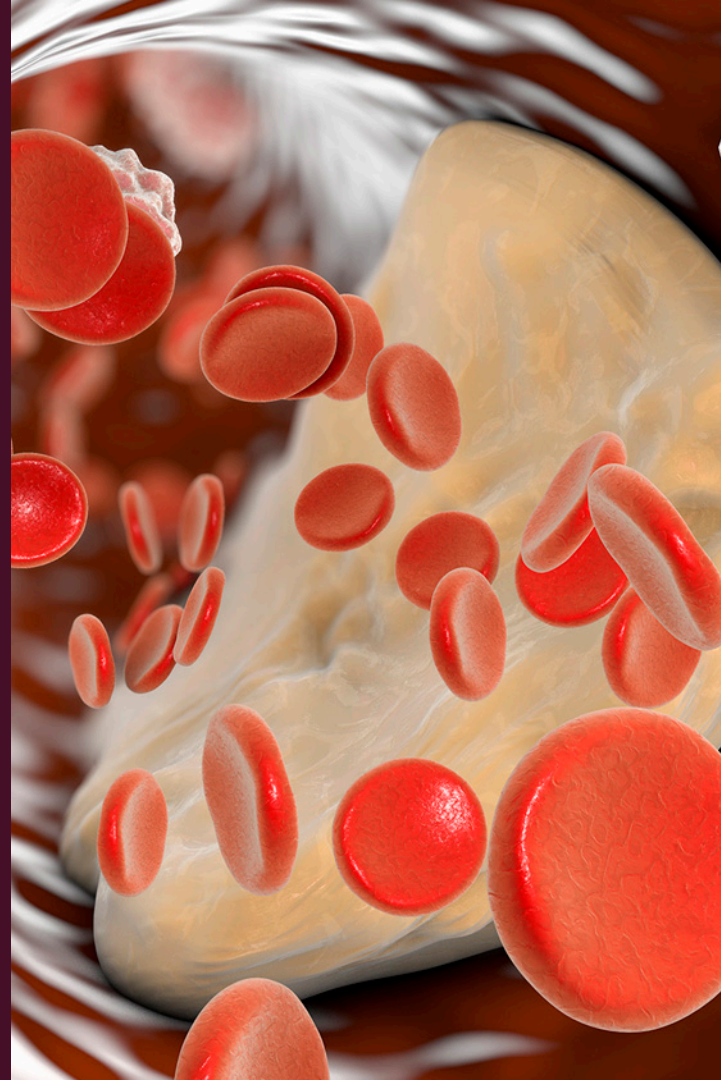


# Clinical Rundown: Hot Topics in Omega-3s and ASCVD Risk Reduction in Diabetes

Yehuda Handelsman, MD,  
FACP, FNLA, FASPC, MACE  
*Chair*



# Yehuda Handelsman, MD, FACP, FNLA, FASPC, MACE

***Medical Director & Principal Investigator***

Metabolic Institute of America

***Program Chair & Director***

4<sup>th</sup> Heart in Diabetes 8/7-9/2020, NYC, NY

18<sup>th</sup> WCIRDC 12/3-5/2019, Los Angeles, CA

**Solo practice**

# **ENDOCRINOLOGY**

---

**Endocrinology, Diabetes, and Metabolism**

Tarzana, California

# Handelsman Disclosures

- **Research Grant** – Amgen, Applied Therapeutic, AZ, BMS, BI, Gan & Lee, Lexicon, Novo Nordisk, Sanofi
- **Advisory/Consultant** – Amarin, Amgen, Applied Therapeutic, AZ, BI, Esperion, Gilead, Janssen, Merck, Merck-Pfizer, Novo Nordisk, Regeneron, Sanofi
- **Speaker's Bureau** – Amarin, Amgen, AZ, Janssen, Merck, Novo Nordisk

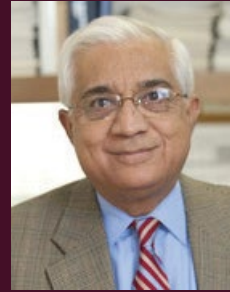
*Dr Handelsman and his immediate family do not have ownership interest and/or stocks of any pharmaceutical or device company*



**Paul D. Rosenblit MD, PhD, FACE, FNLA**  
Private Practice, Director, and Principal Investigator,  
Diabetes/Lipid Management & Research Center  
Huntington Beach, CA  
Clinical Professor of Medicine, Division of  
Endocrinology, Diabetes, and Metabolism  
University of California, Irvine, CA



**Jorge Plutzky, MD**  
Director, Preventive Cardiology  
Cardiovascular Division  
Brigham and Women's Hospital  
Boston, MA



**Om P. Ganda, MD**  
Director, Lipid Clinic  
Chair, Clinical Oversight Committee  
Joslin Diabetes Center  
Associate Professor of Medicine  
Harvard Medical School  
Boston, MA



**Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC**  
Executive Director of Interventional Cardiovascular Programs  
Brigham and Women's Hospital Heart & Vascular Center  
Professor of Medicine  
Harvard Medical School  
Boston, MA

# Clinical Rundown: Hot Topics in Omega-3s and ASCVD Risk Reduction in Diabetes

<b>Welcome, Introductions, and Program Overview</b>	<b>Yehuda Handelsman</b>
<b>Biomarkers, Imaging, and ASCVD: State of the Art</b>	<b>Paul Rosenblit</b>
<b>Who Gains the Most from Intensive Dyslipidemia Therapy?</b>	<b>Om Ganda</b>
<b>Options for Dyslipidemia Therapies in 2020</b>	<b>Yehuda Handelsman</b>
<b>Biology of Omega-3 Fatty Acids in Cardiovascular Disease: What Do We Know?</b>	<b>Jorge Plutzky</b>
<b>Use of Omega-3 Fatty Acids in Patients with Diabetes</b>	<b>Deepak L. Bhatt</b>
<b>Lipid Management Guidelines 2020 Focus on Icosapent Ethyl (IPE)</b>	<b>Yehuda Handelsman</b>
<b>Panel Discussion</b>	<b>Faculty</b>
<b>Diabetes and CVD Management During the COVID-19 Pandemic</b>	<b>Deepak L. Bhatt</b>
<b>Panel Discussion</b>	<b>Faculty</b>
<b>Final Comments, CME information, and Adjourn</b>	<b>Yehuda Handelsman</b>

# Clinical Rundown: Hot Topics in Omega-3s and ASCVD Risk Reduction in Diabetes

## Panel Discussion



Yehuda Handelsman



Paul Rosenblit



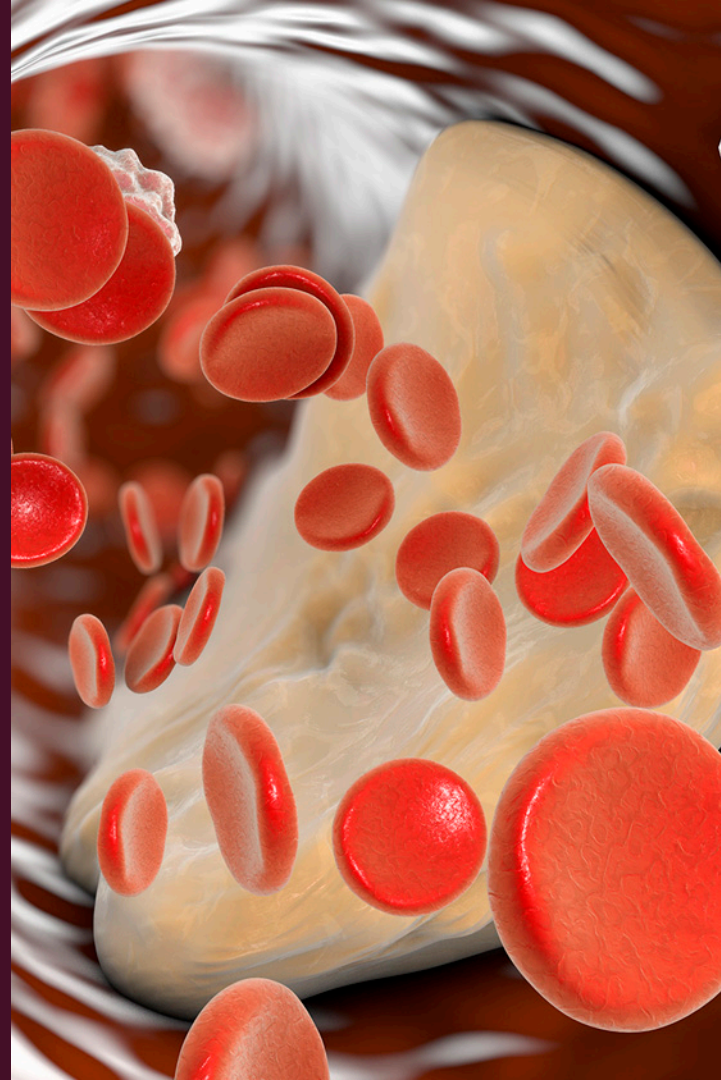
Om Ganda



Jorge Plutzky

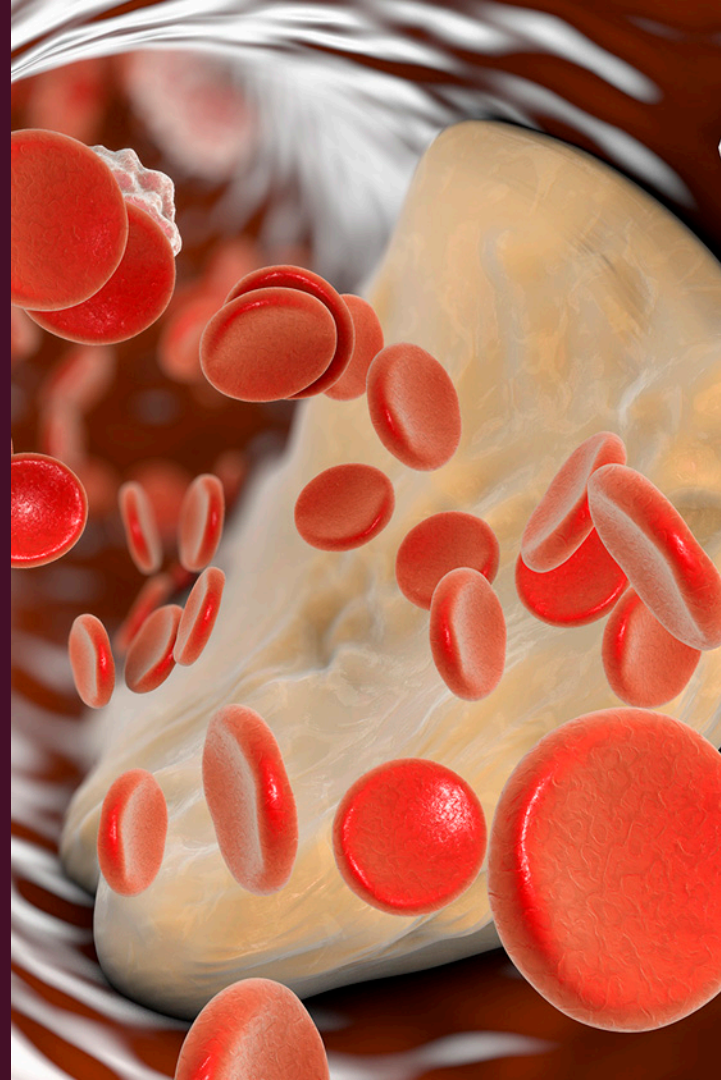


Deepak L. Bhatt



# Lipoprotein Particle Biomarkers and ASCVD

Paul D. Rosenblit, MD



# Lipid Biomarkers and ASCVD

**Paul D. Rosenblit MD, PhD, FACE, FNLA**

**Private Practice, Director, and Principal Investigator,  
Diabetes/Lipid Management & Research Center  
Huntington Beach, CA**

**Clinical Professor of Medicine**

(Division Endocrinology, Diabetes, and Metabolism)

University of California, Irvine (UCI) School of Medicine

**Co-Director, Diabetes Out-Patient Clinic,  
UCI Medical Center, Orange, CA**



# Lipid Biomarkers and ASCVD

## Faculty Disclosures\*

**Dr. Paul D. Rosenblit reported the following relevant financial relationships with commercial interests:**

---

Speaker / Teaching Faculty:           Amarin, Amgen, Merck

---

Clinical Research Site Trials:       Dexcom, Ionis (Akcea), Lilly, Mylan, Novo Nordisk

---

Advisory / Consultant:               Amarin, Akcea

---

\*12 months: January 1, 2019 – December 31, 2019

# NCEP ATP I : Risk Status Based on Presence of CHD Risk Factors Other Than LDL-Cholesterol

NCEP ATP = National Cholesterol Education Program Adult Treatment Program

**High-risk status if has one of the following:**

- **Definite CHD: either**
  - **Definite prior MI or**
  - **Definite myocardial ischemia, such as angina pectoris**
- or
- **Two other CHD risk factors:**
  - **Male**
  - **Family Hx: Premature CHD (definite MI or sudden death of parent or sibling <55 yrs of age)**
  - **Cigarette smoking (currently > 10 cigarettes/day)**
  - **Hypertension**
  - **Low HDL-C (<35 mg/dL) confirmed by repeated measurement)**
  - **Diabetes mellitus**
  - **History of definite cerebrovascular or occlusive peripheral vascular disease**
  - **Severe obesity ( $\geq 30\%$  overweight)**

**For high-risk status:**

**Threshold for drug therapy: LDL-C  $\geq 160$  mg/dL**

**Minimum goal of therapy: LDL-C <130 mg/dL**

**Metabolic Syndrome  
NCEP Expert Panel  
ATP III, 2001**

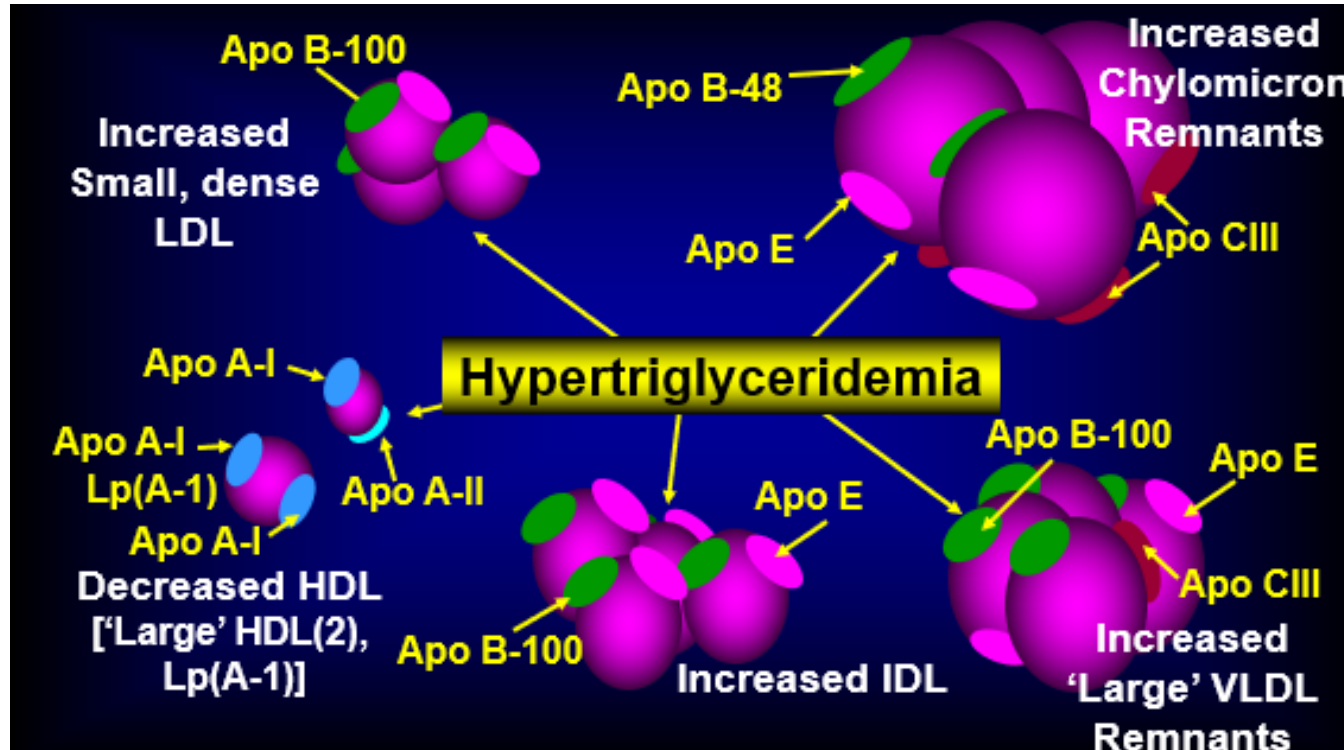
**Syndrome X**

- **Resistance to insulin-stimulated glucose uptake**
  - **Hyperinsulinemia**
  - **Hypertension**
  - **Glucose intolerance**
  - **Increased VLDL-triglycerides**
  - **Decreased HDL cholesterol**

---

  - **Resistance to insulin-stimulated suppression of adipose tissue lipolysis → elevated free fatty acids  
→ ↑ hepatic glucose production and ↑ VLDL-TG**
  - **More common in overweight or obese individuals**
- 3 or more required**
- **BP >130/85**
  - **FBG ≥110 mg/dL**
  - **Fasting TG ≥150 mg/dL**
  - **HDL-C**  
**<40 mg/dL in men**  
**<50 mg/dL in women**
  - **Waist circumference**  
**>102 cm for men**  
**>88 cm for women**

# Atherogenic Lipoprotein Phenotype (ALP): Common Lipoprotein Abnormalities, Accompanying Hypertriglyceridemia, in Cardiovascular Disease

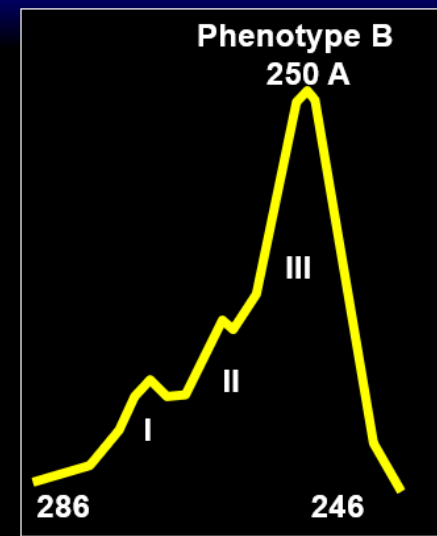
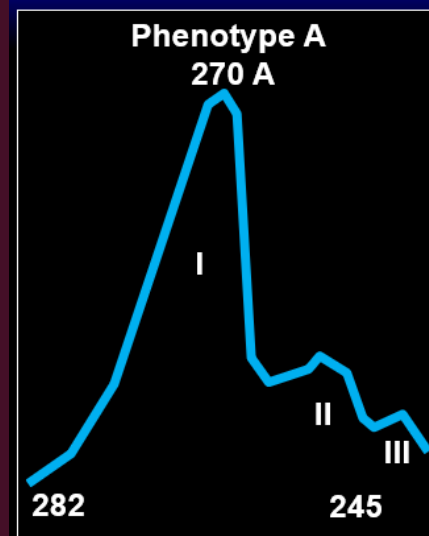


# LDL Fractionation via Gradient Gel Electrophoresis

Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res.* 1982;23(1):97-104.

*J Lipid Res.* 1982;23(1):97-104.

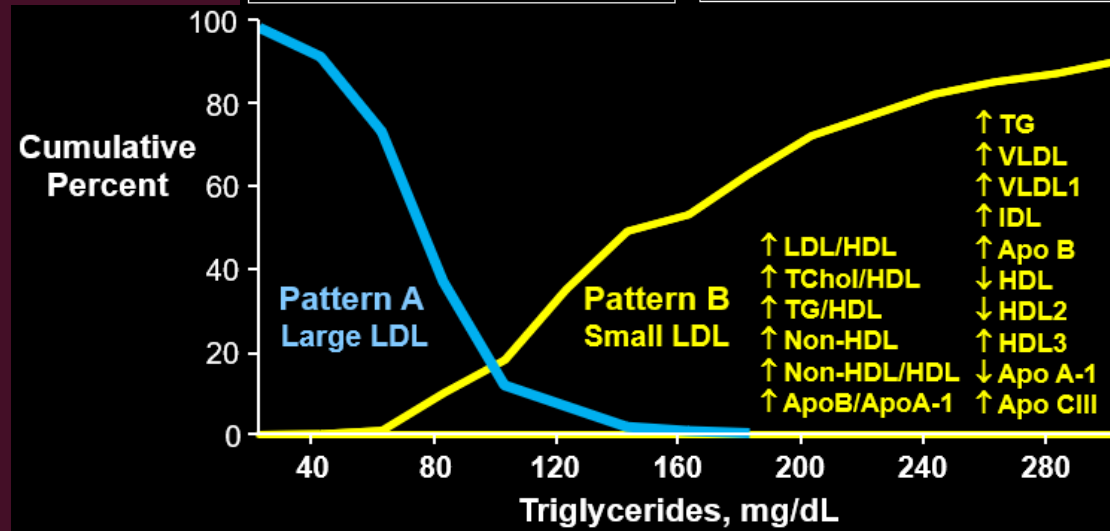
Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. *JAMA.* 1988;260(13):1917-21.



## High Triglycerides Are Associated with LDL Subclass Pattern B, Elevated Apo B, and TG-Rich Remnant Cholesterol (large VLDL, IDL)

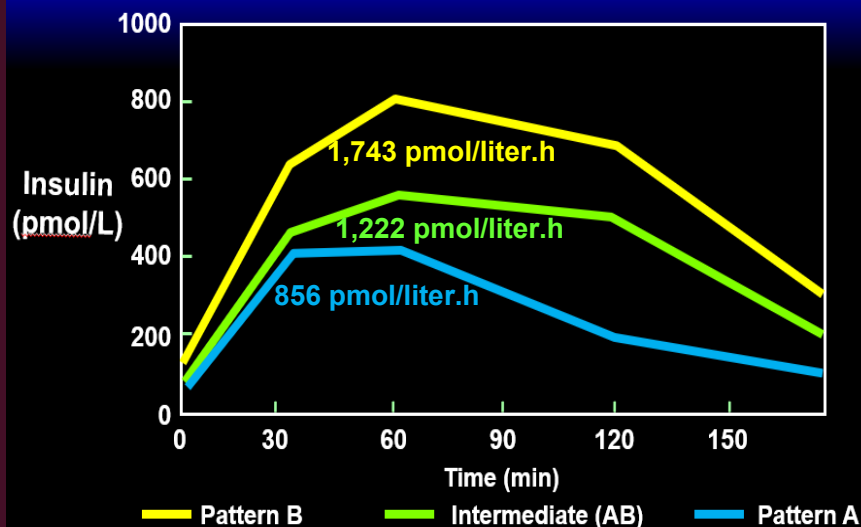
Adapted from

Austin MA, King MC, Vranizan KM, Krauss RM. *Circulation.* 1990;82(2):495-506.



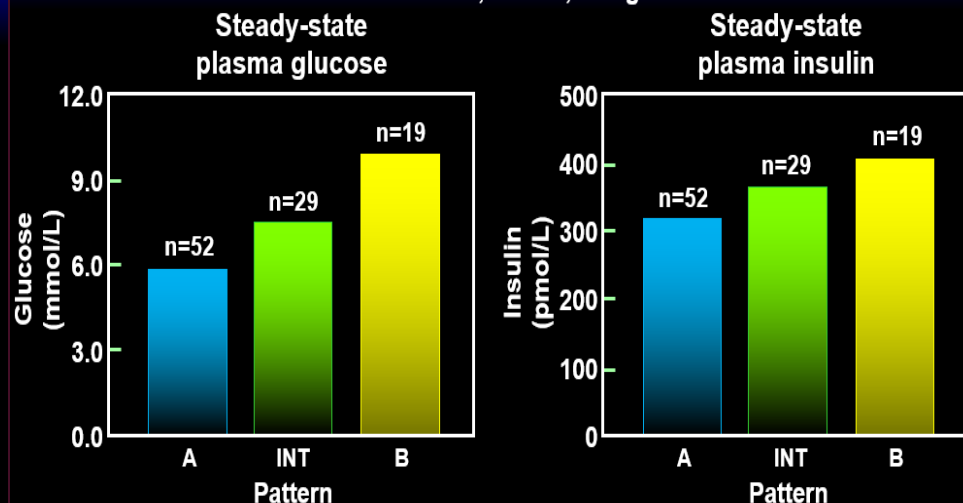
# Individuals with the Atherogenic Small Dense LDL (Pattern B Dyslipidemia) Phenotype Are Insulin Resistant

Insulin Responses to a 75-g Oral Glucose Challenge in 100 Non-Diabetic Healthy Normal Subjects in Relation to LDL Phenotype Pattern A, Intermediate or B

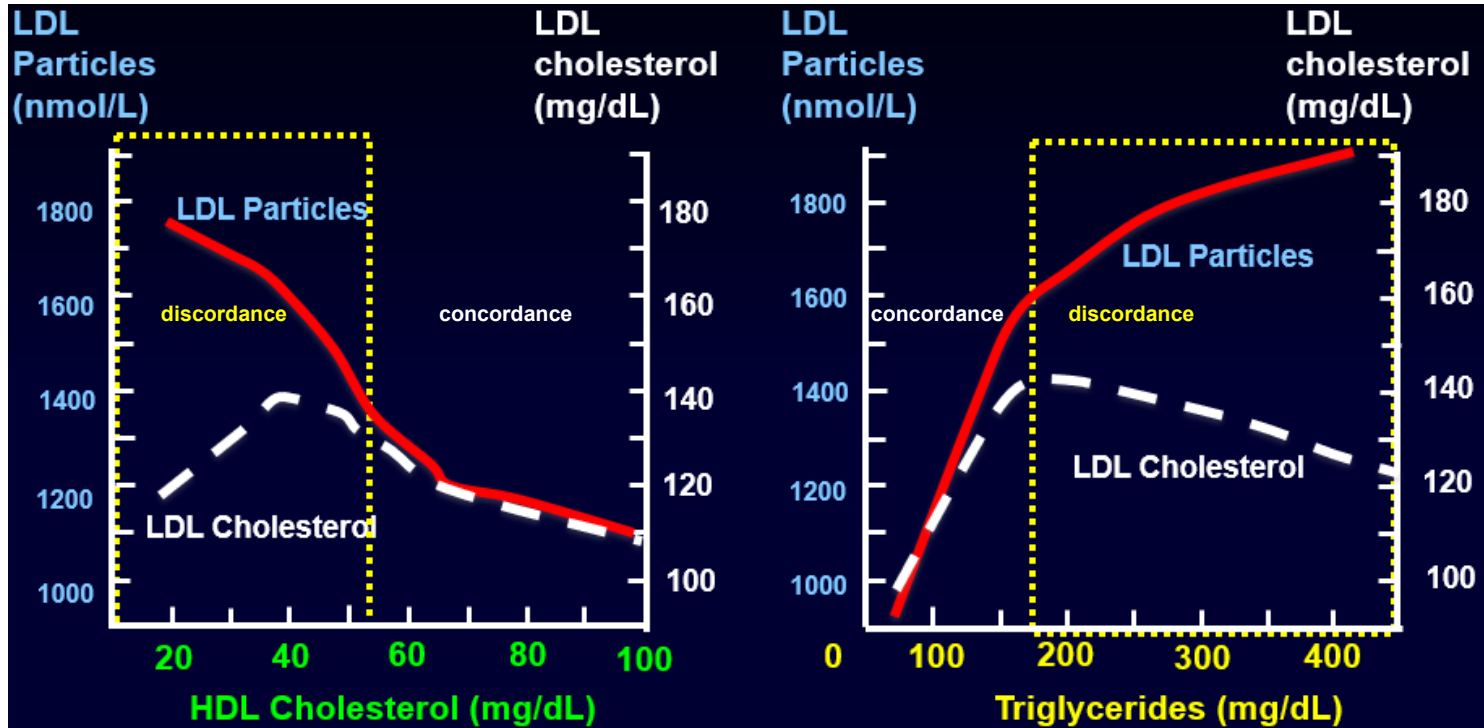


Steady-state Plasma Glucose and Insulin\* of Normal Non-Diabetic Adults Divided According to LDL Subclass Pattern

\*At the end of a 180-min infusion of somatostatin, insulin, and glucose

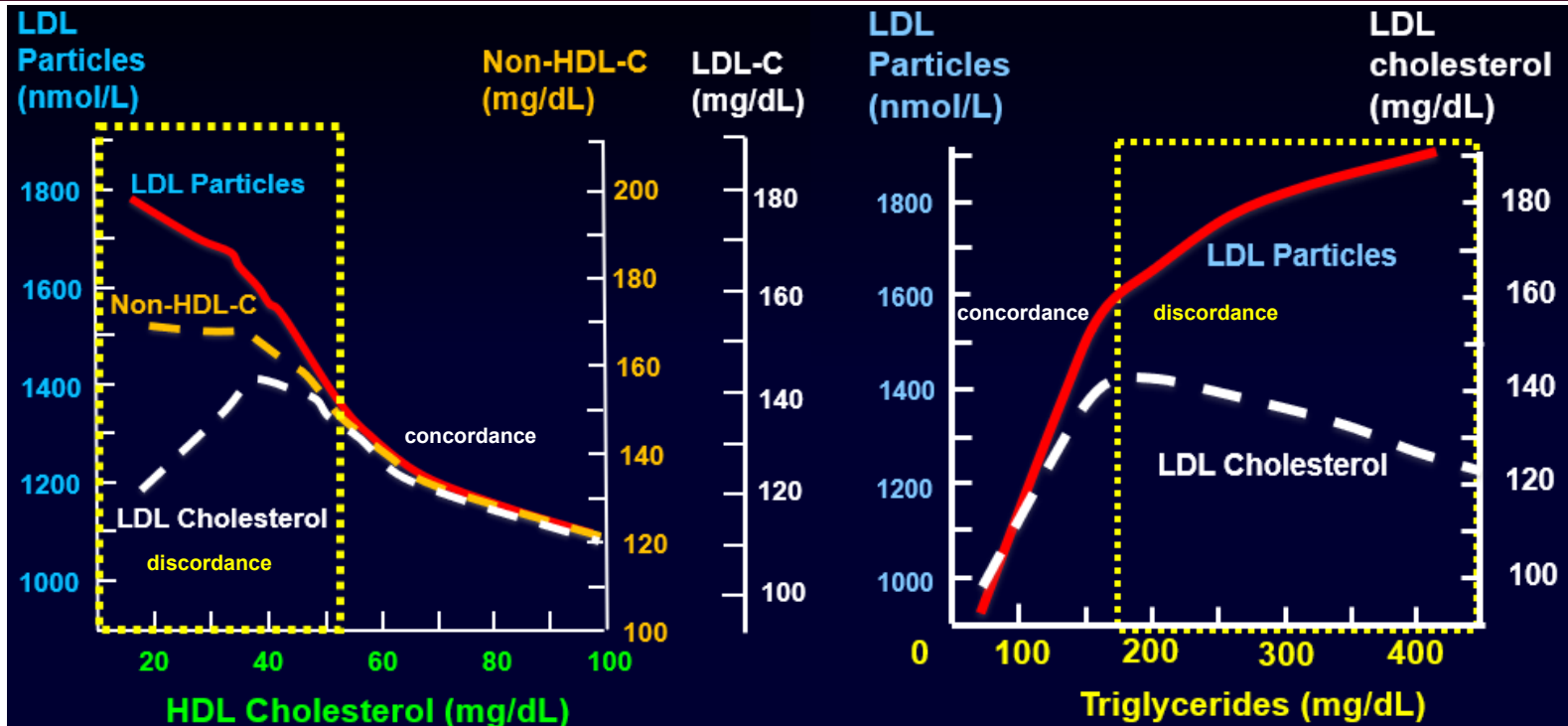


# Framingham Offspring Study: Nuclear Magnetic Resonance, NMR, Spectroscopy, LDL Particle Numbers (LDL-P) & LDL Cholesterol (LDL-C): Relationships to Levels of HDL Cholesterol and Triglycerides



Cromwell WC, Otvos JD. *Curr Atheroscler Rep.* 2004;6(5):381-87.

# Framingham Offspring Study: Nuclear Magnetic Resonance, NMR, Spectroscopy, LDL Particle Numbers (LDL-P) & LDL Cholesterol (LDL-C): Relationships to Levels of HDL Cholesterol and Triglycerides

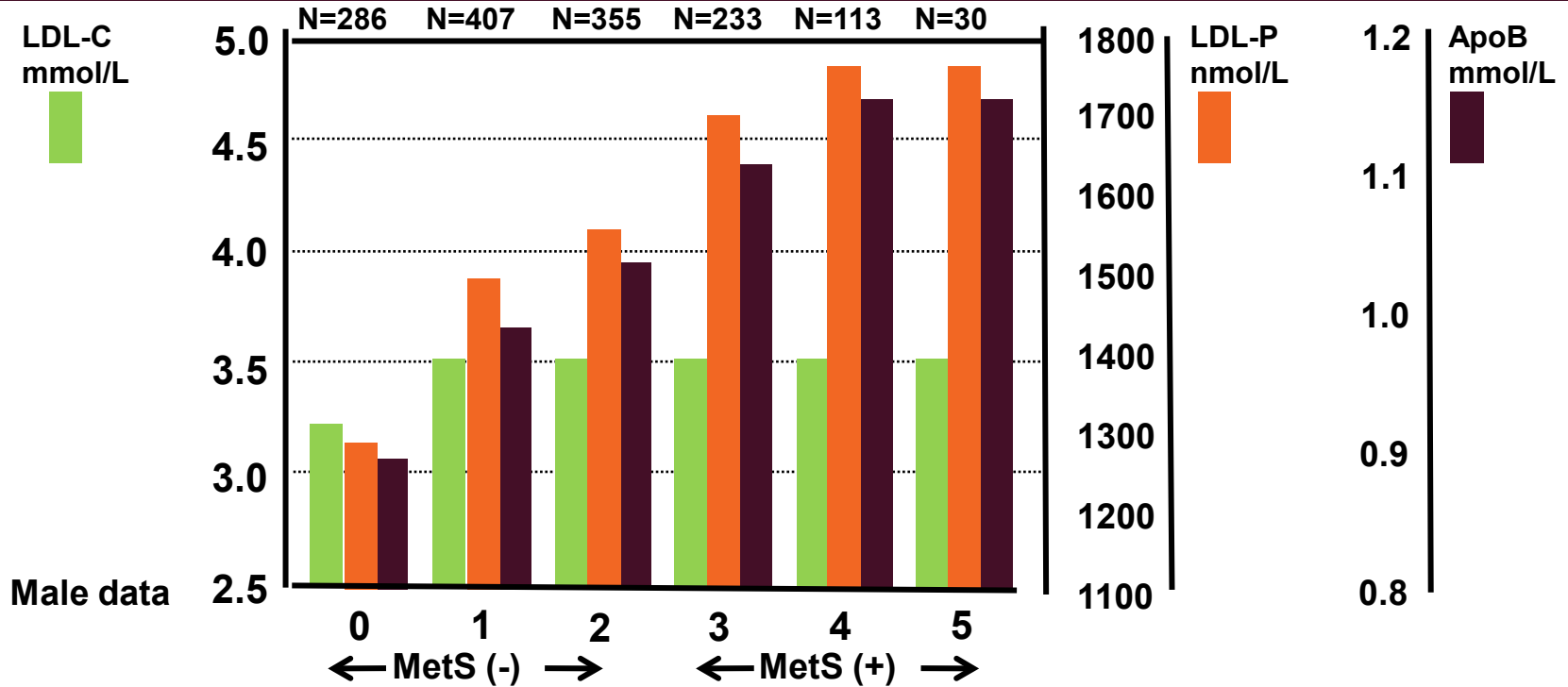


Modified from  
Otvos JD, Jeyarajah EJ, Cromwell WC et al. Am J Cardiol. 2002;90(suppl):22i-29i

Cromwell WC, Otvos JD. *Curr Atheroscler Rep.* 2004;6(5):381-87.



# Framingham Offspring Study (FOS): LDL-C, LDL-P, Apo B with Increasing Number of Metabolic Syndrome Features

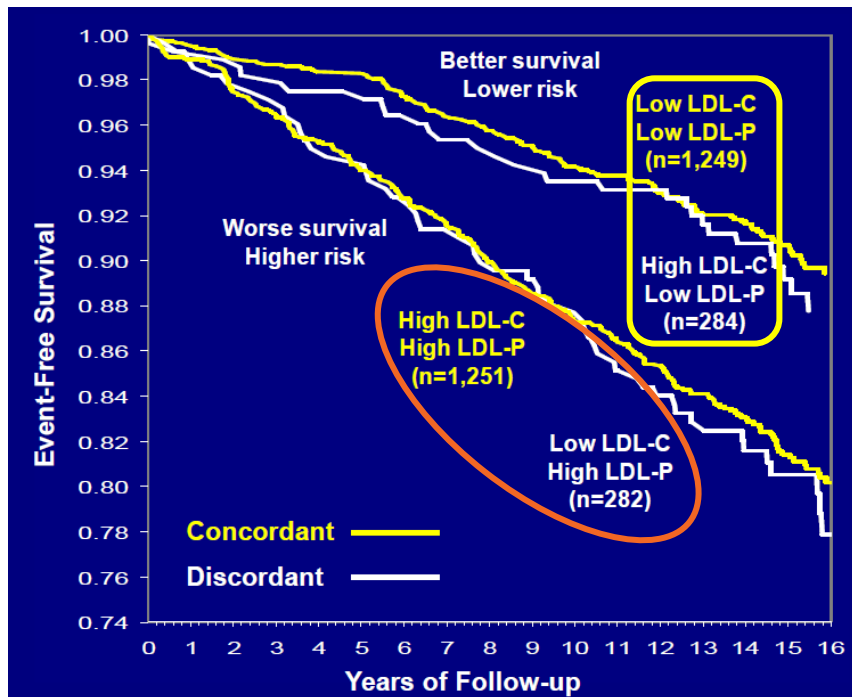


Fruchart JC, et al. *Am J Cardiol.* 2008;102(10 Suppl):1K-34K. ~ 2.3 X risk

Rosenson R, et al. *Atherosclerosis.* 2010;213(1):1-7.

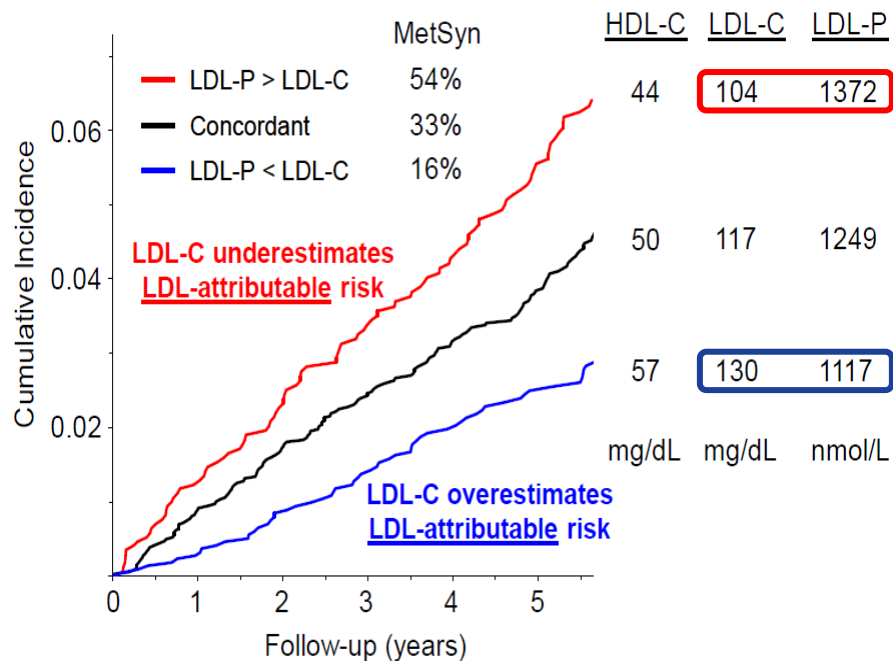
# CHD Event Associations of LDL Particle Numbers (LDL-P) Versus LDL Cholesterol Content (LDL-C): Concordance and Discordance

Framingham Offspring Study (n=3,066)



Cromwell WC, Otvos JD, Keyes MJ et al. *J Clin Lipidol.* 2007;1(6):583-592.

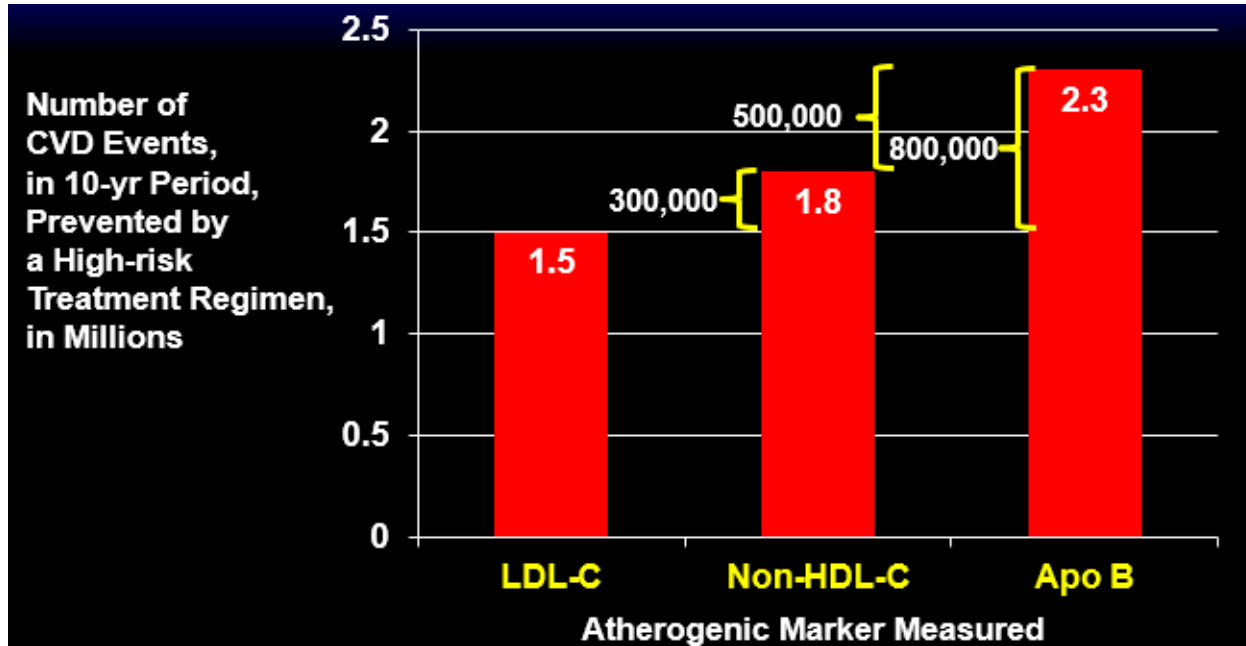
Multi-Ethnic Study of Atherosclerosis, MESA



Otvos JD, Mora S, Shalurova I et al. *J Clin Lipidol.* 2011;5(2):105-13

# Number of CVD Events, in Millions, Prevented by High-risk Tx Regimen of All in 70<sup>th</sup> %'tile of the US Adult Population, in a 10-Year Period, According to Atherogenic Marker: LDL-C vs. Non-HDL-C vs. Apo B

A Meta-Analysis of CV Risk Markers in 15 independent published analyses provided a total of 233,455 subjects and 22,950 CV events.

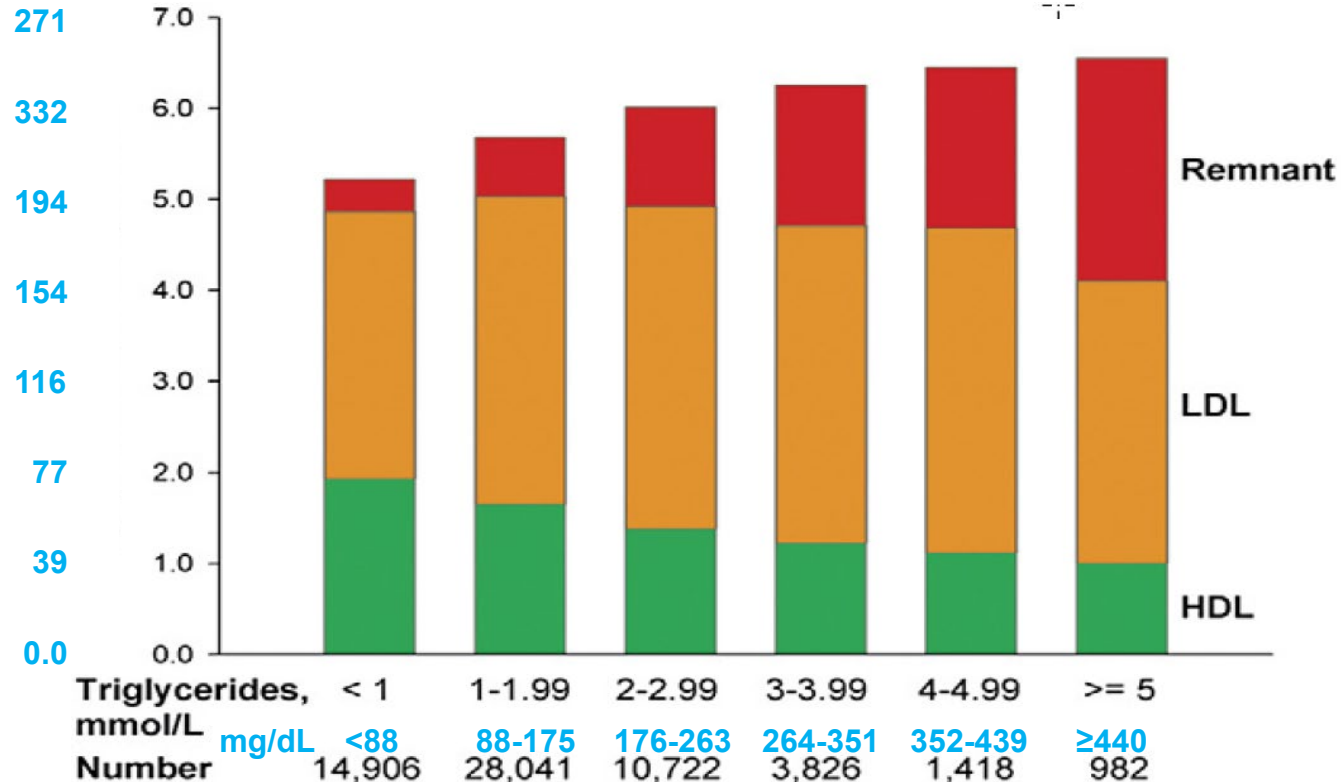


# Lipoprotein Cholesterol as a Function of Increasing Levels of Nonfasting Triglycerides.

Lipoprotein  
Cholesterol,  
mmol/L  
mg/dL

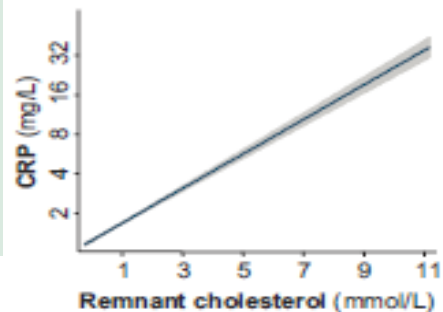
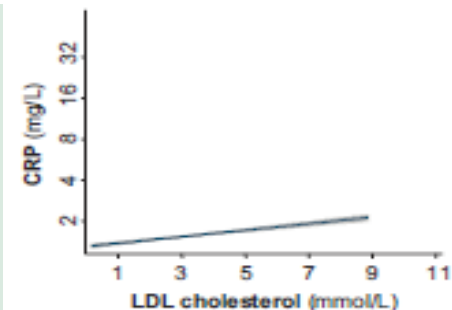
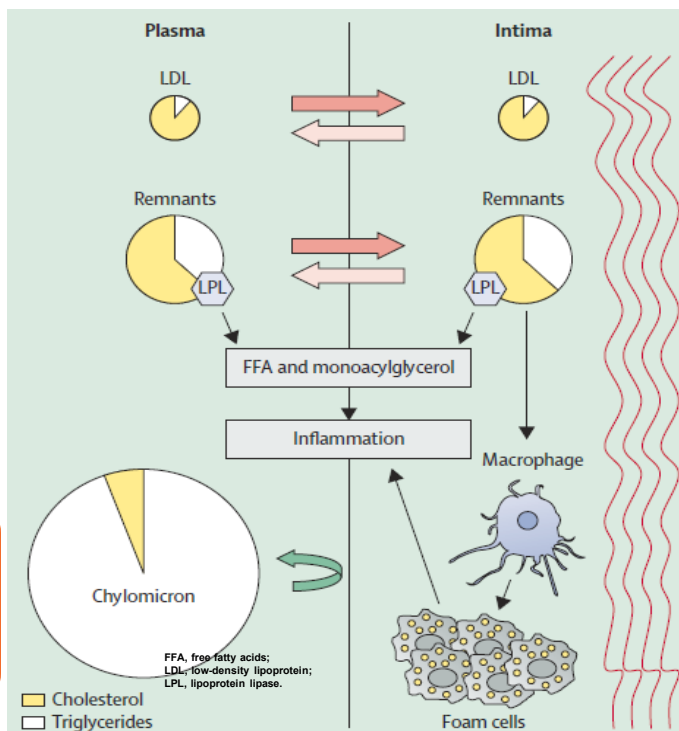
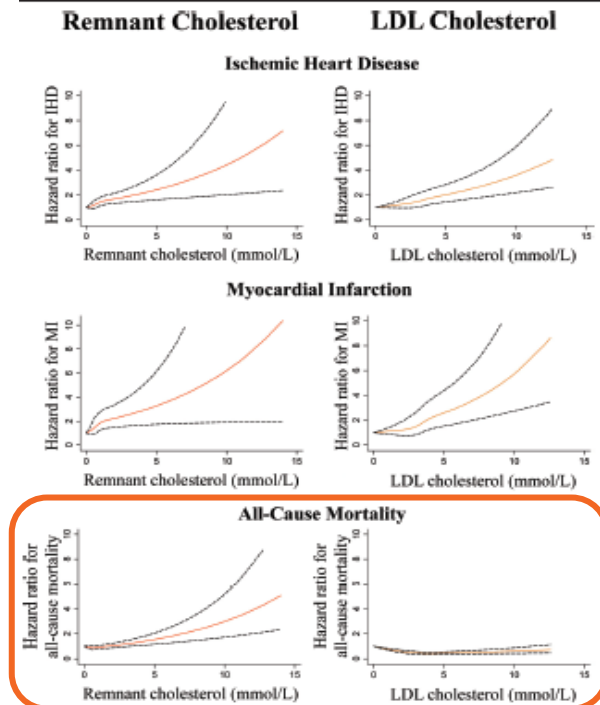
1 mmol TG/L = 88 mg/dL  
5 mmol TG/L = 440 mg/dL

Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease. *J Am Coll Cardiol.* 2013;61(4):427-36.



# Triglyceride-Rich (Remnant) Lipoproteins and ASCVD: New Insights from Epidemiology, Genetics, and Biology

97,962 participants from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) combined.

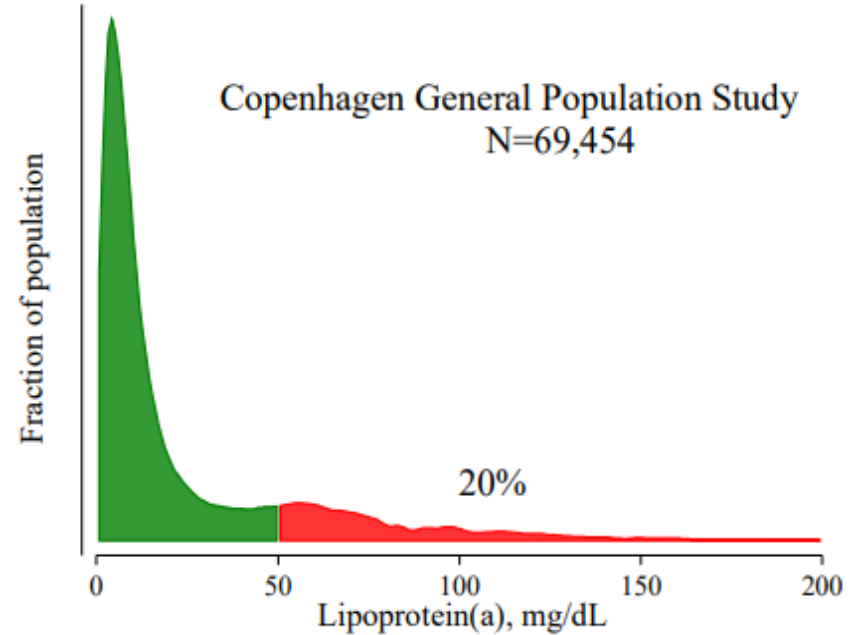
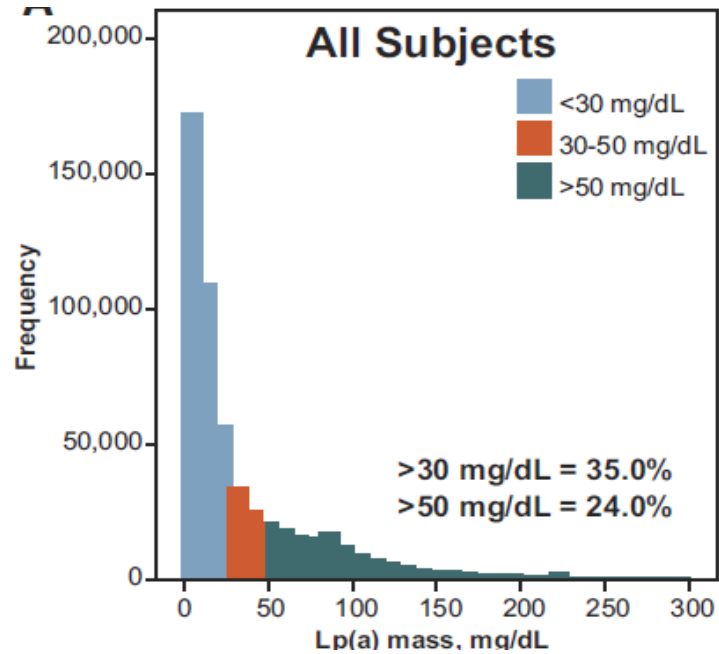
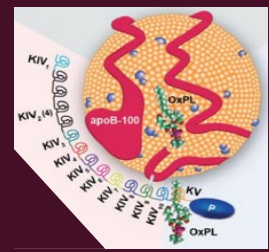


Nordestgaard BG. *Circ Res.* 2016;118(4):547-63.

Varbo A, Freiberg JJ, Nordestgaard BG. *Clin Chem.* 2015;61(3):533-43.

Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* 2014;384(9943):626-35.

# Lipoprotein(a) Is the Most Common Dyslipidemia

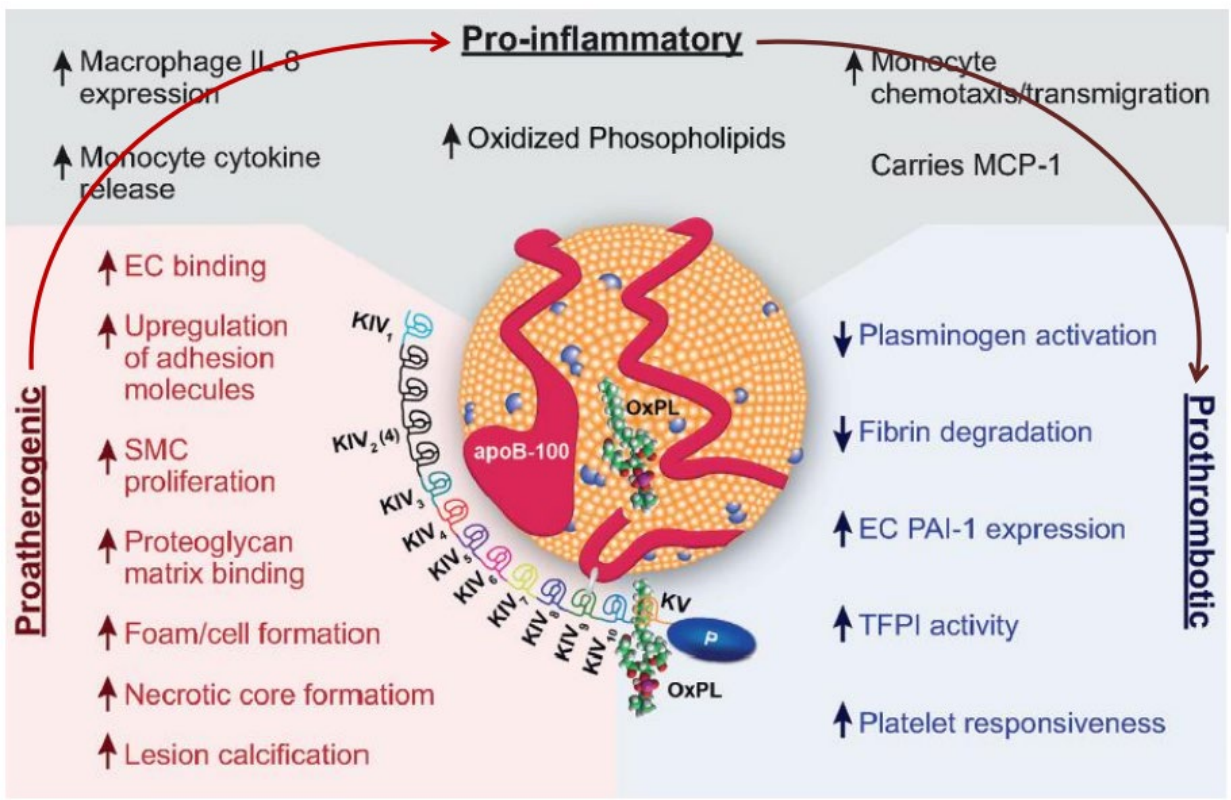


Varvel S, McConnell JP, Tsimikas S. Prevalence of Elevated Lp(a) Mass Levels and Patient Thresholds in 532 359 Patients in the United States. *Arterioscler Thromb Vasc Biol.* 2016;36(11):2239-45. doi: 10.1161/ATVBAHA.116.308011

N Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res.* 2016;57(11):1953-75. doi: 10.1194/jlr.R071233

# Lipoprotein(a) [Lp(a)]

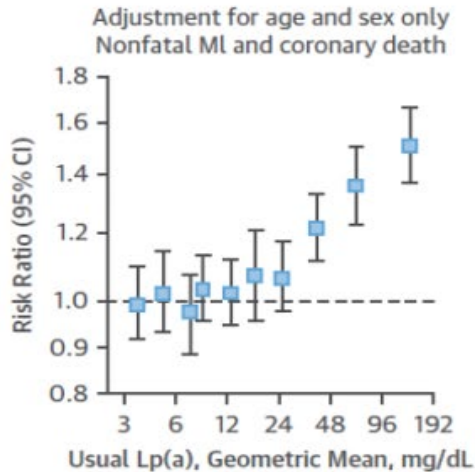
## Pathophysiological Properties



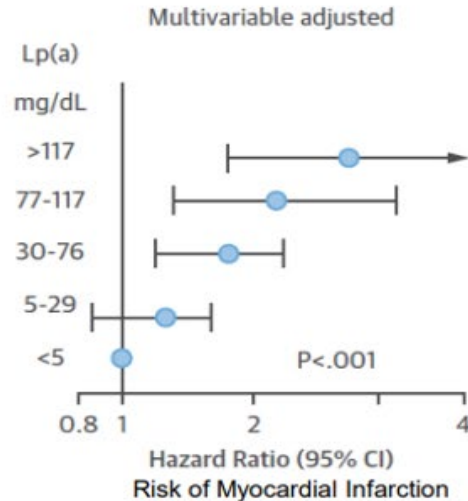
Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies *J Am Coll Cardiol.* 2017;69(6):692-711.

# Lp(a) is an Independent, Causal, Genetic Risk Factor for CVD: The Evidence

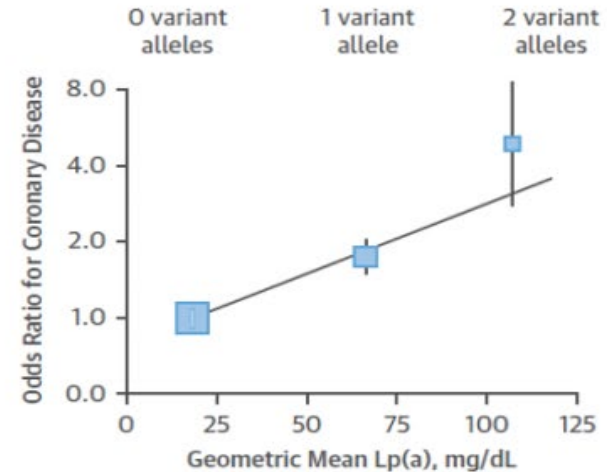
## Meta-analysis



## Mendelian Randomization



## Genome Wide Association



Emerging Risk Factors Collaboration. Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality. *JAMA*. 2009;302(4):412-423.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301(22):2331-9.

Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361(26):2518-28.

Tsimikas S. *J Amer Coll Cardiol*. 2017;69(6):692-711.



# Cumulative Incidence of Major Adverse Cardiovascular Event (MACE) According to Concentrations of Lipoprotein(a) [Lp(a)] among a Secondary Prevention Danish Cohort

Prospective cohort study of Individuals from the Copenhagen General Population Study with CVD at baseline, N = 2,527

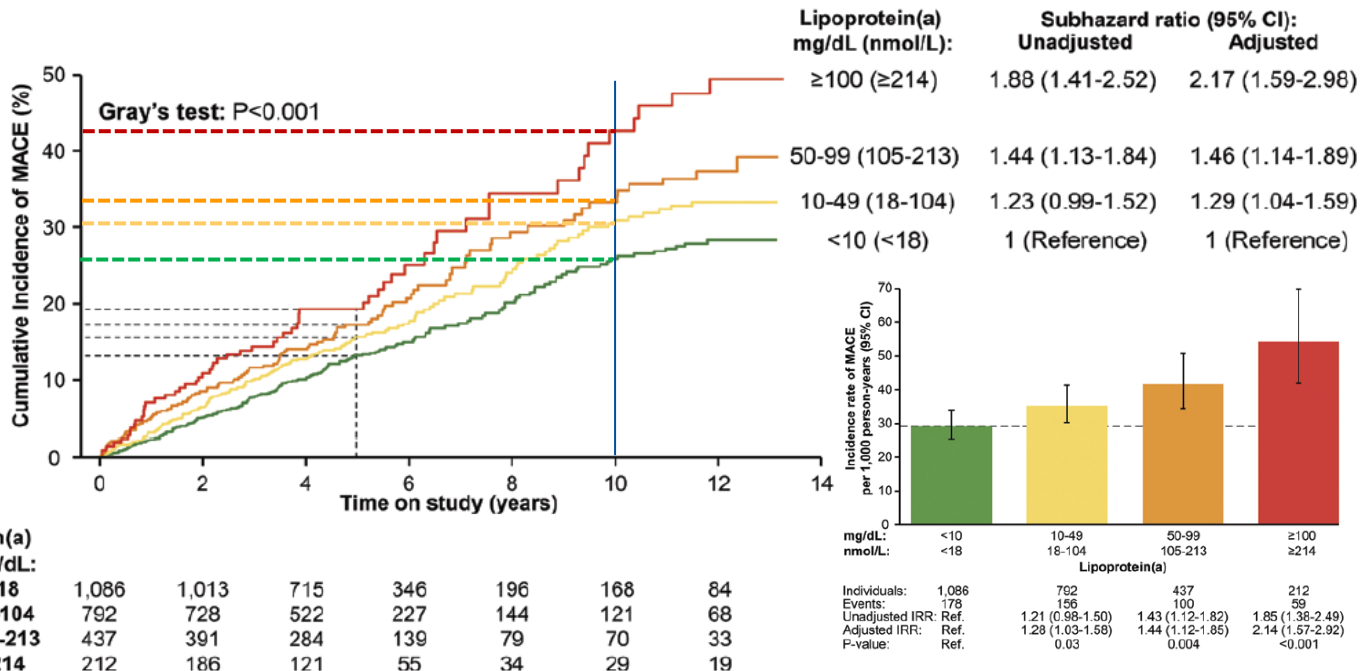
Composite MACE = CV death, nonfatal MI, revascularization (CABG or PTCA), or ischemic stroke

## 4-Point Composite

Lp(a) (mg/dL)	MACE Risk	
	5-yr	10-yr
≥100	19.3	42
50-99	17.2	33
10-49	15.6	30
<10	13.2	26

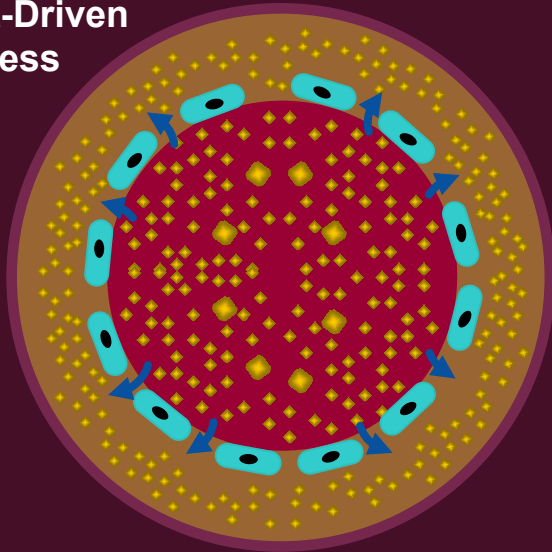
Adapted from:

Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL(105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: A population-based study. *Arterioscler Thromb Vasc Biol.* 2020;40(1):255-66. doi: 10.1161/ATVBAHA.119.312951



# The Fundamental Causal Biomarkers of ASCVD are Apolipoprotein B (Apo B)-Containing Cholesterol Particles Entering the Arterial Wall

Gradient-Driven Process



*A large concentration or 'number' of all atherogenic apo B-containing particles [LDL, Lp(a), TG-rich lipoprotein cholesterol, chylomicron remnants, VLDL-remnants (IDL)] is most predictive of IHD*

Management (Ultimately, Lower Apolipoprotein B)

1. ↓ LDL-C

Lowest is Best (ESC/EAS 2019)

Extreme risk: <40 mg/dL  
Very high risk: <55 mg/dL  
High risk: <70 mg/dL  
Moderate risk: <100 mg/dL  
Low risk: <116 mg/dL

2. ↓ TG-Rich Lp-C

↓ TG (VLDL → IDL → ↑LDL) → ↓ LDL-C

3. ↓ Lp(a)

Lower LDL-C to <50 mg/dL?  
Reduce Lp(a) by 50 or 100 mg/dL →  
for 20% or 40% 5-yr ASCVD RRR  
Lipoprotein [Lp(a)] apheresis  
Await potent Apo(a)-lowering Rx

**Pharmacologic enrichment with EPA\* Rx-grade, non-oxidized \*Eicosapentaenoic acid**

Icosapent Ethyl, 4 grams,

**Thank You!**