

# Oxidized Low-Density Lipoprotein to High-Density Lipoprotein Ratio Predicts Recurrent Stroke in Minor Stroke or Transient Ischemic Attack

Anxin Wang, PhD\*; Shiyu Li, MD\*; Nan Zhang, BS; Liye Dai, MD; Yingting Zuo, MS; Yilong Wang, MD, PhD; Xia Meng, MD, PhD; Yongjun Wang, MD

**Background and Purpose**—Oxidized low-density lipoprotein (oxLDL) level is thought to be associated with recurrent stroke. We aimed to investigate the association between oxLDL to high-density lipoprotein (HDL) ratio and recurrent stroke in patients with minor stroke or transient ischemic attack.

**Methods**—The study included 3019 patients with minor ischemic stroke or high-risk transient ischemic attack from the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events). Baseline oxLDL and HDL levels were measured. The primary outcome was any stroke within 90 days. The secondary outcomes included any stroke within 1 year and ischemic stroke and combined vascular events within 90 days and 1 year. The association between oxLDL/HDL and recurrent stroke was analyzed by using Cox proportional hazards.

**Results**—Patients in the highest oxLDL/HDL quartile had a higher risk of recurrent stroke within 90 days (hazards ratio, 1.50; 95% CI, 1.08–2.08) compared with the lowest quartile after adjusting relevant confounding factors ( $P=0.02$ ). Similar results were found for secondary outcomes ( $P<0.05$  for all). There were no significant interaction between oxLDL/HDL and use of statins agents.

**Conclusions**—Higher serum oxLDL/HDL level in minor stroke or transient ischemic attack was associated with increased risk of recurrent stroke in 90 days and 1 year. OxLDL/HDL may act as a powerful indicator of recurrent stroke in patients with minor stroke or transient ischemic attack.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00979589. (*Stroke*. 2018;49:2637-2642. DOI: 10.1161/STROKEAHA.118.022077.)

**Key Words:** brain ischemia ■ humans ■ ischemic, transient, attack ■ oxidized low density lipoprotein ■ stroke

Oxidative stress appears to be an important pathogenesis of atherosclerosis.<sup>1</sup> Oxidized low-density lipoprotein (oxLDL), the oxidative modification of low-density lipoprotein (LDL) under the oxidative stress, causes vascular endothelial injury, stimulates inflammatory factors release, mediates foam cell formation, damages plaque stability, and promotes thrombosis, playing a crucial role in the initiation and acceleration of atherosclerosis.<sup>1–4</sup> On the contrary, high-density lipoprotein (HDL) protects against the atherosclerotic process by reversing cholesterol transport and inhibiting LDL oxidation.<sup>5,6</sup> The oxLDL/HDL ratio reflects the equilibrium between atherosclerosis and anti-atherosclerosis in the lipid lipoprotein markers. The positive associations between oxLDL and cardiovascular diseases<sup>7–12</sup> and ischemic stroke<sup>13–19</sup> have been verified in many studies. Recent studies have showed that elevated oxLDL/HDL ratio was a strong predictor for coronary heart disease.<sup>20,21</sup> However, no studies have ever investigated the relationship

between oxLDL/HDL and recurrent stroke in patients with minor stroke or transient ischemic attack (TIA).

As the most common manifestations of acute cerebrovascular disease,<sup>22</sup> acute minor ischemic stroke and TIA have high risks of early recurrence.<sup>23,24</sup> Consequently, exploring new predictors of recurrent stroke in these patients contributes to more effective secondary prevention. In our study, we aimed to investigate the association between oxLDL/HDL ratio and recurrent stroke in patients with minor stroke or TIA.

## Methods

### Study Design and Population

The data that support the findings of this study are available from the corresponding author. The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled, multicentric clinical trial, which included 5170 patients in 114 clinical centers in China. The detailed design and main results of the CHANCE trial have been

Received May 16, 2018; final revision received July 31, 2018; accepted August 22, 2018.

From the Department of Neurology (A.W., S.L., N.Z., L.D., Y.Z., Y.W., X.M., Y.W.) and China National Clinical Research Center for Neurological Diseases (A.W., S.L., N.Z., L.D., Y.Z., Y.W., X.M., Y.W.), Beijing Tiantan Hospital, Capital Medical University, China.

\*Drs A. Wang and Li contributed equally.

The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.022077>.

Correspondence to Yongjun Wang, MD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 6 Tiantanxili, Dongcheng Dist, Beijing 100050, China. Email [yongjunwang1962@gmail.com](mailto:yongjunwang1962@gmail.com)

© 2018 American Heart Association, Inc.

*Stroke* is available at <https://www.ahajournals.org/journal/str>

DOI: 10.1161/STROKEAHA.118.022077

described previously.<sup>24–26</sup> Patients with noncardioembolic minor ischemic stroke or high-risk TIA and within 24 hours of symptom onset were randomly assigned to either clopidogrel plus aspirin or placebo plus aspirin group. Among them, a total of 3044 consecutive blood samples from 73 (64%) centers that voluntarily participated in the blood substudy were collected. The approval by the Ethics Committee and written informed consent of participants were both obtained (registration number NCT00979589).

### Basic Clinical Data Collection

Baseline clinical information, including age, sex, smoking status, and medical history, were obtained by a questionnaire on admission. Blood pressure and body mass index were measured by the trained nurses in clinical centers. The National Institutes of Health Stroke Scale and ABCD2 scores were assessed by the trained neurologists on admission who were blinded to patients' clinical information and therapeutic regimen. The medication usages, including antiplatelet, antihypertensive, antidiabetic, and statin agents, were recorded within 90-day follow-up period.

### Measurement of Lipoprotein Markers

Fasting blood samples were collected within 24±12 hours after randomization and isolated, immediately frozen at –80°C in each center. All samples were shipped on dry ice from each center to Beijing Tiantan Hospital, where they were processed and analyzed. Lipid profiles, including total cholesterol, triglyceride, LDL, and HDL, were measured via the enzymatic method, and lipoprotein assay was performed via immunoturbidimetric method using a Roche Modular P800 system (Roche, Basel, Switzerland). Circulating oxLDL was measured in EDTA-plasma samples by using ELISA (mAb-4E6-based ELISA Kit, RapidBio Lab, CALAS, CA).<sup>27</sup> Measurements were conducted according to the manufacturer's guidelines, and laboratory personnel were blinded to the study protocol and patients' information. The intra-assay and interassay coefficient of variation of oxLDL levels test were 1.8% and 1.4%, respectively.

### Outcome Assessment

The primary outcome was a new stroke (ischemic or hemorrhagic) at 90 days. The secondary outcomes included new ischemic stroke and combined vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death) at 90 days and any stroke, ischemic stroke, combined vascular events at 1 year. The outcome assessment was confirmed by a central adjudication committee blinded to the medication assignments.

### Statistical Analysis

Continuous variables were described by medians with interquartile ranges because of skewed distribution. Categorical variables were described by frequencies with percentages. Patients were classified into 4 groups by oxLDL/HDL quartiles. The nonparametric Wilcoxon or Kruskal–Wallis tests were used to compare group differences for continuous variables and  $\chi^2$  tests for categorical variables. The associations of oxLDL/HDL and outcomes were investigated with Cox proportional hazards models. The lowest quartile was defined as the reference group. Variables were adjusted in the multivariable analyses if established as traditional predictors for recurrent stroke, or associated with oxLDL/HDL in univariate analysis, with a  $P<0.2$ . Unadjusted and adjusted hazards ratios and their 95% CI were calculated. The median oxLDL/HDL values of each quartile were entered into the model and treated as a continuous variable to perform trend tests in the regression models. Kaplan–Meier curves by quartiles of oxLDL/HDL were made to verify the association between outcomes and oxLDL/HDL during the follow-up period. To evaluate the incremental predictive value of oxLDL/HDL beyond conventional risk factors, C statistics, integrated discrimination improvement, and net reclassification index were calculated. What's more, we used the Cox proportional hazards models to test the interaction between oxLDL/HDL and statin agents.

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

Among 3044 patients with blood samples, 25 patients without the oxLDL values 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 included had slightly higher levels of blood pressure and National Institutes of Health Stroke Scale, lower proportion of history of angina, diabetes mellitus, and qualifying TIA, and a higher proportion of use of antihypertensive agents (Table I in the [online-only Data Supplement](#)).

Among all the patients included, the median age was 62.3 years, and 1007 (33.4%) patients were women. The median levels of circulating oxLDL and oxLDL/HDL were 14.0  $\mu\text{g}/\text{dL}$  (interquartile range: 6.7–28.8  $\mu\text{g}/\text{dL}$ ) and 4.5 (interquartile range: 2.1–9.3), respectively. Compared with patients with lower oxLDL/HDL, those with higher oxLDL/HDL were more likely to be older, had higher body mass index, LDL, and oxLDL, had lower HDL, had higher proportion of history of ischemic stroke, myocardial infarction, known atrial fibrillation or flutter, hypertension, and diabetes mellitus (Table).

### OxLDL/HDL and Clinical Outcomes

The cumulative occurrence of recurrent stroke, ischemic stroke, and combined vascular events were 9.7%, 9.5%, 9.8% within 90 days' follow-up and 12.1%, 11.6%, 12.4% within 1 year's follow-up. Kaplan–Meier curves by quartiles of oxLDL/HDL levels for stroke within 90 days appeared to separate early and continue to diverge during the follow-up period (Figure 1). The results were similar in the secondary outcomes (Figure I in the [online-only Data Supplement](#)).

In summary, patients with higher oxLDL/HDL quartile had higher incidence of stroke, ischemic stroke, and combined vascular events within 90 days and 1 year ( $P<0.05$ , for all). The association remained significant after adjustment for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, baseline LDL levels, past history of ischemic stroke, myocardial infarction, angina, known atrial fibrillation or flutter, hypertension, diabetes mellitus, and hypercholesterolemia, smoking status, baseline National Institutes of Health Stroke Scale score, medication usage of randomized treatment of aspirin alone or dual antiplatelet therapy, and antihypertensive, antidiabetic, and statin agents (Table II in the [online-only Data Supplement](#)). As Figure 2 showed, the adjusted hazards ratio (95% CI) for the highest versus lowest quartile of oxLDL/HDL was 1.50 (95% CI, 1.08–2.08) for recurrent stroke at 90 days. Similar results were found in the secondary outcomes.

### Incremental Predictive Value of oxLDL/HDL

We evaluated whether oxLDL/HDL would further increased the predictive value of conventional risk factors. Taking recurrent stroke within 90 days as outcome, the C statistic by conventional model did not significantly improve with the addition of oxLDL/HDL (from 0.686 to 0.694;  $P=0.06$ ).

**Table. Characteristics of Patients Included According to oxLDL/HDL Quartiles**

Characteristics	Overall	OxLDL/HDL Quartiles				P Value
		Quartile 1 <5.27	Quartile 2 5.27–11.72	Quartile 3 11.73–24.84	Quartile 4 ≥24.85	
Patients	3019	754	755	755	755	
Age, median (IQR), y	62.3 (54.7–71.2)	60.7 (53.7–69.7)	61.8 (54.2–70.2)	62.3 (54.8–71.2)	64.1 (55.8–73.1)	<0.01
Female, n (%)	1007 (33.4)	265 (35.2)	244 (32.3)	259 (34.3)	239 (31.7)	0.43
SBP, median (IQR), mm Hg	150 (139–164)	150 (137–165)	150 (140–162)	150 (136–160)	150(140–166)	0.55
DBP, median (IQR), mm Hg	90 (80–100)	90 (80–98)	90 (80–100)	90 (80–97)	90 (80–100)	0.10
BMI, median (IQR), kg/m <sup>2</sup>	24.5 (22.8–26.6)	24.2 (22.4–26.0)	24.5 (22.7–26.4)	24.7 (22.9–26.7)	24.8 (22.9–27.3)	<0.01
HDL, median (IQR), mmol/L	1.2 (1.0–1.5)	1.4 (1.2–1.6)	1.2 (1.0–1.5)	1.1 (1.0–1.4)	1.1 (0.9–1.3)	<0.01
LDL, median (IQR), mmol/L	3.1 (2.5–3.8)	3.0 (2.4–3.7)	3.2 (2.6–3.9)	3.2 (2.6–3.8)	3.1 (2.4–3.9)	<0.01
OxLDL, median (IQR), μg/dL	14.0 (6.7–28.8)	3.9 (2.6–5.3)	9.9 (7.8–12.5)	19.5 (15.4–24.7)	48.4 (34.2–75.1)	<0.01
<b>Medical history, n (%)</b>						
Ischemic stroke	577 (19.1)	119 (15.8)	132 (17.5)	145 (19.2)	181 (24.0)	<0.01
TIA	94 (3.1)	17 (2.3)	26(3.4)	24 (3.2)	27 (3.6)	0.45
Myocardial infarction	54 (1.8)	8 (1.1)	10 (1.3)	11 (1.5)	25 (3.3)	<0.01
Angina	92 (3.1)	31 (4.1)	19 (2.5)	21 (2.8)	21 (2.8)	0.26
Congestive heart failure	53 (1.8)	14 (1.9)	12 (1.6)	10 (1.3)	17 (2.3)	0.56
Known atrial fibrillation or flutter	57(1.9)	21 (2.8)	12 (1.6)	6 (0.8)	18 (2.4)	0.02
Valvular heart disease	10 (0.3)	2 (0.3)	2 (0.3)	4 (0.5)	2(0.3)	0.75
Hypertension	1968 (65.2)	449 (59.6)	475 (62.9)	516 (68.3)	528 (69.9)	<0.01
Diabetes mellitus	608 (20.1)	125 (16.6)	139 (18.4)	176 (23.3)	168 (22.3)	<0.01
Hypercholesterolemia	317 (10.5)	66 (8.8)	79 (10.5)	92 (12.2)	80 (10.6)	0.19
Current or previous smoking, n (%)	1293 (42.8)	314 (41.6)	314 (41.6)	321 (42.5)	344 (45.6)	0.36
Time to randomization <12 h, n (%)	1502 (49.8)	366 (48.5)	382 (50.6)	375 (49.7)	379 (50.2)	0.87
<b>Qualifying events, n (%)</b>						
TIA	810 (26.8)	211 (28.0)	206 (27.3)	204 (27.0)	189 (25.0)	0.6
Minor stroke	2209 (73.2)	543 (72.0)	549 (72.7)	551 (73.0)	566 (75.0)	
Baseline NIHSS, median (IQR)	2 (0–2)	2 (0–2)	1 (0–2)	2 (0–2)	2 (0–2)	0.05
<b>Medications within 90-d follow-up period, n (%)</b>						
Aspirin alone	1514 (50.2)	373 (49.5)	380 (50.3)	353 (46.8)	408 (54.0)	0.04
Clopidogrel and aspirin	1505 (49.8)	381 (50.5)	375 (49.7)	402 (53.3)	347 (46.0)	
Antihypertensive agents	1116 (37.2)	276 (36.9)	279 (37.2)	278 (36.9)	283 (37.8)	0.98
Antidiabetic agents	373 (12.4)	74 (9.9)	95 (12.7)	109 (14.5)	95 (12.7)	0.06
Statins	1259 (41.9)	301 (40.2)	325 (43.3)	315 (41.8)	318 (42.5)	0.66

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; 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.

However, the discriminatory power and risk reclassification appear to be significant (integrated discrimination improvement: 5.75%,  $P<0.01$ ; continuous net reclassification index: 19.68%,  $P<0.01$ ). Similar results were found in secondary outcomes (Table III in the [online-only Data Supplement](#)).

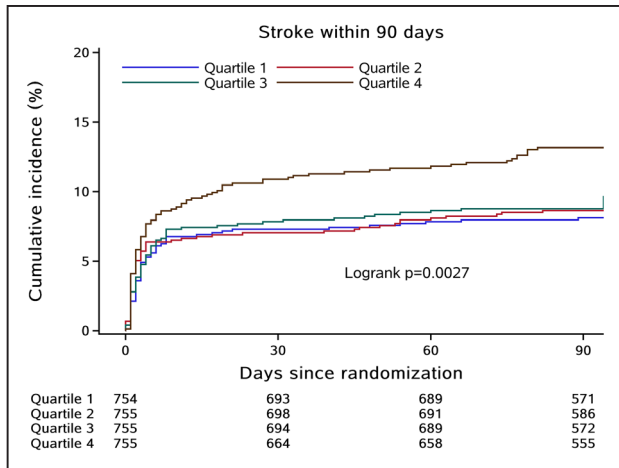
### Effects of OxLDL/HDL and Statins Agents

Many studies had proved statins could influence the level of plasma oxLDL and improve outcomes after acute ischemic

stroke. In our study, there were no interaction between oxLDL/HDL and the use of statins in the recurrent stroke, ischemic stroke, and combined vascular events within 90 days ( $P$  for interaction=0.28, 0.30, 0.31, respectively). Similar results were obtained at 1 year ( $P>0.05$  for all.).

### Discussion

This study proved that elevated level of circulating oxLDL/HDL was an independent predictor of recurrent stroke, ischemic



**Figure 1.** Kaplan-Meier curves of oxidized low-density lipoprotein/high-density lipoprotein for stroke within 90 d.

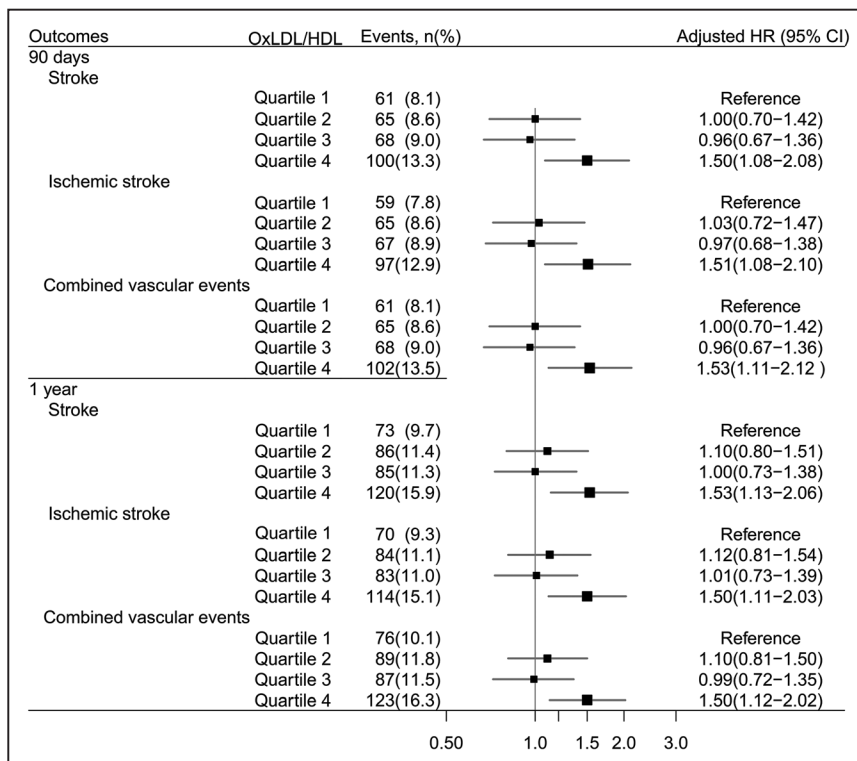
stroke, and combined vascular events in patients with minor stroke or TIA at 90 days and 1 year. There was no significant interaction between oxLDL/HDL and use of statins agents.

Studies about oxLDL/HDL ratio are limited. So far, no study has investigated the relationship between oxLDL/HDL and acute ischemic stroke (AIS). Studies have proved that oxLDL/HDL was a better biomarker than traditional lipid markers (total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol) for coronary artery disease<sup>20,21</sup> and associated with bioprosthetic valve structural degeneration,<sup>28</sup> which was supposed to be related with oxidative stress and inflammation. OxLDL/HDL was significantly higher in type 2 diabetes mellitus patients<sup>29</sup> and correlated with hemoglobin A1c.<sup>30,31</sup> In this study, we demonstrated oxLDL/HDL ratio predicted

recurrent stroke independently in patients with minor stroke or TIA, and the addition of oxLDL/HDL could increase the prediction for recurrent stroke beyond conventional risk factors. In addition, our results showed the association of oxLDL/HDL and adverse vascular outcomes appears only at the highest level, which is in accord with other papers on the association between oxLDL and coronary events.<sup>9,10</sup> There may be a threshold that could differentiate between high and low risk for recurrent stroke.

Many studies have proved the association between oxLDL and ischemic stroke. We have reported that elevated plasma oxLDL level can independently predict recurrent stroke in patients with minor stroke or TIA (Anxin Wang, unpublished data, 2018). There was a significant correlation between plasma and plaque oxLDL level, and elevated plasma oxLDL level was associated with carotid plaques vulnerability.<sup>32,33</sup> A study showed that plasma oxLDL was significantly increased in patients with AIS,<sup>13</sup> and persistently increased oxLDL level was associated with enlargement of the ischemic area in the early phase of AIS.<sup>14</sup> OxLDL level was associated with National Institutes of Health Stroke Scale<sup>14,19</sup> and can independently predict poor outcome after AIS.<sup>34</sup> The predictive value of oxLDL in the cardiovascular field was also confirmed. Many studies have shown circulating oxLDL level was significantly higher in patients with coronary heart disease. Elevated level of oxLDL was predictive of acute cardiovascular disease<sup>9,10</sup> and associated with the severity of coronary heart disease.<sup>7,8,11,12</sup>

OxLDL is supposed to be both proatherogenic and pro-inflammatory and involved in the initiation and progression of atherosclerosis. The pathogenesis that oxLDL involves in the process of atherosclerosis include causing endothelial cell damage, leading to foam cell formation, inducing



**Figure 2.** Adjusted hazards ratios (HR) by quartiles of oxidized low-density lipoprotein (oxLDL)/high-density lipoprotein (HDL) for outcomes within 90 d and 1 y. Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, past history of ischemic stroke, transient ischemic attack, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, diabetes mellitus and hypercholesterolemia, smoking status, time to randomization, baseline National Institutes of Health Stroke Scale score, randomized treatment of aspirin alone or dual antiplatelet therapy, use of antihypertensive, antidiabetic, and statin agents, and baseline low-density lipoprotein level.



leukocyte-endothelial cell adhesion, stimulating increased expression of inflammatory markers, triggering the aggregation of platelet, and so on.<sup>2-4</sup> HDL is considered to be protective against atherosclerosis through reversing cholesterol transport and inhibiting the oxidation of LDL.<sup>5,6</sup> OxLDL and HDL represent roles of atherosclerosis and antiatherosclerosis, respectively, among lipid markers, thus oxLDL/HDL may reflect the oxidative stress level and antioxidant defense comprehensively.

Several studies showed the effect of statins therapy on plasma oxLDL level. A study reported that statins could decrease plasma oxLDL in patients with AIS.<sup>34</sup> Similar results were showed in patients with coronary heart disease.<sup>21,35</sup> The decrease of oxLDL by statins therapy was independent of lowering of LDL cholesterol and total cholesterol, and oxLDL/HDL was also decreased significantly after statins therapy.<sup>21</sup> However, there was no significant interaction between oxLDL/HDL and use of statins agents in our study.

There were several limitations in our study. First, we only obtained the baseline oxLDL level at the acute stage of minor stroke or TIA but could not determine the dynamic change after attack and the response to different therapy. Second, we did not assess the association between oxLDL/HDL and different stroke subtypes or carotid atherosclerosis because of insufficient data. Third, we used the oxLDL-4E6 antibody for detecting circulating oxLDL, which did not specifically bind to LDL oxidation-specific epitopes and thus had a potential cross-reactivity with native LDL. Although the 4E6 antibody binds  $\approx 1000\times$  stronger to oxLDL than native LDL<sup>100</sup><sup>27</sup> and analysis was adjusted for the LDL level, small deviation may existed in the study.

## Conclusions

Our results indicate that higher serum oxLDL/HDL level in minor stroke or TIA was associated with increased risk of recurrent stroke in 90 days and 1 year. OxLDL/HDL may act as a powerful indicator of recurrent stroke in patients with minor stroke or TIA.

## Acknowledgments

We thank all participating hospitals, colleagues, nurses, and imaging and laboratory technicians.

## Sources of Funding

This study is supported by grants from the Ministry of Science and Technology of the People's Republic of China (2013BAI09B03, 2013BAI09B14, 2015BAI12B04, 2015BAI12B02, 2016YFC0901000, 2016YFC0901001, 2016YFC0901002, and 2017YFC1310902), grants from the National Natural Science Foundation of China (no. 81673247, no.816005098), a grant from the Beijing Biobank of Cerebral Vascular Disease (D131100005313003), and a grant from Beijing Institute for Brain Disorders (1152130306).

## Disclosures

None.

## References

- Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation*. 1995;91:2488–2496.
- Itabe H. Oxidative modification of LDL: its pathological role in atherosclerosis. *Clin Rev Allergy Immunol*. 2009;37:4–11. doi: 10.1007/s12016-008-8095-9
- Steinberg D, Witztum JL. Oxidized low-density lipoprotein and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2010;30:2311–2316. doi: 10.1161/ATVBAHA.108.179697
- Steinberg D, Lewis A. Conner memorial lecture. Oxidative modification of LDL and atherogenesis. *Circulation*. 1997;95:1062–1071.
- Mackness MI, Arrol S, Abbott C, Durrington PN. Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis*. 1993;104:129–135.
- Mertens A, Holvoet P. Oxidized LDL and HDL: antagonists in atherothrombosis. *FASEB J*. 2001;15:2073–2084. doi: 10.1096/fj.01-0273rev
- Holvoet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. *Circulation*. 1998;98:1487–1494.
- Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. *Circulation*. 2001;103:1955–1960.
- Shimada K, Mokuno H, Matsunaga E, Miyazaki T, Sumiyoshi K, Miyauchi K, et al. Circulating oxidized low-density lipoprotein is an independent predictor for cardiac event in patients with coronary artery disease. *Atherosclerosis*. 2004;174:343–347. doi: 10.1016/j.atherosclerosis.2004.01.029
- Meisinger C, Baumert J, Khuseynova N, Loewel H, Koenig W. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. *Circulation*. 2005;112:651–657. doi: 10.1161/CIRCULATIONAHA.104.529297
- Anselmi M, Garbin U, Agostoni P, Fusaro M, Pasini AF, Nava C, et al. Plasma levels of oxidized-low-density lipoproteins are higher in patients with unstable angina and correlated with angiographic coronary complex plaques. *Atherosclerosis*. 2006;185:114–120. doi: 10.1016/j.atherosclerosis.2005.05.020
- Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005;353:46–57. doi: 10.1056/NEJMoa043175
- Uno M, Kitazato KT, Nishi K, Itabe H, Nagahiro S. Raised plasma oxidized LDL in acute cerebral infarction. *J Neurol Neurosurg Psychiatry*. 2003;74:312–316.
- Uno M, Harada M, Takimoto O, Kitazato KT, Suzue A, Yoneda K, et al. Elevation of plasma oxidized LDL in acute stroke patients is associated with ischemic lesions depicted by DWI and predictive of infarct enlargement. *Neurol Res*. 2005;27:94–102. doi: 10.1179/016164105X18395
- Vibo R, Körv J, Roose M, Kampus P, Muda P, Zilmer K, et al. Acute phase proteins and oxidized low-density lipoprotein in association with ischemic stroke subtype, severity and outcome. *Free Radic Res*. 2007;41:282–287. doi: 10.1080/10715760601083235
- Guldiken B, Guldiken S, Turgut B, Turgut N, Demir M, Celik Y, et al. The roles of oxidized low-density lipoprotein and interleukin-6 levels in acute atherothrombotic and lacunar ischemic stroke. *Angiology*. 2008;59:224–229. doi: 10.1177/0003319707304134
- Tsai NW, Chang YT, Huang CR, Lin YJ, Lin WC, Cheng BC, et al. Association between oxidative stress and outcome in different subtypes of acute ischemic stroke. *Biomed Res Int*. 2014;2014:256879. doi: 10.1155/2014/256879
- Wang A, Yang Y, Su Z, Yue W, Hao H, Ren L, et al. Association of oxidized low-density lipoprotein with prognosis of stroke and stroke subtypes. *Stroke*. 2017;48:91–97. doi: 10.1161/STROKEAHA.116.014816
- Wang A, Cui Y, Meng X, Su Z, Cao Y, Yang Y, et al. The relationship between oxidized low-density lipoprotein and the NIHSS score among patients with acute ischemic stroke: the SOS-Stroke Study. *Atherosclerosis*. 2018;270:21–25. doi: 10.1016/j.atherosclerosis.2018.01.028
- Huang H, Mai W, Liu D, Hao Y, Tao J, Dong Y. The oxidation ratio of LDL: a predictor for coronary artery disease. *Dis Markers*. 2008;24:341–349.
- Huang H, Ma R, Liu D, Liu C, Ma Y, Mai W, et al. Oxidized low-density lipoprotein cholesterol and the ratio in the diagnosis and evaluation of therapeutic effect in patients with coronary artery disease. *Dis Markers*. 2012;33:295–302. doi: 10.3233/DMA-2012-00941
- von Weitzel-Mudersbach P, Andersen G, Hundborg HH, Johnsen SP. Transient ischemic attack and minor stroke are the most common manifestations of acute cerebrovascular diseases: a prospective, population-based study—the Aarhus TIA study. *Neuroepidemiology*. 2013;40:50–55. doi: 10.1159/000341696
- Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke:

- implications for public education and organisation of services. *BMJ*. 2004;328:326.
24. Wang Y, Johnston SC; CHANCE Investigators. Rationale and design of a randomized, double-blind trial comparing the effects of a 3-month clopidogrel-aspirin regimen versus aspirin alone for the treatment of high-risk patients with acute nondisabling cerebrovascular event. *Am Heart J*. 2010;160:380.e1–386.e1. doi: 10.1016/j.ahj.2010.05.017
  25. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
  26. Wang Y, Pan Y, Zhao X, Li H, Wang D, Johnston SC, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. *Circulation*. 2015;132:40–46. doi: 10.1161/CIRCULATIONAHA.114.014791
  27. Itabe H, Ueda M. Measurement of plasma oxidized low-density lipoprotein and its clinical implications. *J Atheroscler Thromb*. 2007;14:1–11.
  28. Nsaibia MJ, Mahmut A, Mahjoub H, Dahou A, Bouchareb R, Boulanger MC, et al. Association between plasma lipoprotein levels and bioprosthetic valve structural degeneration. *Heart*. 2016;102:1915–1921. doi: 10.1136/heartjnl-2016-309541
  29. Motamed M, Nargesi AA, Heidari B, Mirmiranpour H, Esteghamati A, Nakhjavani M. Oxidized low-density lipoprotein (ox-LDL) to LDL ratio (ox-LDL/LDL) and ox-LDL to high-density lipoprotein ratio (ox-LDL/HDL). *Clin Lab*. 2016;62:1609–1617.
  30. Spessatto D, Brum LMBDP, Camargo JL. Oxidized LDL but not total LDL is associated with HbA1c in individuals without diabetes. *Clin Chim Acta*. 2017;471:171–176. doi: 10.1016/j.cca.2017.06.004
  31. Harmon ME, Campen MJ, Miller C, Shuey C, Cajero M, Lucas S, et al. Associations of circulating oxidized LDL and conventional biomarkers of cardiovascular disease in a cross-sectional study of the Navajo population. *PLoS One*. 2016;11:e0143102. doi: 10.1371/journal.pone.0143102
  32. Nishi K, Itabe H, Uno M, Kitazato KT, Horiguchi H, Shinno K, et al. Oxidized LDL in carotid plaques and plasma associates with plaque instability. *Arterioscler Thromb Vasc Biol*. 2002;22:1649–1654.
  33. Uno M, Kitazato KT, Suzue A, Itabe H, Hao L, Nagahiro S. Contribution of an imbalance between oxidant-antioxidant systems to plaque vulnerability in patients with carotid artery stenosis. *J Neurosurg*. 2005;103:518–525. doi: 10.3171/jns.2005.103.3.0518
  34. Tsai NW, Lee LH, Huang CR, Chang WN, Chang YT, Su YJ, et al. Statin therapy reduces oxidized low density lipoprotein level, a risk factor for stroke outcome. *Crit Care*. 2014;18:R16. doi: 10.1186/cc13695
  35. Tavidou A, Efthimiadis A, Efthimiadis I, Paschalidou H. Antioxidant effects of simvastatin in primary and secondary prevention of coronary heart disease. *Eur J Clin Pharmacol*. 2006;62:485–489. doi: 10.1007/s00228-006-0097-z