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Lp-PLA$_2$ –A Marker For Cardiovascular Risk

Background:

There are a significant number of individuals that develop cardiovascular disease who are not categorized as high risk by the usual risk factors including blood cholesterol levels. Thirty-five percent of patients with cardiovascular disease have total cholesterol levels less than 200 mg/dl. These individuals are frequently not investigated further and their true risk not determined (figure 1).

The current major risk factors (figure 2) uncover an additional group that benefits from aggressive treatment. Tests such as homocysteine, lipoprotein (a), high sensitivity C-reactive protein, fibrinogen and Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$, aka platelet-activating factor acetyl hydrolase) are emerging as additional risk factors. Currently, these tests enhance the estimate of risk determined by the major risk factors.

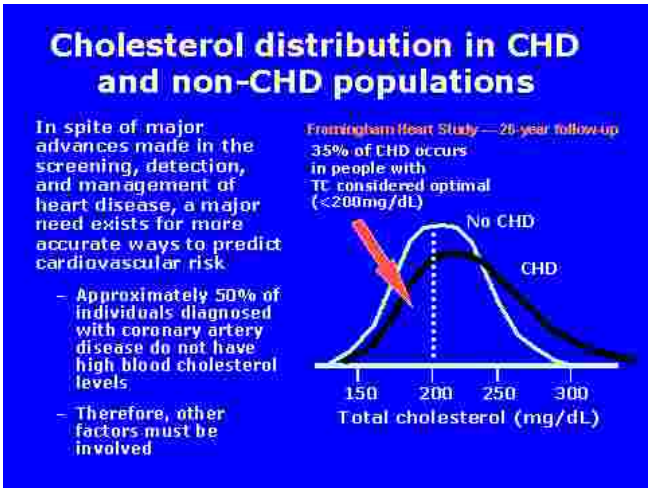

Figure 1- from Castelli W.P., Atherosclerosis 1996.

What is Lp-PLA$_2$?

Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$) is an enzyme that is implicated in the vascular inflammatory pathway that leads to plaque formation. It is produced by circulating monocytes and travels in the plasma attached to LDL-cholesterol. Elevated blood levels serve as a marker for cardiovascular risk.

Risk Factors	
Smoking	High LDL cholesterol
Hypertension	Low HDL cholesterol
Obesity	Elevated hsC-RP
Sedentary life style	High homocysteine
Diabetes	Increased Lp(a)
Family history	High small LDL
Stress	Low large HDL
Metabolic syndrome	High triglycerides

Figure 2

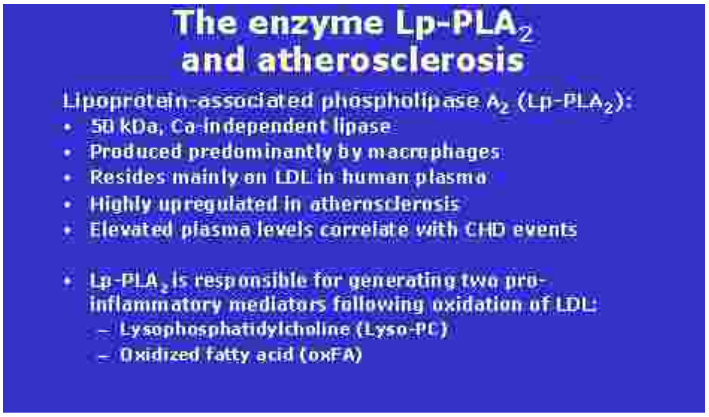

Figure 3 from http://www.plactest.com

Plaque formation and action of Lp-PLA$_2$:

Lp-PLA$_2$ travels attached to LDL-cholesterol in the blood stream. After a tear in the intima of a vessel, LDL-cholesterol enters with Lp-PLA$_2$ to begin plaque formation. Inside the intima, LDL becomes oxidized. Lp-PLA$_2$ hydrolyzes LDL resulting in the formation of powerful pro-inflammatory stimulants and increase in adhesion molecules. These adhesion molecules attract monocytes that transform into macrophages in the intimal wall. Once in the vessel wall, the macrophages engulf oxidized LDL. Upon ingestion of LDL the macrophages develop into foam cells. These aggregate to form a fatty streak, which over time is covered with a fibrous cap. Cytokines and proteases secreted by macrophages cause thinning of the fibrous plaque making it prone to rupture. Plaque rupture results in thrombosis, which can block the artery and lead to a myocardial infarction or ischemic stroke.

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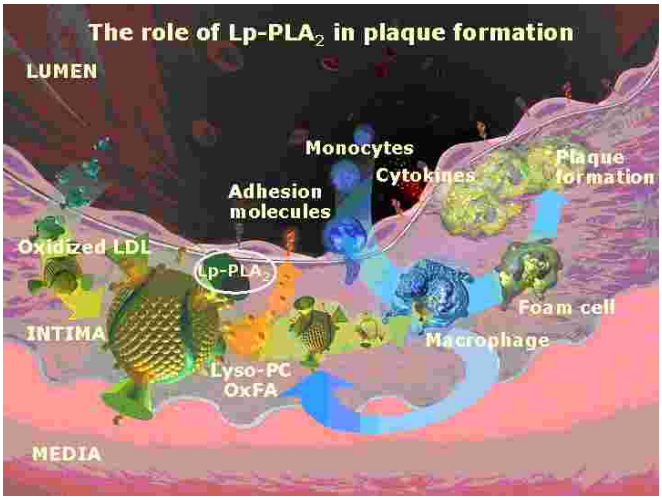

Figure 4 from http://www.plactest.com

Does Lp-PLA$_2$ promote atherogenesis?

Lp-PLA$_2$ creates fragments that are more atherogenic than their parent compounds. These compounds directly participate in the formation of atherosclerotic plaque. If the levels of Lp-PLA$_2$ can be reduced, it is reasonable to conclude that the rate of plaque formation will be reduced. Research to develop an inhibitor to this enzyme is currently in progress. The outcome of this research has implications for prevention and treatment of atherosclerosis and its sequelae.

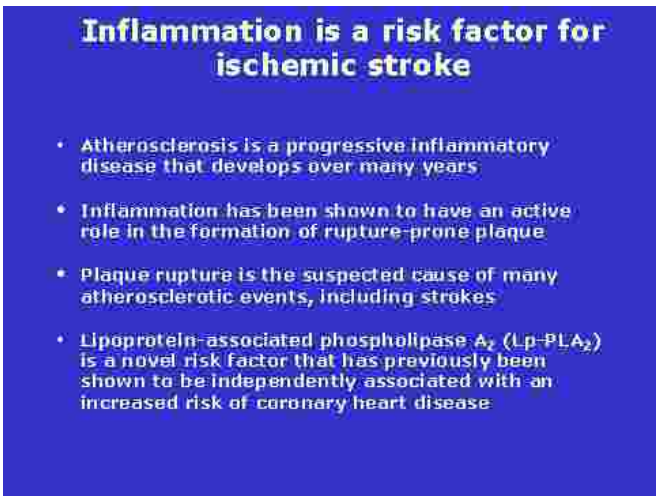

Figure 5 from http://www.plactest.com

Lp-PLA$_2$ versus C-reactive protein.

High sensitivity C-Reactive Protein (hsCRP) and Lp-PLA$_2$ are products of different biological processes. hsCRP is an acute phase reactant produced in response to systemic inflammation. Lp-PLA$_2$, an enzyme predominantly produced by macrophages, travels with LDL and is responsible for generating pro-inflammatory mediators in the vessel wall. In clinical evaluation, these two biomarkers have been shown to be independent of each other. Each provides unique information useful for assessing stroke and coronary heart disease risk. Low but elevated levels of hsCRP are associated with increase cardiovascular risk. Higher levels are seen in acute and chronic systemic inflammatory processes such as rheumatoid arthritis, osteoarthritis and COPD. Lp-PLA$_2$ is a reflection of the degree of vascular inflammation not systemic inflammation.

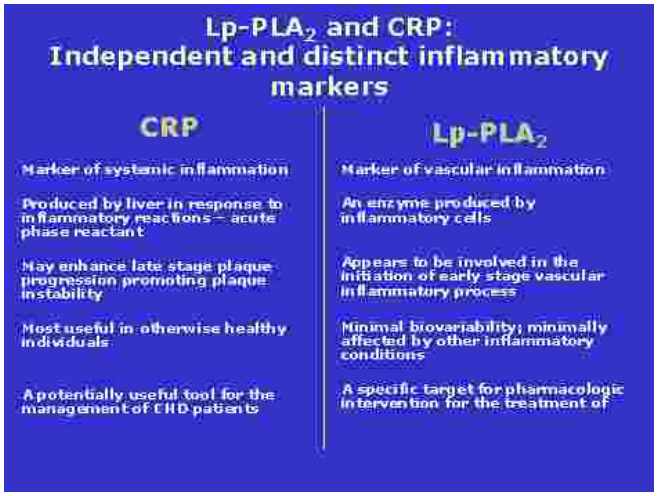

Figure 6 from Packard C.J., et. al. NEJM 2000.

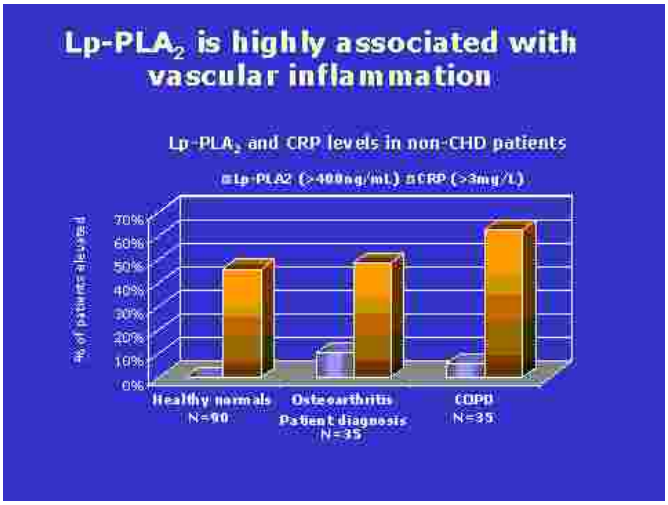

Figure 7 presented at American Heart Association, Nov. 2004

Clinical evidence of Lp-PLA$_2$ as risk factor

Several large studies have demonstrated that inflammatory mediators play an important role in the development of atherosclerosis and potentially indicate an individual's risk for cardiovascular disease. Lp-PLA$_2$ has been shown to have an association with atherogenesis and has independent predictive power to determine coronary heart disease and stroke. The three studies listed below support the usefulness of Lp-PLA$_2$.

1. The WOSCOPS Study (The West of Scotland Coronary Prevention Study)
   a. Five-year trial of 6,595 men with elevated blood cholesterol and no history of heart disease.
   b. Four inflammatory markers were evaluated.
   c. Total of 580 men who went on to have a myocardial infarction or revascularization were compared to 1,160 men who did not have an event (controls).

Conclusion: Lp-PLA$_2$ was shown to be the most powerful predictor of the markers evaluated. The results showed that those with the highest levels of Lp-PLA$_2$ had twice the risk of an event compared to those individuals with the lowest levels, even after adjustment for traditional risk factors and markers of systemic inflammation (hsCRP).

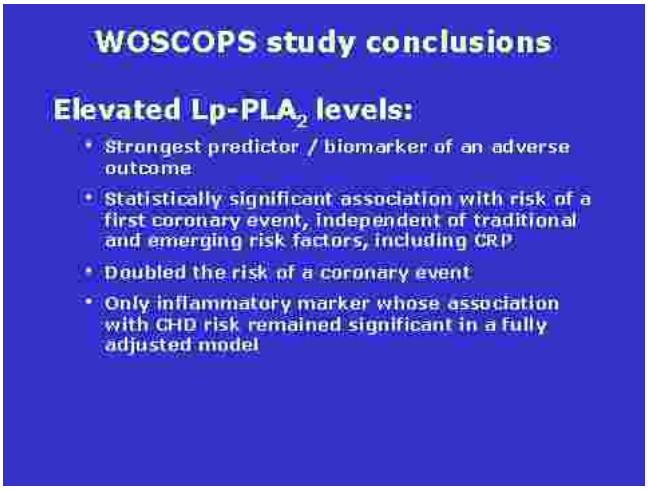

Figure 8 from Packard C.J., et. al. NEJM 2000.

2. The ARIC Study – A case-cohort evaluation based on the Atherosclerosis Risk Communities (ARIC)
   a. NIH sponsored study in four U.S. communities on 12, 819 African American and Caucasian men and women ages 45 – 65.
   b. Lp-PLA$_2$ was evaluated to determine its ability to predict disease.
   c. Six year follow up.

Conclusion: Lp-PLA$_2$ was shown to be the most powerful predictor of the markers that were evaluated. The results showed that those with the highest levels of Lp-PLA$_2$ had twice the risk of an event compared to those individuals with the lowest levels, even after adjustment for traditional risk factors and markers of systemic inflammation.

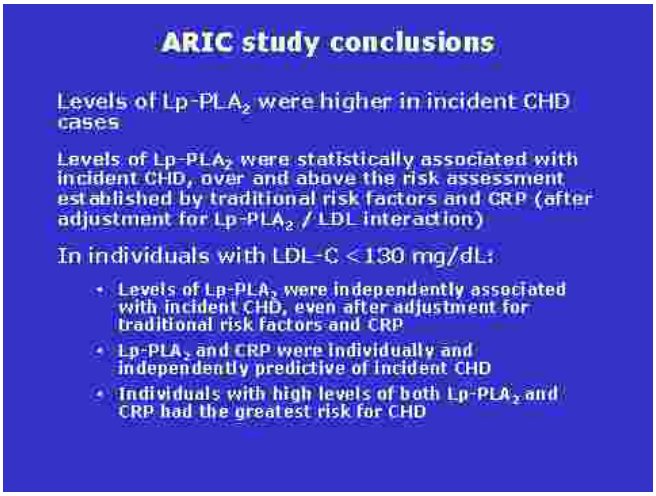

Figure 9 From Ballantyne C.M., et. al. Circulation 2004.

3. The Mayo Heart Study – A study of patient undergoing clinically indicated coronary angiography by researchers at the Mayo Clinic were followed up for major adverse events
   a. 504 consecutive patients.
   b. Four year follow up with 72 major adverse events (deaths, infarctions or revascularizations).
   c. The study evaluated the association of Lp-PLA$_2$ with coronary artery disease risk factors, with the severity of angiographic disease and with the incidence of major adverse events.

Conclusions: The study found that higher Lp-PLA$_2$ levels were associated with a significantly greater risk of events (death, MI, revascularization, stroke). The risk of an event increased by 28% with each standard deviation increase in Lp-PLA$_2$. The association remained significant after adjusting for clinical variables (age, gender, smoking, hypertension) and lipids (total and HDL cholesterol, Lp(a), and triglycerides) as well as CRP and fibrinogen.

4. The Rotterdam Study – A population based follow-up study of 7,983 subjects >55 years of age. The subjects who developed coronary artery disease and ischemic stroke were compared with controls. The Lp-LPA$_2$ levels were found to be an independent predictor of coronary heart disease and ischemic stroke in the general population.

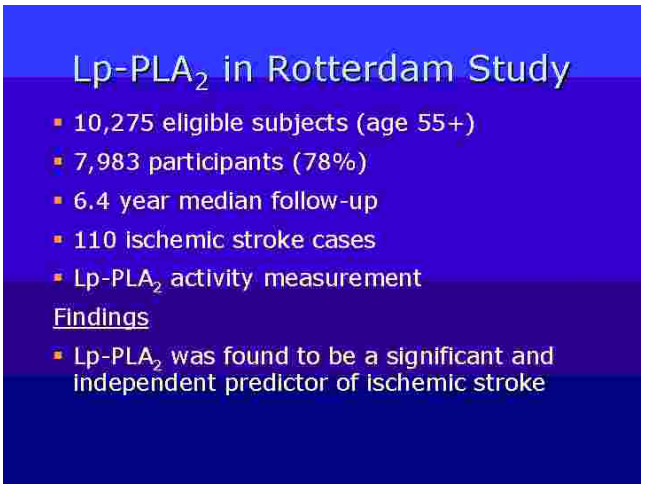

Figure 10 From Oei H.H., et. al. Circulation 2005.

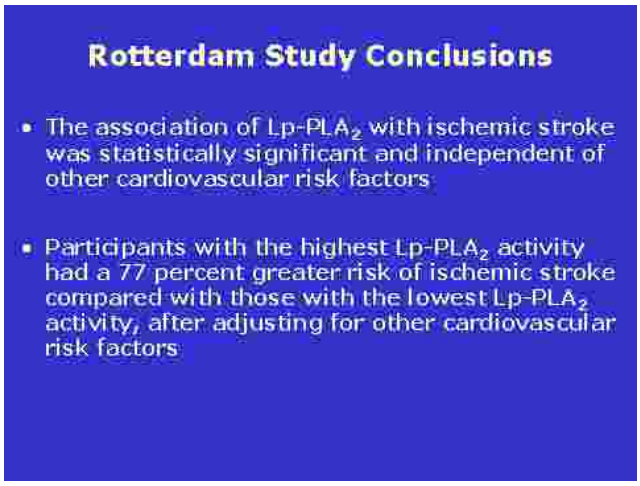

Figure 11 From Oei H.H., et. al. Circulation 2005

When to test for Lp-PLA$_2$

An appropriate candidate is a patient whose preliminary stroke or CHD risk assessment does not provide a clear clinical direction. This may include patients with one major risk factor outside the desirable range or a positive family history. An individual with an occult systemic inflammatory process and an associated elevated high sensitivity C-reactive protein (hsCRP) may cause uncertainty regarding the level of risk. An elevated level of Lp-PLA$_2$ would help decide if more aggressive treatment is necessary in a patient at borderline risk.

Management of elevated Lp-PLA$_2$

Lp-PLA$_2$ is a marker for the inflammatory component of plaque formation. Treatment to lower blood cholesterol, blood pressure, aspirin and perhaps fish oil are likely to be effective in lowering levels of Lp-PLA$_2$ indirectly. A drug that would directly inhibit the action of Lp-PLA$_2$ would likely prevent the formation of an atherosclerotic plaque. Such adrug has not yet been developed but would be of significant benefit.

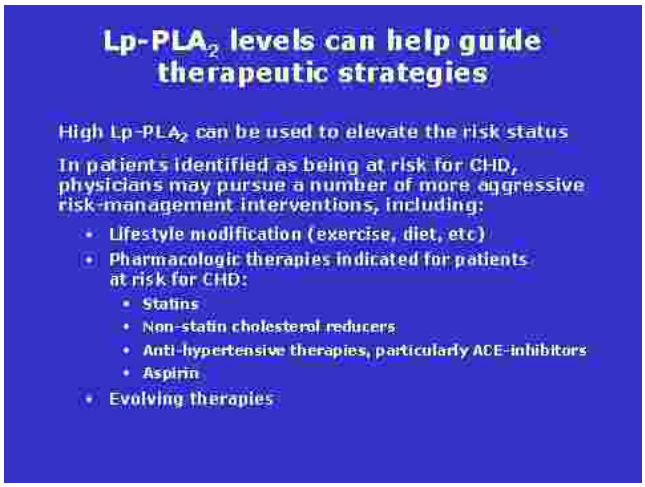

Figure 12 From Ballantyne C.M., et. al. Circulation 2004.

Blood levels of Lp-PLA$_2$:

The level of Lp-PLA$_2$ in the blood is a reflection of the pro-inflammatory activity in the vessel wall. The Mayo Clinic reference range for men is 134 to 480 ng/ml and 93 to 472 ng/ml for women. When interpreting the level of risk of the blood level it is important to keep in mind the reference range of the laboratory. However, in the ARIC Study, individuals with Lp-PLA$_2$ between 310-420 ng/mL had a 1.7-fold increase in risk; those with greater than 420 ng/mL had a 2.1-fold increase in risk.

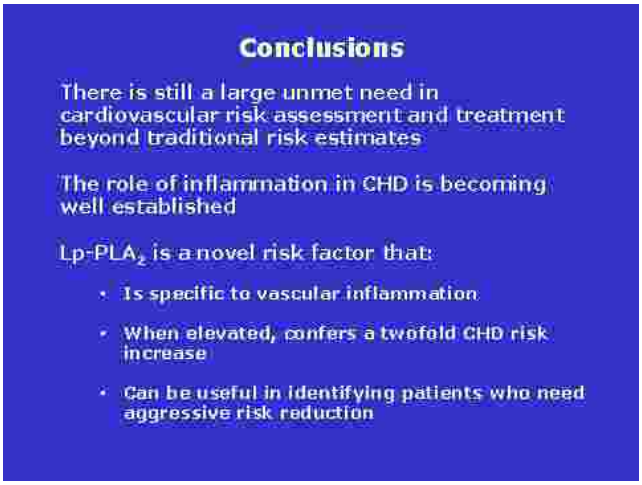

Figure 13 From http://www.plactest.com

How to order Lp-PLA$_2$

A blood level of Lp-PLA$_2$ must be collected in EDTA anticoagulate. A one ml volume of plasma is required. The sample must be kept refrigerated and sent frozen to the reference lab. The assay is an enzyme immunoassay and available at most large reference laboratories. If the specimen is drawn at Rex Lab, the sample will be sent to Mayo Reference Lab. The test number is #81043. The turn around time is 14 days at a cost of $171.00.

Stephen V. Chiavetta, MD

References:

1. *Inflammatory Markers of Coronary Risk, Rader D. J., NEJM 2000, 343:1179 – 1182.*
2. *Lipoprotein-Associated Phospholipase A2 as an Independent Predictor of Coronary Heart Disease, Packard C. J. et. Al., NEJM 2000, 343:1148 – 1155.*
3. *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, Ballantyne C. M. et. al., Circulation 2004, 109: 837 –842*
4. *Association of lipoprotein associated phospholipase A2 levels with coronary artery Disease risk factors, angiographic coronary artery disease and major adverse events at follow up, Brilakis E. S. et. al., European Heart Journal, 2005; 26:137-144.*
5. *Lipoprotein Associated Phospholipid A2 is associated with coronary artery disease and ischemic stroke, The Rotterdam Study, Oei, H. S. et. al., Circulation 2005, 111; 570-575.*

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