Presenter Disclosure Information

Biochemical Surrogates: Are They Valuable for Risk Stratification?

DISCLOSURE INFORMATION:

The following relationships exist related to this presentation:

Stocks & Ownerships: eNOS Pharmaceuticals, Inc.

Consultant: Merck, Pfizer, AstraZeneca, Boehringer-Ingelheim, Bristol Myer Squibb, Asahi-Kasei Corp.

Research Support: AstraZeneca, Asahi-Kasei, Eli Lilly

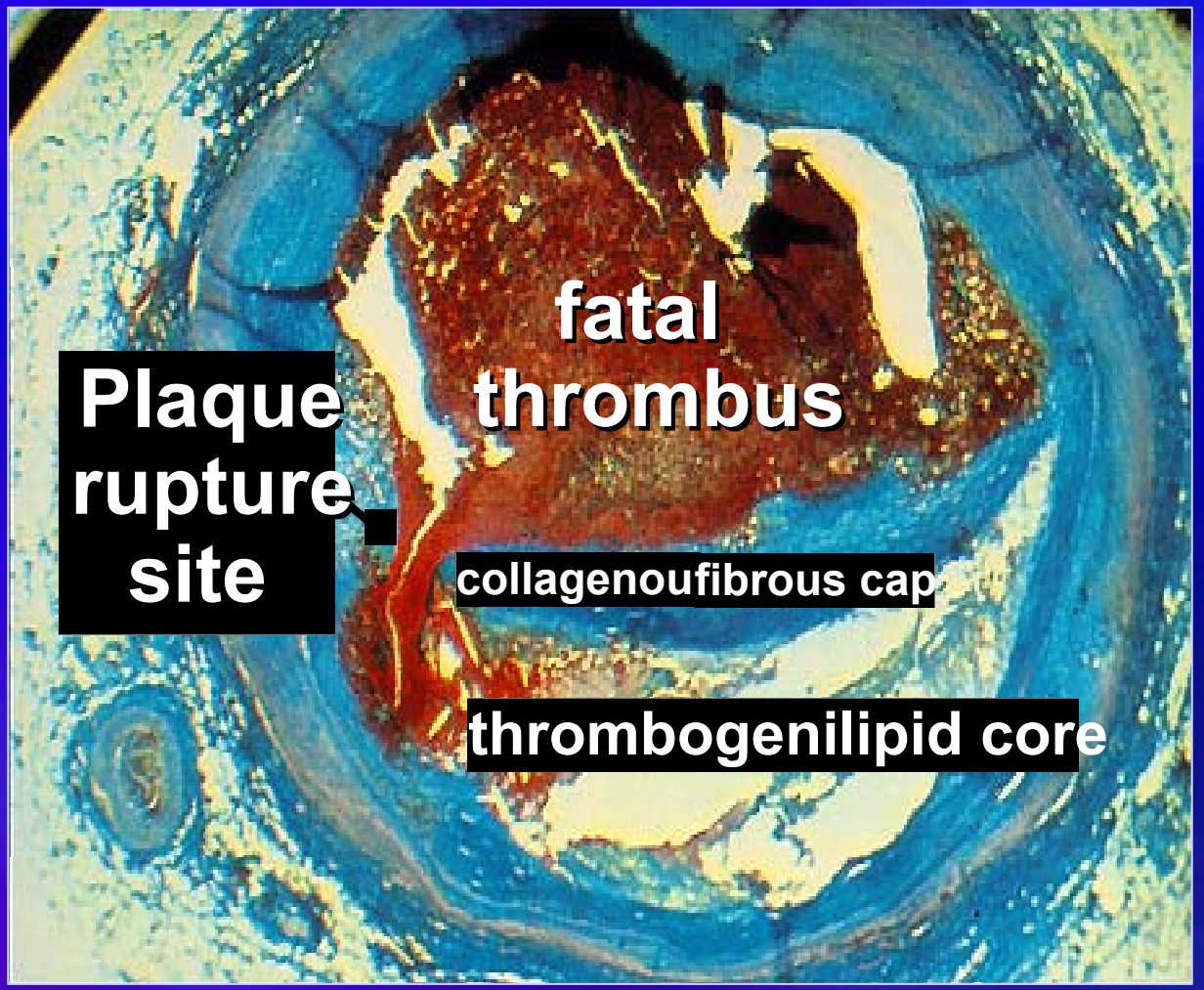
April 25, 2008
Summit TCT - Asia Pacific 2008

Biochemical Surrogates: Are They Valuable for Risk Stratification?

James K. Liao, M.D.
Harvard Medical School
Brigham & Women's Hospital

*The following slides are not prepared by AstraZeneca

Acute Coronary Syndrome
Plaque Rupture

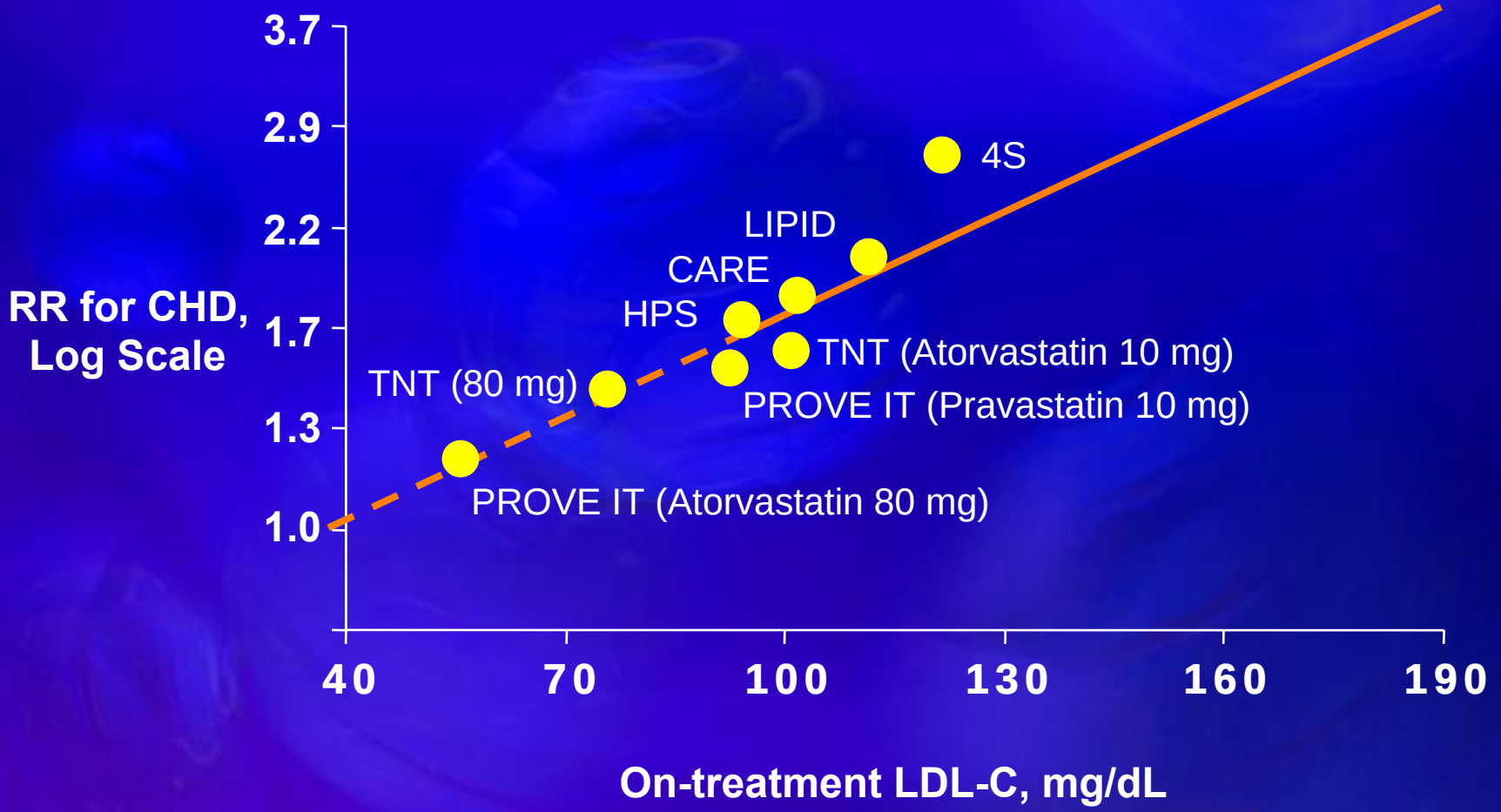


Reprinted from Constantinides P: Plaque hemorrhages, their genesis and their role in supra-plaque thrombosis and atherogenesis. In *Pathobiology of the Human Atherosclerotic Plaque* (Glagov S, Newman WP III, Schaeffer SA, EDS.)
Springer-Verlag, New York, 1990, PP 393-411.

Defining a Biochemical Surrogate

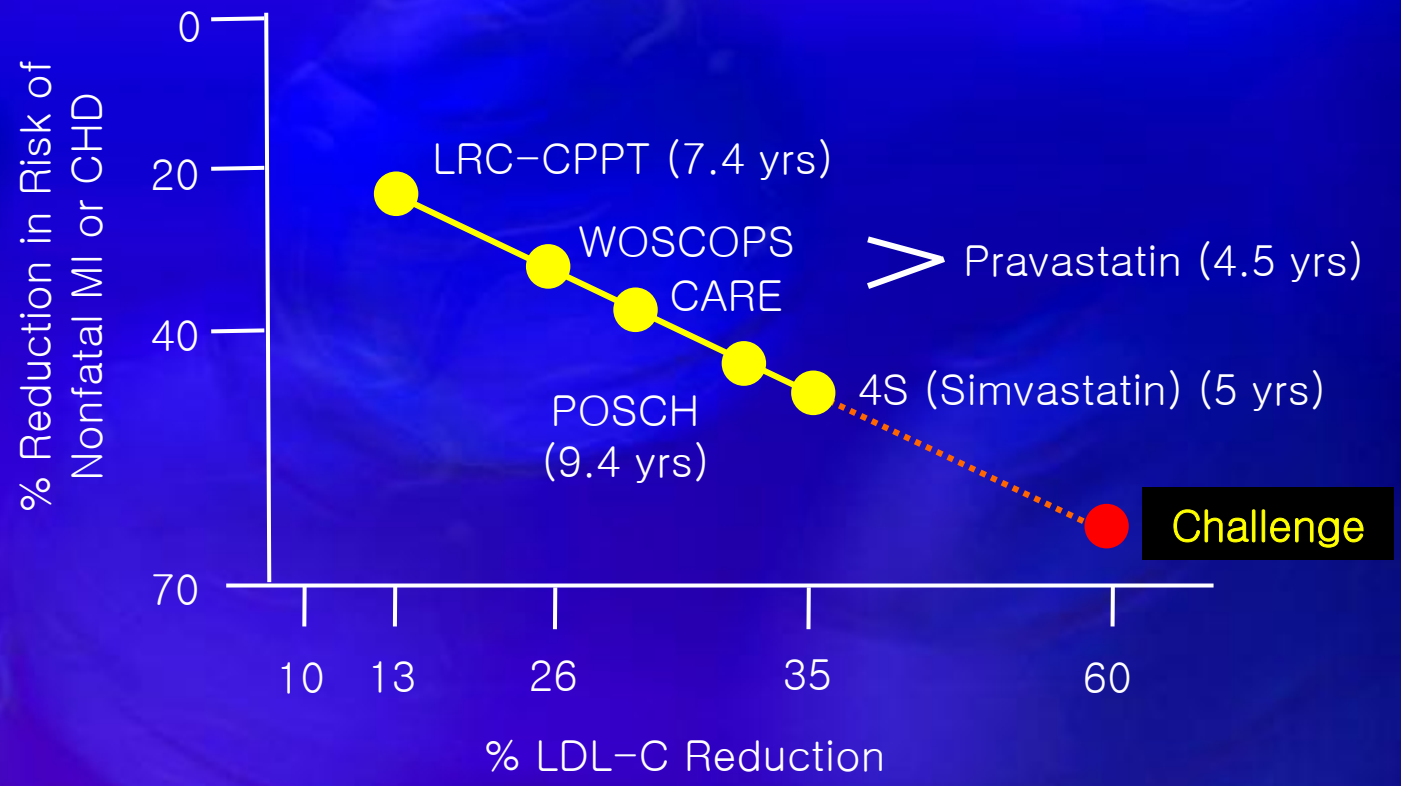
- A biochemical surrogate of a clinical trial is a laboratory measurement that is used as a substitute for a clinical endpoint.
- The validity of using the biochemical surrogate is such that the effect of an intervention on the biochemical surrogate must reliably predict and capture the net effect of the intervention, in part or whole, on the clinical endpoint.

Recent Evidence from Statin Trials Suggests Lower LDL-C Levels Are Better



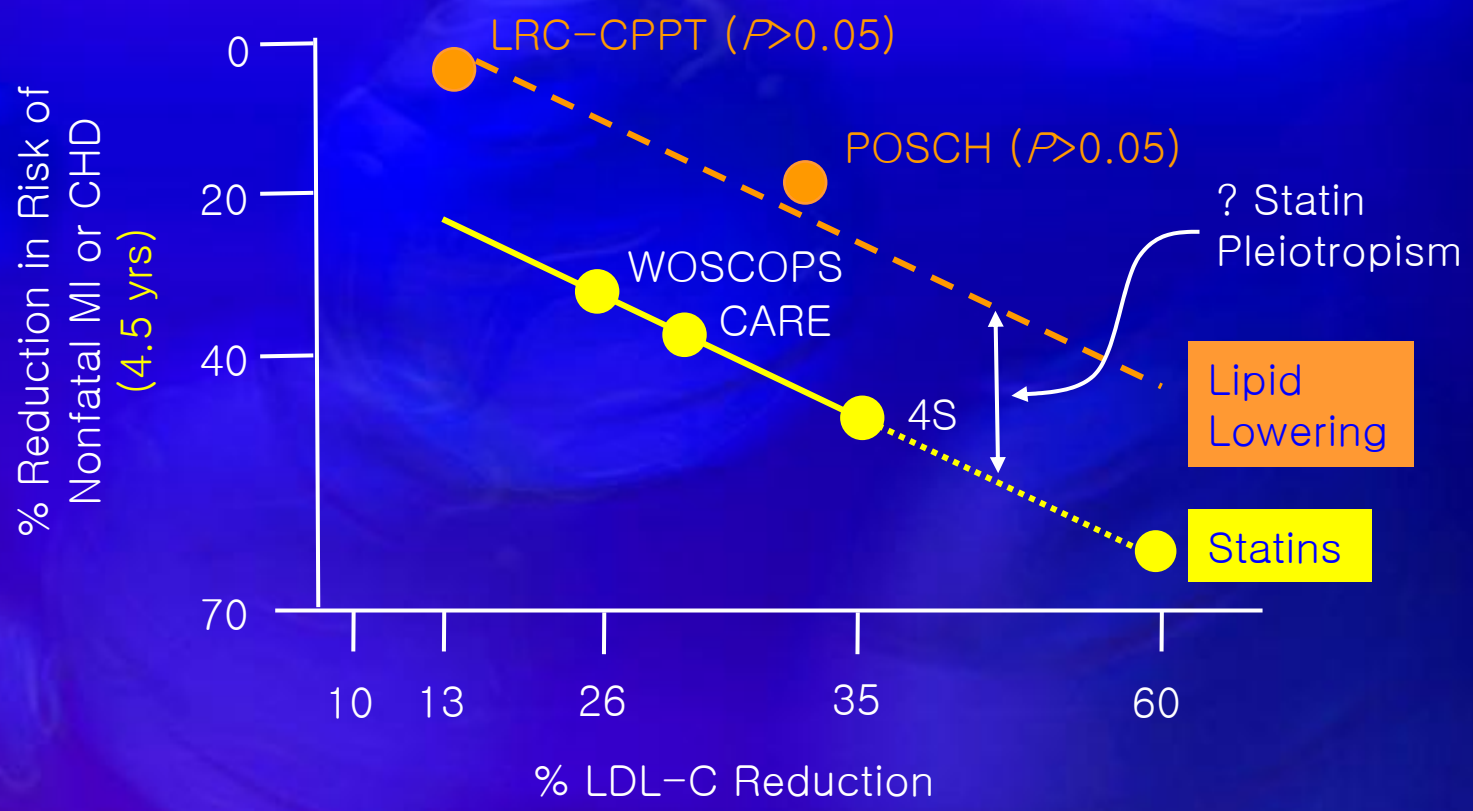
Adpated from Grundy SM, et al, for the Coordinating Committee of the NCEP. *Circulation.* 2004;110:227-239.

Time to Benefit in Lipid Lowering Trials: ↓LDL-C to ↓CHD Risk



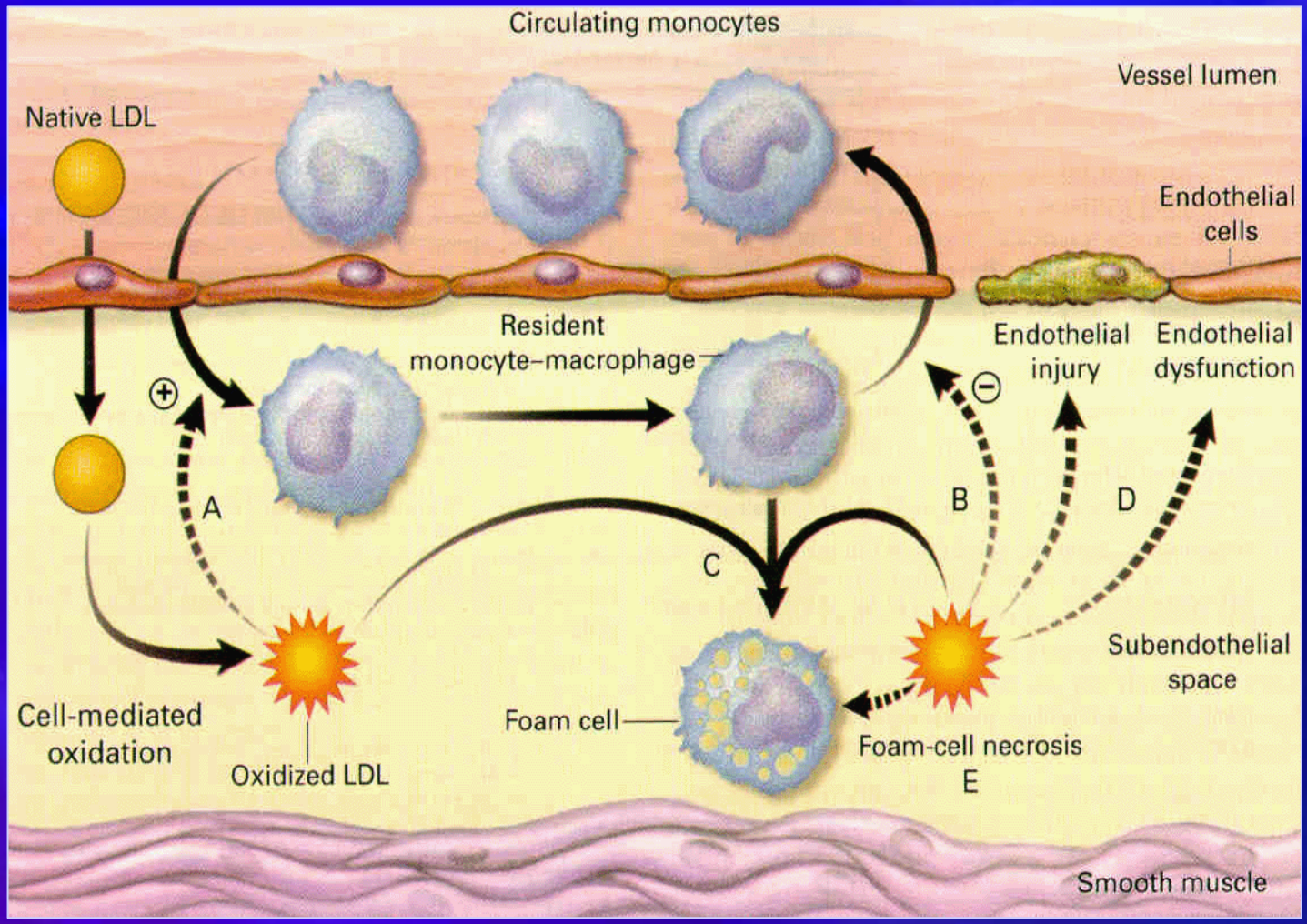
Liao, J.K., *Am. J. Cardiol.* 2005;96:24F-33F.

Time to Benefit in Lipid Lowering Trials: Superiority of Statin Therapy



Liao, J.K., *Am. J. Cardiol.* 2005;96:24F-33F.

Atherosclerosis: 2-Hit Hypothesis?



Diaz et al. *N Engl J Med*. 1997;337:408–416.

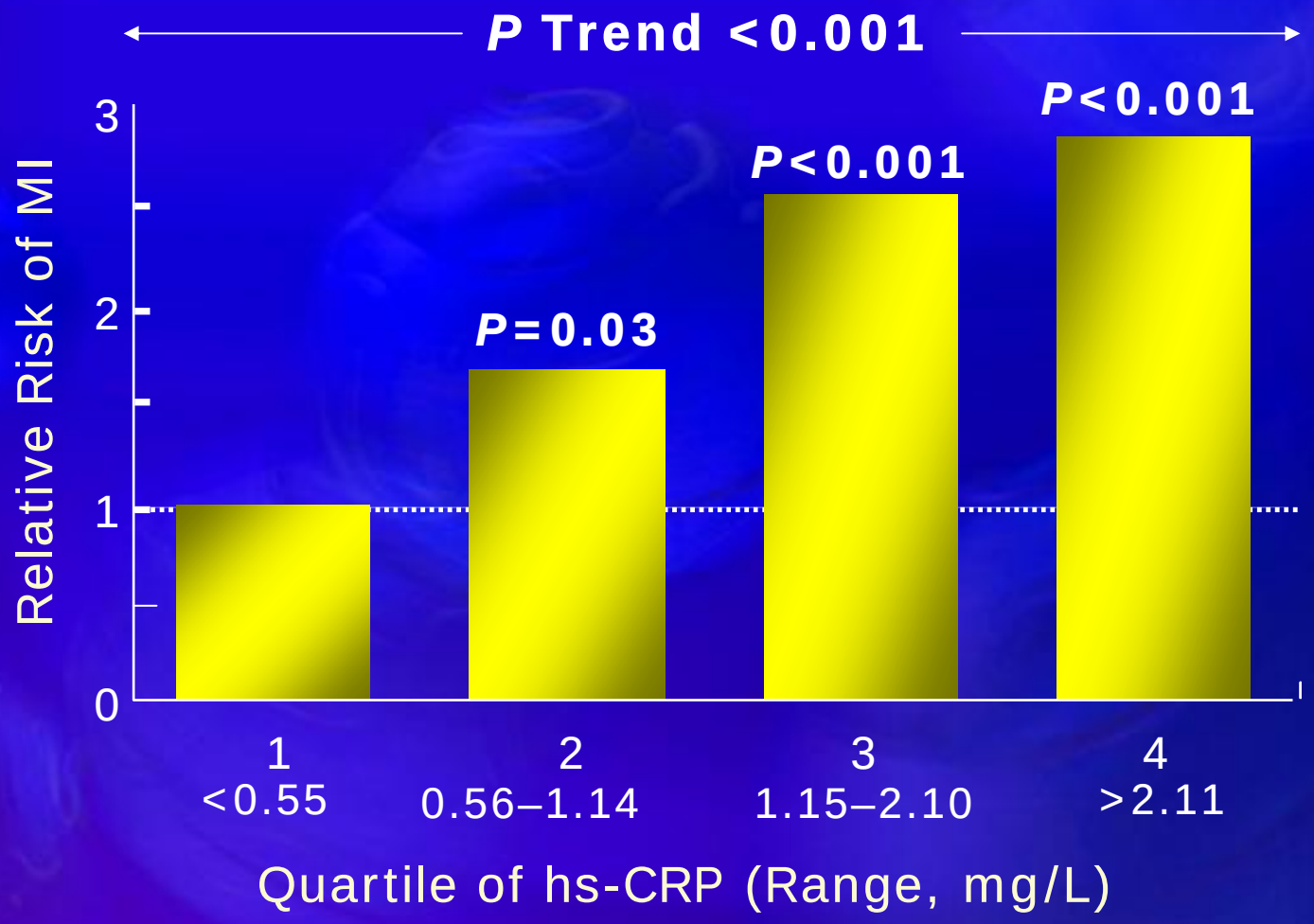
Characteristics of Useful Surrogate Markers

- Consistent with the pathophysiology of the disease
- Sufficiently prevalent in patient populations
- Changes in markers meaningfully correlate with changes in patient outcomes
- Reproducible test and retest characteristics over multiple assessments to allow monitoring of disease
- Extensive clinical availability to support their use

Is a biochemical marker of inflammation such as hsCRP, a useful surrogate marker for cardiovascular disease?

Taylor A, et al. *Atherosclerosis*. 2005;180:1-10.

hs-CRP and Risk of Future MI in Apparently Healthy Men



Ridker PM et al. *N Engl J Med*. 1997;336:973-979.

Association of CRP With Other Risk Factors

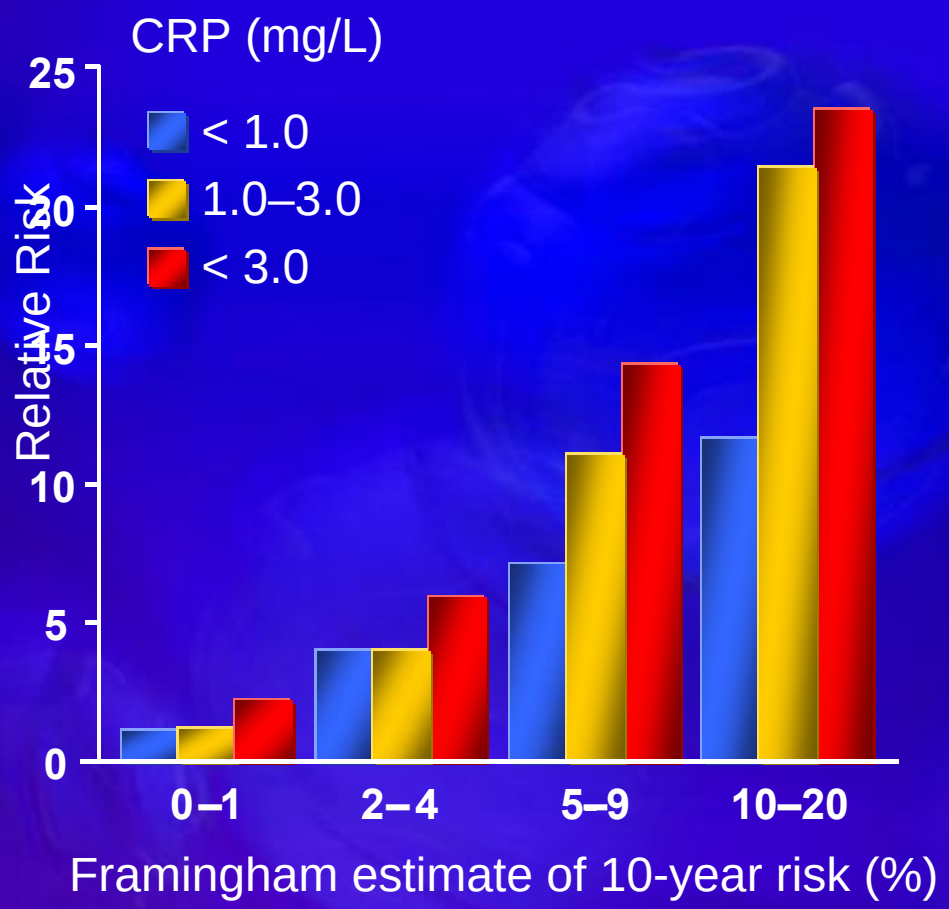
Increased CRP

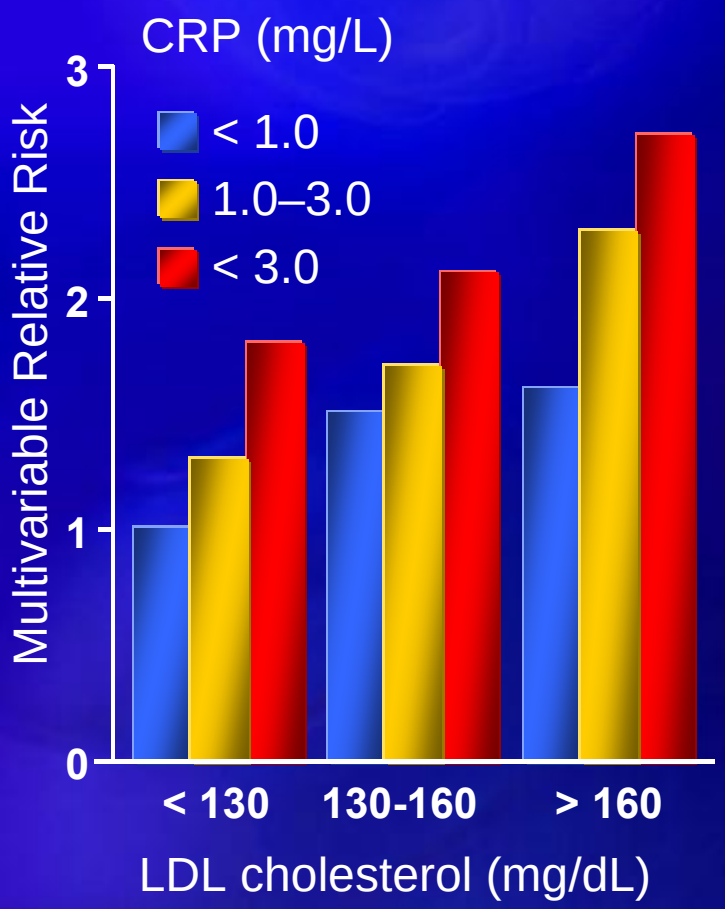
- Hypertension
- BMI
- Obesity
- Diabetes
- Metabolic syndrome
- Smoking

Decreased CRP

- Alcohol consumption
- Physical activity
- Weight loss
- Medications

CRP Adds Prognostic Information at All Levels of LDL-C and Framingham Risk Score

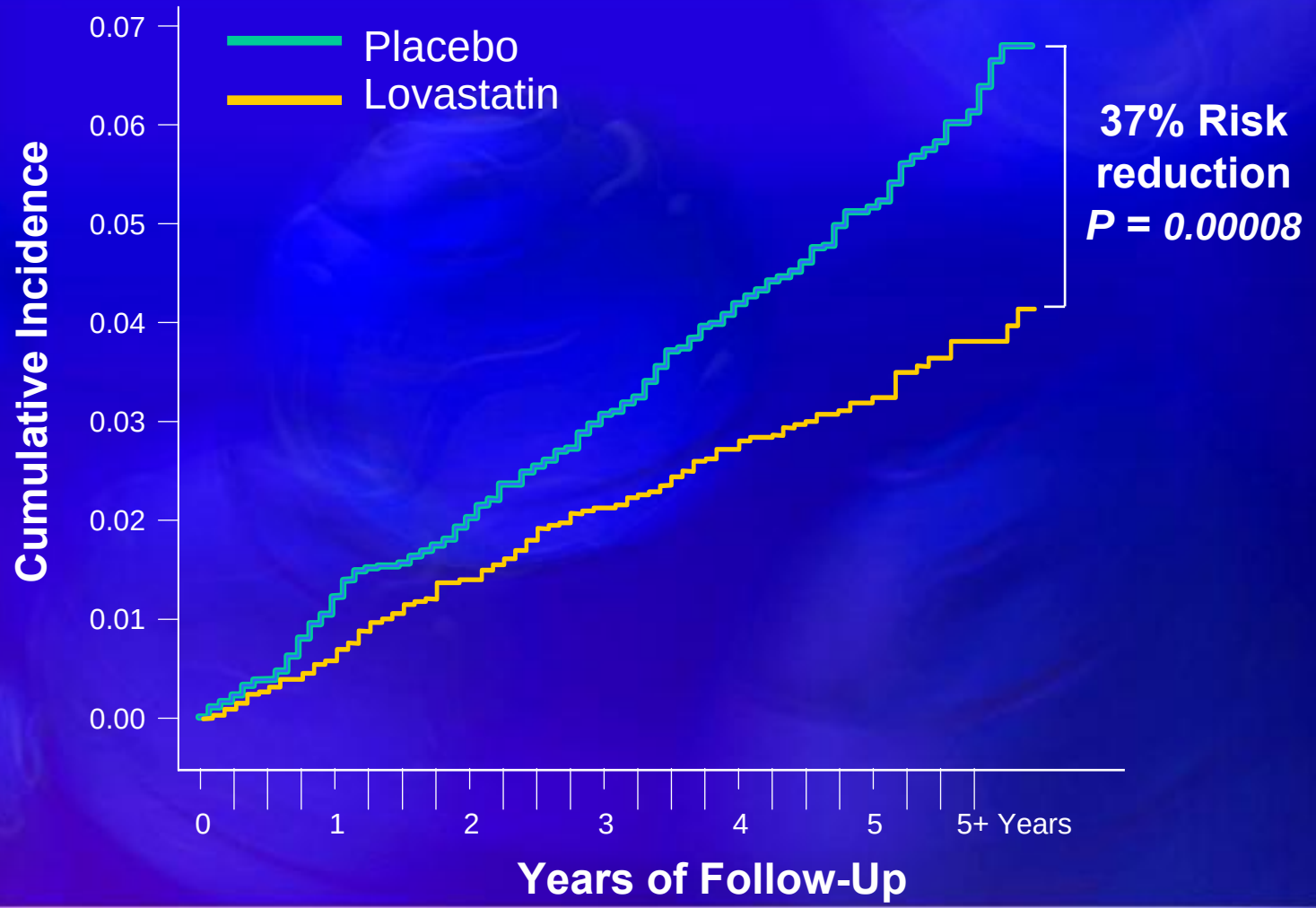




Ridker PM et al. *N Engl J Med*. 2002;347:1557-1565.

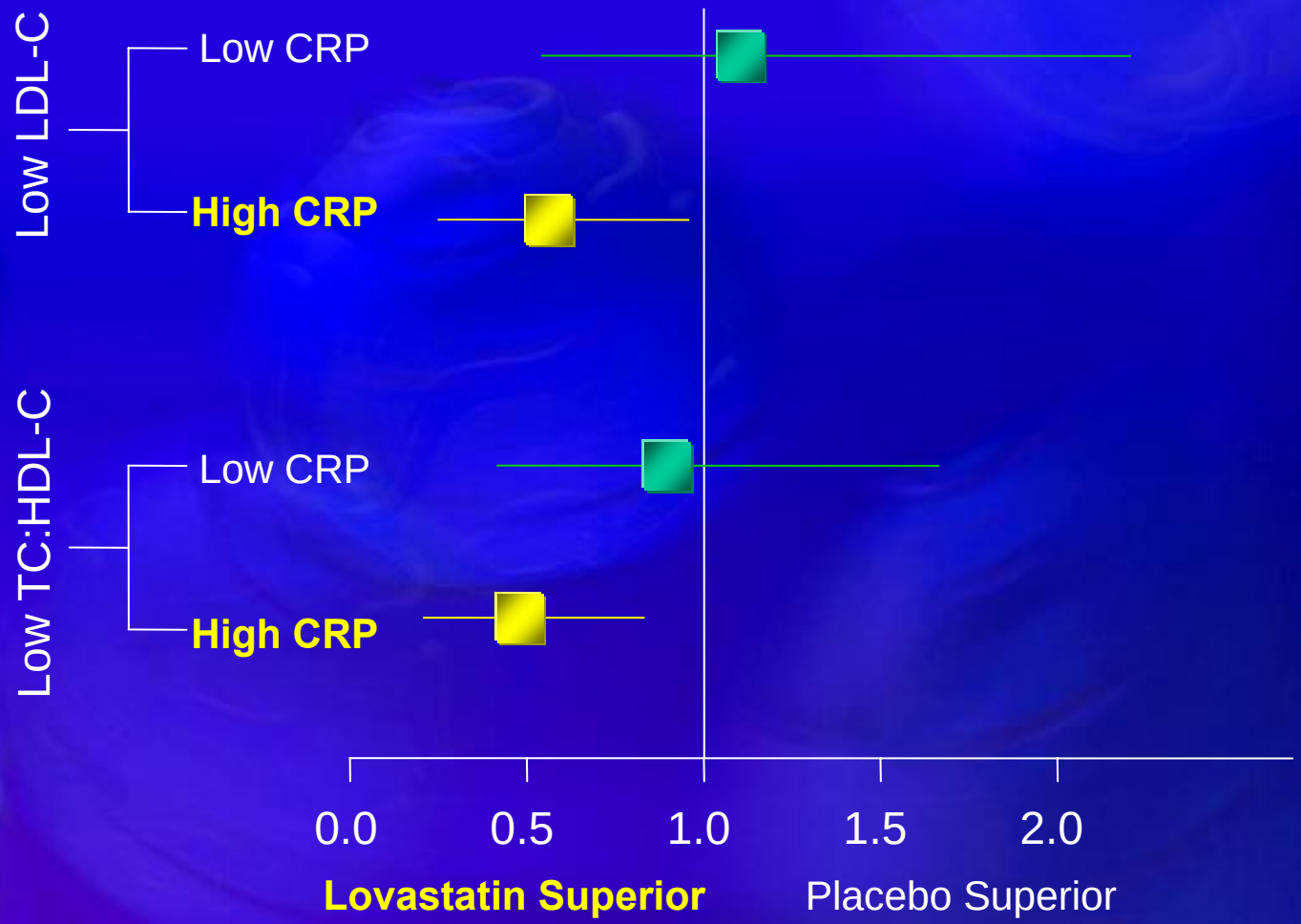
Is CRP a useful surrogate marker, which when combined with lipid evaluation, provides an improved method to target statin therapy in primary prevention?

First Acute Major Coronary Event: AFCAPS/TexCAPS



Downs JR et al. *JAMA*. 1998;279:1615-1622.

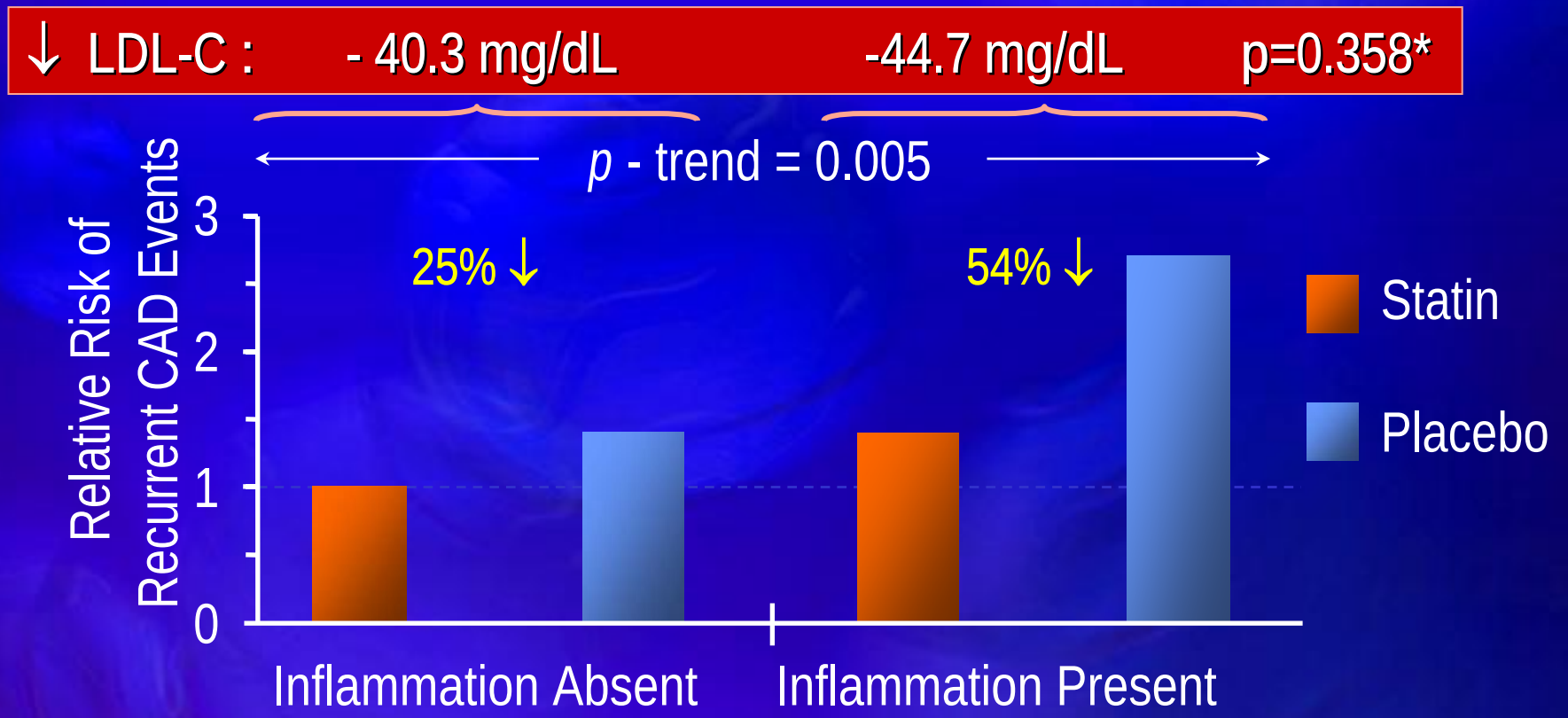
Inflammation Discriminates Between Patients with Low Cholesterol Levels in Primary Prevention Trial



Blake & Ridker Circulation Research, 2001.
Adapted from Ridker PM et al, *New Engl J Med*. 2001:344:1959-1965.

Inflammation, Pravastatin and the Risk of Coronary Events after MI in Patients with Average Cholesterol Levels (CARE)*

* Cholesterol And Recurrent Events trial



Inflammation = both CRP and SAA levels ≥90th percentile

Randomized pravastatin assignment. N = 708

Ridker PM et al. *Circulation.* 98:839–44, 1998

PRIMARY PREVENTION: CDC/AHA Consensus On Inflammatory Markers

1. **hsCRP assay is optimal inflammatory marker thus far**
2. **CRP may be useful in estimating risk of future cardiovascular events in primary prevention, particularly in persons at intermediate risk based on other risk factors**

hsCRP concentration	Risk Level
<1 mg/L	Low
1-3 mg/L	Medium
>3 mg/L	High

Pearson TA et al. *Circulation* 2003;107:499-511.

CDC/AHA Consensus Statement on Inflammatory Markers

Clinical Testing:

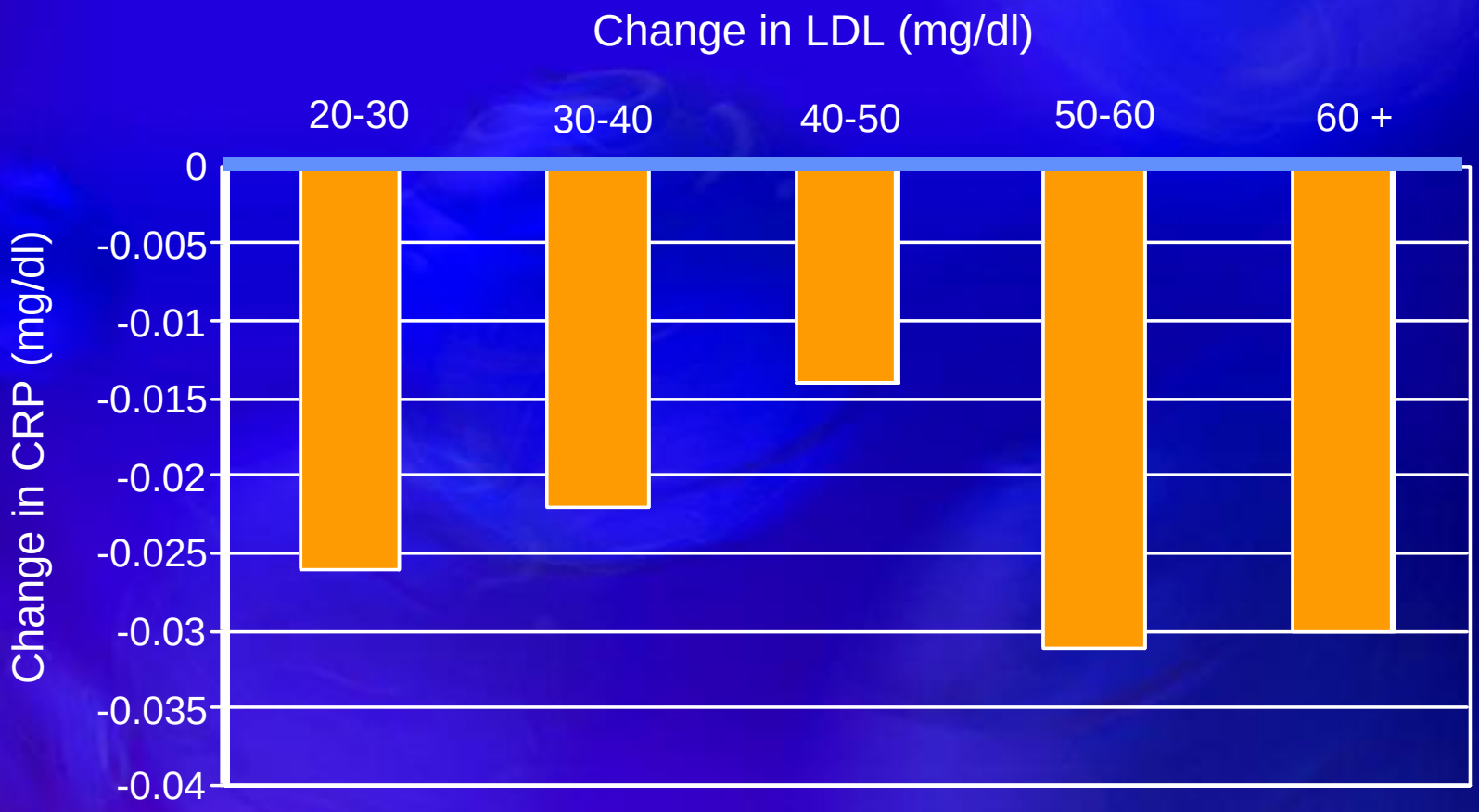
- Standardized assay
- hsCRP should be measured twice 2 weeks apart and averaged
- If hsCRP > 10 mg/L, evaluate for obvious source of infection and repeat in 2 weeks

Pearson TA et al. Circulation 2003;107:499-511

Effects of CV Therapeutics on CRP

CV Therapeutics	Reduction in CRP
ASA	-10%
Fibrates	-10%
Niacin	-15%
PPAR Agonists	-20%
ACE Inhibitors	-25%
ARB	-25%
Ezetimibe	+5%
Statins	-30-50%

Is there a relationship between change in LDL and change in CRP?



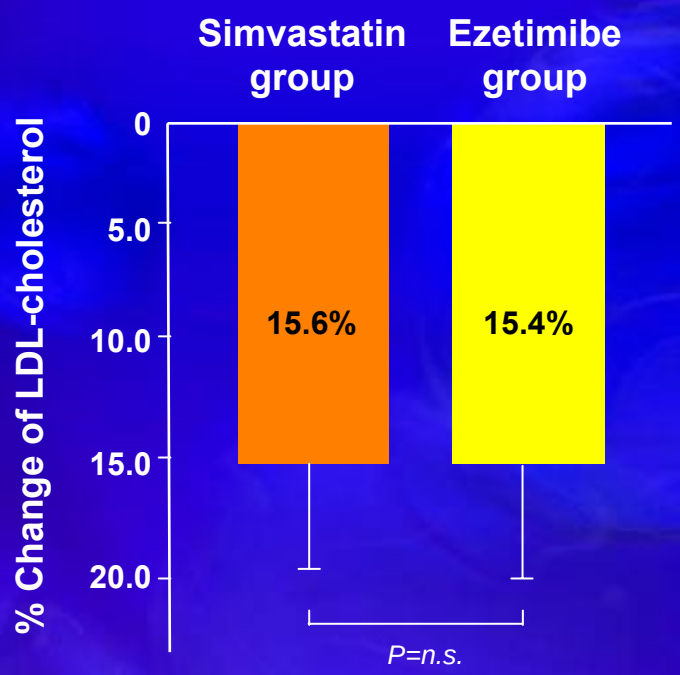
* pravastatin treated patients only

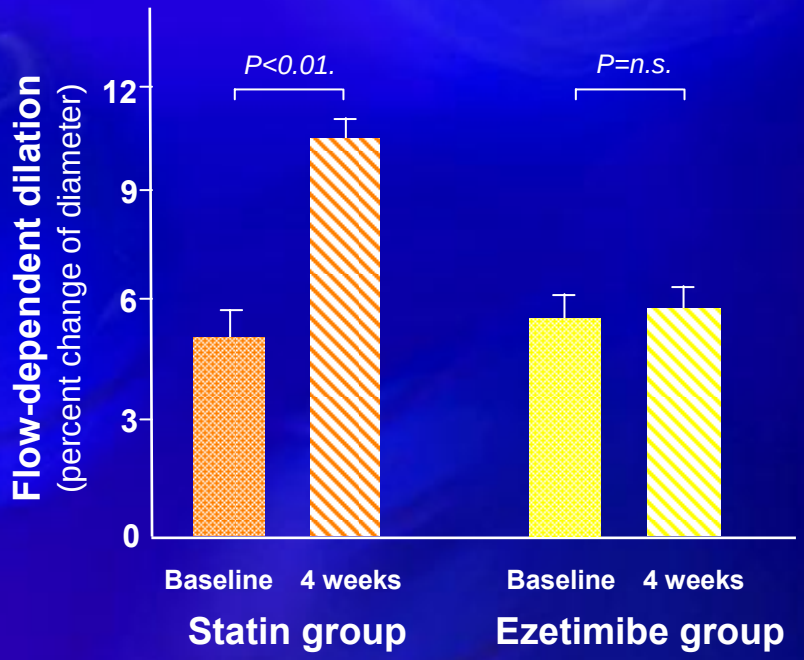
Albert et al, JAMA 2001

Cardiovascular Protective Effects of Statin Therapy

- Lipid-lowering
- ? Pleiotropic effects
  - Improved endothelial function
  - Anti-inflammatory effects
  - Plaque stabilizing effects
  - Antioxidative effects
  - Anti-thrombotic effects
  - Pro-angiogenic effects

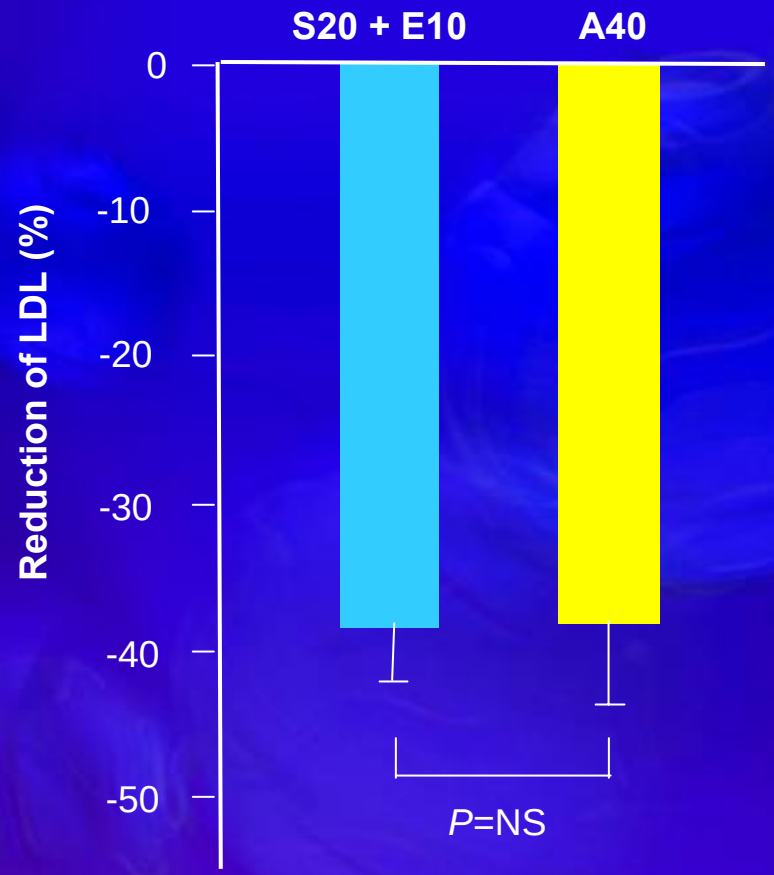
Advantages of Statin vs. Ezetimibe in Endothelial Function

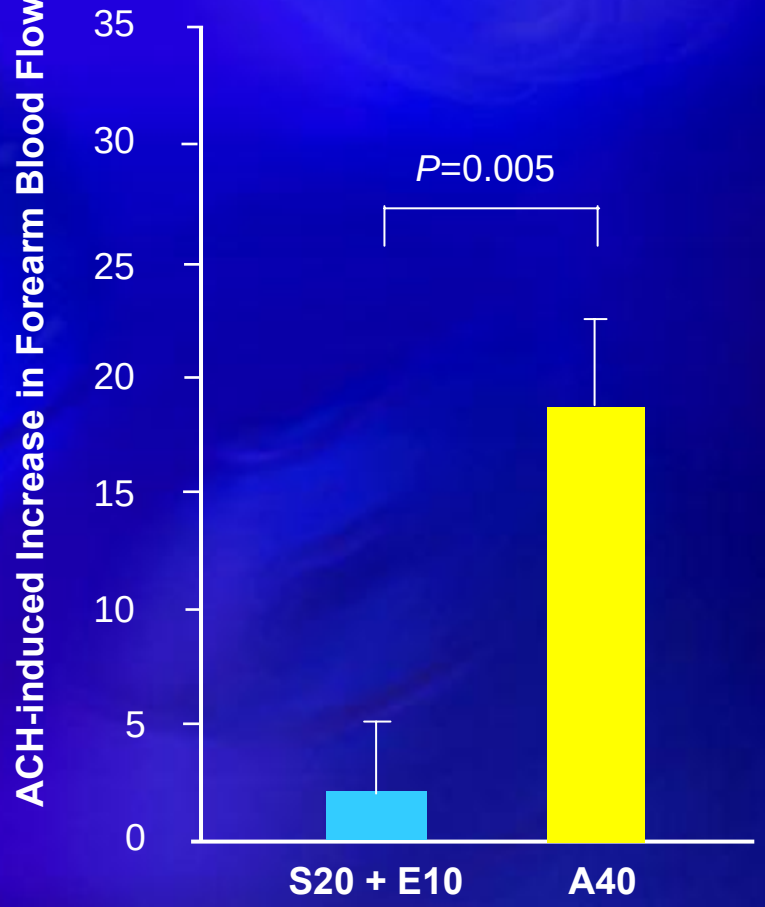




U. Landmesser et al., *Circulation*. 2005;111:2356-63.

Advantages of Mono vs. Dual Therapy in Endothelial Function





A = atorvastatin; S = simvastastin; E = ezetimibe

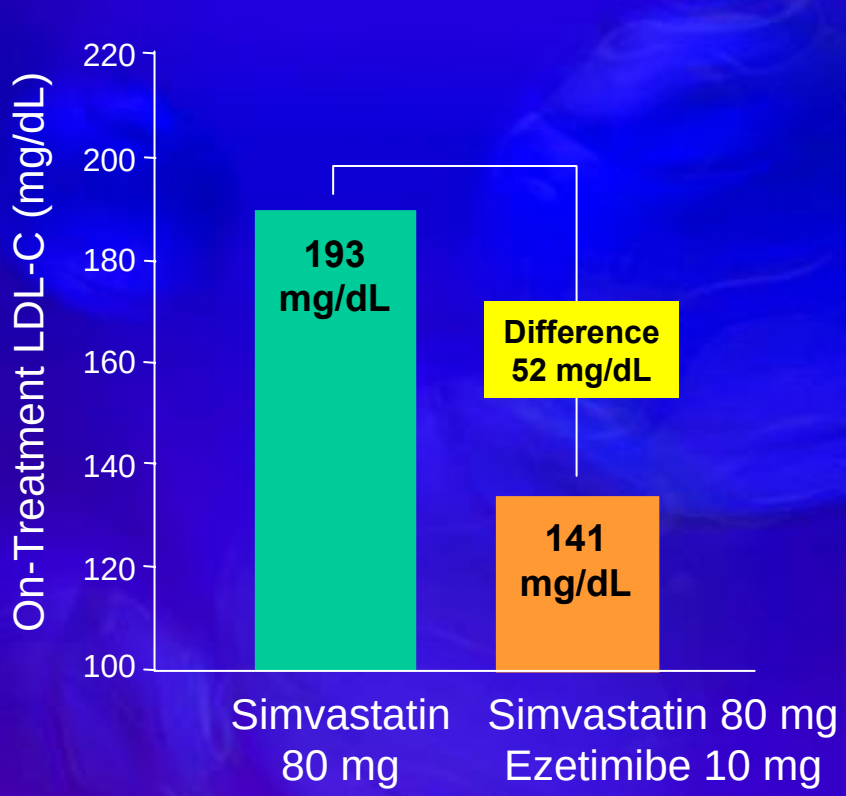
S. Fichtlscherer et al., *Eur. Heart J.* 2006;27:1182-90.

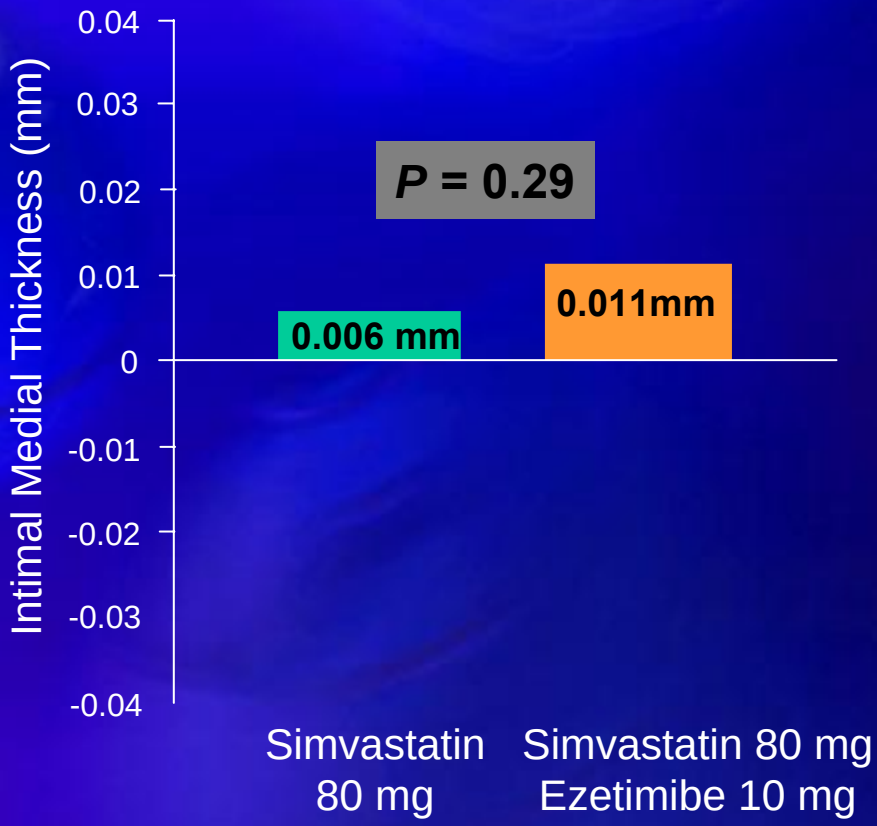
Clinical Outcomes Studies with Combination Therapy

Study	Objectives	Study Groups	Patient Type	N	Duration (yr)
ENHANCE	To evaluate effects of aggressive lipid lowering on carotid artery IMT	Ezetimibe 10 mg/ Simvastatin 80mg Simvastatin 80mg	Hyper-cholesterolemia	725	≥2
SEAS	To assess whether aggressive lipid lowering in patients with moderate AS slows the progression of AS and reduces the number of valve replacements and incidence of CVD outcomes	Ezetimibe 10 mg/ Simvastatin 40mg Placebo	Aortic stenosis (AS)	1,400	≥4
SHARP	To assess the effects of aggressive lipid lowering on vascular events	Ezetimibe 10 mg/ Simvastatin 20mg Placebo	Chronic kidney disease	9,000	>4
IMPROVE IT	To evaluate the effect of aggressive lipid lowering on reduction in risk of death and major coronary events	Ezetimibe 10 mg/ Simvastatin 40mg Simvastatin 40mg	Acute coronary syndrome	10,000	4

ENHANCE=**E**zetimibe a**N**d simvastatin in **H**ypercholesterolemia enh**AN**ces atherosclerosis r**E**gression; IMT=intima media thickness; SEAS=**S**imvastatin and **E**zetimibe in **A**ortic **S**tenosis; SHARP=**S**tudy of **H**eart **A**nd **R**enal **P**rotection; IMPROVE IT=**IMP**roved **R**eduction of **O**utcomes: **V**ytorin™ **E**fficacy **I**nternational **T**rial

ENHANCE Trial:
Ezetimibe Does Not Slow Atherosclerosis Progression Despite Further Reduction in LDL

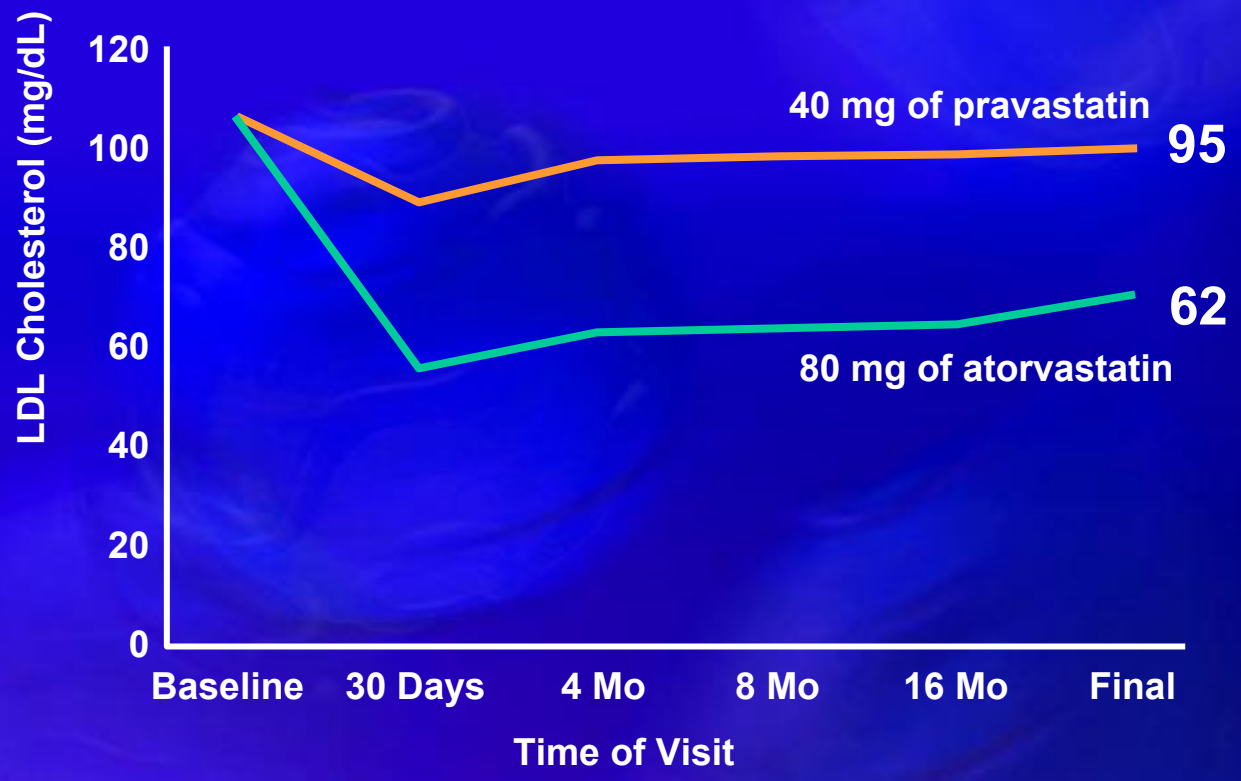




Klastelein JJ et al. *N. Engl. J. Med.* 2008;358:1431-43

Statins as Anti-inflammatory Agents?

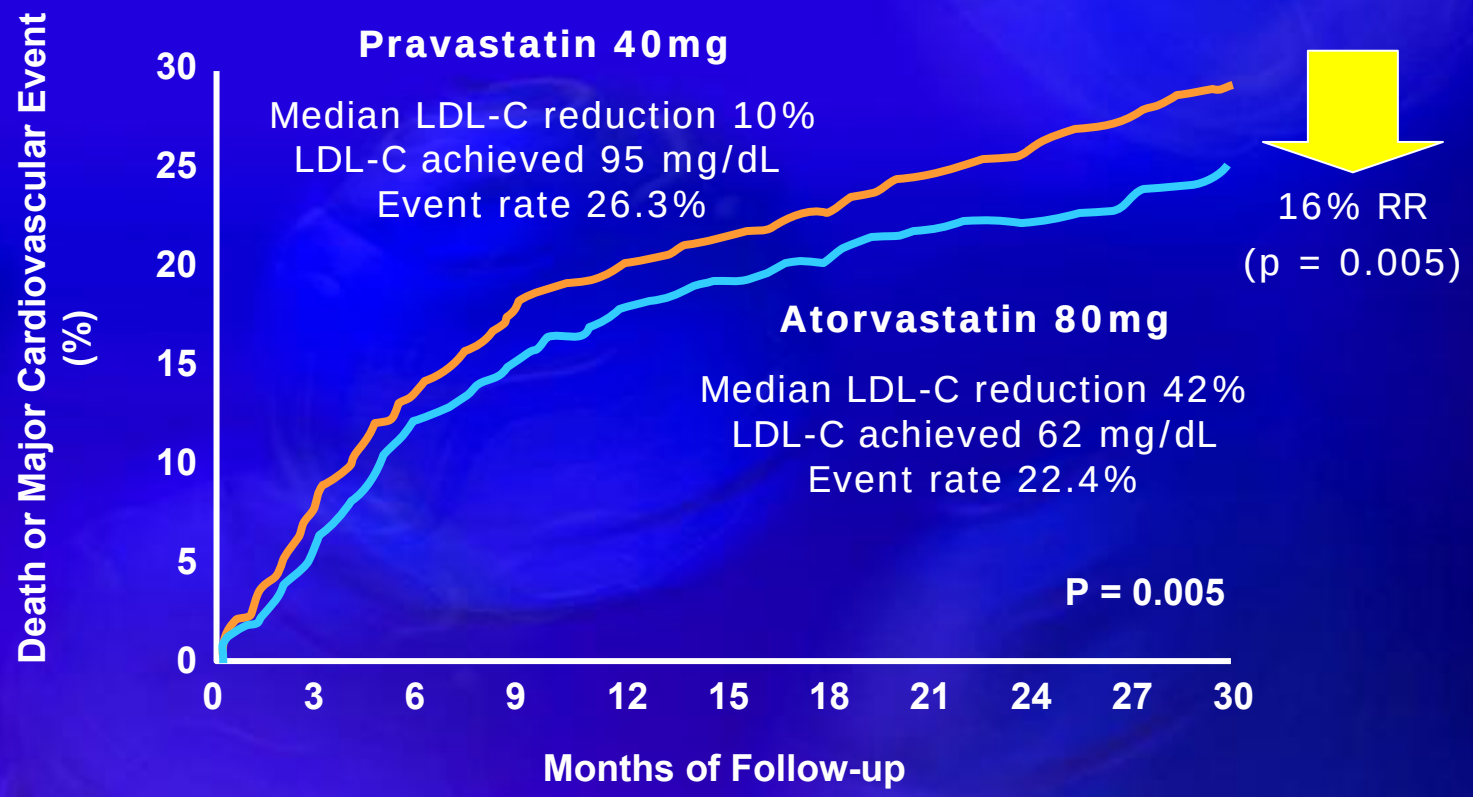
PROVE-IT/TIMI 22: Pravastatin 40 mg vs Atorvastatin 80 mg



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Cannon CP, et al. *N. Engl. J. Med*. 2004;350:1495-1504.

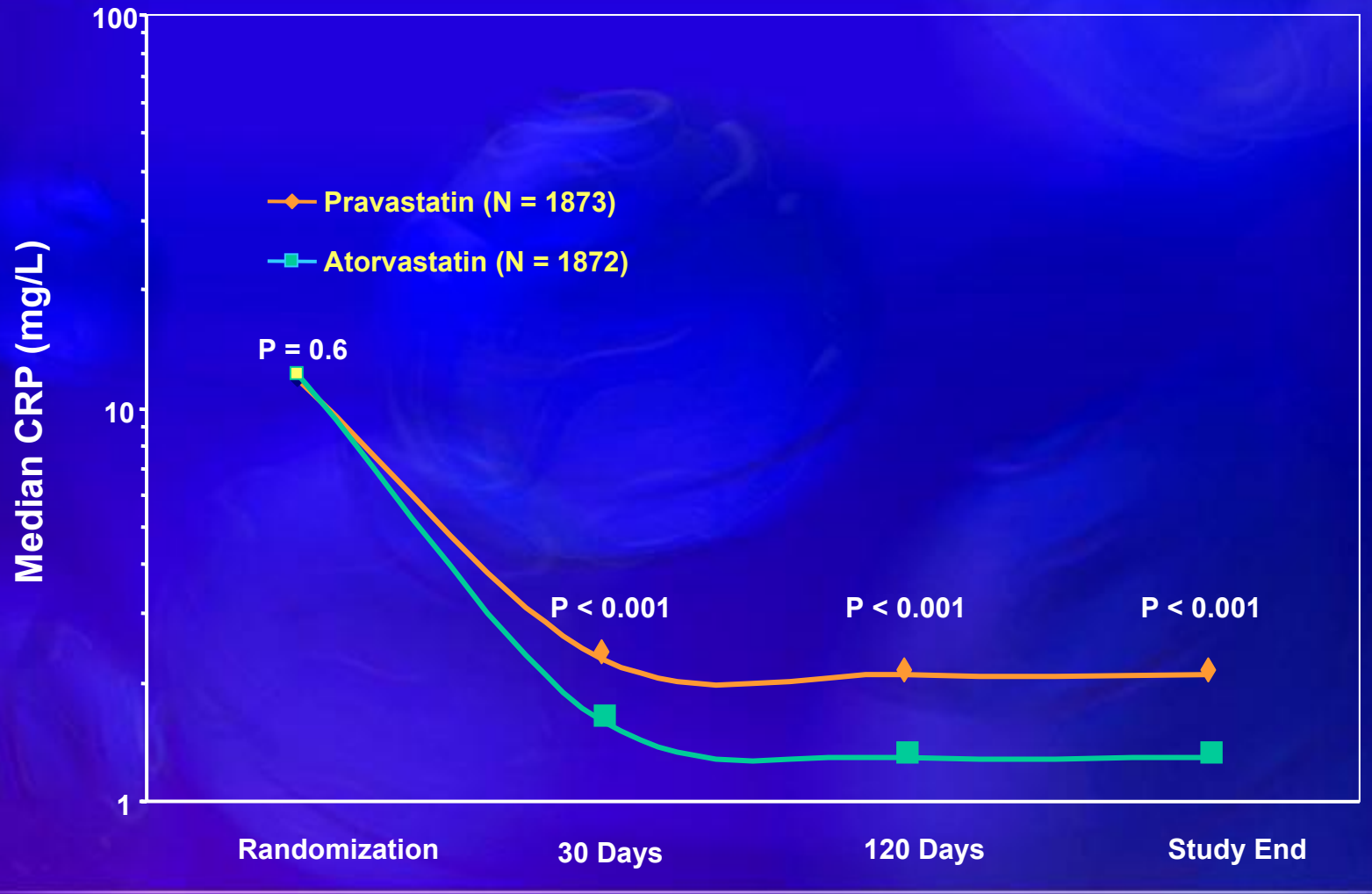
PROVE-IT/TIMI 22: Pravastatin 40 mg vs Atorvastatin 80 mg



No. at Risk						
Pravastatin	2063	1688	1536	1423	810	138
Atorvastatin	2099	1736	1591	1485	842	133

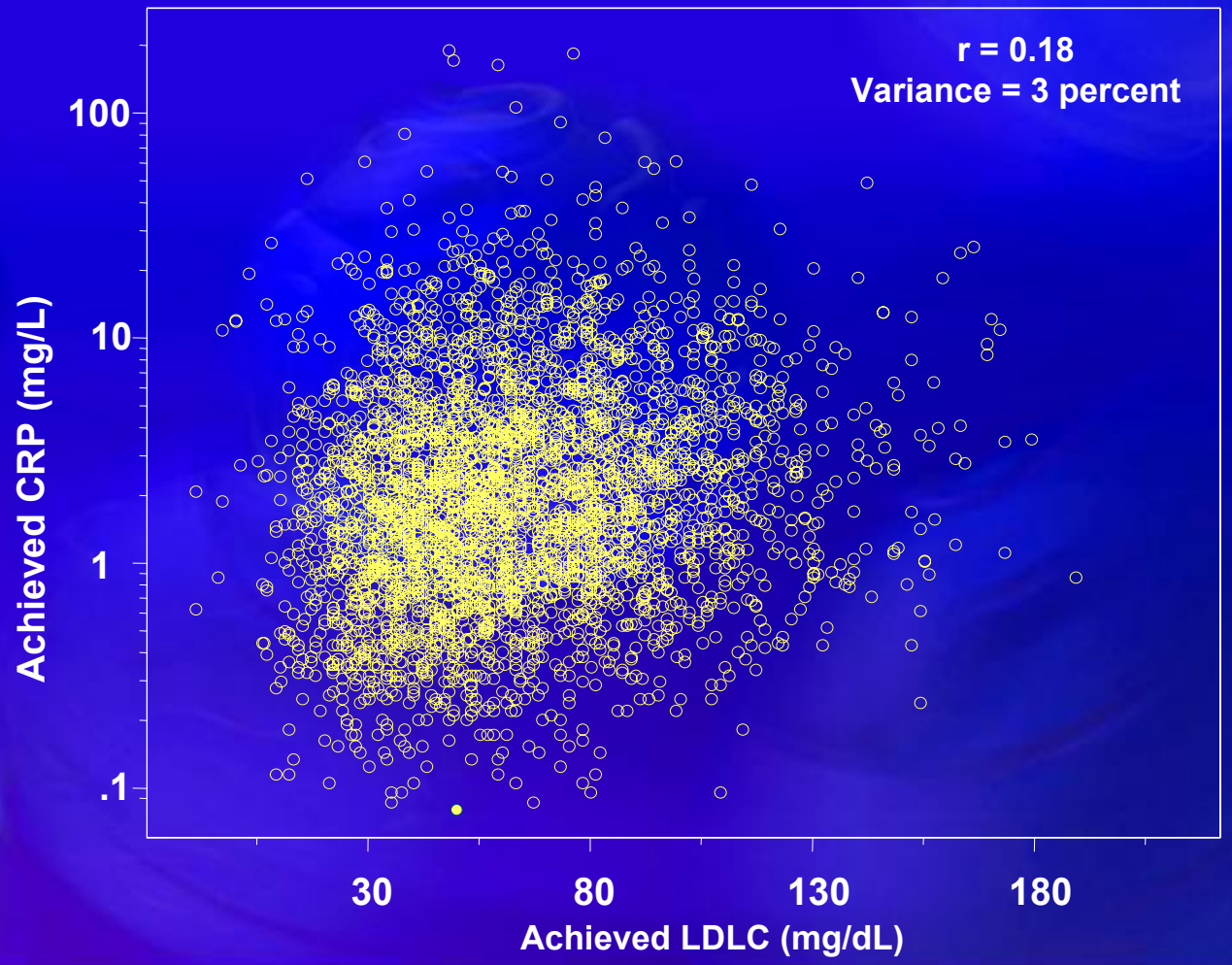
Cannon CP, et al. *N. Engl. J. Med*. 2004;350:1495-1504.

Median CRP Levels According to Treatment Arm Over Duration of Study: PROVE-IT



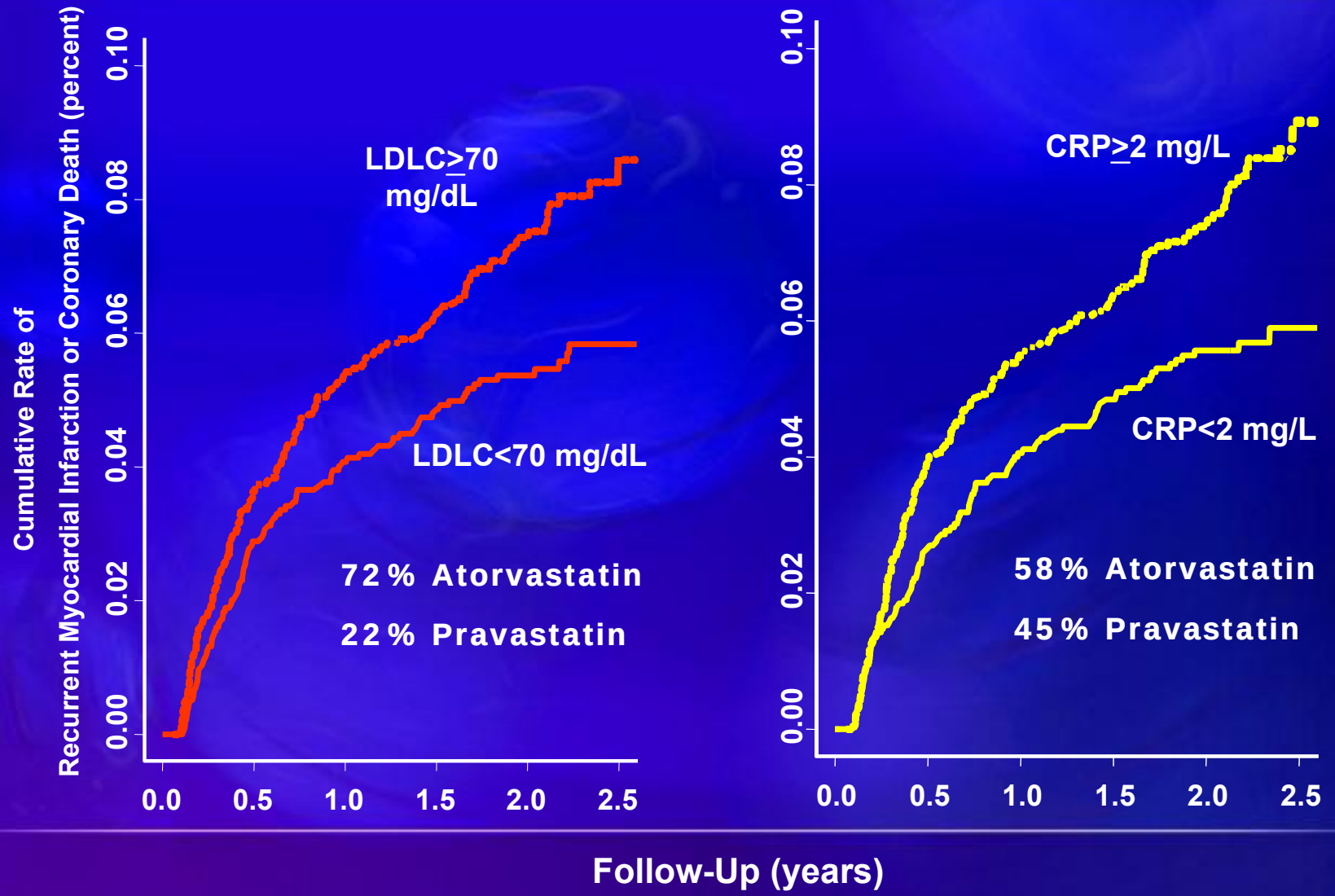
Ridker PM, et al. *N. Engl. J. Med*. 2005;352:20-28.

Minimal Relationship Between LDL and CRP After Initiation of Statin Therapy



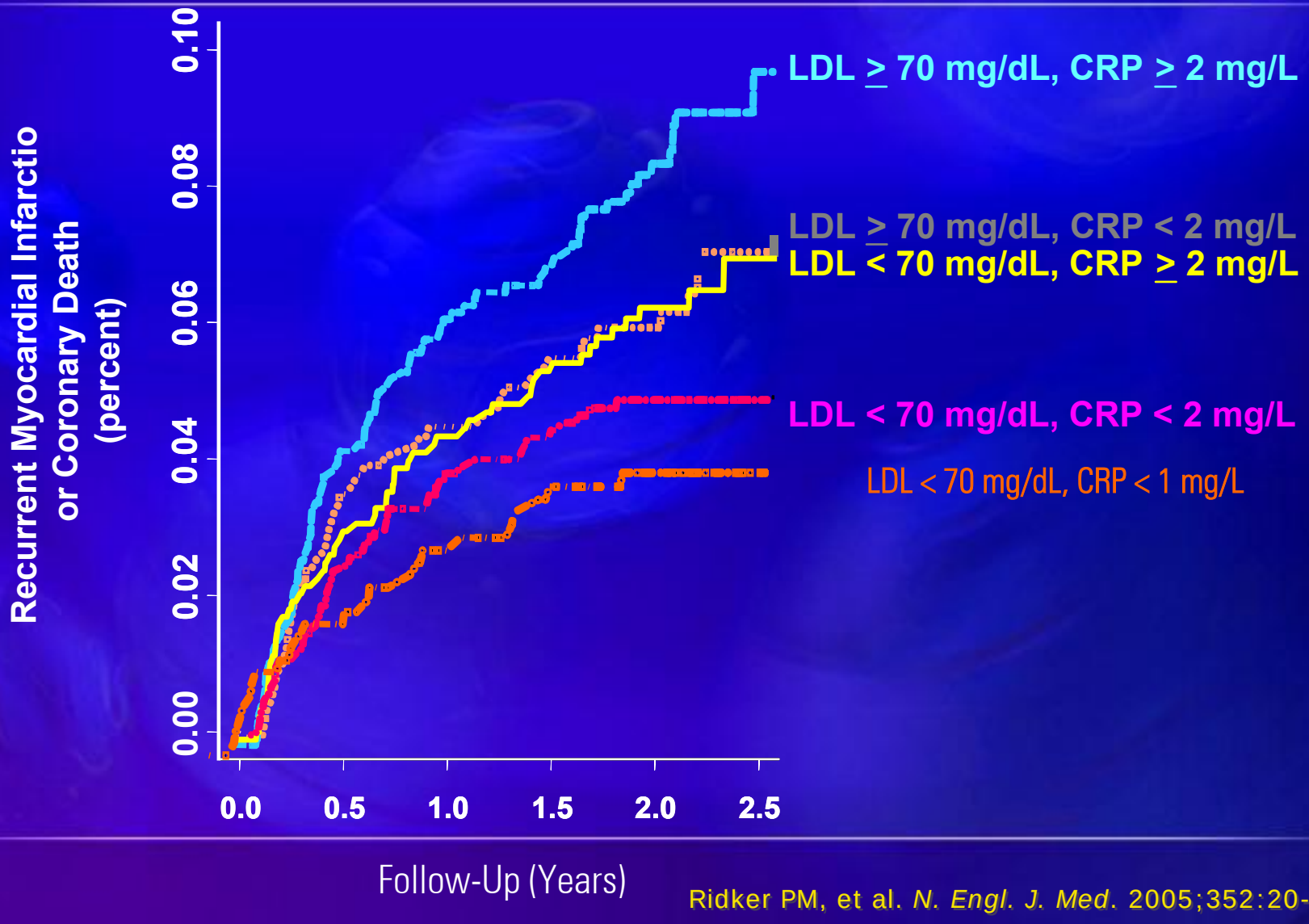
Ridker PM, et al. *N. Engl. J. Med*. 2005;352:20-28.

Clinical Relevance of LDL and CRP After Treatment with Statin Therapy



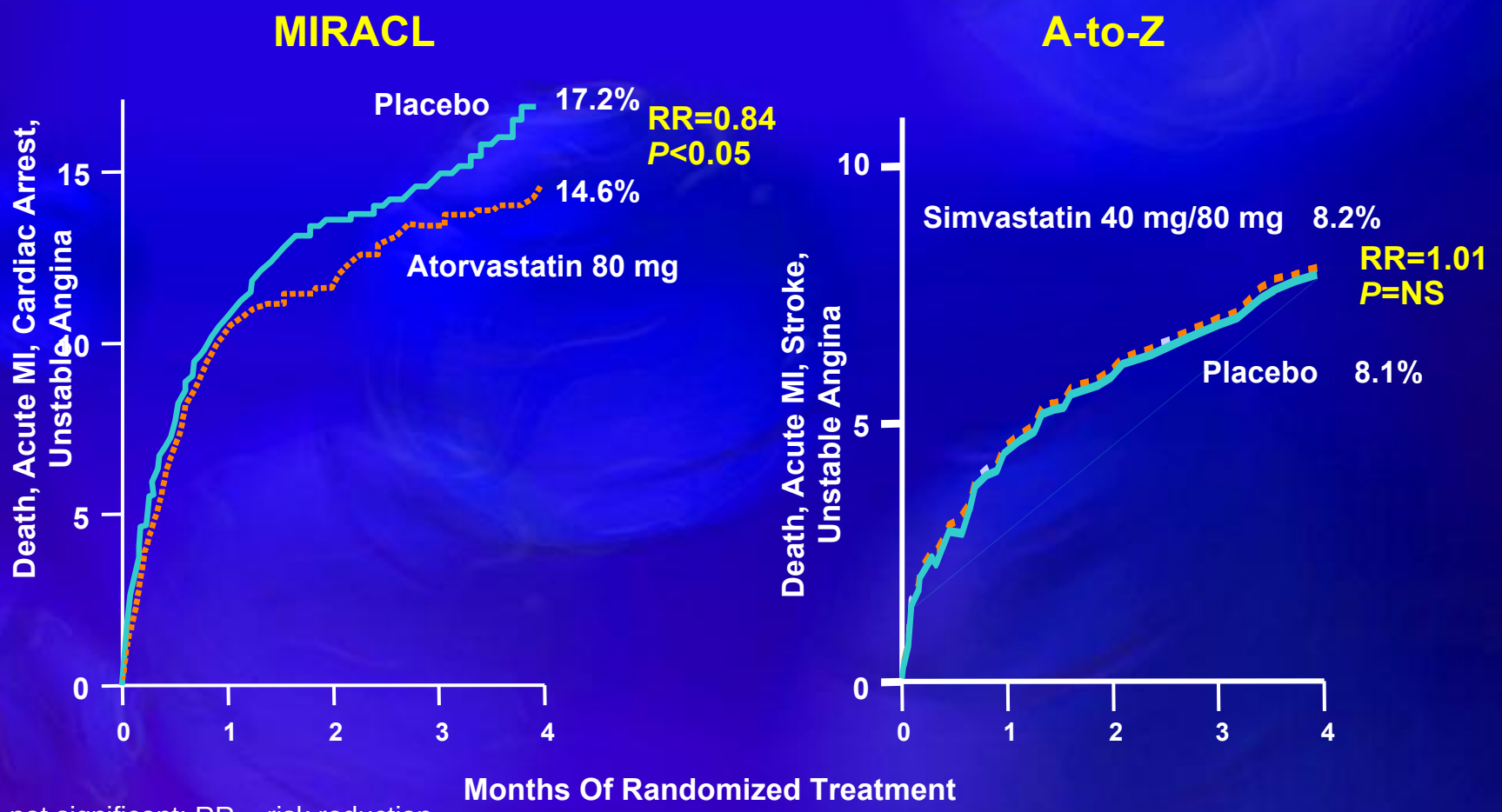
Ridker PM, et al. *N. Engl. J. Med*. 2005;352:20-28.

Clinical Relevance of LDL and CRP After Treatment with Statin Therapy



Ridker PM, et al. *N. Engl. J. Med.* 2005;352:20-28.

MIRACL: Intensive Statin Therapy Reduces Early Events After ACS



NS = not significant; RR = risk reduction.

Adapted from de Lemos et al. *JAMA*. 2004;292:1307, with permission.
Adapted from Schwartz et al. *JAMA*. 2001;285:1711, with permission.
Schwartz and Olsson. *Am J Cardiol*. 2005;96(suppl):45F.

A-to-Z and MIRACL: CRP Appears To Be Correlated With The Early Time To Benefit With Intensive Statin Therapy

	A-to-Z	MIRACL
Number of patients randomized	4497	3086
Early* LDL achieved on treatment, mg/dL	62	72
Early* LDL cholesterol differential, mg/dL	62	63
CRP differential, %	17	34
Early event reduction, %	0*	16*

* Measured 120 days after randomization.
CRP = C-reactive protein.
Adapted from Nissen. *JAMA*. 2004;292:1365, with permission.

PROVE IT-TIMI 22 And MIRACL: CRP Appears To Be Correlated With The Early Time To Benefit With Intensive Statin Therapy

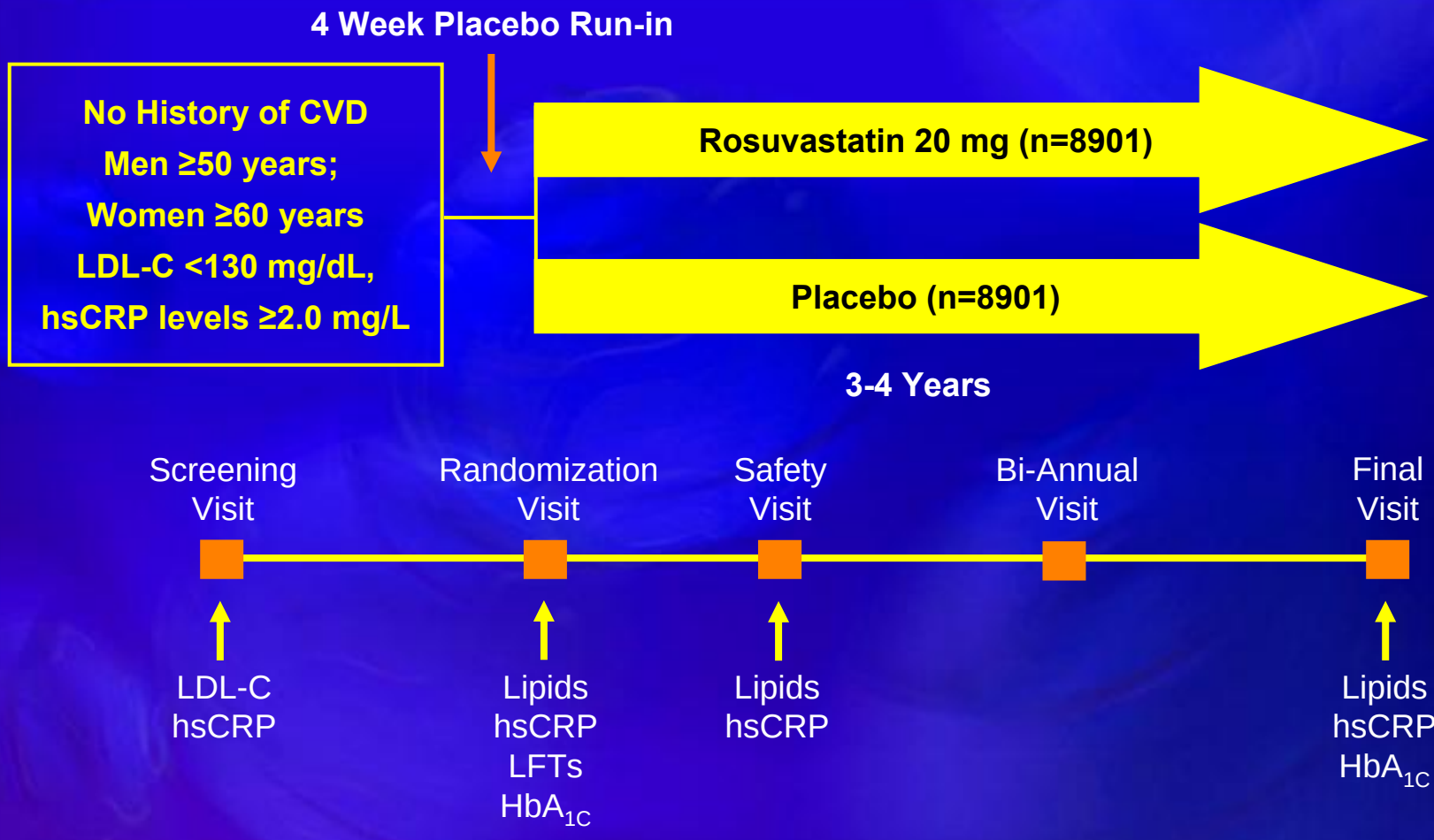
	A-to-Z	MIRACL	PROVE IT
Number of patients randomized	4497	3086	4162
Early* LDL achieved on treatment, mg/dL	62	72	62
Early* LDL cholesterol differential, mg/dL	62	63	33
CRP differential, %	17	34	38
Early event reduction, %	0*	16*	18†

* Measured 120 days after randomization.

† Measured 90 days after randomization.

Adapted from Nissen. *JAMA*. 2004;292:1365, with permission.

JUPITER Study Design



Ridker PM. *Circulation*. 2003;108:2292-2297.
Ridker PM et al. *Am J Cardiol*. 2007;100:1659-1664.

JUPITER: Baseline Characteristics

	Randomized (n=17,802)
Female, %	38.2
Age (range), years	66.3 (60.9-71.8)
Race, %	
Caucasian	71.3
Black	12.5
Asian	1.6
Hispanic	12.7
Other	2.0
Body mass index (range), kg/m^2	28.4 (25.3-32.0)
Blood pressure (range), mmHg	
Systolic/Diastolic	134 (124-145)/80 (75-87)
Smoker, %	15.8

All values are percent or median (interquartile range)

Ridker PM et al. *Am J Cardiol*. 2007;100:1659-1664.

JUPITER: Baseline Laboratory Parameters

	Randomized (n=17,802)
Total cholesterol, mg/dL	185 (169-200)
LDL-C, mg/dL	108 (94-119)
HDL-C, mg/dL	49 (40-60)
Non-HDL-C, mg/dL	134 (118-147)
Triglycerides, mg/dL	118 (85-169)
hsCRP, mg/L	4.3 (2.8-7.1)
Glucose, mg/dL	94 (88-102)
HbA_{1c}, %	5.7 (5.5-5.9)

Values expressed as median (interquartile range). For hsCRP, values are the mean of the screening and randomization visits.
LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; HbA_{1c}=glycosylated hemoglobin

Ridker PM et al. *Am J Cardiol*. 2007;100:1659-1664.

AstraZeneca Disclosure Regarding the JUPITER Study

- On March 31, 2008, AstraZeneca announced that the JUPITER study will be stopped early based on a recommendation from the Independent Data Monitoring Board and the JUPITER Steering Committee, which met on March 29, 2008
- The recommendation to stop the trial is based on unequivocal evidence of a reduction in cardiovascular morbidity and mortality among patients who received rosuvastatin when compared to placebo
- No further information is available at this time

AstraZeneca Website. Crestor Outcomes Study JUPITER Closes Early Due To Unequivocal Evidence Of Benefit. Available at: http://www.astrazeneca.com/pressrelease/5385.aspx. Accessed on March 31, 2008.

Current Concepts Regarding Surrogate Markers and Risk Stratification

- Aggressive lipid lowering is beneficial in the secondary prevention of cardiovascular disease or in patients at high risk.
- Some of the beneficial effects of statin therapy may be due to its non-cholesterol lowering or pleiotropic effects on inflammation.
- Inflammation is an important component of atherosclerosis and cardiovascular disease. Cardiovascular risk reduction with statin therapy depends not only on achieved LDL-C levels, but also on achieved CRP levels.
- Prospective primary prevention trial in patients with low LDL and systemic inflammation (JUPITER) suggests that hsCRP may be a useful surrogate marker in identifying patients who may benefit from statin therapy.