Baptist Health South Florida
Eleventh Annual CVD Prevention Symposium
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LDL and HDL Subclasses
Use and Misuse in the Community

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Clinical Professor - Mercer University School of Pharmaceutical Sciences
Chairman - Cholesterol, Genetics, and Heart Disease Institute (501C3)
Prevention Committee, Saint Joseph’s Hospital of Atlanta

AGENDA:
1. ALP – What is it? What are Subclasses?
2. Risk Prediction: LDL & HDL subclasses
3. Disease Management
4. Use
   Don’t order any “Advanced” tests unless:
   1. the results will change the diagnosis/prognosis
   2. change a therapeutic decision, or
   3. help a family member.
5. Misuse

Disclosures
• Chief Medical Officer – Celera/Quest Diagnostics
• CV Prevention Committee, Saint Joseph’s Hospital Atlanta
• Director, Cholesterol, Genetics, and Heart Disease Institute (501C3 non-profit)
• Clinical Professor - Mercer University School of Pharmaceutical Sciences
• Pharmaceutical Company Lectures – None
• Pharmaceutical Company Consulting – None
• Device Company - None
It’s NOT NEW: LDL Subclass Distribution Test - Historical Perspective

John Gofman, Wei Young, Robert Tandy
Ischemic Heart Disease, Atherosclerosis, and Longevity
Circulation 1966;34:679-697.
1950 analysis of Framingham data at Donner Laboratory (UCB) “Atherogenic Index”
Ron Krauss et. al. Lawrence Berkeley National Laboratory,
University of California, Berkeley

Atherogenic Lipoprotein Profile
ALP - A Nasty Metabolic Stew

- 2-fold rate arteriographic progression
- Thromboxane synthesis
  (Mikszcan 1992)
- Low VIT E Oxidative Susceptibility
  (Tribble 1992, Dejager 1993)
- Insulin Resistance
  (Krauss 1991)
- Inheritance
  (Austin 1994)
- LDL size related to endothelial vasodilator dysfunction
  (Dyce 1993)

- Small LDL Subclass Distribution Test
  - HDL Subclasses
  - IDL Subclasses
  - HDL2b

7-LDL Subclasses 5 HDL Subclasses, 2 IDL Subclasses

ALP Small LDL (predominately) Low HDL2 “Elevated” TG 3-Fold CHD Risk

Defined by DENSITY (AnUC) or DIAMETER (GGE)
GEMMA (Ion Mobility) Components
Ronald M. Krauss, MD University of California
Michael Caulfield, PhD Nichols Institute

Sample Introduction
Spray & Dry
Aerosol analyzer
Detector

Air + CO
+HV
-HV
+1
-1

Liquid Sample
Detector
Condenser
Saturated vapor in
Light beam
Blower
Fiber

Subclasses by Ion Mobility

Pattern A
Larger LDLs
More HDL2
Less IDL

Pattern B
Smaller LDLs
Less HDL2
More IDL

- A subset of high risk patients have a predominance of small, dense LDL particles referred to as “LDL Pattern B”
  - Very high risk for CHD (3-fold)
  - Respond differently to diet and drug therapy than the typical patient with elevated LDL C (pattern A)
  - Better arteriographic response to specific treatment vs pattern A

Hindrance to Large Scale Adoption:
1. Availability of quality laboratory measurements (QC)
2. The Most EFFECTIVE Treatments are the LEAST Expensive.

Ion Mobility Advantage
1. Laws of Physics
2. Quantitative
3. Reproducible
4. Fast
5. Developed by Ronald M. Krauss, MD
6. Multiple clinical trials (Malmo, Jupiter etc)

NCEP ATP-III (May 2001)
Recognizes “Metabolic Syndrome” as Secondary Target of Therapy.
Metabolic Syndrome = > 3 or the following:
1. abdominal obesity (Waist circum > 40 in M, > 35 in F)
2. atherogenic dyslipidemia
elevated Triglycerides (> 150 mg/dl)
low HDL-C (M < 40, F < 50)
small LDL; particles (text description)
3. raised BP (>130/85)
4. insulin resistance (+ glu intolerance  FBS > 110)
5. Prothrombotic and proinflammatory states

(Grundy S. et al. JAMA 2001;285:2486-2496)
Meta Syn Definitions

Old NCEP, Revised NCEP, World Health Organization (WHO), International Diabetes Foundation, European Group for the Study of Insulin Resistance.

<table>
<thead>
<tr>
<th>Defn</th>
<th>Old NCEP</th>
<th>Revised NCEP</th>
<th>WHO</th>
<th>IDF</th>
<th>EU/IDF</th>
<th>US/WHO</th>
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<tbody>
<tr>
<td>HBP</td>
<td>T135/80</td>
<td>T135/80</td>
<td>&gt;140/90</td>
<td>&gt;140/90</td>
<td>&gt;140/90</td>
<td>&gt;140/90</td>
</tr>
<tr>
<td>Trig</td>
<td>≥150</td>
<td>≥150 or Rx</td>
<td>≥150 or Rx</td>
<td>≥150 or Rx</td>
<td>≥150 or Rx</td>
<td>≥150 or Rx</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40/50</td>
<td>&lt;40/50 or Rx</td>
<td>&lt;40/50 or Rx</td>
<td>&lt;40/50 or Rx</td>
<td>&lt;40/50 or Rx</td>
<td>&lt;40/50 or Rx</td>
</tr>
<tr>
<td>Fasting Glu</td>
<td>≥110</td>
<td>≥110</td>
<td>≥110</td>
<td>≥110</td>
<td>≥110</td>
<td>≥110</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>&gt;1.837</td>
<td>&gt;1.837</td>
<td>&gt;1.837</td>
<td>&gt;1.837</td>
<td>&gt;1.837</td>
<td>&gt;1.837</td>
</tr>
<tr>
<td>UAC ratio</td>
<td>&gt;30mg/g</td>
<td>(Hari P et al MetaSyn Related Dis 2011;X:1-9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is the Most Common Cause of Small LDL and Low HDL2?

Obesity Trends* Among U.S. Adults

BRFSS. 1989

(*BMI ≥30, or ~30 lbs overweight for 5' 4" woman)
Obesity Trends* Among U.S. Adults
BRFSS, 2009
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Reversal of Small, Dense LDL Phenotype by Normalization of Adiposity
Randomized controlled trial of moderately overweight (BMI 25-28) healthy men.
N= 37 control, n=96 weight loss (9-wk wgt loss then 4-wk wgt stabilization)
Wgt loss = ~1,000 kcal/day diet (40% CHO), 40% fat, 20% protein, both groups = same exercise.
Wgt loss ~8.5 kg (18.7 lb)
A->A 97% 76%
A->B 3% 24%
B->A 58% 10%
B->B 42% 90%
X2 p<0.0002
Pattern B men who achieved a BMI < 25 -> 81% converted to pattern A.

“Conversion of LDL subclass pattern B to pattern A and reversal of ALP can be achieved in a high proportion of overweight men by normalization of adiposity.”

Misuse and Use #1
Lipoprotein Subclass Distribution and the Metabolic Syndrome
Misuse: Determine LDL subclass as part of Metabolic Syndrome.
The vast majority of MetaSyn patients have small LDL and linked to Trig levels.
Use: In patients with Trig < 150 mg/dl in whom you are concerned about a dyslipoprotein linked to MetaSyn, determination of LDL subclass pattern may be informative.

The most EFFECTIVE Therapy is often the LEAST Expensive!

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Topics:
1. ALP – What is it?
2. Risk Prediction: LDL & HDL subclasses
3. Disease Management
4. Use
5. Misuse

CV Events & Clinical Trials

20-30% RR Reduction is Not Enough

More LDL-C Reduction or SMARTER LDL-C Reduction?

Control group with events
Treatment group with events

Many patients reduce LDL-C yet Continue to have Events!


N=17,832, healthy LDL<130, CRP>2.0
Rosuva 20 vs Placebo 1.5 yr
Stopped early

No. 8901 8901
Events 142 251
N 1.6 2.8
ARR -1.2%

Use of “Advanced Risk Markers”

"... the AHA and other national groups have recommended that the use of these novel modalities should be reserved for refining risk estimates in intermediate-risk patients when there is uncertainty about the need to start drug therapy (1-4).


(Mosca L et al. JACC 2011;57:140A-1433)

Update: Lipoprotein Subclasses

European Consensus Statement on LDL subclasses 2011

A new consensus statement on the clinical significance of LDL subclasses was published in 2011 authored by 18 lipoprotein and coronary heart disease experts.

Current proposed nomenclature for LDL subclasses are based on density or size determined by ultracentrifugation or polyacrylimide gradient gel electrophoresis (SGGE).

The review of large, prospective epidemiologic studies of LDL heterogeneity noted that in respect to the Quebec Cardiovascular Study, “LDL size by GGE predicted the rate of CHD independent of LDL and HDL cholesterol, TGs, Apo B, and total cholesterol to HDL ratio.” In the Epic-North study it was noted that LDL size was inversely related to CHD (OR 0.67, CI 0.67-0.76). However, this is to be expected since the small LDL condition is associated with greater particle number for any given level of LDL-C.

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**LDL Size is a CAD Risk Factor**

*Independent* of TG and HDL-C

Semi-quantitative methods of meta-analysis to:
- Boston Heart Study (ANUC)
- Physicians Health Study (GGE)
- Stanford Five-City Project (GGE)
- Quebec Cardiovascular Study (GGE)

Follow-up 5-13 years

A 10 angstrom decrease in LDL size is associated with a significant increase in CAD risk (~30%) *independent* of TG, TC, HDLC, and other covariates.

(Austin M; Circ 1999;99:1124)

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**Small LDL Predicts CV Events**

<table>
<thead>
<tr>
<th>Study</th>
<th>Boston Area</th>
<th>Stanford</th>
<th>Harvard MD</th>
<th>Quebec</th>
<th>Women's Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Method</td>
<td>ANUC</td>
<td>GGE</td>
<td>GGE</td>
<td>GGE</td>
<td>NMR</td>
</tr>
<tr>
<td>LDL gp</td>
<td>B&lt;257 A</td>
<td>1/5: &lt; 260 A</td>
<td>1/5: &lt; 250</td>
<td>1/5: &lt; 256</td>
<td>1/5: NMR</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>3.0</td>
<td>2.9</td>
<td>2.7</td>
<td>3.6</td>
<td>HR = 1.76</td>
</tr>
<tr>
<td>Covariant</td>
<td>TG</td>
<td>LDL/C</td>
<td>HDL/C</td>
<td>Apo B</td>
<td>HR = 1.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>non-fasting</td>
<td></td>
<td>Apo B</td>
<td>HR = 1.76</td>
</tr>
</tbody>
</table>

* Small LDL predicts CAD risk *independent* of Trig, TC, LDLC, HDLC.

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**Prospective Population Based Study of LDL size and CAD Risk**

Quebec CV Study 2,057 Men followed for 5 years.

<table>
<thead>
<tr>
<th>Yes CAD event</th>
<th>No CAD event</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL size</td>
<td>255.2 A</td>
</tr>
</tbody>
</table>

*Risk & LDL size *NOT* linear. < 256 A risk increased significantly.

*Magnitude* of risk from OTHER risk factors modulated by LDL size.

*Example:* Risk of elevated Apo B or LDLC increased 150%-200% in the presence of small LDL vs those with large LDL.

*Information on LDL size may improve ability to accurately predict IHD risk over traditional lipid variables."

(Lamarche et al. Circ 2000;102(I):853)
Small LDL-C and 13 Years Events

Quebec CV Study: 13 yr follow-up, n=2,072 Men
- GGE: LDL-C > 260 A; LDL-C < 255 A
- Strong and independent relationship of LDL-C < 255 A (small LDL) and CAD risk
- Large LDL (≥ 260 A) NOT associated with risk.

LDL-C > 260 A = LDL-C ≥ %LDL ≥ 260 A

The "Amount" of small LDL is important.
Thus, reduction of LDL mass in LDL pattern B subjects is of extra importance.

Quebec Cardiovascular Study: Small LDL & Apo B

Apo B > 120
LDL dia < 256

Odds Ratio

Is It LDL Particle Size or Number that Correlates with Risk for CVD?
(Superko & Gadesam, Curr Athero Reports 2008;10:377-385)

This is Not a Competition
It’s Both
**Triglycerides are Unreliable for Predicting LDL Subclass Pattern in Individual Patients**

Trig Range
70 - 250 mg/dl
r=0.55
p<0.0001
A > 263 A
B < 257 A

Regression Plot
Y = 1512.055 - 5.281 * X; R^2 = .306

A > 263 A
B < 257 A

**LDLC/Apo B and LDL PPD (A)**

Atlanta Cardiology
N = 543
R = 0.41
P = 0.0001

How does this apply to YOUR INDIVIDUAL patient?

**HDL2b: CAD Severity and Progression**

A. Hyper Trig Male
B. Normo Trig Male
C. Normo Trig Male
D. Healthy Normo Trig Female

HDL2b-GGE = HDL2 ANUC
(Gradient Gel Electrophoresis)

Update: HDL Subclass

1. Fifty-three year follow-up of coronary heart disease vs. HDL2 and other lipoproteins in Gofman's Livermore Cohort.
   Paul T. Williams, Ph.D. J or Lipid Research 2012;53:266-72.
   1329 men (69.8%) who died through 2008, 408 with CHD listed as a cause of death, and 113 who died prematurely (≤age 65) with CHD listed as a cause. When adjusted for age, the risk associated with the lowest HDL2 quartile increased 22% for all-cause (P=0.001), 63% for total CHD (P<10^{-5}), and 117% for premature CHD mortality (P=0.0001). Thus low HDL2 is associated with increased CHD risk.

2. High-density lipoprotein Subclasses and their Relationship to Cardiovascular Disease.
   HR Superko, L Pendyala, PT Williams, KM Momary, SB King III, BC Garrett. J or Clinical Lipidology 2012;
   Measurements of HDL2b by gradient gel electrophoresis provided more consistent evidence of CHD risk than measurement of HDL2 cholesterol.
   HDL2 and HDL3 cholesterol do not distinguish cardioprotective differences between HDL subclasses. More extensive characterization of HDL particles by GGE, ionmobility, or ultracentrifugation may provide more specific information about CHD risk than the measurement of HDL-C, HDL3 cholesterol, or HDL2 cholesterol.

HDLb is Most Informative when HDL-C is “Normal”

Misure use and Use #2

Misuse: Determine LDL subclass pattern in all patients to determine CAD risk.
The presence of the small LDL pattern B trait can be predicted in many patients based on elevated Trigs (> 200 mg/dl), or low HDLC (< 40 mg/dl in men < 50 mg/dl in women).

Use: If the presence of the small LDL trait would affect the diagnosis, further evaluation, treatment decisions, or family screening, then determination of LDL subclass distribution in patients with “normal” standard lipids may be informative.
AGENDA:
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Arteriographic Trial Evidence
ALP or Metabolic Syndrome

<table>
<thead>
<tr>
<th>Funding</th>
<th>Year</th>
<th>NIH (ID)</th>
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<tbody>
<tr>
<td>NHLBI Type II (NHLBI + UCBerkeley)</td>
<td>1987</td>
<td>NHL (Sf12-20, 0-7)</td>
</tr>
<tr>
<td>CLAS (TG break points) (USC+UCBerkeley)</td>
<td>1993</td>
<td>NIH</td>
</tr>
<tr>
<td>STARS (London, England)</td>
<td>1993</td>
<td>Nat'l Health</td>
</tr>
<tr>
<td>MARS (USC + UCBerkeley)</td>
<td>1994</td>
<td>NIH+Merck</td>
</tr>
<tr>
<td>SCRIP (Stanford + UCBerkeley)</td>
<td>1996</td>
<td>NIH (Sf0-7,PPD)</td>
</tr>
<tr>
<td>FATS (Univ. Washington)</td>
<td>1996</td>
<td>NIH (RF)</td>
</tr>
<tr>
<td>SCRIP (Stanford + UCBerkeley)</td>
<td>2000</td>
<td>NIH (LDL IIIa+b)</td>
</tr>
<tr>
<td>EAST (Emory University+UCBerkeley)</td>
<td>2000</td>
<td>NIH (LDL IIIa+b)</td>
</tr>
<tr>
<td>HATS (Univ. Washington)</td>
<td>2001</td>
<td>NIH (LpA1,HDL2)</td>
</tr>
<tr>
<td>SCRIP (Stanford + UCBerkeley)</td>
<td>2003</td>
<td>NIH (LDL IVb)</td>
</tr>
<tr>
<td>DAIS (Finland)</td>
<td>2003</td>
<td>Fournier Labs (PPD)</td>
</tr>
</tbody>
</table>

SCRIP / LBNL Subclasses 1996
(Miller et al. Circulation 1996;94:2146-2153)

Subjects: Dense LDL = > 1.0378 n=92, Buoyant LDL = < 1.0378; n=121
(Analytic ultracentrifugation and GGE)

Outcome: Significant reduction in the rate of arteriographic CAD progression in patients with Dense but not Buoyant LDL.
LDLC reduction was the same in Dense and Buoyant RR subgroups.

“Distinct metabolic processes may give rise to different types of LDLs and to different responses to a specific therapy. LDL profiles may be useful indicators of optimal therapy for individual patients.”
The SAME

St. Thomas Atheroma Regression Study (STARS)

90 male CAD pts randomized to usual care (UC) or dietary intervention (D) or diet + cholestyramine (DC) for 3.3 yrs in England. Baseline LDLC ~ 194 mg/dl (reduced to 130 mg/dl in the DC group). The general results were a significant reduction in the arteriographic rate of progression (p=0.01).

A follow-up analysis revealed that the most dense LDL subfraction (DLDS on density gradient ultracentrifugation (d = 1.040-1.063 kg/L)) was "the plasma lipoprotein subfraction that exerts the single most powerful effect on the course of CAD in middle-aged men with hypercholesterolemia".

(Watts et al. Metabolism 1995;44:1461-1467)
Change in LDL Density in FATS

Familial Atherosclerosis Treatment Study (FATS)

n=88 (subset of FATS) Groups = Niacin+colestipol, lovastatin+colestipol, colestipol, placebo.

LDL buoyancy by Density Gradient Ultracentrifugation

Decrease in Hepatic Lipase assoc with increased LDL buoyancy.

"Changes in LDL buoyancy with drug therapy were the best correlates of changes in coronary stenosis" Accounts for 37% of change while apol accounts for an additional 5%.

"LDL density appears to be a realistic and rewarding additional therapeutic target for CAD prevention."

(Zambon et al Circ 1999;99:1959-1964)

FATS and LDL Buoyancy

Changes in LDL buoyancy and HL activity were associated with changes in disease severity (p<0.0005). In a multivariate analysis, an increase in LDL buoyancy was most strongly associated with CAD regression, accounting for 37% of the variance of change in coronary stenosis (p<0.001) followed by reduction in apolipoprotein B (5% of variance p<0.05).

These studies support the hypothesis that therapy-associated changes in HL alter LDL density, which favorably influences CAD progression. This is a new and potentially clinically relevant mechanism linking lipid-altering therapy to CAD improvement.

(Zambon et al Circ 1999;99:1959-1964)

Results of multiple linear regression analysis by best-subset technique, showing the percent variance of changes in coronary stenosis accounted for by changes in each of the variables sequentially added (see "Statistical Analyses" in the Methods section).

New Lessons from EAST

Emory Angioplasty versus Surgery Trial (EAST)  
(King S. et al. NEJM 1994;331:1044-1050)  
PTCA vs. CABG in multivessel CAD, 3 yrs, n=392  
PTCA vs CABG does not differ significantly in the composite end point (death, Q wave MI, thallium).  
More additional revascularization required in PTCA group.  
No Drug Treatment. Mean TC did not change over the course of the investigation.

EAST: New Lesions and LDL IIIa,b IVa,b

<table>
<thead>
<tr>
<th>Pattern</th>
<th>YES n=57</th>
<th>NO n=288</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern A</td>
<td>23(51%)</td>
<td>153(66%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pattern B</td>
<td>18(40%)</td>
<td>58(23%)</td>
<td></td>
</tr>
<tr>
<td>LDL IIIa,b,IVa,b</td>
<td>30.9%</td>
<td>24.9%</td>
<td>0.016</td>
</tr>
<tr>
<td>LDL Pla dia (A)</td>
<td>262.3</td>
<td>265.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Tgcy</td>
<td>13.1</td>
<td>12.6</td>
<td>0.61</td>
</tr>
</tbody>
</table>

"These data confirmed that small, dense LDL particles are significantly associated with CAD progression. Therefore, lipid management for atherosclerosis should include LDL particle size and distribution modification as well as LDLc level reduction."


Small LDL and Fenofibrate (DAIS)

Correlates of on-treatment with Δ mean lumen dia

<table>
<thead>
<tr>
<th>Correlation</th>
<th>All</th>
<th>Feno</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL PPD</td>
<td>-0.10</td>
<td>-0.21*</td>
<td>0.00</td>
</tr>
<tr>
<td>LDLc</td>
<td>0.11*</td>
<td>0.20*</td>
<td>0.03</td>
</tr>
<tr>
<td>LDLc/ApoB</td>
<td>-0.05</td>
<td>-0.10</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

*In subjects with low LDLc a preponderance of small LDL increased progression. Focusing only on LDLc as a therapeutic target may be misleading in these subjects.

(Yakkilainen et al. Circ 2003;107:1733-1737)
Figure 2. Kaplan-Meier survival curves for quartiles of HDL2 (top) and HDL3 (bottom) cholesterol (C) concentrations expressed as the estimated probability of not having IHD during the 10-year follow-up. The log-rank test showed that the difference in estimated probability was different over the four HDL2 cholesterol quartiles (P=0.01). The test did not reach statistical significance for HDL3 cholesterol quartiles (P=0.06).

(Salonen JT et al. Circulation 1991;84:129-139)

Don’t be Satisfied with “AVERAGE” values.

HL Gene Promoter variant Determines Response to Lipid Lowering Rx

N = 49 dyslipidemic men with CAD in FATS. QCA 2.5 yr FIIU.
HL C>T genotypes: CC n=25 (51%), TC n=20 (41%), TT n=4 (8%)
Rx 1) lovastatin (40 mg/d) + colestipol (30 g/d),
or 2) niacin (4 g/d) + colestipol (30 g/d)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CC (51%)</th>
<th>TC (41%)</th>
<th>TT (8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trig %</td>
<td>-19%</td>
<td>-18%</td>
<td>-27%</td>
</tr>
<tr>
<td>LDL C %</td>
<td>-38%</td>
<td>-37%</td>
<td>-40%</td>
</tr>
<tr>
<td>HDL C %</td>
<td>+35%</td>
<td>+22%</td>
<td>+14%</td>
</tr>
<tr>
<td>HDL2 C %</td>
<td>+335%</td>
<td>+128%</td>
<td>+49%</td>
</tr>
<tr>
<td>Apo A1 %</td>
<td>+12%</td>
<td>+11%</td>
<td>+5%</td>
</tr>
<tr>
<td>LDL Rf %</td>
<td>+12%</td>
<td>+6%</td>
<td>+1%</td>
</tr>
<tr>
<td>HL %</td>
<td>-18%</td>
<td>-9%</td>
<td>-5%</td>
</tr>
<tr>
<td>Coronary stenosis</td>
<td>-2.1%</td>
<td>-1.1%</td>
<td>+4.0%</td>
</tr>
</tbody>
</table>

Conclusions:
Screening for HL promoter region variants id’s CAD pts who benefit most from lipid lowering Rx
Those “resistant” to HL mediated lipid lowering may benefit from aggressive LDLC lowering.
Clinically relevance: a) arteriographic change correlated with clinical events, b) 20-47% of CAD population have HL polymorphism, c) screening could become important parameter in choice of treatment strategies and cost effectiveness.

(Zambon et al. Circ 2001;103:792-798)
Simultaneous LDL-C Lowering and HDL-C Elevation for Optimal CVD Reduction

Meta-analysis of 23 Lipid Trials; n= 83,000

- The cardiovascular event rate reductions associated with a decrease in LDL-C and an increase in HDL-C are statistically independent.

- Meta-analysis revealed that the sum of % increase in HDL-C and % decrease in LDL-C (%ΔHDL + %ΔLDL) predicts cardiovascular benefits more effectively than either component alone.

- This analysis supports the notion that a readily attainable 40% reduction in LDL-C combined with a 30% elevation in HDL-C will result in ~70% CHD risk reduction and a revolution in cardiovascular prevention.

- A NEW GOAL? 40% LDLC reduction + 30% HDLC increase

So What Happened to AIMHIGH and HPS-Thrive?
### Nicotinic Acid, Dose, and Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>CDP</td>
<td>2-3 gm/d</td>
<td>Decreased events</td>
</tr>
<tr>
<td>1987</td>
<td>CLAS</td>
<td>3-12 gm/d</td>
<td>Regression</td>
</tr>
<tr>
<td>1993</td>
<td>FATS</td>
<td>4 gm/d</td>
<td>Regression</td>
</tr>
<tr>
<td>1994</td>
<td>SCRIPS</td>
<td>2-3 gm/d</td>
<td>Lack of Progression</td>
</tr>
<tr>
<td>2001</td>
<td>HATS</td>
<td>2-4 gm/d</td>
<td>Regression</td>
</tr>
<tr>
<td>2005</td>
<td>Armed Forces</td>
<td>3 gm/d</td>
<td>Lack of Progression</td>
</tr>
<tr>
<td>2011</td>
<td>AIMHIGH</td>
<td>1.5 gm/d</td>
<td>No effect</td>
</tr>
<tr>
<td>2013</td>
<td>HPSThrive</td>
<td>1.5 gm/d</td>
<td>No effect</td>
</tr>
</tbody>
</table>

### AGENDA:

1. ALP – What is it?
2. Risk Prediction: LDL & HDL subclasses
3. Disease Management
4. Use
5. Misuse

### LDL Subclass Testing

Over thirty years of both prospective and case-control studies (NIH) have verified that high concentration of small, dense LDL particles (i.e., LDL pattern B) substantially increases the risk of heart disease [3*], peripheral arterial disease [4*], control artery thickness [5*] and accelerated atherosclerosis of coronary arteries [6*].

The increases in risk have been shown to be independent of LDL-cholesterol [7*, 8*], HDL-cholesterol [7*, 8*], triglyceride [8*], and total/HDL-cholesterol concentrations [8*].

Small, dense LDL particle measurements have been reported to be the strongest predictors of CHD among all lipoproteins examined prospectively in epidemiological studies and angiographic studies that measure disease progression directly [15*], and cross-sectionally [3*].

An increase in LDL buoyancy was most strongly associated with CAD regression [15*].

**Treatment:** Diet, Exercise, Weight loss, nicotinic acid, fibrates, omega-3 fatty acids.

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LDL Use and Misuse

Use:
1. Diagnosis of LDL pattern B when Trigs between 70-200 mg/dl
2. CVD risk prediction in appropriate TG and HDLc range. TG >70 mg/dl and < 250 mg/dl for LDL size
   HDLc >40 and < 60 males; >50 and < 70 females* for HDLc
3. Identify CAD patients who have greater rate of arteriographic progression and new lesion formation
4. Identification of CAD patients who respond (arteriographically) well to multi lifestyle and drug therapy
5. Guide Therapy for more than just statin induced LDL-C reduction
6. Assess family members of patients with LDL pattern B when family members have
   "normal" trig values.
7. Evaluate effectiveness of Diet (CHO vs fat) and exercise/weight on risk attributed to
   LDL and HDL subclasses.

Misuse:
1. Population wide screening for CVD risk.
2. Premenopausal women have a low likelihood of exhibiting LDL subclass pattern B
   even when inheritance of the trait is suggested by family history [18].
3. Diagnosis of Metabolic Syndrome
4. Curiosity
5. Financial gain

Conclusions

Secondary Prevention and Small LDL Pattern B

<table>
<thead>
<tr>
<th>Study</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI-II (NHLBI)</td>
<td>Reduction in IDL and dense LDL associated with arteriographic benefit</td>
</tr>
<tr>
<td>EAST (Emory Univ - NHL)</td>
<td>Small LDL independently associated with arteriographic change. Every 5% increase in small LDL associated with 5% increase in all major CV events and independent of LDL-C.</td>
</tr>
<tr>
<td>STARS (Great Britian)</td>
<td>Dense LDL was best predictor of arteriographic change.</td>
</tr>
<tr>
<td>SORP (Stanford Univ - NHL)</td>
<td>Dense LDL associated with 2-fold greater rate of arteriographic progression in placebo group. LDL pattern B subjects had greater arteriographic benefit from treatment.</td>
</tr>
<tr>
<td>FATS [NHL]</td>
<td>Change in LDL density was best predictor of arteriographic change.</td>
</tr>
<tr>
<td>DIAS</td>
<td>Diabetic patients with low LDL-C (&lt;117 mg/dl) but small LDL exhibited significant arteriographic progression.</td>
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