Published Ahead of Print on August 8, 2018 as 10.1212/WNL.0000000000006118

ARTICLE

Oxidized low-density lipoprotein predicts recurrent stroke in patients with minor stroke or TIA

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Neurology® 2018;00:e1-e9. doi:10.1212/WNL.0000000000006118

Abstract

Objective
To investigate the association between oxidized low-density lipoprotein (oxLDL) and recurrent stroke in patients with minor stroke or TIA.

Methods
In the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial, baseline oxLDL levels were blindly measured in plasma with the 4E6 antibody in the core laboratory. 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 associations of oxLDL with recurrent stroke were analyzed by Cox proportional hazards.

Results
Among 3,019 patients included in this study, the median (interquartile range) of oxLDL was 13.96 (6.65–28.81) μg/dL. After adjustment for conventional confounding factors, patients in the highest oxLDL quartile (≥28.81 μg/dL) had a higher risk of recurrent stroke within 90 days (hazard ratio 1.43, 95% confidence interval 1.03–1.98) compared to those in the lowest oxLDL quartile (<6.65 μg/dL). Similar results were found for secondary outcomes. We also found a J-shaped association between oxLDL and risk of each outcome. There were no significant interactions between oxLDL and low-density lipoprotein and use of dual antiplatelet, antihypertensive, antidiabetic, and statins agents.

Conclusions
Elevated oxLDL levels can independently predict recurrent stroke in patients with minor stroke or TIA.

ClinicalTrials.gov identifier:
NCT00979589.

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Glossary

BMI = body mass index; **BP** = blood pressure; **CHANCE** = Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events; **CI** = confidence interval; **CVD** = cardiovascular disease; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **NIHSS** = NIH Stroke Scale; **oxLDL** = oxidized low-density lipoprotein.

The oxidized low-density lipoprotein (oxLDL), which is the major modified form of low-density lipoprotein (LDL), has been identified as an important contributing factor to atherosclerotic lesions. It has been reported that there was a significant correlation between plaque and circulating oxLDL levels.[1] In apparently healthy individuals, the levels of circulating oxLDL were indicative of levels of inflammatory response and oxidative stress in systemic arteries.[2] In patients with acute coronary artery diseases, the elevated levels of circulating oxLDL were directly related to the release of modified LDL from ruptured plaques.[3] Some studies have reported the predictive value of circulating oxLDL for future cardiac events in the general population, as well as in patients with prior cardiovascular diseases (CVDs).[2,4,5] OxLDL level was also increased in patients with acute ischemic stroke[6] and was related to poor functional outcome after stroke.[7] However, its role to predict a new vascular event in patients who already had a stroke remains unclear.

It is well known that patients with minor stroke or TIA are at high immediate risk for recurrent stroke.[8] Approximately 10% to 20% of these patients would have a new stroke within the first 3 months.[8,9] In the present study, we sought to investigate whether circulating oxLDL could predict recurrent stroke using data from the cohort of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial.

Methods

Study design and population

The detailed design and main results of the CHANCE trial have been described previously.[10–12] In brief, the CHANCE trial was a randomized, double-blind, placebo-controlled clinical trial. It enrolled 5,170 patients with acute minor stroke (NIH Stroke Scale [NIHSS] score ≤3) or high-risk TIA ($ABCD^2 \geq 4$) within 24 hours after onset and aimed to assess whether a combination of clopidogrel and aspirin was superior to aspirin alone in reducing the risk of recurrent stroke. Between October 2009 and July 2012, this trial was conducted at 114 centers across China. Among them, 73 (64%) centers voluntarily participated in the blood substudy. A total of 3,044 consecutive blood samples were collected.

Standard protocol approvals, registrations, and patient consents

The CHANCE trial has been approved by the ethics committee of each center and is registered at clinicaltrials.gov (NCT00979589). All participants or their legal proxies have provided written informed consent.

Outcome assessment

Patients were followed up at 90 days and 1 year. All visits were in person by trained site coordinators.[11,12] The primary outcome was any stroke (including ischemic or hemorrhagic stroke) within 90 days. The secondary outcomes included any stroke within 1 year and new ischemic stroke and combined vascular events (including ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death) within 90 days and 1 year. The definition of the above-mentioned outcomes was consistent with those previously described in the CHANCE trail.[11,12] All events were reviewed and confirmed by a central adjudication committee blinded to the study treatment assignments.

Measurement of circulating OxLDL

Blood samples were collected from fasting patients within 24 ± 12 hours after randomization. At each participating hospital, plasma samples were isolated and immediately frozen at −80°C. All isolated samples were shipped on dry ice from each center to Beijing Tiantan Hospital, where they were processed and analyzed. The level of circulating oxLDL was measured in EDTA plasma samples with the mAb-4E6-based[13] ELISA Kit (RapidBio Laboratory, Calabasas, CA). Measurements were conducted according to the manufacturer's guidelines. The intra-assay and inter-assay coefficients of variation of oxLDL level tests were 1.8% and 1.4%, respectively. All tests were performed in the clinical core laboratory of Beijing Tiantan Hospital, and all testing personnel were blinded to the study clinical data.

Assessment of demographic, behavioral, and clinical characteristics

Baseline demographic characteristics (including age and sex), smoking status, and medical history were self-reported on a questionnaire on admission. Blood pressure (BP) and body mass index (BMI) were measured by trained nurses on admission according to the unified standard report per CHANCE protocol.[11] The NIHSS and $ABCD^2$ scores were assessed by the trained neurologists on admission. The LDL level was measured in serum samples with a Roche Modular P800 analyzer (Roche, Basel, Switzerland). Medication use (including use of antiplatelet, antihypertensive, antidiabetic, and statin agents) was recorded within the 90-day follow-up period.

Statistical analysis

Continuous variables were described by medians and interquartile ranges because of skewed distribution. Categorical variables were described by frequencies and percentages. Patients were classified into 4 groups by oxLDL quartiles. The nonparametric Wilcoxon or Kruskal-Wallis test was used to compare group differences for continuous variables, and χ^2 tests were used for categorical variables.

The associations of oxLDL 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 in univariate analysis with a value of $p < 0.2$. Unadjusted and adjusted hazards ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Trend tests were performed in the regression models after the median oxLDL values of each quartile were entered into the model and treated as a continuous variable. In addition, we used restricted cubic splines to examine the shape of the association between oxLDL and outcomes with 4 knots (at the 5th, 35th, 65th, and 95th percentiles).[14] The reference point for oxLDL was the median (3.85 μg/dL) of the reference group (the lowest quartile), and the HR was adjusted for all confounding variables. Additionally, we used C statistics, integrated discrimination improvement, and net reclassification index to evaluate the incremental predictive value of oxLDL beyond conventional risk factors.

Interaction analysis was performed with Cox proportional hazards models. We tested the interactions between oxLDL and LDL (categorical variable <3.37 and ≥3.37 mmol/L) and medications such as dual antiplatelet, antihypertensive, antidiabetic, and statin agents as the outcomes of interest.

Overall, a 2-sided value of $p < 0.05$ was considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics

Of 3,044 patients with blood samples, 25 patients without the oxLDL value were excluded. Thus, a total of 3,019 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 of BP levels and NIHSS scores; lower proportions of history of angina, diabetes mellitus, and qualifying TIA; and a higher proportion of use of antihypertensive agents (table e-1, links.lww.com/WNL/A647).

Among the 3,019 patients included, the median age was 62.31 years, and 1,007 (33.36%) patients were female. The median level of circulating oxLDL was 13.96 μg/dL (interquartile range 6.65–28.81 μg/dL). Compared to patients with lower oxLDL, those with higher oxLDL were more likely to be older; had slightly higher BMI and LDL; had higher proportions of history of ischemic stroke, myocardial infarction, known atrial fibrillation or flutter, diabetes mellitus, and hypercholesterolemia; and had a lower proportion of history of angina (table 1).

Circulating oxLDL and clinical outcomes

The cumulative occurrence of recurrent stroke, ischemic stroke, and combined vascular events was 9.74%, 9.54%, and 9.80% within 90 days of follow-up and 12.06%, 11.63%, and 12.42% within 1 year of follow-up. All Kaplan-Meier curves by quartiles of oxLDL levels appeared to separate early and to continue to diverge throughout the follow-up period (figure 1). Patients with higher oxLDL quartile showed a higher incidence of stroke, ischemic stroke, and combined vascular events within 90 days and at 1 year (log-rank test $p < 0.01$ for all).

After adjustment for age, sex, BMI, history of ischemic stroke, myocardial infarction, angina, known atrial fibrillation or flutter, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, baseline NIHSS score, randomized treatment of aspirin alone or dual antiplatelet therapy, use of antihypertensive agents, antidiabetic agents, and statin agents, and baseline LDL levels, higher oxLDL level was associated with increased risk of recurrent stroke within 90 days (table 2). The association remained significant at 1 year. The adjusted HR for the highest vs lowest quartile of oxLDL was 1.43 (95% CI 1.03–1.98) for recurrent stroke at 90 days and 1.43 (95% CI 1.06–1.92) at 1 year. Similar results were observed for ischemic stroke and combined vascular events within 90 days and 1 year (table 2).

Multivariable-adjusted spline regression models showed J-shaped associations between oxLDL levels and the risk of recurrent stroke, ischemic stroke, and combined vascular events within 90 days and 1 year (figure 2).

Incremental predictive value of oxLDL

We evaluated whether oxLDL would further increase the predictive value of conventional risk factors (table 3). For recurrent stroke within 90 days as the outcome of interest, the C statistic by the conventional model did not significantly improve with the addition of oxLDL (from 0.676 to 0.685, $p = 0.1365$). However, the discriminatory power and risk reclassification appeared to be substantially better (integrated discrimination improvement 5.10%, $p = 0.0196$; continuous net reclassification index 18.38%, $p = 0.0018$). Similar results were found in secondary outcomes.

Effects of LDL and medication use

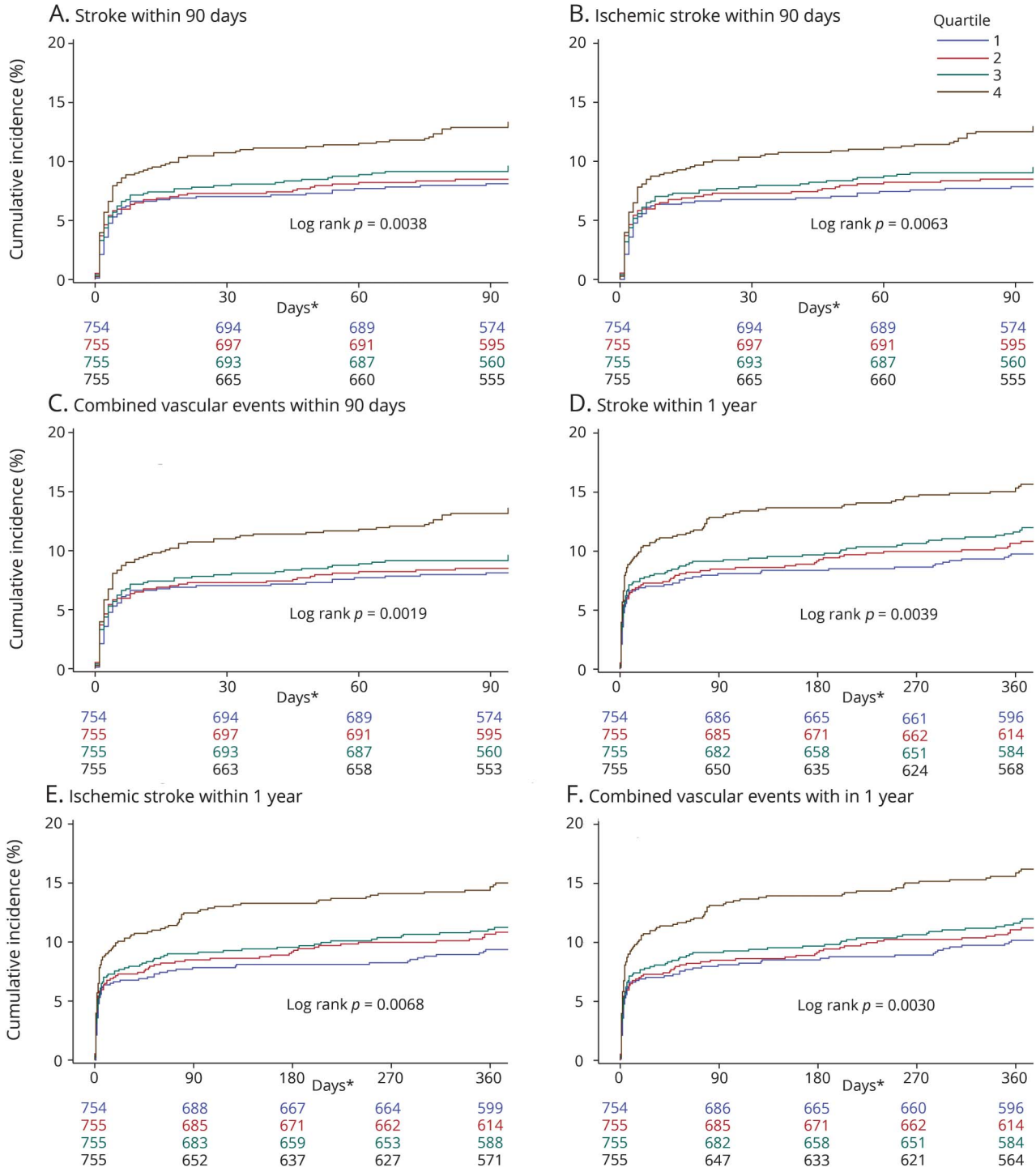
For recurrent stroke within 90 days as the outcome of interest, there was no interaction between oxLDL and LDL (p for interaction = 0.9593). Moreover, we found that there

Table 1 Characteristics of Patients Included According to oxLDL quartiles

Characteristics	Overall	oxLDL quartiles				*p* Value
		Quartile 1, <6.65 μg/dL	Quartile 2, 6.65–13.95 μg/dL	Quartile 3, 13.96–28.80 μg/dL	Quartile 4, ≥28.81 μg/dL	
Patients, n	3,019	754	755	755	755	
Age, median (IQR), y	62.31 (54.74–71.18)	60.44 (53.41–68.75)	61.46 (53.73–70.45)	62.73 (55.16–71.18)	64.72 (56.25–73.28)	<0.0001
Female, n (%)	1,007 (33.36)	242 (32.10)	236 (31.26)	271 (35.89)	258 (34.17)	0.2170
SBP, median (IQR), mm Hg	150 (139–164)	150 (137–165)	150 (139–160)	150 (138–164)	150 (140–166)	0.2675
DBP, median (IQR), mm Hg	90 (80–100)	90 (80–97)	90 (80–100)	90 (80–98)	90 (80–100)	0.3640
BMI, median (IQR), kg/m^2	24.49 (22.76–26.56)	24.22 (22.49–25.95)	24.51 (22.84–26.56)	24.75 (22.84–26.61)	24.51 (22.86–27.08)	0.0005
LDL, median (IQR), mmol/L	3.12 (2.49–3.82)	2.95 (2.38–3.56)	3.16 (2.53–3.93)	3.24 (2.62–3.87)	3.16 (2.46–3.91)	<0.0001
Medical history, n (%)						
Ischemic stroke	577 (19.11)	116 (15.38)	143 (18.94)	138 (18.28)	180 (23.84)	0.0004
TIA	94 (3.11)	18 (2.39)	26 (3.44)	24 (3.18)	26 (3.44)	0.5988
Myocardial infarction	54 (1.79)	7 (0.93)	14 (1.85)	10 (1.32)	23 (3.05)	0.0122
Angina	92 (3.05)	33 (4.38)	20 (2.65)	12 (1.59)	27 (3.58)	0.0114
Congestive heart failure	53 (1.76)	11 (1.46)	16 (2.12)	10 (1.32)	16 (2.12)	0.5019
Known atrial fibrillation or flutter	57 (1.89)	16 (2.12)	18 (2.38)	3 (0.40)	20 (2.65)	0.0055
Valvular heart disease	10 (0.33)	2 (0.27)	2 (0.26)	1 (0.13)	5 (0.66)	0.3068
Hypertension	317 (10.50)	67 (8.89)	82 (10.86)	94 (12.45)	74 (9.80)	0.1303
Diabetes mellitus	608 (20.14)	133 (17.64)	135 (17.88)	179 (23.71)	161 (21.32)	0.0075
Hypercholesterolemia	1,968 (65.19)	450 (59.68)	489 (64.77)	500 (66.23)	529 (70.07)	0.0004
Current or previous smoking, n (%)	1,293 (42.83)	325 (43.10)	336 (44.50)	302 (40.00)	330 (43.71)	0.3088
Time to randomization <12 h, n (%)	1,502 (49.75)	355 (47.08)	392 (51.92)	381 (50.46)	374 (49.54)	0.2913
Qualifying events, n (%)						
TIA	810 (26.83)	217 (28.78)	206 (27.28)	200 (26.49)	187 (24.77)	0.3591
Minor stroke	2,209 (73.17)	537 (71.22)	549 (72.72)	555 (73.51)	568 (75.23)	
Baseline NIHSS score, median (IQR)	2 (0–2)	1 (0–2)	1 (0–2)	2 (0–2)	2 (1–2)	0.0622
Medications within 90-d follow-up period, n (%)						
Aspirin alone	1,514 (50.15)	383 (50.80)	358 (47.42)	371 (49.14)	402 (53.25)	0.1338
Clopidogrel and aspirin	1,505 (49.85)	371 (49.20)	397 (52.58)	384 (50.86)	353 (46.75)	
Antihypertensive agents	1,116 (36.97)	273 (36.21)	278 (36.82)	277 (36.69)	288 (38.15)	0.8804
Antidiabetic agents	373 (12.36)	80 (10.61)	90 (11.92)	109 (14.44)	94 (12.45)	0.1524
Statins	1,259 (41.70)	298 (39.52)	329 (43.58)	311 (41.19)	321 (42.52)	0.4152

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; IQR = interquartile range; LDL = low-density lipoprotein; NIHSS = NIH Stroke Scale; oxLDL = oxidized low-density lipoprotein; SBP = systolic blood pressure.

Figure 1 Cumulative incidence of recurrent stroke, ischemic stroke, and combined vascular events by oxLDL quartiles within 90 days and 1 year



(A–C) Kaplan-Meier curves of incidence of recurrent stoke, ischemic stroke, and combined vascular events by oxidized low-density lipoprotein (oxLDL) quartiles within 90 days. (D–F) Kaplan-Meier curves of incidence of recurrent stoke, ischemic stroke, and combined vascular events by oxLDL quartiles within 1 year. *The x-axis label in all panels is days since randomization.

were no interactions between oxLDL and use of dual antiplatelet (p for interaction = 0.7578), antihypertensive (p for interaction = 0.1494), and antidiabetic (p for interaction = 0.3834) agents. However, we noted a potential interaction between oxLDL and the use of statins (p for interaction = 0.0849). The oxLDL level tended to be a stronger predictor for recurrent stroke within 90 days in patients not taking statins (HR 1.92, 95% CI 1.26–2.94) (table e-2, links.lww.com/WNL/A647). We found similar results for secondary outcomes of interest.

Table 2 HRs (95% CIs) for outcomes according to oxLDL quartiles

Outcomes	oxLDL quartiles	Outcomes within 90 d			Outcomes within 1 y		
		Events, n (%)	Unadjusted model	Adjusted model[a]	Events, n (%)	Unadjusted model	Adjusted model[a]
Stroke	Quartile 1	61 (8.09)	Reference	Reference	74 (9.81)	Reference	Reference
	Quartile 2	64 (8.48)	1.05 (0.74–1.49)	0.98 (0.69–1.40)	83 (10.99)	1.12 (0.82–1.54)	1.06 (0.77–1.45)
	Quartile 3	70 (9.27)	1.15 (0.82–1.62)	0.97 (0.69–1.38)	89 (11.79)	1.21 (0.89–1.64)	1.04 (0.76–1.43)
	Quartile 4	99 (13.11)	1.65 (1.20–2.27)	1.43 (1.03–1.98)	118 (15.63)	1.63 (1.22–2.18)	1.43 (1.06–1.92)
	p for trend	0.0010	0.0003	0.0054	0.0006	0.0003	0.0063
Ischemic stroke	Quartile 1	59 (7.82)	Reference	Reference	71 (9.42)	Reference	Reference
	Quartile 2	64 (8.48)	1.09 (0.76–1.55)	1.01 (0.71–1.45)	83 (10.99)	1.17 (0.85–1.61)	1.10 (0.80–1.51)
	Quartile 3	69 (9.14)	1.18 (0.83–1.66)	0.99 (0.69–1.40)	84 (11.13)	1.19 (0.87–1.63)	1.01 (0.74–1.40)
	Quartile 4	96 (12.72)	1.66 (1.20–2.29)	1.43 (1.03–1.99)	113 (14.97)	1.63 (1.21–2.19)	1.40 (1.04–1.90)
	p for trend	0.0013	0.0006	0.0082	0.0013	0.0007	0.0138
Combined vascular events	Quartile 1	61 (8.09)	Reference	Reference	77 (10.21)	Reference	Reference
	Quartile 2	64 (8.48)	1.05 (0.74–1.49)	0.98 (0.69–1.40)	86 (11.39)	1.12 (0.82–1.52)	1.06 (0.77–1.44)
	Quartile 3	70 (9.27)	1.15 (0.82–1.62)	0.97 (0.69–1.38)	90 (11.92)	1.17 (0.87–1.59)	1.02 (0.75–1.39)
	Quartile 4	101 (13.38)	1.69 (1.23–2.32)	1.46 (1.06–2.02)	122 (16.16)	1.62 (1.22–2.16)	1.42 (1.06–1.91)
	p for Trend	0.0006	0.0002	0.0030	0.0006	0.0002	0.0052

Abbreviations: CI = confidence interval; HR = hazard ratio; oxLDL = oxidized low-density lipoprotein.
[a] Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, history of ischemic stroke, TIA, 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 NIH Stroke Scale score, randomized treatment of aspirin alone or dual antiplatelet therapy, use of antihypertensive, antidiabetic, and statin agents, and baseline low-density lipoprotein levels.

Discussion

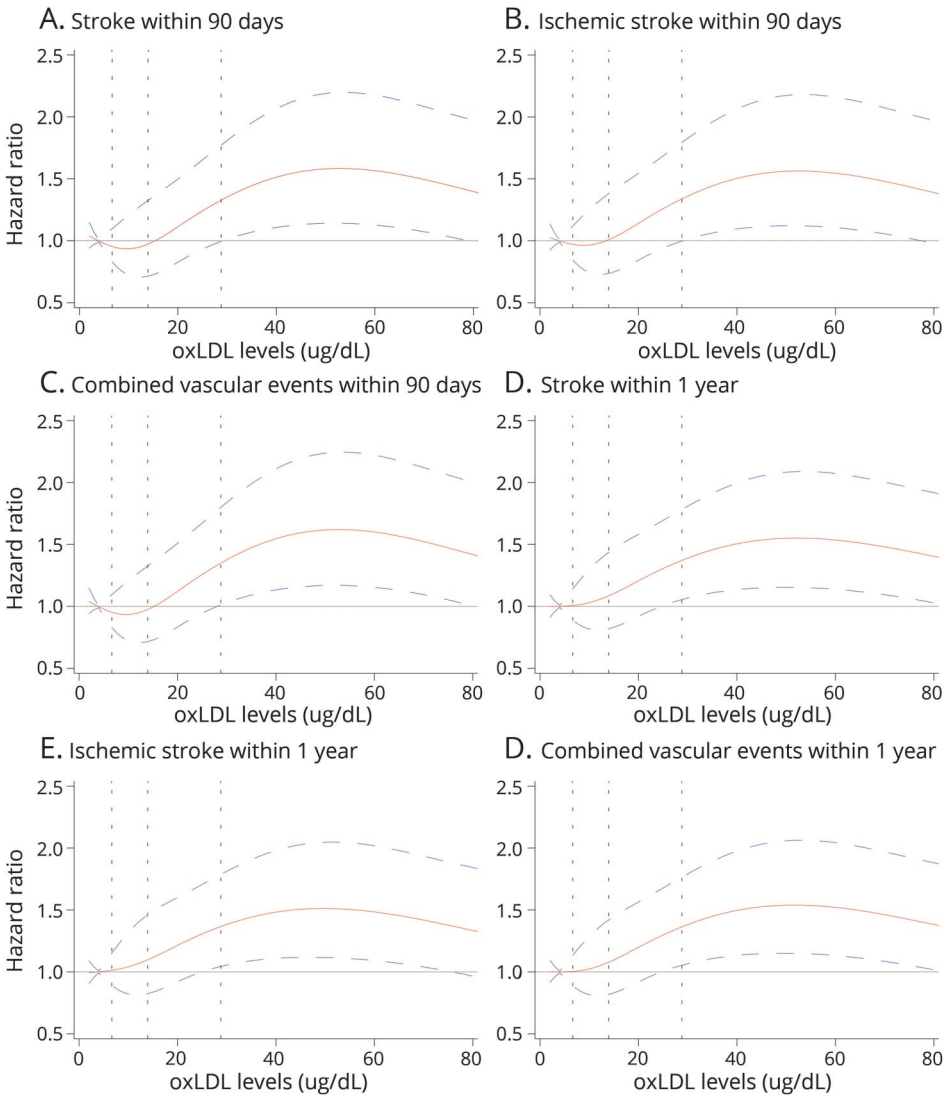
The major finding of this study was that a higher level of circulating oxLDL was an independent predictor of recurrent stroke, as well as ischemic stroke and combined vascular events, in patients with minor stroke or TIA during the first 90 days and 1 year. There were no significant interactions between oxLDL and LDL and use of dual antiplatelet, antihypertensive, antidiabetic, and statins agents. However, oxLDL tended to be a stronger predictor for each outcome in patients not taking statins.

Several studies have proved the predictive value of circulating oxLDL for recurrent cardiac events in patients with prior CVDs.[2,4,5] The predictive value of circulating oxLDL for recurrent stroke has never been reported. Nevertheless, some previous studies conducted to investigate the associations between oxLDL and conventional risk factors of CVDs suggested some possible underlying mechanism. A population-based study reported that higher circulating oxLDL was associated with increased incidence of metabolic syndrome after 5 years of follow-up.[15] In particular, oxLDL was related to its components of abdominal obesity,[16] hyperglycemia,[17] and hypertriglyceridemia.[15] In a large sample of CVD-free adults, an association of oxLDL with elevated systolic and diastolic BP was found in patients with prehypertension.[18] Circulating oxLDL could reflect the levels of inflammatory response and oxidative stress in systemic vasculature. It is a reasonable hypothesis that the elevated level of circulating oxLDL is a common pathway of a variety of conventional risk factors that contribute to the incidence of vascular events, including stroke.[19]

The mechanisms responsible for the association of oxLDL and atherosclerosis include damage of endothelial cells, migration and proliferation of smooth muscle cells, and inflammatory effects. Circulating oxLDL is related to plaque oxLDL and suggests an atherosclerotic burden in systemic vasculature.[1,19] Circulating oxLDL has correlated to carotid intimal-media thickening among patients with type 1 diabetes mellitus.[20] In patients with minor stroke or TIA, those with more atherosclerotic burden are more likely to have recurrent stroke. In addition, studies in patients undergoing carotid endarterectomy imply that higher circulating levels of oxLDL were related to greater carotid plaque instability,[1] which increased their risk of having a recurrent stroke.

We demonstrated that adding oxLDL to conventional risk factors could increase the discriminatory power and risk reclassification for future vascular events. This possibly is

Figure 2 Association of oxLDL levels with risk of recurrent stoke, ischemic stroke, and combined vascular events within 90 days and 1 year



(A–C) Recurrent stoke, ischemic stroke, and combined vascular events within 90 days. (D–F) Recurrent stroke, ischemic stroke, and combined vascular events within 1 year. oxLDL = oxidized low-density lipoprotein.

related to some of its pathophysiologic characteristics such as increasing platelet reactivity[21] and autoimmune response. This result implies that atherosclerosis may play an important role in the recurrence of stroke.

In our study, no interaction between oxLDL and LDL was detected. No interactions between oxLDL and use of dual antiplatelet, antihypertensive, and antidiabetic agents were detected either, although the effects of these treatments on reducing circulating oxLDL have been reported.[22,23] A potential interaction between oxLDL and use of statins was seen with regard to recurrent stroke within 90 days and 1 year. Circulating oxLDL was a predictor for recurrent stroke in patients not taking statins but not in patients on statins. The a priori hypothesis was that the use of statins within the first 90 days reduced the level of oxLDL and affected the incidence of vascular events in the follow-up period. This hypothesis was supported by several studies.[24–26] One study reported that treatment with atorvastatin resulted in a decrease in oxLDL levels among patients with type 2 diabetes mellitus.[26] Another study reported that the levels of circulating oxLDL were significantly decreased by statin therapy (atorvastatin 10 mg/d) in patients with hypercholesterolemia.[24] Similar results were seen in patients on 40 mg simvastatin.[25] However, these findings were related to the antibodies used for testing.[2] Studies using the antibody of oxLDL-4E6 and oxLDL-DLH3 supported this association.[24–26] Those that used oxLDL-E06 yielded conflicting results.[27] Overall, the tendency for interaction between oxLDL and statins for recurrent stroke is a topic worth further investigation.

There were several limitations to our study. First, we used the oxLDL-4E6 antibody (used most in trials) to determine circulating oxLDL levels. However, the oxLDL-4E6 antibody

Table 3 Reclassification and discrimination statistics for outcomes within 90 days and 1 year by oxLDL

	C statistic		IDI		NRI (continuous)		NRI (categorical)[a]	
	Estimate (95% CI)	*p* Value	Estimate (95% CI), %	*p* Value	Estimate (95% CI), %	*p* Value	Estimate (95% CI), %	*p* Value
Outcomes within 90 d								
Stroke								
Conventional model[b]	0.676 (0.644–0.707)		Reference		Reference		Reference	
Conventional model + oxLDL	0.685 (0.651–0.717)	0.1365	5.10 (0.79–9.30)	0.0196	18.38 (6.48–29.11)	0.0018	3.62 (−2.37 to 19.32)	0.21305
Ischemic stroke								
Conventional model	0.681 (0.644–0.711)		Reference		Reference		Reference	
Conventional model + oxLDL	0.689 (0.652–0.719)	0.1592	4.51 (0.56–8.97)	0.0352	17.61 (6.40–29.10)	0.0028	2.40 (−4.89 to 8.43)	0.9452
Combined vascular events								
Conventional model	0.676 (0.644–0.709)		Reference		Reference		Reference	
Conventional model + oxLDL	0.686 (0.652–0.718)	0.1090	5.76 (0.62–9.58)	0.0104	19.40 (6.83–29.48)	0.0011	3.28 (−4.67 to 8.96)	0.3422
Outcomes within 1 y								
Stroke								
Conventional model	0.662 (0.637–0.708)		Reference		Reference		Reference	
Conventional model + oxLDL	0.669 (0.648–0.717)	0.3106	5.11 (0.78–9.37)	0.0196	17.14 (6.92–29.20)	0.0031	5.66 (−4.29 to 9.94)	0.1177
Ischemic stroke								
Conventional model	0.670 (0.638–0.706)		Reference		Reference		Reference	
Conventional model + oxLDL	0.676 (0.647–0.715)	0.4074	4.65 (0.79–9.24)	0.0299	14.71 (6.42–28.98)	0.0122	1.23 (−4.11 to 9.61)	0.7270
Combined vascular events								
Conventional model	0.658 (0.635–0.706)		Reference		Reference		Reference	
Conventional model + oxLDL	0.667 (0.644–0.714)	0.3964	5.82 (0.91–9.39)	0.00686	17.66 (6.59–29.00)	0.0022	5.77 (−3.96 to 10.04)	0.1074

Abbreviations: CI = confidence interval; IDI = integrated discrimination improvement; NRI = net reclassification index; oxLDL = oxidized low-density lipoprotein.
[a] Patients were divided into 4 risk categories by oxLDL quartiles.
[b] Conventional model: age, sex, body mass index, history of ischemic stroke, myocardial infarction, angina, known atrial fibrillation or flutter, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, baseline NIH Stroke Scale score, randomized treatment of aspirin alone or dual antiplatelet therapy, use of antihypertensive agents, antidiabetic agents, and statin agents, and baseline low-density lipoprotein levels.

has a potential cross-reactivity with native LDL and relies on enough lysine modifications on apolipoprotein B-100.[13] Although the analysis was adjusted for the LDL levels in this study, there could still be antibody reaction variation. Second, we did not collect data on history of carotid stenosis and vascular status at admission. The association of oxLDL with recurrent stroke for different etiologies was not assessed in this study. However, our prior study showed that the oxLDL level was related to poor prognosis only in patients with large artery atherosclerosis and small artery occlusion, not in those with cardioembolism.[7] We speculated that the oxLDL level could fail to predict the incidence of cardioembolic type of stroke. Further sensitivity analyses are needed. Third, we measured the baseline oxLDL level only at the acute stage of minor stroke or TIA. The dynamic change of oxLDL at different stages could not be presented in this study. Notably, circulating oxLDL was found to increase after stroke but to decrease over the following months.[6] For analyzing the

predictive role of oxLDL at different stages, further studies with repeated measurement intervals are needed. Fourth, the medical histories were reported by patients themselves on a questionnaire. However, the data from self-reported information was less accurate than from queriable medical records.

This substudy of CHANCE trial suggests that elevated oxLDL levels could independently predict recurrent stroke in patients with minor stroke or TIA. This finding may be significant because there currently are no other biomarkers that can predict the risk of recurrent stroke.

Author contributions

Anxin Wang performed the experiments, conducted the statistical analysis, interpreted the data, and drafted the manuscript. Jie Xu and Guojuan Chen interpreted the data and commented on the drafts. David Wang and S. Claiborne Johnston supervised the analysis, interpreted the data, and commented on the drafts. Xia Meng, Jinxi Lin, Hao Li, and Yibin Cao revising the manuscript for intellectual content. Nan Zhang, Caiyun Ma, and Liye Dai performed the experiments and interpreted the data. Xingquan Zhao and Liping Liu designed and supervised the analysis. Yongjun Wang and Yilong Wang had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Yilong Wang designed and conceptualized this study.

Study 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, and 2016YFC0901002), grants from the National Natural Science Foundation of China (81673247 and 816005098), a grant from the Beijing Biobank of Cerebral Vascular Disease (D131100005313003), and a grant from Beijing Institute for Brain Disorders (1152130306).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received October 23, 2017. Accepted in final form May 10, 2018.

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Neurology published online August 8, 2018
DOI 10.1212/WNL.0000000000006118