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

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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.

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

Oxidative stress appears to be an important pathogenesis of atherosclerosis.[1] 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.[1–4] On the contrary, high-density lipoprotein (HDL) protects against the atherosclerotic process by reversing cholesterol transport and inhibiting LDL oxidation.[5,6] The oxLDL/HDL ratio reflects the equilibrium between atherosclerosis and antiatherosclerosis in the lipid lipoprotein markers. The positive associations between oxLDL and cardiovascular diseases[7–12] and ischemic stroke[13–19] have been verified in many studies. Recent studies have showed that elevated oxLDL/HDL ratio was a strong predictor for coronary heart disease.[20,21] 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,[22] acute minor ischemic stroke and TIA have high risks of early recurrence.[23,24] 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

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described previously.[24–26] 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 informations, 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 immunoturbidmetric 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).[27] 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 χ^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 μg/dL (interquartile range: 6.7–28.8 μg/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^2	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
Medical history, n (%)						
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
Qualifying events, n (%)						
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
Medications within 90-d follow-up period, n (%)						
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

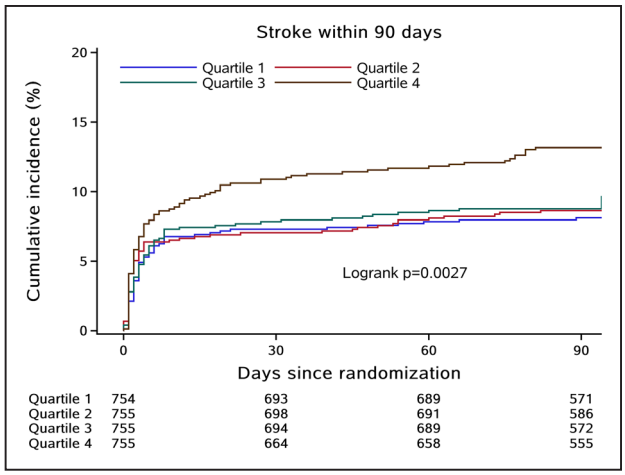

Figure 1. Kaplan-Meier curves of oxidized low-density lipoprotein/high-density lipoprotein for stroke within 90 d.

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[20,21] and associated with bioprosthetic valve structural degeneration,[28] which was supposed to be related with oxidative stress and inflammation. OxLDL/HDL was significantly higher in type 2 diabetes mellitus patients[29] and correlated with hemoglobin A1c.[30,31] 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.[9,10] 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.[32,33] A study showed that plasma oxLDL was significantly increased in patients with AIS,[13] and persistently increased oxLDL level was associated with enlargement of the ischemic area in the early phase of AIS.[14] OxLDL level was associated with National Institutes of Health Stroke Scale[14,19] and can independently predict poor outcome after AIS.[34] 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[9,10] and associated with the severity of coronary heart disease.[7,8,11,12]

OxLDL is supposed to be both proatherogenic and proinflammatory 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

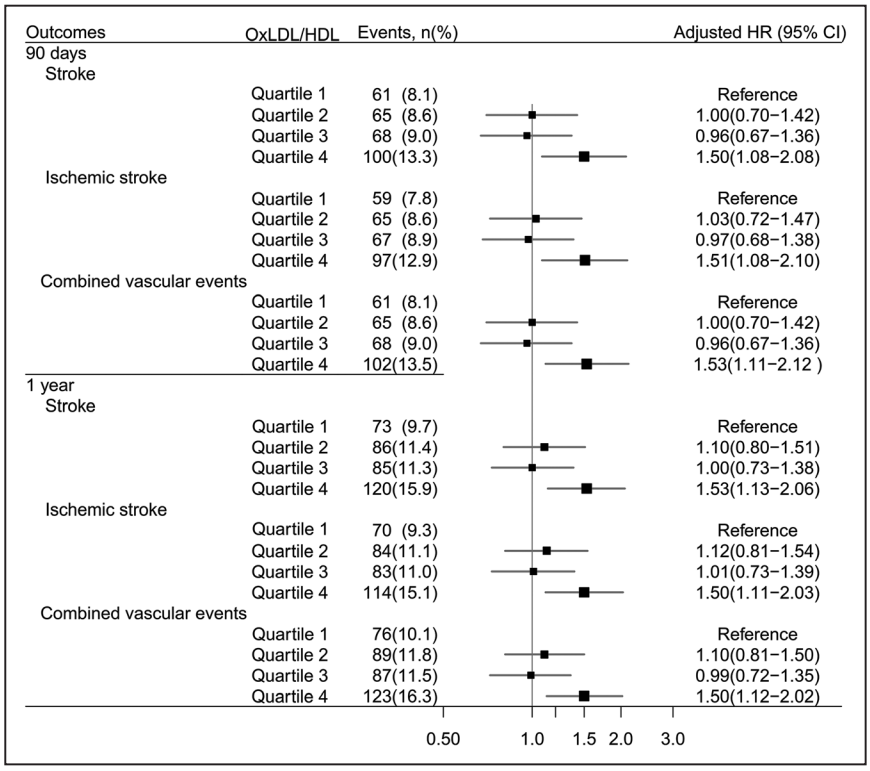

Figure 2. Adjusted hazards ratios (HR) by quartiles of oxidized low-density lipoprotein (oxLDL)/high-density lipoprotein (HDL) for outcomes within 90 d and 1 y. Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, past history of ischemic stroke, transient ischemic 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.[2–4] HDL is considered to be protective against atherosclerosis through reversing cholesterol transport and inhibiting the oxidation of LDL.[5,6] 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.[34] Similar results were showed in patients with coronary heart disease.[21,35] 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.[21] 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 ≈1000× stronger to oxLDL than native LDL100[27] 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.

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Disclosures

None.

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