

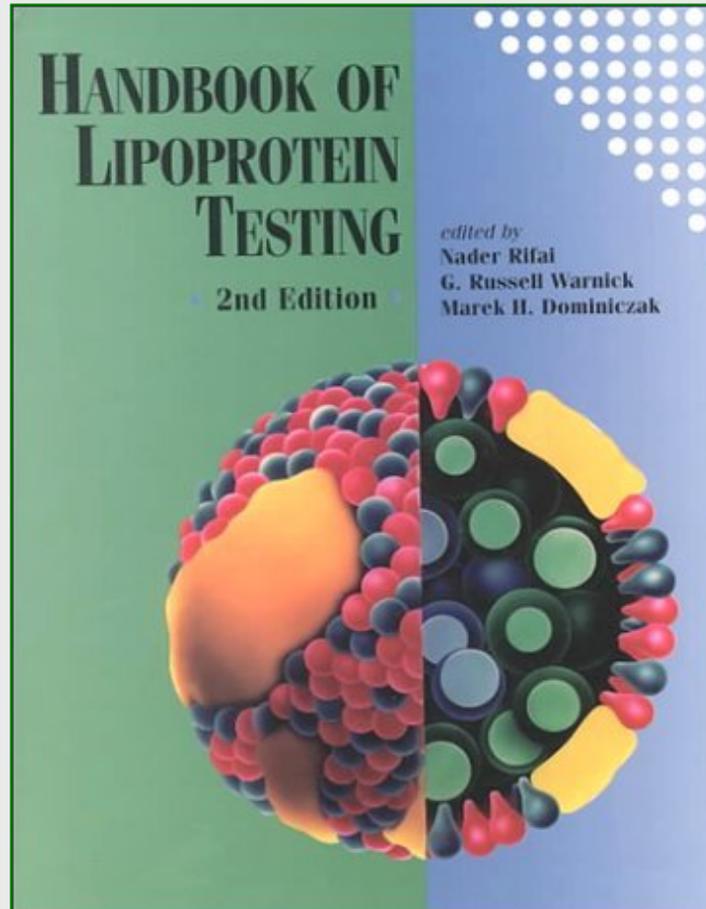
# **Lipid Panel to Lipoprotein Subclasses: Time for a Paradigm Shift**



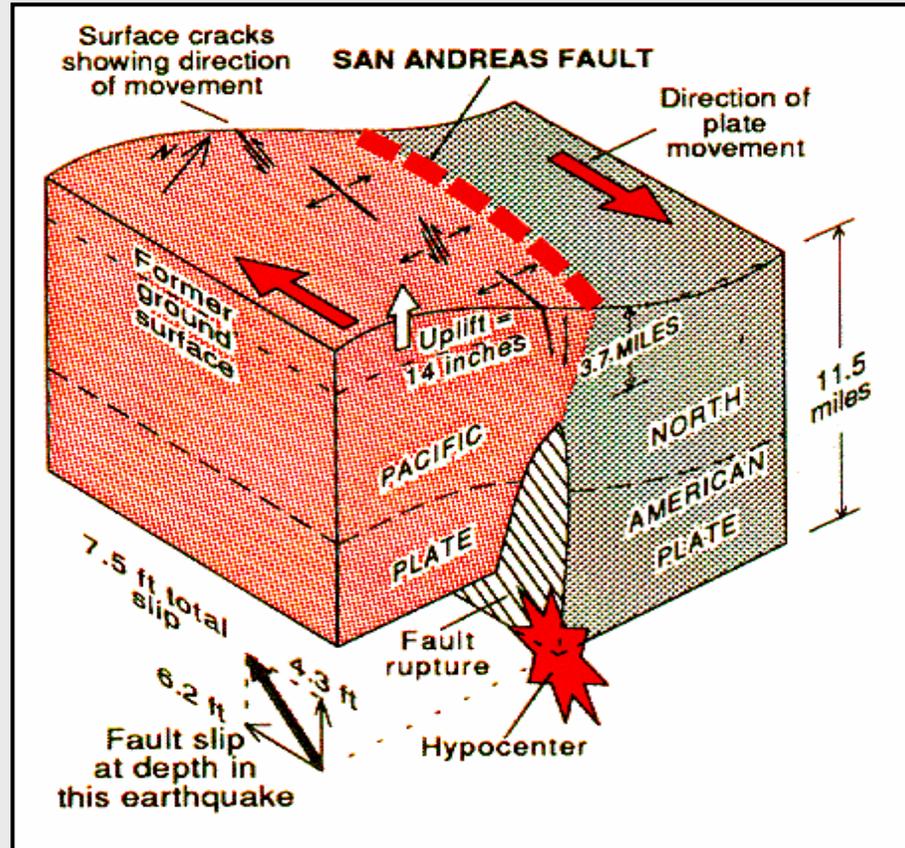
**G. Russell Warnick, MS, MBA Vice President for Laboratory  
Operations, Berkeley HeartLab, Inc.**

# My 35 Years Experience Driving Improvements in Lipid/Lipoprotein Testing

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# Anatomy of an Earthquake



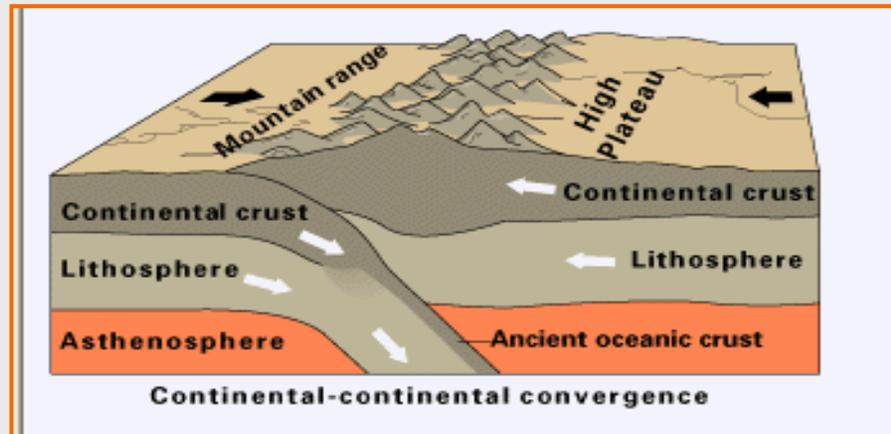
# From Scientific Research to Clinical Practice

## PUSH

- Evolving Research/Technology
- Innovators
- Early Adopters
- Financial Incentives

## OPPOSITION

- Resistance to Change
- Bureaucratic Inertia
- Achieving Consensus
- Vested Interests

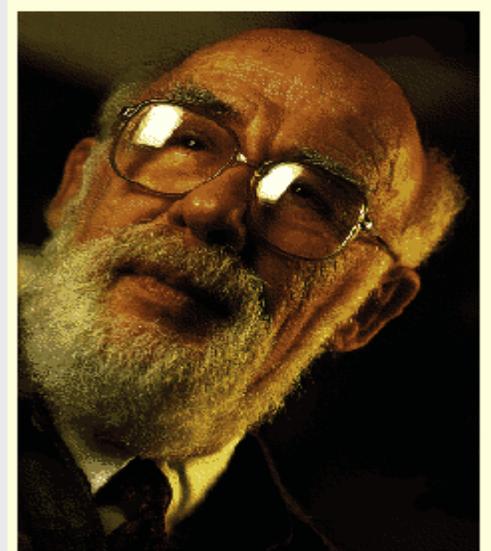


# A Lesson from History

## John Gofman – Pioneered Lipoproteins/CAD

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- \* As a physicist at UC Berkeley purified plutonium for “Manhattan” project
- \* 1947 - received MD; organized Donner Laboratory research on CAD
- \* 1950s - developed analytical ultracentrifugation and demonstrated independent relationships of LDL and HDL to CAD
- \* 1956 NIH Consensus Conference **rejected** observation of differential association of lipoproteins w/ CAD and concluded measurement of total cholesterol adequate, i.e. lipoprotein characterization unnecessary
- \* Consequence - Gofman abandoned lipoprotein research, began studying effects of radiation
- \* Protective role of **HDL** was **forgotten** until rediscovered in the mid-1970’s, i.e. practice lagged 2 decades



# Lipid Panel – 3 Decades Later

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- \* Total cholesterol, triglycerides, HDL-C, LDL-C
- \* Endorsed by NCEP Adult Treatment Panel
- \* Lipid panel has been standard for longer than the career of many in this audience
- \* LDL-C by calculation or direct assay **unreliable**
- \* These now **traditional biomarkers miss about half** of patients at risk for CVD

# BHL Patients with Diagnosed CVD

- \* **4,406 patients** with known CVDs - Male 2886 (66%), 4406 Female 1520 (34%)
- \* Biomarkers measured  $\pm$ 3 months of diagnosis
- \* Mean Age = 67 years old

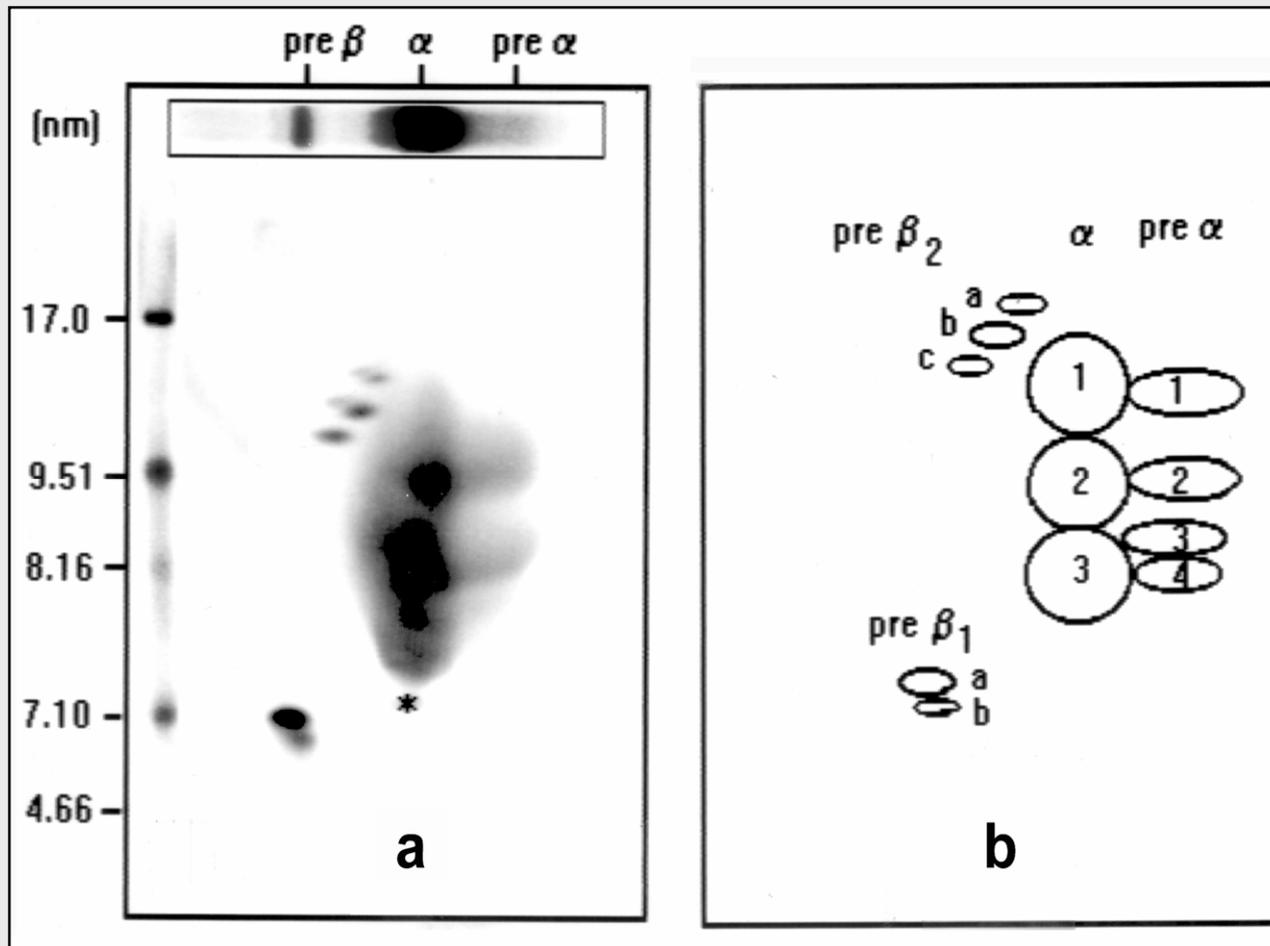
Subject Number by Disease		
<b>IMT</b>	<b>155</b>	<b>3.5%</b>
<b>Angina</b>	<b>96</b>	<b>2.2%</b>
<b>CABG</b>	<b>1079</b>	<b>24.5%</b>
<b>CHF</b>	<b>330</b>	<b>7.5%</b>
<b>MI</b>	<b>1242</b>	<b>28.2%</b>
<b>PCI</b>	<b>835</b>	<b>19.0%</b>
<b>EBCT</b>	<b>151</b>	<b>3.4%</b>
<b>PVD</b>	<b>54</b>	<b>1.2%</b>
<b>Stroke/TIA</b>	<b>464</b>	<b>10.5%</b>
<b>Total</b>	<b>4,406</b>	

# LDL/HDL Subclasses Better Identify CVDs

Biomarker	Cutpoint	Pt. #	Sensitivity	Patients <b>NOT</b> identified by Biomarker
TRIG	≥ 150 mg/dL	1,723	39%	61%
HDL-C	≤ 40 mg/dL	1,768	40%	60%
TCHOL	≥ 200 mg/dL	1,015	23%	77%
LDL-C	≥ 130 mg/dL	481	11%	89%
HDL 2b	≤ 20 %	3,065	70%	30%
LDL IIIa+b	≥ 15%	4,036	92%	8%

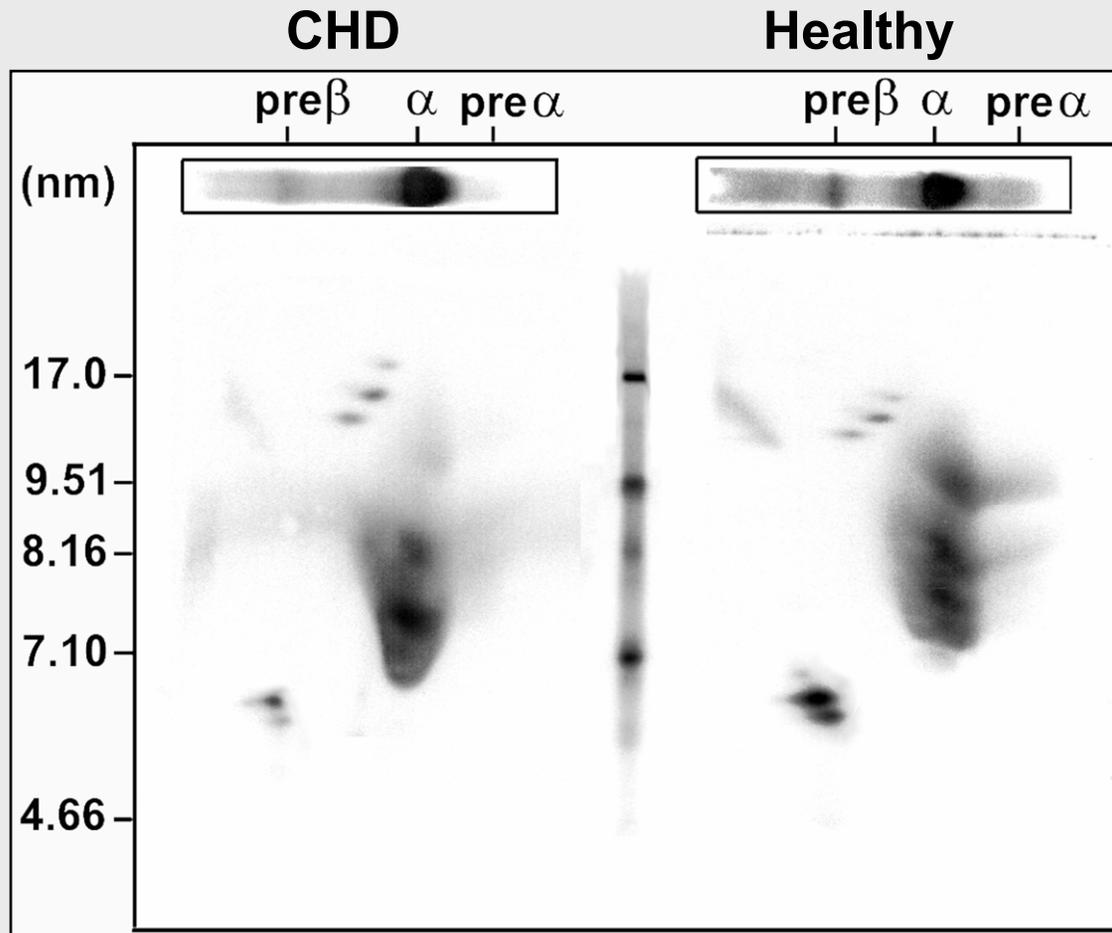
# HDL is Highly Heterogeneous

## APOA-I-Containing HDL Subclasses by 2d Electrophoresis



Asztalos et. al. BBA.1993;1169:291-300

# HDL Subclasses Differentially Associated with CVD risk



# Reports of Differential Association of HDL Subclasses with CVD Risk

(Using High Resolution Electrophoresis)

- \* CHD vs controls
  - Asztalos BF, Roheim PS, Milani RL, et al. Distribution of Apo-AI-Containing HDL Subpopulations in Patients With Coronary Artery Disease. *Arterioscler Thromb Vasc Biol.* 2000;20:2670- 2676.
  
- \* HATS
  - Asztalos BF, Batista M, Horvath KV, et al. Change in  $\alpha$ 1 HDL Concentration Predicts Progression in Coronary Artery Stenosis. *Atheroscler Thromb Vasc Biol.* 2003;23:847-852
  
- \* CETP Deficients
  - Asztalos BF, Horvath KV, Kajinami K, et al. Apolipoprotein Composition Of HDL In Cholesteryl Ester Transfer Protein Deficiency. *J. Lipid Res.* 2004;45:448-455..
  
- \* Framingham
  - Asztalos BF, Cupples LA, Demissie S, et al. High-Density Lipoprotein Subpopulation Profile and Coronary Heart Disease Prevalence in Male Participants of the Framingham Offspring Study. *Atheroscler Thromb Vasc Biol.* 2004;24:2181-2187.
  
- \* VA-HIT
  - Asztalos BF, Collins D, Cupples, et al. Value of High-Density Lipoprotein (HDL) Subpopulations in Predicting Recurrent Cardiovascular Events in the Veterans Affairs HDL Intervention Trial. *Atheroscler Thromb Vasc Biol.* 2005;25:2185-2191.

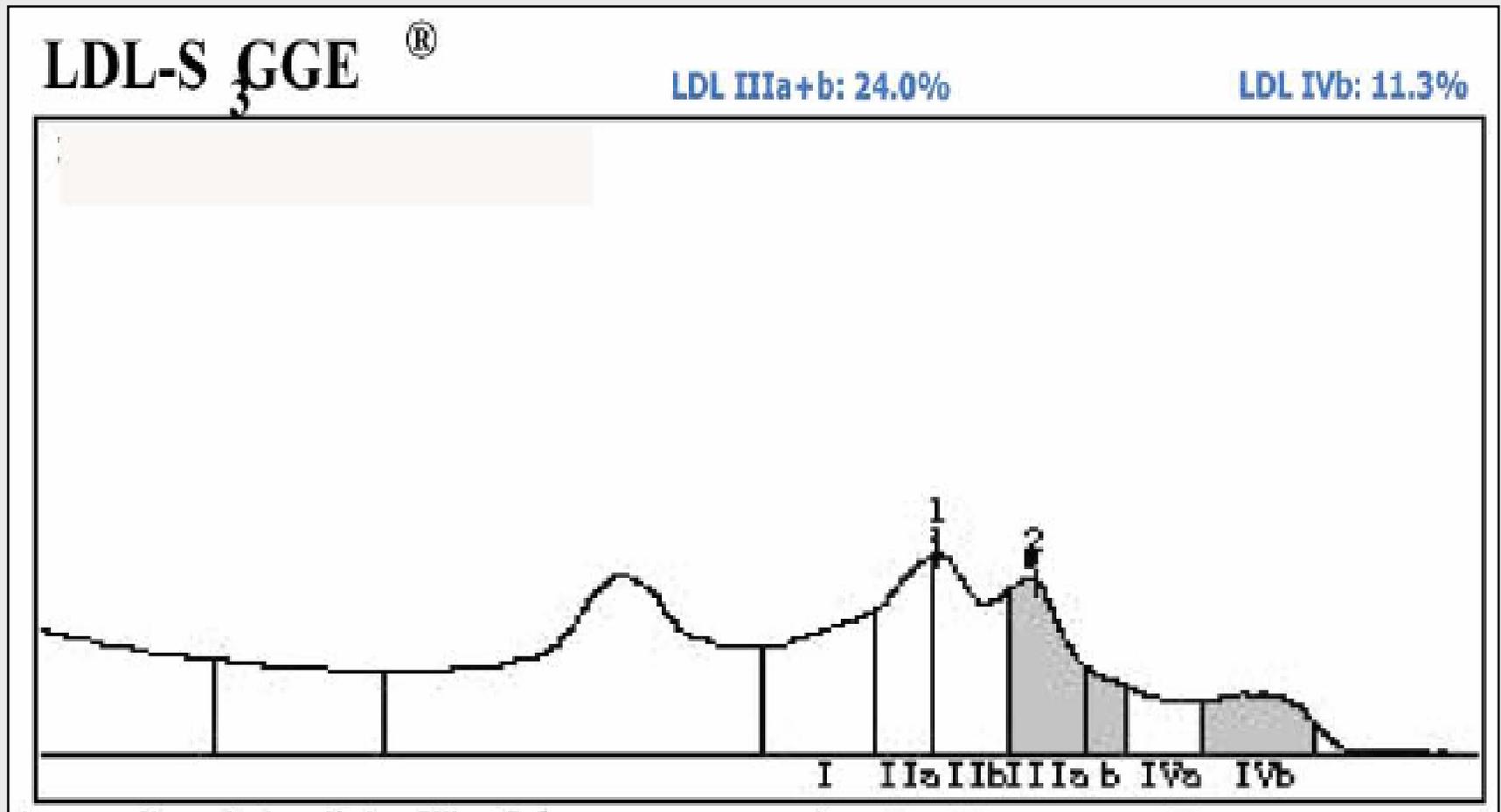
# Experts: HDL Subclasses more Definitive

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- \* “In both the **Framingham** Offspring Study and the **VA-HIT** study, we have clearly documented that low levels of  **$\alpha$ -1 and  $\alpha$ -2 HDL** are much better at CHD risk prediction than is HDL cholesterol”
- \* “In the HAT Study substantial increases in large a-1 particles with the niacin/simvastatin combination were correlated with less progression or more regression of coronary atherosclerosis”

Schaefer, Asztalos Current Opinion Lipidology 2006;17:394-8

# LDL Subclass Heterogeneity



# LDL Subclasses

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- \* Small, dense LDL are more atherogenic because
  - Increased susceptibility to oxidation <sup>1</sup>
  - Increased arterial wall uptake <sup>1</sup>
  - Conformational change of Apo B <sup>1,2</sup>
  - Decreased affinity for LDL receptors <sup>1,3</sup>
  - Increased binding to proteoglycans <sup>4</sup>
- \* LDL size has been observed to be a CAD risk factor independent of TG and HDL-C
- \* In multiple regression LDL size was a better predictor than LDL-C <sup>5</sup>
  - LDL density change accounted for 48% of stenotic change

1. *Curr Opin Lipidol* 1996; 7: 167-171.

2. *J. Biol. Chem* 1994; 69: 511-519.

3. *J. Lipid Res* 1996; 37: 1924-1935.

4. *J. Lipid Res* 1998. 39: 1263-1273.

5. *Circulation* 1996;94;I-539

# UNMET Medical Need

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- \* Current LDL-C and HDL-C measurements are not adequate to characterize patients and manage therapy
- \* HDL-C assay does not identify differential association of subclasses
  - Emerging HDL therapeutics will require new assays of HDL properties.
- \* LDL-C assays can be unreliable and do not distinguish the most atherogenic subclasses
- \* Subclass characterization better characterizes risk and facilitates prevention of secondary events
- \* Increasingly effective treatment options are available if patients can be identified.

# Conclusions

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- \* Lipid panel has dominated practice for over 20 years
- \* Panel fails to identify half the patients at risk for CVD
- \* Lipoprotein subclasses better characterize risk
- \* Time for a paradigm shift?