



Lp-PLA₂ – Clinical Backgrounder

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is an enzyme that has been identified as a novel risk factor for coronary events and stroke. The PLAC™ test, an enzyme immunoassay developed by diaDexus, Inc., has received marketing clearance from the U.S. Food and Drug Administration for measuring the level of Lp-PLA₂ in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease (CHD), and ischemic stroke associated with atherosclerosis. The following major research studies support the hypothesis that Lp-PLA₂ is an important predictor of major cardiovascular events, especially in patients not identified as high risk by traditional risk assessment.

American Heart Association 2004 Scientific Sessions, November, 2004.

Oral Presentation #2798: “The Relation of Lipoprotein-Associated Phospholipase A₂ and C-Reactive Protein and Risk for Ischemic Stroke in Middle-Aged Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study”.

In a prospective, case cohort study of 12,773 apparently healthy middle-aged men and women in the ARIC study, Christie M. Ballantyne, MD, Director of the Center for Cardiovascular Disease Prevention at Baylor College of Medicine and the Methodist DeBakey Heart Center, Houston, and his team examined the relationship between Lp-PLA₂, C-reactive protein, traditional risk factors and stroke over approximately six years. Dr. Ballantyne and his team used the PLAC test to measure levels of Lp-PLA₂ in the participants’ blood.

The study showed:

- Mean Lp-PLA₂ levels were higher in the 194 ischemic stroke cases than the 812 noncases, whereas LDL-C levels were not significantly different.
- Elevated levels of Lp-PLA₂ were independently associated with stroke even after adjustment for all traditional risk factors, as well as C-reactive protein, body mass index and triglycerides.
- Those with elevated levels of Lp-PLA₂ were nearly twice as likely to experience a stroke.
- Individuals with high levels of both Lp-PLA₂ and CRP were greater than ten times more likely to suffer a stroke than individuals with low levels of both Lp-PLA₂ and CRP.

Circulation Volume 110(14), October 2004, Pages 1903-1908.

“Lipoprotein-Associated Phospholipase A₂ Adds to Risk Prediction of Coronary Events by C-Reactive Protein in Apparently Healthy Middle-Aged Men from the General Population. Results from the 14 Year Follow-up of a Large Cohort from Southern Germany”.

This study involved 934 apparently healthy men, aged 45 to 64, from the general population. During the 14 year period of the study, 97 men suffered a coronary event. Wolfgang Koenig, MD, Department of Internal Medicine II–Cardiology, University of Ulm Medical Center, Ulm, Germany, and his team evaluated baseline

levels of Lp-PLA₂ in conjunction with traditional risk factors and C-reactive protein. The researchers used the PLAC test to measure levels of Lp-PLA₂ in the participants' blood.

The study showed:

- Elevated levels of Lp-PLA₂ were independently predictive of coronary events in men with moderately elevated cholesterol.
- Baseline levels of Lp-PLA₂ were higher in subjects who experienced an event compared to the event free subjects.
- Each standard deviation increase in Lp-PLA₂ levels was associated with a 37% increased risk of a coronary event.
- Even after correction for all traditional risk factors and CRP, those individuals with elevated levels of Lp-PLA₂ had a 23% increased risk of coronary event per one standard deviation increase.
- Lp-PLA₂ and CRP were additive in their ability to predict risk of coronary heart disease.

Circulation Volume 109(7), February 2004, Pages 837-842.

“Lipoprotein-Associated Phospholipase A₂, High-Sensitivity C-Reactive Protein, and Risk for Incident Coronary Heart Disease in Middle-Aged Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study”.

In this prospective, case-cohort study of 12,819 apparently healthy middle-aged American men and women in the ARIC study, Christie M. Ballantyne, MD, Director of the Center for Cardiovascular Disease Prevention at Baylor College of Medicine and the Methodist DeBakey Heart Center, Houston, and his team examined the relationship between Lp-PLA₂, C-reactive protein (CRP), traditional risk factors and incident CHD over the course of six years, stratified by low-density lipoprotein (LDL) cholesterol. Dr. Ballantyne and his team used the PLAC test to measure the levels of Lp-PLA₂ in the participants' blood.

The study showed that:

- Mean levels of Lp-PLA₂ and CRP were higher in the 609 cases of CHD events than the 741 controls, after adjustment for age, sex and race.
- In individuals with normal LDL cholesterol levels (<130mg/dL):
 - Levels of Lp-PLA₂ were independently associated with incident CHD, even after adjustment for traditional risk factors and CRP.
 - Those with elevated levels of Lp-PLA₂ were approximately twice as likely to experience a coronary event as individuals without elevated levels of Lp-PLA₂.
 - Lp-PLA₂ and CRP were individually and independently predictive of incident CHD.
 - Individuals with elevated levels of both Lp-PLA₂ and CRP have the greatest risk for CHD.

New England Journal of Medicine Volume 343, October 2000, Pages 1148-1155.

“Lipoprotein-Associated Phospholipase A₂ as an Independent Predictor of Coronary Heart Disease”

The authors of this paper evaluated the association of Lp-PLA₂ levels with relative risk of CHD in a prospective case-control study using baseline samples from hypercholesterolemic men, median LDL value 190mg/dL (580 cases and 1,160 age- and smoking-matched controls) in the West of Scotland Coronary Prevention Study (WOSCOPS). WOSCOPS was a large and significant clinical trial that evaluated the use of pravastatin therapy to reduce cardiac events in nearly 6,600 men.

The study showed that:

- An individual's risk of having a coronary event increased with elevated levels of Lp-PLA₂.
- Individuals with high levels of Lp-PLA₂ had as much as a twofold elevated risk for CHD compared to patients with low levels of Lp-PLA₂.
- Lp-PLA₂ was shown to be statistically independent of traditional risk factors and markers of systemic inflammation, including CRP, white cell count, and fibrinogen.

For more information or for copies of the above research, please contact Daryl Messinger at (415) 999-2361 or daryl@weisscommpartners.com

###