

Beyond Statins: Is there something

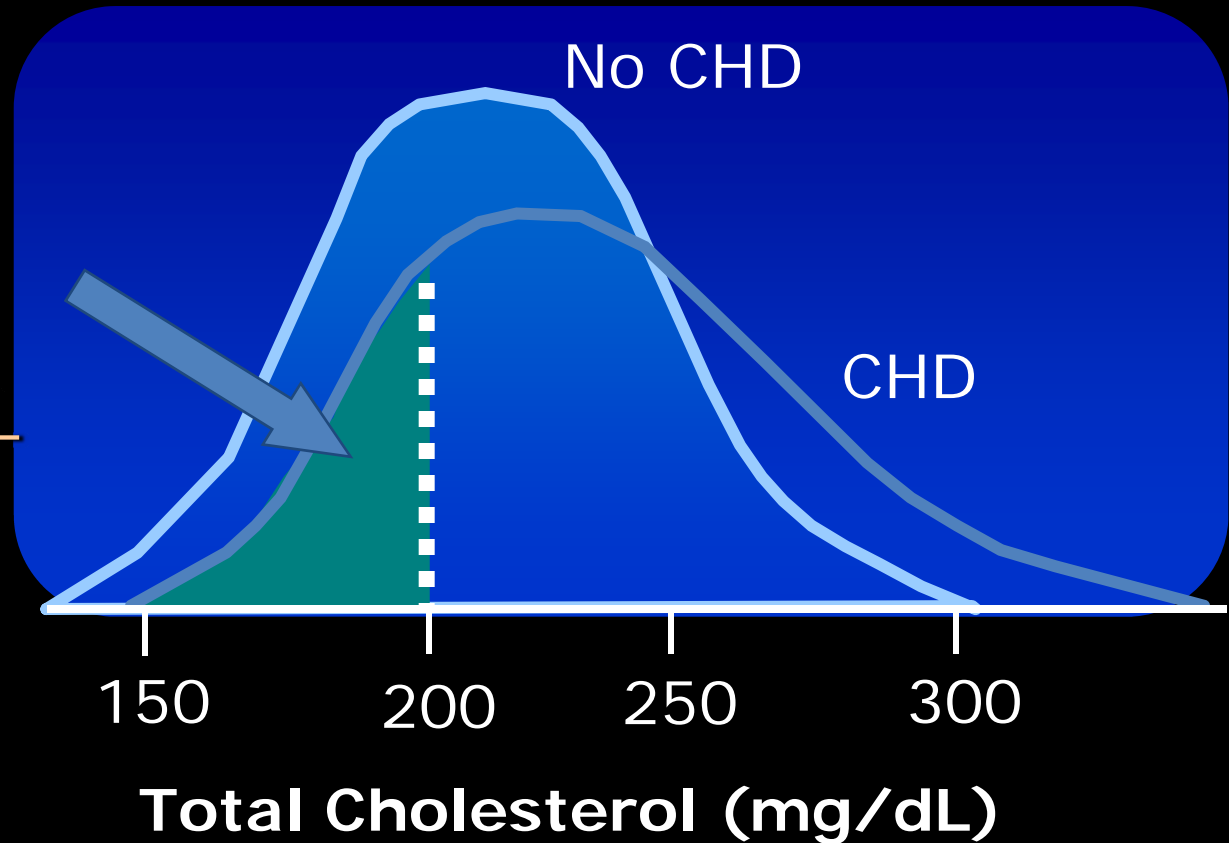
Dr Ramesh Babu MD DM FACC

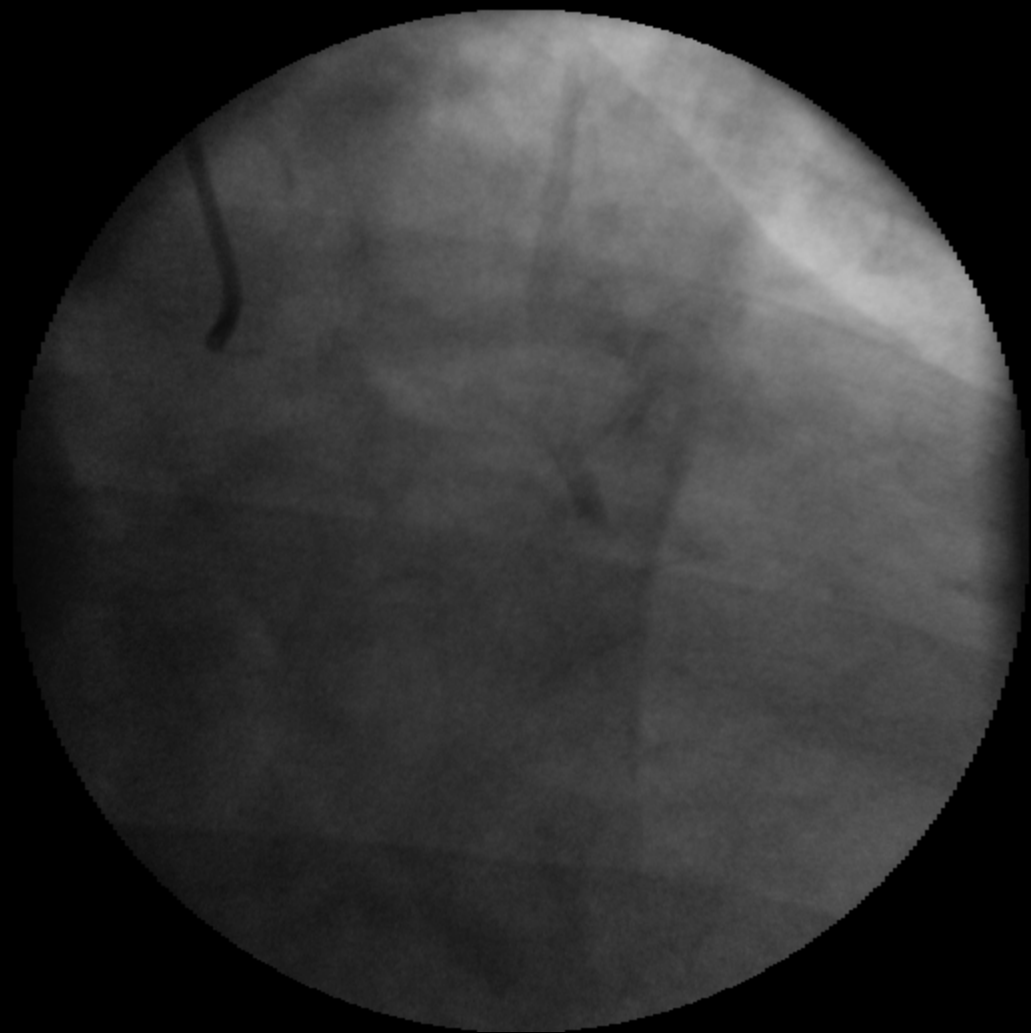
Chief of Cardiology

Total Cholesterol Distribution: *CHD vs Non-CHD Population*

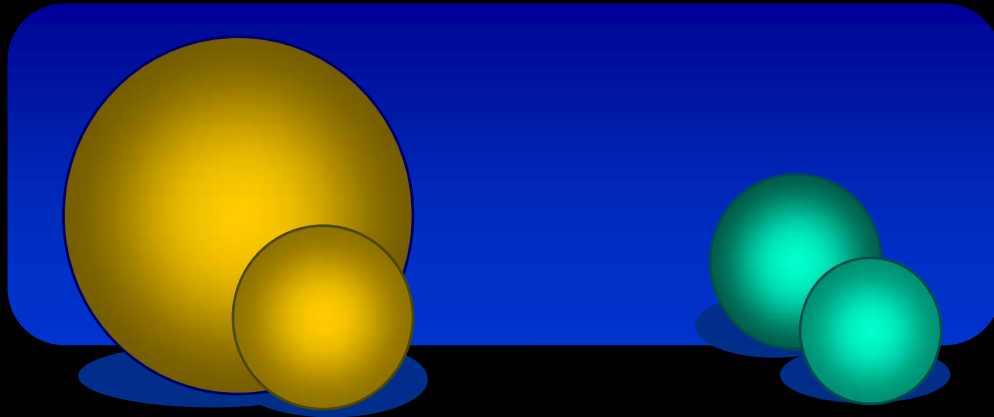
Framingham Heart Study—26-Year Follow-up

35% of CHD occurs in people with TC < 200 mg/dL



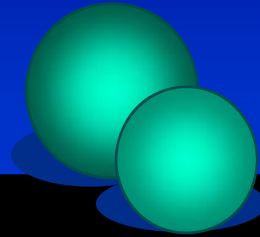


Lipoprotein Classes and Inflammation



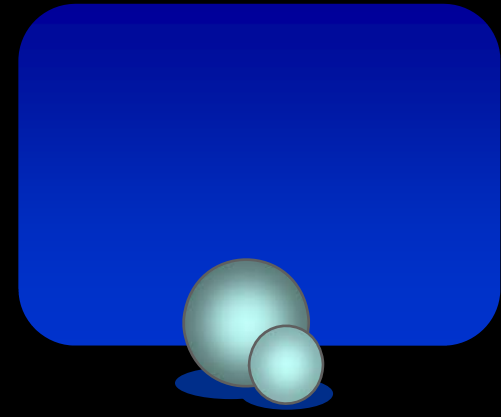
Chylomicrons,
VLDL, and
their catabolic
remnants

> 30 nm



LDL

20–22 nm



HDL

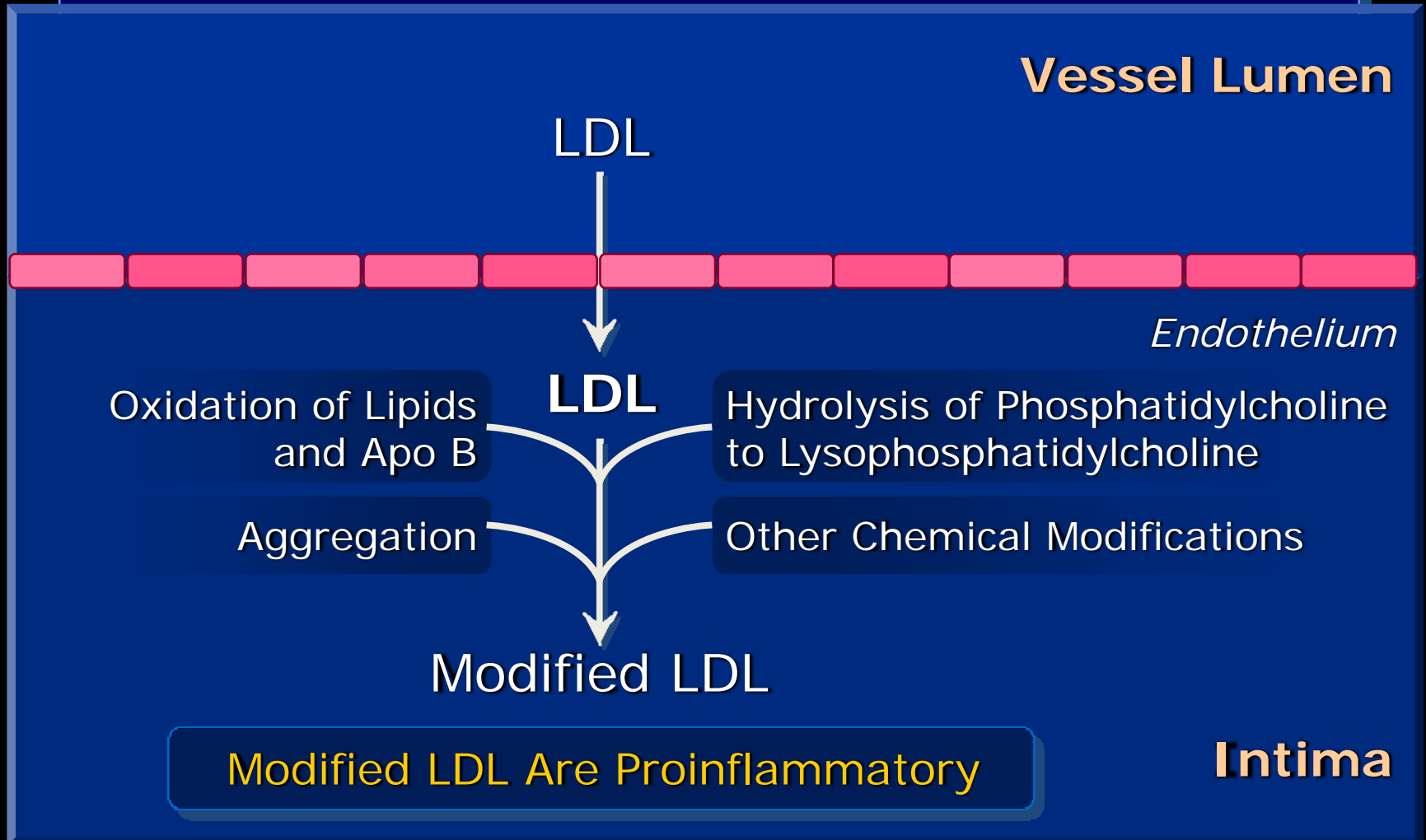
9–15 nm

Potentially proinflammatory

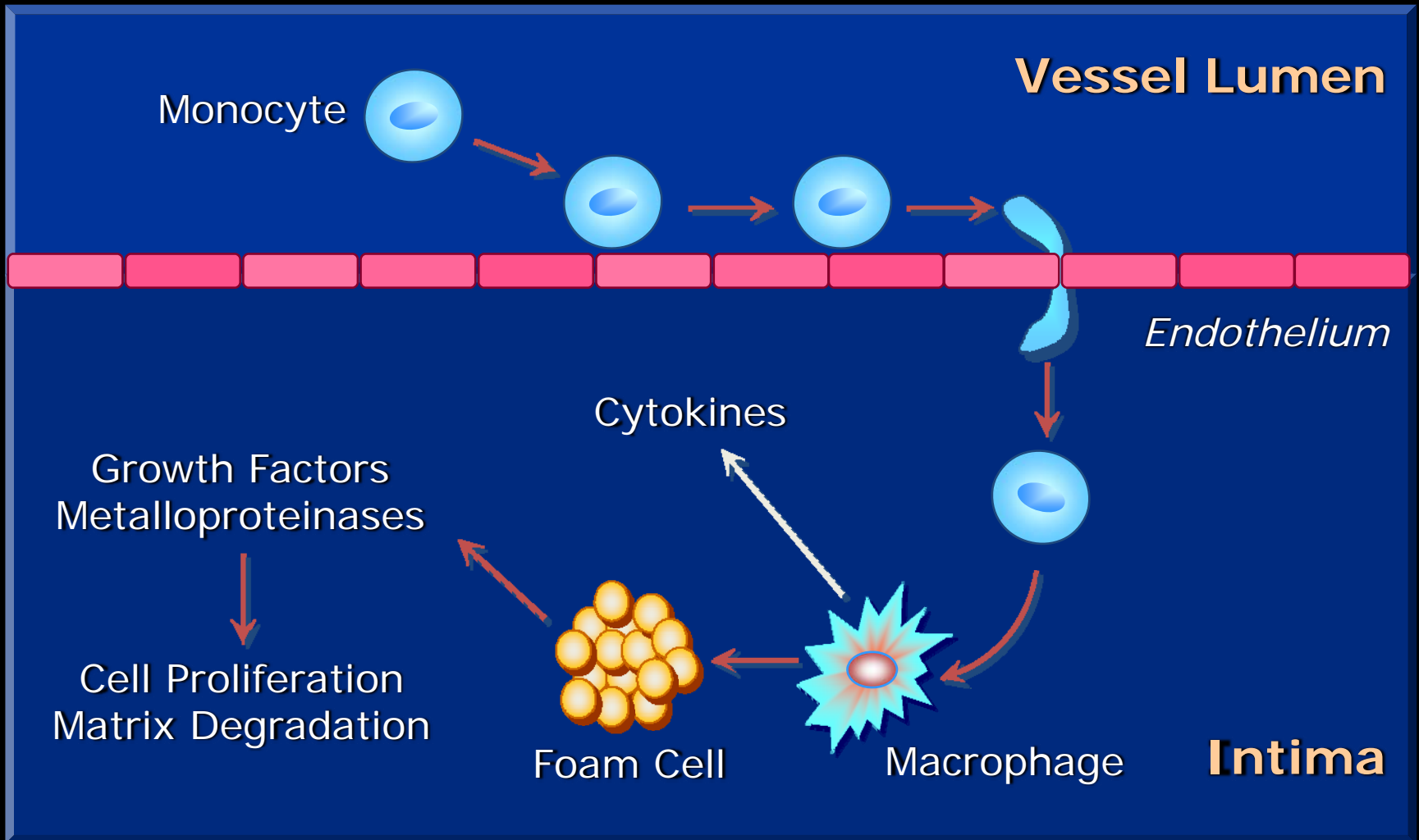
Potentially anti-
inflammatory

Role of LDL in Inflammation

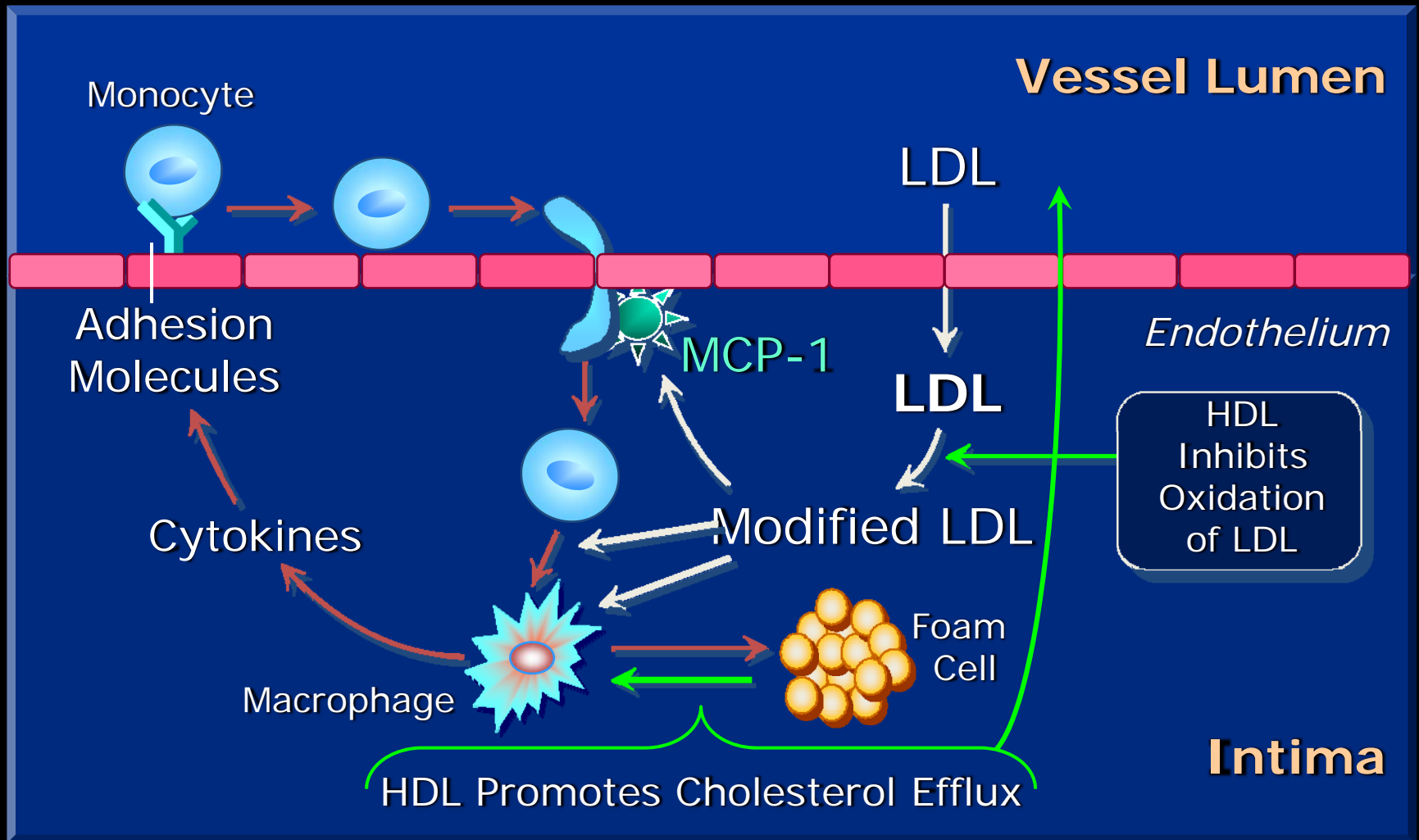
LDL Readily Enter the Artery Wall Where They May Be Modified



Atherosclerosis Is an Inflammatory Disease



HDL Inhibits the Oxidative Modification of LDL



Success in the Statin Era

50,000 Patients Randomized to Statin or Placebo

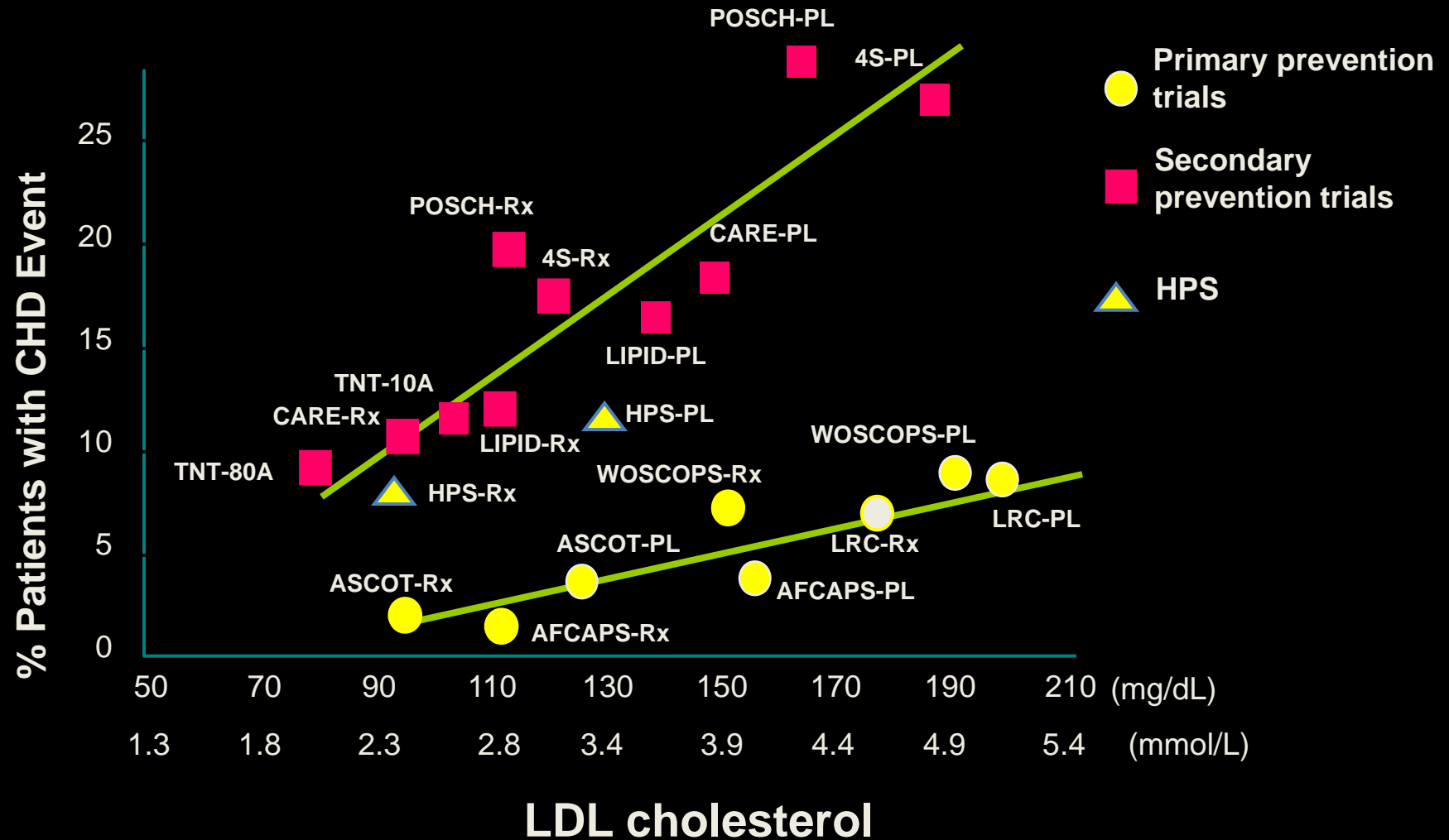
Trial (Duration [yr]; N)	Base LDL-C mg/dL	LDL-C Decrease (%)	In-Rx LDL-C mg/dL	Statin Event Rate	Placebo Event Rate	RRR	Absolute Risk Reduction	# Need to Rx
4S (5.4; 4.4K)	188	35%	122	19.4%	28.0%	34%	8.6%	12
HPS* (5.0; 20K)	131	30%	94	19.8%	25.2%	24%	3.4%	18
LIPID (6.1; 9.0K)	150	25%	112	12.3%	15.9%	24%	3.6%	28
CARE (5.0; 4.2K)	139	32%	98	10.2%	13.2%	24%	3.0%	34
WOSCOP (4.9; 6.6K)	192	26%	159	5.3%	7.5%	29%	2.2%	46
AFCAPS (5.2; 6.6K)	150	25%	115	3.5%	5.5%	37%	2.0%	50

*HPS Collaborative Group. *Lancet*. 2002;360:7–22.

RRR=relative risk reduction

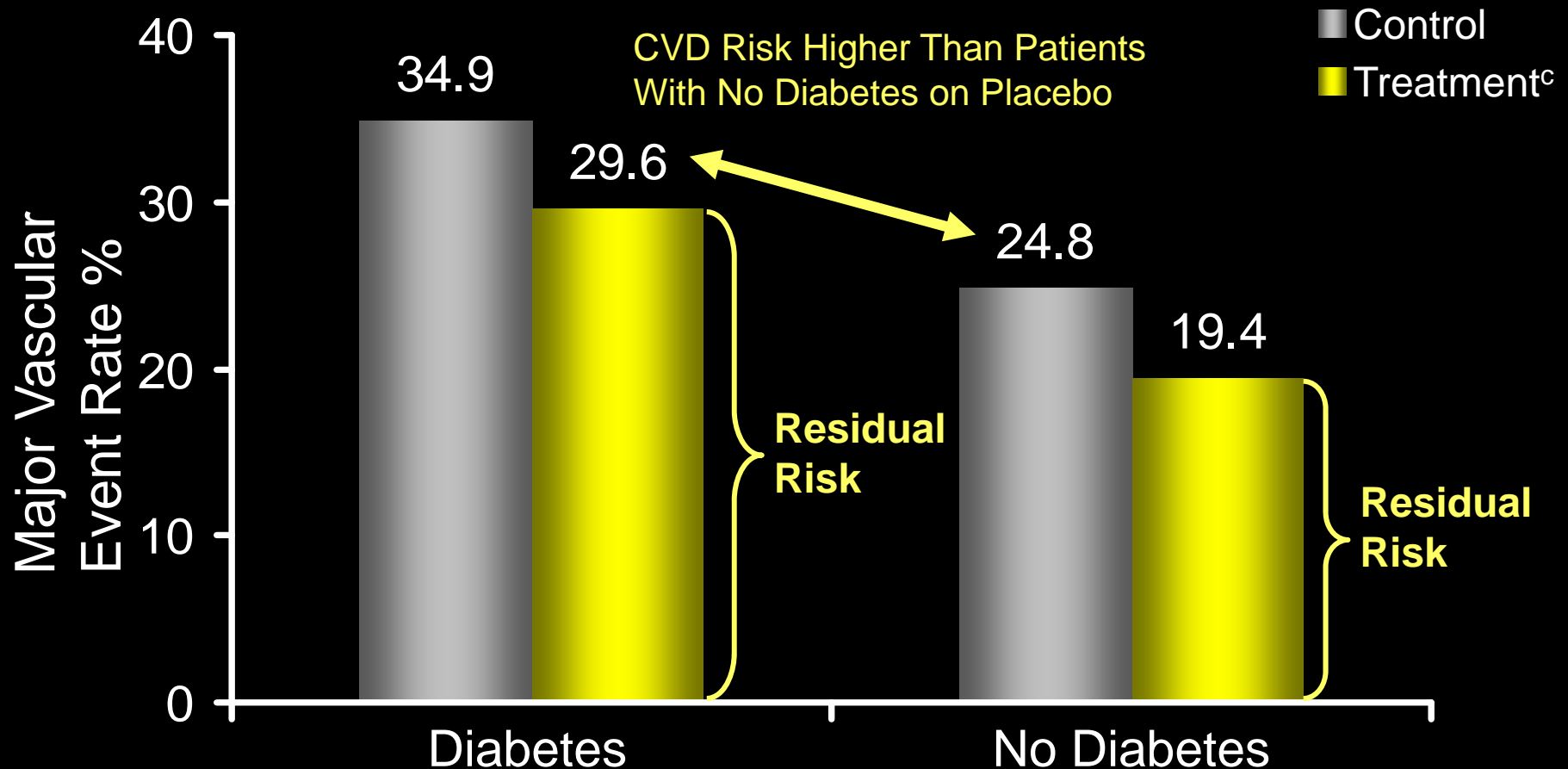
LaRosa JC, et al. *JAMA*. 1999;282:2340–2346.

Statins : Gold Standard of Therapy



Statin Therapy Reduces CVD Events

CTT Meta-Analysis of 14 Statin Trials^a



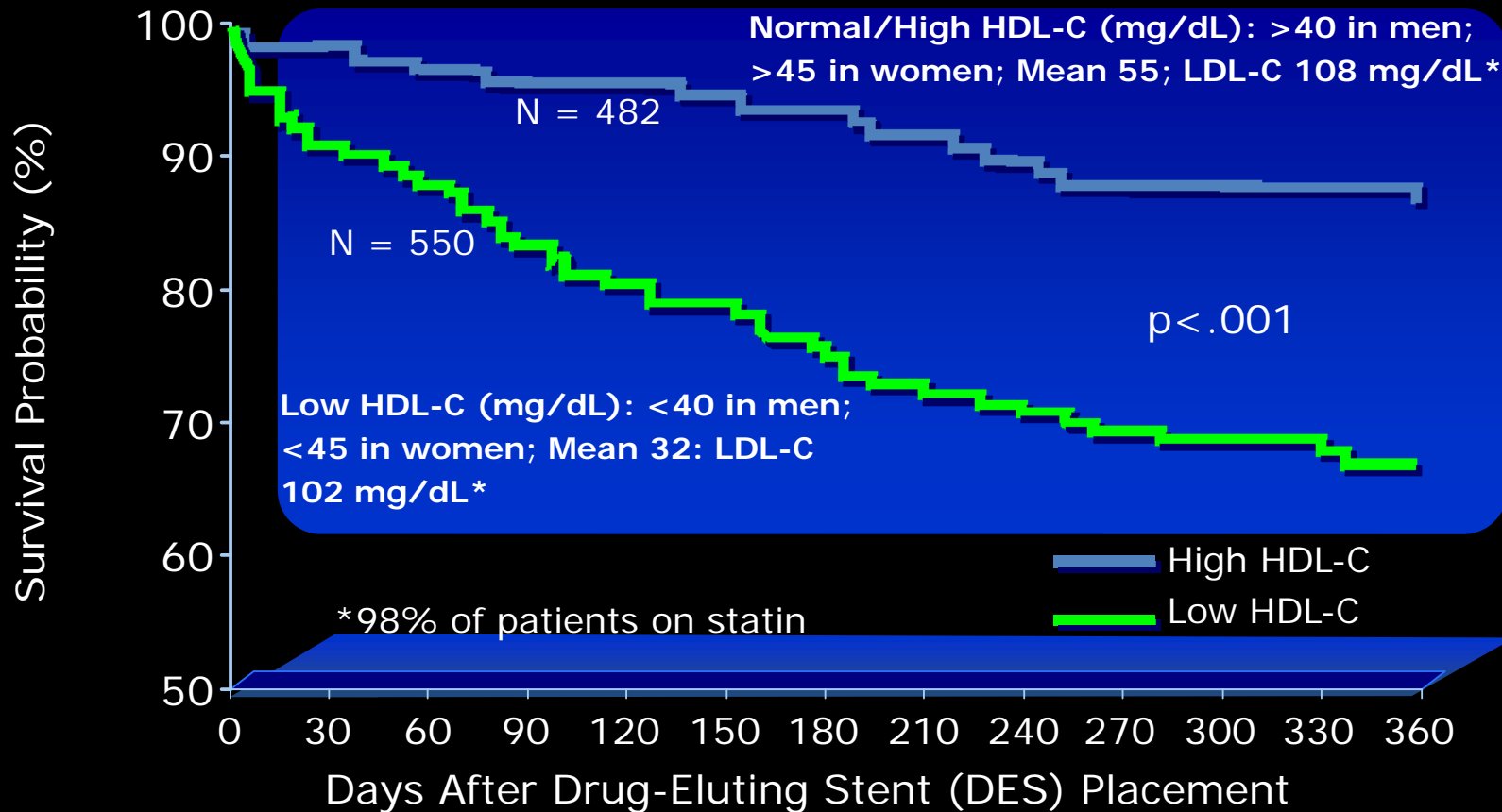
^a4.3-year mean follow-up of 18 686 patients with diabetes; n = 71 370 patients with no diabetes

^bNonfatal MI, CHD death, stroke, or coronary revascularization

^cEvent rate per 1 mmol/L (39 mg/dL) reduction in LDL-C

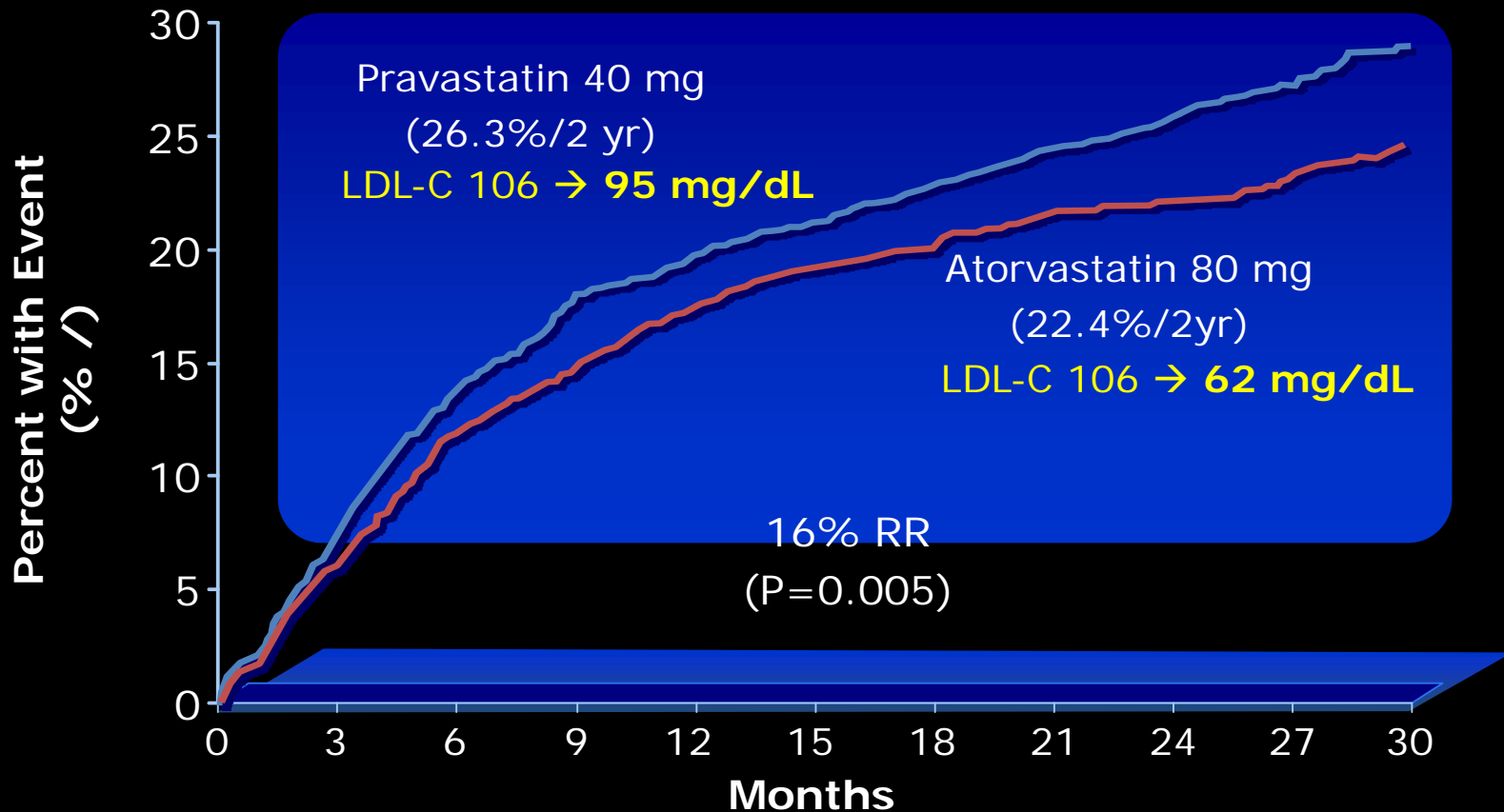
CTT Collaborators. *Lancet*. 2008;371:117-125.

1-Year Event-Free Survival Post-DES: Low vs. High HDL at Baseline TLR/MACE Survival Curves



TLR=target lesion revascularization; MACE=major adverse cardiac event

PROVE-IT Study: 4,162 AMI/ACS Patients and Incidence of Death, Myocardial Infarction, and Revascularization

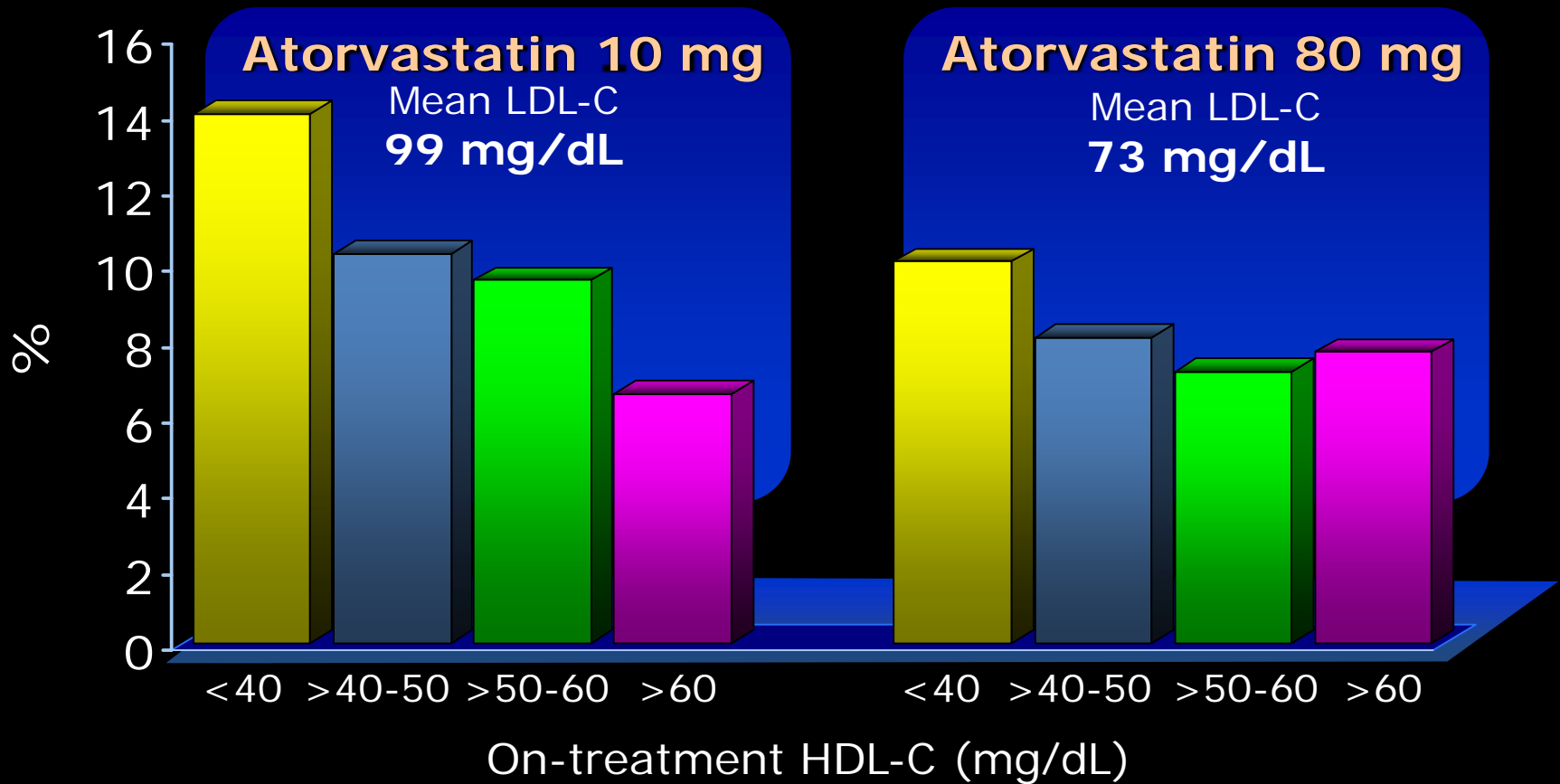


ACS = acute coronary syndrome; AMI = acute myocardial infarction

Cannon CP, et al. *N Engl J Med*. 2004;350:1495–1504. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

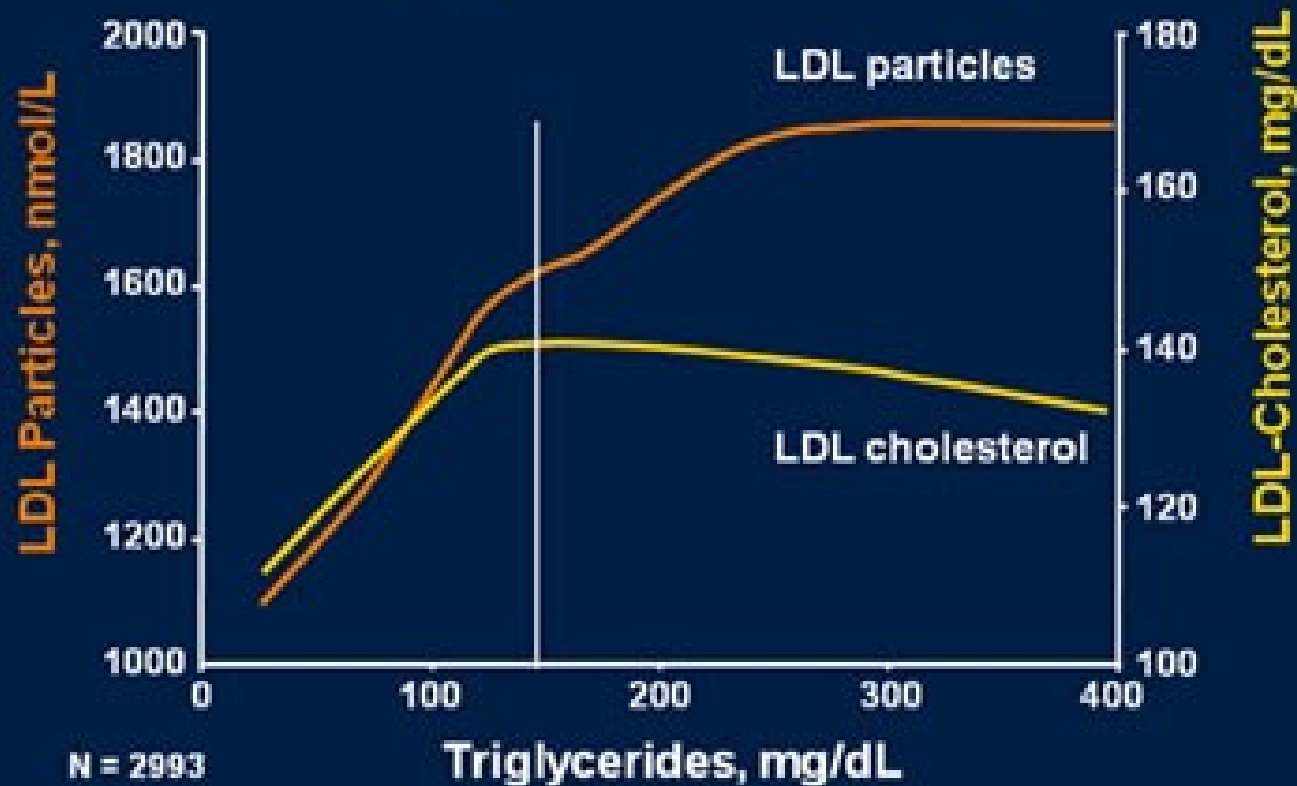


Major Cardiovascular Events According to On-treatment HDL-C: *Treating to New Targets (TNT) Trial*



Barter PJ, Kastelein JJ. *J Am Coll Cardiol.* 2006;47:492–499. |
Waters DD, et al. *J Am Coll Cardiol.* 2006;48:1793–1799.

Relationship Between Elevated Triglycerides, LDL-C, and LDL Particle Number: Framingham Heart Study



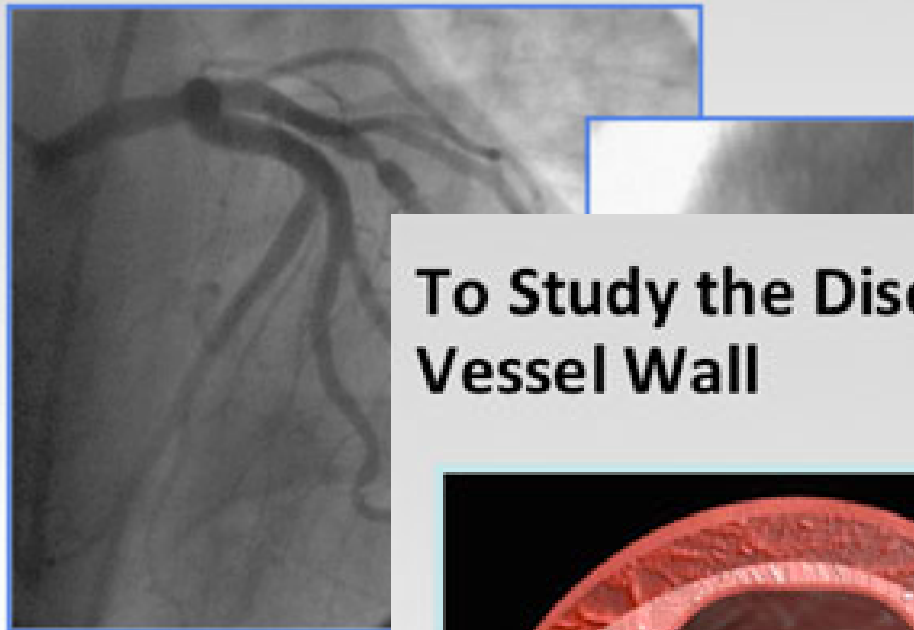
Relationship Between HDL-C and CHD (Meta-Analysis of 68 Prospective Population- Based Studies With at Least 1 Year of Follow-Up)

Emerging Risk Factors Collaboration

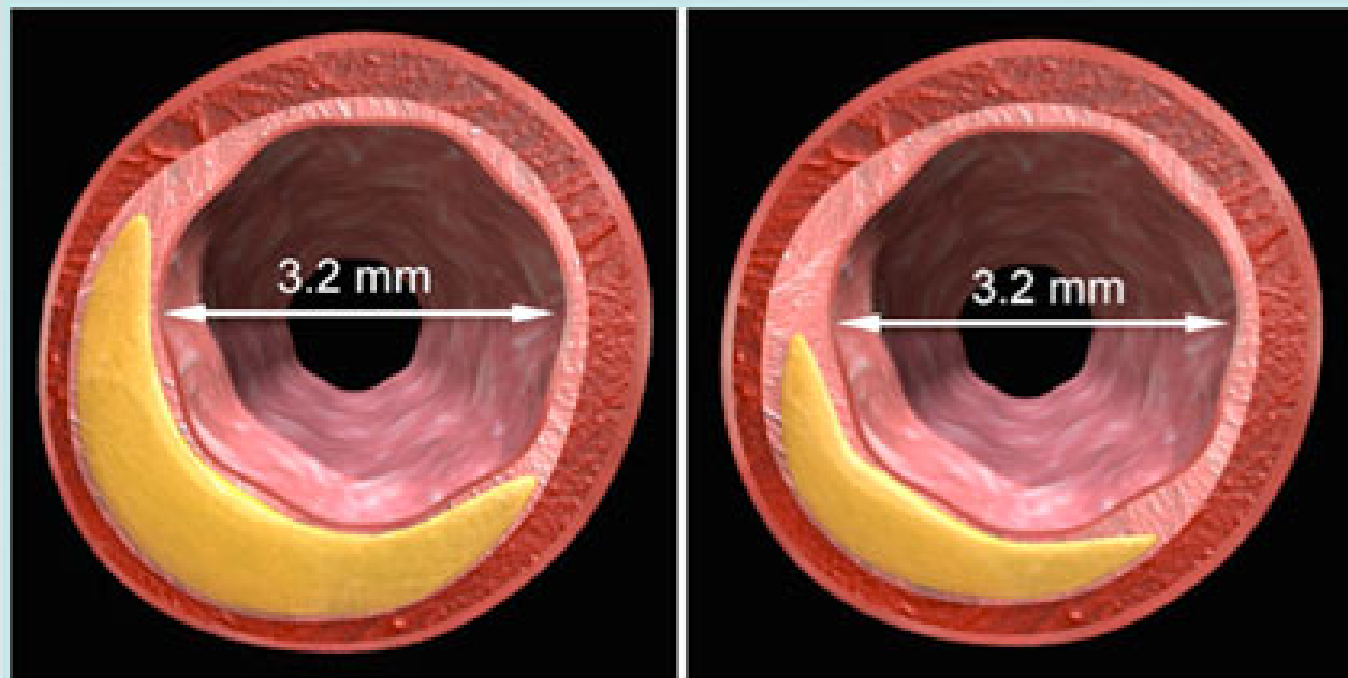
	No. subjects/ No. CHD cases	15 mg/dL increase in HDL-C		
		Hazard ratio (95% CI)	Wald χ^2	I^2 (95% CI)
Adjusted for non-lipid risk factors*	302,430/12,785	0.71 (0.68-0.75)	149	60 (48-69)
Adjusted for non- HDL-C and \log_{10} triglycerides		0.78 (0.74-0.82)	84	40 (20-55)

*Age, sex, systolic blood pressure, smoking status, body mass index, and the presence or absence of a history of diabetes.

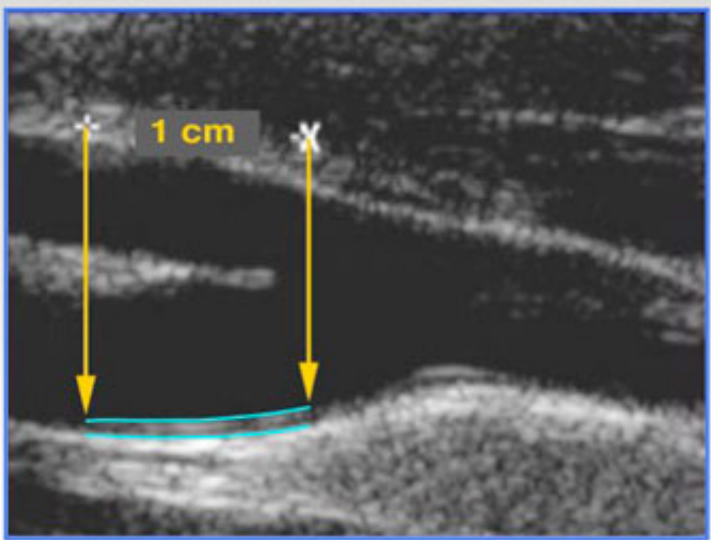
50 Years of Coronary Angiography



To Study the Disease, You Need to Image the Vessel Wall

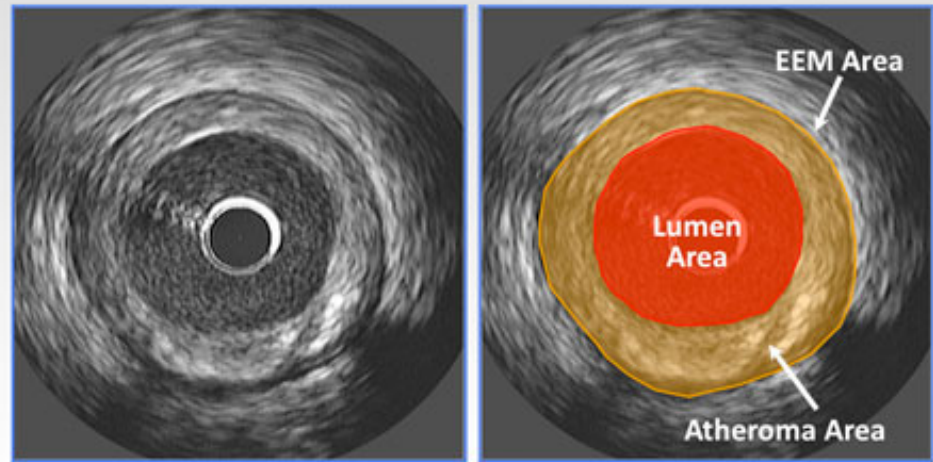


Carotid Intima Medial Thickness

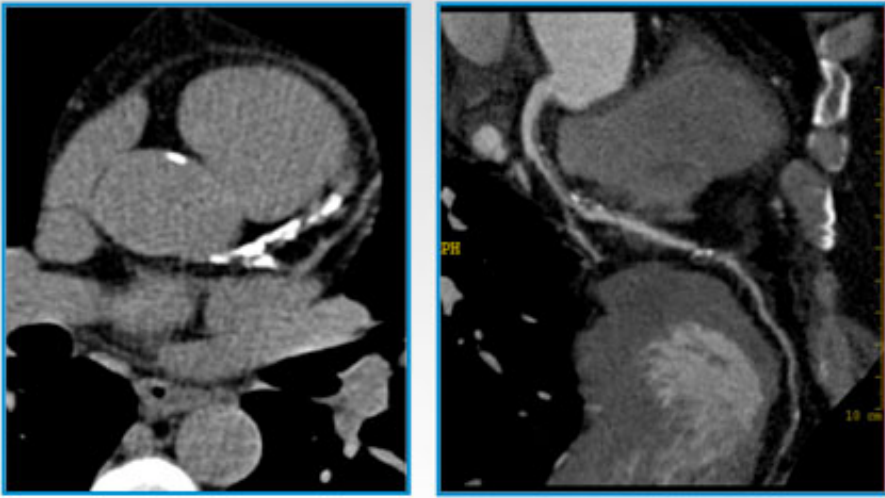


Ultrasound Determination of Atheroma Area

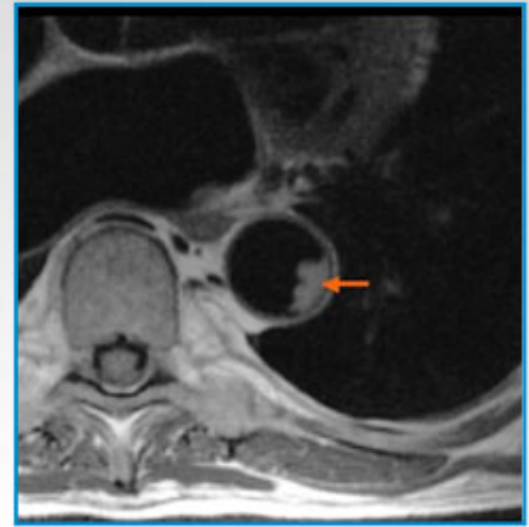
Precise planimetry of external elastic membrane (EEM) and lumen borders with calculation of atheroma cross-sectional area



Computed Tomography Angiography



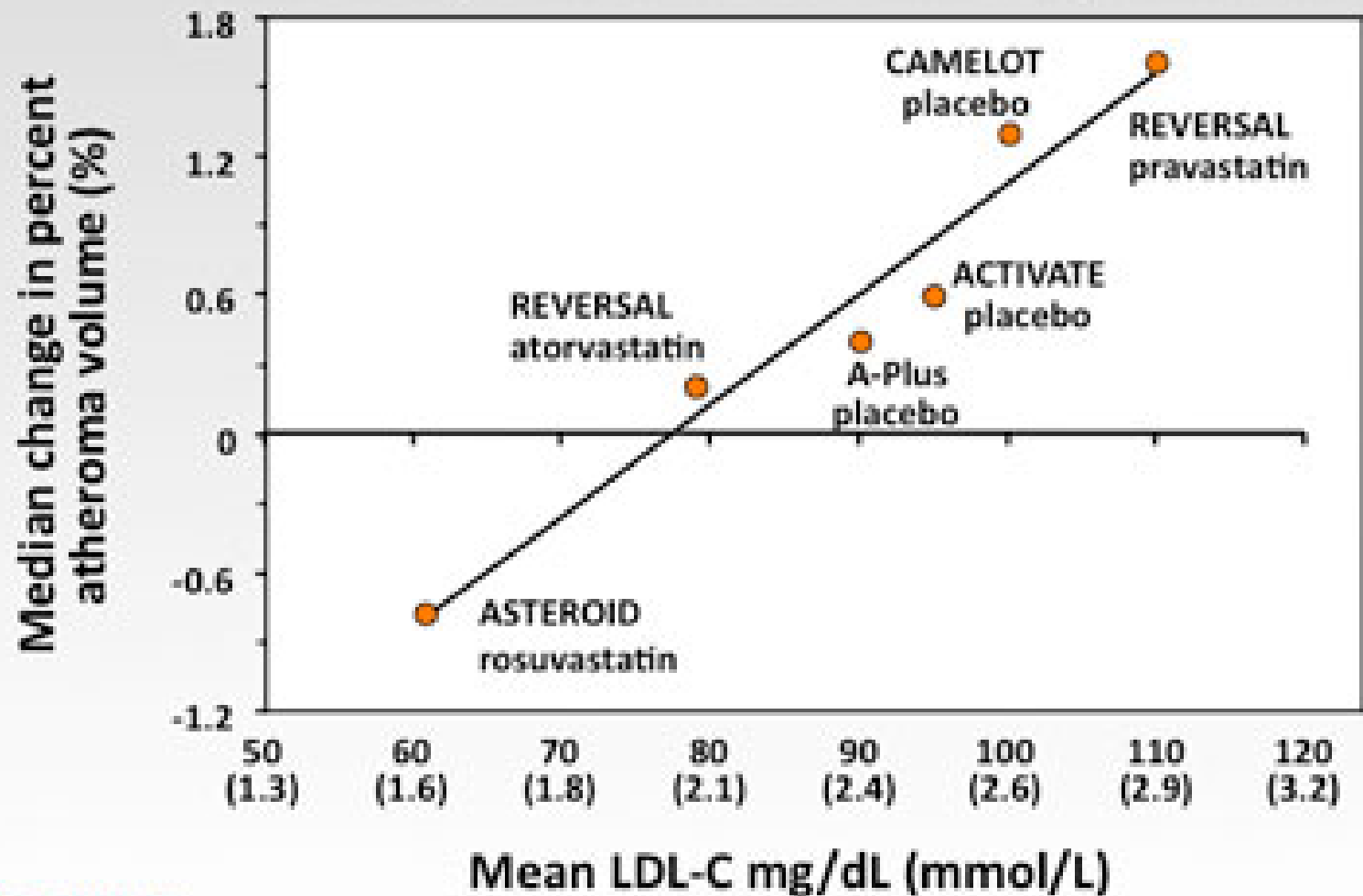
Magnetic Resonance Imaging



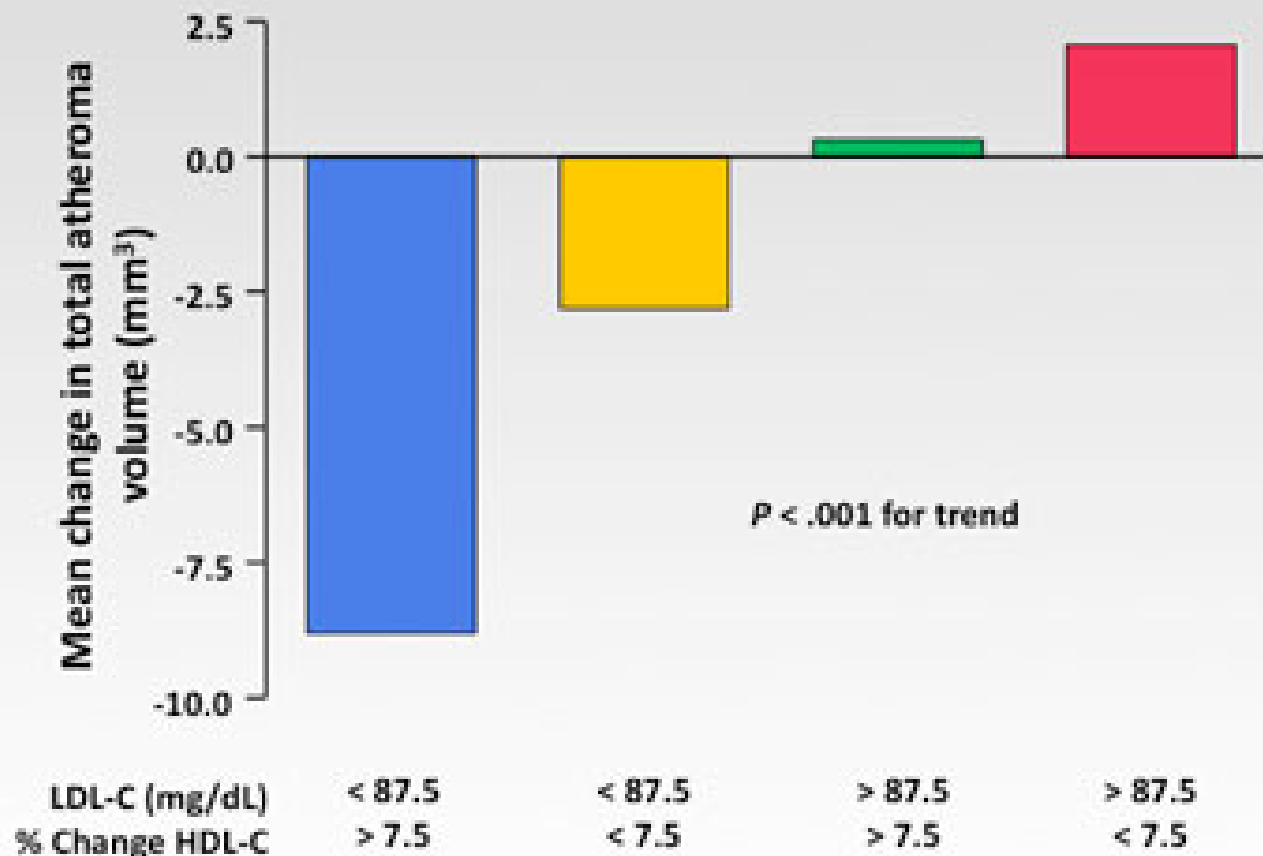


Recent Coronary IVUS Progression Trials

Relationship between LDL-C and Progression Rate



Benefit of Combination HDL Raising and LDL Lowering With Statins



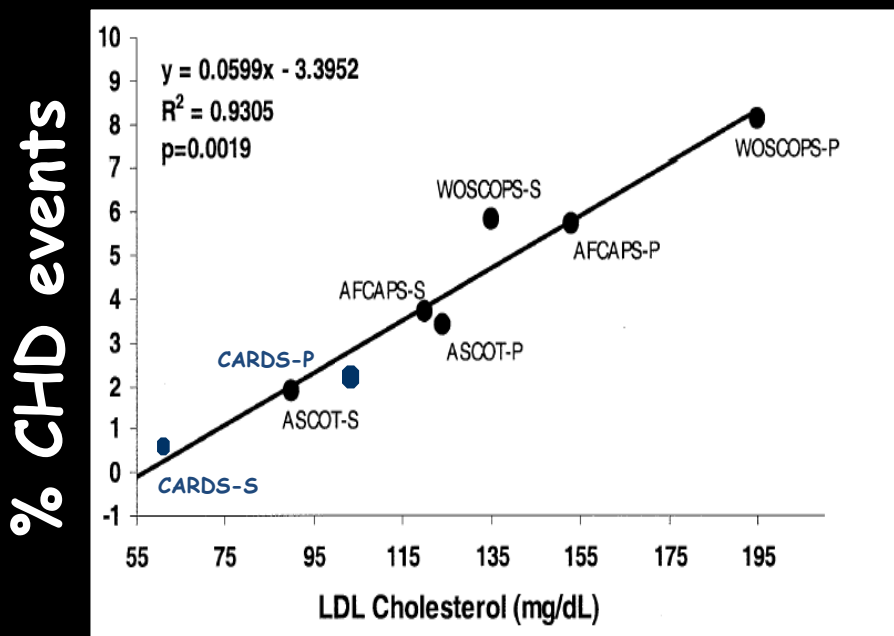
Lipid Monotherapy Options: *Clinical and Lipid Expectations*

Drug Class	CV Event Reduction (%)	LDL-C Decrease (%)	HDL-C Increase (%)	TG Decrease (%)	LDL Size/ Buoyancy
Statins	25% - 35% (4S, CARE, LIPID)	++++	+ 5%	+	+
Niacin	16% - 35% (CDP, Stockholm)	++	++++ 30%	++++	+++
Fibrates	11% - 24% (FIELD, VA-HIT)	+	++ 10%	++++	+
Torcetrapib	61%↑ (???????)	+	++++ 40%	+	+

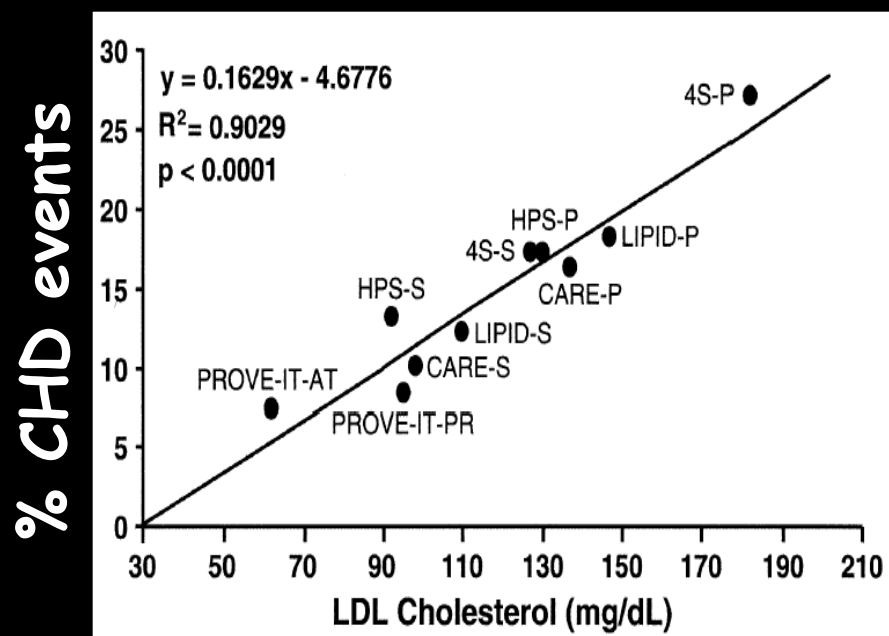
CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride

Compiled by Brown BG, December 2006.

LDL Debate; How low?

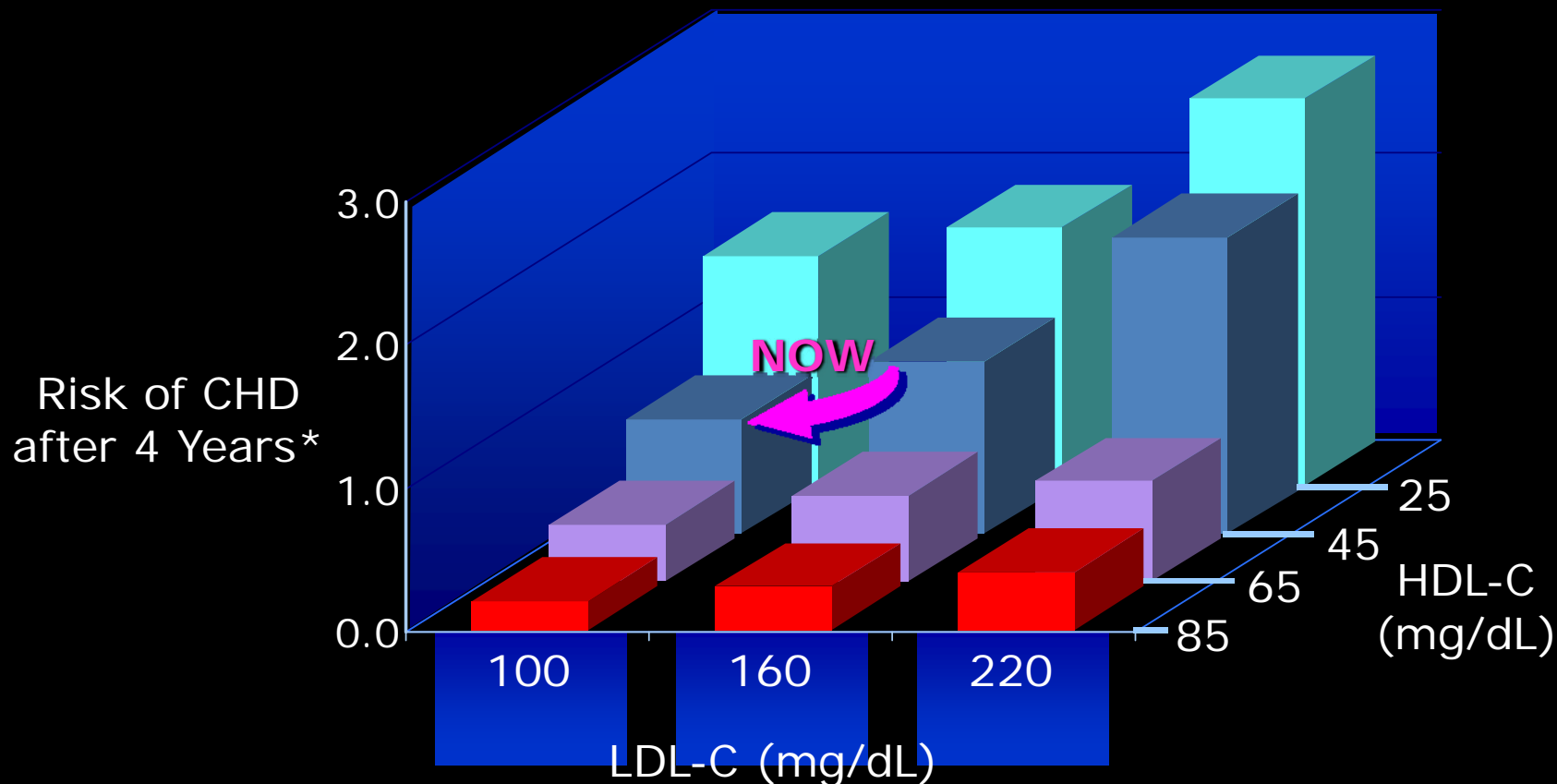


"in primary prevention the event rate is predicted to approach zero at LDL of 57 mg/dl = 1.5 mmol/L"



"in secondary prevention the event rate is predicted to approach zero at LDL of 30 mg/dl = 0.8 mmol/L"

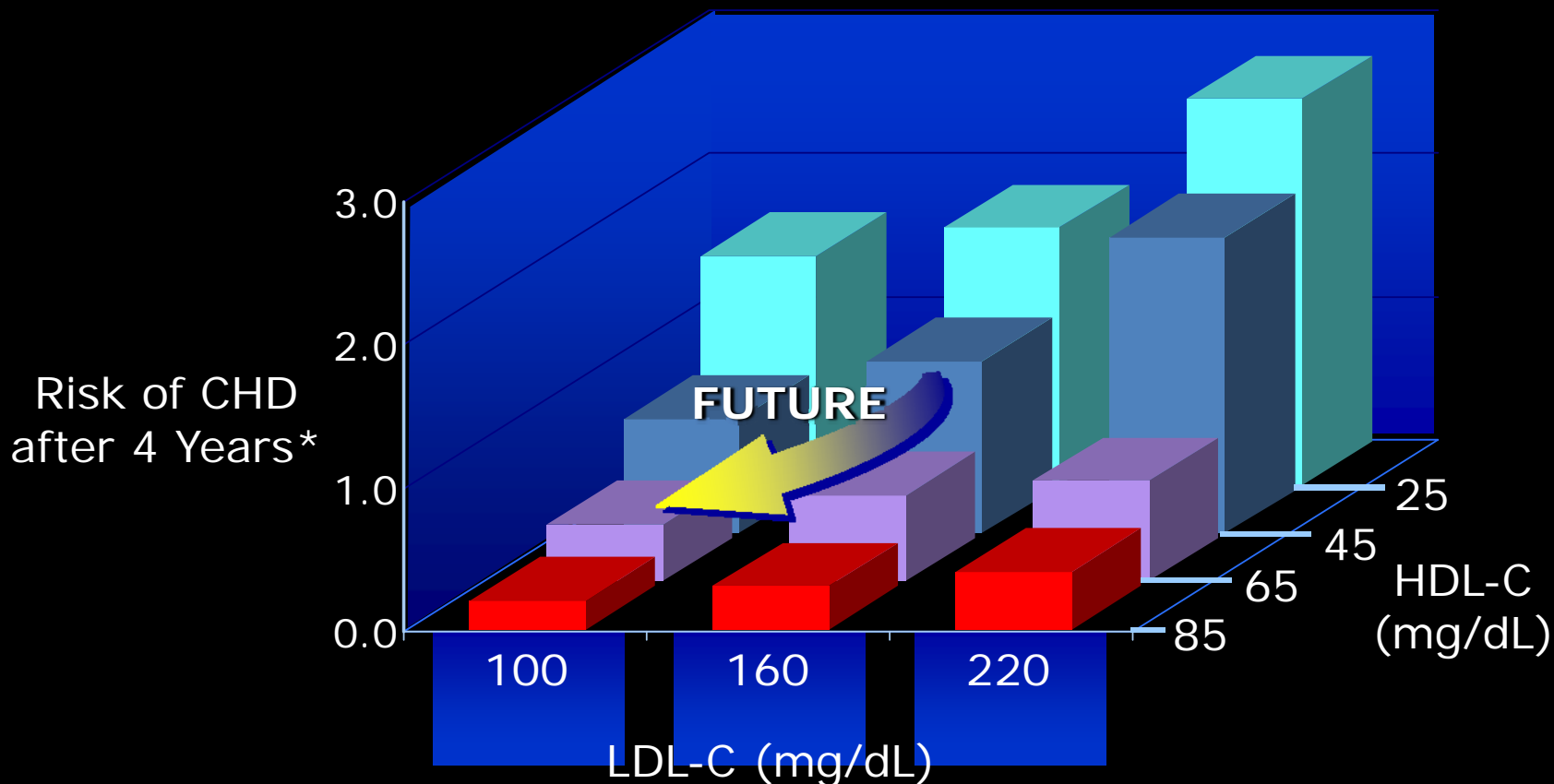
Framingham Study



*Risk of coronary heart disease (CHD) over 4 years of follow-up for men ages 50 to 70

Reprinted from Castelli WP. *Can J Cardiol.* 1988;4(Suppl A): 5A-10A, with permission from Pulsus Group Inc.

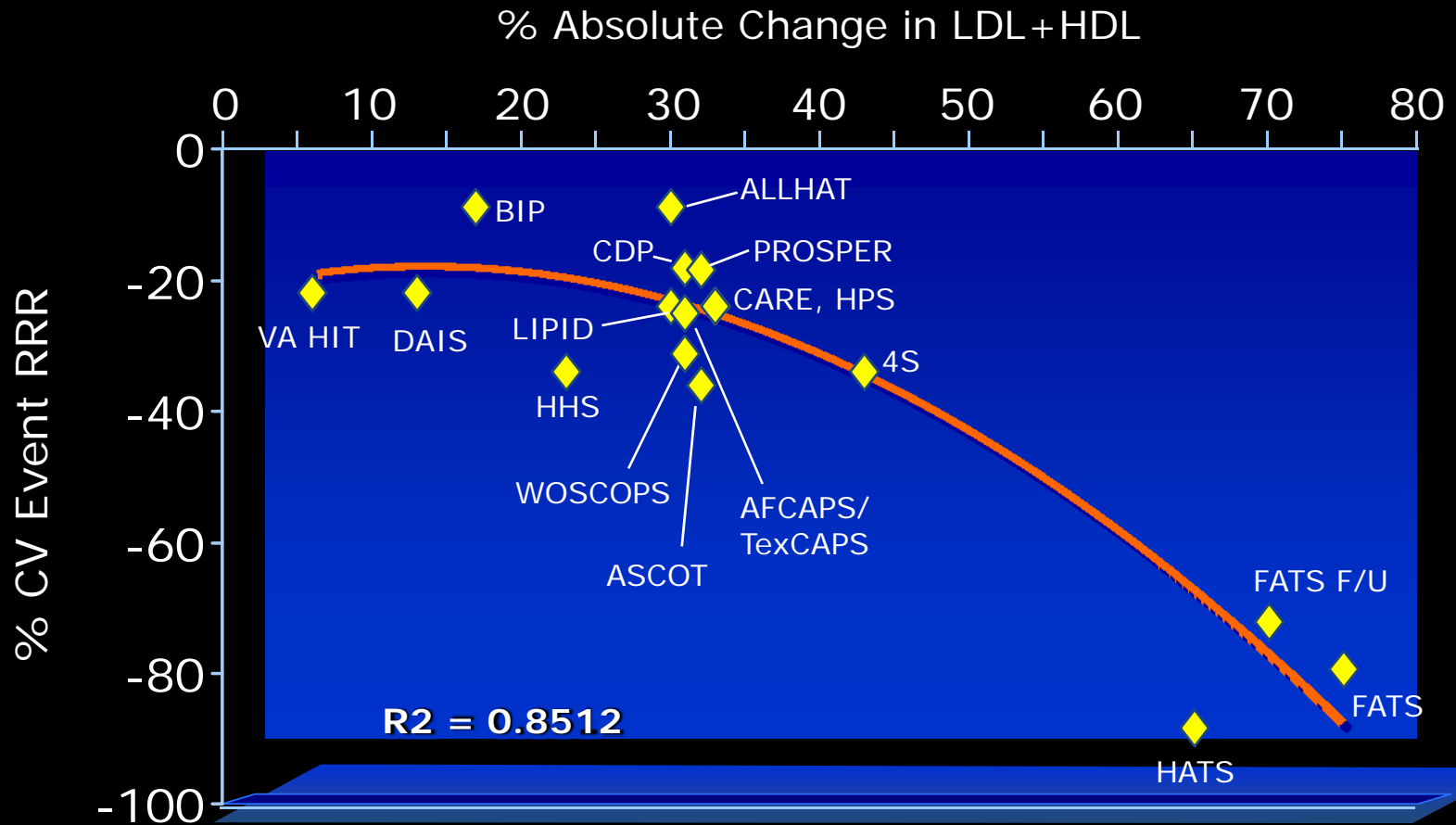
Framingham Study



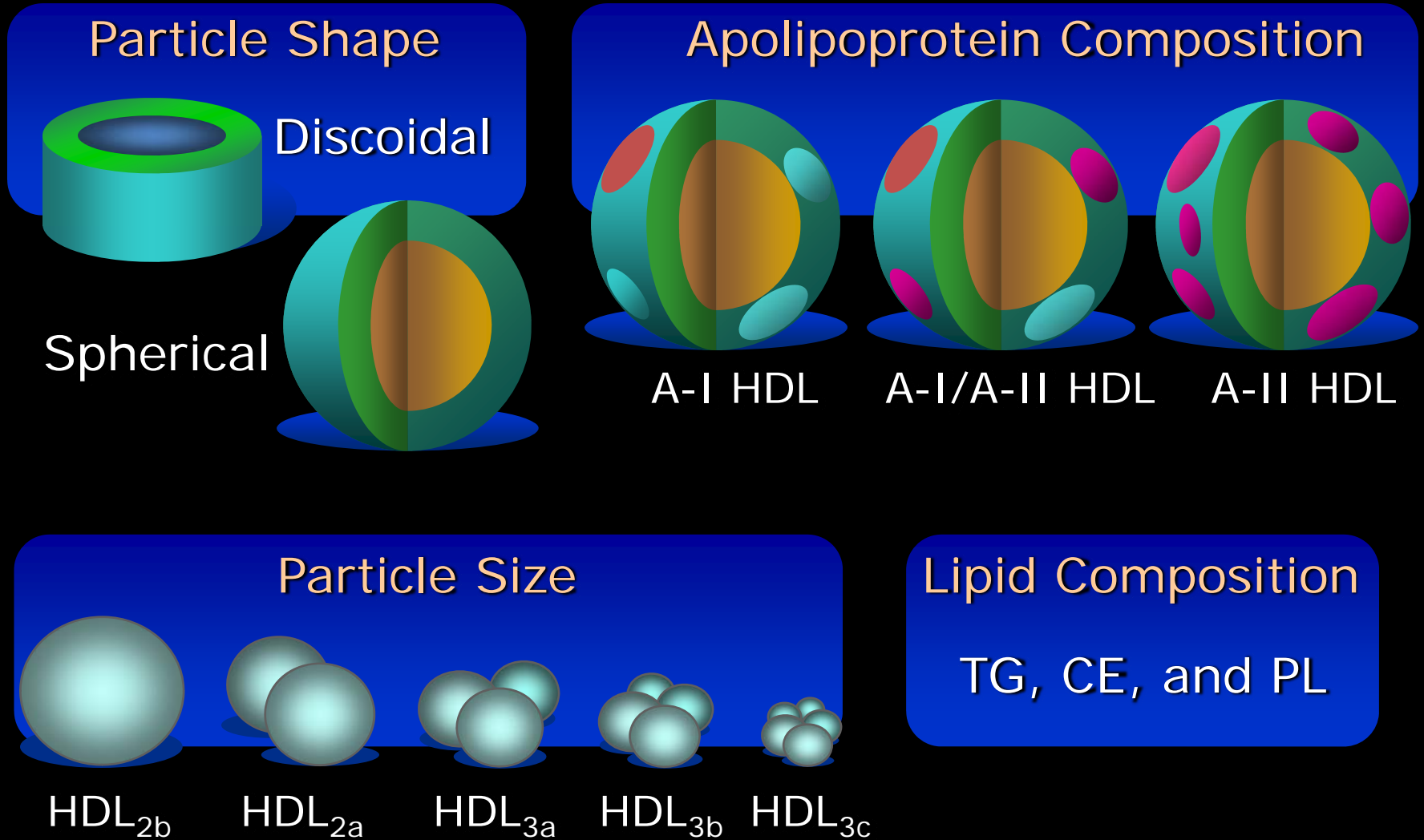
*Risk of coronary heart disease (CHD) over 4 years of follow-up for men ages 50 to 70

Reprinted in adapted form from Castelli WP. *Can J Cardiol*. 1988;4(Suppl A):5A-10A, with permission from Pulsus Group Inc.

Are LDL and HDL Effects Additive? 2nd Order Relationship



Heterogeneity of HDL



So, What's New in Lipids Since the ATP III Update in 2004?

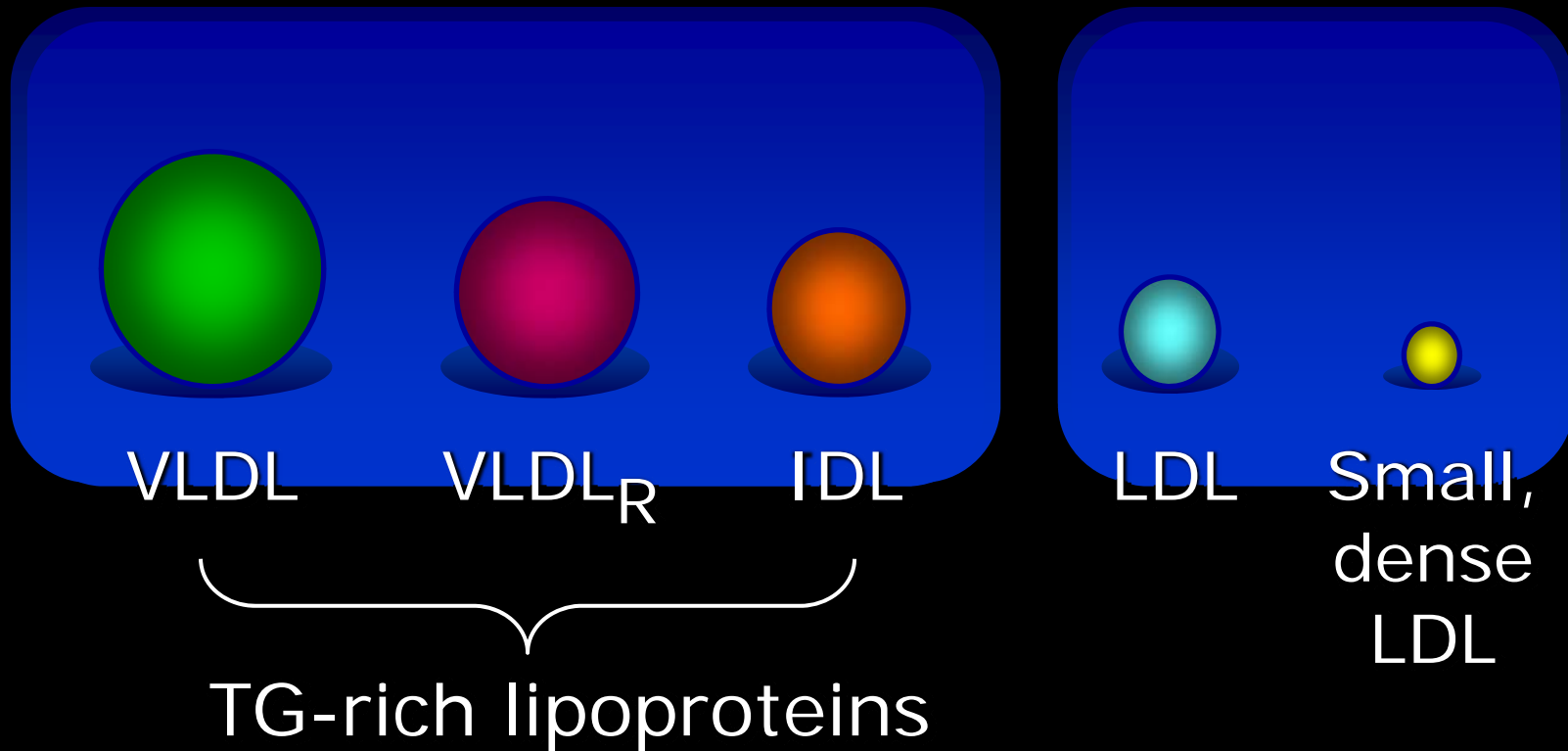
- AHA endorsed LDL-C < 70 mg/dL as a reasonable target in secondary prevention
- Defining level for HDL-C as a risk is based on gender (< 40 mg/dL men, < 50 mg/dL women)
- Primary prevention with statin (JUPITER) is beneficial, especially in women, and age > 70
- Limited or no data from statins in ESRD, class 3/4 HF, and aortic stenosis
- Incremental benefit of niacin and fibrates combined with statin (ACCORD, ARBITER 6)

What Will the NCEP ATP IV Look Like in 2011?

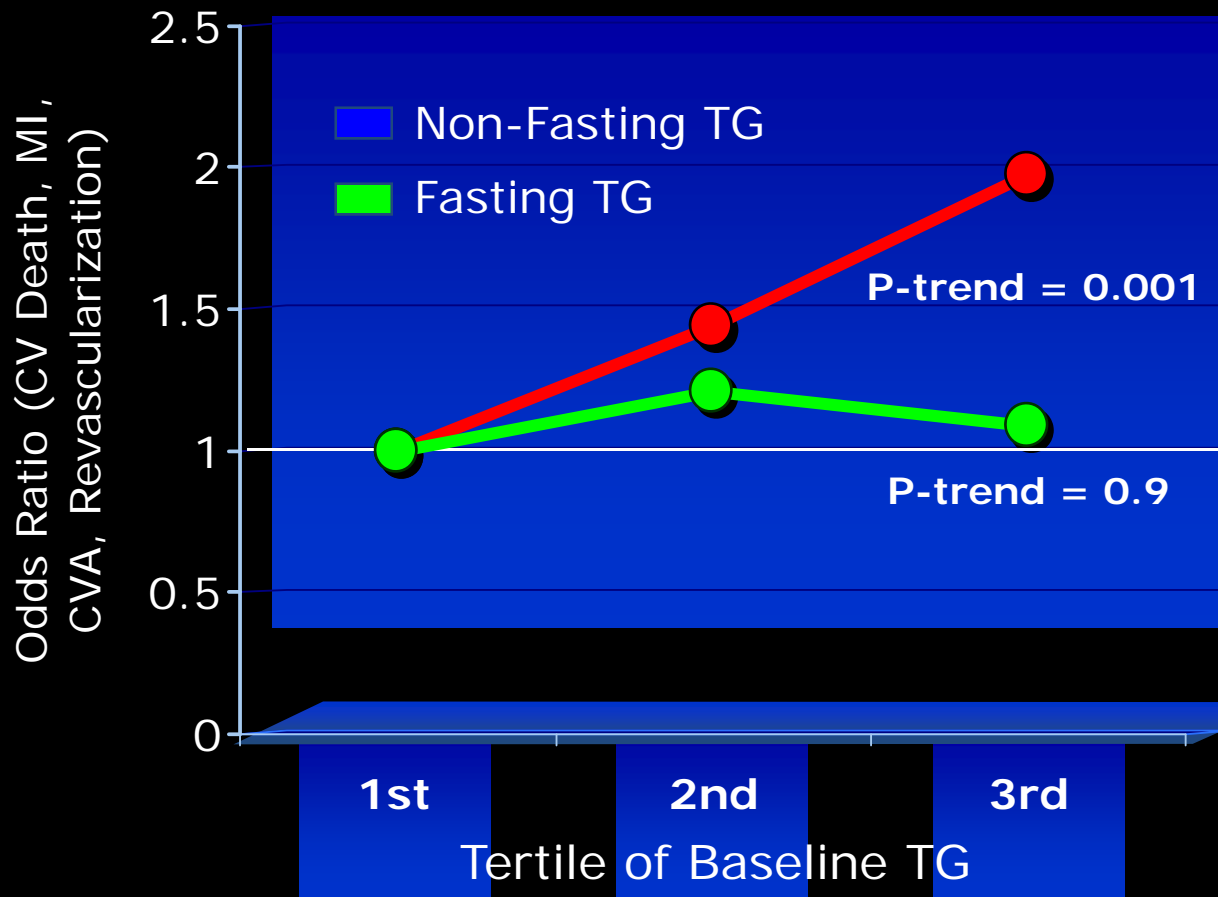
- More emphasis on the identification of primary CVD prevention patients for treatment?
- Do apoB, non-HDL-C, and/or particle number become targets along with LDL-C? In which patients?
- Incremental benefit with optimal statin treatment (to LDL-C goal):
 - Niacin?
 - Fenofibrate?
 - Omega 3s?
- What is the driver of incremental benefit?
 - ↑ HDL-C
 - ↓ apoB or LDL-P
 - Both?

Atherogenic Particles

MEASUREMENTS: Apolipoprotein B
Non-HDL-C



Population CVD Risk Attributable to TGs



Women's Health Initiative

- 20,118 Fasting
- 6,319 Non-fasting (<8 hr)
- Baseline demographics
- Baseline bloods
- 11.4-year mean F/U
- Fasting time documented
- Endpoint: CV death, MI, CVA, Revascularization
- 1,001 events
- Best risk discriminant = TG drawn @ 2–4 hours

Triglyceride Levels as an Independent Risk Factor for CHD?

Study	Results
PROCAM	High TG levels predict major coronary events <i>independent</i> of HDL-C
Copenhagen Male Study	High TG levels predict major coronary events <i>independent</i> of HDL-C
Lipid Research Clinics Follow-up Study	Coronary mortality related to TG levels, but <i>not independent</i> of HDL-C and LDL-C
Helsinki Heart Study	The effect of TG levels on CHD is jointly influenced by LDL-C and HDL-C levels
COLTS	“Normal” TG levels (1.1–2.2 mmol/L [100–199 mg/dL]) predict new cardiovascular events independent of HDL-C
Framingham Heart Study	TG were a CHD risk factor only when HDL-C was ≤ 1.03 mmol/L (≤ 40 mg/dL)

Ongoing “Events” Trials of Combined LDL-C Lowering and HDL-C Raising

Study	Sponsor	Rx vs. Control	N total*	\$ total (mil)*	Median Follow	Finish Year*
ACCORD	NIH & Pharma	Feno + St vs. Statin	5900	300 M	5.6 years	Q3-'09
AIM-HIGH	NIH & Kos	Nia + Sim vs. Sim	3300	42 M	4.0 years	Q3-'10
HPS-THRIVE	Merck, USA	Nia + Sim + FI † vs. Sim	20000	????	4+ years	Q4-'12

* Approximate

Drug Codes: Feno = fenofibrate, St = statin, Tor = torcetrapib, Ator = atorvastatin, Sim = simvastatin, Nia = extended release niacin

†FI = flush inhibitor (Pgd2 receptor blocker).

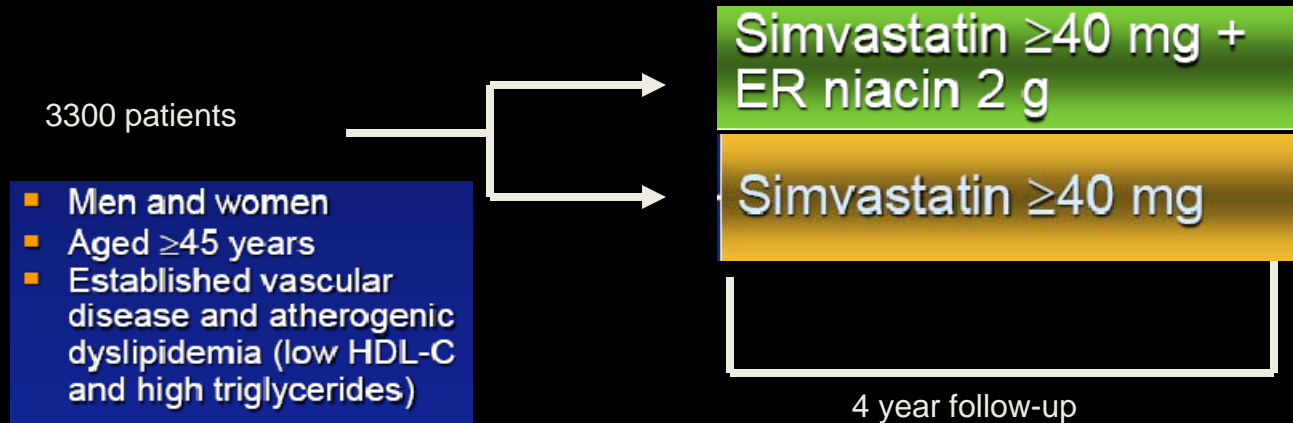
Compiled by Brown BG, 2007.

Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71%
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5%
FIELD (Fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27%
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

AIM-HIGH

Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes



Primary End Point

Composite of CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk ACS with objective evidence of ischemia

Key Secondary End Points

Composite of CHD death, nonfatal MI, or ischemic stroke

HPS2 – THRIVE

Treatment of HDL to Reduce the Incidence of Vascular Events

20 000 patients

- Men and women
- Aged 50-80 years
- History of MI, stroke or PAD
- ~ 7000 patients with diabetes
- Coordinating centers in UK, China and Scandinavia

Statin therapy
to optimal
LDL-C level

ER niacin + MK-0524A
combination tablet

Placebo

4-year follow-up

Primary End Point

- MI, stroke, revascularization procedures

Reports ~ 2012



Timeline

Cholesterol Guideline Update (ATP IV)

Expected availability for public review and comment: Spring 2011

Expected release date: Fall 2011

Hypertension Guideline Update (JNC 8)

Expected availability for public review and comment: Spring 2011

Expected release date: Fall 2011

Obesity Guideline Update (Obesity 2)

Expected availability for public review and comment: Spring 2011

Expected release date: Fall 2011

Integrated Cardiovascular Risk Reduction Guideline

Timeline TBD



Summary

- LDL-C remains the primary target of lipid-altering therapies
- HDL-C is an important CHD risk factor
- Non-HDL cholesterol or atherogenic cholesterol is also important
- Even small increases in HDL-C may confer substantial benefit
- Intervention to raise HDL-C levels should be considered in high-risk patients