Lipoprotein-Associated Phospholipase A_2 and Risk of Stroke

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Stroke is the second-leading cause of death worldwide and is a disabling disease of both older and younger adults. Stroke is also among the most highly preventable disorders because there are well-defined risk factors and preventatives. The establishment of new risk markers or factors for stroke risk assessment provides a new avenue for stroke prevention. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme that hydrolyzes oxidized phospholipids, releasing lysophosphatidylcholine, which has proinflammatory properties thought to be involved in the development of atherosclerosis and plaque rupture. In 2005, the Lp-PLA_2 blood test was approved by the US Food and Drug Administration (FDA) for assessing the risk of ischemic stroke and coronary artery disease. In epidemiologic studies, low-density lipoprotein cholesterol and other lipid factors have not been shown to be consistent predictors of stroke risk. Lp-PLA_2 measures, on the other hand, have shown a consistent association with stroke risk, conferring about a 2-fold increase in stroke occurrence. This relation has been studied in both first and recurrent stroke and is reviewed in this article. Importantly, a recent study has now shown that Lp-PLA_2 may increase the area under the curve beyond that of traditional cardiovascular risk factors and C-reactive protein. Therefore, Lp-PLA_2 determination may provide a pivotal opportunity to appropriately classify previously misclassified persons who are actually at high risk of stroke and in need of aggressive stroke intervention. **(Am J Cardiol 2008;101[suppl]:34F–40F)**

The global burden of stroke is immense. Stroke is the second-leading cause of death throughout the world. Of the 5.7 million annual stroke deaths worldwide, 87% occur in low- and middle-income countries. There are about 16 million first-ever strokes annually. Globally, there are >50 million stroke and transient ischemic attack (TIA) survivors, and ≥1 in 5 survivors will have another stroke within 5 years.[1]

In the United States, stroke is the third-leading cause of death, after heart disease and cancer. Stroke accounts for 6% of all deaths in the United States, with as many as 150,000 deaths per year.[2,3] There are about 780,000 new strokes annually, of which 600,000 are first attacks and 180,000 are recurrent strokes. There are approximately 5–6 million stroke survivors in the United States. Stroke is the leading cause of adult disability, with 15%–30% of stroke victims experiencing permanent disability and 20% requiring institutional care at 3 months after onset.[3] Not surprisingly, stroke is very costly, with recent estimates suggesting that the total direct and indirect costs are $62.7 billion.[3]

A number of populations are at risk for stroke. It should no longer be considered a disease confined to the elderly because about a third of stroke victims are <65 years of age.[4] Blacks have twice the risk of stroke compared with whites.[3] Hispanics are also at higher risk. Women are at higher risk of stroke mortality because, on average, they live longer than men. In adults, we have seen an exponential increase in stroke at age 55, with about a doubling of stroke risk for every 5- to 10-year period thereafter.[3] However, anyone is at risk for stroke if they have vascular risk factors, a history of other vascular diseases, such as myocardial infarction (MI) or peripheral vascular disease, or if there is a family history of stroke. Interestingly, stroke kills more than twice as many US women every year than breast cancer, and more women than men die of stroke.[5] Black women are also at an increased risk of stroke. Finally, it is estimated that 30% of strokes in women occur in those <65 years of age.[4]

Modifiable stroke risk factors include medical and lifestyle factors.[6] Lifestyle factors, such as smoking, heavy alcohol consumption, poor diet, and physical inactivity or lack of exercise, are also believed to elevate the risk of stroke. The important modifiable medical risk factors are hypertension, MI, atrial fibrillation, diabetes mellitus, blood lipids, and asymptomatic carotid stenosis. A history of TIA also elevates risk. The risk of stroke is 24%–29% 5 years after a TIA, which is comparable to the 25%–40% risk of having a second stroke after an initial stroke has occurred.[7–10]

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Table 1
Elevated lipoprotein-associated phospholipase A_2 (Lp-PLA_2) as a predictor of risk for first or recurrent ischemic stroke in 6 prospective studies*

Stroke Study	Year	Population
Atherosclerosis Risk in Communities (ARIC)[13]	2005	Healthy middle-aged adults
Rotterdam Study[14]	2005	Healthy men and women aged >55 yr
Northern Manhattan Stroke Study (NOMAS)[15]	2006	Recurrent stroke
Veterans Affairs HDL Intervention Trial (VA-HIT)[16]	2006	Recurrent CV events, low LDL and low HDL
Furie et al[17]	2007	Stroke 6 mo after TIA or first stroke
Women's Health Initiative Observational Study[18]	2007	Postmenopausal women

CV = cardiovascular; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TIA = transient ischemic attack.

* Published or presented in peer-reviewed articles, showing a consistent association between Lp-PLA_2 elevation and risk of stroke.

Lipoprotein-Associated Phospholipase A_2: An Independent Risk Factor

Approximately 87% of strokes are ischemic.[3] In 2005, the US Food and Drug Administration (FDA) approved a lipoprotein-associated phospholipase A_2 (Lp-PLA_2) blood test for assessing patients at risk for ischemic stroke. This blood test fills an important unmet need because low-density lipoprotein (LDL) and other lipid measurements may not be reliable predictors of stroke risk.[11] Inflammatory processes are involved in atherosclerosis and plaque rupture, which in turn contribute to the development of ischemic stroke.[12] Lp-PLA_2 is an enzyme that hydrolyzes oxidized phospholipids, releasing lysophosphatidylcholine, which has proinflammatory properties.[12] Recently, 6 important stroke studies looked at Lp-PLA_2 as a risk predictor for ischemic stroke (Table 1).[13–18]

The Atherosclerosis Risk in Community (ARIC) study was a case-cohort analysis under National Institutes of Health (NIH) sponsorship involving 4 communities in Maryland, Minnesota, Mississippi, and North Carolina. The study population was 45–64 years of age at entry and included 12,773 middle-aged healthy men and women, with both blacks and whites represented.[13] Lp-PLA_2 and C-reactive protein (CRP) were evaluated to determine their ability to predict future stroke. A total of 194 individuals experienced ischemic stroke; there were 766 noncases for comparison, and there was a 6- to 8-year follow-up period. LDL cholesterol levels were similar between the stroke cases and noncases (136.6 mg/dL and 132 mg/dL, respectively; 1 mg/dL = 0.02586 mmol/L). In contrast, elevated Lp-PLA_2 in the highest versus the lowest tertile was associated with a hazard ratio (HR) of 1.97 (95% confidence interval [CI], 1.16–3.33; $p = 0.01$) in relation to stroke.[13] These results were adjusted for age, sex, race, current smoking status, systolic blood pressure, diabetes, and levels of LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein (hs-CRP). Lp-PLA_2 was a predictor of stroke, regardless of LDL cholesterol level.

Because Lp-PLA_2 appears to be independent of traditional risk factors, including hypertension, the ARIC study also examined whether increased Lp-PLA_2 and increased blood pressure were synergistic risk factors for stroke (Figure 1). Tertiles of systolic blood pressure were <113 mm Hg, 113–130 mm Hg, and >130 mm Hg. Once patients were identified as having blood pressure values >130–139 mm Hg, their stroke risk was 3.5-fold higher than patients in the bottom tertile for systolic blood pressure. In general, at every level of blood pressure, an Lp-PLA_2 value above the median approximately doubled the risk for stroke. In the top tertile of systolic blood pressure, which included patients with prehypertension, stroke risk increased from 3.5-fold to almost 7-fold.[13]

CRP provided additive predictive power in assessing stroke risk, according to the ARIC study.[13] Generally, as the CRP level increases, there is some increase in the risk of stroke. When used together, Lp-PLA_2 and CRP have a synergism and substantially increase the risk of stroke approximately 11-fold when both are elevated in the top tertile versus both at low levels (ie, bottom tertile).

Thus, according to the ARIC study findings, Lp-PLA_2 levels are higher in individuals who have a stroke; lipid parameters were not predictive of stroke; elevated Lp-PLA_2 levels conferred an approximate 2-fold increase in risk independently of traditional risk factors, including lipids; and, elevated Lp-PLA_2 and elevated CRP levels were complementary beyond traditional risk factors in identifying individuals at greatly increased risk for ischemic stroke.

The Rotterdam Study was the first population-based study to assess the impact of elevated Lp-PLA_2 on stroke risk.[14] This case-cohort study included 7,983 participants with a 6.4-year median follow-up duration for incident ischemic stroke and a 7.2-year median follow-up duration for incident coronary artery disease (CAD). A random cohort of 1,820 subjects was selected for comparison. This group included 308 patients with CAD and 110 patients with incident ischemic stroke. Quartiles of Lp-PLA_2 activity were developed, and the lowest quartile served as the reference category. Lp-PLA_2 activity showed a graded, stepwise increased risk of stroke risk based on HR. Compared with the first quartile of Lp-PLA_2 activity, age- and sex-adjusted HRs for the second, third, and fourth quartiles were 1.06, 1.56, and 1.97, respectively (p for trend = 0.02). After an additional adjustment for cardiovascular risk factors, the corresponding HRs were 1.08, 1.58, and 1.97, respectively (p for trend = 0.03). The study found Lp-PLA_2 to be an independent predictor of stroke in the general population, including those patients with non-HDL cholesterol levels below the median. Total cholesterol and non-HDL cholesterol levels were identical in the stroke patients compared with the controls. Thus, the association between Lp-PLA_2

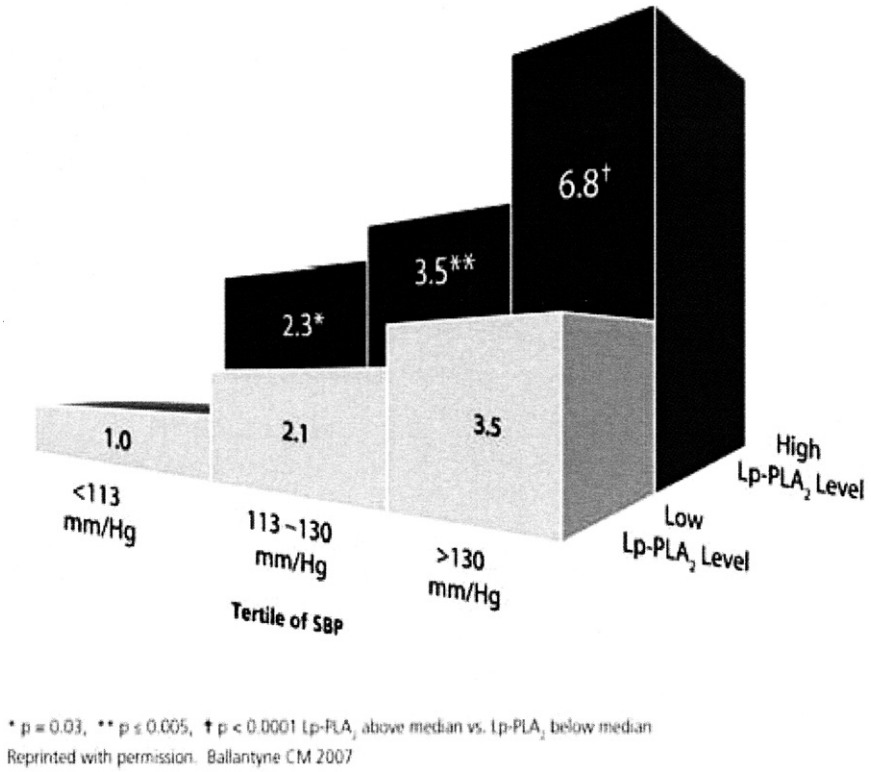

Figure 1. Risk ratios for ischemic stroke based on lipoprotein-associated phospholipase A_2 (Lp-PLA_2) level and systolic blood pressure (SBP). In the Atherosclerosis Risk in Community (ARIC) study of apparently healthy middle-aged men and women, Lp-PLA_2 increases the risk for ischemic stroke in borderline hypertension. An Lp-PLA_2 value above the median plus SBP in the top tertile (>130 mm Hg) further increased stroke risk by a cumulative 6- to 7-fold. *p = 0.03, **p ≤0.005, †p <0.0001 Lp-PLA_2 above median vs Lp-PLA_2 below median. (Reprinted with permission from *Ballantyne CM, 2007.*[13])

activity and stroke suggests that although Lp-PLA_2 is carried by LDL particles, it may convey a different risk. Furthermore, adjusting for baseline and incident MI and heart failure did not change the risk estimates, suggesting that these conditions are not intermediate pathways linking Lp-PLA_2 to stroke.[14]

The Northern Manhattan Stroke Study looked at how Lp-PLA_2 drawn at the time of initial stroke might predict the risk of recurrent stroke (90% of patients had blood drawn within 6 days of their initial stroke).[15] The study population was urban, multiethnic, and included 467 patients. Patients were ≥40 years of age, had a first ischemic stroke, and were identified by a surveillance system at Columbia University Medical Center and other local hospitals. The NIH stroke scale at baseline was categorized in the study subjects, and laboratory analyses were performed for both hs-CRP and Lp-PLA_2 levels. Laboratory personnel were blinded to patient status and outcomes. The primary outcome was recurrent stroke, and the secondary outcomes included recurrent stroke, MI, and vascular death.

Figure 2 shows the association between Lp-PLA_2 and recurrent stroke after a first ischemic stroke. CRP and Lp-PLA_2 appear to provide complementary prognostic information after a first ischemic stroke. The study showed that although CRP provided information about mortality risk, it was not a good predictor of stroke risk (HR, 0.67; 95% CI, 0.34–1.32). In contrast, Lp-PLA_2 conferred about a 2.1-fold increase in recurrent stroke risk (HR, 2.08; 95% CI, 1.04–4.18). In addition, only Lp-PLA_2 predicted the combined vascular end point of recurrent stroke, MI, or vascular death (HR, 1.86; 95% CI, 1.01–3.42). There was a nonsignificant trend toward Lp-PLA_2 being a more robust recurrent stroke predictor in patients with LDL cholesterol levels <130 mg/dL.[15]

Furie and colleagues[17] at the Massachusetts General Hospital studied Lp-PLA_2 activity in patients with acute ischemic stroke. The study compared 685 consecutive ischemic stroke/TIA patients and 586 stroke/TIA-free comparably aged control subjects from a primary care clinic. Major outcomes—early recurrent stroke and recurrent stroke, MI, or death—were measured at 6 months. Patients with stroke or TIA were tested at baseline (≤7 days after stroke) and 6 months after stroke (n = 148). Lp-PLA_2 enzyme activity was measured using a colorimetric activity method.[17] When baseline and 6-month Lp-PLA_2 levels were compared, the mean difference was not statistically significant, suggesting that there may not be suppression of Lp-PLA_2 after stroke as there may be after acute coronary syndromes. There were 23 recurrent strokes in the 6-month short-term follow-up period. However, when cases and controls were compared at baseline, Lp-PLA_2 activity levels were 139.7 and 130.2 nmol/min per mL, respectively, which

was statistically significant ($p < 0.001$). Lp-PLA_2 was a significant predictor of risk of early stroke recurrence at 6 months and remained significant after multivariate adjustment for diabetes, hypertension, hyperlipidemia, atrial fibrillation, smoking, and stroke subtype.

The Veterans Affairs HDL Intervention Trial (VA-HIT) examined Lp-PLA_2 as a predictor of major cardiovascular events in a high-risk secondary prevention population with a uniformly low LDL cholesterol and low HDL cholesterol (mean LDL cholesterol, 111 mg/dL; mean HDL cholesterol, 32 mg/dL) level.[19] The Lp-PLA_2 analysis was performed using plasma from 927 subjects attending the 6-month follow-up visit (cardiovascular event rate with placebo, 24.7%) and 1,267 subjects with placebo at baseline (cardiovascular event rate, 25.2%). CAD patients were randomized to gemfibrozil or placebo. In the overall study, the average age was 64 years. Baseline Lp-PLA_2 was obtained at the 6-month follow-up visit.

The VA-HIT study found that for every standard deviation increase in Lp-PLA_2, there was a significant association with an increase in *all* cardiovascular events (HR, 1.13; $p = 0.018$).[16] For stroke, the results were even more significant compared with coronary events, with a relative risk per standard deviation in Lp-PLA_2 mass concentration of 1.38 ($p = 0.002$).

Finally, the Women's Health Initiative (WHI) looked at the risk of ischemic stroke in postmenopausal women. It is the largest study to date to look at Lp-PLA_2 and risk of stroke. The WHI study was conducted at 40 clinical centers across the United States and was designed to examine the impact of a number of factors on many of the major causes of morbidity and mortality in postmenopausal women.[20] The study used a nested case-control design with all participants 50–79 years of age.[18] There was a total of 929 incident strokes and 935 matched controls. In this population, the risk of incident stroke was statistically significantly greater in study participants with elevated Lp-PLA_2 compared with controls ($p < 0.003$). The relative risk per standard deviation increase in the risk of ischemic stroke was 1.07 (95% CI, 1.01–1.14). This statistically significant association was driven by an increase in large-vessel stroke (HR, 1.34; 95% CI, 1.10–1.64) but not small-vessel stroke (HR, 1.02; 95% CI, 0.90–1.15). Interestingly, the relative risk per standard deviation of Lp-PLA_2 among current users of hormone therapy was 1.05 (95% CI, 0.95–1.17), and among nonusers, it was 1.10 (95% CI, 1.02–1.19).[18] There was no association between the risk of stroke and elevated levels of CRP, in contrast to previous smaller studies.

Perspectives on Lipoprotein-Associated Phospholipase A_2 in Clinical Practice

The 2006 American Stroke Association statement on cholesterol as a risk for stroke states that "plasma lipids and lipoproteins affect the risk of ischemic stroke, but the exact relationships are still being clarified. In general, increasing levels of total cholesterol are associated with higher rates of ischemic stroke. Low HDL is a risk factor for ischemic stroke in men, but more data are needed to determine the effect in women . . . ."[6] In the ARIC study of apparently healthy middle-aged persons, neither high LDL cholesterol nor low HDL cholesterol levels were reliable predictors of stroke risk. The investigators concluded that, "The relation of circulating cholesterol to ischemic stroke does not resemble its well-known relation to coronary artery disease."[11]

Thus, as a predictor for stroke, cholesterol measurements may be a less reliable risk factor, as demonstrated by a number of studies, including the Framingham Heart Study and the Honolulu Heart Study,[21] the Physicians Health Study,[22] and the ARIC Study.[11] In each case, there is a nonstatistically significant relation between cholesterol level and stroke risk. However, the use of statins may reduce stroke incidence. A number of studies demonstrated statistically significant reductions in stroke risk of 19%–48% through statin therapy, including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[23] the Cholesterol and Recurrent Events (CARE) study,[24] the Heart Protection Study (HPS),[25] the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study,[26] the Scandinavian Simvastatin Survival Study,[27] and the Collaborative Atorvastatin Diabetes Study (CARDS).[28] Perhaps, the statins affect stroke reduction through their pleiotropic anti-inflammatory actions.[29] This is quite consistent with the fact that statins reduce Lp-PLA_2 very significantly.

The question has lingered as to whether recurrent strokes can be prevented by statin administration in patients with no previous CAD. Most studies have addressed first stroke prevention and were conducted predominantly in patients with CAD. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study[30] investigated the impact of atorvastatin 80 mg/day on the risk of stroke in patients with prior stroke or TIA but no history of CAD. The study was a prospective multicenter international double-blind, randomized placebo-controlled trial. Patients in the study had ischemic stroke or TIA within 6 months and had modified ranking scores of <3 (functionally independent), with LDL cholesterol measurements of 100–190 mg/dL. The median follow-up period was almost 5 years.[30]

The primary end point was time to fatal or nonfatal stroke. There was a statistically significant 16% reduction in fatal or nonfatal stroke in the atorvastatin treatment group, with an adjusted HR of 0.84 (95% CI, 0.71–0.99; $p = 0.03$).

The secondary end point, time to any CAD event, was also reduced. Coronary events decreased by a full 42% in the atorvastatin treatment group, with an adjusted HR of 0.58 (95% CI, 0.46–0.73; $p < 0.001$). This was a surprising finding because patients who entered the trial had no overt history of CAD. However, as the old familiar adage goes, "Rotten in the basement, rotten in the attic." If there is vulnerable plaque in the coronary arteries, such plaque may also be present in the cerebral arteries and vice versa (Figure 3).

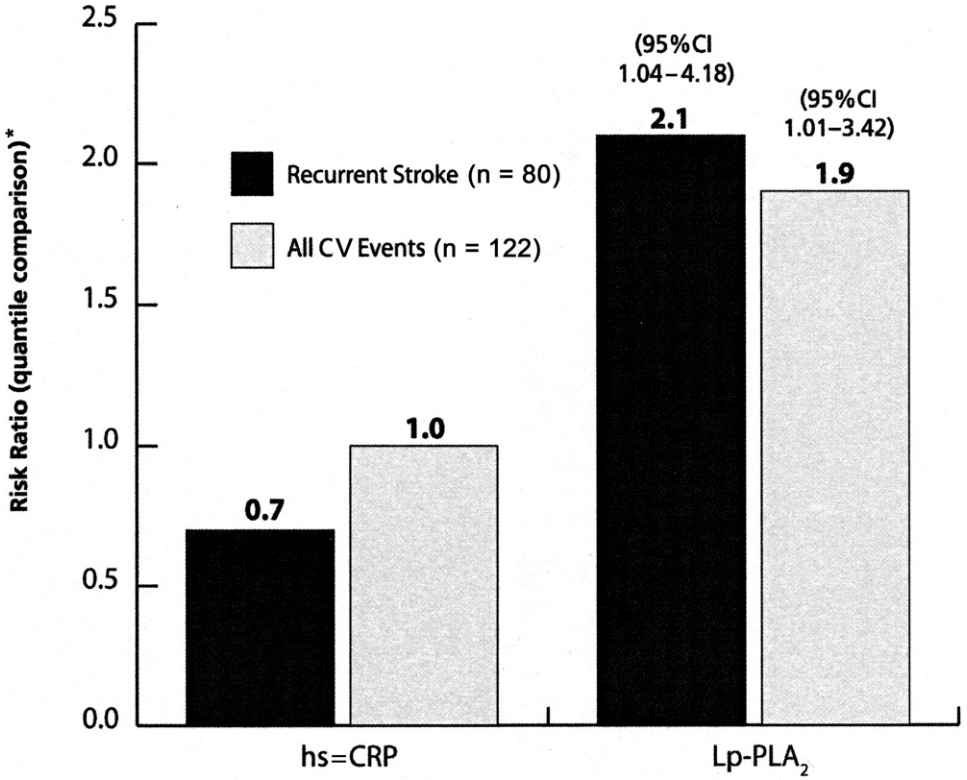

Figure 2. Association of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) with high risk of recurrent stroke after first ischemic stroke. Elevated Lp-PLA_2 drawn in the acute setting of first stroke in the Northern Manhattan Stroke Study (NOMAS) independently predicted a doubling of risk for recurrent stroke and almost a doubling of risk for any hard cardiovascular event, including myocardial infarction, stroke, or vascular death. In contrast, high-sensitivity C-reactive protein (hs-CRP) was not associated with risk for recurrent stroke or incidence of cardiovascular events (CV) after stroke. CI = confidence interval. *Adjusted for demographics, traditional risk factors, stroke severity, and both markers. (Adapted from *Arch Intern Med*.[15])

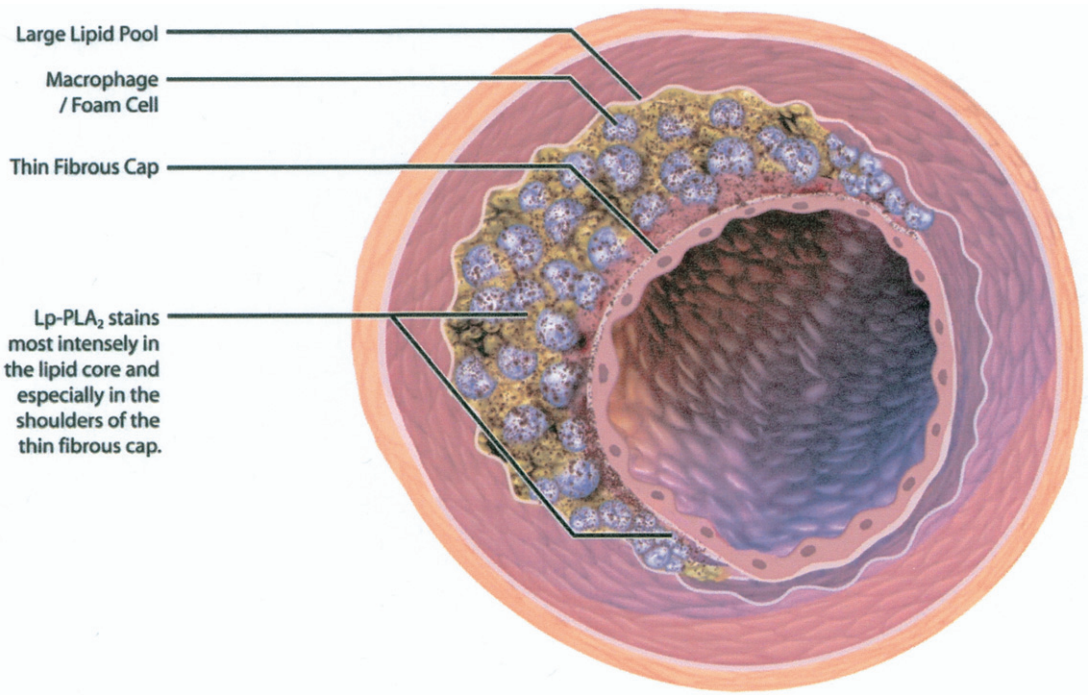

Figure 3. Expression of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in atherosclerotic carotid plaques. Tissue staining of carotid atherosclerotic plaques for Lp-PLA_2 in 2 different studies has shown that rupture-prone, thin fibrous cap lesions exhibit intense staining for the biomarker. Advanced carotid atheromas are similar to advanced coronary atheromas in this respect. (illustration by Scott Barrows, medical illustrator, University of Illinois at Chicago.)

In fact, among hospital-based patients undergoing carotid endarterectomy including symptomatic and asymptomatic patients, Mannheim et al[31] have shown that Lp-PLA_2 expression was significantly higher in the plaque of symptomatic patients than asymptomatic patients, in particular in those with TIA. Lp-PLA_2 expression localized primarily to the shoulder and necrotic lipid core areas of the plaque co-localized with oxidized LDL and macrophage content. In addition, the Lp-PLA_2 product lysophosphatidylcholine plaque concentration was higher in the plaque of symptomatic than asymptomatic patients, particularly in TIA patients.

Data from the ARIC study determined the area under the curve (AUC) in patients to be 0.747 when using traditional risk factors.[32] When CRP is added to traditional risk factors, the AUC in receiver operating characteristic analysis increases to 0.759, for a total increase of about 0.012. When Lp-PLA_2 is added to traditional risk factors and CRP, there is a further AUC increase to 0.778, for a total increase of about 0.031. Finally, with traditional risk factors, CRP, Lp-PLA_2, and an interaction factor accounting for both inflammatory markers, the AUC is raised substantially to 0.793, for a total increase of almost 0.05 over traditional risk factors alone. Note that for both markers to increase the AUC, they are identifying stroke risk in different subsets of patients, in addition to being complementary when both are elevated. It has been suggested that a better statistical evaluation of a cardiovascular risk biomarker is whether the biomarker changes the patient's risk category over time.[33] This was recently reported in the ARIC study, where persons with a $<2\%$ 5-year risk for stroke were classified as low risk, persons with 2%–5% 5-year risk were classified as moderate risk, and persons with a $>5\%$ risk of stroke were classified as high risk. Lp-PLA_2 and CRP did not reclassify low-risk persons, but they did reclassify 37% of persons originally misclassified as moderate risk, using traditional risk factors alone.[32] In this study, 26% were reclassified as low risk and 11% were reclassified as high risk. Assuming that all patients with an estimated 5-year stroke risk $\geq 2\%$ may need statin treatment and lifestyle modification, a determination of Lp-PLA_2 and CRP values may be useful in intermediate-risk persons, with elevated levels leading to reclassification of these individuals to high risk.

Conclusion

A number of important studies have been presented looking at the association between Lp-PLA_2 and stroke risk, and it appears that the risk conferred by an elevation in Lp-PLA_2 in the top quartile or tertile versus bottom quartile or tertile is about 2-fold, as it is for coronary event risk in various studies. A commercial immunoassay for the quantitative determination of Lp-PLA_2 in human plasma is available and can be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for CAD and ischemic stroke associated with atherosclerosis. This immunoassay may prove to be especially useful for proper risk classification of persons with stroke or cardiovascular diseases who are found to be at moderate risk. It appears useful in overall cardiovascular risk classification and may lead to more aggressive therapeutic approaches with statin agents for lipid control or with other approaches in high-risk patients for cardiovascular disease reduction. Accurate classification of these persons into low-, moderate-, or high-risk disease categories may prove important in relation to administration of appropriate risk reduction therapies, which include lifestyle modification and statin medication. The American Heart Association/American College of Cardiology guidelines advocate for aggressive lowering of lipids and other factors to new targets, for example, in patients with established atherosclerotic vascular diseases.[34]

Author Disclosures

The author who contributed to this article has disclosed the following industry relationships.

Philip B. Gorelick, MD, serves as a consultant for Bayer; is on the Speakers' Bureau, and a Stroke Steering Committee Member for Boehringer Ingelheim; and is a study adjudicator for Pfizer, Inc.

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