

Are Lipid Measurements
Falling Short?
Evaluating Lipoprotein Pathology

Michael Richman M.D., F.A.C.S.
CEO and Director,
The Center for Cholesterol Management
Los Angeles, California

www.lipidcenter.com

LDL-C is the focus of clinical attention for historical and analytical reasons

“... all **abnormalities** in plasma lipid concentrations, or dyslipidemia, can be translated into **dyslipoproteinemia.**”

“... the **shift** of **emphasis** to **lipoproteins** offers distinct advantages in the **recognition** and **management** of such disorders.”

Explanation of LDL

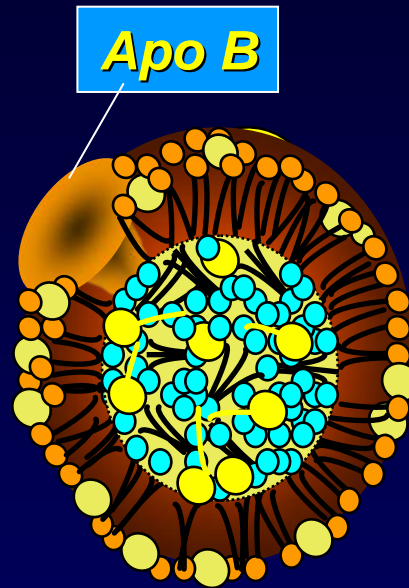
LDL = Low Density Lipoprotein

LDL-C = the amount of cholesterol contained in
all LDL particles

LDL-P = LDL particle concentration

Lipids vs. Lipoproteins

This is an LDL Particle



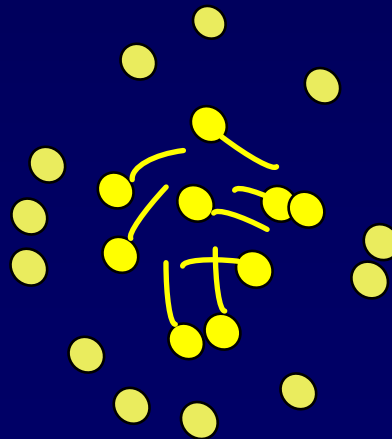
**POLAR
SURFACE COAT**

Phospholipid 
Free cholesterol 

**NONPOLAR
LIPID CORE**

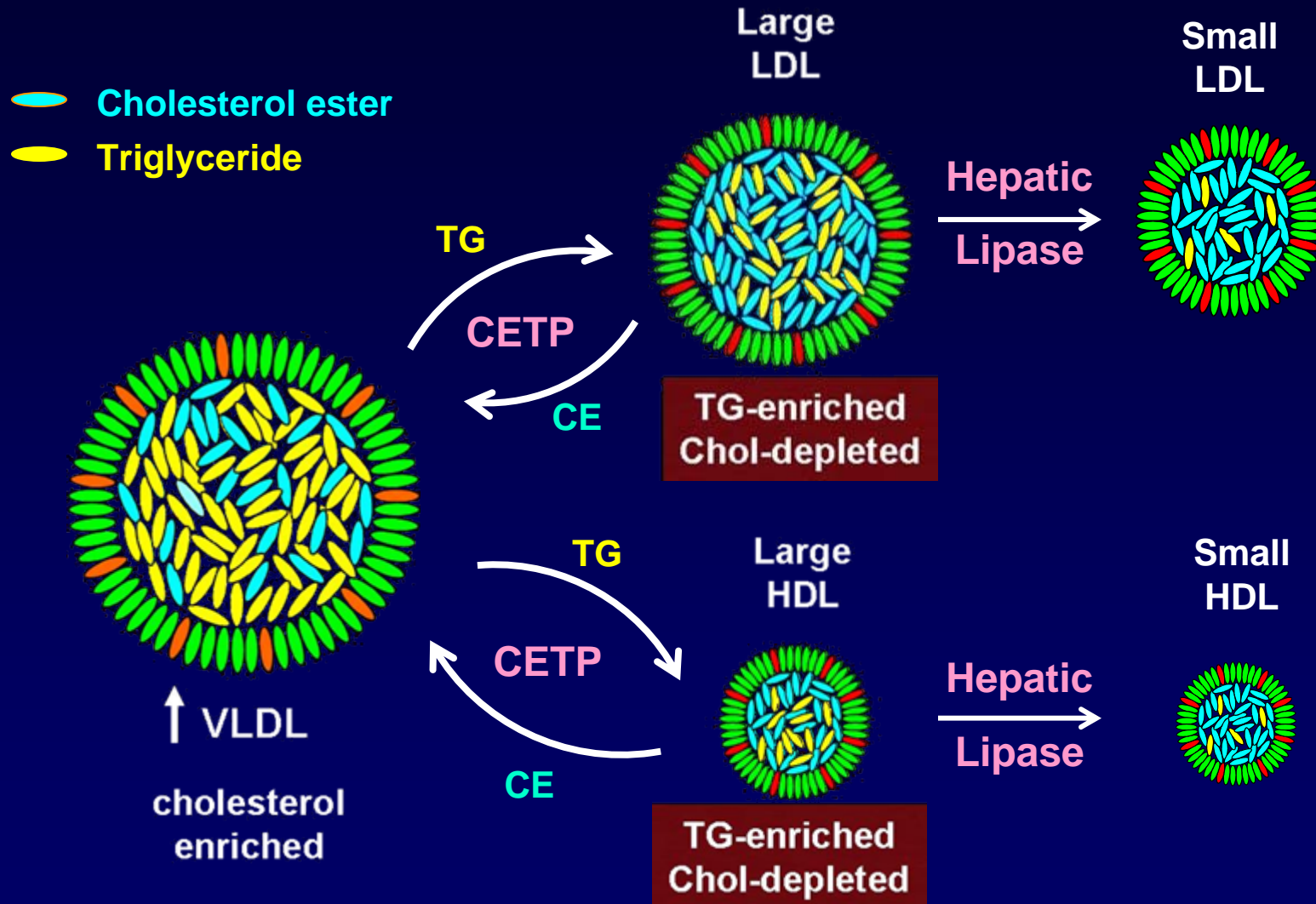
 Cholesterol Ester
 Triglyceride

This is LDL
Cholesterol



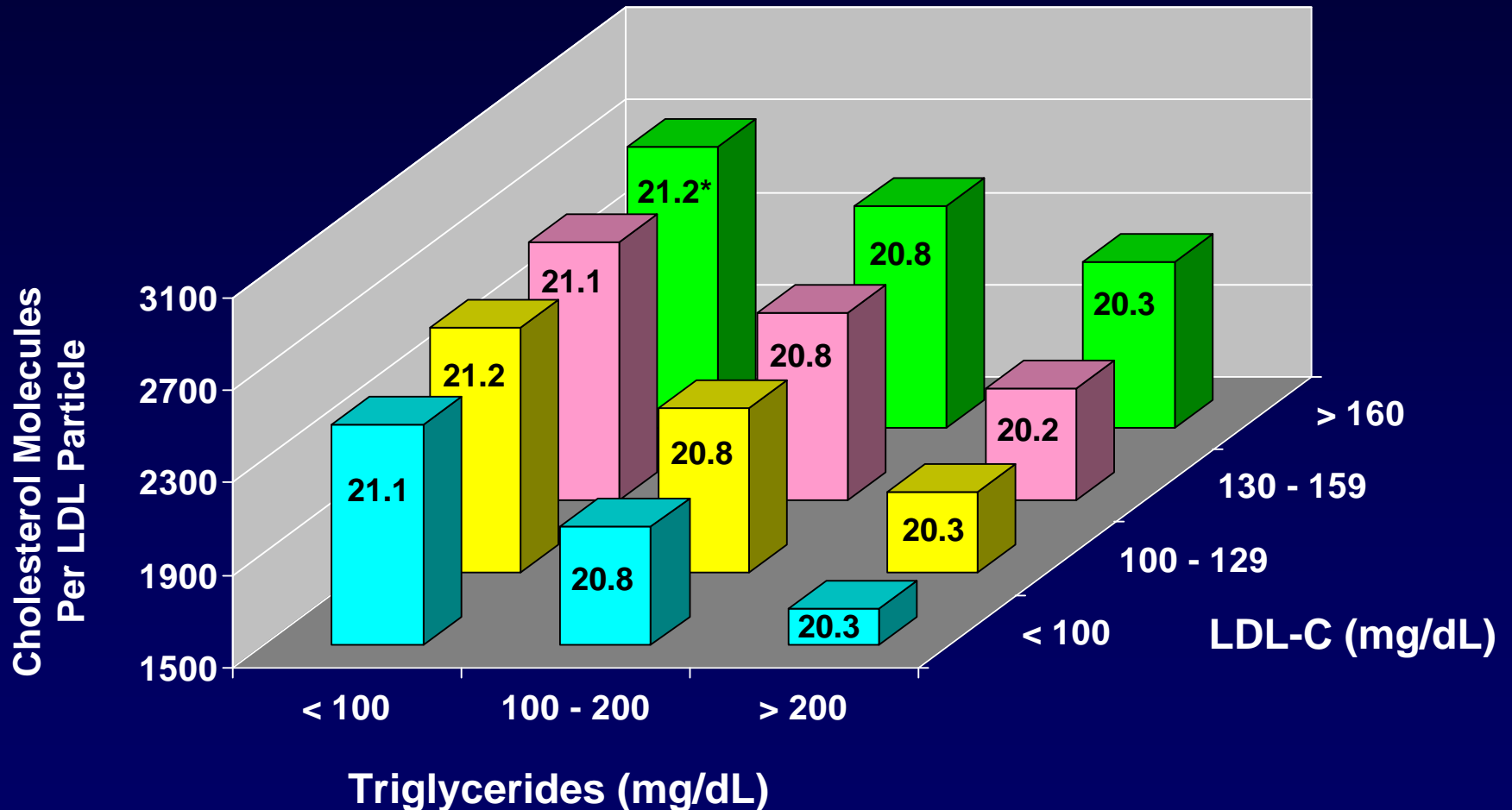
A convenient
analytic surrogate
of LDL since 1972

Cholesterol Carried Inside Lipoprotein Particles Is Highly Variable



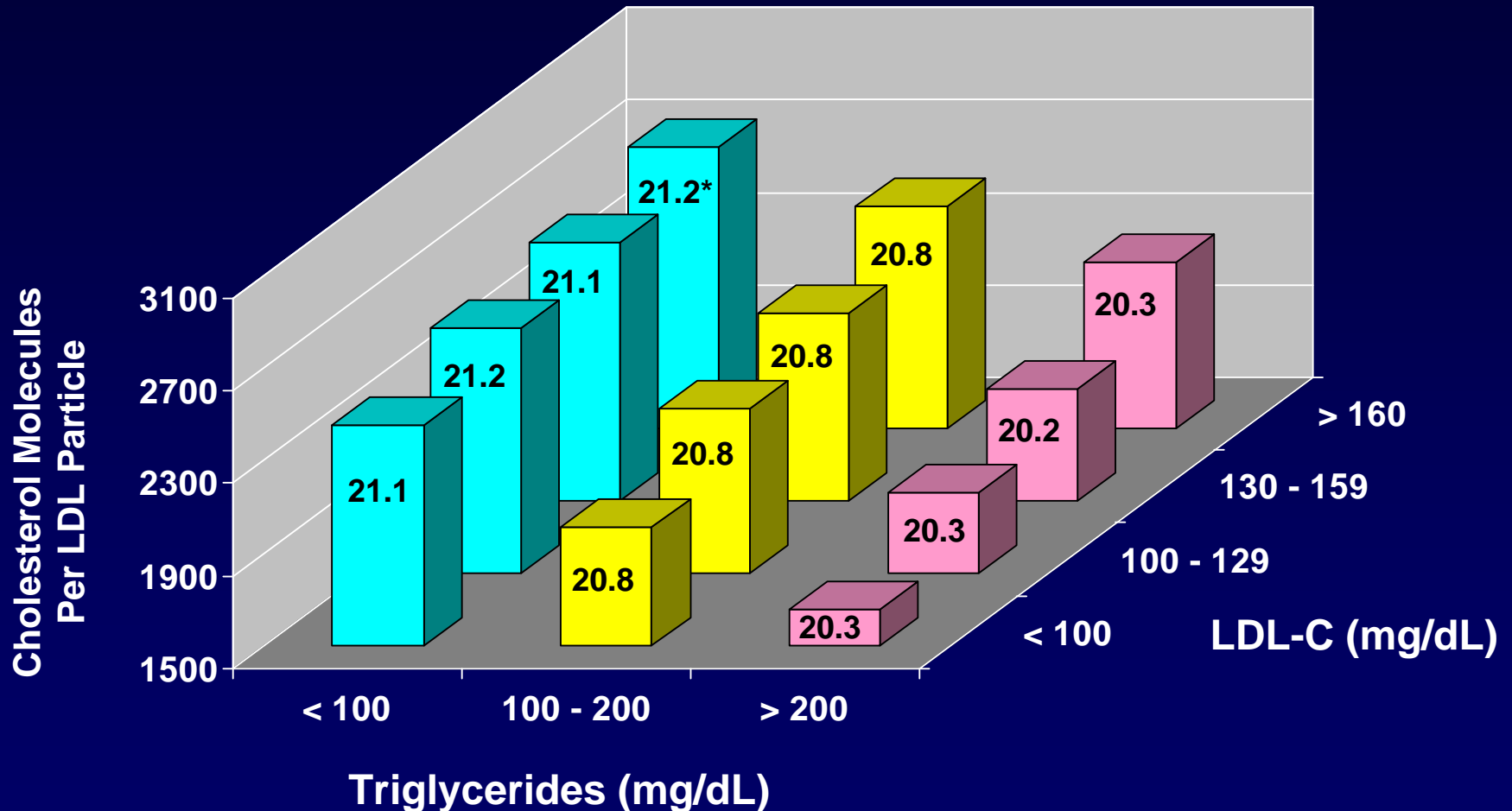
Cholesterol Content Variability of LDL is Driven Partly by LDL Size Differences

Framingham Offspring Study (n=3,066)

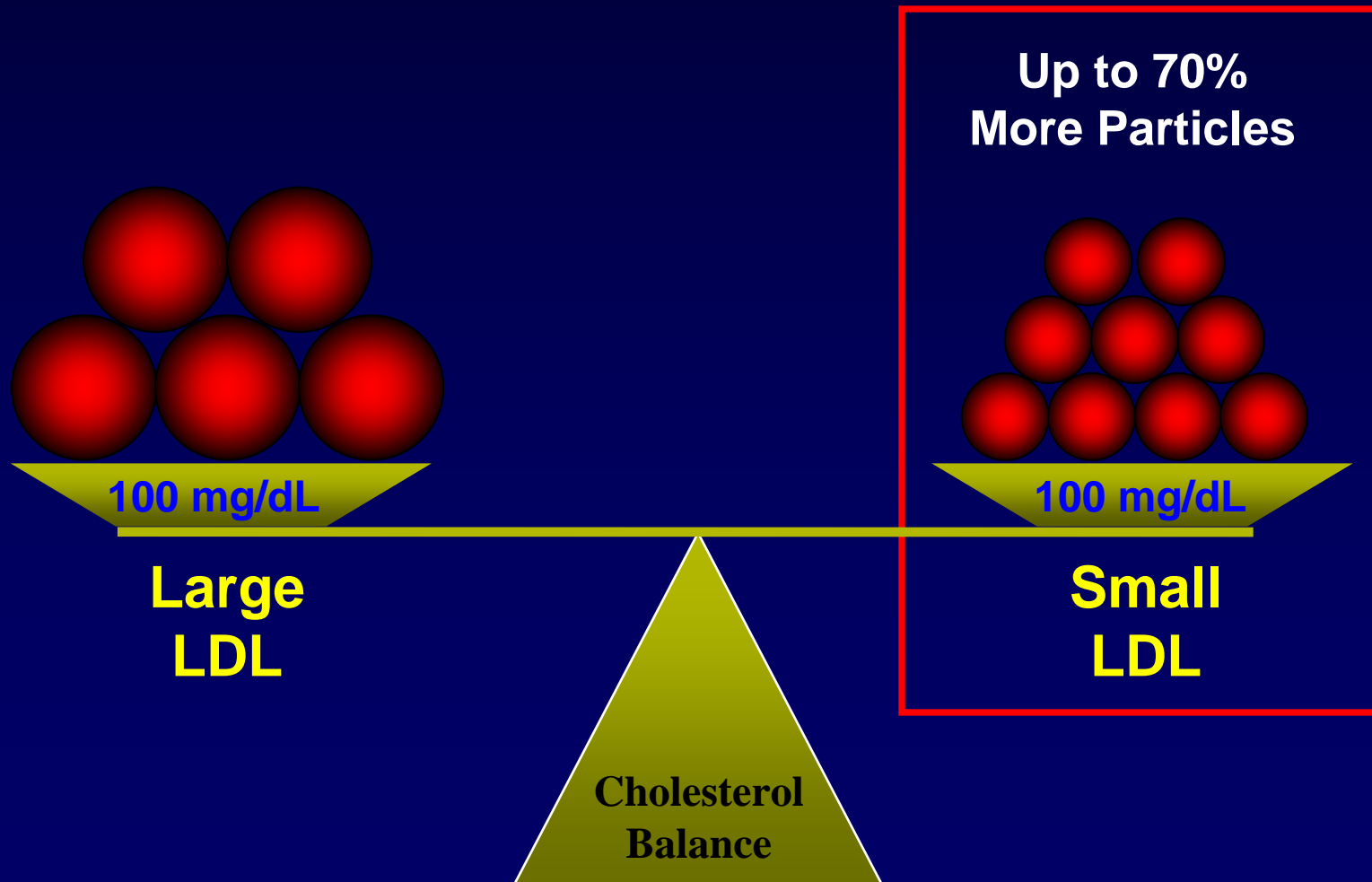


Cholesterol Content Variability of LDL is Driven Also by LDL Concentration!

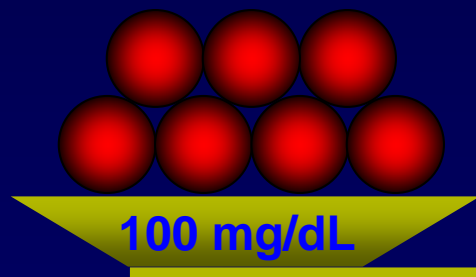
Framingham Offspring Study (n=3,066)



Among Individuals At The Same LDL-C Level, The Number of LDL Particles Varies

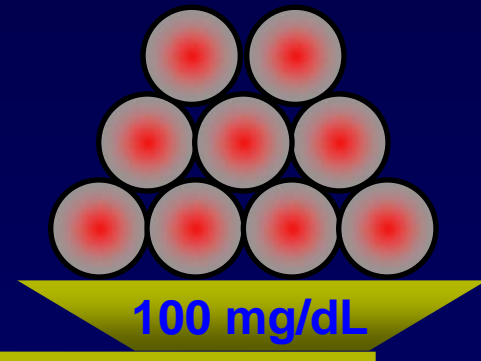


Among Individuals At The Same LDL-C Level, The Number of LDL Particles Varies



Normal Cholesterol
Carried Per Particle

Up to 40%
More Particles

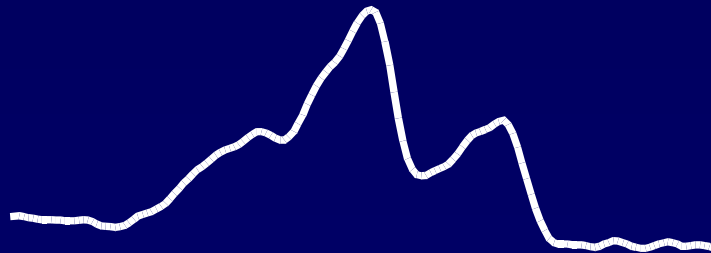
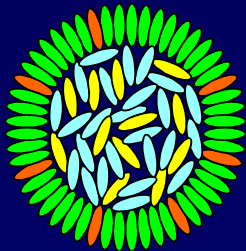
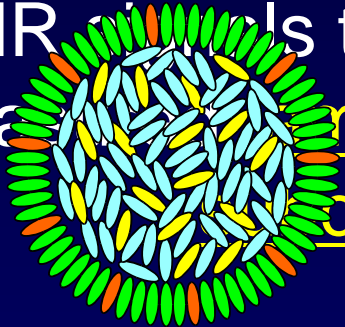


Less Cholesterol
Carried Per Particle

Cholesterol
Balance

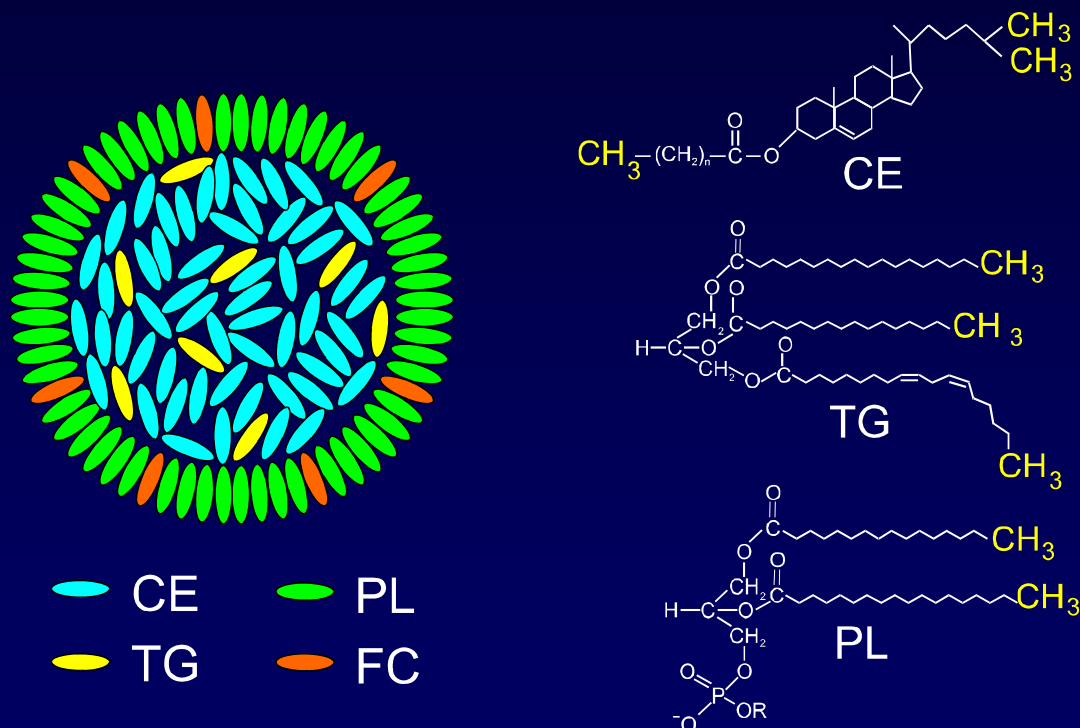
NMR Lipoprotein Analysis

Lipoprotein subclasses of different size broadcast lipid NMR signals that are naturally distinguishable. The measured amplitudes of these signals provide class quantification.



NMR Lipoprotein Analysis

Each subclass NMR signal comes from the aggregate number of terminal methyl groups on the lipids in the particle shell and core.



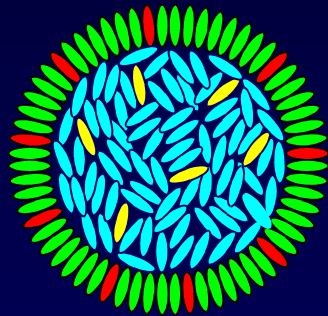
The number of methyl groups in a particle of given size is unaffected by lipid compositional variation.



NMR Measures LDL Particle Number Not LDL Cholesterol

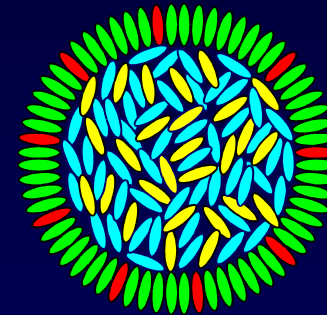
Normal LDL

Cholesterol-poor LDL

Measured
LDL-C
90 mg/dL

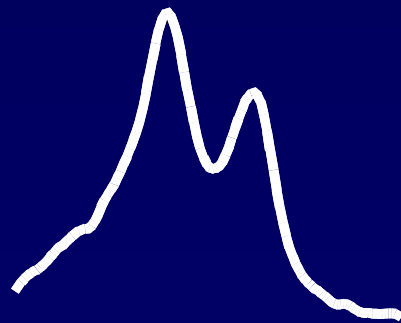


 cholesterol ester
 triglyceride

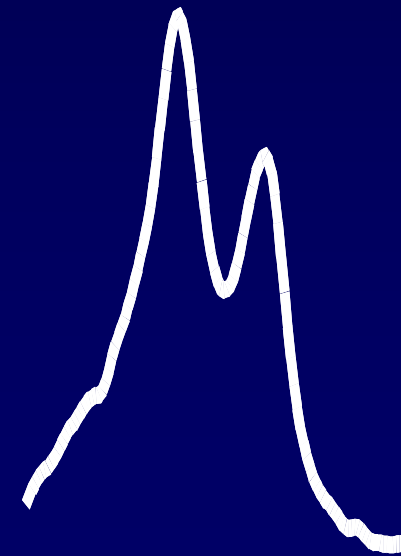


Measured
LDL-C
90 mg/dL

LDL particles
900 nmol/L

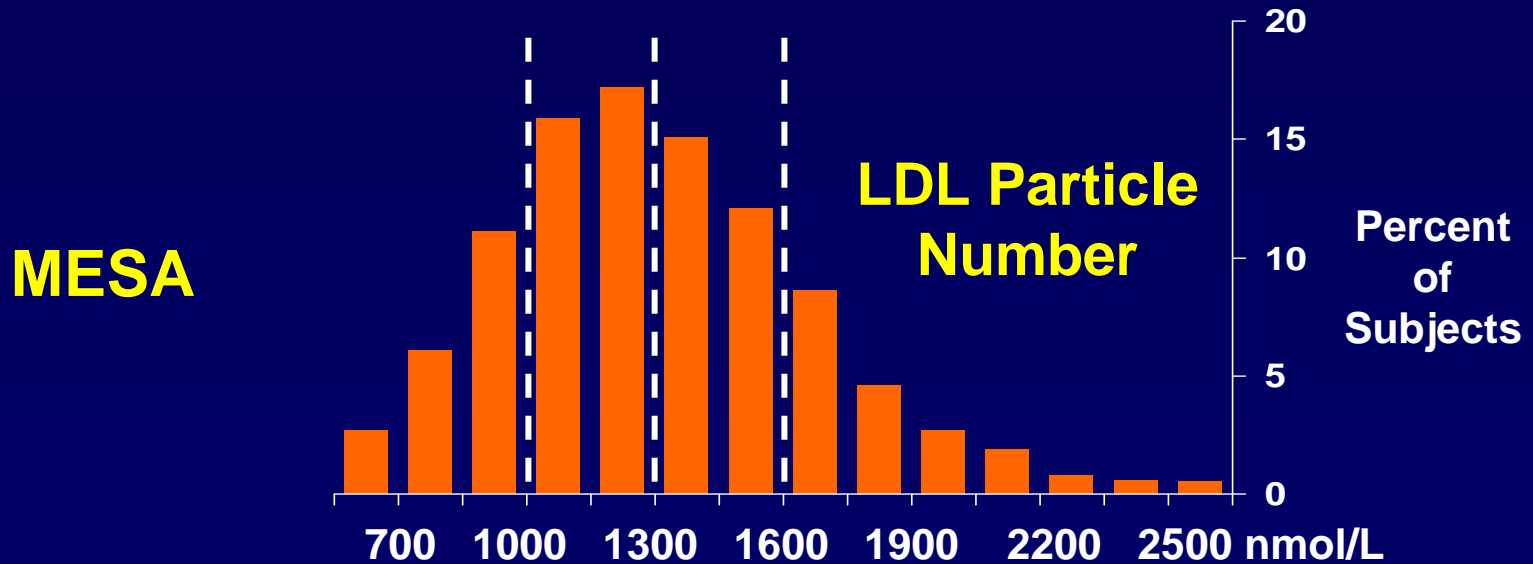
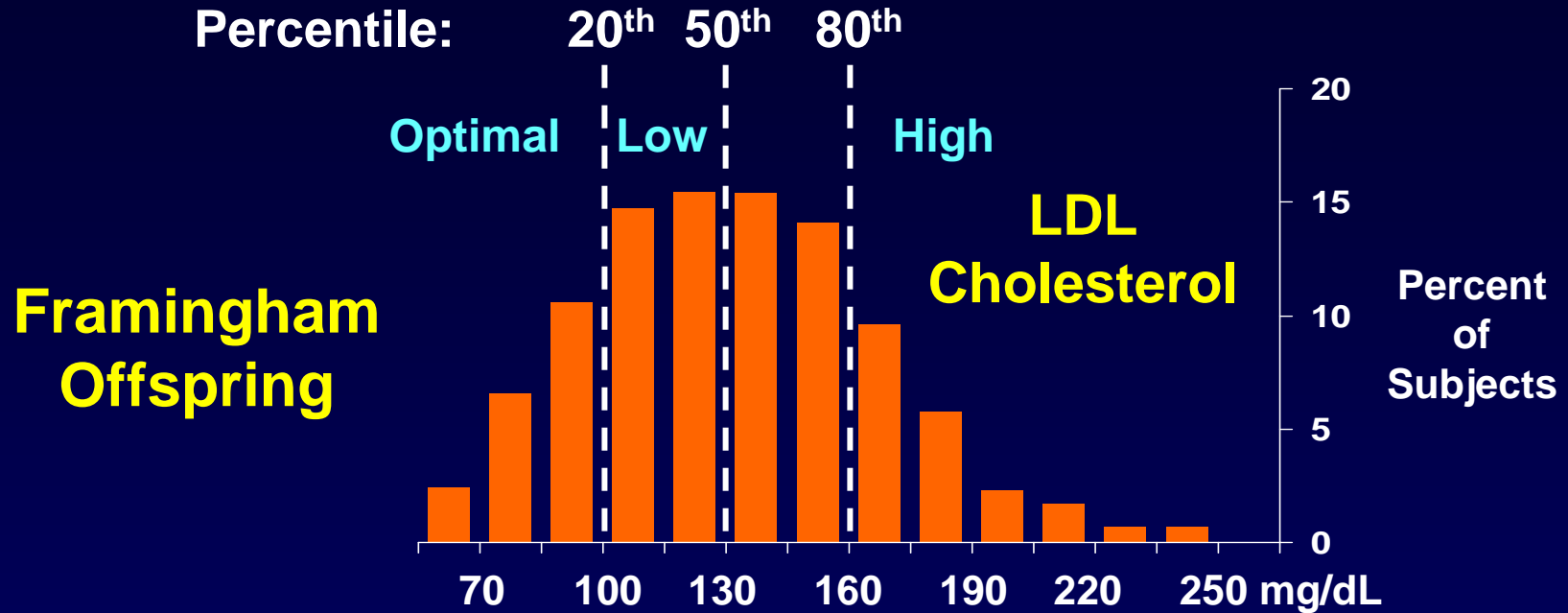


LDL
NMR
Signals



LDL particles
1600 nmol/L

LDL treatment targets are consensus, population-based (not derived from clinical trials comparing different targets)

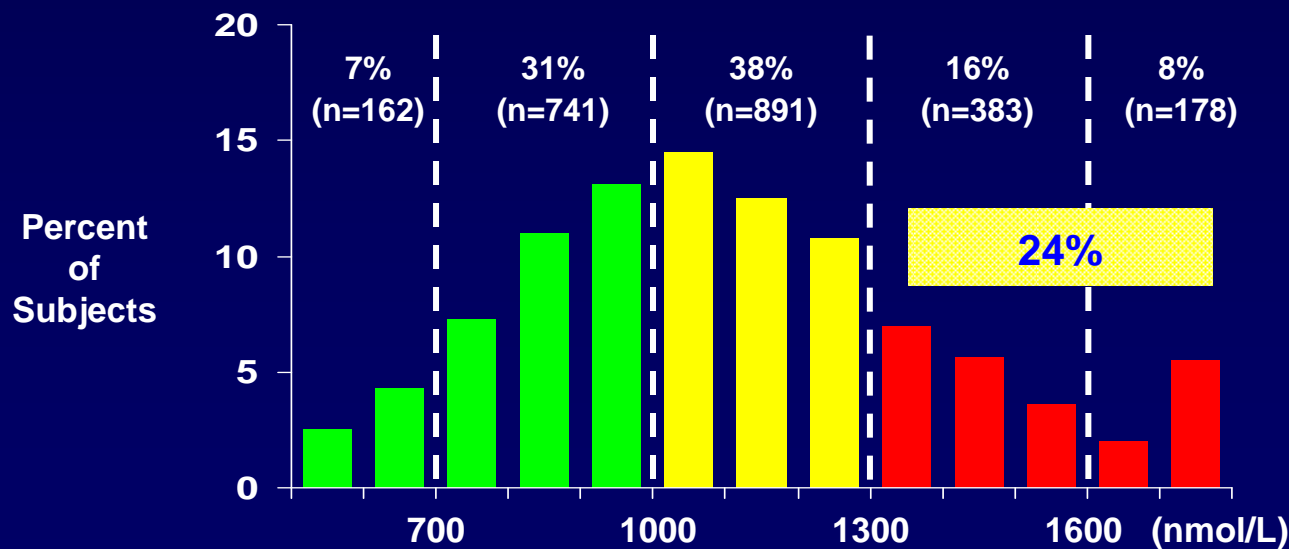
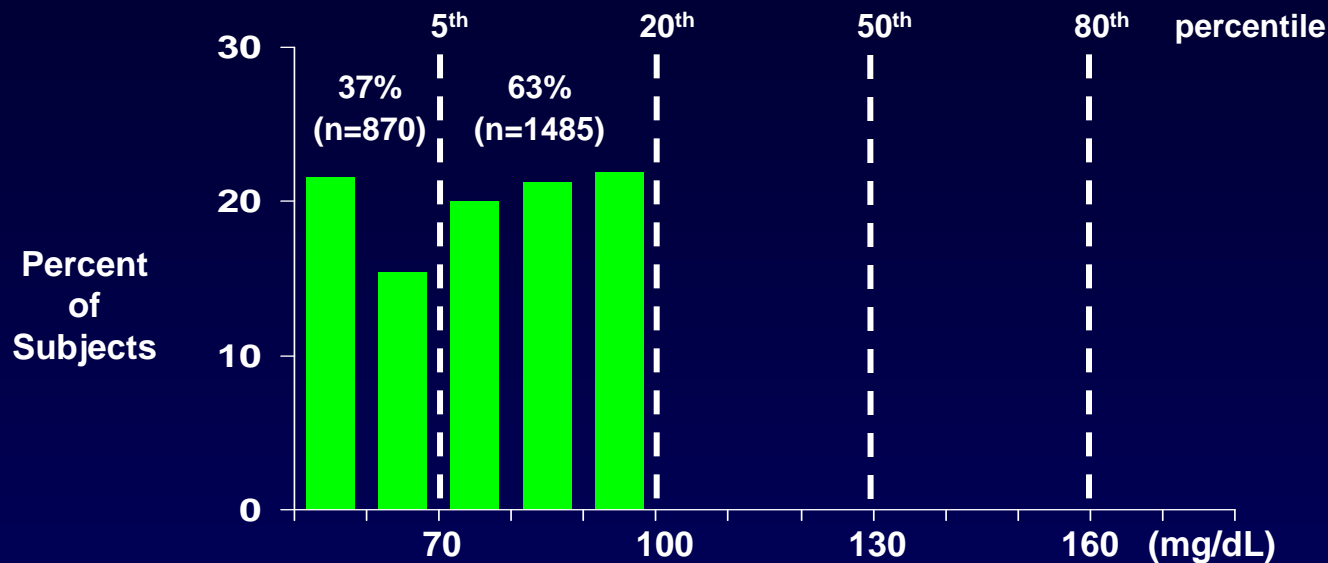


**LDL Particle Number is Highly Heterogeneous
Among Patients with Type 2 Diabetes Mellitus at
LDL Cholesterol Target Goal <100 mg/dL**

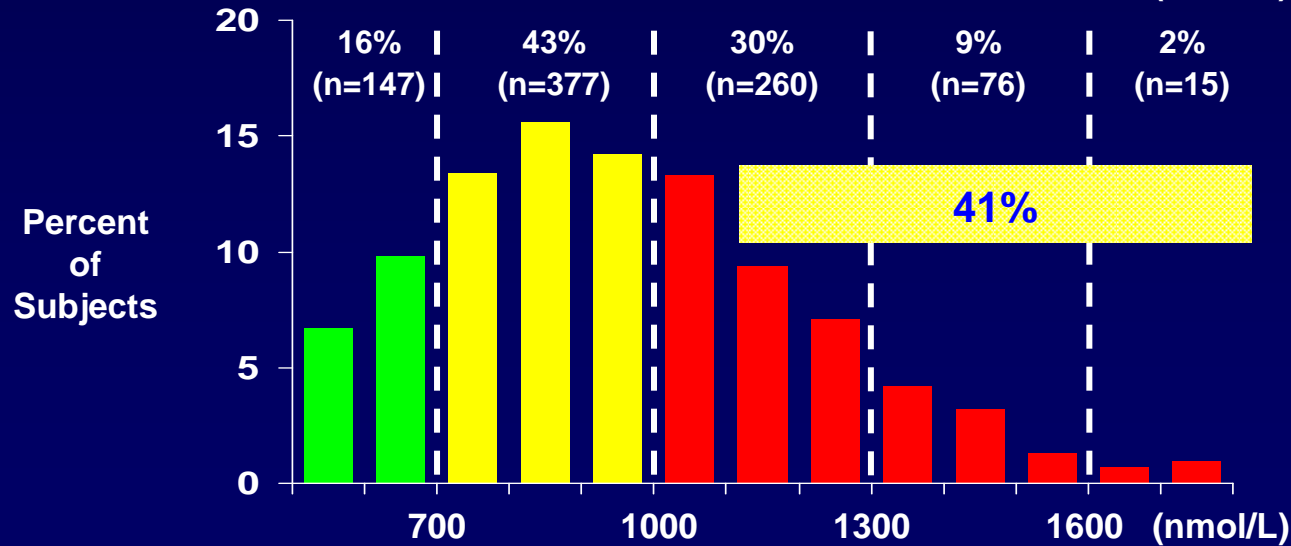
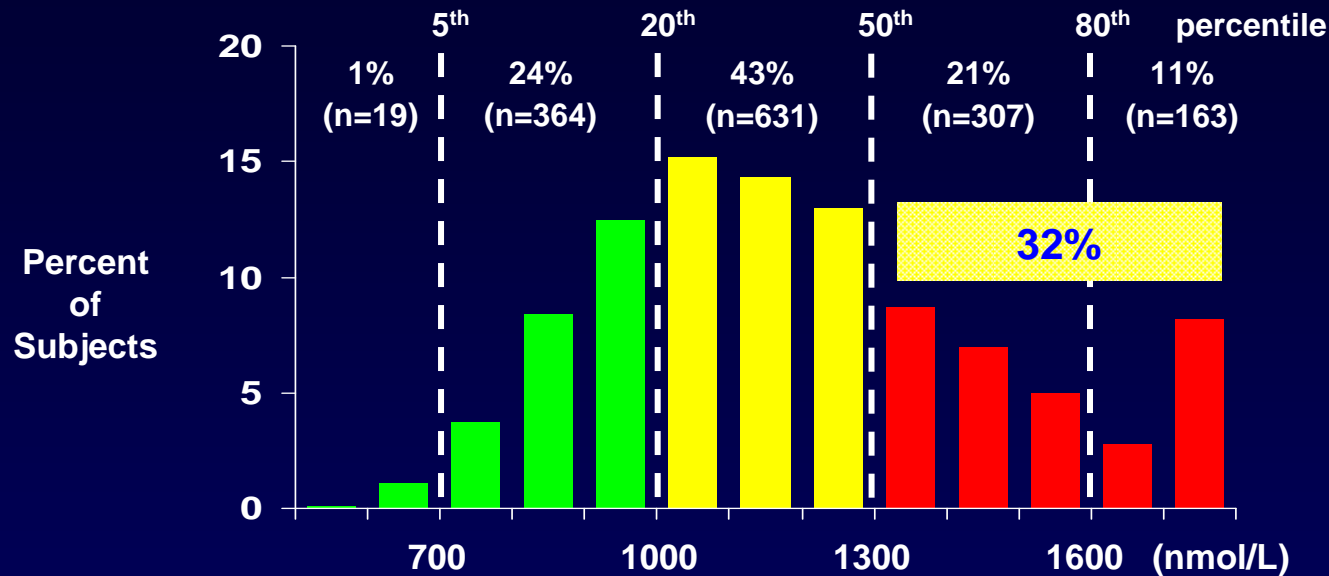
W.C. Cromwell and J.D. Otvos

Am J Cardiol. 2006;98:1599-1602

LDL Cholesterol and LDL Particle Numbers in T2DM Patients with LDL-C < 100 mg/dL (n=2,355)



LDL Particle Number Distribution in T2DM Subjects



Weight of Evidence

CVD OUTCOMES STUDIES	LDL-P MORE PREDICTIVE THAN LDL-C	CVD ENDPOINTS	PATIENT TYPE
Framingham Offspring Study Cromwell et al. J Clin Lipidology 2007	YES	Incident MI, Stroke, CHD Death, Angina	Healthy Men & Women n=3,066
Multi-Ethnic Study of Atherosclerosis (MESA) Mora et al. Atherosclerosis 2007	YES	Carotid Intima-Media Thickness (IMT)	Healthy Men & Women n=5,538
Veterans Affairs HDL Intervention Trial (VA-HIT) Otvos et al. Circulation 2006	YES	Nonfatal MI or CHD Death	Men with Known CHD & Low HDL-C n=1,061
Pittsburgh Epidemiology of Diabetes Complications Study Soedamah-Muthu et al. Diabetologia 2003	YES	MI, CHD Death, Coronary Revascularization	Type I Diabetic Men and Women n=118
Cardiovascular Health Study (CHS) Kuller et al. Arterioscler Thromb Vasc Biol 2002	YES	Incident MI or Angina	Elderly n=1,175
Women's Health Study (WHS) Blake et al. Circulation 2002	YES	Incident MI, CHD Death, Stroke	Healthy Women n=260
Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC-1) Rosenson et al. Am J Cardiol 2002	YES	Angiographic Minimum Lumen Diameter	Patients with Known CHD n=241
Healthy Women Study (HWS) Mackey et al. Am J Cardiol 2002	YES	EBCT Coronary Calcification Score	Post Menopausal Healthy Women n=286

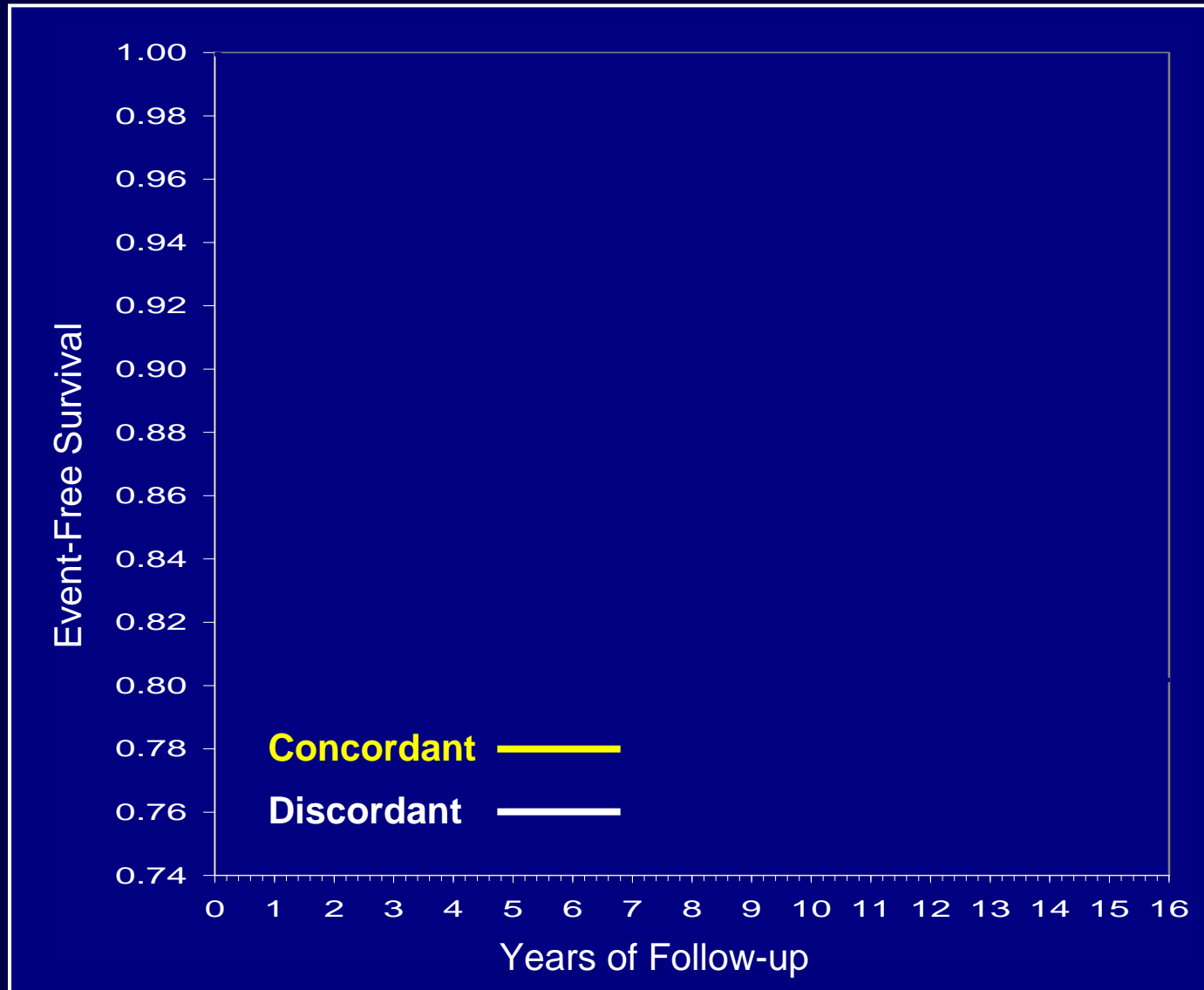
Original Contributions

LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management

William C. Cromwell, MD,* James D. Otvos, PhD, Michelle J. Keyes, PhD, Michael J. Pencina, PhD, Lisa Sullivan, PhD, Ramachandran S. Vasan, MD, Peter W. F. Wilson, MD, Ralph B. D'Agostino, PhD

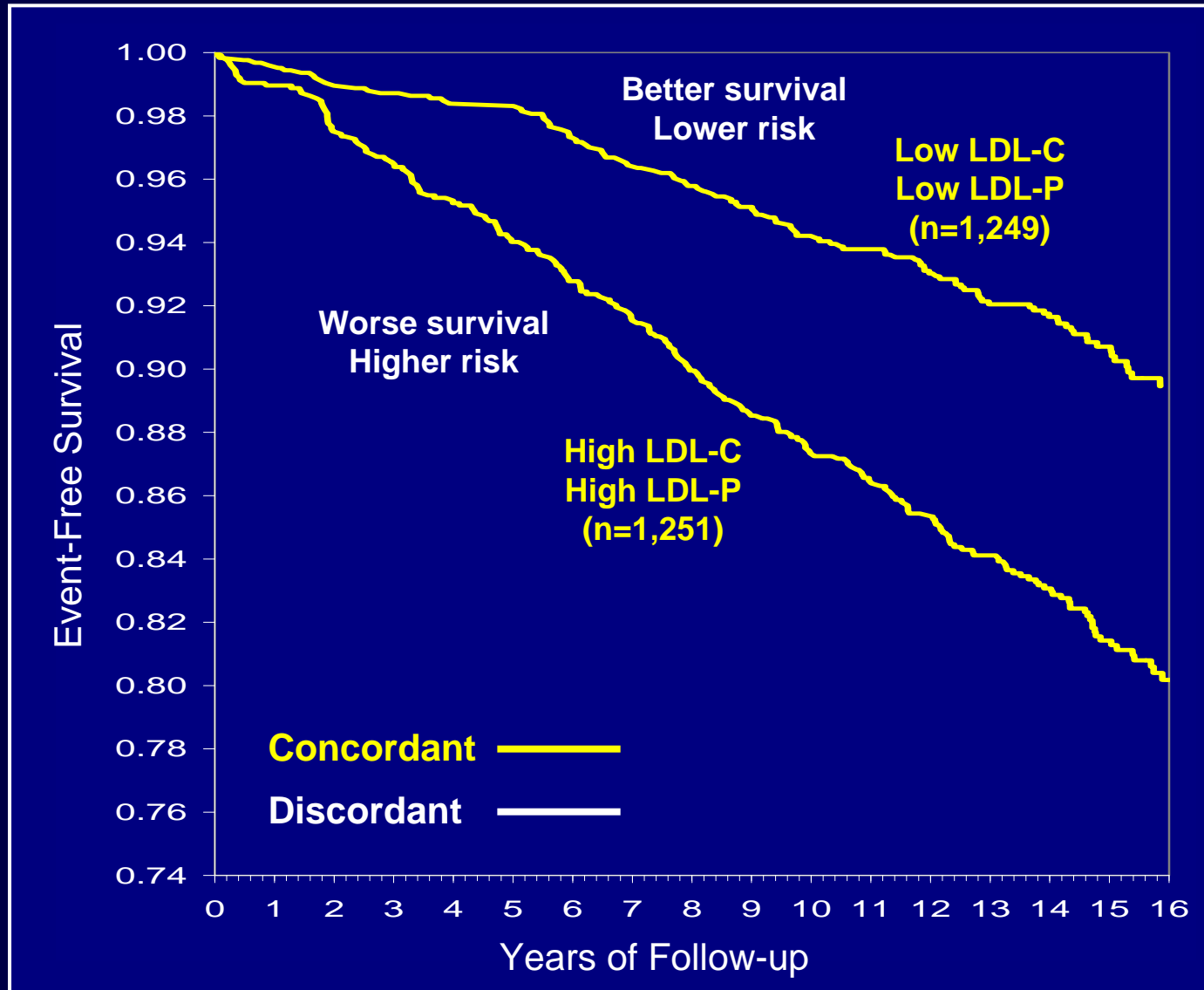
CHD Event Associations of LDL-P versus LDL-C

Framingham Offspring Study (n=3,066)



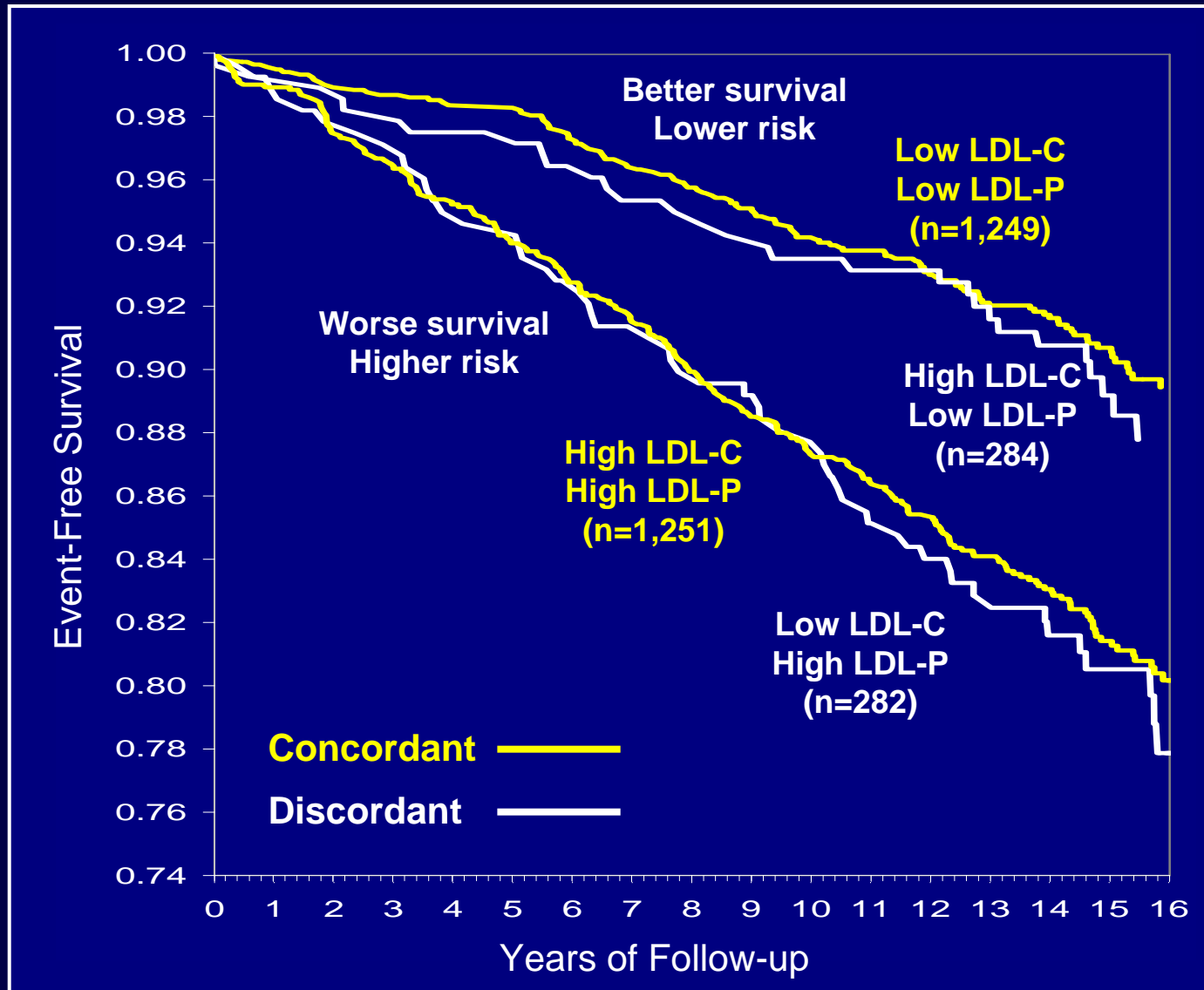
CHD Event Associations of LDL-P versus LDL-C

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CHD Event Associations of LDL-P versus LDL-C

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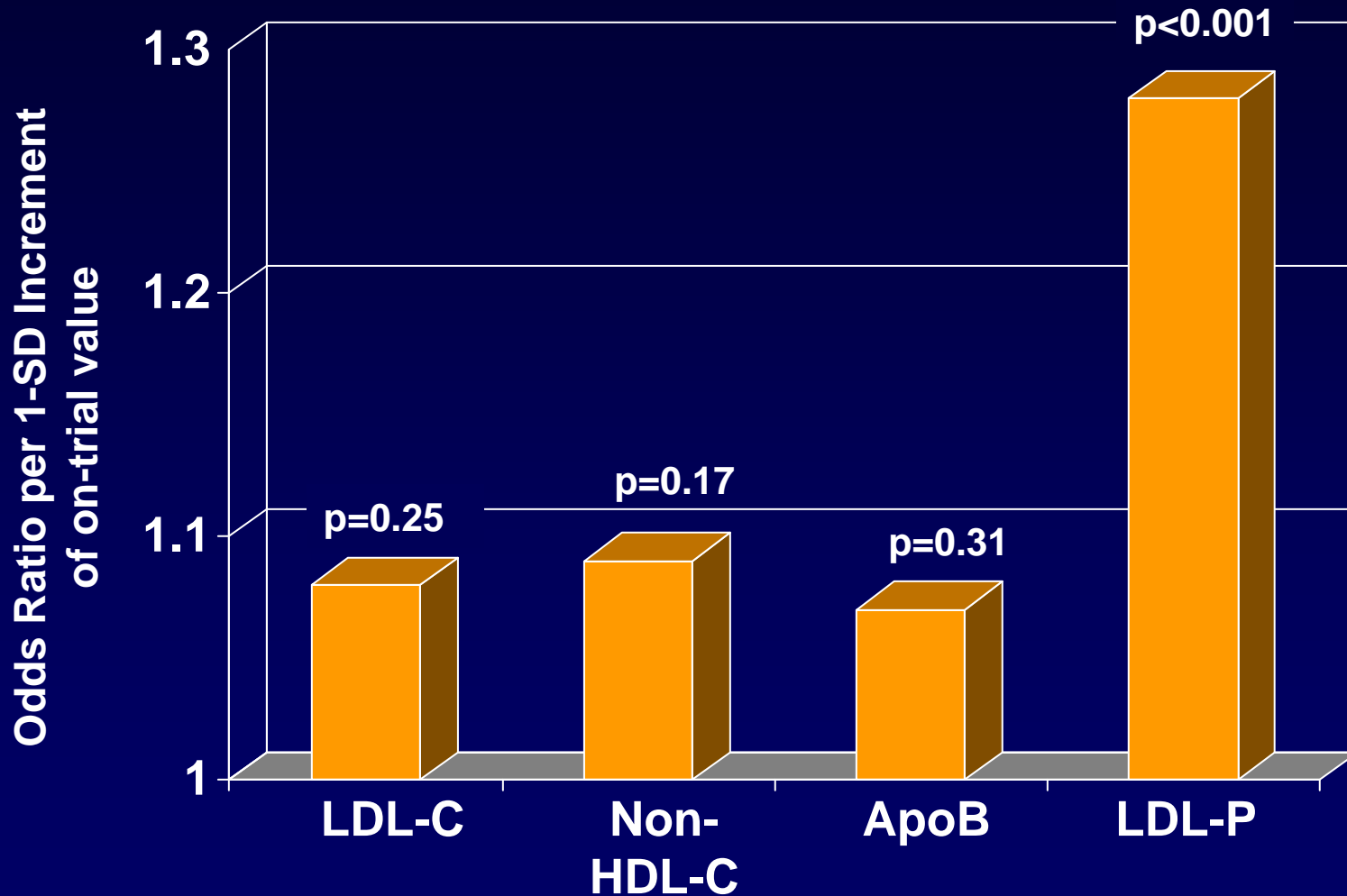


**LDL and HDL Particle Subclasses Predict
Coronary Events and are Favorably Changed
by Gemfibrozil Therapy in the Veterans
Affairs HDL Intervention Trial (VA-HIT)**

Otvos JD, Collins D, Freedman DS, Shalaurova I,
Schaefer EJ, McNamara J, Bloomfield HE, Robins SJ

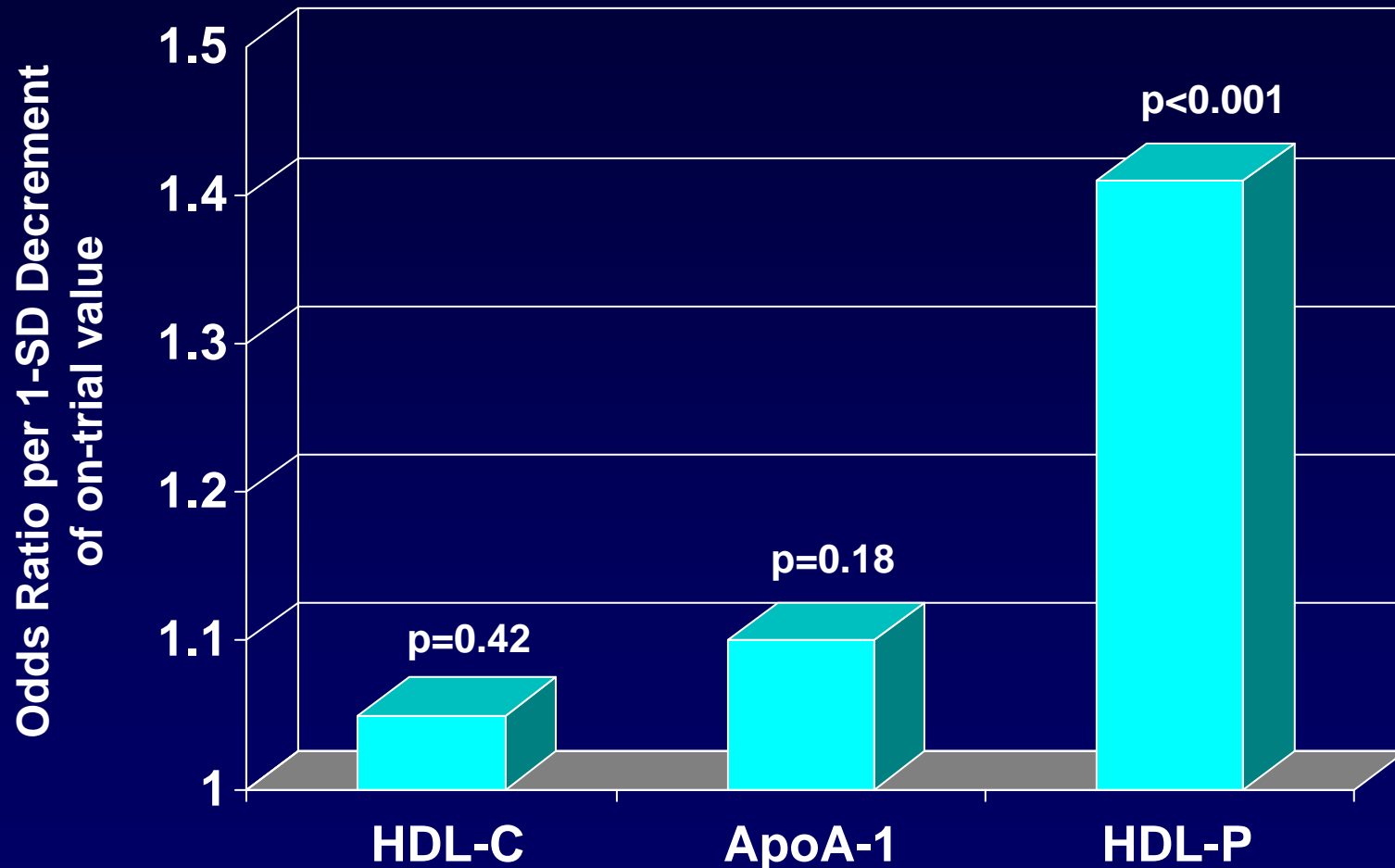
Circulation 2006;113:1556-63

Alternative Measures of LDL as Predictors of CHD Events in VA-HIT



Adjusted for treatment, age, hypertension, smoking, BMI, and diabetes

Alternative Measures of HDL as Predictors of CHD Events in VA-HIT



Adjusted for treatment, age, hypertension, smoking, BMI, and diabetes

Circulation 2006;113:1556-63

Conclusion

In this nested case-control sub-study of VA-HIT, NMR-measured HDL and LDL particle numbers were significant independent predictors of incident CHD events, whereas levels of HDL and LDL cholesterol (or apolipoproteins A-1 and B) were not.

Conclusions

1. The cholesterol content of LDL is far more variable than generally appreciated.
2. Cholesterol-depleted LDL is prevalent not only in individuals with elevated TG/low HDL etc., but also in those with low LDL.
3. LDL-P is a more sensitive indicator of low risk than LDL-C or non-HDL-C, and therefore a more discriminating LDL treatment target.

ADA/ACC Consensus Statement

A need for better lipoprotein Management

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CONSENSUS CONFERENCE REPORT

Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus Conference Report From the American Diabetes Association
and the American College of Cardiology Foundation

Writing Committee Members

John D. Brunzell, MD, FACP*
Michael Davidson, MD, FACC†
Curt D. Furberg, MD, PhD‡
Ronald B. Goldberg, MD§

Barbara V. Howard, PhD||
James H. Stein, MD, FACC, FACP¶
Joseph L. Witztum, MD#

ADA/ACC Consensus Statement

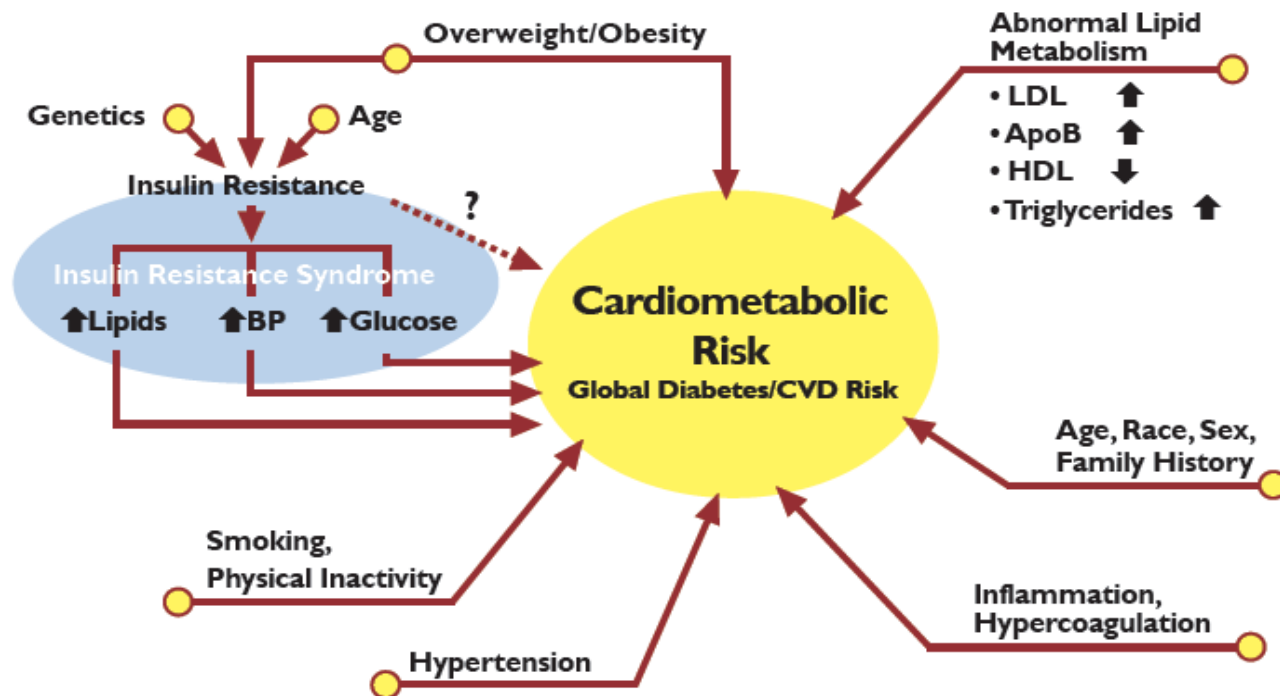
A need for better lipoprotein management

- Lipoprotein abnormalities are common findings in patients with CMR. Measurement of LDL cholesterol may not accurately reflect the true burden of atherogenic LDL particles, especially in those with typical lipoprotein abnormalities of CMR.
- Even with adequate LDL cholesterol lowering, many patients on statin therapy have significant residual CVD risk. Treatment targets and the best approach for CVD risk reduction in this population need to be better defined.
- Some have advocated that assessment of other lipoprotein parameters might be more helpful than assessment limited to LDL-C or non-HDL cholesterol in these populations.

ADA/ACC Consensus Statement

A need for better lipoprotein management

Factors Contributing to Cardiometabolic Risk



Reprinted with permission from Brunzell JD, et al., Lipoprotein Management in Patients with Cardiometabolic Risk Consensus Statement from the American Diabetes Association and the American College of Cardiology Foundation. *JACC*. 2008;51:1513.

ADA/ACC Consensus Statement

Key Findings on LDL-P by NMR

- “A more accurate way to capture the risk posed by LDL may be to measure the number of LDL particles directly using nuclear magnetic resonance (NMR).”
- “Measurements of apoB or LDL particle number by NMR may more closely quantitate the atherogenic lipoprotein load.
- “ApoB and LDL particle number also appear to be more discriminating measures of the adequacy of LDL lowering therapy than are LDL cholesterol or non-HDL cholesterol.”

Approach to Clinical Utilization of NMR LDL-P

Step 1: Assess clinical CHD risk: Very-High, High, Moderate-High Risk

Step 2: Establish targets of therapy appropriate for degree of clinical risk present

Very-High and High Risk

LDL-P < 1000 nmol/L

Moderately-High Risk

LDL-P NMR < 1300 nmol/L

Step 3: Laboratory evaluation

Step 4: Clinical intervention as indicated to achieve targets:

Primary target: LDL

Secondary targets: HDL and TG

Step 5: Assess response to therapy and modify intervention as indicated to achieve LDL-P target

LDL Lowering Drugs Reduce LDL-P

Change in Laboratory Values

Adapted from *Therapeutic Lipidology*, 2006

Lipid-altering agent	LDL-P (%)	LDL-C (%)
Statins	18-55 ▼	18-55 ▼
Nicotinic acid (Niacin)	10-25 ▼	05-25 ▼
Fibric acids (Fibrates)	05-20 ▼	05-20 ▼
Ezetimibe	15-25 ▼	17-22 ▼
Bile acid sequestrants	15-30 ▼	15-30 ▼
Fish oils	Trials in progress	No change/increase
Phytosterols/phytostanols	Trials in progress	10-15 ▼

Treatments that Alter the Cholesterol Content of LDL Change LDL-C and LDL-P Differentially

Cholesterol per particle decreases with:

- statins
- statin + ezetimibe
- estrogen replacement therapy
- anti-retrovirals (some)
- low fat, high carb diet

↓ LDL-C More

Cholesterol per particle increases with:

- fibrates
- niacin
- glitazones
- omega 3 FAs
- exercise
- low carb diet

↓ LDL-P More

Conclusions

- Unrecognized (and under-treated) LDL particle elevations are common and a significant contributor to the residual risk of many patients with “acceptable” levels of LDL-C.
- Achievement of LDL-P treatment goals ensures that the patient has achieved adequate LDL reduction.
- LDL size (“quality”) does not contribute to risk once LDL particle number is taken into account.
- LDL-P may be lowered not only by statins, but by lifestyle change and combination drug therapy.

Relationship of LDL Particle Size and CHD Outcomes

1. The relationship of small LDL size with CHD risk is intertwined with a complex physiologic syndrome that includes high TG, low HDL-C and increased LDL particle number.
2. LDL size is a strong risk marker, but has no significant association with CVD once LDL particle number is taken into account (Quebec, MESA, Framingham, EPIC-Norfolk, VA-HIT, Women's Health Study).
3. Following adjustment for confounding (all in data analysis), small LDL particles do not appear to be more atherogenic than large LDL particles (MESA, VA-HIT).