Are Lipid Measurements Falling Short? Evaluating Lipoprotein Pathology

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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."

Fredrickson et al., NEJM 1967; 276: 148

Explanation of LDL

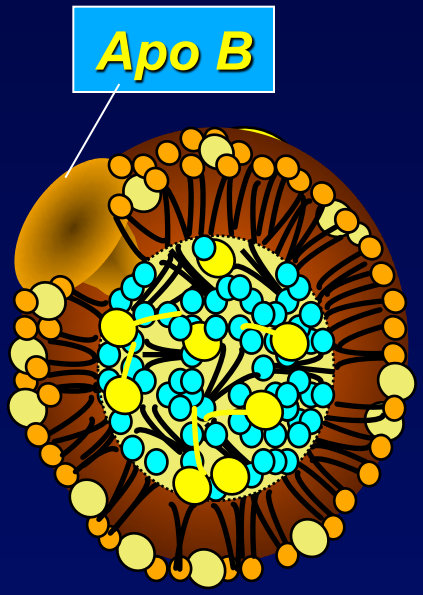
LDL = Low Density Lipoprotein

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

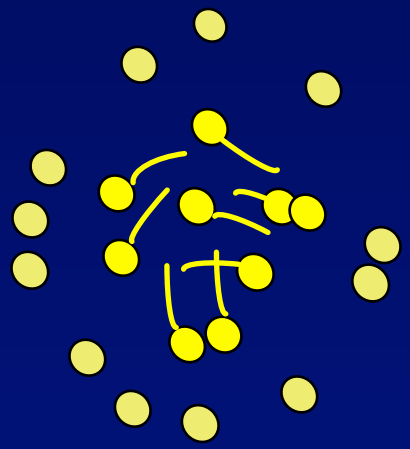
Free cholesterol

NONPOLAR LIPID CORE

Cholesterol Ester

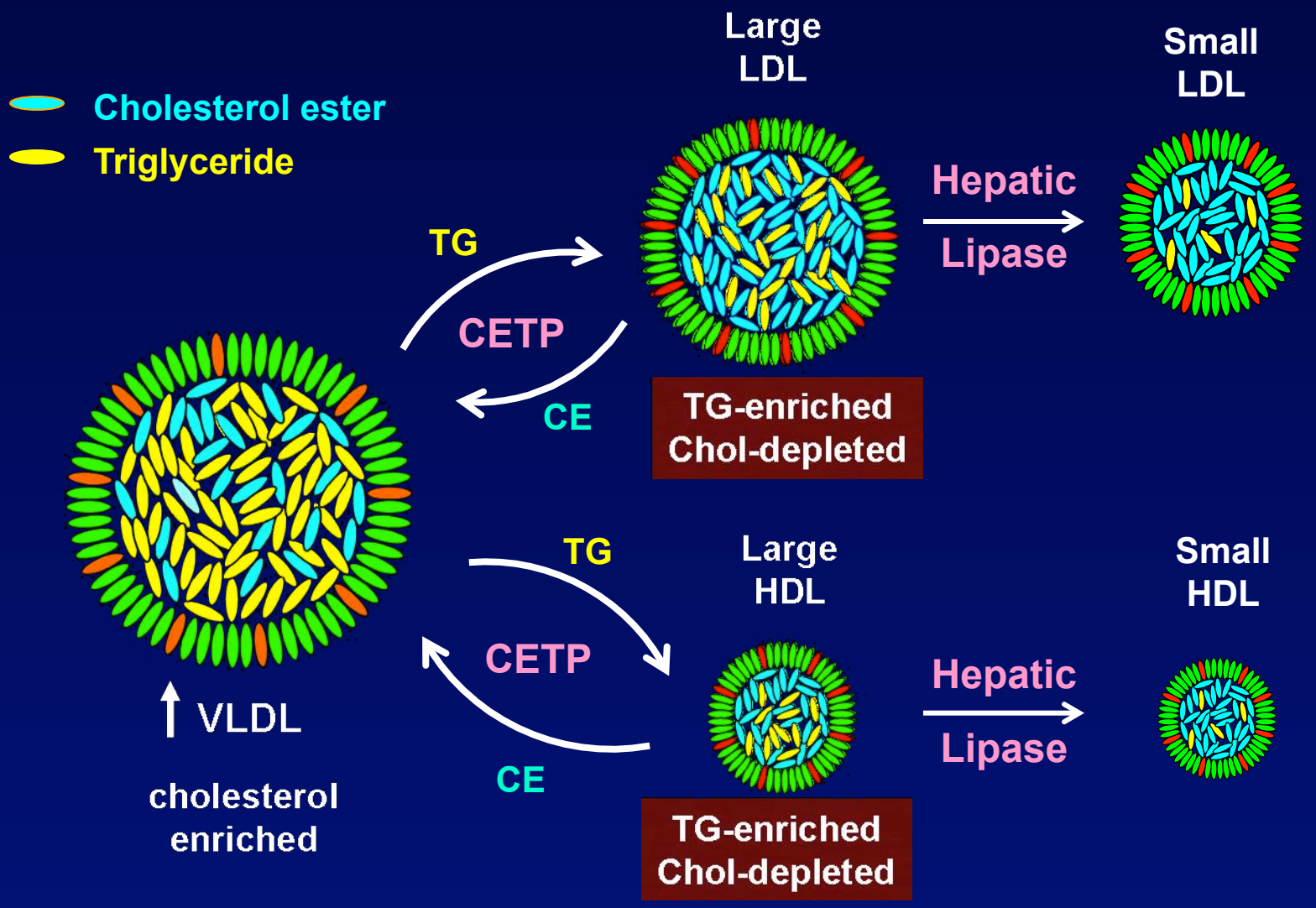
Triglyceride

This is LDL Cholesterol



A convenient analytic surrogate of LDL since 1972

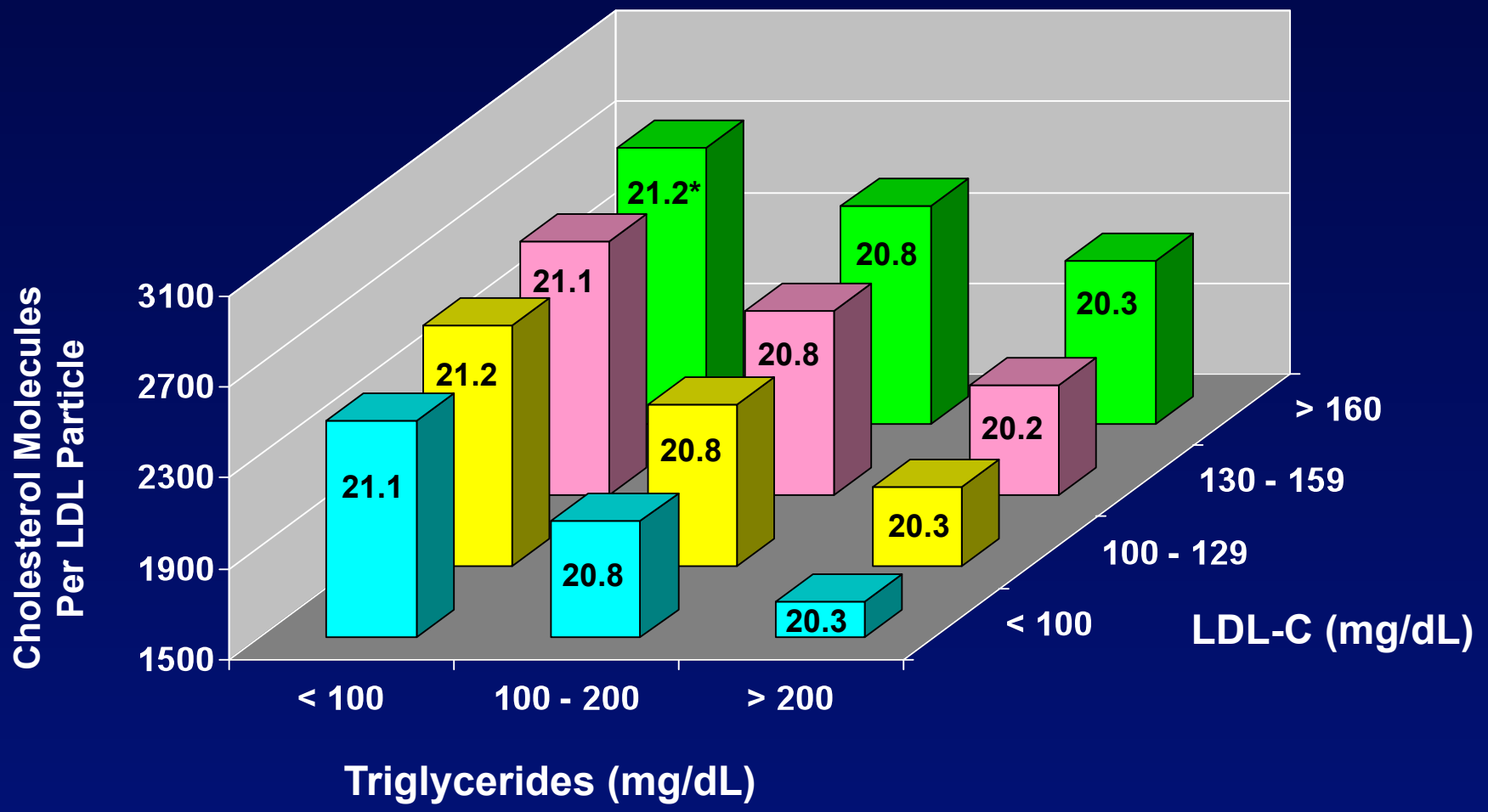
Cholesterol Carried Inside Lipoprotein Particles Is Highly Variable



Otvos JD, Jayarajah E, Cromwell, WC. *AJC* 2002;90(8A):22i-29i

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

Framingham Offspring Study (n=3,066)

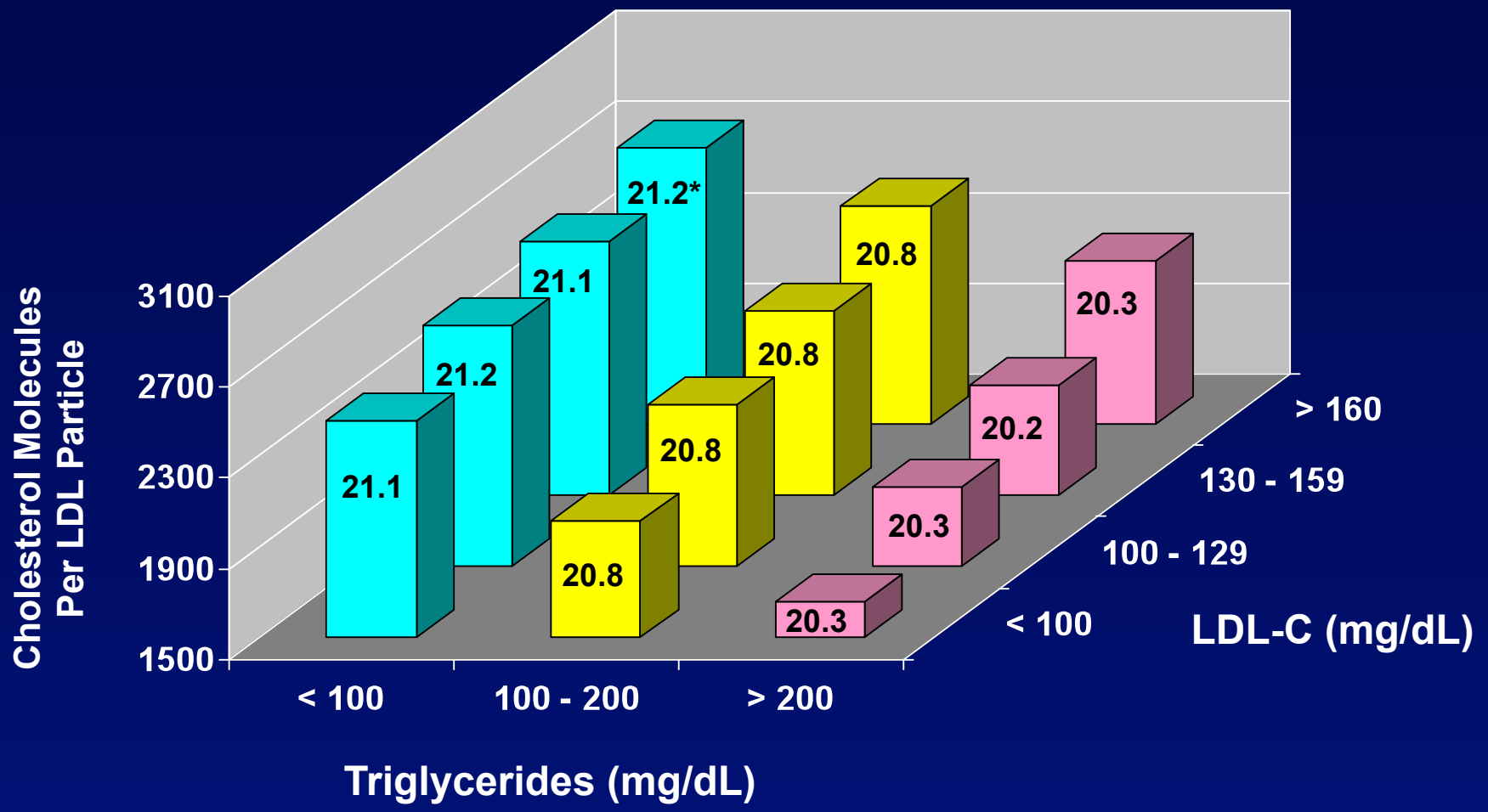


Cromwell WC et al. *J Clin Lipidology* 2007;1(6):583-592.

* Numbers are mean LDL sizes (nm)

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

Framingham Offspring Study (n=3,066)



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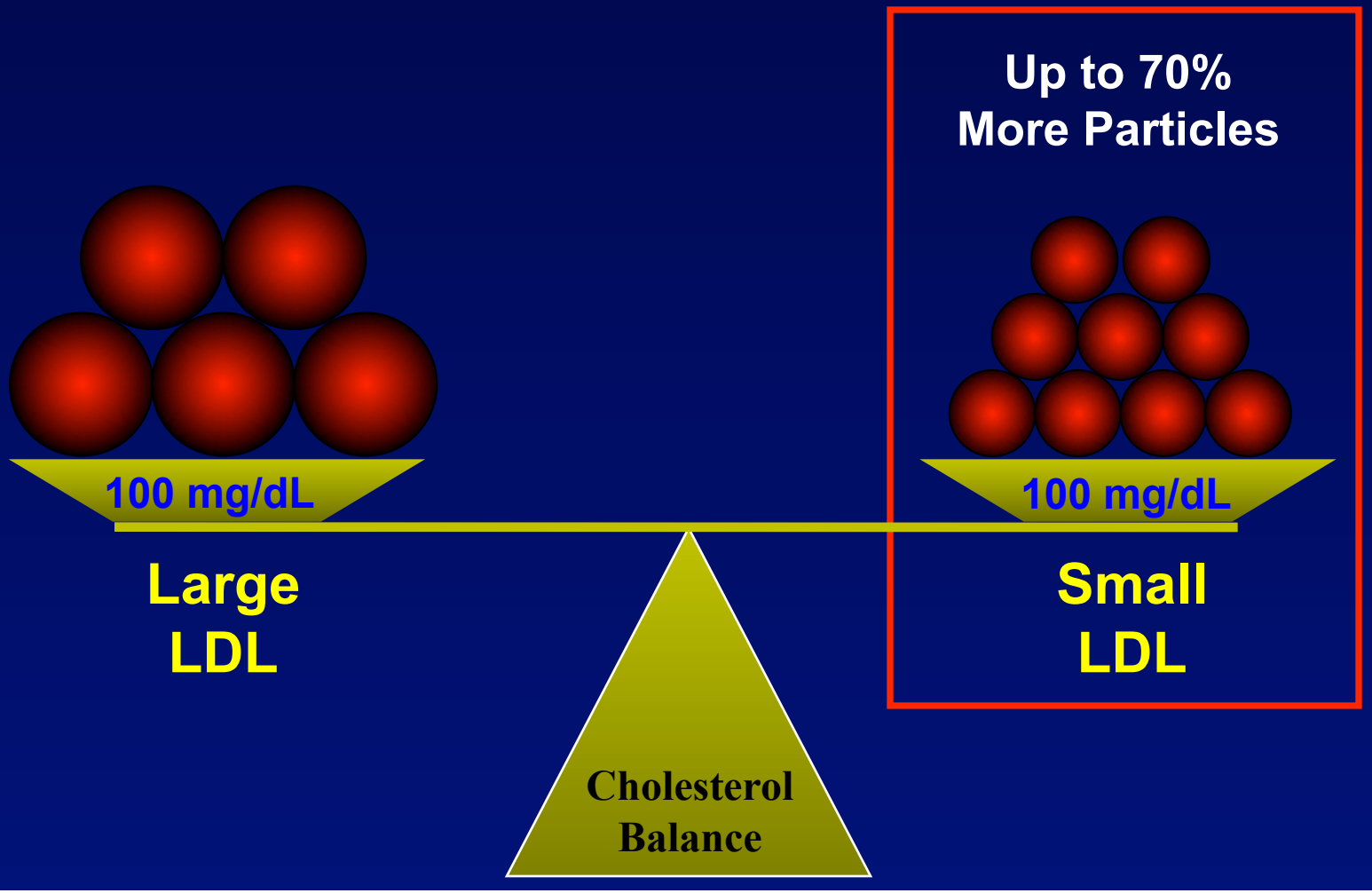
* Numbers are mean LDL sizes (nm)

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



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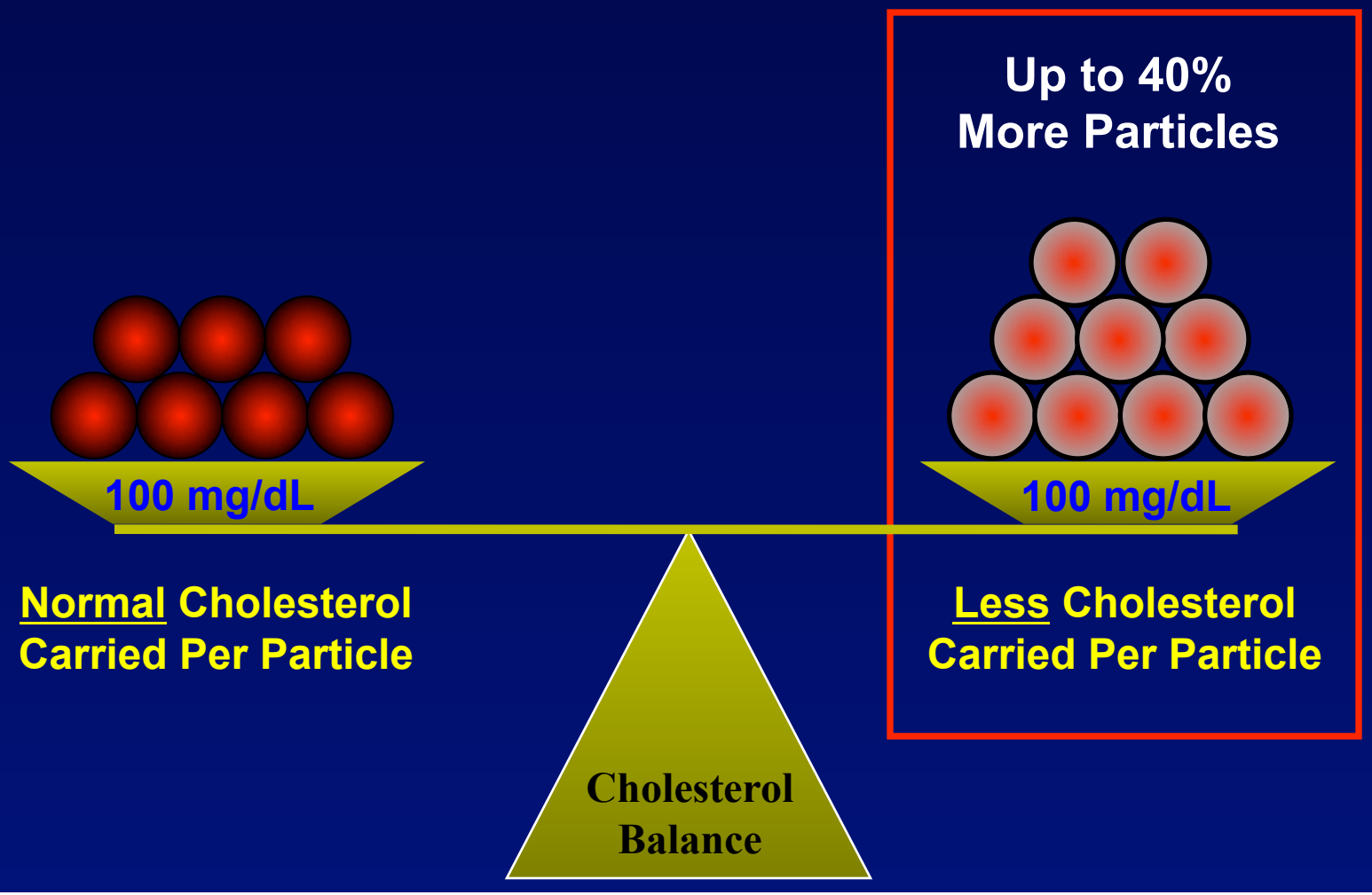


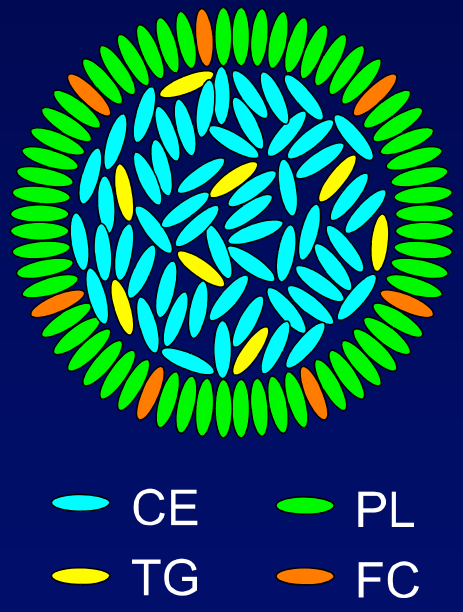
NMR Lipoprotein Analysis

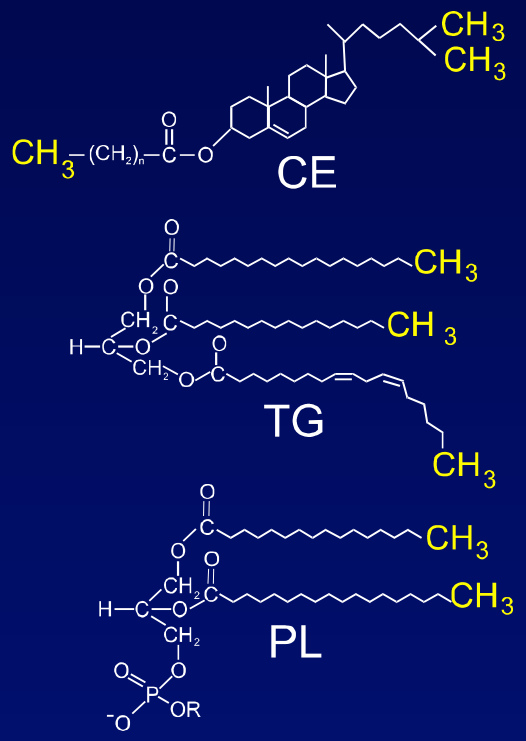
Lipoprotein subclasses of different size broadcast lipid NMR signals that are naturally distinguishable. The measured amplitudes of these signals provide subclass quantification.

Otvos JD. Handbook of Lipoprotein Testing. AACC Press 2000

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.

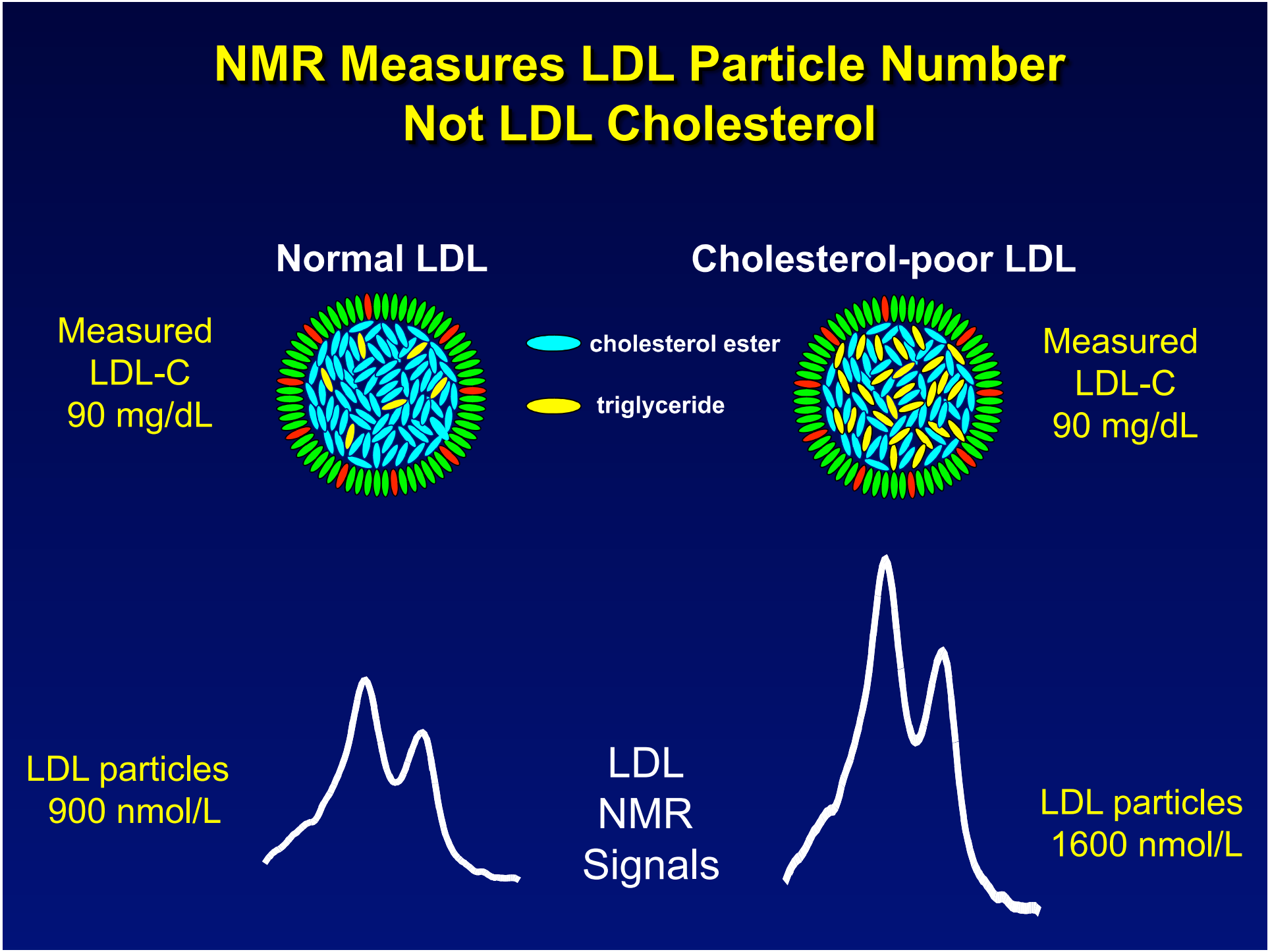




The number of methyl groups in a particle of given size is unaffected by lipid compositional variation.

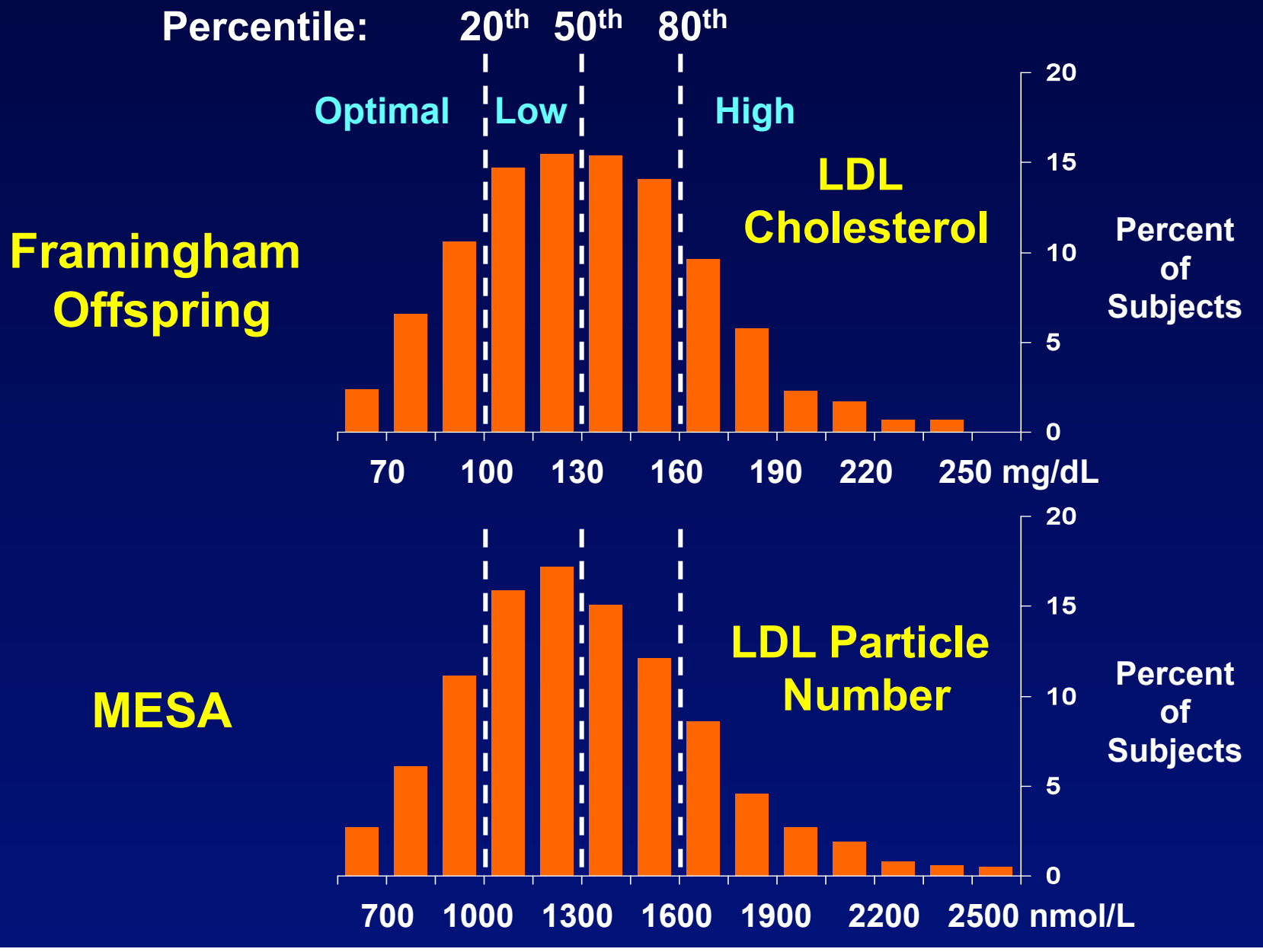
Otvos JD. Handbook of Lipoprotein Testing. AACC Press 2000

NMR Measures LDL Particle Number Not LDL Cholesterol



LDL treatment targets are consensus, population-based

(*not derived from clinical trials comparing different targets*)

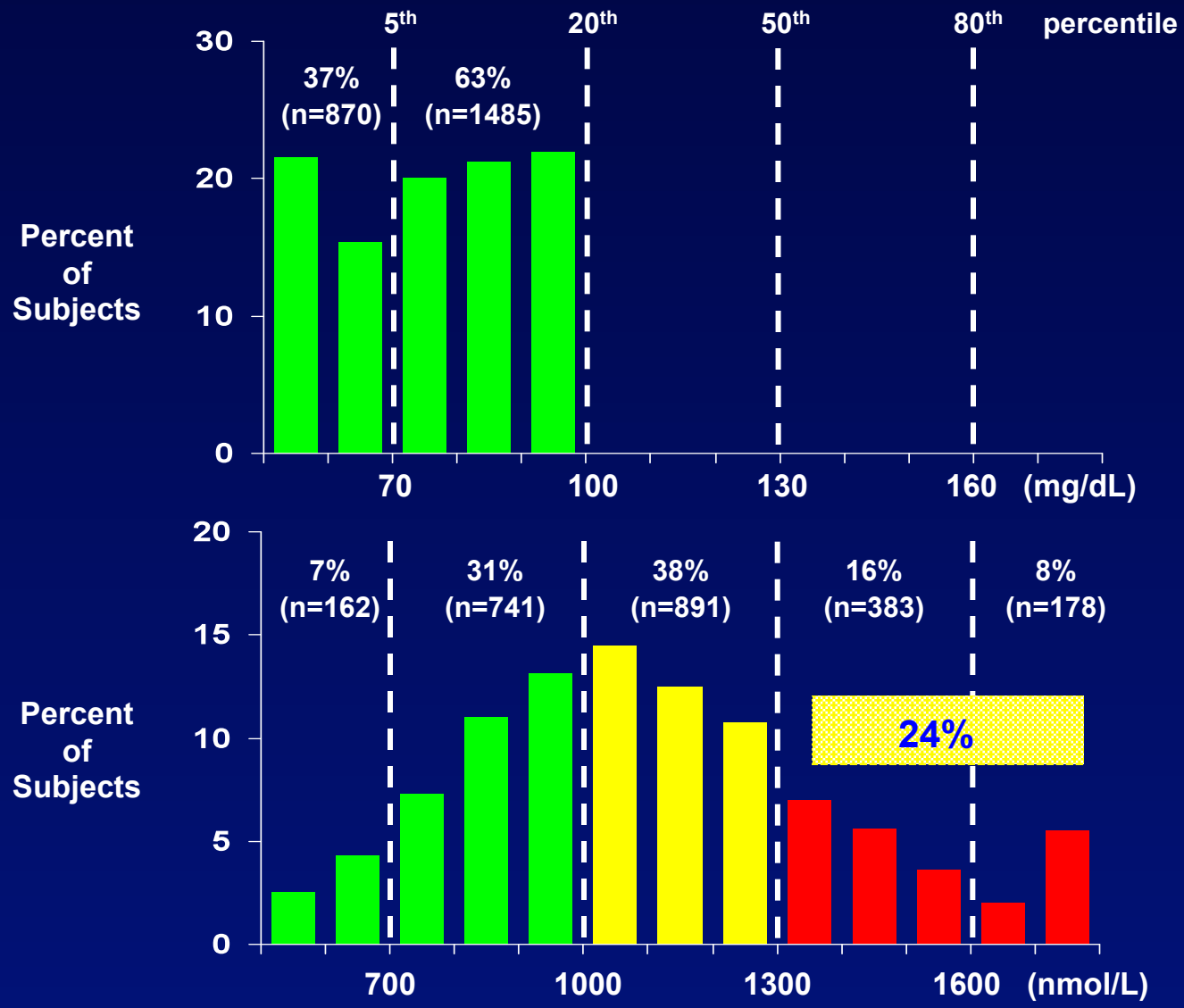


LDL Particle Number is Highly Heterogeneous Among Patients with Type 2 Diabetes Mellitus at LDL Cholesterol Target Goal <100 mg/dL

W.C. Cromwell and J.D. Otvos

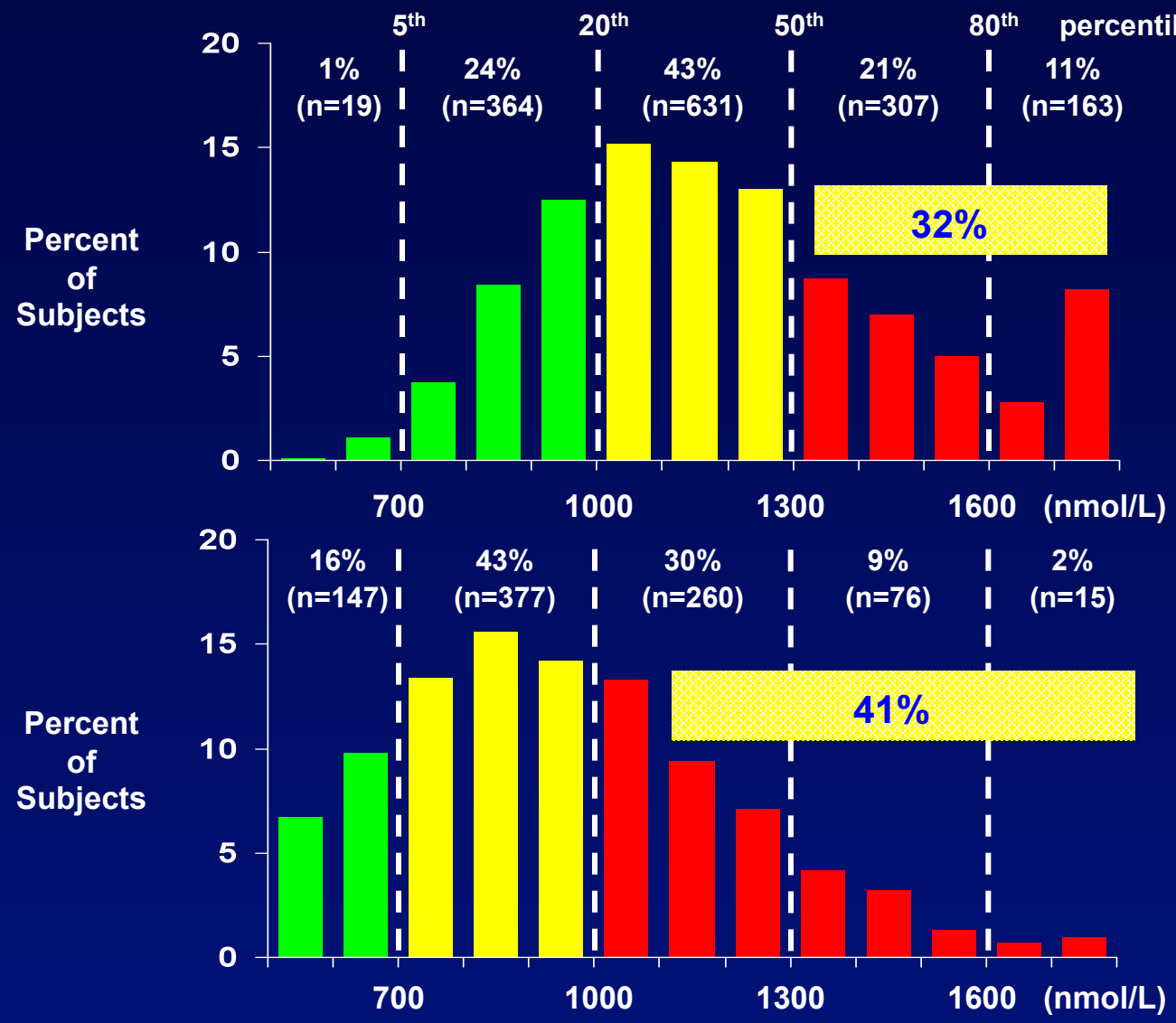
Am J Cardiol. 2006;98:1599-1602

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



Am J Cardiol. 2006;98:1599-1602

LDL Particle Number Distribution in T2DM Subjects



LDL-C
71-99 mg/dL
(n=1,484)

LDL-C
≤ 70 mg/dL
(n=871)

Am J Cardiol. 2006;98:1599-1602

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

Journal of Clinical Lipidology (2007) 1, 583–592

Journal of Clinical Lipidology

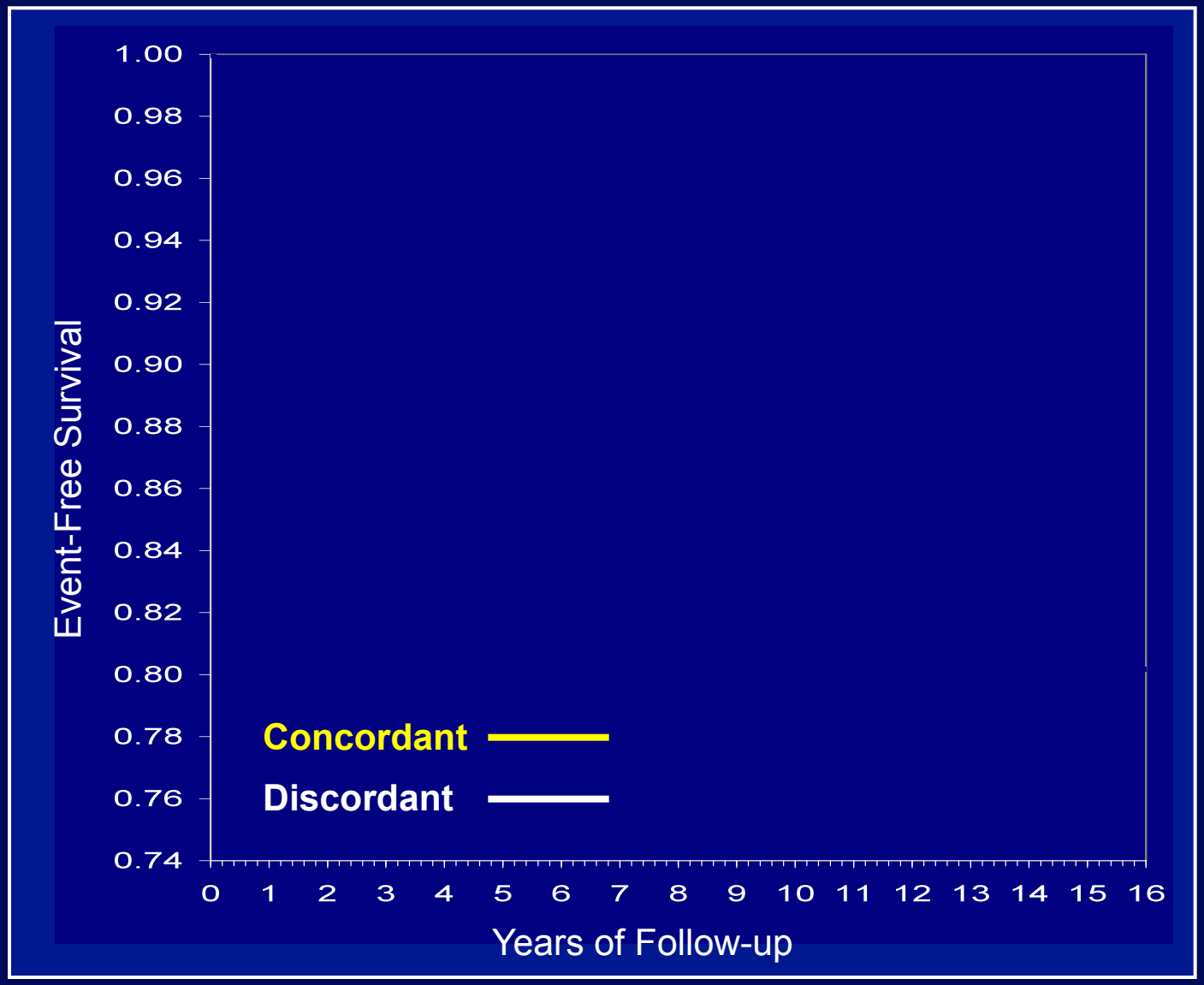
Original Contributions

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)



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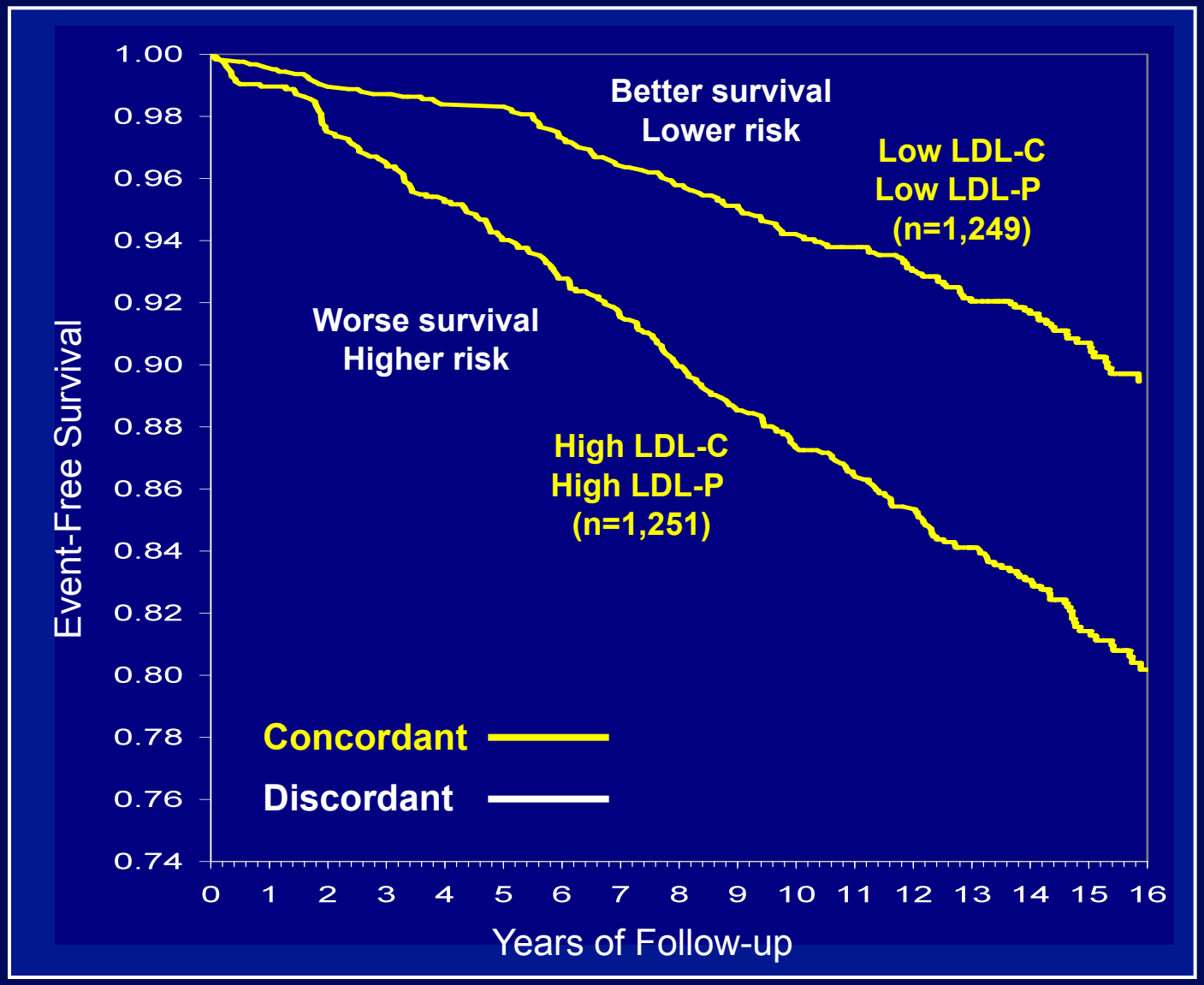

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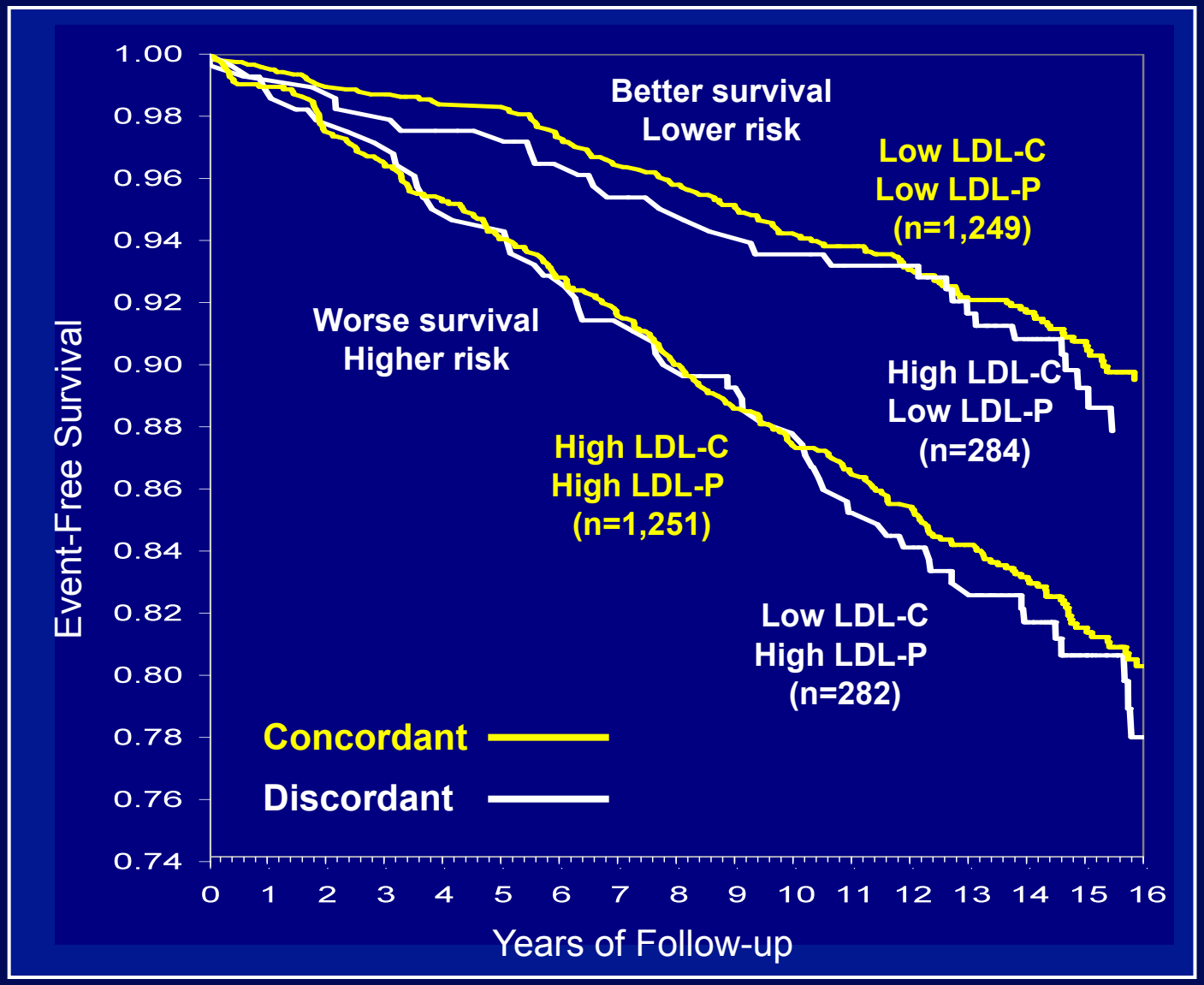


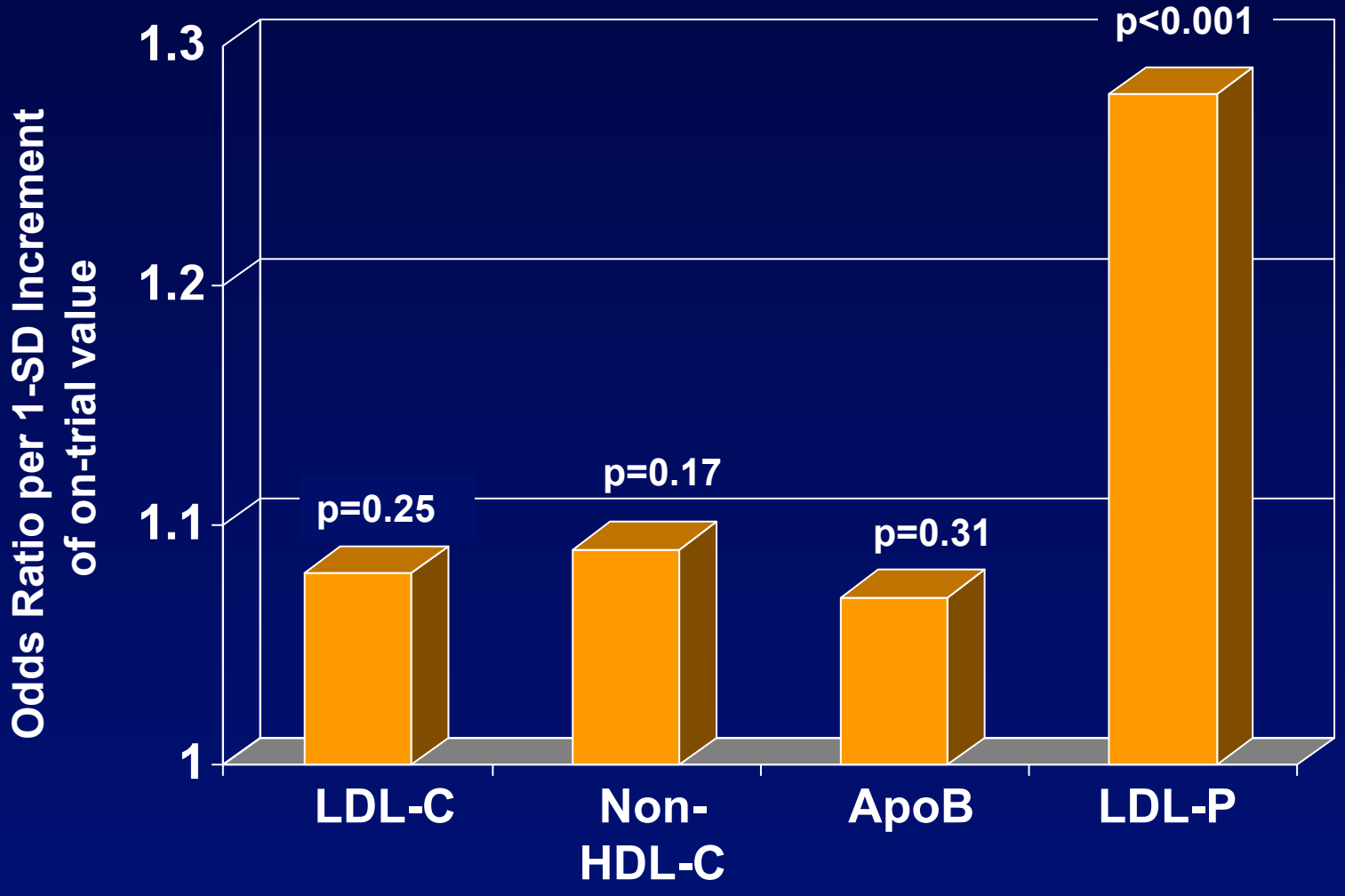
Cromwell WC et al. *J Clin Lipidology* 2007;1(6):583-592.

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

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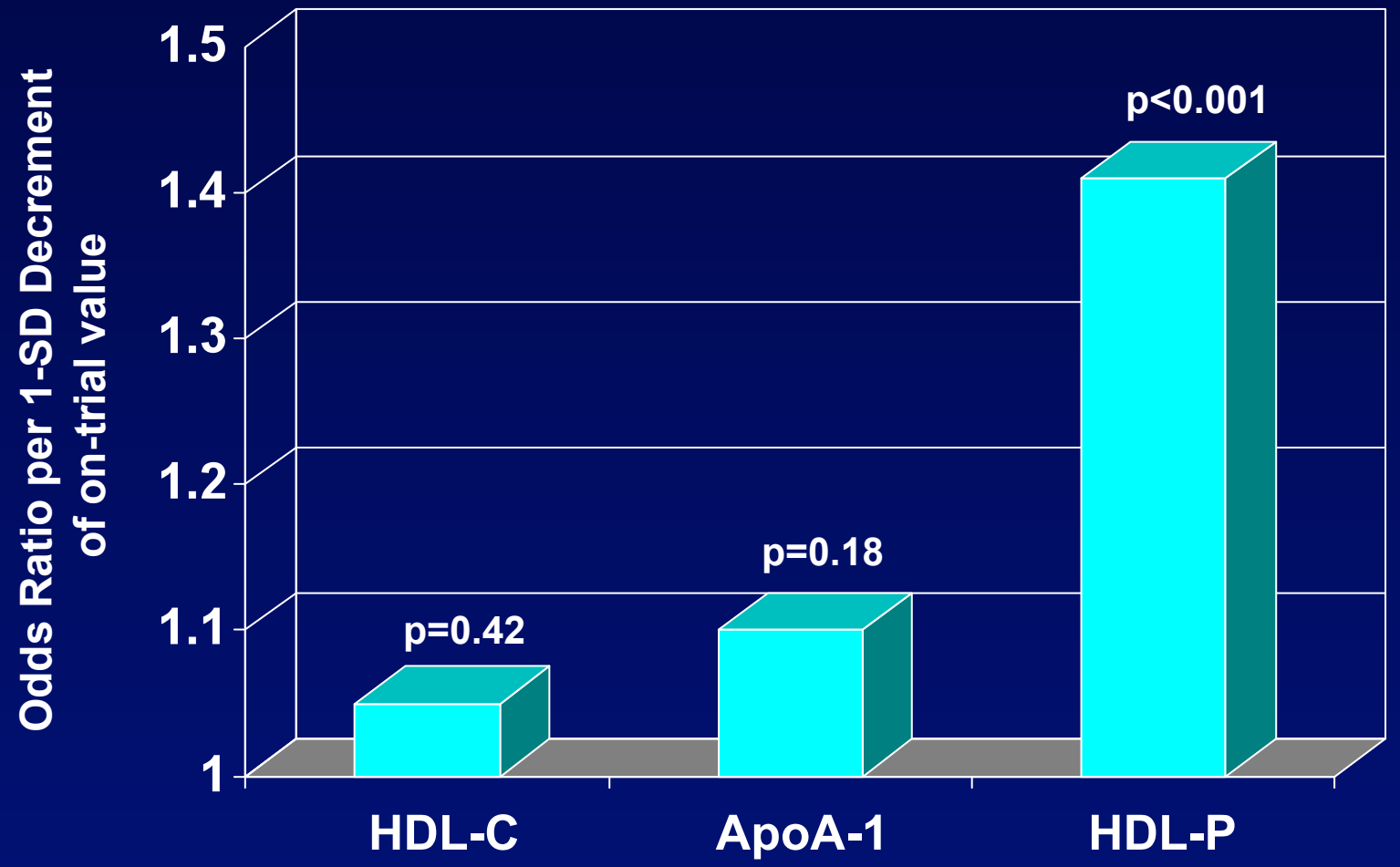

Adjusted for treatment, age, hypertension, smoking, BMI, and diabetes

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.

Circulation 2006;113:1556-63

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

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ADA/ACC Consensus Statement

A need for better lipoprotein management

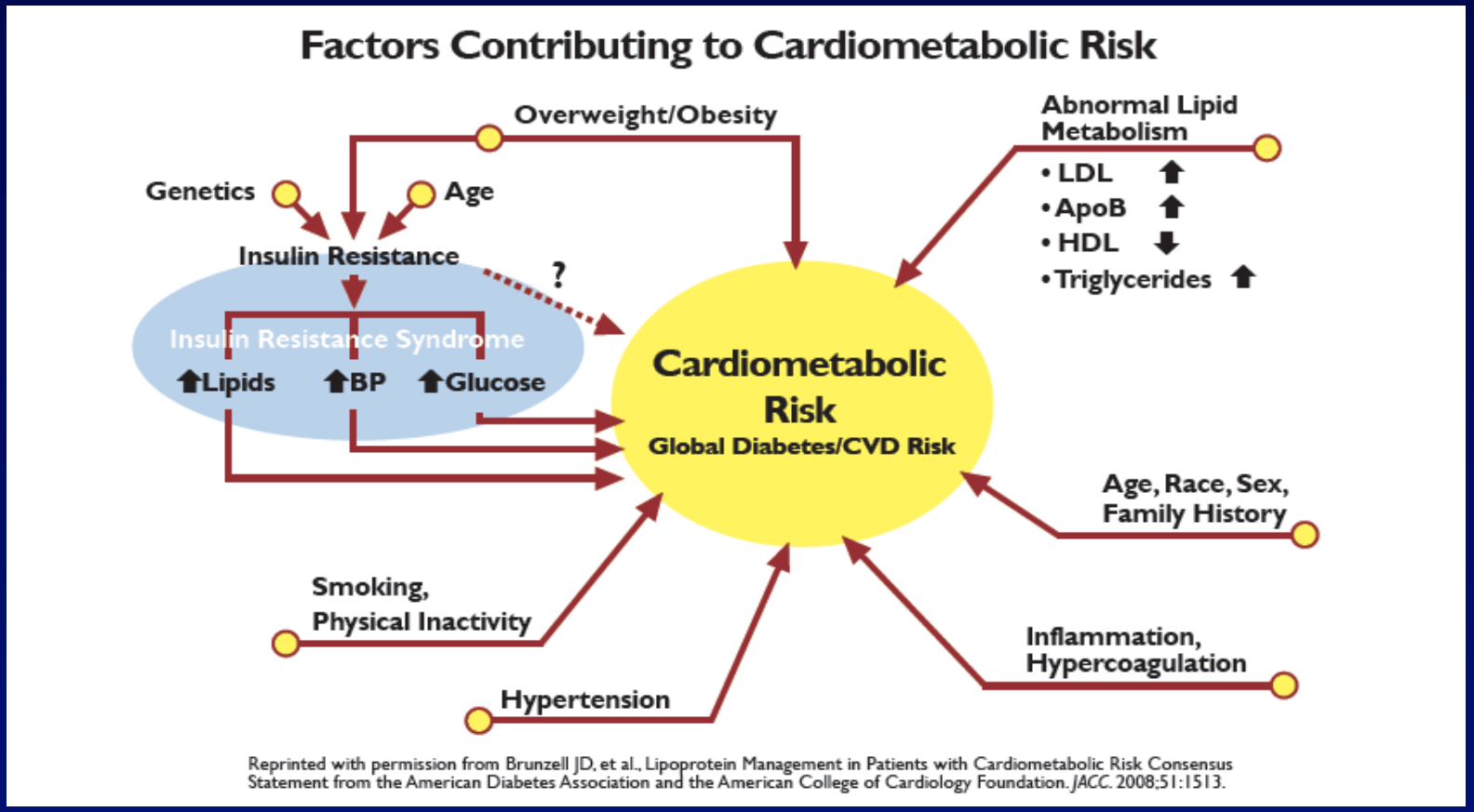
- Lipoprotein abnormalities are common findings in patients with CMR. Measurement of LDL cholesterol may not accurately reflect the true burden of atherogenic LDL particles, especially in those with typical lipoprotein abnormalities of CMR.

- 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



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).