adjusted hazard ratio, 1.52; 95% CI, 1.17–1.97), compared with those with oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L, after adjusting relevant confounding factors (P=0.002). Similar results were observed for secondary outcomes (P<0.05 for all).

CONCLUSIONS: In patients with minor stroke or transient ischemic attack, joint high levels of oxLDL and hs-CRP was associated with increased risk of recurrent stroke, combined vascular events, and poor functional outcome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00979589.

Key Words: high-sensitivity C-reactive protein ■ oxidized low-density lipoprotein ■ poor functional outcome ■ recurrence ■ stroke

Atherosclerosis is the main pathological basis of most ischemic stroke. The role of inflammation and oxidative stress in the pathological progression of atherosclerosis and cardiovascular disease have been widely addressed before. Specific mediators such as hs-CRP (high-sensitivity C-reactive protein)
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and low-density lipoprotein link these pathophysiological pathways. Hs-CRP is a well-recognized inflammatory biomarker, its high level reflects the instability of atherosclerotic plaque and is associated with a worse outcome after ischemic stroke including recurrent vascular events. The oxidative modification of low-density lipoprotein under the oxidative stress resulting in oxidized low-density lipoprotein (oxLDL), which is another factor induces proinflammatory and proatherogenic effects and is involved in the initiation and acceleration of atherosclerosis lesions. Our previous study found that elevated concentrations of oxLDL could be a strong predictor of recurrent stroke in patients with minor stroke or transient ischemic attack (TIA). Studies showed the levels of oxLDL positively correlated with hs-CRP in men from the general population and in patients with coronary heart disease, implying they may be involved in some of the same pathophysiological pathways in the process of atherogenesis. One observational study showed the combined use of oxLDL and hs-CRP have better predictive value for prognosis after acute coronary syndrome. However, no studies have ever investigated the relationship between combined oxLDL and hs-CRP levels and recurrent stroke and poor functional outcomes in patients with minor stroke or TIA.

Acute minor ischemic stroke and TIA are the most common cerebrovascular diseases, with a high risk of recurrent stroke or other vascular events in the early stage. Identifying more comprehensive and reliable predictors is crucial to treat patients precisely to reduce stroke burden. Thus, we aimed to investigate whether oxLDL and hs-CRP have combined effects on outcomes of acute minor ischemic stroke or TIA, using the data derived from the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events).

**METHODS**

The data and methods that support the findings of this study are available from the corresponding authors upon reasonable request.

**Study Population**

Details on the rationale, design, and results of the CHANCE trial have been published previously. In brief, CHANCE was a randomized, double-blind, placebo-controlled clinical trial conducted at 114 centers in China between October 1, 2009, and July 30, 2012, with the aim to assess the efficacy of combined treatment with clopidogrel (loading dose of 300 mg followed by 75 mg daily for 90 days) plus aspirin (loading dose of 75–300 mg followed by 75 mg daily for 21 days) versus aspirin alone (loading dose of 75–300 mg followed by 75 mg daily for 90 days) in reducing the risk of recurrent stroke after 90 days of follow-up. This trial enrolled 5170 patients with minor ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] ≤3) or high-risk TIA (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes ≥4) within 24 hours after symptom onset. A total of 73 (64%) centers voluntarily participated in the blood substudy, and 3044 consecutive blood samples were collected. The CHANCE trial was registered with ClinicalTrials.gov (NCT00979589). Written informed consent was obtained from all participants or their legal proxies. The CHANCE protocol was approved by the ethics committee at each study center.

**Data Collection**

Baseline data on demographics, smoking status, and medical history of ischemic stroke, TIA, diabetes, hypertension, hyperlipidemia, myocardial infarction, angina, congestive heart failure, known atrial fibrillation, and valvular heart disease, were collected through face-to-face interviews by trained interviewers. Blood pressure and body mass index were measured by the
group differences for continuous variables, and $\chi^2$ tests for categorical variables. There is no consensus on the best cutoff value of oxLDL and hs-CRP; our previous study showed patients in the highest oxLDL quartile had a higher risk of recurrent stroke within 90 days compared with those in the lowest oxLDL quartile. Thus, we used the upper quartile to indicate high risk in the current study. Patients were classified into 4 groups: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L, group 2: oxLDL ≤28.81 μg/dL and hs-CRP >4.20 mg/L, group 3: oxLDL >28.81 μg/dL and hs-CRP ≤4.20 mg/L, group 4: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L. Cox proportional hazards model was used to calculate hazards ratios (HRs) and 95% CIs for the associations of oxLDL and hs-CRP with recurrent stroke, ischemic stroke, and combined vascular events. For poor functional outcomes, logistic regression was used to estimate odds ratios (ORs) and 95% CIs. Patients with oxLDL level ≤28.81 μg/dL and hs-CRP level ≤4.20 mg/L were set as the reference group. Variables including age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline NIHSS score, randomized treatment of aspirin alone or clopidogrel with aspirin, and the qualifying events of minor stroke or TIA, were adjusted in the multivariable regression analyses. The Kaplan–Meier analyses were used to generate survival plots of recurrent stroke, ischemic stroke, and combined vascular events, and groups were compared by the log-rank test. We further performed sensitivity analysis by changing the cutoff points of oxLDL and hs-CRP. Because previous study suggested patients with hs-CRP >3 mg/L was associated with increased risk of recurrent stroke, we used hs-CRP cutoff of 3 mg/L to define high risk. For oxLDL, median value (13.96 μg/dL) was used. Totally, 3 sensitivity analyses were conducted with different combinations of oxLDL and hs-CRP (patients were classified into 4 groups based on: (1) the upper quartile of oxLDL and hs-CRP levels of 3.0 mg/L; (2) the median of oxLDL and the upper quartile of hs-CRP; (3) the median of oxLDL and hs-CRP levels of 3.0 mg/L). Also, subgroup analysis was performed according to statin agents and qualifying events of minor stroke or TIA with an interaction test. Overall, a 2-sided $P<0.05$ was considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS
Baseline Characteristics
Of the 5170 patients who participated in the CHANCE trial, 2151 cases without oxLDL or hs-CRP measurements were excluded. Thus, a total of 3019 patients...
were included in the final analysis. The baseline characteristics of patients included and excluded were well balanced, except that the patients enrolled had slightly higher blood pressure levels, NIHSS scores, lower proportion of history of angina, diabetes, qualifying TIA, and were more likely to receive antihypertensive agents during follow-up (Table 1). Of the 3019 patients included in this study, the median age was 62.31 (interquartile ranges, 54.74–71.18), and 1007 (33.36%) patients were women. Elevated oxLDL (>28.81 μg/dL) and hs-CRP (>4.20 mg/L) was observed in 624 (20.67%) of the 3019 patients. Table 2 shows the baseline characteristics of the patients by oxLDL and hs-CRP levels. Compared with patients with both lower oxLDL and hs-CRP levels, those with both higher oxLDL and hs-CRP levels were more likely to be older, have higher NIHSS score, and higher proportion of history of ischemic stroke, myocardial infarction, and hypertension.

### Associations of oxLDL and hs-CRP With Recurrent Vascular Events
Overall, the cumulative incidence of recurrent stroke, ischemic stroke, combined vascular events was 9.74%,

| Characteristics | Overall | Excluded | Included | P value |
|-----------------|---------|----------|----------|---------|
| Patients, n     | 5170    | 2151     | 3019     |         |
| Age, median (IQR), y | 62.29 (54.69–71.27) | 62.29 (54.61–71.38) | 62.31 (54.74–71.18) | 0.865 |
| Women, n (%)    | 1750 (33.85) | 743 (34.54) | 1007 (33.36) | 0.374 |
| BMI, median (IQR), kg/m² | 24.49 (22.72–26.45) | 24.49 (22.67–26.32) | 24.49 (22.76–26.56) | 0.285 |
| SBP, median (IQR), mm Hg | 150 (136–161) | 150 (135–160) | 150 (139–164) | 0.003 |
| DBP, median (IQR), mm Hg | 90 (80–100) | 90 (80–98) | 90 (80–100) | 0.021 |
| HDL, median (IQR), mmol/L | 1.2 (1.00–1.46) | 1.21 (1.06–1.60) | 1.2 (0.99–1.46) | 0.551 |
| LDL, median (IQR), mmol/L | 3.12 (2.49–3.82) | 3.12 (2.56–4.23) | 3.12 (2.49–3.82) | 0.586 |
| oxLDL, median (IQR), μg/dL | 13.96 (6.65–28.81) | - | 13.96 (6.65–28.81) | 0.586 |
| hs-CRP, median (IQR), mg/L | 1.7 (0.8–4.2) | 1.4 (0.6–4.3) | 1.7 (0.8–4.2) | 0.476 |
| Medical history, n (%) | | | | |
| Ischemic stroke | 1033 (19.98) | 456 (21.20) | 577 (19.11) | 0.064 |
| TIA | 174 (3.37) | 80 (3.72) | 94 (3.11) | 0.234 |
| Myocardial infarction | 96 (1.86) | 42 (1.95) | 54 (1.79) | 0.667 |
| Angina | 184 (3.56) | 92 (4.28) | 92 (3.05) | 0.019 |
| Congestive heart failure | 80 (1.55) | 27 (1.26) | 53 (1.76) | 0.151 |
| Known atrial fibrillation | 96 (1.86) | 39 (1.81) | 57 (1.89) | 0.844 |
| Valvular heart disease | 14 (0.27) | 4 (0.19) | 10 (0.33) | 0.322 |
| Hypertension | 3399 (65.74) | 1431 (66.53) | 1968 (65.19) | 0.317 |
| Diabetes | 1093 (21.14) | 485 (22.55) | 608 (20.14) | 0.037 |
| Hypercholesterolemia | 573 (11.08) | 256 (11.90) | 317 (10.50) | 0.114 |
| Current or previous smoking, n (%) | 2221 (42.96) | 928 (43.14) | 1293 (42.83) | 0.822 |
| Time to randomization <12 h, n (%) | 2573 (49.77) | 1071 (49.79) | 1502 (49.75) | 0.978 |
| Qualifying events, n (%) | | | | |
| TIA | 1445 (27.95) | 635 (29.52) | 810 (26.83) | 0.034 |
| Minor stroke | 3725 (72.05) | 1516 (70.48) | 2209 (73.17) | 0.034 |
| Baseline NIHSS score, median (IQR) | 2 (0–2) | 1 (0–2) | 2 (0–2) | 0.036 |
| Antiplatelet assignment, n (%) | | | | |
| Clopidogrel and aspirin | 2584 (49.98) | 1079 (50.16) | 1505 (49.85) | 0.586 |
| Aspirin alone | 2586 (50.02) | 1072 (49.84) | 1514 (50.15) | 0.825 |
| Medications within 90-d follow-up period, n (%) | | | | |
| Antihypertensive agents | 1814 (35.09) | 698 (32.45) | 1116 (36.97) | 0.001 |
| Hypoglycemic agents | 656 (12.69) | 283 (13.16) | 373 (12.36) | 0.393 |
| Stain agents | 2171 (41.99) | 912 (42.40) | 1259 (41.70) | 0.617 |

BMI indicates body mass index; CHANCE, clopidogrel in high-risk patients with acute nondisabling cerebrovascular events; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; oxLDL, oxidized low-density lipoprotein; SBP, systolic blood pressure; and TIA, transient ischemic attack.
9.54%, 9.80%, within 90 days of follow-up and 12.06%, 11.63%, 12.42% within 1 year of follow-up. All Kaplan–Meier curves by oxLDL and hs-CRP levels appeared to separate early and to continue to diverge throughout the follow-up period (Figure 1). Patients with oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L showed a higher incidence of recurrent stroke, ischemic stroke, and combined vascular events within 90 days and at 1 year.

| Characteristics                         | Overall | Group 1* | Group 2* | Group 3* | Group 4* | P value |
|-----------------------------------------|---------|----------|----------|----------|----------|---------|
| Patients, n                             | 3019    | 2138     | 132      | 12       | 624      |         |
| Age, median (IQR), y                    | 62.31 (54.74–71.18) | 61.36 (54.10–70.19) | 62.58 (55.24–70.58) | 65.34 (56.36–73.43) | <0.001  |
| Women, n (%)                            | 1007    | 700      | 48       | 37       | 222      | 0.182   |
| BMI, median (IQR), kg/m²                | 24.49 (22.76–26.56) | 24.49 (22.72–26.37) | 24.46 (22.65–26.99) | 24.28 (22.72–26.74) | 0.226   |
| SBP, median (IQR), mmHg                 | 150 (139–164) | 150 (138–162) | 150 (140–160) | 150 (140–160) | 0.297   |
| DBP, median (IQR), mmHg                 | 90 (80–100) | 90 (80–100) | 90 (80–95) | 90 (80–100) | 0.731   |
| HDL, median (IQR), mmol/L               | 1.2 (1.09–1.46) | 1.21 (1.01–1.48) | 1.21 (1.06–1.41) | 1.14 (0.91–1.35) | 0.009   |
| LDL, median (IQR), mmol/L               | 3.28 (2.61–3.95) | 3.12 (2.50–3.78) | 3.28 (2.61–3.95) | 3.19 (2.53–3.79) | 0.331   |
| oxLDL, median (IQR), μg/dL              | 13.96 (6.65–28.81) | 9.46 (5.01–15.62) | 19.88 (12.44–25.23) | 35.19 (30.88–45.6) | <0.001  |
| hs-CRP, median (IQR), mg/L              | 1.7 (0.8–4.2) | 1.1 (0.6–2.0) | 5.8 (4.7–8.4) | 2.9 (1.5–3.7) | 0.001   |

**Table 2.** Baseline Characteristics of Patients According to oxLDL and hs-CRP Levels

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; oxLDL, oxidized low-density lipoprotein; SBP, systolic blood pressure; and TIA, transient ischemic attack.

*Patients were classified into 4 groups based on the upper quartile of oxLDL and hs-CRP levels: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 2: oxLDL ≤28.81 μg/dL and hs-CRP >4.20 mg/L; group 3: oxLDL >28.81 μg/dL, hs-CRP ≤4.20 mg/L; group 4: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L.
CI, 1.17–1.97]; HR, 1.44 [95% CI, 1.14–1.83]). Similar results were observed for ischemic stroke and combined vascular events within 90 days and 1 year (Table 3). Figure 2 shows the sensitivity analysis results by using oxLDL cutoff of 13.96 μg/dL and hs-CRP cutoff of 3 mg/L. Consistent with the main results, patients with both elevated levels of oxLDL and hs-CRP had higher risk of recurrent stroke, ischemic stroke, and combined vascular events when applying different combinations of oxLDL and hs-CRP in the sensitivity analysis.

Associations of oxLDL and hs-CRP With Poor Functional Outcome

Totally, there were 200 (6.67%) and 130 (4.45%) patients who had poor functional outcome (defined as mRS of 3–6) at 90 days and 1 year, respectively. The corresponding values of patients had mRS of 2–6 were 316 (10.53%) and 281 (9.61%) at 90 days and 1 year, respectively. The risk of poor functional outcome (defined as mRS 3–6) significantly increased in patients with oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L, the adjusted OR (95% CI) was 1.76 (1.34–2.30) at 90 days and 1.62 (1.22–2.16) at 1 year, respectively. Robust results were observed in sensitivity analysis (Figure 2).

Subgroup Analysis

The associations of oxLDL and hs-CRP with recurrent stroke within 90 days were consistent with respect to the use of statins agents (yes or no) (P for interaction=0.542; Table 5) and the qualifying events of minor stroke or TIA (P for interaction=0.794; Table 6). We found similar results for secondary outcomes of interest (all P for interactions >0.05).

DISCUSSION

In this subgroup analysis of the CHANCE trial, we found that patients with joint high levels of oxLDL and hs-CRP had higher risk of stroke recurrence, ischemic stroke, combined vascular events, and poor functional outcome at 90 days and 1 year than both low levels of oxLDL and hs-CRP. Further analysis by changing the cut-off value of oxLDL to 13.96 μg/dL and hs-CRP to 3 mg/L in sensitivity analysis showed consistent results. The role of oxLDL and hs-CRP in the pathophysiological pathway of stroke has been widely explored in previous studies. Both oxLDL and hs-CRP are
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A recent animal study found that oxLDL treatment contributes to the inflammatory response and oxidative stress in human aortic endothelial cells, linking oxLDL and C-reactive protein to atherosclerosis, endothelial dysfunction, oxidative stress, and inflammatory response from a molecular perspective. However, the evidence on the association of combined oxLDL and hs-CRP with poor prognosis after stroke is limited. In the current study, we used the upper quartile of oxLDL and hs-CRP to differentiate between high and low risk, and found the association of oxLDL and hs-CRP and adverse vascular outcomes appears only at both high levels, when both low levels treated as the reference group, which is in accord with other studies on the association of oxLDL and hs-CRP with coronary events.

Table 3. Associations of oxLDL and hs-CRP Levels With Stroke, Ischemic Stroke, and Combined Vascular Events Within 90 Days and 1 Year

| Outcomes                      | Outcomes within 90 d | Outcomes within 1 y |
|-------------------------------|----------------------|---------------------|
|                               | Events, n (%)        | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | Events, n (%)        | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
| Stroke                        |                      |                     |                     |                      |                     |                     |
| Group 1                       | 182 (8.51)           | Reference           | Reference           | 230 (10.76)          | Reference           | Reference           |
| Group 2                       | 12 (9.60)            | 1.21 (0.63–2.01)    | 1.06 (0.59–1.90)    | 15 (12.00)           | 1.13 (0.67–1.90)    | 1.09 (0.64–1.83)    |
| Group 3                       | 14 (10.61)           | 1.25 (0.73–2.15)    | 1.21 (0.70–2.08)    | 17 (12.88)           | 1.20 (0.73–1.97)    | 1.16 (0.71–1.91)    |
| Group 4                       | 86 (13.78)           | 1.65 (1.28–2.13)    | 1.52 (1.17–1.97)    | 102 (16.35)          | 1.56 (1.24–1.97)    | 1.44 (1.14–1.83)    |
| Ischemic stroke               |                      |                     |                     |                      |                     |                     |
| Group 1                       | 179 (8.37)           | Reference           | Reference           | 222 (10.38)          | Reference           | Reference           |
| Group 2                       | 12 (9.60)            | 1.14 (0.64–2.05)    | 1.07 (0.60–1.93)    | 15 (12.00)           | 1.17 (0.69–1.97)    | 1.12 (0.66–1.89)    |
| Group 3                       | 14 (10.61)           | 1.27 (0.74–2.19)    | 1.23 (0.71–2.11)    | 17 (12.88)           | 1.25 (0.76–2.04)    | 1.20 (0.73–1.97)    |
| Group 4                       | 83 (13.30)           | 1.62 (1.25–2.10)    | 1.49 (1.15–1.94)    | 97 (15.54)           | 1.54 (1.21–1.95)    | 1.41 (1.11–1.79)    |
| Combined vascular events      |                      |                     |                     |                      |                     |                     |
| Group 1                       | 182 (8.51)           | Reference           | Reference           | 237 (11.09)          | Reference           | Reference           |
| Group 2                       | 12 (9.60)            | 1.21 (0.63–2.01)    | 1.06 (0.59–1.90)    | 15 (12.00)           | 1.10 (0.65–1.85)    | 1.05 (0.62–1.78)    |
| Group 3                       | 14 (10.61)           | 1.25 (0.72–2.15)    | 1.21 (0.70–2.08)    | 17 (12.88)           | 1.17 (0.71–1.91)    | 1.12 (0.69–1.84)    |
| Group 4                       | 88 (14.10)           | 1.69 (1.31–2.18)    | 1.56 (1.21–2.03)    | 106 (16.99)          | 1.58 (1.26–1.99)    | 1.46 (1.16–1.84)    |

Adjusted hazard ratio (95% CI) was calculated after adjusting for age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline National Institutes of Health Stroke Scale score, randomized treatment of aspirin alone or clopidogrel with aspirin, and the qualifying events of minor stroke or transient ischemic attack. Patients were classified into 4 groups based on the upper quartile of oxidized low-density lipoprotein (oxLDL) and hs-CRP levels: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 2: oxLDL >28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 3: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L; group 4: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L. HR indicates hazard ratio; hs-CRP, high-sensitivity C-reactive protein; and oxLDL, oxidized low-density lipoprotein.
stroke or TIA, which would be beneficial for the stroke risk stratification approaches and further identifying individuals in high-risk. However, although we observed a higher incidence of recurrent stroke, ischemic stroke, and combined vascular events in patients with high oxLDL and low hs-CRP levels, or high hs-CRP with low oxLDL levels, than those with both low oxLDL and hs-CRP levels, the HRs were not significant in this study.

**Figure 2.** Sensitivity analysis of oxidized low-density lipoprotein (oxLDL) and hs-CRP (high-sensitivity C-reactive protein) levels with clinical outcomes at 90 days and 1 year.

Adjusted hazard ratio/odds ratio (95% CI) was calculated after adjusting for age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline National Institutes of Health Stroke Scale score, randomized treatment of aspirin alone or clopidogrel with aspirin, and the qualifying events of minor stroke or transient ischemic attack. Sensitivity analysis I: Patients were classified into 4 groups based on the upper quartile of oxLDL and hs-CRP levels of 3.0 mg/L: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤3.0 mg/L; group 2: oxLDL ≤28.81 μg/dL and hs-CRP >3.0 mg/L; group 3: oxLDL >28.81 μg/dL, hs-CRP ≤3.0 mg/L; group 4: oxLDL >28.81 μg/dL and hs-CRP >3.0 mg/L. Sensitivity analysis II: Patients were classified into 4 groups based on the median of oxLDL and the upper quartile of hs-CRP: group 1: oxLDL ≤13.96 μg/dL and hs-CRP ≤4.2 mg/L; group 2: oxLDL ≤13.96 μg/dL and hs-CRP >4.2 mg/L; group 3: oxLDL >13.96 μg/dL, hs-CRP ≤4.2 mg/L; group 4: oxLDL >13.96 μg/dL and hs-CRP >4.2 mg/L. Sensitivity analysis III: Patients were classified into 4 groups based on the median of oxLDL and hs-CRP levels of 3.0 mg/L: group 1: oxLDL ≤13.96 μg/dL and hs-CRP ≤3.0 mg/L; group 2: oxLDL ≤13.96 μg/dL and hs-CRP >3.0 mg/L; group 3: oxLDL >13.96 μg/dL, hs-CRP ≤3.0 mg/L; group 4: oxLDL >13.96 μg/dL and hs-CRP >3.0 mg/L. mRS indicates modified Rankin Scale.

**Table 4.** Associations of oxLDL and hs-CRP Levels With Poor Functional Outcomes at 90 Days and 1 Year

| Outcomes | Outcomes at 90 d | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Outcomes at 1 y | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|----------|----------------|------------------------|----------------------|----------------|------------------------|----------------------|
| mRS 3–6  | Events, n (%)  |                        |                      |                |                        |                      |
| Group 1  | 118 (5.55)     | Reference               | Reference            | 71 (3.43)      | Reference               | Reference            |
| Group 2  | 3 (2.40)       | 0.42 (0.13–1.34)        | 0.35 (0.11–1.12)     | 3 (2.54)       | 0.73 (0.23–2.37)        | 0.60 (0.18–1.95)     |
| Group 3  | 9 (6.87)       | 1.26 (0.62–2.53)        | 1.19 (0.59–2.42)     | 7 (5.43)       | 1.62 (0.73–3.59)        | 1.46 (0.65–3.30)     |
| Group 4  | 70 (11.33)     | 2.17 (1.59–2.97)        | 1.90 (1.38–2.61)     | 49 (8.09)      | 2.48 (1.70–3.61)        | 1.98 (1.35–2.93)     |
| mRS 2–6  | Events, n (%)  |                        |                      |                |                        |                      |
| Group 1  | 189 (8.89)     | Reference               | Reference            | 168 (8.12)     | Reference               | Reference            |
| Group 2  | 10 (8.00)      | 0.89 (0.46–1.73)        | 0.75 (0.38–1.47)     | 8 (6.78)       | 0.82 (0.40–1.72)        | 0.68 (0.32–1.44)     |
| Group 3  | 16 (12.21)     | 1.43 (0.83–2.46)        | 1.33 (0.77–2.31)     | 17 (13.18)     | 1.72 (1.01–2.93)        | 1.63 (0.94–2.81)     |
| Group 4  | 101 (16.34)    | 2.00 (1.54–2.60)        | 1.76 (1.34–2.30)     | 88 (14.52)     | 1.92 (1.46–2.53)        | 1.62 (1.22–2.16)     |

Adjusted odds ratio (95% CI) was calculated after adjusting for age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline National Institutes of Health Stroke Scale score, randomized treatment of aspirin alone or clopidogrel with aspirin, and the qualifying events of minor stroke or transient ischemic attack. Patients were classified into 4 groups based on the upper quartile of oxidized low-density lipoprotein (oxLDL) and hs-CRP (high-sensitivity C-reactive protein) levels: group 1: oxidized low-density lipoprotein ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 2: oxidized low-density lipoprotein >28.81 μg/dL and hs-CRP >4.20 mg/L; group 3: oxidized low-density lipoprotein >28.81 μg/dL, hs-CRP ≤4.20 mg/L; group 4: oxidized low-density lipoprotein >28.81 μg/dL and hs-CRP >4.20 mg/L. hs-CRP indicates high-sensitivity C-reactive protein; mRS, modified Rankin Scale; OR, odds ratio; and oxLDL, oxidized low-density lipoprotein.
### Table 5. Subgroup Analysis According to Stain Agents Within 90-Day Follow-up Period for Associations of oxLDL and hs-CRP Levels With Clinical Outcomes At 90 Days and 1 Year

| Outcomes | Outcomes within 90 d |  | Outcomes within 1 y |  |
|----------|----------------------|---|---------------------|---|
|          | Group 1 | Group 2 | Group 3 | Group 4 | \( P_{nt} \) | Group 1 | Group 2 | Group 3 | Group 4 | \( P_{nt} \) |
| **Stroke** |  |  |  |  |  |  |  |  |  |  |
| No       | Reference | 0.95 (0.44–2.05) | 1.32 (0.67–2.61) | 1.74 (1.27–2.39) | 0.542 | Reference | 1.03 (0.52–2.04) | 1.32 (0.71–2.45) | 1.61 (1.20–2.17) | 0.645 |
| Yes      | Reference | 1.17 (0.47–2.91) | 1.06 (0.43–2.63) | 1.16 (0.73–1.84) |  | Reference | 1.16 (0.51–2.66) | 1.09 (0.43–2.27) | 1.18 (0.80–1.76) |  |
| **Ischemic stroke** |  |  |  |  |  |  |  |  |  |  |
| No       | Reference | 0.98 (0.45–2.10) | 1.33 (0.67–2.63) | 1.71 (1.24–2.36) | 0.538 | Reference | 1.06 (0.54–2.09) | 1.35 (0.73–2.50) | 1.58 (1.16–2.13) | 0.655 |
| Yes      | Reference | 1.18 (0.48–2.95) | 1.07 (0.43–2.66) | 1.13 (0.71–1.80) |  | Reference | 1.19 (0.52–2.74) | 1.02 (0.45–2.35) | 1.14 (0.76–1.72) |  |
| **Combined vascular events** |  |  |  |  |  |  |  |  |  |  |
| No       | Reference | 0.96 (0.44–2.06) | 1.32 (0.67–2.61) | 1.78 (1.29–2.44) | 0.582 | Reference | 1.00 (0.51–1.97) | 1.28 (0.69–2.38) | 1.65 (1.23–2.20) | 0.599 |
| Yes      | Reference | 1.17 (0.47–2.91) | 1.06 (0.43–2.63) | 1.21 (0.77–1.91) |  | Reference | 1.13 (0.49–2.58) | 0.96 (0.42–2.20) | 1.18 (0.80–1.75) |  |
| **mRS 3–6** |  |  |  |  |  |  |  |  |  |  |
| No       | Reference | 0.19 (0.03–1.43) | 0.73 (0.22–2.42) | 1.97 (1.29–3.01) | 0.518 | Reference | 1.08 (0.32–3.71) | 0.88 (0.20–3.79) | 2.06 (1.20–3.52) | 0.807 |
| Yes      | Reference | 0.57 (0.13–2.44) | 1.65 (0.66–4.11) | 1.80 (1.10–2.94) |  | Reference | 1.95 (0.71–5.34) | 1.89 (1.07–3.34) |  |  |
| **mRS 2–6** |  |  |  |  |  |  |  |  |  |  |
| No       | Reference | 0.48 (0.17–1.37) | 0.87 (0.36–2.08) | 1.84 (1.29–2.62) | 0.261 | Reference | 1.22 (0.55–2.69) | 1.24 (0.54–2.83) | 1.82 (1.25–2.65) | 0.612 |
| Yes      | Reference | 1.15 (0.47–2.84) | 1.89 (0.90–3.97) | 1.64 (1.08–2.49) |  | Reference | 1.99 (0.90–4.27) | 1.39 (0.89–2.18) |  |  |

Adjusted hazards ratio or odds ratio (95% CI) was calculated after adjusting for age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline National Institutes of Health Stroke Scale score, randomized treatment of aspirin alone or clopidogrel with aspirin, and the qualifying events of minor stroke or transient ischemic attack. Patients were classified into 4 groups based on the upper quartile of oxidized low-density lipoprotein (oxLDL) and hs-CRP (high-sensitivity C-reactive protein) levels: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 2: oxLDL ≤28.81 μg/dL and hs-CRP >4.20 mg/L; group 3: oxLDL >28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 4: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L. Hs-CRP indicates high-sensitivity C-reactive protein; mRS, modified Rankin Scale; oxLDL, oxidized low-density lipoprotein; \( P_{nt} \), \( P \) for interaction; and TIA, transient ischemic attack.
Table 6. Subgroup Analysis According to Qualifying Events for Associations of oxLDL and hs-CRP Levels With Clinical Outcomes At 90 Days and 1 Year

| Outcomes                        | Outcomes within 90d | Outcomes within 1y | P_int |
|---------------------------------|---------------------|---------------------|-------|
|                                 | Group 1     | Group 2     | Group 3    | Group 4     | Group 1     | Group 2     | Group 3    | Group 4     | P_int       |
| Stroke                          | Reference   | 0.98 (0.50–1.94) | 1.28 (0.69–2.37) | 1.58 (1.18–2.13) | 0.794       | Reference   | 0.96 (0.52–1.77) | 1.16 (0.66–2.03) | 1.44 (1.10–1.89) | 0.853       |
| TIA                             | Reference   | 1.33 (0.41–4.27) | 0.94 (0.29–3.07) | 1.22 (0.71–2.10) | Reference   | 1.61 (0.58–4.46) | 1.16 (0.42–3.22) | 1.33 (0.81–2.17) | reference   | 0.857       |
| Ischemic stroke                 | Reference   | 1.00 (0.51–1.98) | 1.31 (0.71–2.43) | 1.57 (1.16–2.13) | 0.729       | Reference   | 0.99 (0.54–1.83) | 1.20 (0.68–2.12) | 1.42 (1.07–1.87) | 0.880       |
| TIA                             | Reference   | 1.32 (0.41–4.25) | 0.95 (0.29–3.09) | 1.15 (0.66–2.01) | Reference   | 1.62 (0.58–4.49) | 1.17 (0.42–3.25) | 1.27 (0.77–2.10) | 0.880       |
| Combined vascular events        | Reference   | 0.98 (0.50–1.94) | 1.28 (0.69–2.37) | 1.61 (1.20–2.17) | 0.840       | Reference   | 0.92 (0.50–1.70) | 1.10 (0.63–1.94) | 1.42 (1.09–1.86) | 0.880       |
| mRS 3–6                         | Reference   | 0.39 (0.12–1.26) | 1.30 (0.61–2.78) | 1.92 (1.35–2.72) | 0.962       | Reference   | 0.64 (0.20–2.11) | 1.38 (0.57–3.31) | 1.82 (1.20–2.77) | 0.742       |
| mRS 2–6                         | Reference   | 0.71 (0.09–5.57) | 1.67 (0.75–3.72) | Reference   | 2.06 (0.23–18.39) | 2.96 (0.98–8.95) | 0.463       |

Adjusted hazards ratio or odds ratio (95% CI) was calculated after adjusting for age, sex, body mass index, high-density lipoprotein, history of ischemic stroke, myocardial infarction, hypertension, baseline National Institutes of Health Stroke Scale score, and randomized treatment of aspirin alone or clopidogrel with aspirin. Patients were classified into 4 groups based on the upper quartile of oxidized low-density lipoprotein (oxLDL) and hs-CRP (high-sensitivity C-reactive protein) levels: group 1: oxLDL ≤28.81 μg/dL and hs-CRP ≤4.20 mg/L; group 2: oxLDL ≤28.81 μg/dL and hs-CRP >4.20 mg/L; group 3: oxLDL >28.81 μg/dL, hs-CRP ≤4.20 mg/L; group 4: oxLDL >28.81 μg/dL and hs-CRP >4.20 mg/L. Hs-CRP indicates high-sensitivity C-reactive protein; mRS, modified Rankin Scale; oxLDL, oxidized low-density lipoprotein; P_int, P for interaction; and TIA, transient ischemic attack.
This may be partly because of the different definition of the study population, in which we considered the role of both factors at the same time, and the low sample size in the 2 groups. In connection with the existing studies on combined oxLDL and hs-CRP levels, we speculate on the plausible path-physiological mechanisms linking them to minor stroke or TIA include the following. High concentrations of oxLDL can induce macrophage differentiation and stimulate endothelial cell production of CRP. CRP forms a positive feedback loop with oxLDL by activating the complement system, continuously enhancing phagocytosis of oxLDL by macrophages and promoting foam cell formation, and causing cellular autophagy under oxidative stress conditions. On the other hand, activation of the inflammatory response also triggers atherosclerotic protective fibrous membrane rupture. Both of these aspects cause atherosclerotic plaque instability. In addition, imbalances in the oxidative-antioxidant system play an important role in increasing the risk of recurrence, vascular events, and poor functional prognosis in patients with stroke. OxLDL and hs-CRP together induce endothelial cell damage, expose blood to procoagulant tissues, and promote lipoprotein oxidation in a vicious cycle. Furthermore, it has been reported that CRP can bind phosphatidylinositol on oxLDL in a calcium-dependent manner, forming a CRP/oxLDL complex with positive or negative effects on the progression of atherosclerosis. However, there is no conclusive evidence about the effect of such complexes on atherosclerosis.

Many studies have demonstrated the cholesterol-lowering, anti-inflammatory and anti-oxidant effects of statins, which have a positive prognostic effect on acute ischemic stroke. Both oxLDL and hs-CRP alone levels were reported to be lower in patients with stroke receiving statin therapy than in those not receiving statin therapy. In JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a clinical trial among apparently healthy people without hyperlipidemia but with elevated hs-CRP levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. Besides, it was reported that high statin doses could reduce adiponectin’s capacity to suppress intracellular cholesterol ester levels in oxLDL-loaded macrophages. However, there was no significant interaction between combined oxLDL and hs-CRP and use of statins agents in our study, which was in line with the previously reported relationship between oxLDL/HDL and statins.

Our study had some limitations. First, although most trials use oxLDL-4E6 antibody to determine oxLDL levels, in fact there may be antibody reaction variation because of potential cross-reactivity of oxLDL-4E6 antibodies with natural low-density lipoprotein and lysine modification of apoB100. Second, oxLDL and hs-CRP levels were obtained by fasting venous blood collection after admission in all patients, so oxLDL and hs-CRP levels at acute onset could not be recorded, and potential differences in acute and post-acute oxLDL and hs-CRP levels could not be investigated. Third, oxLDL and hs-CRP levels during follow-up were not recorded in this study, so we could not assess changes in plasma oxLDL and hs-CRP levels over time and their effect on stroke outcomes.

CONCLUSIONS

In summary, this substudy of CHANCE trial suggested that joint higher levels of oxLDL and hs-CRP was associated with increased risk of recurrent stroke, combined vascular events, and poor functional outcome in patients with minor stroke or TIA. The application of this combined test in the clinical practice of stroke diseases may help clinical decision making and further improve the prognosis of patients with stroke.

ARTICLE INFORMATION

Received August 1, 2022; accepted September 8, 2022.

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Sources of Funding

This work was supported by National Natural Science Foundation of China (81870905, U20A20358), Beijing Municipal Science & Technology Commission (D171100003017002), Beijing Municipal Administration of Hospitals Incubating Program (PX2020021).

Disclosures

None.

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