Effects of HMG-CoA Reductase Inhibitors on Inflammation and Endothelial Function

Dr. R. Preston Mason

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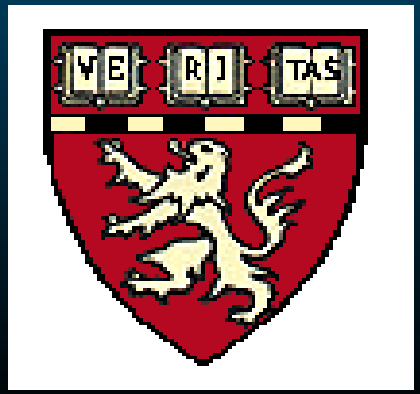
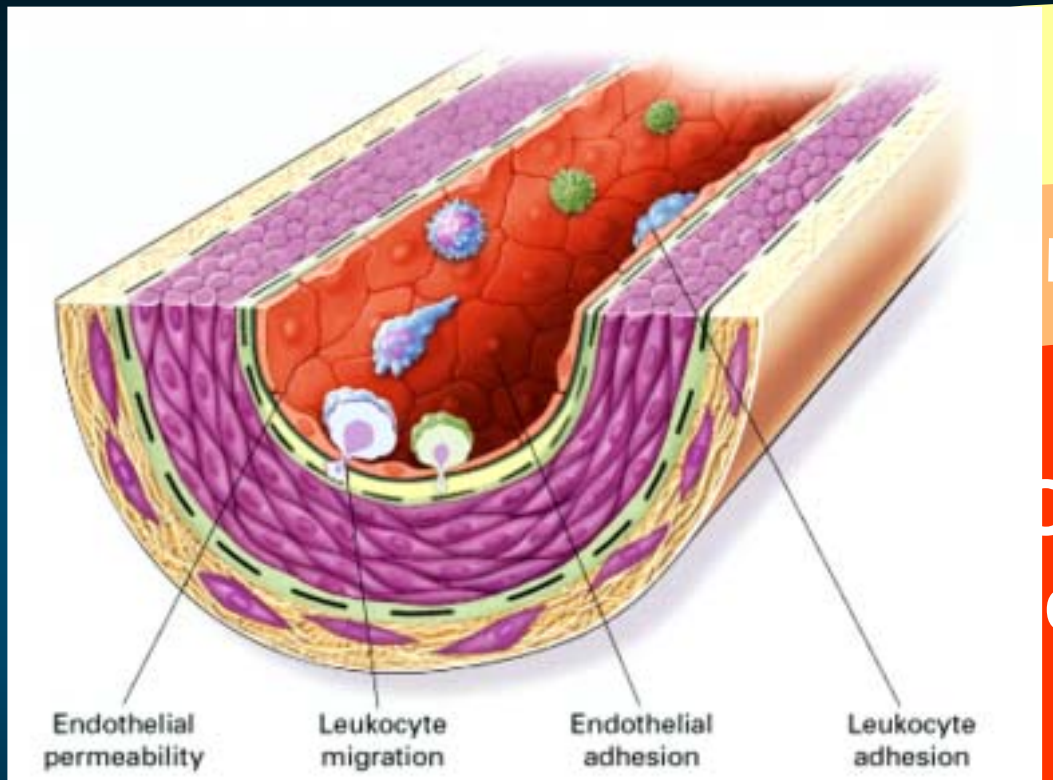


Integrated Perspective on CV Risk Factors and Vascular Disease



Ross R. *N Engl J Med*. 1999;340:115-126

Endothelial Dysfunction

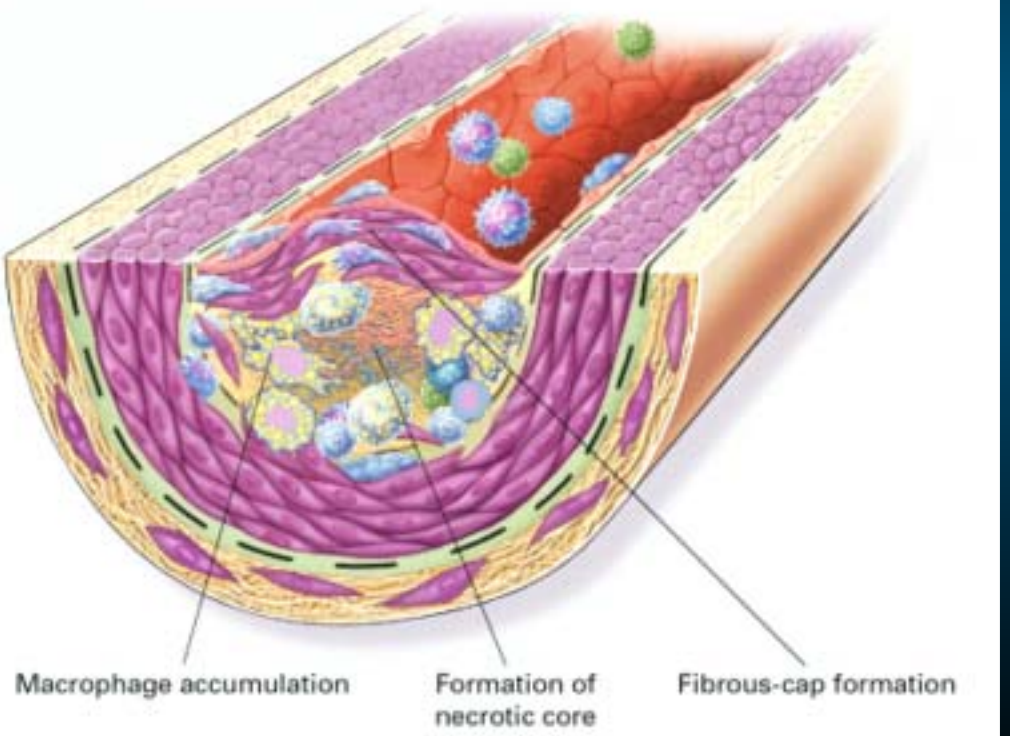
Dyslipi

Dysfun

Oxidative Stress & Inflammation

Diabete

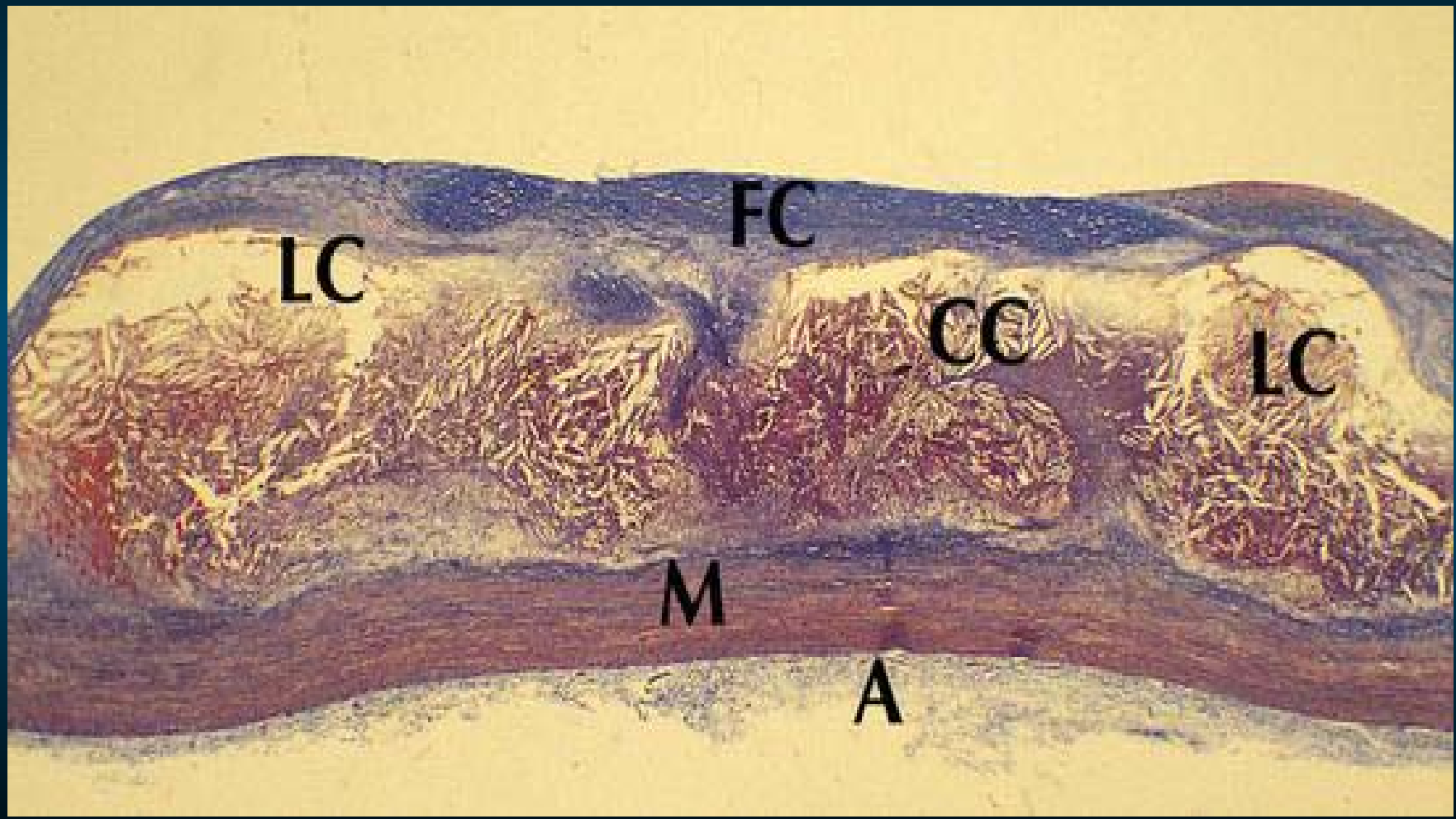
Inflam



Ross R. *N Engl J Med*. 1999;340:115-126

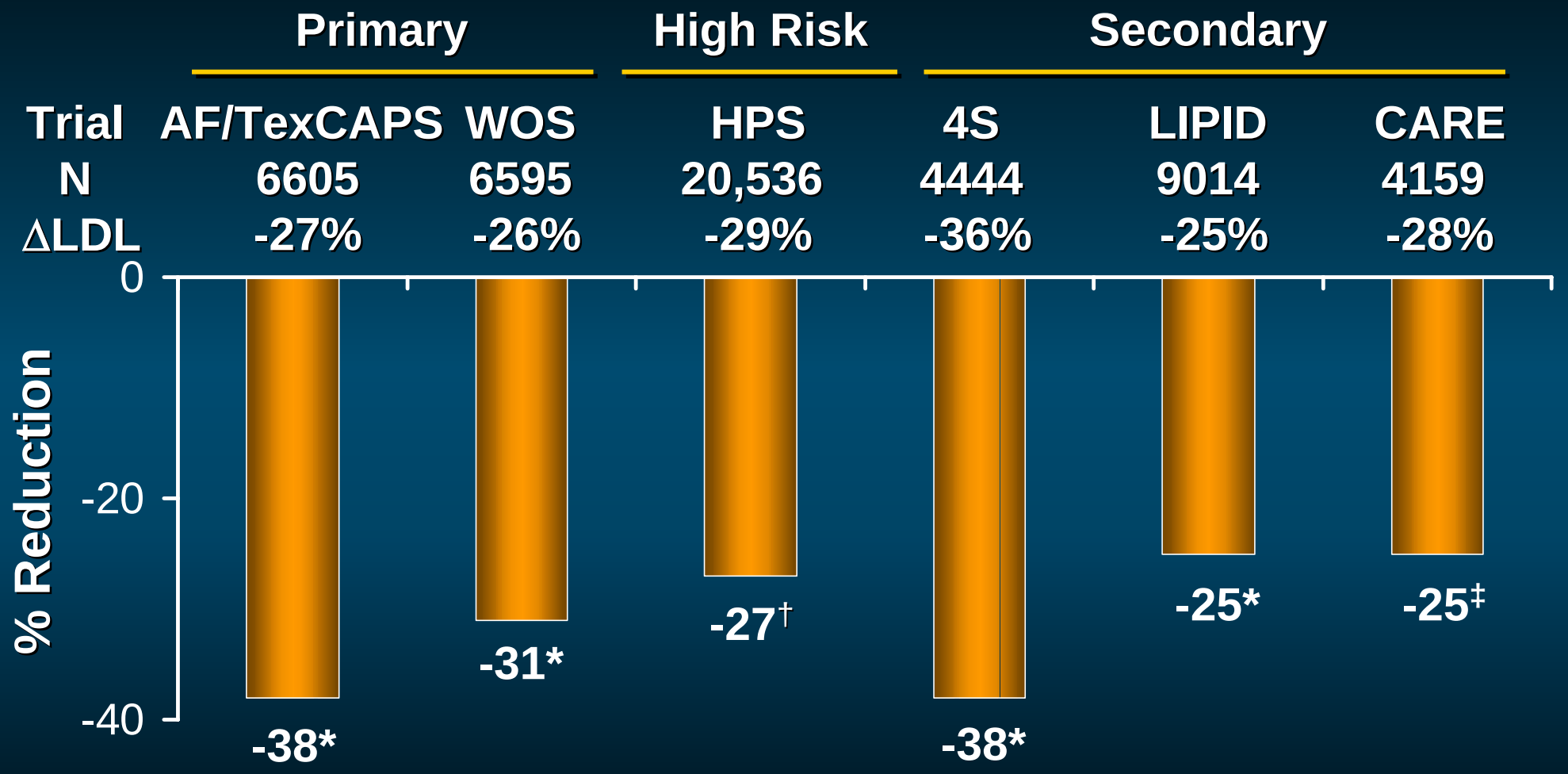
RP Mason and RF Jacob

An Established Fibrofatty Plaque with Excessive Lipid Core



Statins Reduce Morbidity and Mortality with Atherosclerosis

Reduction in Major Coronary Events: Statin Trials



*P<0.001; †P<0.0001; ‡P=0.002.

HPS Collaborative Group. *Lancet*. 2002;360:7-22; LaRosa et al. *JAMA*. 1999;282:2340-2346.

The Forgotten Majority

Study	Deaths *Not* Prevented
4S	70%
WOSCOPS	78%
CARE	80%

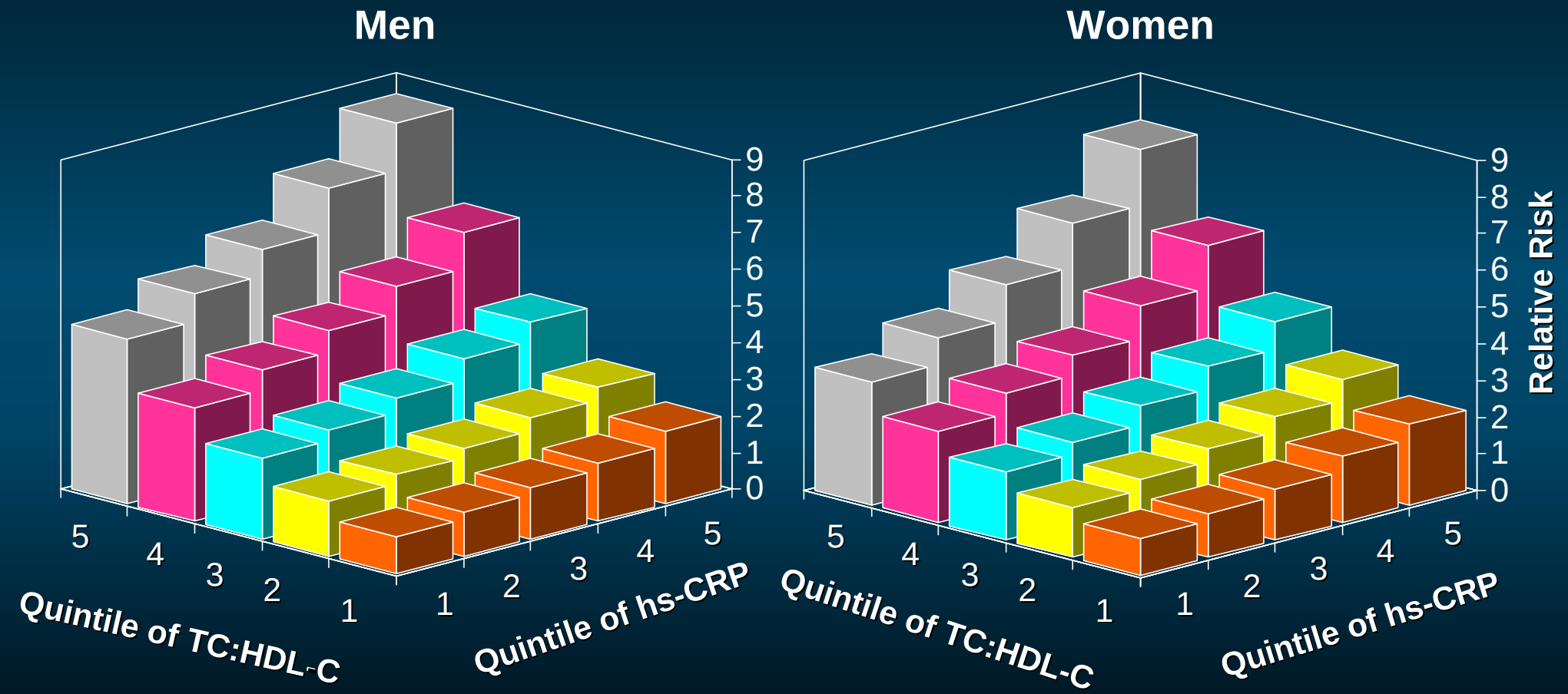
P Libby

The Challenge of Residual Morbidity and Mortality due to Atherosclerotic Disease

Beyond LDL

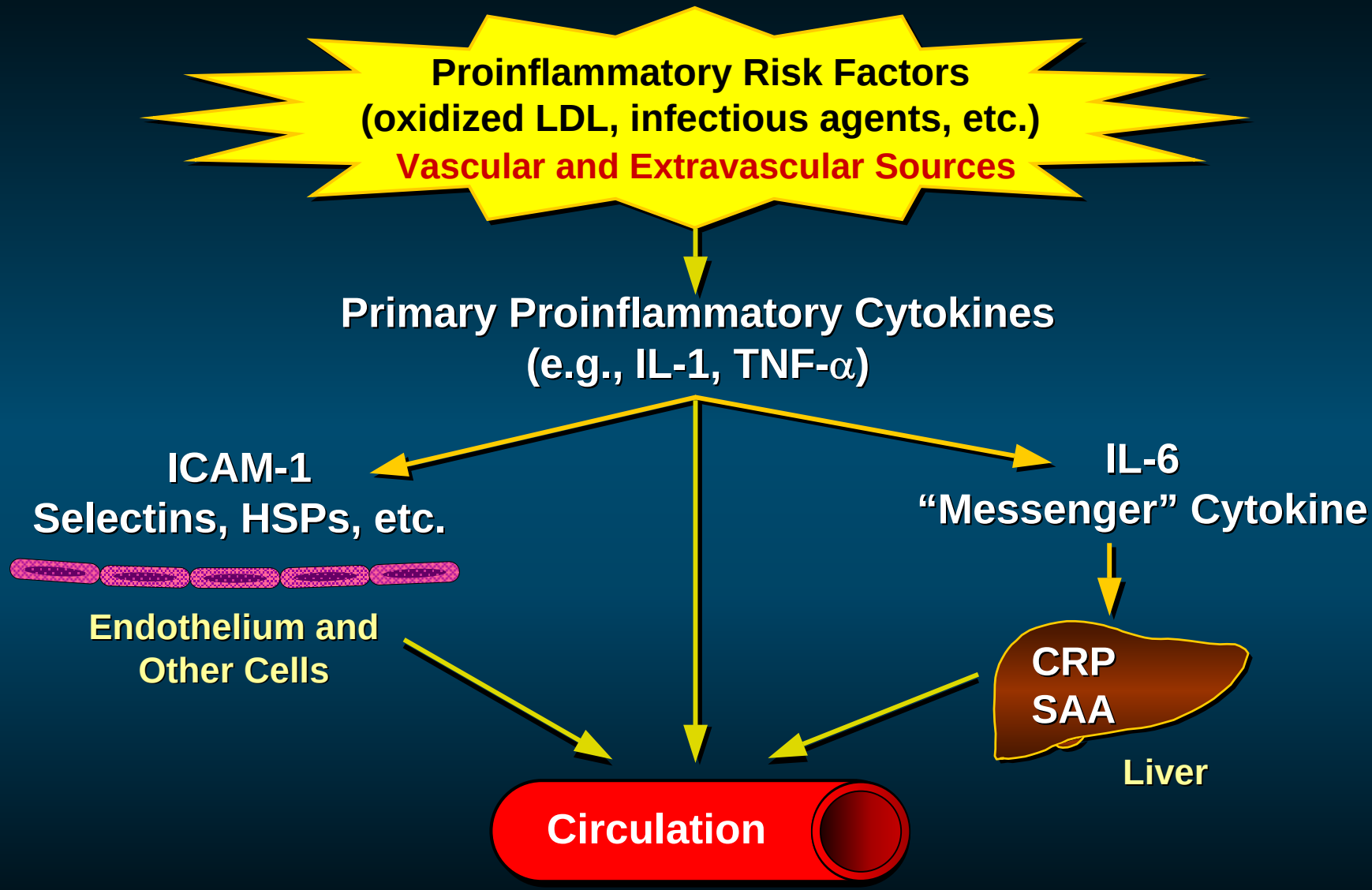
Statins and Inflammation: CRP Additive With Lipids

Data From NHANES



Ridker. *Circulation*. 2001;103:1813-1818.

Inflammatory Markers of Coronary Risk

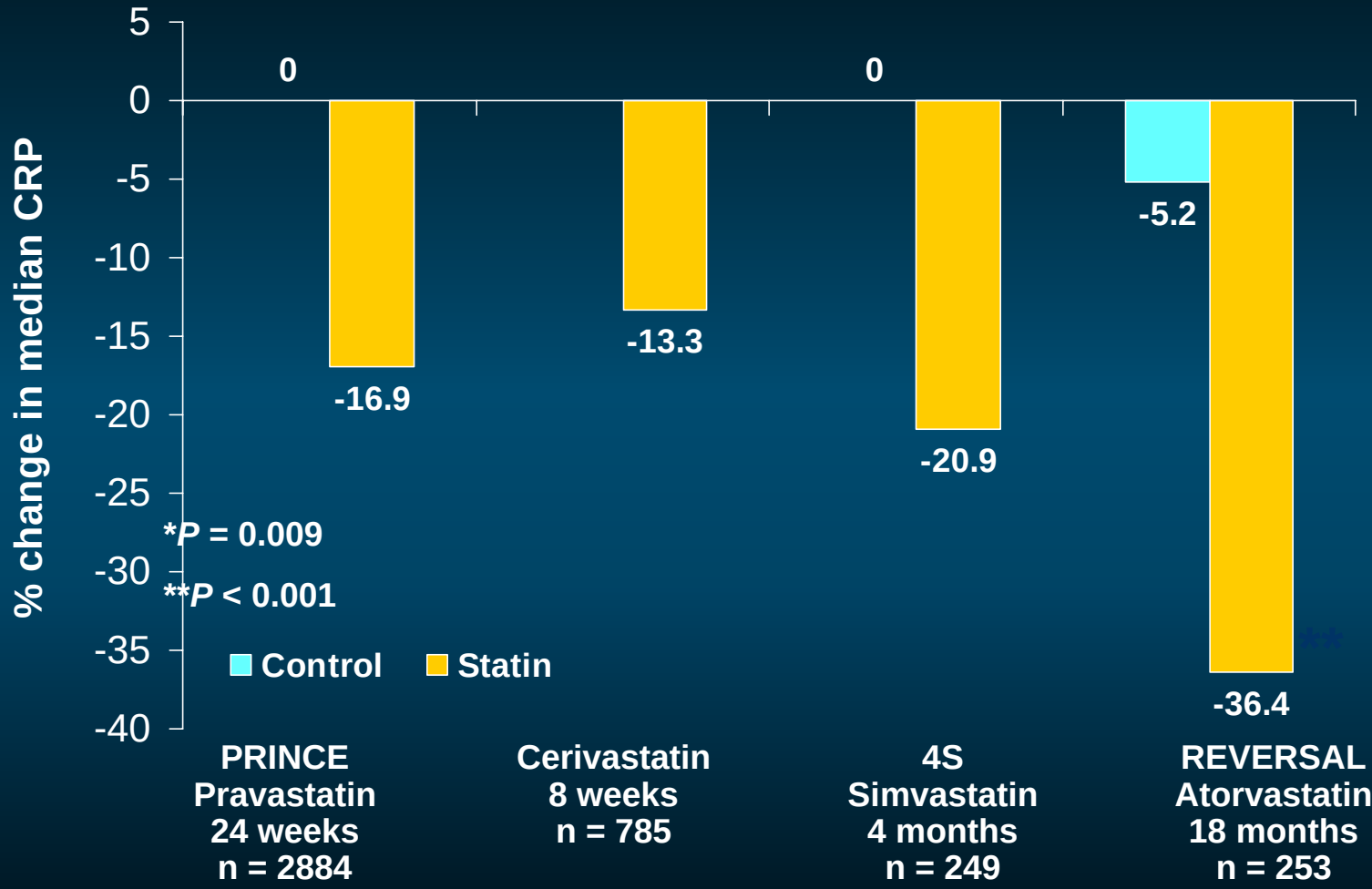


Libby and Ridker. *Circulation*. 1999;100:1148-1150.

Statins have Anti-inflammatory Actions:

A Novel Mechanism of Action

Statin Therapy and hsCRP



Albert MA, et al. *JAMA.* 2001;286:64-70; Ridker PM, et al. *Circulation*. 2001;103:1191-1193; Crea F, et al. *Clin Cardiol.* 2002;25:461-466; Nissen SE, et al. *JAMA.* 2004;291:1071-1080.

Lipophilic Statins have Anti-inflammatory Actions that Accelerate Benefit

SUPPLEMENT TO VOLUME 96, NUMBER 5

The American Journal of Cardiology®

SEPTEMBER 5, 2005

Time to Benefit in Lipid-Lowering Trials

GUEST EDITORS:
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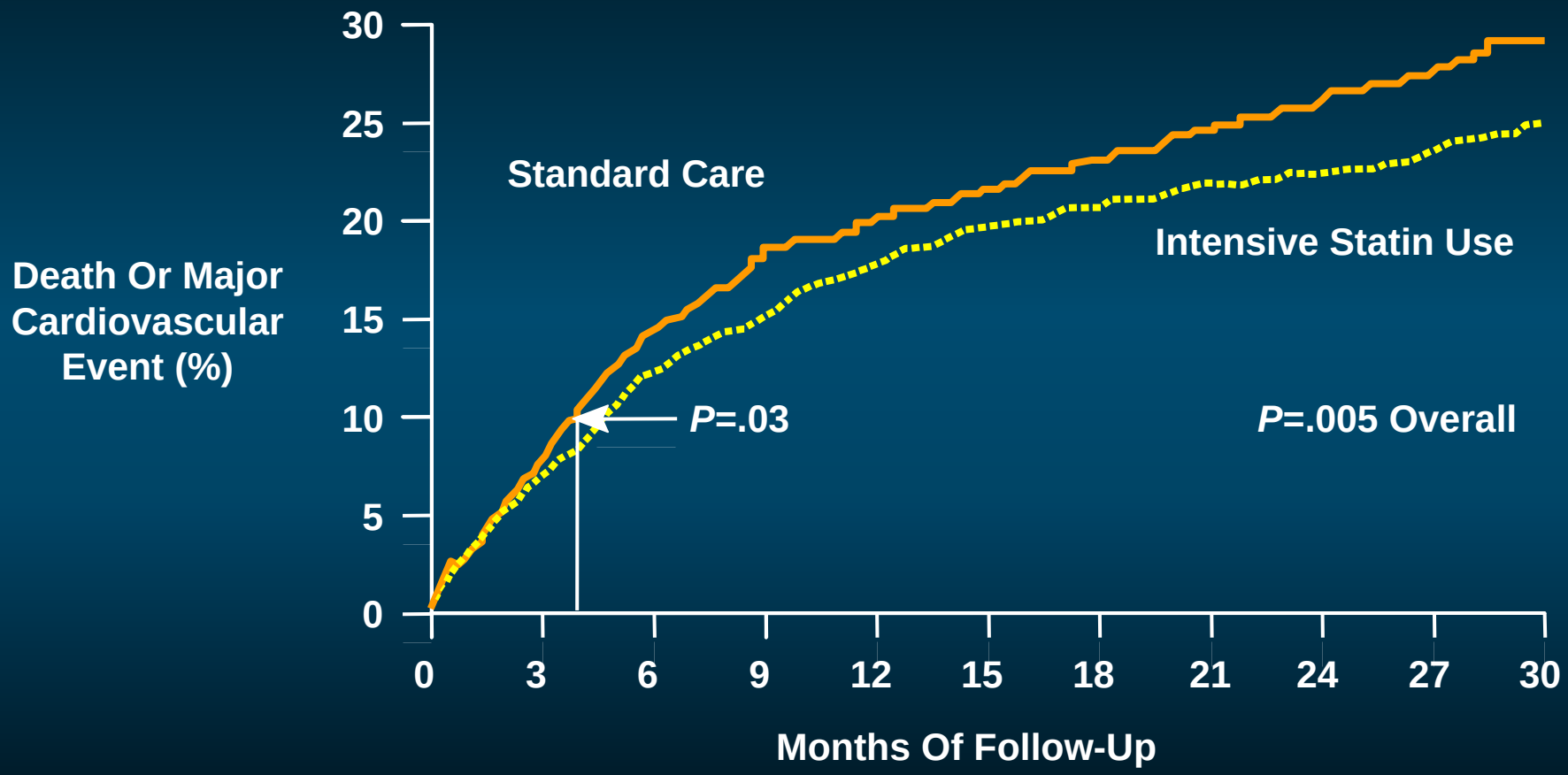
PROVE IT-TIMI 22
Study Design

- N = 4162
- Randomized to standard (40 mg/day pravastatin) or intensive (80 mg/day atorvastatin) therapy for 2 years
- Primary outcome: composite of time to all-cause mortality, MI, unstable angina requiring hospitalization, revascularization ≥30 days after randomization, and stroke

Cannon et al. *N Engl J Med*. 2004;350:1495.

PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause

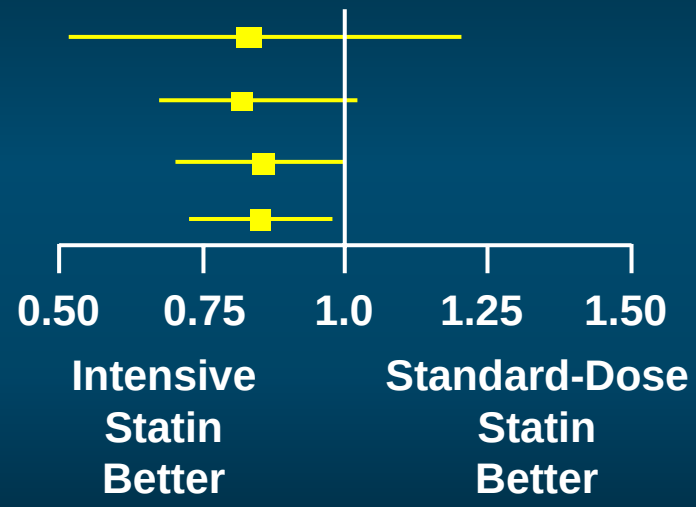
Primary End Point



Adapted from Cannon et al. *N Engl J Med*. 2004;350:1495, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause At Different Censoring Times

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction (%)	Event Rate (%)	
			Intensive	Standard
30 days		17	1.9	2.2
90 days		18	6.3	7.7
180 days		14	12.2	14.1
End of follow-up		16	22.4	26.3

Reproduced from Cannon et al. *N Engl J Med*. 2004;350:1495, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

PROVE IT-TIMI 22: Effect Of Different Statin Regimens On LDL Cholesterol And CRP

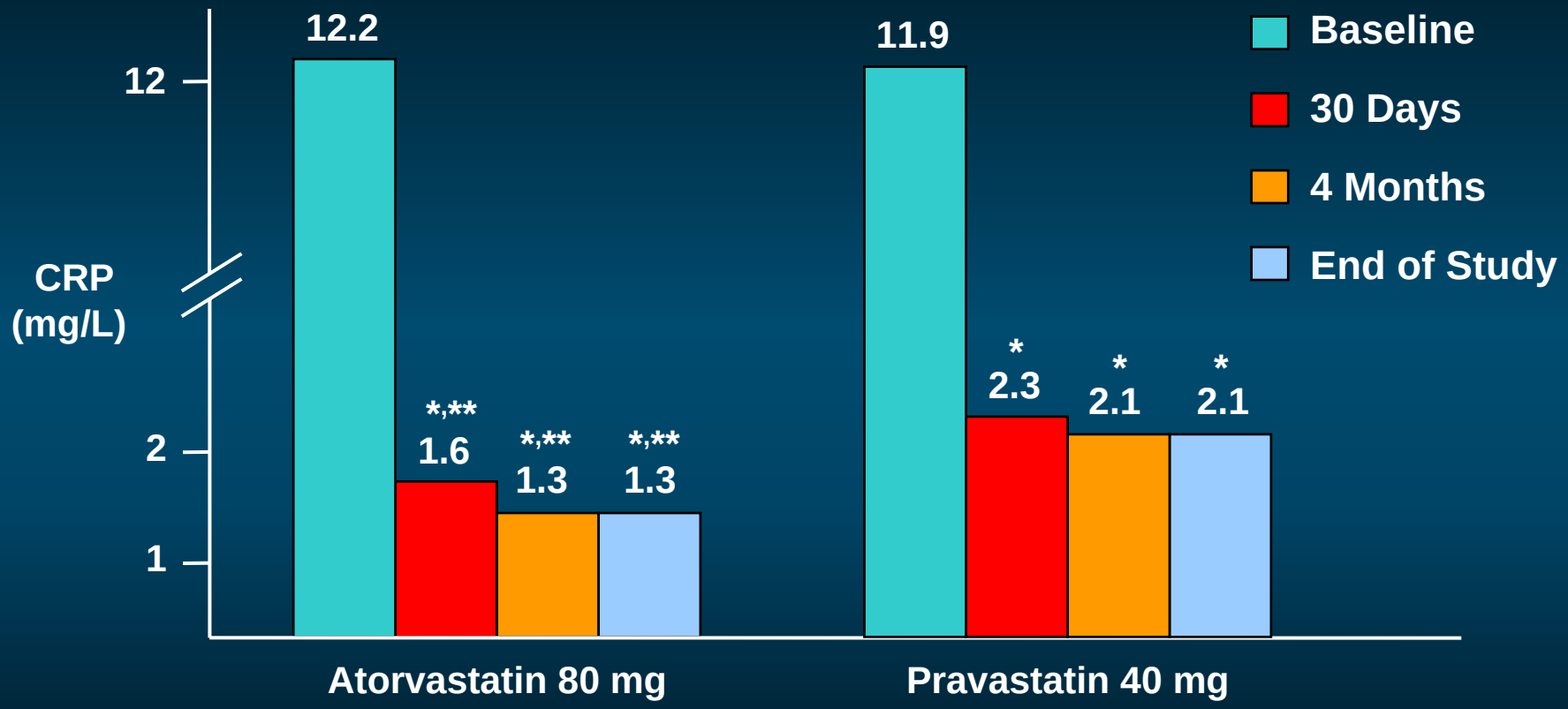
Biological Response	Statin Regimen	Baseline	30 Days	4 Months
LDL mg/dL (mean)	Standard	106	88	97
	Intensive	106	60	67
	P value	NS	<.001	<.001
CRP mg/L (median)	Standard	11.9	2.3	2.1
	Intensive	12.2	1.6	1.3
	P value	NS	<.001	<.001

Cannon et al. *N Engl J Med*. 2004;350:1495.

Ridker et al. *N Engl J Med*. 2005;352:20.

Reproduced from Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F, with permission.

PROVE IT-TIMI 22: CRP Levels At Enrollment And During Follow-Up



* *P*<.001 vs baseline.

** *P*<.001 vs pravastatin.

Ridker et al. *N Engl J Med*. 2005;350:20.

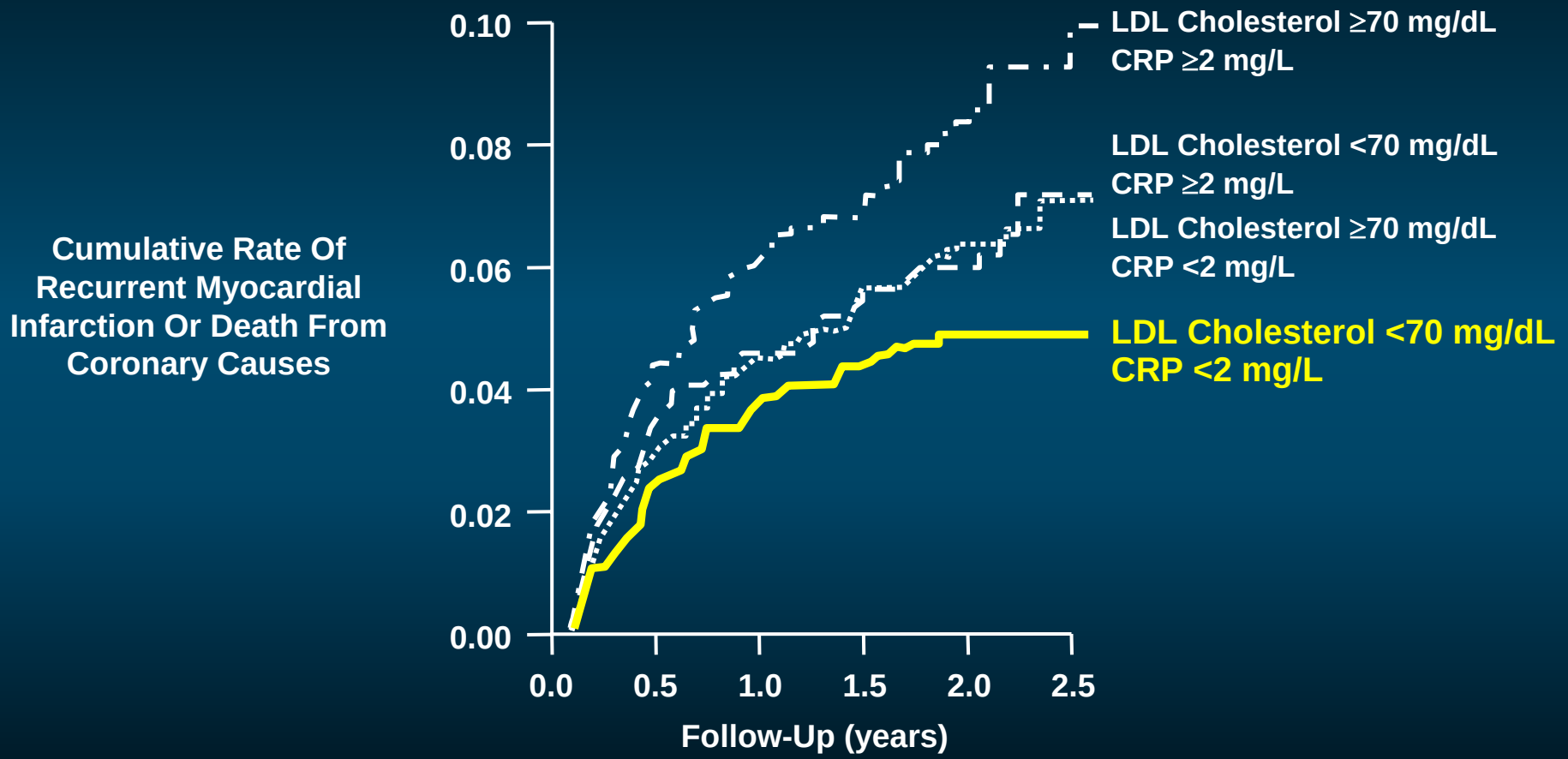
Reproduced from Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F, with permission.

PROVE IT-TIMI 22: Relationship Between CRP And Clinical Outcomes

- CRP is a clinical marker of inflammation
- CRP as an independent predictor of cardiovascular risk may be more important than LDL
- Early and large decreases in CRP following intensive statin therapy (80 mg/day atorvastatin) were closely related to reduced morbidity and slower progression of atherosclerosis

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

PROVE IT-TIMI 22: Prognostic Value Of 30-Day Achieved LDL And CRP On Recurrent MI Or Death From Cardiovascular Causes



Reproduced from Ridker et al. *N Engl J Med*. 2005;352:20, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

PROVE IT-TIMI 22

Conclusions

- Intensive statin therapy with resulted in apparent clinical benefit observed as early as 30 days
- Significant reduction in all-cause mortality, MI, unstable angina, revascularization ≥30 days, and stroke apparent at 4 months (*P*=.03)
- Additional benefits gained in patients with concurrent reductions in CRP beyond LDL reduction

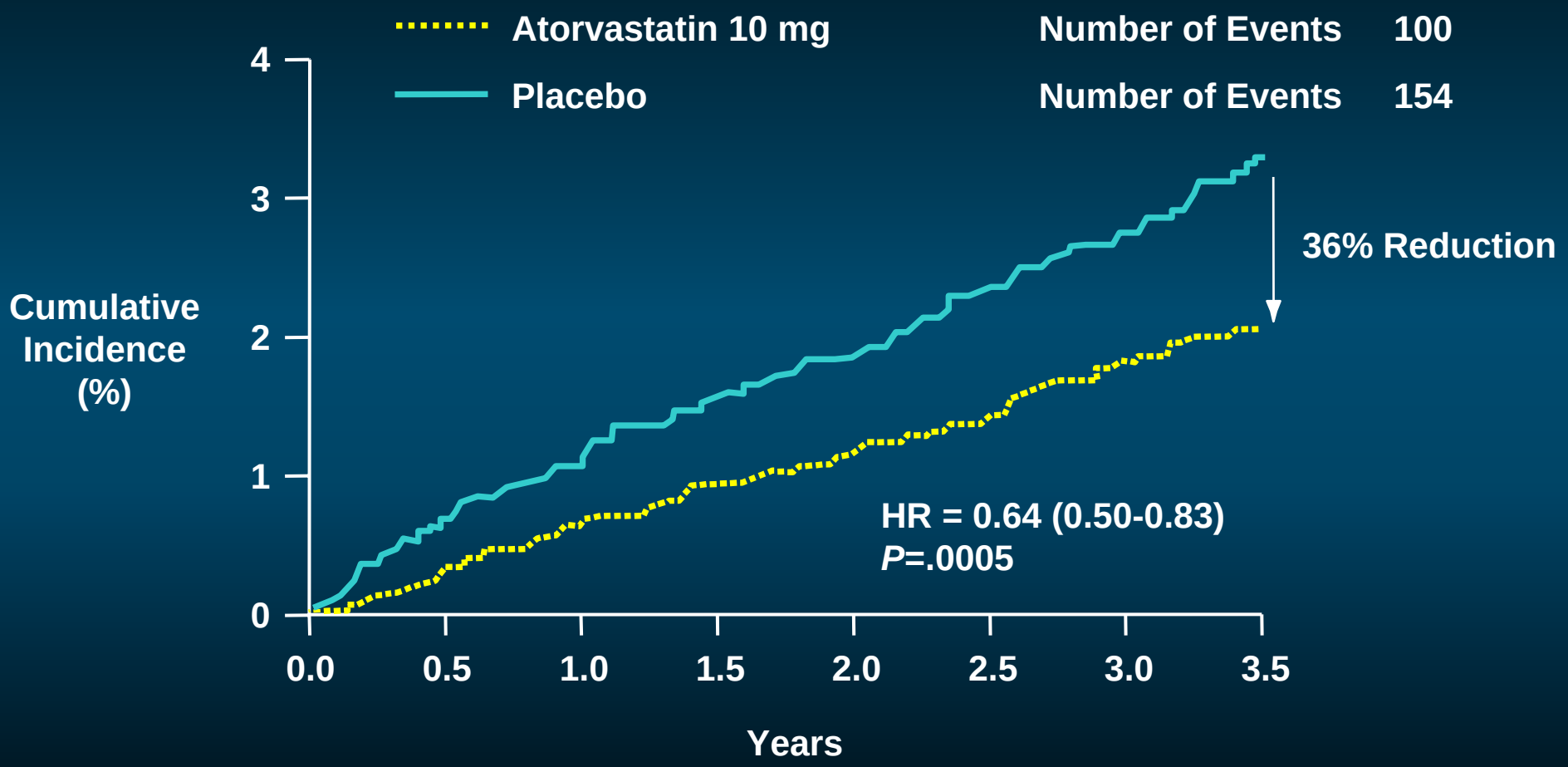
ASCOT-LLA
Study Design

- N = 10,305
- Randomized to atorvastatin 10 mg/d or placebo for 5 years (stopped after 3.3 years)
- Primary outcome: time to first nonfatal MI and fatal CAD

Sever et al. *Lancet*. 2003;361:1149.

ASCOT-LLA: Nonfatal MI And Fatal CAD

Primary End Point

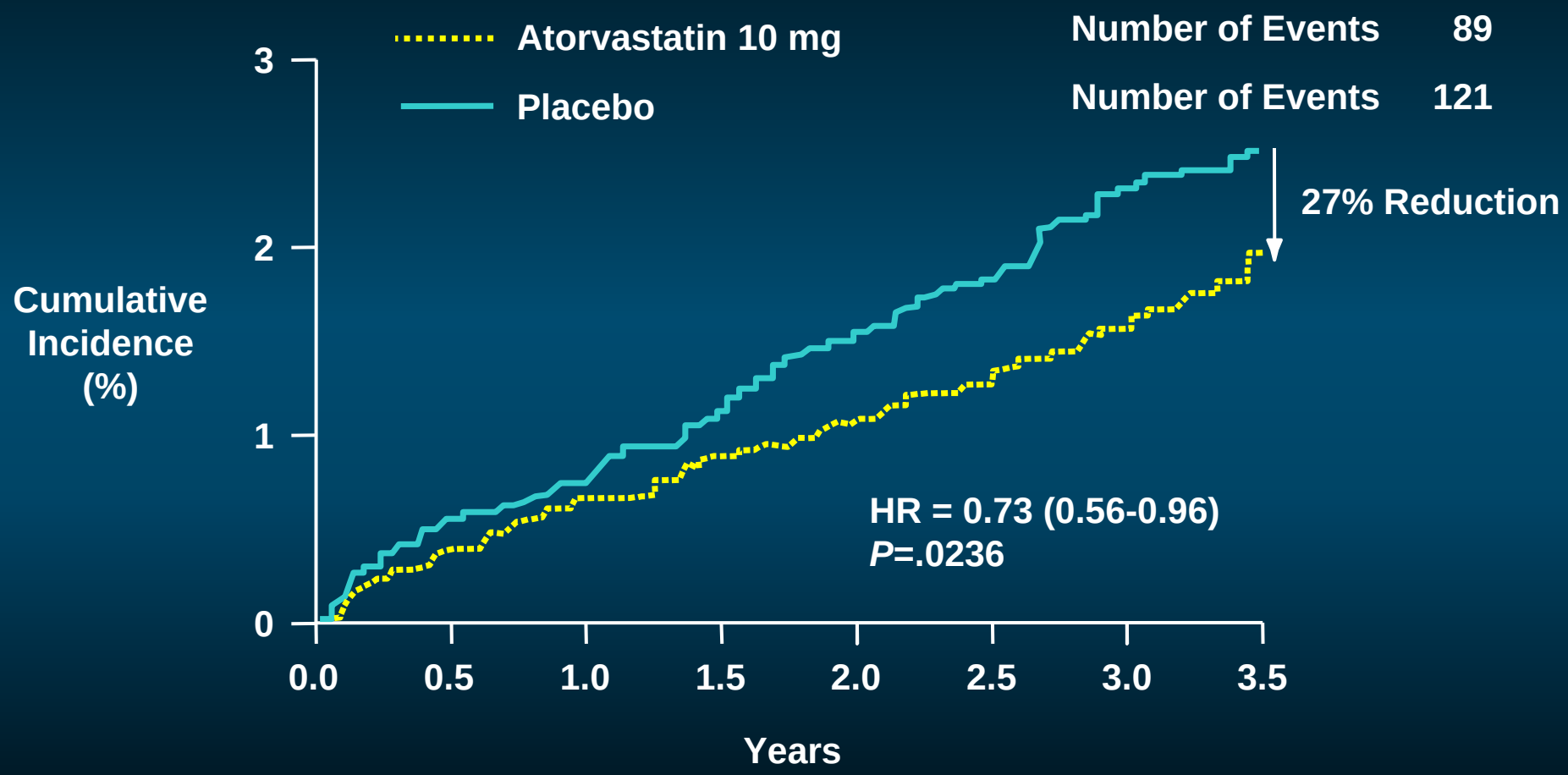


Adapted from Sever et al. *Lancet*. 2003;361:1149, with permission.

Sever et al. *Am J Cardiol*. 2005;96(suppl):39F.

ASCOT-LLA: Fatal And Nonfatal Stroke

Secondary End Point



HR = hazard ratio.

Adapted from Sever et al. *Lancet*. 2003;361:1149, with permission.

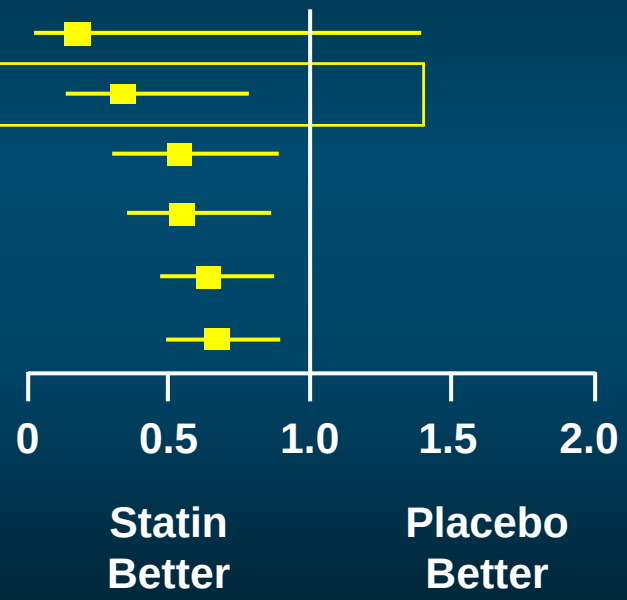
Sever et al. *Am J Cardiol*. 2005;96(suppl):39F.

ASCOT-LLA
Post Hoc Analysis Of Time To Benefit

- To assess benefit at specific time points (30 days, 90 days, 180 days, 1 y, 2 y, end of study), cumulative hazard ratio was calculated at different censoring times
- Time to 1st primary end point event in the atorvastatin and placebo groups was compared in an intention-to-treat basis
- Log-rank procedure and Cox proportional hazards model was used to calculate confidence interval

Sever et al. *Am J Cardiol*. 2005;96(suppl):39F.

ASCOT-LLA Time-To-Benefit Analysis: Cardiac Events



Censoring Time	Hazard Ratio (95% CI)	Risk Reduction (%)	Event Rate*	
			Statin	Placebo
30 days		83	2.4	14.2
90 days		67	5.5	16.6
180 days		48	7.5	14.3
1 year		45	6.6	12.0
2 years		38	5.9	9.5
End of study		36	6.0	9.4

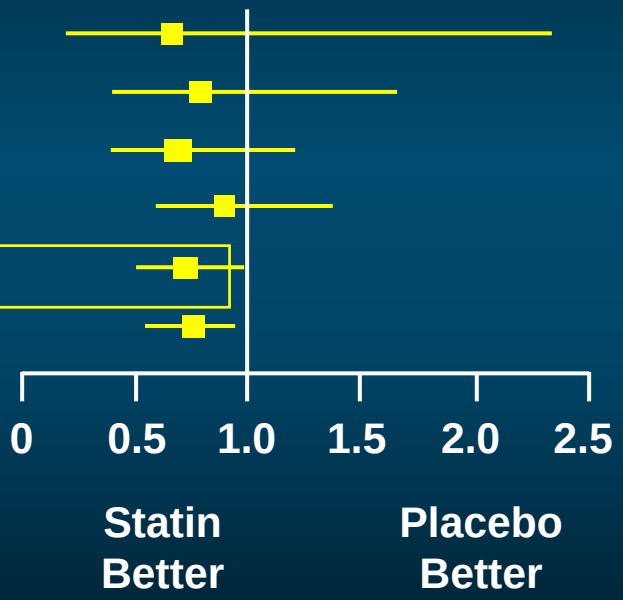
* Per 1000 patient-years.

CI = confidence interval.

Reproduced from Sever et al. *Am J Cardiol*. 2005;96(suppl):39F, with permission.

ASCOT-LLA Time-To-Benefit Analysis: Stroke Events

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction (%)	Event Rate*	
			Statin	Placebo
30 days		34	9.4	14.3
90 days		19	10.2	12.7
180 days		31	7.9	11.5
1 year		11	6.6	7.5
2 years		29	5.5	7.7
End of study		27	5.4	7.4



* Per 1000 patient-years.

Reproduced from Sever et al. *Am J Cardiol*. 2005;96(suppl):39F, with permission.

ASCOT-LLA Time-To-Benefit Analysis

Conclusions

- CAD risk reduction with atorvastatin occurred much earlier than expected based on lipid-lowering effects only
  - CAD relative risk reduction with statin was noticeable at 30 days and was significant at 3 months (*P*=.008) and through termination of trial (3.3 years)
  - stroke relative risk reduction with statin was noticeable at 30 days, and was significant at 2 years (*P*=.05) and termination (*P*=.02)

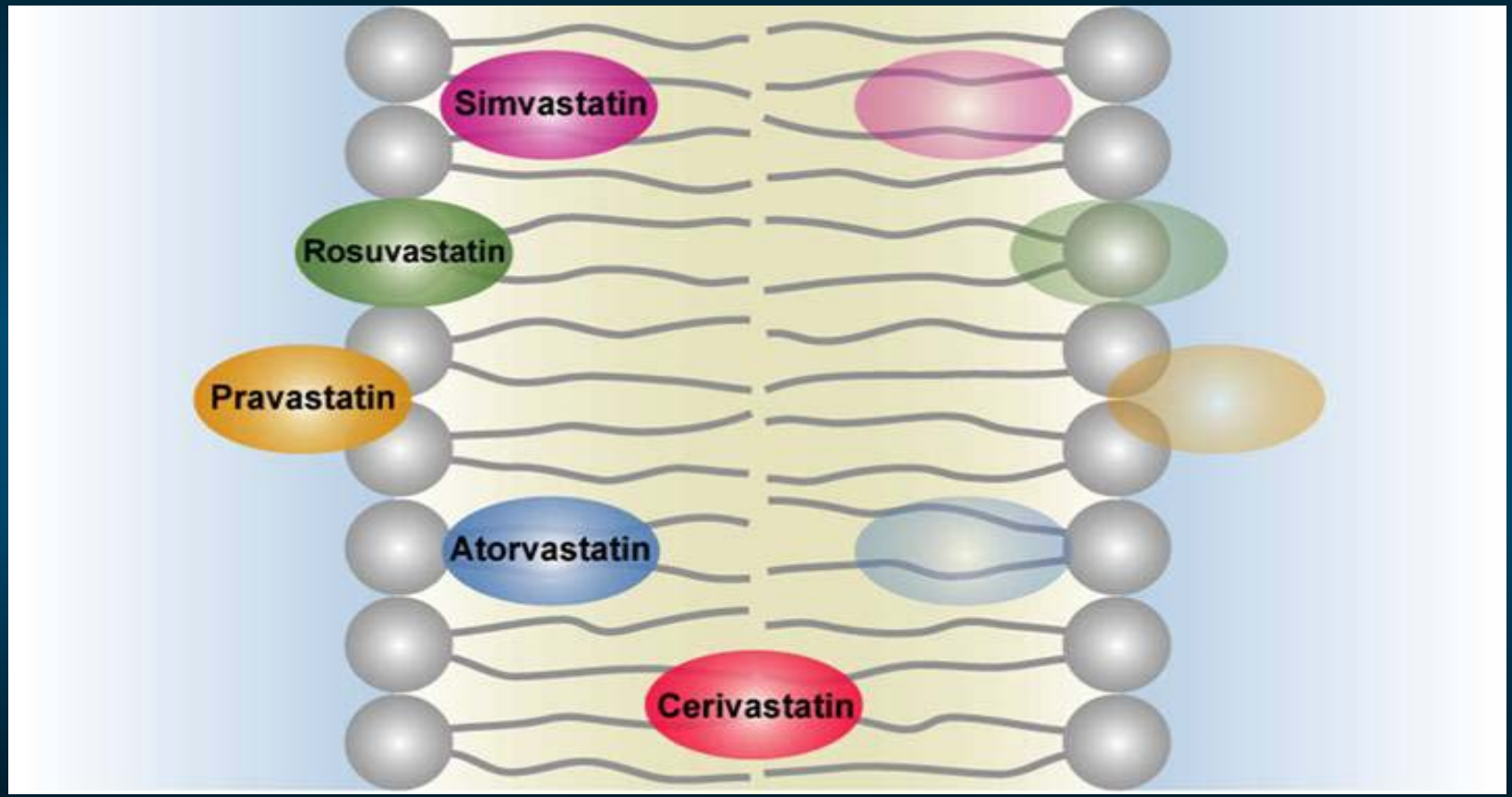
Intermolecular Differences of Statins Contribute to Distinct Actions

Intermolecular Similarities And Differences Of Statins

- Intermolecular similarities
  - all statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase
  - all statins share a common dihydroxy group necessary for HMG-CoA reductase enzyme inhibition
- Intermolecular difference
  - substituents on pharmacophore moiety are responsible for pharmacokinetic and pharmacodynamic differences, which in turn affect efficacy, safety, and pleiotropic effects

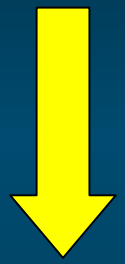
Mason et al. *Am J Cardiol*. 2005;96(suppl):11F.

Equilibrium Molecular Locations Of Statins Based On X-Ray Diffraction Analysis



Reproduced from Mason et al. *Am J Cardiol*. 2005;96(suppl):11F, with permission.

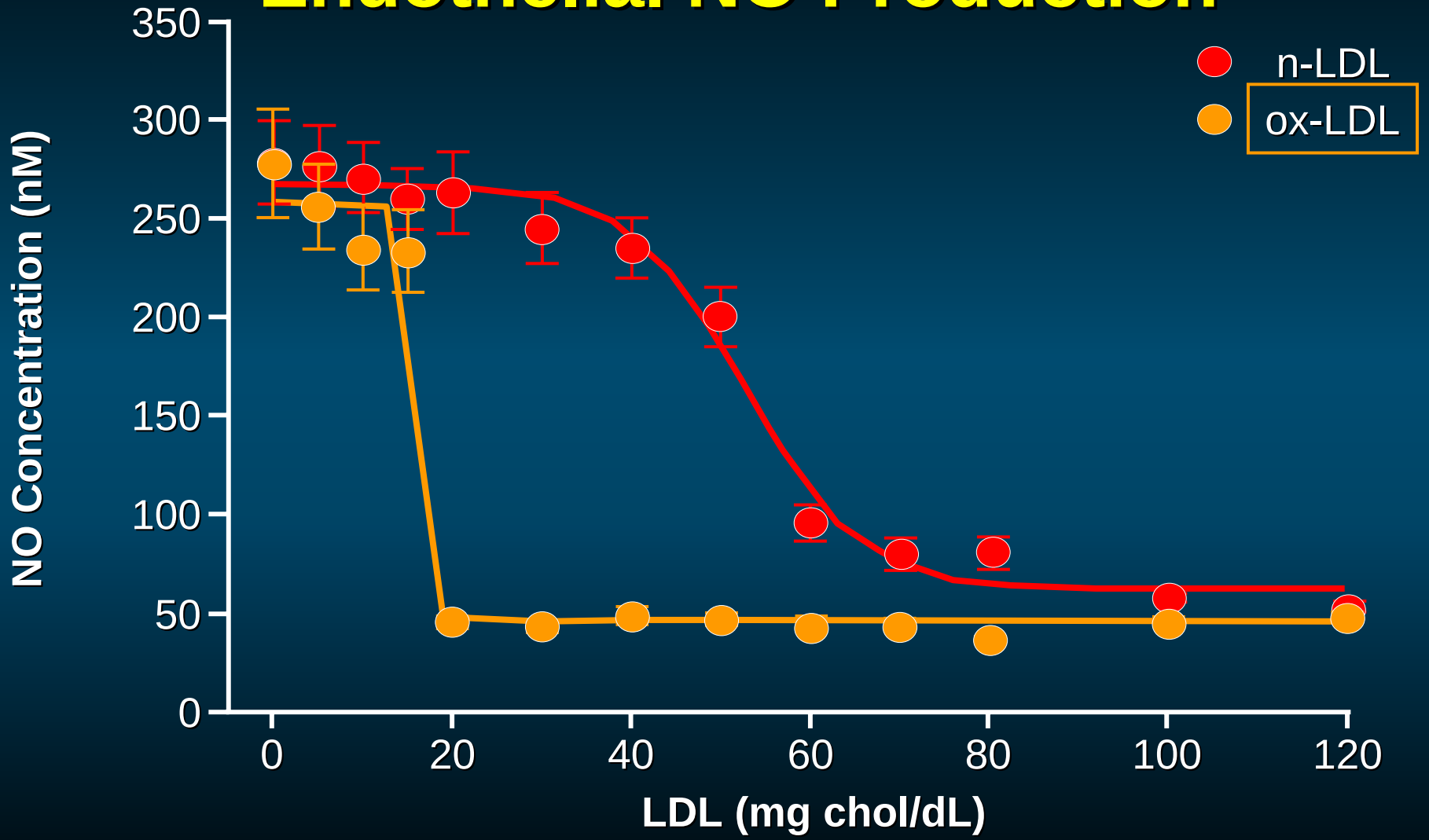
Oxidative Stress



Endothelial Dysfunction

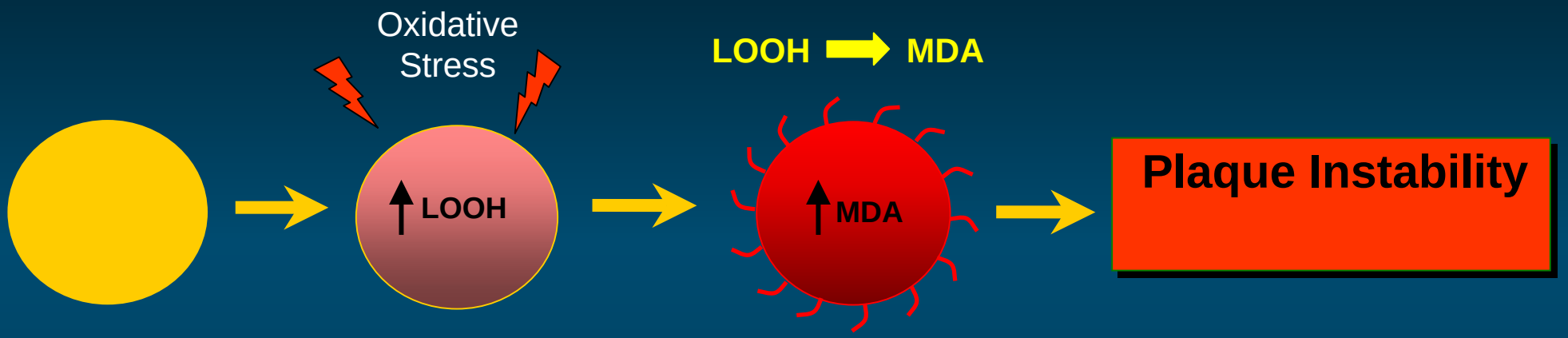
Inflammation

Effect of Native and Oxidized LDL on Endothelial NO Production



Vergnani et al. *Circulation.* 2000;101:1261.

Early (LOOH) Versus Late (MDA) Markers of LDL Oxidation



Native LDL

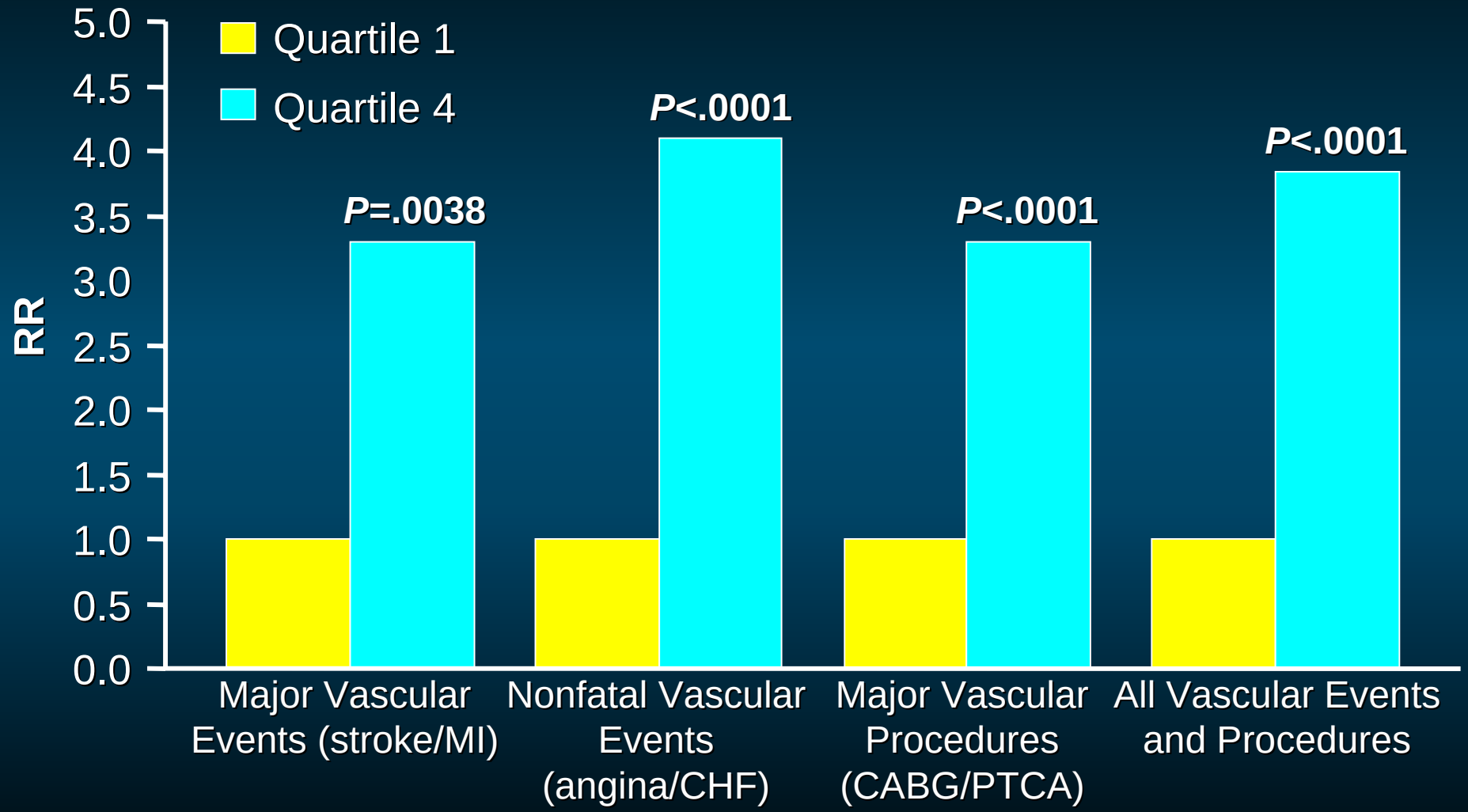
"Susceptible" LDL

MDA-modified LDL apo B

- Foam-cell formation
- Monocyte motility
- Endothelial adhesion
- Chemoattraction
- Free-radical production

RP Mason

Analysis of CV Risk Prediction With MDA-LDL in 634 Pts with Stable CAD



Walter MF, Mason RP. *JACC* 44:1996;2004

Plasma Lipid Oxidation Markers: An Independent Biomarker of CV Risk?

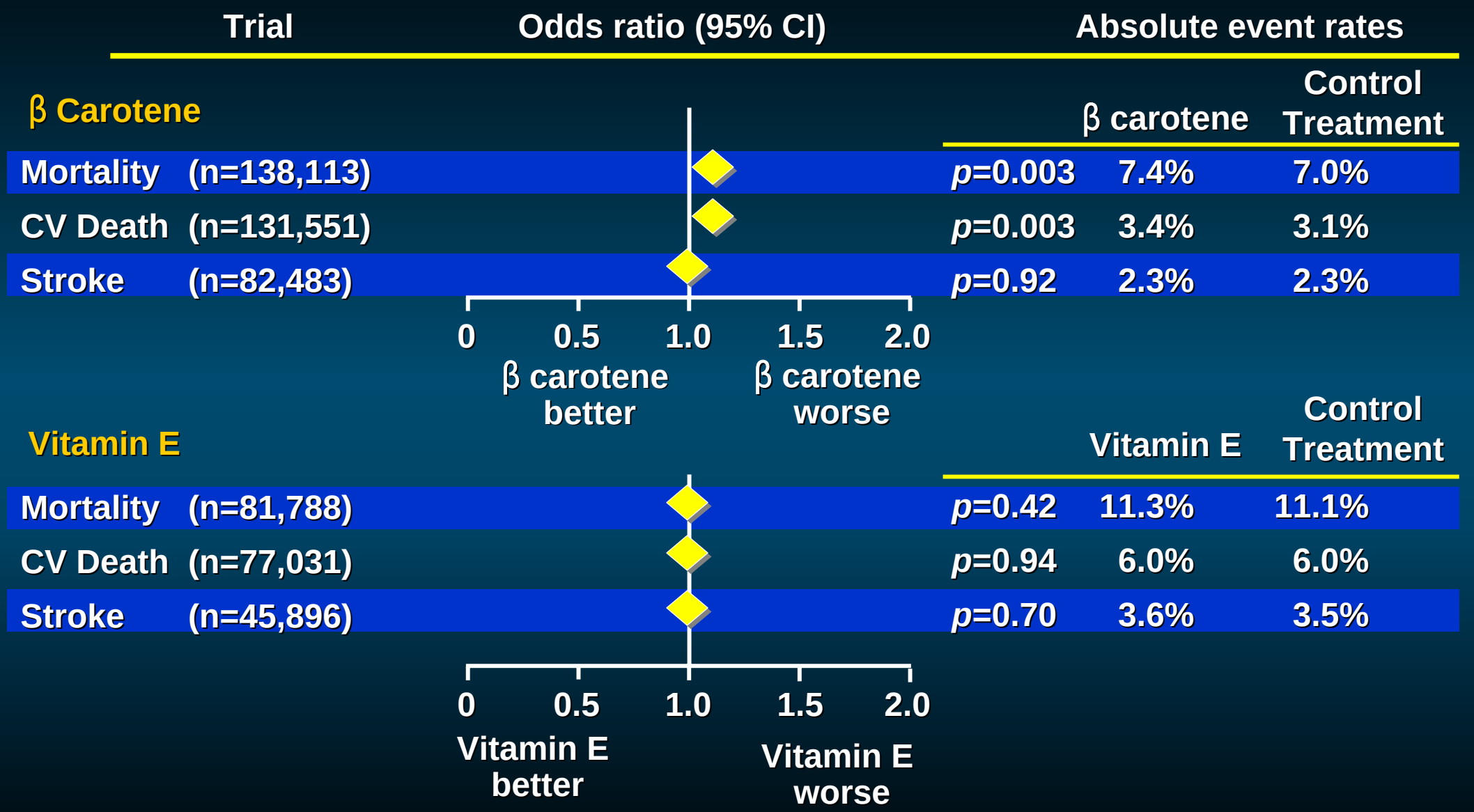
oxLDL Predicted Events Independently of other Risk Factors:

1) Lipids (LDL, HDL, triglycerides)
2) Blood Pressure (SBP, DBP)
3) Age
4) Body Mass Index (BMI)
5) Inflammatory Marker: hsCRP

Walter MF, Mason RP. *JACC* 44:1996;2004

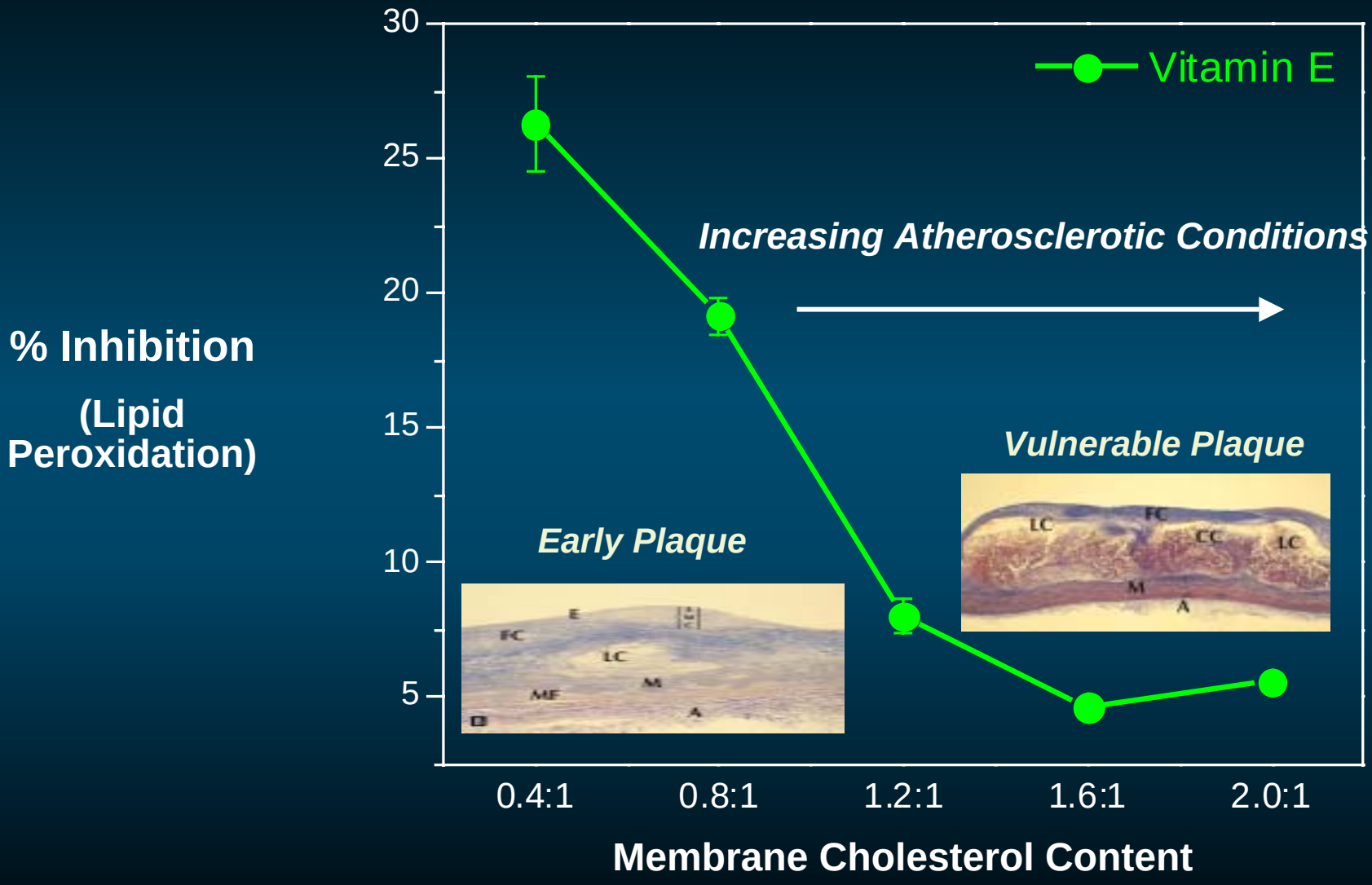
What’s Wrong with Natural Antioxidants?

Antioxidant Vitamins and CVD



Antioxidant, Meta-analysis. *Lancet*. 2003;361:2017-2023.

Antioxidant Effects of Vitamin E Diminished Under Atherosclerotic Conditions



Mean ± S.D. (n=5-6)

Walter WF, Mason RP. American College of Cardiology (2004)

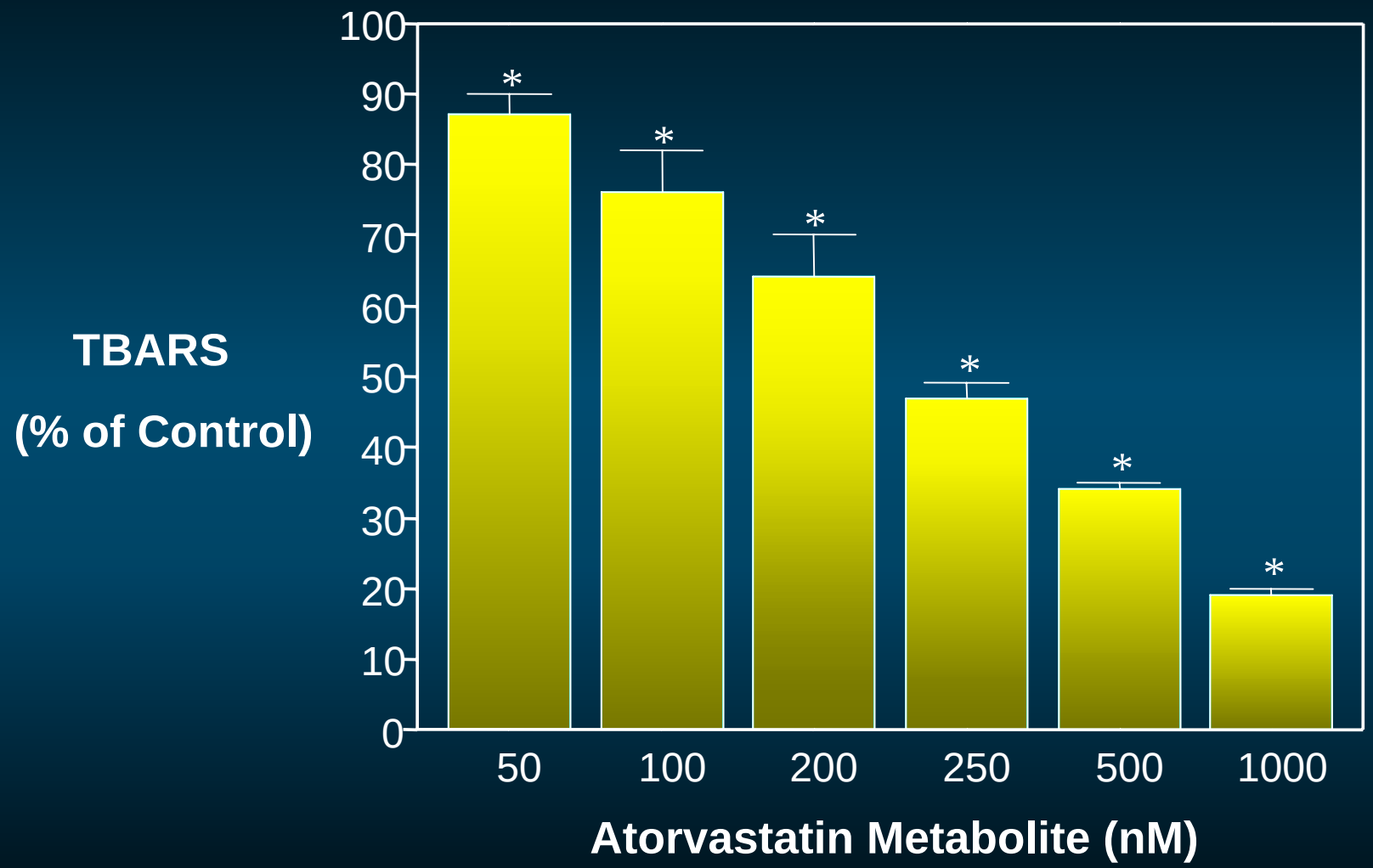
Statins Interfere with Oxidation Pathways

Mechanisms by which Statins Interfere with Oxidative Stress

- Reduce Expression of NADPH Oxidase Subunits
- Block isoprenylation of rac-1
- Reduce LDL levels
- Enhance catalase levels

Bokoch GM et al. *J. Clin. Invest.* 1992;89:402-408; Wassmann S et al. *Arterioscler. Thromb. Vasc. Biol.* 2002;22:300-305; Yamamoto A et al. *Eur. J. Pharmacol.* 1998;361:143-149.

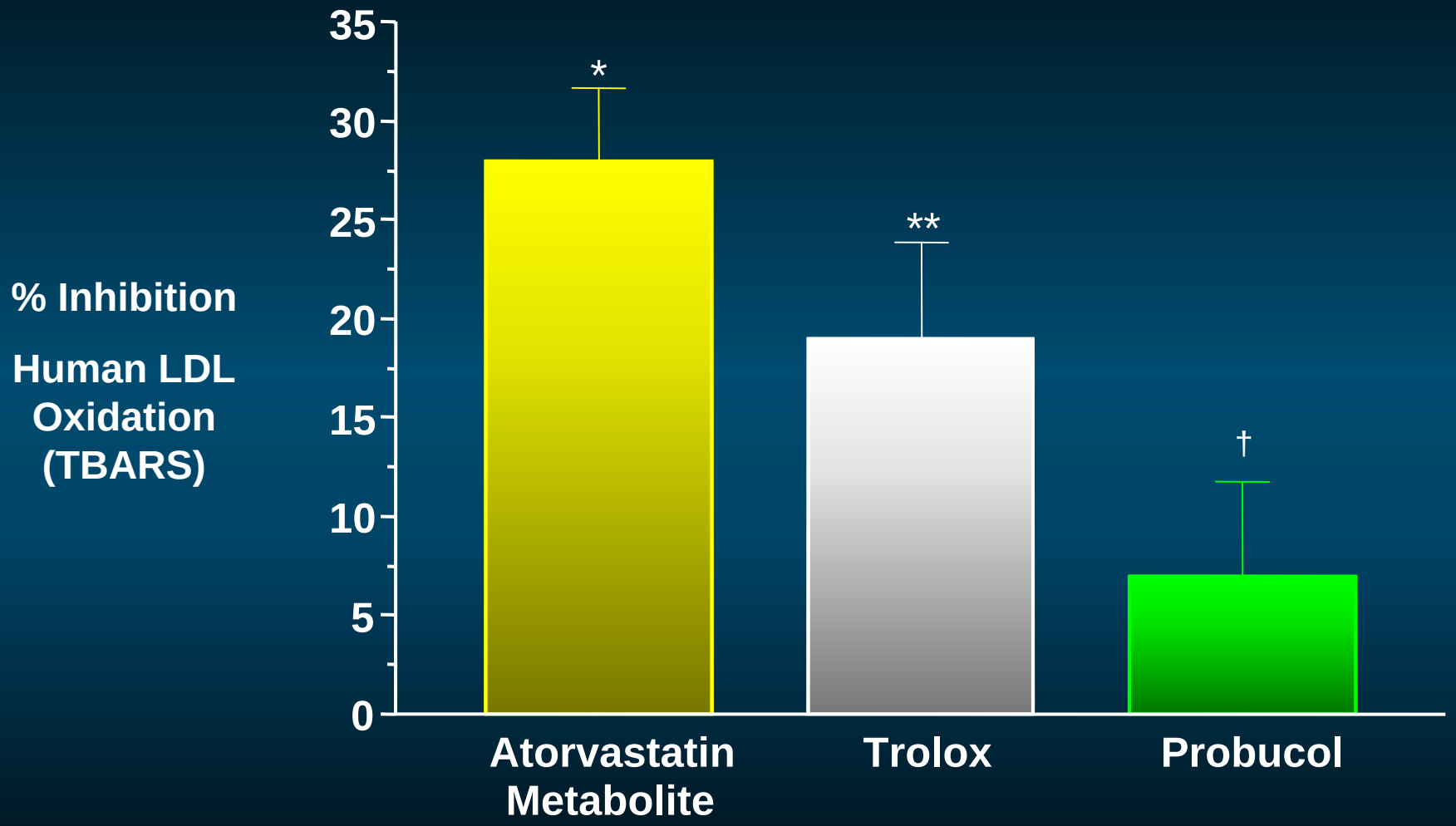
Effect of Atorvastatin o-Hydroxy Metabolite on Human LDL Oxidation



***p < 0.05 versus untreated.**

Mason RP et al. *Circulation* (June, 2004).

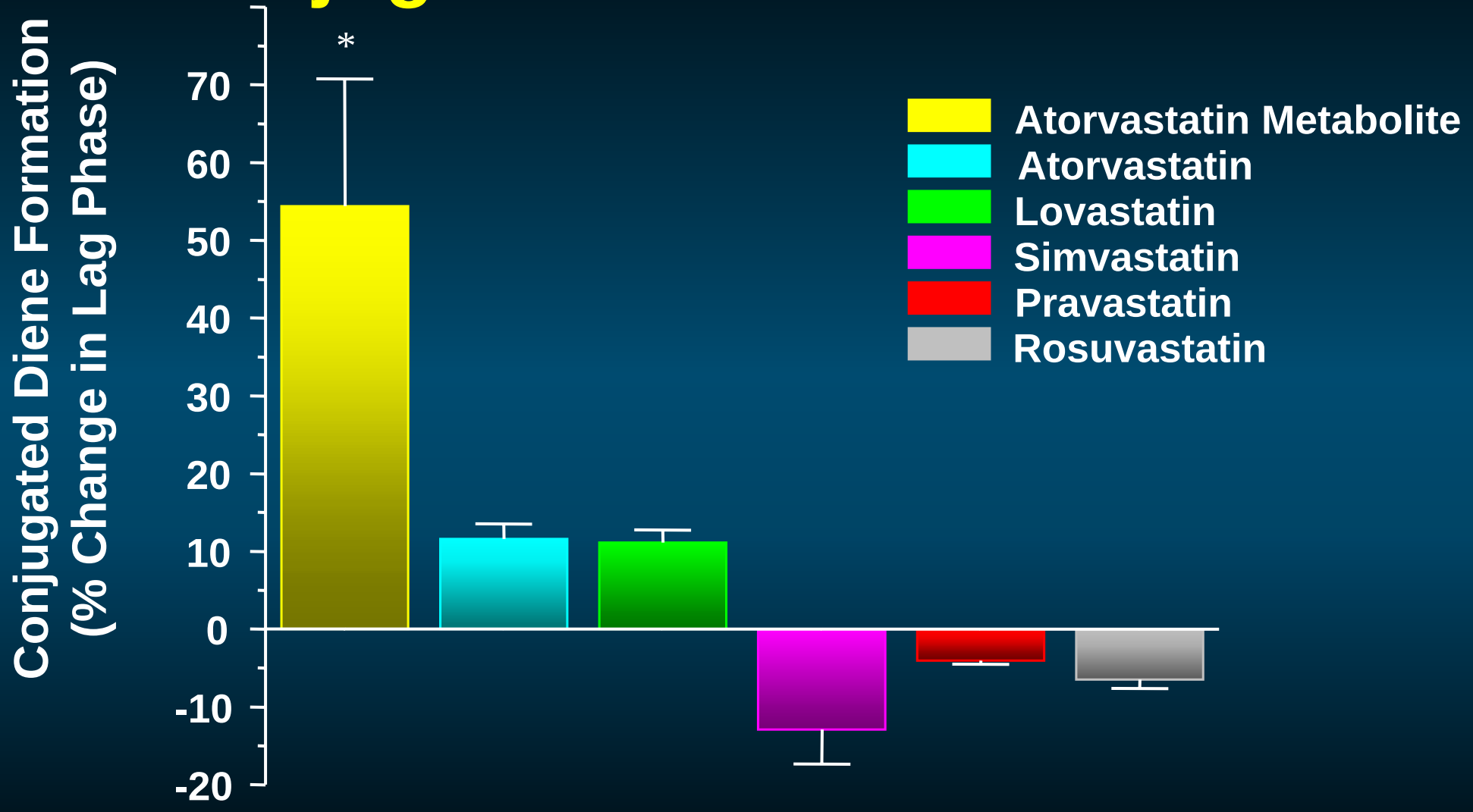
Effects of Atorvastatin Active Metabolite vs Antioxidants on Cu^{2+}-Induced LDL Oxidation



***p* < 0.001, ****p* < 0.001 and † *p* < 0.0001 versus Control**

Reproduced from Mason et al. *Am J Cardiol*. 2005;96(suppl):11F, with permission.

Effects of Statins on Human LDL Conjugated Diene Formation

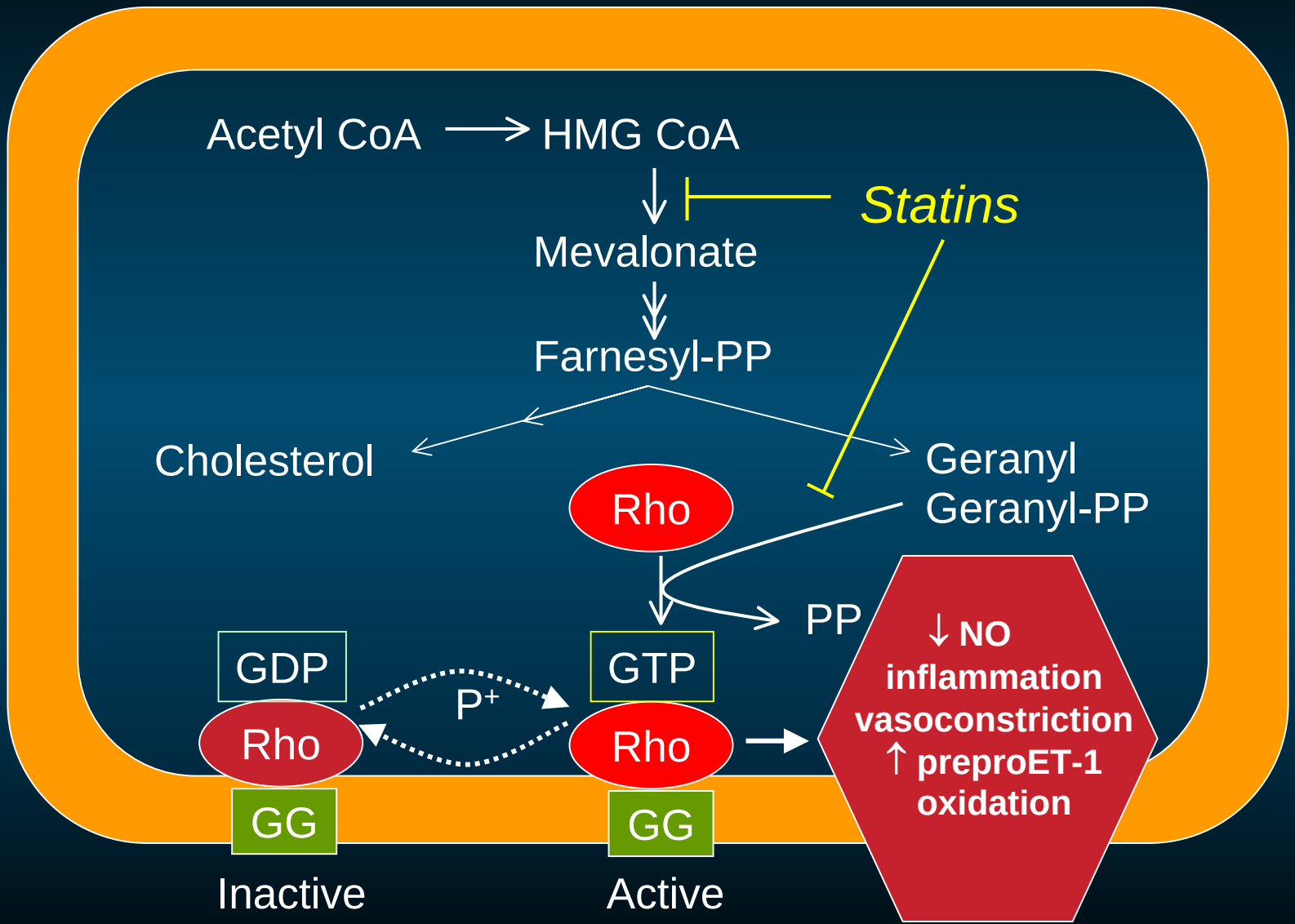


*p<0.005 vs untreated.

Walter MF, Mason RP. American College of Cardiology (2004)

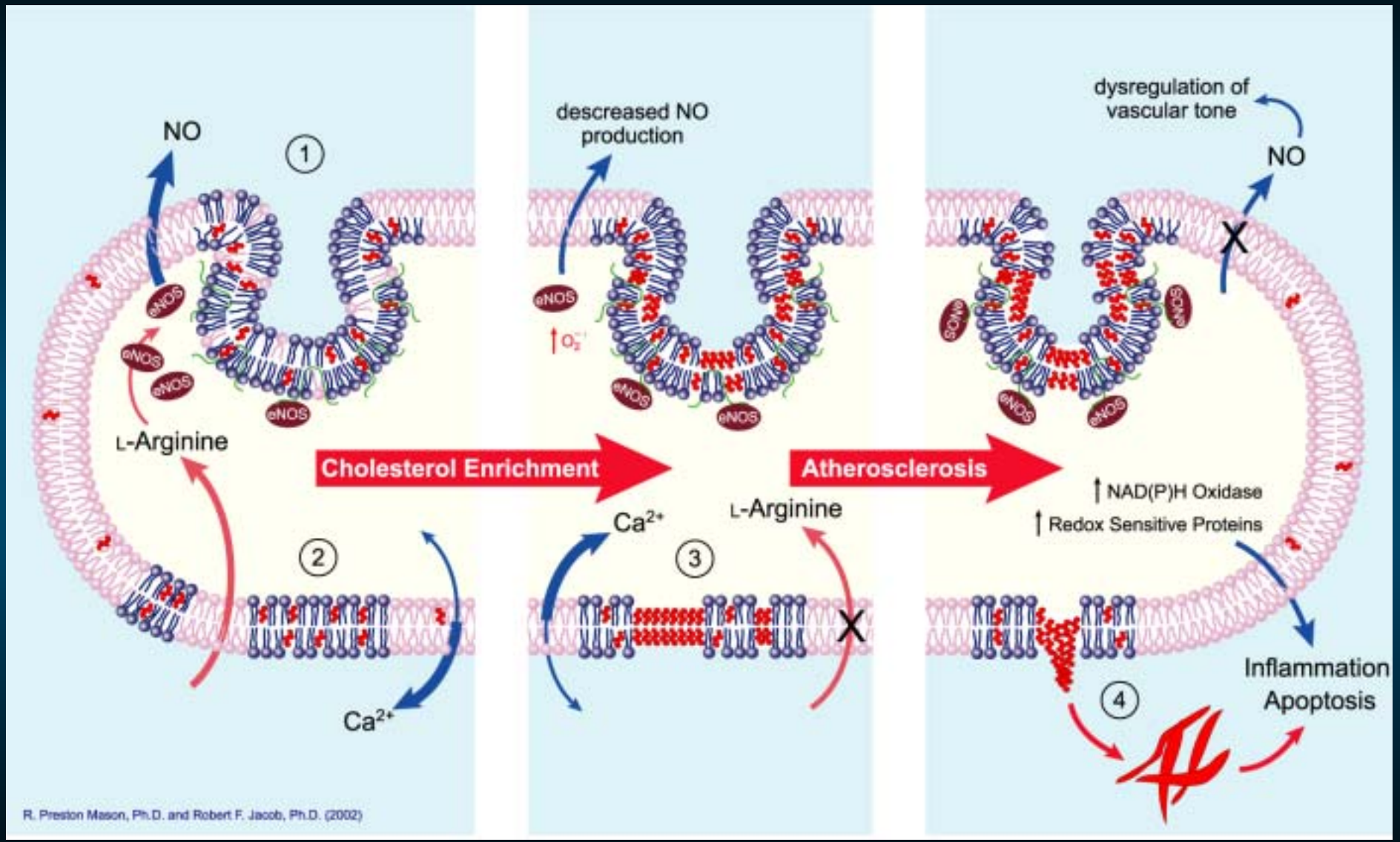
Statins Improve Endothelial Function

Prenylation of the G-Protein Rho is Central for Mediating Many Pleiotropic Effects of Statins



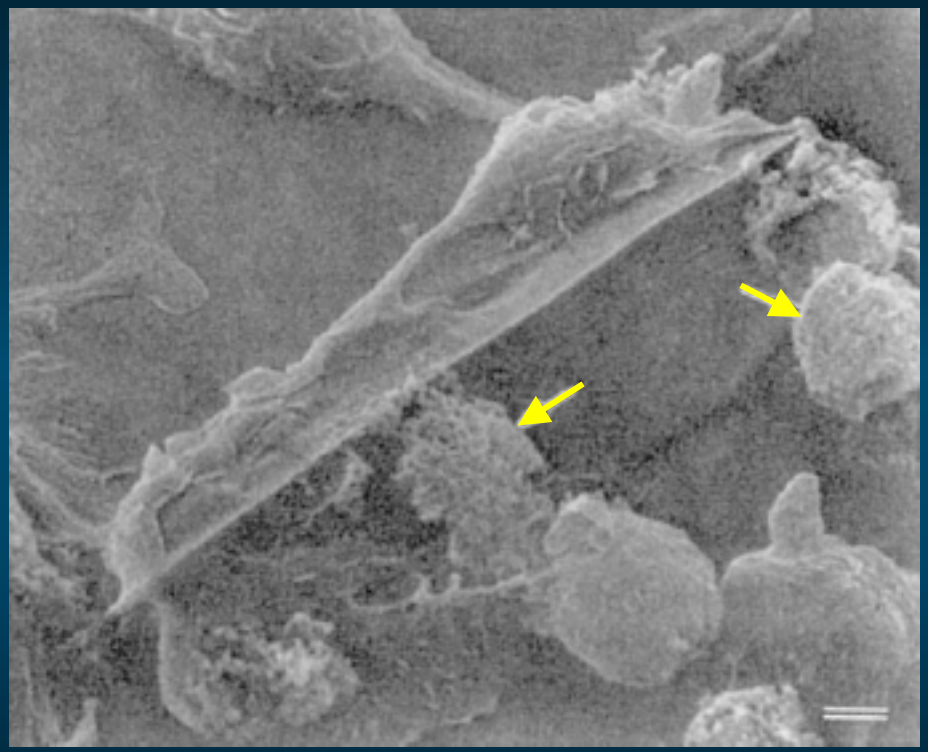
KINLAY S et al. Curr Opin Lipidol 12:383, 2001

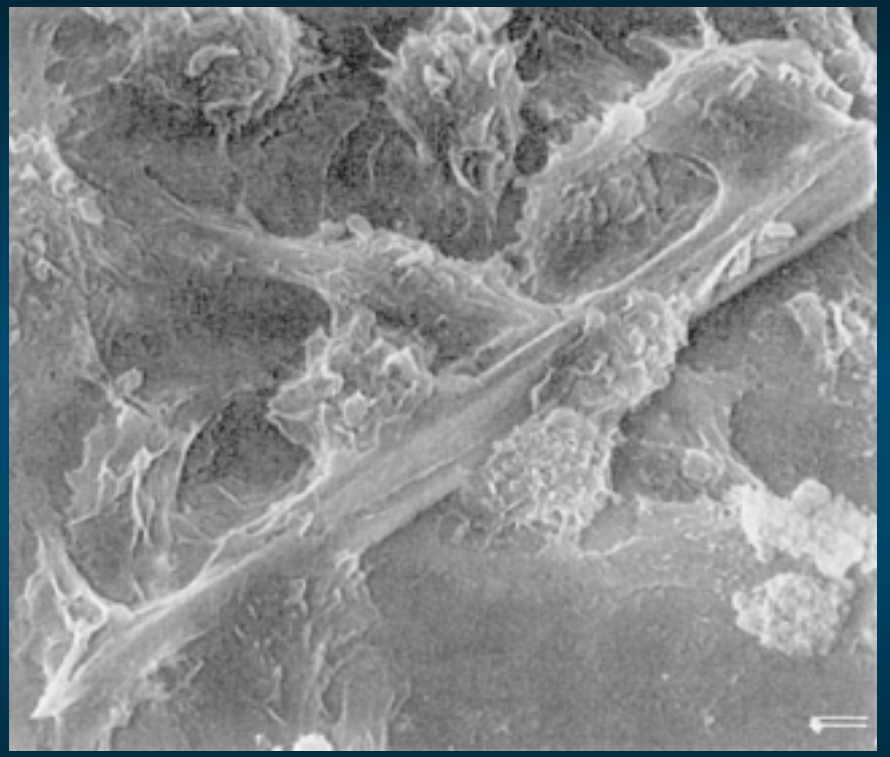
Role of Microdomains in Atherosclerosis



Mason RP and Jacob RF. *Circulation*. 2004.

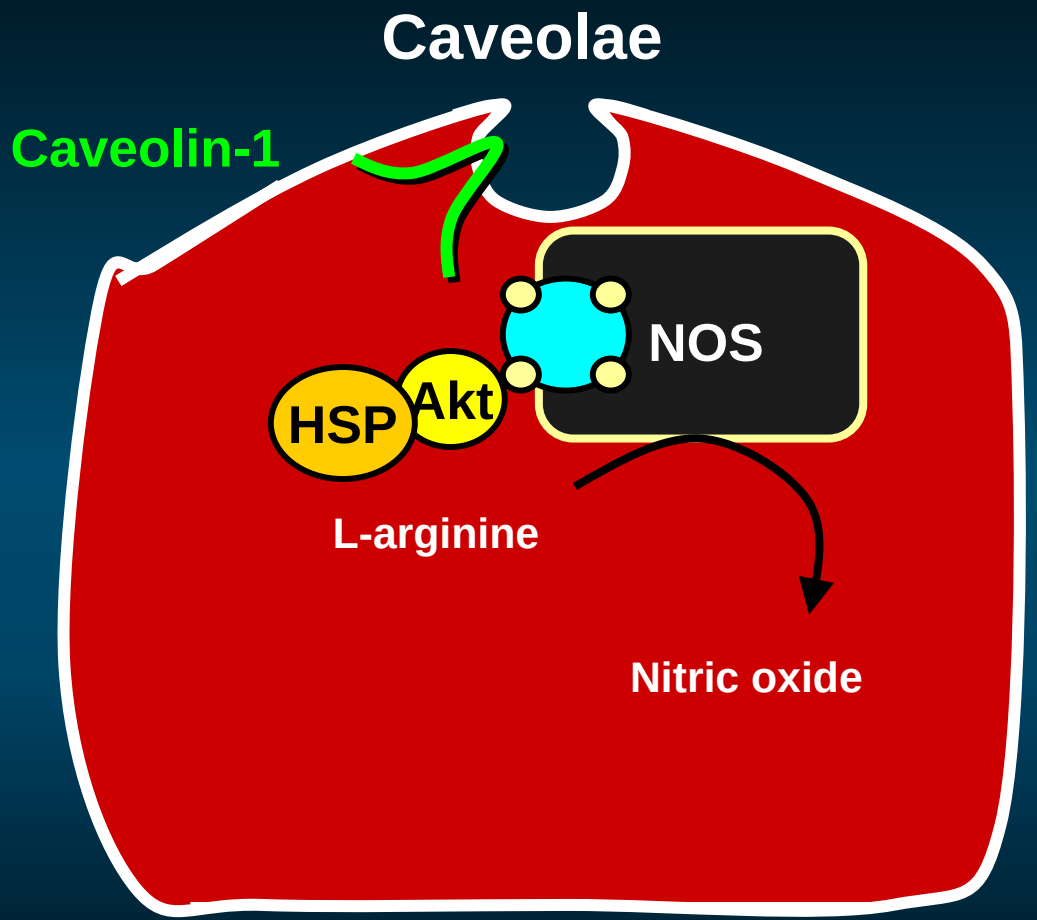
Cholesterol Crystals Associated with Apoptotic Cell Death





Kellner-Weibel G. *Arterioscler Thromb Vasc Biol.* 1999;19:1891-1898.

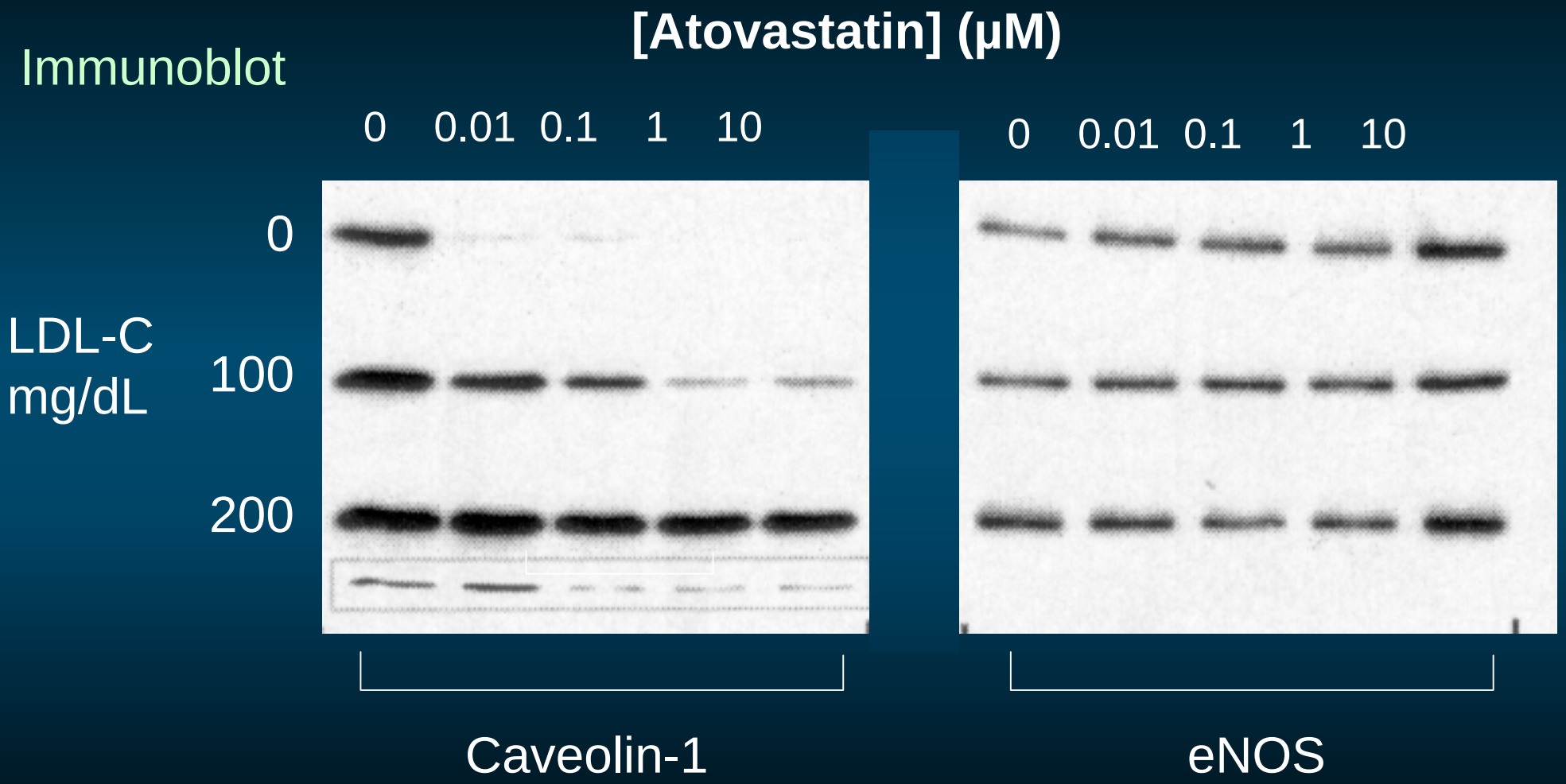
Caveolin and HSP/Akt and eNOS Activation



1. Statins decrease caveolin expression
2. Statins increase eNOS activation by ⬆ HSP/Akt phosphorylation
3. Activated eNOS increases NO production

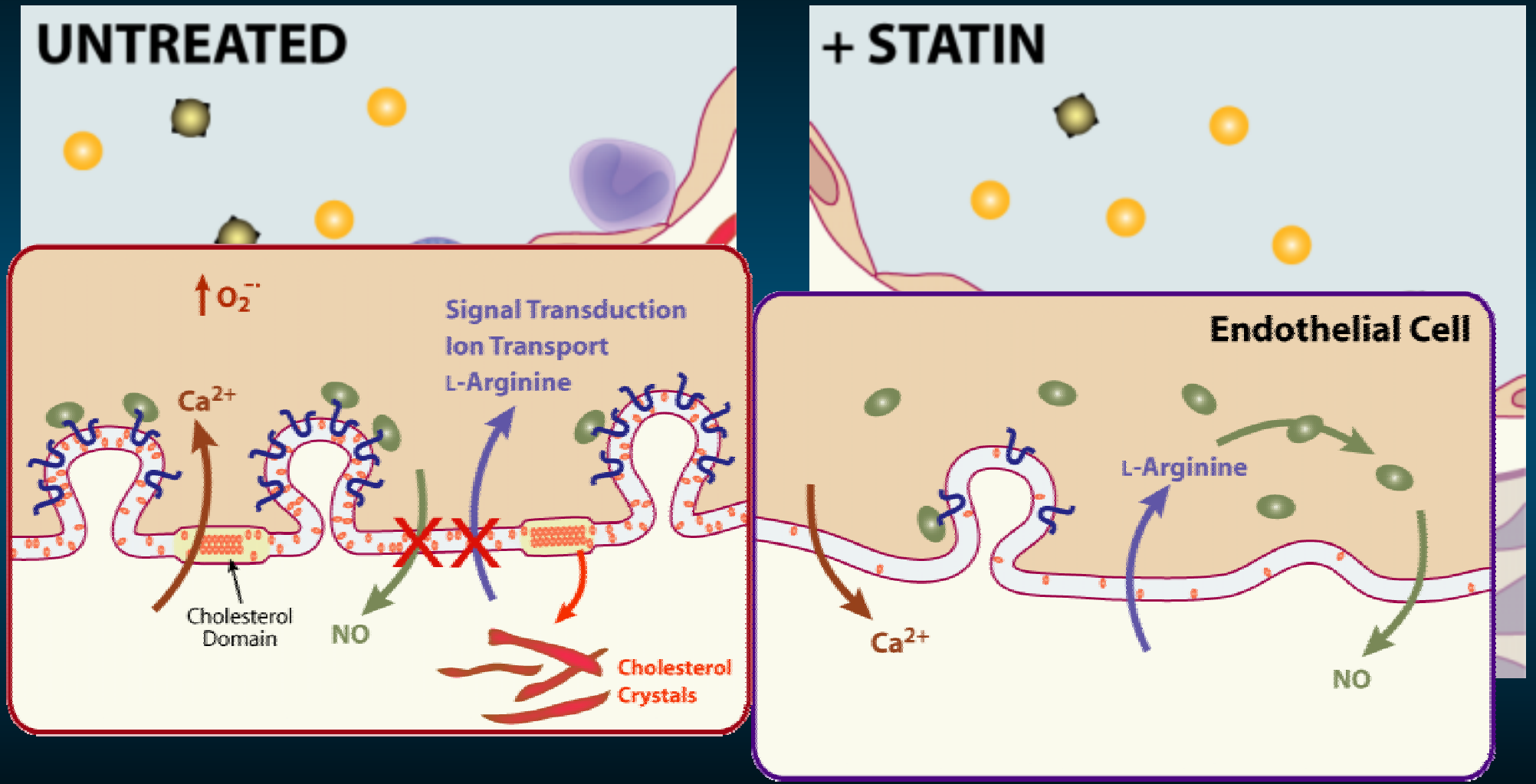
Adapted from Kinlay S, et al. *Curr Opin Lipidol.* 2001;12:383.
Brouet A. *Circ Res.* 2001;89:866.

Statin Promotes eNOS Activation: Decrease in Caveolin Abundance in EC



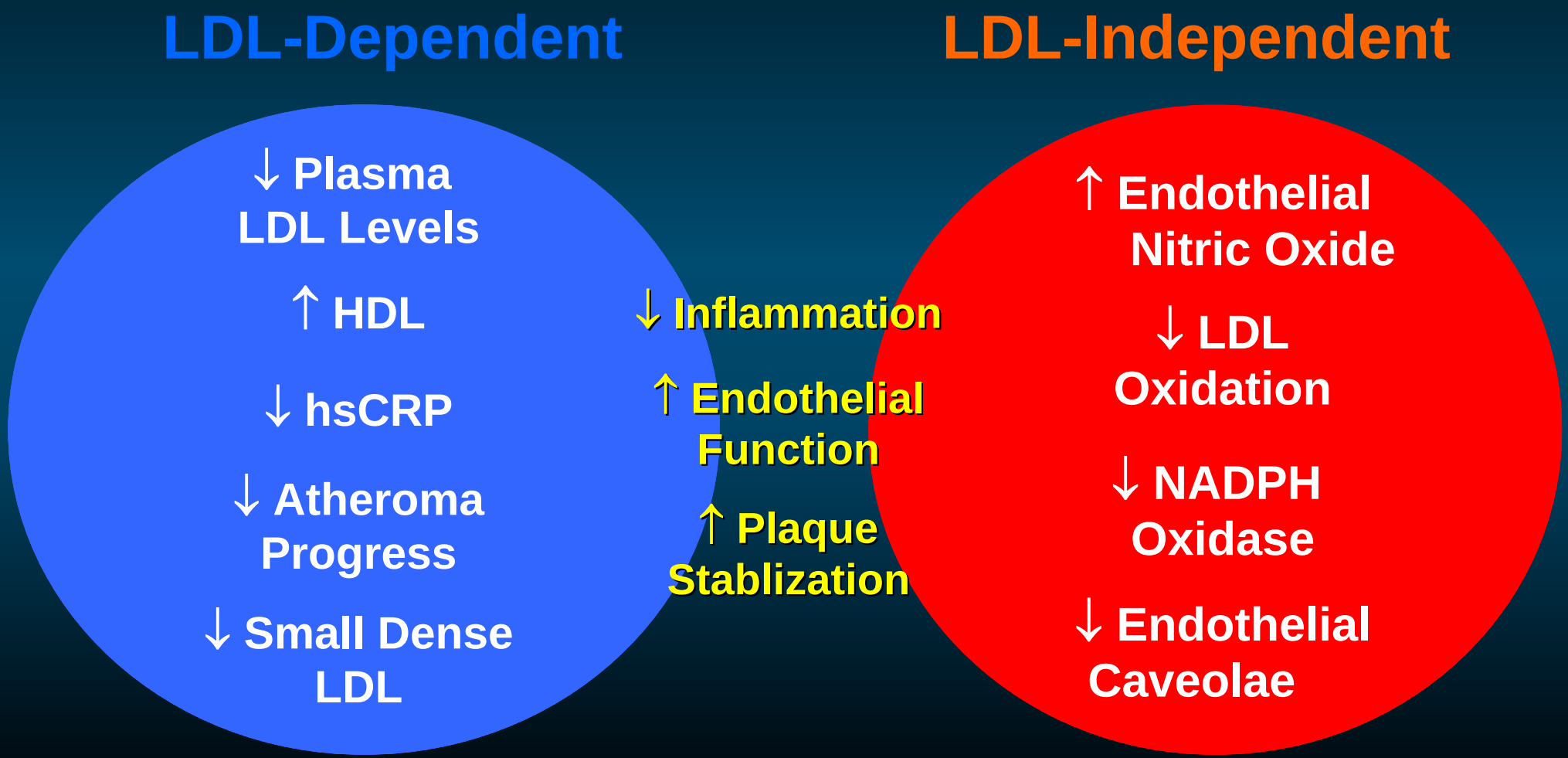
Feron O et al. Circulation 103:113, 2001

Effects of Statin Treatment on Endothelial Cell Membranes and Vasculature in Atherosclerosis



Mason RP et al. *Circulation*. (June, 2004)

Atheroprotection with Lipophilic Statin: HMG-CoA Inhibition and Beyond



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