Detection and Treatment of Patients with Vulnerable Plaque

Nicholas Palladino, MD, JD
Director of the South Jersey Lipid Clinic

Plaque rupture - NOT stenosis - causes most acute MIs and Ischemic Strokes

Lp-PLA2 at the “Scene of the Crime”: As Lesions Progress so Does Staining (Reddish-Black) Intensity

Lp-PLA2 - a causative enzyme in vulnerable plaque formation

Multiple inflammatory markers for multiple purposes

The Problem with a Non-specific Inflammatory Marker: 40% Fluctuation in Risk Category in a Single Month
Intradividual % CV
Lp-PLA2 - HS-CRP LDL HDL TG


Elevated Lp-PLA2, Independently Doubles the Patient’s Baseline Risk for CHD & Stroke Events

*Angiographic CHD only

Prevalence of major risk factors in CHD
Khot, et al. JAMA 2003

4 Major modifiable risk factors: hypertension, smoking, hypercholesterolemia, diabetes
The PLAC® Test Identifies Stroke-Prone Prehypertensive Patients: ARIC Study

Risk Ratios for Ischemic Stroke Based on Lp-PLA₂ Level and SBP

Ballantyne C, et al; Arch Int Med Nov 2005

Endothelial Dysfunction in Coronary Arteries Worsens as Lp-PLA₂ Rises >240 ng/mL


Lp-PLA₂ Predicts CHD Outcomes: Mayo Heart Study

95% of patients with Lp-PLA₂ < 200 ng/mL were Event Free at 4 years

Brilakis ES et al, Mayo Heart Study, Euro J Card 2005
Event-free Survival in 1,051 Patients S/P ACS or Revasc. and on Statins (LDL 100 mg/dl), by Lp-PLA₂ Tertiles

KAROLA Study

Lp-PLA₂ in 1,051 Rehab Pts S/P ACS or Revascularization doubles risk of recurrent NFMI/CVA/Cardiac Death

Fully adjusted for traditional risk factors, LDL and HDL, statin Rx, CRP, age, BMI, etc.
Koenig W. KAROLA Heart Study, ACC abstract 2005

Effect of lipid treatment on Lp-PLA₂ levels

Albert M., et al., JACC 2005
Tsimihodimos V. et al., JACC 2004
S. Winkler, et al., JACC 2004
PRINCE – Pravastatin lowers both LDL and Lp-PLA2, and these reductions do not correlate

Niaspan Further Reduces Vascular Inflammation, Additionally to Statin Rx

Statin Monotherapy RX -vs- Statin+Niacin Combination RX

Brown BG et al. NEJM 1999; 323:1268-98
Brown BG et al. NEJM 2001;345(22):1583-92
Brown BG. Circulation Suppl 1997
**ADVOCATE:**

**HDL Subfractions at Week 16**

% Change from Baseline

- HDL<sub>2</sub>
  - Advicor® 1000/40 mg
  - Advicor® 2000/40 mg
  - Simvastatin 40 mg

- HDL<sub>3</sub>
  - Atorvastatin 40 mg

† P≤0.05 vs Simvastatin
‡ P≤0.05 vs Atorvastatin

HDL<sub>2</sub> and HDL<sub>3</sub> are mean values.

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**LDL has Three Components**

- **Lp(a)** is 10X more atherogenic than LDL on a mg/dL basis
- **IDL** is more atherogenic than LDL alone
- **LDL-R** is the LDL component most affected by statin drug therapy

Total LDL-C = LDL-R + Lp(a) + IDL

LDL has Three Components

- LDL 20%
- Lp(a) 20%
- LDL-R 60%

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**The Three LDL Components Require Different Treatments**

- Statin + Niacin or Fibrate Combination Therapy
- Statins Target LDL-R
- Niacin, Estrogen, Raloxifene, ASA
- Pattern Density is in LDL-R - consider Niacin, TZDs, Omega-3-FA, Fibrates, Statin drugs ineffective

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Lipoprotein Sub-Classes

Chylomicron
VLDL
Remnants
LDL-R
HDL2
HDL3
Particle Size (nm)
Density (g/ml)

Friedewald LDL is Clinically Inaccurate When Trigs >200 mg/dL

<table>
<thead>
<tr>
<th>Triglyceride mg/dL</th>
<th>Percent Correct (Within ± 10%)</th>
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<tbody>
<tr>
<td>151-200</td>
<td>84%</td>
</tr>
<tr>
<td>201-300</td>
<td>77%</td>
</tr>
<tr>
<td>301-400</td>
<td>59%</td>
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</tbody>
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* Percent calculated LDL-C values within ± 10% of the ultracentrifuge values

Clin Chem: 1990; 36:36-42

Friedewald Clinically Misclassifies Risk When Trigs Elevated

In 20,224 samples, Friedewald underestimated LDL an average of 19.5%.
Cameron; Pharmacotherapy 24:167 (2004)

36% of patients had an error >5% (underestimation) of LDL using the Friedewald formula

Resulted in 28% of patients being classified to the wrong CHD risk category
NCEP ATP III Expanded Risk Factors That Can Modify LDL Risk

“Trigs >200 mg/dL indicate a need to identify Non-HDL cholesterol (LDL + VLDL) as a secondary target of lipid-lowering therapy” (II-13)

“Increased remnant lipids (IDL and small VLDL) are candidates for intervention and can heighten CHD risk substantially beyond that predicted by LDL alone” (II-10,7)

“The metabolic syndrome (low-HDL, small LDL, elevated trigs) taken in the aggregate enhances risk for CHD at any given LDL level” (II-26)

“Elevated presence of Small LDL is an indication for atherogenic dyslipidemia and metabolic syndrome” (II-22)

Elevations of Lp(a) and LDL have been reported to have a synergy in elevating risk (II-21)

For Clinical Judgment: NCEP Referenced Lipids That May be Targeted to Reduce Absolute Risk

Lipoprotein Sub-Fraction Treatment Recommendations - VAP

LDL:
- LDL (real): Statin, Ezetimibe, Bile Acid Sequestrant
- IDL: Statin + Niacin, then Statin + Fibrates
- Lp(a): Niacin, Estrogen, Fish Oils
- Pattern Density: (Pattern A – Large, Fluffy, Buoyant, Desirable vs. Pattern B – Small, Dense Atherogenic)
- Pattern A: Niacin, TZDs, Fish Oils, Fibrates
- Pattern B: Niacin, Estrogen, Fish Oils

HDL:
- HDL.2 (Large, Buoyant Most Cardioprotective): Niacin
- HDL.3 (Smaller, dense Less Cardioprotective): Fibrates

TRIGLYCERIDES:
- <600: Niacin
- >600: Fibrates
- VLDL.1,2,3: Statin + Fibrates, then Statin + Niacin
Lp-PLA<sub>2</sub> is Strongly Expressed within Atherosclerotic Plaque

Human coronary artery cross-section with monoclonal Ab staining (reddish-brown) for Lp-PLA<sub>2</sub>

Advances in the Prevention of CHD

- LDL-C
- Lp-PLA<sub>2</sub>
- HDL-C
- Lipid subclasses
- Combination therapy