Association of Lp-PLA$_2$-A and early recurrence of vascular events after TIA and minor stroke

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ABSTRACT

Objective: To determine the association of lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) measured in the acute period and the short-term risk of recurrent vascular events in patients with TIA or minor stroke.

Methods: We measured Lp-PLA$_2$ activity (Lp-PLA$_2$-A) in a subset of 3,201 participants enrolled in the CHANCE (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) trial. Participants with TIA or minor stroke were enrolled within 24 hours of symptom onset and randomized to single or dual antiplatelet therapy. In the current analysis, the primary outcome was defined as the composite of ischemic stroke, myocardial infarction, or death within 90 days.

Results: The composite endpoint occurred in 299 of 3,021 participants (9.9%). The population average Lp-PLA$_2$-A level was 209 ± 59 nmol/min/mL (95% confidence interval [CI] 207–211). Older age, male sex, and current smoking were associated with higher Lp-PLA$_2$-A levels. Lp-PLA$_2$-A was significantly associated with the primary endpoint (adjusted hazard ratio 1.07, 95% CI 1.01–1.13 for every 30 nmol/min/mL increase). Similar results were seen for ischemic stroke alone. Adjustment for low-density lipoprotein cholesterol attenuated the association between Lp-PLA$_2$-A and the primary endpoint (adjusted hazard ratio 1.04, 95% CI 0.97–1.11 for every 30 nmol/min/mL increase).

Conclusions: Higher levels of Lp-PLA$_2$-A in the acute period are associated with increased short-term risk of recurrent vascular events. *Neurology*® 2015;85:1585–1591

GLOSSARY

ABCD² = age, blood pressure, clinical features, duration of TIA, and presence of diabetes; **ACS** = acute coronary syndrome; **CHANCE** = Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events; **CI** = confidence interval; **HR** = hazard ratio; **LDL-C** = low-density lipoprotein cholesterol; **Lp-PLA$_2$** = lipoprotein-associated phospholipase A$_2$; **Lp-PLA$_2$-A** = lipoprotein-associated phospholipase A$_2$ activity; **MIRACL** = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; **PROVE-IT** = Pravastatin or Atorvastatin Evaluation and Infection Therapy.

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$), an enzyme associated with metabolism of low-density lipoprotein to proinflammatory mediators, has been linked to atherosclerotic plaque inflammation and instability.[1,2] In pathologic studies of plaque specimens obtained following carotid endarterectomy, expression of Lp-PLA$_2$ is increased in patients with recent stroke or TIA compared with asymptomatic patients.[3] Both Lp-PLA$_2$ mass and activity can be easily measured in blood samples, and elevated levels have been shown to predict long-term risk of stroke and myocardial infarction.[4] Less is known about the relationship between Lp-PLA$_2$ levels and the short-term risk of recurrent vascular events, although several small studies have suggested that Lp-PLA$_2$-A, but not Lp-PLA$_2$ mass, may predict short-term risk of recurrent stroke after TIA.[5,6] The aim of the present study was to examine the association of Lp-PLA$_2$-A with short-term risk of recurrent vascular events in a large cohort of patients with acute TIA or minor stroke.

Supplemental data at Neurology.org

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CHANCE coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS The study population consisted of participants enrolled in the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial for whom stored blood samples were available for testing. Details about study rationale, design, and results have been published previously.[7,8] Briefly, CHANCE was a randomized, double-blind, multicenter trial conducted in China that enrolled patients with acute TIA or minor stroke within 24 hours of symptom onset. TIA participants were required to be at moderate to high risk of stroke as categorized by an $ABCD^2$ score of ≥4. The $ABCD^2$ score is a clinical risk score that stratifies risk of stroke after TIA.[9] Stroke participants were required to have minor stroke as defined by an NIH Stroke Scale score of ≤3. Participants were randomized to one of 2 groups. The first received clopidogrel (loading dose of 300 mg followed by 75 mg daily for 3 months) plus aspirin (loading dose of 75–300 mg followed by 75 mg daily for 21 days), while the second group received aspirin (loading dose of 75–300 mg followed by 75 mg daily for 3 months). The selection of the aspirin loading dose between 75 and 300 mg was at the discretion of the treating investigator in both groups. The primary outcome measure was the risk of any stroke, including both ischemic and hemorrhagic stroke, within a 3-month period. Secondary outcomes included incidence of any vascular event or death. For the current analysis, the primary outcome measure was specified as a composite of ischemic stroke, myocardial infarction, and death, with ischemic stroke alone as a secondary outcome measure.

Standard protocol approvals, registrations, and patient consents. The CHANCE trial is registered with clinicaltrials.gov (NCT00979589). All of the participants or their legal proxies provided written informed consent. The CHANCE protocol was approved by the ethics committee at each study center.

Blood sampling. A subset of 73 CHANCE centers participated in blood sample collection. Venous blood samples were obtained under sterile conditions within 48 hours of symptom onset. Samples were collected in serum-separation tubes and centrifuged within 2 hours at 1,500*g* for 15 minutes. Serum was extracted and samples were stored at −80°C until testing was performed. Lp-PLA_2-A was measured with an automated enzyme assay system run on a Hitachi 7,600 analyzer (PLAC test for Lp-PLA_2-A; diaDexus Inc., San Francisco, CA). The intra-assay coefficient of variation for the Lp-PLA_2-A assay is ≤2.9% and the interassay

Table 1 Baseline characteristics of study patients overall and dichotomized by Lp-PLA_2-A level threshold of 225 nmol/min/mL

Variable	Overall	Lp-PLA_2-A <225 nmol/min/mL	Lp-PLA_2-A ≥225 nmol/min/mL	*p* Value
No.	3,021	1,815	1,206	
Age, y	62.6 ± 10.7	62.2 ± 10.5	63.2 ± 10.9	0.0137
Male	2,001 (66.2)	1,132 (62.4)	869 (72.1)	<0.0001
Systolic blood pressure, mm Hg	151.5 ± 22.4	151.6 ± 22.7	151.4 ± 21.9	0.8689
Diastolic blood pressure, mm Hg	88.9 ± 13.2	89.1 ± 13.4	88.7 ± 12.8	0.4365
BMI, kg/m²	24.7 ± 3.0	24.7 ± 3.1	24.7 ± 2.9	0.7343
LDL-cholesterol	3.2 ± 1.1	3.0 ± 1.0	3.6 ± 1.1	<0.0001
Current smoker	990 (32.8)	567 (31.2)	423 (35.1)	0.0279
History of stroke	578 (19.1)	326 (18.0)	252 (20.9)	0.0447
History of TIA	96 (3.2)	61 (3.4)	35 (2.9)	0.4815
History of hypertension	1,967 (65.1)	1,171 (64.5)	796 (66.0)	0.4015
History of diabetes	620 (20.5)	368 (20.3)	252 (20.9)	0.6794
History of hyperlipidemia	316 (10.5)	188 (10.4)	128 (10.6)	0.8222
History of myocardial infarction	55 (1.8)	27 (1.5)	28 (2.3)	0.0931
History of angina	99 (3.3)	60 (3.3)	39 (3.2)	0.9134
History of heart failure	54 (1.8)	30 (1.7)	24 (2.0)	0.4934
Minor stroke	2,217 (73.4)	1,323 (72.9)	894 (74.1)	0.4513
TIA	804 (26.6)	492 (27.1)	312 (25.9)	
$ABCD^2$ score 4–5	661 (82.2)	406 (82.5)	255 (81.7)	0.7754
$ABCD^2$ score 6–7	143 (17.8)	86 (17.5)	57 (18.3)	
Aspirin alone	1,517 (50.2)	901 (49.6)	616 (51.1)	0.4395
Clopidogrel plus aspirin	1,504 (49.8)	914 (50.4)	590 (48.9)	
Composite endpoint	299 (9.9)	161 (8.9)	138 (11.4)	0.0204
Ischemic stroke	192 (66.0)	101 (64.3)	91 (67.9)	0.5206

Abbreviations: BMI = body mass index; LDL = low-density lipoprotein; Lp-PLA_2-A = lipoprotein-associated phospholipase A_2 activity.
Data are mean ± SD or n (%).

Table 2 Univariate analysis of factors associated with primary endpoint (ischemic stroke, MI, or death)

Variable	Hazard ratio (95% CI)	p Value
Age per 10 y	1.16 (1.04–1.29)	0.0076
Male	0.81 (0.64–1.02)	0.0693
Systolic blood pressure per 20 mm Hg	1.23 (1.12–1.35)	<0.0001
Diastolic blood pressure per 10 mm Hg	1.09 (1.00–1.18)	0.0432
BMI	1.03 (0.92–1.14)	0.6406
Current smoker	0.86 (0.67–1.10)	0.2415
History of stroke	0.95 (0.71–1.27)	0.7049
History of TIA	1.39 (0.80–2.42)	0.2446
History of hypertension	1.39 (1.08–1.79)	0.0109
History of diabetes	1.44 (1.12–1.86)	0.0052
History of hyperlipidemia	0.95 (0.65–1.39)	0.7942
History of MI	0.18 (0.02–1.26)	0.0835
History of angina	0.92 (0.47–1.78)	0.7956
History of heart failure	0.75 (0.28–2.02)	0.5732
Minor stroke	1.09 (0.84–1.41)	0.5239
TIA ABCD^2 score 6–7 vs 4–5	1.06 (0.53–1.75)	0.8930
Dual antiplatelet vs aspirin monotherapy	0.65 (0.52–0.83)	0.0003
Lp-PLA$_2$-A per 30 nmol/min/mL	1.06 (1.00–1.13)	0.0351
Lp-PLA$_2$-A ≥225 nmol/min/mL	1.31 (1.05–1.65)	0.0193

Abbreviations: BMI = body mass index; CI = confidence interval; Lp-PLA$_2$-A = lipoprotein-associated phospholipase A$_2$ activity; MI = myocardial infarction.

coefficient of variation is ≤3.0%. Low-density lipoprotein cholesterol (LDL-C) was measured using a Roche Modular P800 system (Roche, Basel, Switzerland). All assays were performed at a central laboratory at Tiantan Hospital with laboratory personnel blinded to clinical data.

Statistical analysis. Variables were summarized using means and 95% conference intervals (CIs) for continuous variables, with frequencies and percentages for categorical variables. Student *t* test was used to compare group differences for continuous variables, and χ^2 tests for dichotomous variables. Cox proportional hazard models were applied to examine the association between patient characteristics and the primary endpoint. Lp-PLA$_2$-A levels were dichotomized to ≤225 or >225 nmol/min/mL. This threshold was prespecified based on prior studies of acute stroke and TIA that suggested a substantially increased risk of recurrence associated with levels >150 nmol/min/mL using an older microplate Lp-PLA$_2$-A assay run at room temperature.[5,10,11] The newer-generation Lp-PLA$_2$-A assay used in the present study runs at 37°C on automated analyzers and produces values approximately 1.5 times higher than the previous microplate assay. The choice of the 225 nmol/min/mL threshold was thus based on a calculation of the level from the newer-generation assay equivalent to the 150 nmol/min/mL threshold using the older-generation assay. To examine whether there is a nonlinear relationship between Lp-PLA$_2$-A levels and outcome, we also tested the association between the quadratic and cubic term and the primary endpoint. A treatment by Lp-PLA$_2$-A level interaction was also tested. Multivariable models were constructed with adjustment for imbalances between groups in demographic factors, risk factors, enrolling event (TIA vs stroke), and study intervention. Variables were included in the model if there was imbalance across groups with $p < 0.10$. All variables that were associated with the composite outcome in univariate analysis with $p < 0.10$ were also included in the final model. A post hoc analysis adjusting for LDL-C in a subset of patients with available LDL-C measurements was also performed. All tests were 2-sided. An association was considered statistically significant if $p < 0.05$. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS From 2009 to 2012, 5,170 patients were enrolled in the CHANCE trial. Of these, 3,021 patients from 73 sites participated in the blood biomarker substudy. Among the 3,021 participants, the mean Lp-PLA$_2$-A level was 209.3 nmol/min/mL (95% CI 207.2–211.4) and 1,206 (39.9%) had Lp-PLA$_2$-A levels ≥225 nmol/min/mL. Baseline characteristics of the 3,021 included patients are shown in table 1. Comparing those with Lp-PLA$_2$-A levels above vs below the 225 nmol/min/mL threshold, those with higher levels were more likely to be older, be male, smoke, have a history of prior stroke, and have higher LDL-C (table 1).

Outcomes. The composite endpoint of ischemic stroke, myocardial infarction, or death occurred in 299 of 3,021 participants (9.9%). Ischemic stroke occurred in 291 participants (9.6%), myocardial infarction in 2 participants (0.07%), and death in 6 participants (0.2%). Older age, higher systolic and diastolic blood pressures, history of hypertension, history of diabetes, higher Lp-PLA$_2$-A level, and assignment to aspirin alone were associated with a greater risk of the composite outcome (table 2). Nearly identical results were seen for ischemic stroke alone (table e-1 on the *Neurology*® Web site at Neurology.org).

Lp-PLA$_2$-A levels and outcome. When tested as a linear variable, Lp-PLA$_2$-A levels were higher in older patients, men, current smokers, and those with a history of myocardial infarction (table 3). After adjustment for age, sex, systolic blood pressure, hypertension, diabetes, prior myocardial infarction, and antiplatelet treatment, Lp-PLA$_2$-A level was significantly linearly associated with the primary endpoint (hazard ratio [HR] 1.07, 95% CI 1.01–1.13, per 30 nmol/min/mL increase) (table 4). This linear association also indicated that the treatment assignment did not modify the effect of Lp-PLA$_2$-A on the given outcome ($p = 0.32$ for the treatment by Lp-PLA$_2$-A interaction). Using a threshold Lp-PLA$_2$-A level of 225 nmol/min/mL, we found that the patient group with Lp-PLA$_2$-A at or above this level had a 30% increased risk of the primary endpoint (adjusted HR 1.30, 95% CI 1.03–1.63, $p = 0.026$). Similar results were found for ischemic stroke alone (table e-2).

For the test of the goodness of the multivariable model fit, we found that neither the quadratic ($p = 0.86$) nor the cubic ($p = 0.62$) trend of Lp-PLA$_2$-A

Table 3 Lp-PLA$_2$-A levels by patient characteristics

Variable	No.	Mean (95% CI), nmol/min/mL	p Value
Age, y			0.0472
<62	1,496	207.2 (204.2–210.2)	
≥62	1,525	211.4 (208.5–214.4)	
Sex			<0.0001
Female	1,020	199.7 (196.1–203.3)	
Male	2,001	214.2 (211.7–216.8)	
BMI			0.0112
Underweight	154	196.1 ± 56.1	
Normal	1,683	209.2 ± 58.5	
Overweight	1,184	211.2 ± 59.2	
Smoking			0.0024
No or former smoker	2,031	207.1 (204.5–209.6)	
Current smoker	990	214.0 (210.3–217.6)	
History of stroke			0.0923
No	2,443	208.5 (206.1–210.8)	
Yes	578	213.0 (208.2–217.8)	
History of TIA			0.1307
No	2,925	209.6 (207.5–211.8)	
Yes	96	200.4 (188.7–212.2)	
History of hypertension			0.4005
No	1,054	210.6 (207.0–214.1)	
Yes	1,967	208.7 (206.1–211.3)	
History of diabetes			0.9029
No	2,401	209.3 (206.9–211.6)	
Yes	620	209.6 (205.0–214.2)	
History of hyperlipidemia			0.5900
No	2,705	209.1 (206.9–211.4)	
Yes	316	211.0 (204.5–217.5)	
History of myocardial infarction			0.0209
No	2,966	209.0 (206.9–211.1)	
Yes	55	227.5 (211.9–243.0)	
History of angina			0.1985
No	2,922	209.6 (207.5–211.7)	
Yes	99	201.9 (190.3–213.4)	
History of heart failure			0.5812
No	2,967	209.3 (207.1–211.4)	
Yes	54	213.7 (198.0–229.4)	
Recruit event			0.1832
Minor stroke	2,217	210.2 (207.7–212.6)	
TIA	804	207.0 (202.9–211.0)	
ABCD^2 score			0.1587
4–5	661	205.6 (201.1–210.1)	
6–7	143	213.2 (203.6–222.8)	

Continued

level was found to be associated with the primary endpoint, which meant that the model was constructed successfully.

Interaction between LDL-C and Lp-PLA$_2$-A. LDL-C levels were available in a subset of 2,936 patients. Mean LDL-C was 3.22 (SD: 1.07) and median LDL-C was 3.12 (IQR: 2.49–3.82). LDL-C and Lp-PLA$_2$-A were highly correlated (Pearson r = 0.36, $p < 0.0001$). In univariate analysis, LDL-C was associated with the primary endpoint (HR 1.14, 95% CI 1.02–1.27, $p = 0.025$). When LDL-C was entered into the multivariable model, the association between Lp-PLA$_2$-A and the primary endpoint was attenuated and was no longer significant (adjusted HR 1.04, 95% CI 0.97–1.11). Analysis comparing the association between Lp-PLA2-A, used as a categorical or continuous variable, and the primary endpoint stratified by LDL-C above or below the median LDL-C level showed no significant difference between those with high compared with low LDL-C (table 5).

DISCUSSION Considerable data support an association between Lp-PLA$_2$ measured in clinically stable patients and the long-term risk of stroke and other vascular events. In a pooled, collaborative analysis of 79,036 participants in 32 separate prospective studies, Lp-PLA$_2$-A and mass were both associated with a continuous increased risk of stroke and myocardial infarction.[4] Much less is known about the short-term risk of recurrence associated with Lp-PLA$_2$ levels drawn in the setting of an acute vascular event. Several small studies have examined Lp-PLA$_2$ levels measured in the acute period after TIA or stroke. For example, a US study of patients with acute TIA (n = 167) found that elevated Lp-PLA$_2$ activity and mass were both associated with a large vessel TIA etiology, and that Lp-PLA$_2$-A was associated with early recurrent stroke or death.[5] Similar findings were reported in a Spanish cohort with acute TIA, with Lp-PLA$_2$-A being associated both with large vessel disease and with early recurrent cerebrovascular events within 7 and 30 days.[6] A somewhat larger study including patients with both acute stroke and TIA found Lp-PLA$_2$-A to be associated with recurrent events at 6 months.[11] The results of the present study are consistent with these prior data. Lp-PLA$_2$-A level was significantly associated with the primary endpoint such that the risk of recurrence increased 7% for every 30 nmol/min/mL increase of Lp-PLA$_2$-A.

In contrast, 2 studies examining Lp-PLA$_2$-A measured in the setting of acute coronary syndromes (ACS) did not find an association with outcome. In the Myocardial Ischemia Reduction with Aggressive

Table 3 Continued

Variable	No.	Mean (95% CI), nmol/min/mL	p Value
Treatment			0.7168
Aspirin monotherapy	1,517	209.7 (206.8–212.7)	
Clopidogrel + aspirin	1,504	208.9 (206.0–211.9)	

Abbreviations: BMI = body mass index; CI = confidence interval; Lp-PLA_2-A = lipoprotein-associated phospholipase A_2 activity.

Cholesterol Lowering (MIRACL) trial, there was no relationship between baseline Lp-PLA_2-A and vascular events within 16 weeks.[12] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, there was no relationship between baseline Lp-PLA_2-A and recurrent events over an average of 2 years of follow-up.[13] There are important differences between the TIA/minor stroke and ACS populations, as well as differences in individual studies, which might account for these discrepant findings. Stroke and TIA have heterogeneous causes, ranging from cardioembolism to large vessel atherosclerotic stenosis to small vessel disease, in contrast to ACS, which has a more homogeneous pathophysiology. Risk of recurrent events is dramatically higher in stroke and TIA due to large vessel stenosis as opposed to other causes.[14] As a marker of unstable atherosclerotic plaque, Lp-PLA_2-A may therefore be identifying those TIA and stroke patients with a large vessel mechanism and thus higher risk. In contrast, as most patients with ACS have large vessel atherosclerotic disease with unstable plaque, the ability to discriminate risk among patients on this basis may be reduced. In addition, differences in the timing of blood sampling might be important, as Lp-PLA_2-A levels change dynamically early after a vascular event. In a study of longitudinal samples collected in the NOMAS (Northern Manhattan Study), Lp-PLA_2-A levels dropped about 10% in the days following acute ischemic stroke and about 30% following acute myocardial infarction.[15] Samples in the MIRACL study were obtained 24 to 96 hours after hospital admission, and in PROVE-IT within 10 days of the index event; in contrast, in CHANCE and other TIA/minor stroke studies, samples were obtained <48 hours from symptom onset.

Table 4 Multivariable analysis of factors associated with primary endpoint (ischemic stroke, MI, or death)

Variable	Hazard ratio (95% CI)	p Value
Age per 10 y	1.15 (1.03–1.28)	0.0138
Male	0.88 (0.69–1.12)	0.2963
BMI	1.03 (0.99–1.07)	0.0977
Systolic blood pressure per 20 mm Hg	1.20 (1.09–1.33)	0.0003
History of hypertension	1.23 (0.94–1.59)	0.1256
History of diabetes	1.42 (1.10–1.85)	0.0081
History of MI	0.14 (0.02–1.02)	0.0519
Dual antiplatelet	0.64 (0.51–0.81)	0.0002
Lp-PLA_2-A per 30 nmol/min/mL	1.07 (1.01–1.13)	0.0319

Abbreviations: BMI = body mass index; CI = confidence interval; Lp-PLA_2-A = lipoprotein-associated phospholipase A_2 activity; MI = myocardial infarction.

The observed association of Lp-PLA_2-A with short-term vascular risk in our cohort is consistent with the hypothesis that Lp-PLA_2-A, as measured in peripheral blood, may reflect plaque instability and therefore early risk of recurrence. This suggests that therapies designed to suppress Lp-PLA_2 might have a role in the treatment of acute cerebrovascular disease.[16] Statin therapy significantly reduces Lp-PLA_2 levels, and this could represent one potential biological mechanism by which early administration of statin therapy might reduce the risk of recurrence in patients with acute TIA or minor stroke. However, the specific Lp-PLA_2 inhibitor darapladib has been tested in patients with coronary artery disease in 2 recently published large randomized studies (SOLID-TIMI and STABILITY), neither of which demonstrated benefit.[17,18] The results of these trials suggest the possibility that Lp-PLA_2 may be merely a marker of unstable plaque rather than having an important mechanistic role in clinical atherothrombotic events.

We found a strong correlation between LDL-C and Lp-PLA_2, and the association between Lp-PLA_2 and vascular events was attenuated after adjustment for LDL-C. Some prior studies have suggested that the association between Lp-PLA_2 and vascular events is strongest in patients with lower LDL-C levels,[19] whereas others have found no significant difference in the predictive value of Lp-PLA_2 based on baseline LDL-C level.[20] In our cohort, there was no evidence of variability in the association between Lp-PLA_2 and vascular risk based on baseline LDL-C.

Our study has several limitations. First, data on specific TIA/stroke mechanisms were not available, so we were not able to examine whether Lp-PLA_2-A levels correlated with a large vessel atherosclerotic mechanism as has been reported in earlier studies. Second, we did not have detailed information on baseline and subsequent statin use. Statin therapy both lowers Lp-PLA_2 levels and has been associated with an attenuation of the risk associated with elevated Lp-PLA_2-A.[16] For instance, in the JUPITER trial, rosuvastatin lowered Lp-PLA_2-A levels by 33%; while there was a significant relationship between Lp-PLA_2-A and cardiovascular events in patients randomized to placebo, there was

Table 5 Multivariable analysis of factors associated between Lp-PLA$_2$-A category or Lp-PLA$_2$-A level and the primary endpoint stratified by LDL-C above or below the median of LDL-C level

	Lp-PLA$_2$-A category				Lp-PLA$_2$-A level			
	LDL-C < median		LDL-C ≥ median		LDL-C < median		LDL-C ≥ median	
Variable	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Age per 10 y	1.15 (0.97–1.36)	0.1195	1.13 (0.97–1.31)	0.1142	1.15 (0.97–1.36)	0.1172	1.13 (0.97–1.31)	0.1143
Male	0.78 (0.53–1.15)	0.2127	1.03 (0.75–1.41)	0.8692	0.78 (0.53–1.14)	0.2005	1.03 (0.75–1.41)	0.8705
BMI	1.02 (0.96–1.08)	0.5742	1.04 (0.99–1.10)	0.123	1.02 (0.96–1.08)	0.5825	1.04 (0.99–1.10)	0.1171
Systolic blood pressure per 20 mm Hg	1.22 (1.05–1.43)	0.0117	1.20 (1.05–1.36)	0.0077	1.22 (1.05–1.43)	0.0113	1.20 (1.05–1.37)	0.0071
History of hypertension	1.61 (1.04–2.48)	0.0316	1.07 (0.76–1.50)	0.6946	1.61 (1.04–2.48)	0.0312	1.08 (0.77–1.51)	0.6662
History of diabetes	1.27 (0.82–1.95)	0.2853	1.44 (1.03–2.01)	0.0337	1.27 (0.83–1.96)	0.2746	1.44 (1.03–2.01)	0.0341
Dual antiplatelet	0.66 (0.46–0.95)	0.0271	0.63 (0.46–0.86)	0.0036	0.66 (0.46–0.95)	0.027	0.63 (0.46–0.86)	0.0034
Lp-PLA$_2$-A ≥225 nmol/min/mL	1.19 (0.80–1.77)	0.384	1.18 (0.86–1.60)	0.3044				
Lp-PLA$_2$-A per 30 nmol/min/mL					1.05 (0.95–1.16)	0.318	1.04 (0.95–1.12)	0.3942

Abbreviations: BMI = body mass index; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$-A = lipoprotein-associated phospholipase A$_2$ activity.

no relationship in those receiving rosuvastatin.[21] Third, comparison with prior studies of Lp-PLA$_2$ may be limited by the different populations studied. The CHANCE trial was conducted exclusively in China, whereas most of the earlier data are derived from Western populations. Different patterns of atherosclerotic disease, for instance the greater prevalence of intracranial stenosis as opposed to extracranial stenosis in Asian populations, may limit extrapolation to other groups. Fourth, patients with a known cardioembolic source at presentation were excluded from enrollment in CHANCE, so the population of TIA/stroke patients in the present study may differ from that included in purely observational studies that had broader inclusion criteria.

Our results demonstrate an association between Lp-PLA$_2$-A measured in the acute period after TIA or minor stroke and the short-term risk of recurrent vascular events. This association remained significant after adjustment for traditional prognostic factors. Future studies to better understand the mechanistic link between Lp-PLA$_2$-A levels and early recurrence might lead to greater insight into the biological basis of early recurrent cerebrovascular events.

AUTHOR CONTRIBUTIONS

Jinxi Lin performed the experiments, interpreted the data, and wrote drafts of the manuscript. Hongwei Zheng interpreted the data and commented on drafts. Brett L. Cucchiara supervised the analysis, interpreted the data, and commented on drafts. Jiejie Li performed the experiments and interpreted the data. Xianhong Liang performed the experiments and interpreted the data. Xingquan Zhao and Chunxue Wang supervised the analysis. Hao Li and Michael T. Mullen conducted the statistical analyses and interpreted the data. S. Claiborne Johnston designed and supervised the analysis. Yilong Wang and Yongjun Wang formulated the research question and designed and supervised the analysis.

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DISCLOSURE

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