Lipoprotein-Associated Phospholipase A_2 and C-Reactive Protein for Risk-Stratification of Patients With TIA

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Background and Purpose—Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a marker of unstable atherosclerotic plaque, and is predictive of both primary and secondary stroke in population-based studies.

Methods—We conducted a prospective study of patients with acute TIA who presented to the ED. Clinical risk scoring using the $ABCD^2$ score was determined and Lp-PLA_2 mass ($LpPLA_2$-M) and activity ($LpPLA_2$-A) and high-sensitivity C-reactive protein (CRP) were measured. The primary outcome measure was a composite end point consisting of stroke or death within 90 days or identification of a high-risk stroke mechanism requiring specific early intervention (defined as ≥50% stenosis in a vessel referable to symptoms or a cardioembolic source warranting anticoagulation).

Results—The composite outcome end point occurred in 41/167 (25%) patients. $LpPLA_2$-M levels were higher in end point–positive compared to –negative patients (mean, 192±48 ng/mL versus 175±44 ng/mL, $P=0.04$). $LpPLA_2$-A levels showed similar results (geometric mean, 132 nmol/min/mL, 95% CI 119 to 146 versus 114 nmol/min/mL, 95% CI 108 to 121, $P=0.01$). There was no relationship between CRP and outcome ($P=0.82$). Subgroup analysis showed that both $LpPLA_2$-M ($P=0.04$) and $LpPLA_2$-A ($P=0.06$) but not CRP ($P=0.36$) were elevated in patients with >50% stenosis. In multivariate analysis using cut-off points defined by the top quartile of each marker, predictors of outcome included $LpPLA_2$-A (OR 3.75, 95% CI 1.58 to 8.86, $P=0.003$) and $ABCD^2$ score (OR 1.30 per point, 95% CI 0.97 to 1.75, $P=0.08$).

Conclusion—Many patients with TIA have a high-risk mechanism (large vessel stenosis or cardioembolism) or will experience stroke/death within 90 days. In contrast to CRP, both Lp-PLA_2 mass and activity were associated with this composite end point, and $LpPLA_2$-A appears to provide additional prognostic information beyond the $ABCD^2$ clinical risk score alone. **(*Stroke*. 2009;40:00-00.)**

Key Words: transient ischemic attack ■ lipid and lipoprotein metabolism ■ secondary prevention

Despite the development of clinical risk prediction scores such as the $ABCD^2$ score, risk stratification of patients with TIA remains imperfect.[1,2] Biomarkers indicating the presence of unstable atherosclerotic plaque might represent a useful supplement to improve risk prediction. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and C-reactive protein are 2 candidate markers which have been associated with inflammation and plaque instability in histopathologic studies of the carotid arteries.[3,4] The primary aims of this study were to determine whether measurement of $LpPLA_2$ and high-sensitivity C-reactive protein (CRP) could improve risk-stratification of patients with TIA and to examine the relationship between these blood markers and TIA mechanism.

Typically, risk stratification schemes for patients with TIA have been tested in observational studies evaluating subsequent stroke occurrence. However, these studies occur on a background of variable diagnostic testing and therapeutic intervention which alter patient outcome.[5] Ideally, risk stratification schemes would identify both patients who will experience stroke and those with a high-risk cause for which specific early intervention (such as carotid endarterectomy or initiation of anticoagulant therapy) is warranted and would alter subsequent stroke risk. For the purposes of this study, therefore, the primary outcome measure was a composite end point consisting of: (1) the presence of a treatment-emergent mechanism for which a specific therapy other than an antiplatelet agent is indicated (ie, >50% large vessel stenosis or cardioembolic source warranting anticoagulation) or (2) occurrence of subsequent stroke or death despite currently available standard therapy.

Methods

We conducted a prospective study of patients with suspected TIA evaluated within 48 hours of symptom onset. TIA was defined as acute onset of focal cerebral or monocular symptoms lasting <24 hours and thought to be attributable to a vascular cause in the opinion of the neurologist evaluating the patient. All patients for whom there

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was sufficient clinical suspicion to justify diagnostic testing for a neurovascular cause were eligible for inclusion in this study, with 2 exceptions. First, patients with severe or terminal illness likely to preclude full evaluation and follow-up were excluded. Second, patients taking warfarin with an INR ≥1.5 were excluded because of concerns that therapeutic anticoagulation might confound measurement of marker levels. A detailed description of our study methodology has been published previously.[6] Informed consent was obtained from all subjects and the protocol was approved by our local Institutional Review Board.

On enrollment, a standardized case report form was completed collecting data on clinical features of the TIA, medical history, and examination findings. Subsequently, all relevant diagnostic testing was recorded and an assessment of the presumed cause of the TIA was determined at hospital discharge and 90-day follow-up. Clinical events and therapeutic interventions were determined at hospital discharge and 90-day follow-up. The primary outcome measure was a composite end point including stroke or death within 90 days, ≥50% stenosis in a vessel referable to symptoms, or a cardioembolic source warranting anticoagulation. This outcome measure was prespecified as the primary end point at the time of study conception and design, before patient enrollment or data analysis.

Findings on early MRI (when performed) were also evaluated, though MRI evaluation was not a study requirement, and patient selection for MRI was not systematic but based on individual clinician practice and resource availability. Patients with acute infarction on diffusion weighted imaging (DWI) were classified as DWI+, and those without infarction as DWI−.

Determination of $ABCD^2$ risk score was performed in a manner identical to that reported by the originators of this score.[1] This 7-point score incorporates age (≥60 years=1 point), blood pressure (SBP ≥140 mm Hg or DBP ≥90 mm Hg=1 point), clinical features (unilateral weakness=2 points; speech disturbance without weakness=1 point; other symptoms=0 points), duration of symptoms (≥60 minutes=2 points; 10 to 59 minutes=1 point; <10 minutes=0 points), and history of diabetes (1 point). Although the actual $ABCD^2$ score was computed retrospectively, all components of the score were prospectively collected as part of the described data set. Categorization of $ABCD^2$ scores into 3 groups (0 to 3, 4 to 5, 6 to 7) were used as was done in the initial $ABCD^2$ publication.[1]

Collection of all clinical and radiographic information, and final determination of outcome category, was performed blinded to results of biomarker testing.

Blood Sampling

Venous blood samples were obtained under sterile conditions. Samples were collected in tubes containing 3.2% sodium citrate and immediately centrifuged at 1300*g* for 10 minutes. Plasma was then extracted and additionally centrifuged at 10 000*g* for 3 minutes. Samples were promptly frozen at −80°C until testing was performed.

Lp-PLA_2 mass ($LpPLA_2$-M) was assayed using a microplate-based enzyme linked immunosorbent assay (diaDexus Inc). Lp-PLA_2 activity ($LpPLA_2$-A) was measured with a colorimetric activity method (diaDexus Inc). This method measures a kinetic rate over time and verification of the linearity of the kinetics is necessary to ensure accurate measurement; samples with nonlinear kinetics represent unreliable measurements attributable to interference in the assay and results are not reported. High-sensitivity C-reactive protein (CRP) was measured on a Hitachi 917 analyzer (Roche Diagnostics) using a turbidimetric immunoassay (Kamiya K assay, Kamiya Biomedical Corp). All assays were performed at a central laboratory at diaDexus Inc with laboratory personnel blinded to all clinical data. Twenty percent of $LpPLA_2$-M and $LpPLA_2$-A samples were tested in duplicate, and the coefficient of variation was <10% in 97% of $LpPLA_2$-A samples and 92% of $LpPLA_2$-M samples. All of the $LpPLA_2$-M and $LpPLA_2$-A samples had coefficients of variation of <15%.

Statistical Analysis

Groups of patients were compared with χ^2 tests, Wilcoxon ranked sum tests, or logistic regression, as indicated. In analyses using $LpPLA_2$-A as a continuous variable, log-transformed values were used given the nonnormal distribution of $LpPLA_2$-A. For descriptive purposes, geometric means of $LpPLA_2$-A levels are presented which closely represent the mean of a ln sample.[7] Median and intraquartile range were used for analysis of CRP, as this was not normally distributed even after log transformation. Separate analysis of the association between marker levels and outcome category was performed using (1) threshold levels defined by the top quartile of levels within the study population, and (2) using previously reported threshold levels for general cardiovascular risk for $LpPLA_2$-M and CRP (there is no currently accepted threshold value for $LpPLA_2$-A). Both 200 ng/mL and 235 ng/mL have been recommended as appropriate threshold levels for $LpPLA_2$-M.[8,9] We therefore included analysis using both of these cut points. For CRP, a threshold value of 300 μg/dL has been recommended.[10] For both $LpPLA_2$-M and CRP, the threshold values used are recommended for improving classification of general cardiovascular risk, and not specifically for risk-stratification after TIA. Odds ratios (OR) and 95% confidence intervals were reported for all comparisons when appropriate. C-statistics (area under receiver-operator characteristic curves) were calculated to estimate predictive discriminatory ability. All tests were 2-sided. An association was considered significant if $P<0.05$. All statistical analyses were performed using STATA version 10.0 (Stata Corporation).

Table 1. Patient Characteristics

Age, mean (SD)	62±14
Systolic BP, mean (SD)	153±28
Diastolic BP, mean (SD)	83±15
Hypertension	107 (64%)
Clinical features	
Unilateral weakness	60 (36%)
Speech disturbance without weakness	40 (24%)
Other	67 (40%)
Duration of symptoms	
≥60 minutes	101 (60%)
10 to 59 minutes	42 (25%)
<10 minutes	24 (14%)
Diabetes	36 (22%)
Male sex	75 (45%)
CAD/MI	21 (13%)
Hyperlipidemia	68 (41%)
Prior stroke	29 (17%)
Peripheral vascular disease	8 (5%)
Current smoker	27 (16%)
Migraine	17 (10%)
Time onset to enrollment, hours (mean)	26.4±12.7

Results

From November 2002 to June 2007, 167 patients were enrolled. Three patients could not be reached for follow-up at 90 days; 1 of these was diagnosed with carotid occlusion at presentation and thus included in the end point–positive group, and the other 2 had no identified cause of their TIA and an unremarkable hospital course and were included in the end point–negative group. Characteristics of enrolled patients are shown in Table 1.

Time from symptom onset to blood sampling was a mean of 26.2±12.7 hours. Overall, the composite end point oc-

Table 2. Levels of Lp-PLA$_2$ Mass (LpPLA$_2$-M), Lp-PLA$_2$ Activity (LpPLA$_2$-A), and High-Sensitivity C-Reactive Protein (CRP) by Selected Characteristics of the Patient Population

	LpPLA$_2$-M (ng/mL) Mean±SD (n=162)	*P*	LpPLA$_2$-A (nmol/min/ml) GEM (n=136)	*P*	CRP (ug/dL) Median (IQR) (n=162)	*P*
Overall	179±46		118 (113–124)		120 (41–351)	
Outcome category		0.04		0.01		0.82
Endpoint negative	175±44		114 (108–121)		121 (39–369)	
Endpoint positive	192±48		132 (119–146)		116 (50–322)	
ABCD^2 score		0.64		0.17*		0.14†
0 to 3	183±43		123 (114–132)		99 (37–216)	
4 to 5	178±44		119 (111–127)		128 (40–339)	
6 to 7	174±57		105 (87–126)		392 (49–934)	
Large vessel stenosis						
Present	197±40	0.04	132 (118–148)	0.06	167 (100–409)	0.36
Absent	176±40		116 (110–122)		111 (40–351)	
Cardioembolism		0.37		0.65		0.28
Present	190±60		123 (102–149)		62 (42–221)	
Absent	178±44		118 (112–124)		124 (40–360)	
Stroke/death		0.82		0.001		0.64
Present	183±38		178 (132–240)		95 (47–181)	
Absent	179±46		116 (111–122)		121 (41–369)	
MRI DWI		0.84		0.15		0.31
DWI+	181±47		126 (108–147)		145 (46–433)	
DWI−	175±46		112 (104–121)		122 (37–483)	

Variables were tested with χ^2 tests or Wilcoxon ranked sum tests as appropriate. **P* value based on ANOVA; †*P* value based on Kruskal–Wallis test.

curred in 41 patients (25%). Clinical events occurred in 8 patients (5%), including 5 strokes and 3 deaths; 6 of these patients also had a high-risk cause of TIA. Four of the 5 strokes occurred within 48 hours after TIA onset; the other stroke occurred 9 days after TIA. Two of 3 deaths were attributable to cardiac disease; the cause of death in the remaining case was unknown. A ≥50% stenosis in a vessel referable to the patients' symptoms was found in 25 patients (15%), of which 21 were attributable to atherosclerosis and 4 attributable to arterial dissection, and a cardioembolic source warranting anticoagulation was found in 14 patients (8%). Increasing ABCD^2 scores were associated with increasing risk (*P* for trend=0.017). When comparing groupings of ABCD^2 scores (0 to 3, 4 to 5, 6 to 7) and outcome, higher scores were associated with greater risk (OR 1.9 per group, 95% CI 1.1 to 1.3, *P*=0.018).

Blood samples for analysis were available for 162 subjects; in 4 subjects blood samples could not be obtained, and 1 subject had insufficient sample volume for testing. Results for LpPLA$_2$-M and CRP were available for 162 subjects. Results for LpPLA$_2$-A were available for 136 patients; 26 samples had nonreportable results because of interference in the assay. Table 2 summarizes the results of biomarker testing. LpPLA$_2$-M levels were normally distributed and were increased in end point–positive compared to end point–negative patients (mean, 192 ng/mL versus 175 ng/mL, *P*=0.04). LpPLA$_2$-A levels were normally distributed when log-transformed and showed similar results (geometric mean, 132 nmol/min/mL versus 114 nmol/min/mL, *P*=0.01). There was no relationship between CRP and outcome (median 116 μg/dL versus 121 μg/dL, *P*=0.82). Subgroup analysis showed that both LpPLA$_2$-M (*P*=0.04) and LpPLA$_2$-A (*P*=0.06) but not CRP (*P*=0.36) were elevated in patients with large vessel stenosis. LpPLA$_2$-A levels were also increased in patients with stroke or death (*P*=0.001). There was no relationship between any of the markers and presence of a cardioembolic source, MRI DWI lesion, or ABCD^2 score.

In univariate analysis using cut-off points defined by the top quartile of each marker (LpPLA$_2$-M ≥208 ng/mL, LpPLA$_2$-A ≥143 nmol/min/mL, CRP ≥351 μg/dL), predictors of outcome category included ABCD^2 score (OR 1.37 per point, *P*=0.02) and LpPLA$_2$-A (OR 3.68, *P*=0.003) with a trend for LpPLA$_2$-M (OR 2.11, *P*=0.06). In multivariate analysis, LpPLA$_2$-A remained predictive of outcome (OR 3.75, 95% CI 1.58 to 8.86, *P*=0.003) and there was a trend for ABCD^2 score (OR 1.30 per point, 95% CI 0.97 to 1.75, *P*=0.08). The C-statistic for ABCD^2 score alone predicting outcome was 0.63; this improved to 0.68 with LpPLA$_2$-A added to the model.

Exploratory analysis of LpPLA$_2$-M and LpPLA$_2$-A dichotomized by top quartile versus bottom 3 quartiles stratified by ABCD^2 category is presented in Table 3. The additive predictive value of both LpPLA$_2$-M and LpPLA$_2$-A seemed to be greatest in patients classified as moderate risk by the ABCD^2 clinical risk score. Similar analysis for CRP is presented in Table 4, in which there was no additive predictive value within any ABCD^2 score category. Similar results were seen using the previously reported threshold levels. For

Table 3. No. of Patients With Composite End Point in ABCD^2 Categories Stratified by Lp-PLA$_2$ Activity (LpPLA$_2$-A, nmol/min/ml) and Lp-PLA$_2$ Mass (LpPLA$_2$-M, ng/ml)

	No. With End Point/Total (%)					
ABCD^2 score	LpPLA$_2$-A<143	LpPLA$_2$-A≥143	*P*	LpPLA$_2$-M<208	LpPLA$_2$-M≥208	*P*
0 to 3	5/36 (13.9%)	2/11 (18.2%)	0.66	8/43 (18.6%)	2/16 (12.5%)	0.71
4 to 5	10/53 (18.9%)	10/19 (52.6%)	0.008	12/62 (19.4%)	10/21 (47.6%)	0.02
6 to 7	3/13 (23.1%)	3/4 (75.0%)	0.12	5/15 (33.3%)	3/5 (60.0%)	0.35

instance, using the threshold value of 200 ng/mL for LpPLA$_2$-M, there was a trend toward LpPLA$_2$-M predicting outcome category (21% end point–positive with LpPLA$_2$-M <200 ng/mL versus 32% end point–positive with LpPLA$_2$-M ≥200, P=0.12). Using the previously reported threshold level of 235 ngm/mL, LpPLA$_2$-M was significantly predictive of outcome category (22% end point–positive with LpPLA$_2$-M <235 versus 47% end point–positive with LpPLA$_2$-M ≥235, P=0.02). Using the reported threshold level of 300 μg/dL for CRP, there was no association with outcome category (28% end point–positive with CRP <300 μg/dL versus 28% end point–positive with CRP ≥300, P=0.99).

Discussion

A number of prior studies assessing the long-term prognostic value of Lp-PLA$_2$ mass and activity have shown both markers to be predictive of future stroke, both in patients with and without a previous history of cerebrovascular disease.[11–14] An additional study assessing shorter-term risk (at 6 months after an index stroke or TIA) found Lp-PLA$_2$-A to be a significant predictor of recurrent stroke.[15] In contrast, in the VA-HIT study, Lp-PLA$_2$-A was not predictive of stroke, though it was predictive of myocardial infarction and vascular death, whereas Lp-PLA$_2$-M was strongly predictive of subsequent stroke.[16,17]

Our results suggest a potential role for measurement of both Lp-PLA$_2$ mass and activity to improve short-term risk stratification of patients with TIA. This is particularly true for patients classified as moderate-risk using the ABCD^2 clinical risk score (score of 4 to 5), in which there was a substantially greater likelihood of subsequent stroke or death or harboring a high-risk TIA mechanism among patients in the highest quartile of LpPLA$_2$-M and LpPLA$_2$-A levels. This may also be the case for patients in the highest risk ABCD^2 category (scores of 6 to 7), although the number of patients available for analysis was too small to reach firm conclusions. Conversely, it does not appear that Lp-PLA$_2$ adds prognostic value to patients classified as low risk by ABCD^2 scoring. In addition to our prespecified composite end point, LpPLA$_2$-A was also significantly associated with subsequent stroke or death, possibly suggesting that it is a more powerful predictor of short-term clinical events than LpPLA$_2$-M, although this conclusion is limited by the smaller number of patients for which LpPLA$_2$-A could be tested.

Table 4. No. of Patients With Composite End Point in ABCD^2 Categories Stratified by High-Sensitivity CRP (CRP, ug/dL) Levels

ABCD^2 Score	No. With End Point/Total (%)		
	CRP<351	CRP≥351	*P*
0 to 3	9/49 (18.4%)	1/10 (10.0%)	1.0
4 to 5	17/63 (27.0%)	5/20 (25.0%)	1.0
6 to 7	5/9 (55.6%)	3/11 (27.3%)	0.36

It appears that the most likely basis by which Lp-PLA$_2$ predicts stroke is as a biomarker of unstable atherosclerotic plaque. A recent analysis of plaque specimens obtained after carotid endarterectomy demonstrated increased Lp-PLA$_2$ expression in patients with recent TIA or stroke compared to asymptomatic patients, and a correlation between Lp-PLA$_2$ content and markers of oxidative stress, inflammation and instability.[3] The results of our study provide further support for the role of Lp-PLA$_2$ as a biomarker of unstable atherosclerotic plaque. Both Lp-PLA$_2$ mass and activity were significantly associated with symptomatic >50% large vessel stenosis, but not with cardioembolism, consistent with a specific role in atherosclerotic disease.

Unlike Lp-PLA$_2$, we did not find CRP useful for risk stratification of patients with TIA. The role of CRP in predicting recurrent events in patients with cerebrovascular disease is controversial.[18] In a cohort of 467 patients with ischemic stroke from the Northern Manhattan Stroke Study, CRP was not associated with recurrent stroke or the composite of stroke, MI, and vascular death, but was associated with mortality.[11] In several smaller cohorts of patients with acute ischemic stroke, CRP has been predictive of recurrent vascular events or death, but with variable results depending on the timing of CRP measurement.[19–21] We are aware of only 1 study that evaluated CRP exclusively in patients with acute TIA. In this study, 135 patients with acute TIA were followed up for one year, and an association between CRP and risk of recurrent ischemic events was found.[22] However, the supplemental value of CRP measurement in addition to clinical risk scoring was not assessed, and given the longer time of follow-up, these results are less applicable to early risk stratification.

Strengths of our study include its prospective design, detailed follow-up and data collection, and patient population reflective of the type of patients in whom a biomarker for risk-stratification would most likely be used. The enrollment of only patients with TIA also largely eliminates the confounding effect of stroke severity on marker levels, which has been shown to be a relevant concern with CRP measurement, although not with LpPLA$_2$.[11] There are also some limitations to our study, most notably the sample size and small number of clinical events. Additionally, the effect of the timing of marker measurement in relation to TIA onset remains uncertain. One study evaluating stroke patients demonstrated stability of inflammatory biomarkers, including CRP, over

multiple time points within the first month after stroke onset, suggesting this may not be a major concern.[23] To our knowledge, similar data are not currently available for Lp-PLA_2 however.

In conclusion, our results suggest a potential clinical role for measurement of Lp-PLA_2, but not CRP, for short-term risk stratification of patients with acute TIA. Further, our results support the idea that Lp-PLA_2 reflects the presence of unstable atherosclerotic plaque.

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Disclosures

None.

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