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:
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     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

Funding

- National Heart, Lung, and Blood Institute (501C3)

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Atherogenic Lipoprotein Profile
ALP - A Nasty Metabolic Stew

Thromboxane synthesis
(Weisser 1992)

PPL
(Superko 1992)

Sialic Acid content
Proteoglycan binding
(Schulte 1990, Sever 1992)

Insulin Resistance
(Krauss 1991)

Inheritance
(Austin 1994)

Arterial Wall Uptake by 40%
(Nordstad 1989)

Low Vit E
Oxidative Susceptibility
(Tribble 1992, Dejager 1993)

High Trig
Low HDLC

LDL size related to endothelial vasodilator dysfunction
(Toye 1990)

3-fold CHD Risk
Defined by DENSITY (AnUC) or DIAMETER (GGE)

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** = \( \geq 3 \) 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 (f glu intolerance FBS > 110)
5. Prothrombotic and proinflammatory states


---

**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>Defin</th>
<th>Old NCEP</th>
<th>Revised NCEP</th>
<th>WHO</th>
<th>IDF</th>
<th>ESC</th>
<th>IDF proposes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu or HOMA-IR &gt;75%</td>
<td>3+</td>
<td>3+</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abol Ob or BMI &gt;35</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>WHt-R &gt;50</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>HDL-C &lt;40</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trig &gt;150</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>SBP &gt;140</td>
<td>2</td>
<td>2</td>
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<td>Fasting Glu &gt;100</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>Fasting Insu &gt;8mU/L</td>
<td>2</td>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>BHRR &gt;150</td>
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<td>2</td>
<td></td>
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<tr>
<td>UAC ratio &gt;30mg/g</td>
<td>2</td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

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**Obesity Trends* Among U.S. Adults**

*BMI >30, or ~ 30 lbs overweight for 5’4” woman*

---

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

Obesity Trends* Among U.S. Adults
BRFSS, 2009

(*)BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person

Obesity is like Kudzu

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)
Wgt Loss Control
A->A 57% 75%
A->B 3% 24%
B->A 58% 10%
B->B 42% 90%
X^2 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.”

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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;57:1404-1423)
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>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>TC/HDLc</td>
<td>apo-B</td>
<td>apo-B</td>
<td>HR 1.4/ HDLc 0.82</td>
</tr>
</tbody>
</table>

* SFC = Stanford 5 Cities Project (Gardner et al., JAMA 1996;276:875-881.)
* PHS = Physician's Health Survey (Stampfer & Krauss et al., JAMA, 1996: 276:882-8.)
* Quebec = Quebec Cardiovascular Study (Lamarche et al., Can 1997;95:69-75)
* Women's Health =Mora et al Circ 2009;119:931-939

Prospective Population Based Study of LDL size and CAD Risk

- Quebec CV Study, 2,057 Men followed for 5 years.  
  - Yes CAD event
  - No CAD event

- LDL size
  - 255.2 A
  - 257.0 A
  - 0.002

- Independent of Trig, TC, LDLc, HDLC

* 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."

(Austin M; Circ 1999;99:1124)
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 < 251 A

-Strong and independent relationship of LDL C < 255 A (Small LDL) and CAD risk
- Large LDL > 260 A NOT associated with risk
GGE = LDLC + LDL C X NLDL > 260 A

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

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
(Superko HR, Circulation 2009;119:2383-2391)
**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, 409 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), 65% for total CHD (P=0.015), 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 Suppanto, L Pendyala, PF Williams, KM Momary, SB King III, BC Garrett. J or Clinical Lipidology 2012: http://dx.doi.org/10.1016/j.jacl.2012.03.001

   Literature review of 80 published investigations.

   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, immobility, or ultracentrifugation may provide more specific information about CHD risk than the measurement of HDL-C, HDL2 cholesterol, or HDL2b cholesterol.

---

**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)


---

**HDL2b is Most Informative when HDL-C is “Normal”**

Stanford Coronary Risk Intervention Project (NIH)
N = 300 CAD pts
R = 0.72
P<0.001

Low HDLC ~ Low HDL2
High HDLC ~ High HDL2

HDL2 measurements most useful in middle range!
Misuse 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 HDL (< 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.

---

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**Arteriographic Trial Evidence**

<table>
<thead>
<tr>
<th>ALP or Metabolic Syndrome</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI Type II (NHLBI + UC Berkeley)</td>
<td>NIH (Sf12-20, 0-7)</td>
</tr>
<tr>
<td>CLAS (TG break points) (USC + UC Berkeley)</td>
<td>1993 NIH</td>
</tr>
<tr>
<td>STARS (London, England)</td>
<td>1993 Nat'l Health</td>
</tr>
<tr>
<td>MARS (USC + UC Berkeley)</td>
<td>1994 NIH+Merck</td>
</tr>
<tr>
<td>SCRAP (Stanford + UC Berkeley)</td>
<td>1996 NIH (Sf0-7, PPD)</td>
</tr>
<tr>
<td>FATS (Univ. Washington)</td>
<td>1996 NIH (RF)</td>
</tr>
<tr>
<td>SCRAP (Stanford + UC Berkeley)</td>
<td>2000 NIH (LDL IIIa+b)</td>
</tr>
<tr>
<td>EAST (Emory University + UC Berkeley)</td>
<td>2000 NIH (LDL IIIa+b)</td>
</tr>
<tr>
<td>HATS (Univ. Washington)</td>
<td>2001 NIH (LpA2, HDL2)</td>
</tr>
<tr>
<td>SCRAP (Stanford + UC Berkeley)</td>
<td>2003 NIH (LDL IVb)</td>
</tr>
<tr>
<td>DAIS (Finland)</td>
<td>2003 Fournier Labs (PPO)</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."
### St. Thomas Atheroma Regression Study (STARS)

90 male CAD pts randomized to usual care (UC) or dietary intervention (DI) or diet + cholestyramine (DC) for 3.3 yrs in England. Baseline LDL-C ~ 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 (LDL3 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* 1993;42:1461-1467)

### Change in LDL Density in FATS

Familial Atherosclerosis Treatment Study (FATS)

m=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 apoB 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<0.0001). 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<0.01) followed by reduction in apolipoprotein B (5% of variance p<0.05).

These studies support the hypothesis that therapy-associated changes in HL after 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)

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.

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).

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

<table>
<thead>
<tr>
<th>New Lesion Formation (3 years)</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 I</td>
<td>4(9%)</td>
<td>27(12%)</td>
<td></td>
</tr>
<tr>
<td>Pattern II</td>
<td>18(40%)</td>
<td>53(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 Pr dia (A)</td>
<td>262.2</td>
<td>265.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Multivariate analysis LDL IIIa,b IVa,b significant predictor new lesions (p<0.01)

"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."


"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

All Feno Placebo

LDL PPD -0.10 -0.21* 0.00
LDL C 0.11* 0.20* 0.03
LDLC/ApoB -0.05 -0.10 -0.05

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

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

(Vakkilainen 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<.01). The test did not reach statistical significance for HDL3 cholesterol quartiles (P=.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 F/U.
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>CC</th>
<th>TC</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trig</td>
<td>-19%</td>
<td>-18%</td>
</tr>
<tr>
<td>LDL C</td>
<td>-38%</td>
<td>-37%</td>
</tr>
<tr>
<td>HDLC</td>
<td>+35%</td>
<td>+32%</td>
</tr>
<tr>
<td>HDL2C</td>
<td>+3.5%</td>
<td>+12%</td>
</tr>
<tr>
<td>Apo A1</td>
<td>+12%</td>
<td>+11%</td>
</tr>
<tr>
<td>LDL Rf</td>
<td>+12%</td>
<td>+6%</td>
</tr>
<tr>
<td>HL</td>
<td>-18%</td>
<td>-9%</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 LDL C lowering.

Clinically relevant: 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.
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?
AGENDA:
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LDL Use and Misuse

Use:
1. Diagnosis of LDL pattern B when triglycerides between 70-200 mg/dl
2. CVD risk prediction in appropriate TG and HDL range.
3. Identify CAD patients who have greater rate of atheromatous 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” triglycerides.
7. Evaluate effectiveness of diet (cholesterol 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

LDL Subclass Testing

Over thirty years 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 [2**, peripheral arterial disease [4**], carotid 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 [*5**] and cross-sectionally [*7**].

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.

References:

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 - NIH)</td>
<td>Small LDL independently associated with arteriographic change. Every 5% increase in small LDL associated with 14% increase in all major CV events and independent of LDL-C</td>
</tr>
<tr>
<td>STARS (Great Britain)</td>
<td>Dense LDL was best predictor of arteriographic change.</td>
</tr>
<tr>
<td>SCRIP (Stanford Univ - NIH)</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 (NIH)</td>
<td>Change in LDL density was best predictor of arteriographic change.</td>
</tr>
<tr>
<td>DAIS</td>
<td>Diabetic patients with low LDL-C (&lt;117 mg/dl) but small LDL exhibited significant arteriographic progression.</td>
</tr>
</tbody>
</table>