# ADVANCED LIPID TESTING

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Diplomate of the American Board of Clinical Lipidology

## COMPARISON OF LIPID PANELS

<table>
<thead>
<tr>
<th>STANDARD LIPID PANEL</th>
<th>ADVANCED LIPID PANEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strongest components are:</td>
<td>• APO B</td>
</tr>
<tr>
<td>– TC/HDL RATIO</td>
<td>• APO B/APO A1</td>
</tr>
<tr>
<td>– NON-HDL CHOLESTEROL</td>
<td>• LDL SUBFRACTIONATION</td>
</tr>
<tr>
<td>– LDL-C</td>
<td>• HDL SUBTYPE</td>
</tr>
<tr>
<td></td>
<td>• Lp(a)</td>
</tr>
<tr>
<td></td>
<td>• Hs-CRP</td>
</tr>
<tr>
<td></td>
<td>• LP-PLA2</td>
</tr>
<tr>
<td></td>
<td>• NT-proBNP</td>
</tr>
<tr>
<td></td>
<td>• CYSTATIN C</td>
</tr>
</tbody>
</table>
Prevalence of Emerging Cardiovascular Risk Factors in Younger Individuals with a Family History of Premature Coronary Heart Disease and Low Framingham Risk Score

**TABLE 1**: Mean values and standard deviations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of men and women (y)</td>
<td>47 y of age (5.9)</td>
</tr>
<tr>
<td>Men</td>
<td>58%</td>
</tr>
<tr>
<td>Women</td>
<td>62%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>77%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 mm Hg (14.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73 mm Hg (9.4)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>247 mg/dL (43-52)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>110 mg/dL (608)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>144 mg/dL (127-160)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>51 mg/dL (53.7)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, TR = triglycerides.

**TABLE 2**: Emerging clinical and lipid risk factors

<table>
<thead>
<tr>
<th>Emerging clinical risk factors</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP &gt; 3</td>
<td>24%</td>
</tr>
<tr>
<td>Positive calcium score</td>
<td>32%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emerging lipid risk factors</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid elevation</td>
<td>22%</td>
</tr>
<tr>
<td>Low HDL2 in women</td>
<td>72%</td>
</tr>
<tr>
<td>Low HDL2 in men</td>
<td>67%</td>
</tr>
<tr>
<td>Small, dense LDL pattern</td>
<td>19%</td>
</tr>
<tr>
<td>Mixed LDL pattern</td>
<td>43%</td>
</tr>
<tr>
<td>Elevated remnant lipoproteins</td>
<td>49%</td>
</tr>
</tbody>
</table>

Abbreviations: HDL = high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL = apolipoprotein B.


GOFMAN’S LIVERMORE COHORT

- Prospective study of 1905 men with 29 yr follow-up
- Low HDL2 was independently associated with CV events after multivariate analysis. HR= 1.67 for total CHD.
- Premature CHD was increased 60% by low HDL2

Atherosclerosis 214 (2011) 196–202
Apo B has been shown to be superior to LDL-C in predicting risk of CV events in the following trials:

- Quebec Cardiovascular Study
- AMORIS Study
- Thrombo Study
- Thrombo Metabolic Syndrome Study
- Northwick Park Heart Study
- Nurses’ Health Study
- Health Professionals’ Follow-up Study
- AFCAPS/TEXCAPS
- Leiden Heart Trial
- INTERHEART Study
- Women’s Health Study
- Ideal and TNT Studies
- ISIS
- COPENHAGEN
- LIPID
- FIELD (PLACEBO GROUP ONLY)
# LDL-C VS APO B

1.) **AMORIS**  
   - n=172,000  
   - F/U=5.5 yrs  
   - RR of LDL-C = 1.14 (RR Female = 0.85)  
   - RR of apo B = 1.33 (RR Female = 1.53)  

2.) **ISIS**  
   - n = 3510  
   - controls = 9805  
   - RR of LDL-C = 2.21  
   - RR of apo B = 2.66  

3.) **Health Professional Study**  
   - n=18,225  
   - F/U=6yr  
   - RR of LDL-C = 1.81  
   - RR of apo B = 3.01  

4. **Copenhagen Study**  
   - n = 9231  
   - F/U=8 yrs  
   - RR of LDL-C = 1.4 (Female RR = 1.4)  
   - RR of apo B = 1.6 (Female RR = 1.8)  

5.) **Nurses Health Study**  
   - n=33,000  
   - F/U = 8yrs  
   - LDL-C RR = 2.73  
   - apo B RR = 4.7  

6.) **LIPID**  
   - n=9014  
   - R/U 6.1yrs  
   - LDL-C RR = 1.15  
   - apo B RR = 1.64  

7.) **AFCAPS/TEXCAPS**  
   - n=6505  
   - F/U= 5.2 yrs  
   - LDL-C RR = 1.29  
   - apo B RR = 1.6  

8.) **TNT and IDEAL**  
   - n=18,018  
   - F/U=4.8 yrs  
   - LDL-C RR = 0.95  
   - Apo B RR = 1.24  

9.) **FRAMINGHAM**  
   - n = 3322  
   - F/U = 15 yrs  
   - LDL-C HR = 1.11  
   - APO B HR = 1.37
LDL-C VS APO B

10.) Quebec Cardiovascular Study n=2155  F/U = 5 yrs
    LDL-C RR = NS
    APO B RR = 1.4 (p<0.001)

11.) Thrombo Study n=1045  F/U = 2.16 yrs
    LDL-C RR = NS
    APO B RR = 1.82 (p= 0.018)

12.) Northwick Park Heart Study n=2508  F/U = 6 yrs
    LDL-C RR =4.4  (multivariate 1.31)
    APO B RR = 4.64  (multivariate 1.42)

13.) Leiden Heart Study N=848  F/U = 2.95 yrs
    LDL-C RR = 1.16
    APO B RR =3.21 (P=0.033)

14.) FIELD STUDY PLACEBO GROUP N= 4900  F/U = 5 YRS
    LDL-C HR = 1.05
    APO B HR = 1.14 (P=0.001)

Total patient yrs of follow-up is 1,826,71

LDL-C VS APO B
NEGATIVE STUDIES

1.) NHANES III
    LDL-C vs apo B  RR=NS

2.) ARIC n=12,300  F/U=10 yrs
    LDL-C RR= 1.42
    apo B RR= 1.31

3.) PREVEND N= 6948  F/U = 7.9 yrs
    LDL-C RR = 1.24  (HDL = 52 and TG = 98)
    apo B RR = 1.13  (Diabetes = 2.8%)

4.) FIELD STUDY FENOFIBRATE SUBGROUP
    LDL-C  HR = 1.16
    APO B HR = 1.22
Advanced Lipid Management
Douglas Triffon, MD

Framingham Study ROC curves analysis:
- APO B HR = 1.37 AUC = 0.73
- LDL-C HR = 1.11 AUC = 0.71

Amoris Study ROC curve analysis:
- APO B RR = 1.33 AUC = 0.65
- LDL-C RR = 1.14 AUC = 0.6

Field Study ROC curve analysis:
- APO B HR = 1.14 AUC = 0.545
- LDL-C HR = 1.05 AUC = 0.530

JAMA, August 15, 2007—Vol 298, No. 7
SUMMARY OF LDL-C STUDIES

- LDL-C, in the majority of studies, is inferior in risk prediction to apo B.
- On-treatment LDL-C is not predictive of subsequent events in most statin trials while apo B remains predictive. (LIPID, AFCAPS/TEXCAPS, Leiden Heart Study, and TNT-IDEAL.)
- The difference between LDL-C and apo B in ROC analysis is small.
THE EMERGING RISK FACTOR COLLABORATION

91307 SUBJECTS FROM 22 TRIALS

JAMA, November 11, 2009—Vol 302, No. 18

NON-HDL CHOLESTEROL AND APO B

• Non-HDL cholesterol and apo B are highly correlated with correlation coefficients of 0.93-0.94.

• Elevated triglycerides decrease this correlation to 0.69

• Statin treatment changes this relationship

• Non-HDL-C and apo B can become discordant in risk prediction
**APO B VS NON-HDL CHOLESTEROL**

- Distribution of apoB:
  - VLDL: 7%
  - LDL: 93%
- Distribution of non-HDL-C:
  - VLDL: 85%
  - LDL: 60%

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**APO B VERSUS NON-HDL CHOLESTEROL**

Target levels reached:

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NON-HDL-C VS APO B

Figure 2 Illustration demonstrating the variance or discordance between non-HDL-C and apoB from the US population survey National Health and Nutrition Examination Survey 2005-2006. On the left (A), non-HDL-C and apoB are depicted as percentiles whereas on the right (B), the HRs for each are calculated on the basis of the range values for both reported by the Emerging Risk Factors Collaboration study. For a 75th percentile level of non-HDL-C, apoB may vary from the 40th to the 90th percentile. The variance of non-HDL-C for the equivalent level of apoB is just as great. Similarly, for a HR of non-HDL-C of 2.75, the HR of apoB may vary from 1.90 to 3.45.

APO B AND NON-HDL CHOLESTEROL

Baseline and treatment correlations for non–high-density lipoprotein cholesterol and apolipoprotein B and low-density lipoprotein cholesterol and apolipoprotein B by baseline triglyceride tertiles

<table>
<thead>
<tr>
<th>TG Tertile</th>
<th>Baseline</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL cholesterol vs. ApoB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low TG</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>Middle TG</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>High TG</td>
<td>0.69</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Am J Cardiol 2009;104:548–553
### APO B AND NON-HDL CHOLESTEROL

**Baseline** | **Treatment**
---|---
APO B and non-HDL cholesterol vs. ApoB

<table>
<thead>
<tr>
<th>TG Level</th>
<th>Baseline</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TG</td>
<td>0.93</td>
<td>0.96</td>
</tr>
<tr>
<td>Middle TG</td>
<td>0.91</td>
<td>0.93</td>
</tr>
<tr>
<td>High TG</td>
<td>0.69</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Am J Cardiol 2009;104:548–553*

### APO B VS NON-HDL CHOLESTEROL

- **A**: Baseline
- **B**: On Statin

*J Am Coll Cardiol 2008;52:626–32*
APO B VS NON HDL CHOLESTEROL

Table 3  Linear Regression of ApoB Versus Non-HDL-C at Baseline (Untreated) and on Statin Therapy

<table>
<thead>
<tr>
<th></th>
<th>Slope</th>
<th>Intercept</th>
<th>r²</th>
<th>Non-HDL-C (ApoB = 0)</th>
<th>mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Tg</td>
<td>1.92</td>
<td>98.8</td>
<td>0.70</td>
<td>190.7</td>
<td></td>
</tr>
<tr>
<td>High Tg</td>
<td>1.92</td>
<td>-44.1</td>
<td>0.71</td>
<td>135.8</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.96</td>
<td>-34.4</td>
<td>0.70</td>
<td>129.8</td>
<td></td>
</tr>
<tr>
<td>On statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Tg</td>
<td>1.27</td>
<td>-10.0</td>
<td>0.92</td>
<td>104.6</td>
<td></td>
</tr>
<tr>
<td>High Tg</td>
<td>1.25</td>
<td>-8.3</td>
<td>0.92</td>
<td>104.1</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.26</td>
<td>-8.9</td>
<td>0.92</td>
<td>104.4</td>
<td></td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2008;52:626–32

Preventive Cardiology

Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment

John J. Kostis, MD, PhD; Wen A. van der Steeg, MD; Jager Horne, PhD; Michael Gaffney, PhD; Nils B. Cates, MD; Philip Morton, MD, PhD; Prakash Babu Amruthur, MD, PhD; Peter G. Visscher, MD; Michael Scarchilli, MD; John C. Libby, MD; Terje R. Pedersen, MD, PhD; Scott M. Grundy, MD, PhD, for the TNT and IDEAL Study Groups

Background—Low-density lipoprotein (LDL) cholesterol is the principal target of lipid-lowering therapy, but recent evidence has suggested more appropriate targets. We compared the relationships of cardiovascular events with LDL cholesterol, non-HDL cholesterol, high-density lipoprotein (HDL) cholesterol, and apolipoprotein B, as well as ratios of total/HDL cholesterol, LDL/HDL cholesterol, and apoB/apoA-1, with the occurrence of cardiovascular events in patients receiving statin therapy.

Methods and Results—A post hoc analysis was performed that combined data from 2 prospective, uncontrolled clinical trials in which 30,691 (“Treating to New Targets”) and 6038 (“Incremental Decrease in End Points Through Aggressive Lipid Lowering”) patients with established coronary heart disease were assigned to usual care or a high-intensity lipid-lowering treatment. In models with LDL cholesterol, non-HDL cholesterol, and apoB/apoA-1, a positive relationship with cardiovascular outcome, whereas a positive relationship with LDL cholesterol was lost. In a model that combined non-HDL cholesterol and apoB/apoA-1, neither was significant owing to collinearity. Total/HDL cholesterol ratio and the apoB/apoA-1 ratio in particular were each more closely associated with outcome than any of the individual atherogenic lipoprotein parameters.

Conclusions—In patients receiving statin therapy, cardiovascular event-free treatment of non-HDL cholesterol and apoB/apoA-1 may be more closely associated with cardiovascular outcome than levels of LDL cholesterol. Inclusion of measurements of the atherogenic lipoprotein fraction further strengthened the relationship. These data support the use of non-HDL cholesterol or apoB/apoA-1 as novel treatment targets for statin therapy. Given the absence of intervention that have been proven to consistently reduce cardiovascular disease risk through raising plasma levels of HDL cholesterol or apoB/apoA-1, these measures to consider the ratio variables as clinically useful. (Circulation. 2010;121:302-309.)
Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study

Lancet Jul 2008; 372: 224-33
INTERHEART

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>TC/HDL C ratio (95% CI) 1</th>
<th>ApoB/ApoA1 ratio (95% CI) 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.17 (1.13-1.20)</td>
<td>1.59 (1.50-1.64)</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.34 (1.24-1.45)</td>
<td>1.77 (1.64-1.92)</td>
</tr>
<tr>
<td>European</td>
<td>1.31 (1.25-1.37)</td>
<td>1.47 (1.37-1.58)</td>
</tr>
<tr>
<td>South Asian</td>
<td>1.19 (1.04-1.37)</td>
<td>1.53 (1.42-1.64)</td>
</tr>
<tr>
<td>Latin American</td>
<td>1.00 (0.90-1.10)</td>
<td>1.27 (1.17-1.37)</td>
</tr>
<tr>
<td>Arab</td>
<td>1.12 (0.99-1.25)</td>
<td>1.21 (1.09-1.32)</td>
</tr>
<tr>
<td>Other Asian</td>
<td>1.08 (0.93-1.25)</td>
<td>1.59 (1.42-1.77)</td>
</tr>
<tr>
<td>Coloured African</td>
<td>1.43 (1.16-1.77)</td>
<td>1.98 (1.60-2.49)</td>
</tr>
<tr>
<td>Black African</td>
<td>1.69 (1.29-2.20)</td>
<td>1.59 (1.35-1.97)</td>
</tr>
</tbody>
</table>

**Lancet** Jul 2008; 372: 224-33
AMORIS STUDY

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (n = 1160)</th>
<th>Female (n = 536)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1. ApoB/apoA-I</td>
<td>1.53</td>
<td>1.45–1.61</td>
</tr>
<tr>
<td>2. IDL C/HDL C</td>
<td>1.16</td>
<td>1.13–1.19</td>
</tr>
<tr>
<td>3. TC/HDL C</td>
<td>1.15</td>
<td>1.12–1.18</td>
</tr>
<tr>
<td>4. Non-HDL C/HDL C</td>
<td>1.15</td>
<td>1.12–1.18</td>
</tr>
<tr>
<td>P-values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. vs. 2.</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1. vs. 3.</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1. vs. 4.</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All other combinations</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

LIPID RATIOS

- The relationship between apo B and risk is continuous where the relationship with HDL is more complex at the extremes of values.
- Do LDL and HDL contribute equally and continuously at all values?
CONTINGENT EFFECT OF HDL ON CV RISK

Current Atherosclerosis Reports 2007, 9:261–265

ROC CURVE ANALYSIS

1.) GOES STUDY (593 statin treated pts)
   - APO B/APO A-1 HR = 3.77  AUC = 0.655
   - TC/HDL HR = 1.19  AUC = 0.65

2.) EPIC NORFOLK STUDY (NO STATINS AND AODM)
   - HDL = 52 MG/DL  TG = 141 MG/DL
   - APO B/APOA-1 OR = 2.08  AUC = 0.673 (FRS)
   - TC/HDL OR = 1.85  AUC = 0.67

3.) FRAMINGHAM HEART STUDY n=3332 f/u=15yrs
   - APO B/APO A1 HR = 1.39  AUC = 0.74
   - TC/HDL HR = 1.39  AUC = 0.73

4.) FIELD N= 9795 F/U = 5 YRS
   - APO B/APO A1 HR = 1.2  AUC = 0.589
   - TC/HDL HR = 1.21  AUC = 0.592
ROC CURVE ANALYSIS

AMORIS STUDY

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL C &lt;3.6 (n = 23931)</td>
<td>LDL C &gt;3.6 (n = 40799)</td>
</tr>
<tr>
<td>1. ApoB/apoA-I</td>
<td>0.641</td>
<td>0.702</td>
</tr>
<tr>
<td>2. LDL/HDL</td>
<td>0.585</td>
<td>0.557</td>
</tr>
<tr>
<td>3. TC/HDL</td>
<td>0.572</td>
<td>0.565</td>
</tr>
<tr>
<td>#AMI</td>
<td>257</td>
<td>73</td>
</tr>
<tr>
<td>P-values</td>
<td>0.017</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Errors using ratios

- **EPIC NORFOLK STUDY** - APO B/APO A1 The percent of reclassified cases was incorrect 41% of the time and controls reclassified in error 50% of the time.

- **FRAMINGHAM STUDY** - APOB/APOA1 had net improvement of reclassification of risk of 9.2%

- **AMORIS STUDY** - TC/HDL underestimates risk in 69% of men and 85% of women and overestimates risk in 26% of men and 12% of women.

Lp(a): LDL with apolipoprotein(a) attached

- Binds LDL receptor and oxidized LDL receptor
- Binds vascular matrix and cells
- Inhibits fibrinolysis
- Promotes smooth muscle cell activity


Lp(a) – cholesterol in Framingham

Odds Ratio for CHD 2.3x higher when Lp(a) cholesterol > 10mg/dL, after adjusting for age, HDL, LDL, smoking, diabetes, BP, and BMI.

Clinical Chemistry 1999; 45(7):1039-1046
Lp(a) CHOLESTEROL VS Lp(a) MASS

Steven R. Jones, Johns Hopkins Hospital, Baltimore, MD; Krishnaji Kulkarni, Atherotech

- Lipoprotein (a) Cholesterol, But Not Lp(a) Mass, Is An Independent Predictor Of Angiographic Coronary Artery Disease And Subsequent Cardiovascular Events In Patients Referred For Coronary Angiography.

  - Joseph P McConnell1; Linnea M Baudhuin1; Peter B Berger2; Iftikhar J Kullo3; John F O'Brien3; Sandra C Bryant3; Stacy J Hartman3; Jennie N Ward3; Ryan J Lennon3; Virend K Somers3; George G Klee3; Allan S Jaffe3
504 patients undergoing coronary angiography had both Lp(a) cholesterol and mass measured and were followed for 4.0 years for CV events.

- Elevated Lp(a) cholesterol and Lp(a) mass were significantly associated with extent of angiographic CAD (P < 0.001).
- High Lp(a) cholesterol was also significantly associated with CV events (p= 0.01), while high Lp(a) mass approached but did not reach statistical significance (P=0.06).

In a multiple regression analysis model adjusting for age, gender, LDL cholesterol, HDL, triglyceride, Lp(a) mass, and Lp(a) cholesterol; Lp(a) cholesterol remained a significant predictor of angiographic CAD (OR 1.54, 95% CI 1.24 –1.91, P <.001) and CV events (OR 1.34, 95% CI 1.06 –1.67, P = 0.01), while Lp(a) mass was no longer significantly associated with CAD (p=0.96) or events (p=0.28).
Oxidized Phospholipids, Lipoprotein(a), Lipoprotein-Associated Phospholipase A2 Activity and 10-Year Cardiovascular Outcomes: Prospective Results from the Bruneck Study

- 765 inhabitants of Bruneck, Italy were studied over a 10 year period.
- The primary end-point was CV death, MI, CVA, and TIA.
- OXPL/apo B, Lp(a), and Lp-PLA2 were measured.

ATVB 2007;27;1788-95
ADDITIVE EFFECTS OF Lp(a) AND PLA2

BRUNECK STUDY
- Prospective population based survey
  - 765 subjects with CAD
  - 10 year follow-up (82 events)
  - End point was CV death, MI, CVA or TIA
  - RR was elevated in highest tertiles of both Lp(a) and Lp-PLA2 activity versus lowest tertiles RR=3.5 vs 1.0

EPIC NORFOLK STUDY
- Nested Case Control Study
  - 763 cases
  - 1397 controls
  - 6 year follow-up
  - End point was fatal and non-fatal CAD
  - RR was elevated in highest tertiles of both Lp(a) and sPLA2 activity versus lowest tertiles RR=2.97 vs 1.00

ATVB 2007;27;1788-95

JACC Vol,56, No. 12,2010
Sept 14,2010:946-55
**MULTIPLE BIOMARKERS**

- Uppsala Longitudinal Study of Adult Men
  - N=1135 men (Mean age = 70 yrs)
  - Follow-up 10 years
  - Assessed additive effects of troponin I, pro-BNP, cystatin C, and hs-CRP on death from all causes and CV death.
  - All the biomarkers predicted total mortality and CV death.
  - Subjects with elevated levels of any two biomarkers tripled the risk of CV death.
  - Subjects with 3 biomarkers = 7 fold increased risk
  - C statistic was increased from 0.664 to 0.766 with addition of the 4 biomarkers to established risk factors.
Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death

- Measured 10 biomarkers in 3209 participants in the Framingham Heart Study with 7.4 yrs of follow-up.
- Measured CRP, BNP, NT-pro-ANP aldosterone, renin, fibrinogen, d-dimer, PAI-1, homocysteine, and urinary albumin to creat ratio
- Endpoints were total mortality, and major CV events

n engl j med 355;25;2631-2639

Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death

<table>
<thead>
<tr>
<th>Multimarker Score</th>
<th>Death</th>
<th>Major Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>adjusted hazard ratios (95% CI)</em></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.0 (reference group)</td>
<td>1.0 (reference group)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.34 (0.83–2.18)</td>
<td>1.54 (0.98–2.40)</td>
</tr>
<tr>
<td>High</td>
<td>4.08 (2.31–6.62)</td>
<td>1.84 (1.11–3.05)</td>
</tr>
</tbody>
</table>

P value for trend: <0.001 0.02

N ENGL J MED 355;25;2631-2639
SUMMARY

Cholesterol Risk
– Apo B or Non-HDL Cholesterol  Treat with statins

Inflammatory Risk  Treat with combination Rx
– HS-CRP
– Lp(a)
– Lp-Pla2

Cardiorenal Risk  Treat with ACE-I, ARB, DRI
– Microalbumin
– BNP

Figure 2. Association of standard lipids, NMR lipoproteins, and immunoassay apolipoproteins with incident CVD in 27,673 initially healthy women in the Women’s Health Study. *p < 0.0001 for each lipoprotein compared with total HDL cholesterol (control) after adjustment for other lipids. **p < 0.01 for each lipoprotein compared with all other lipoproteins after adjustment for other lipids.