Role of Lipoproteins and Inflammation in the Progression/Regression of Atherosclerosis

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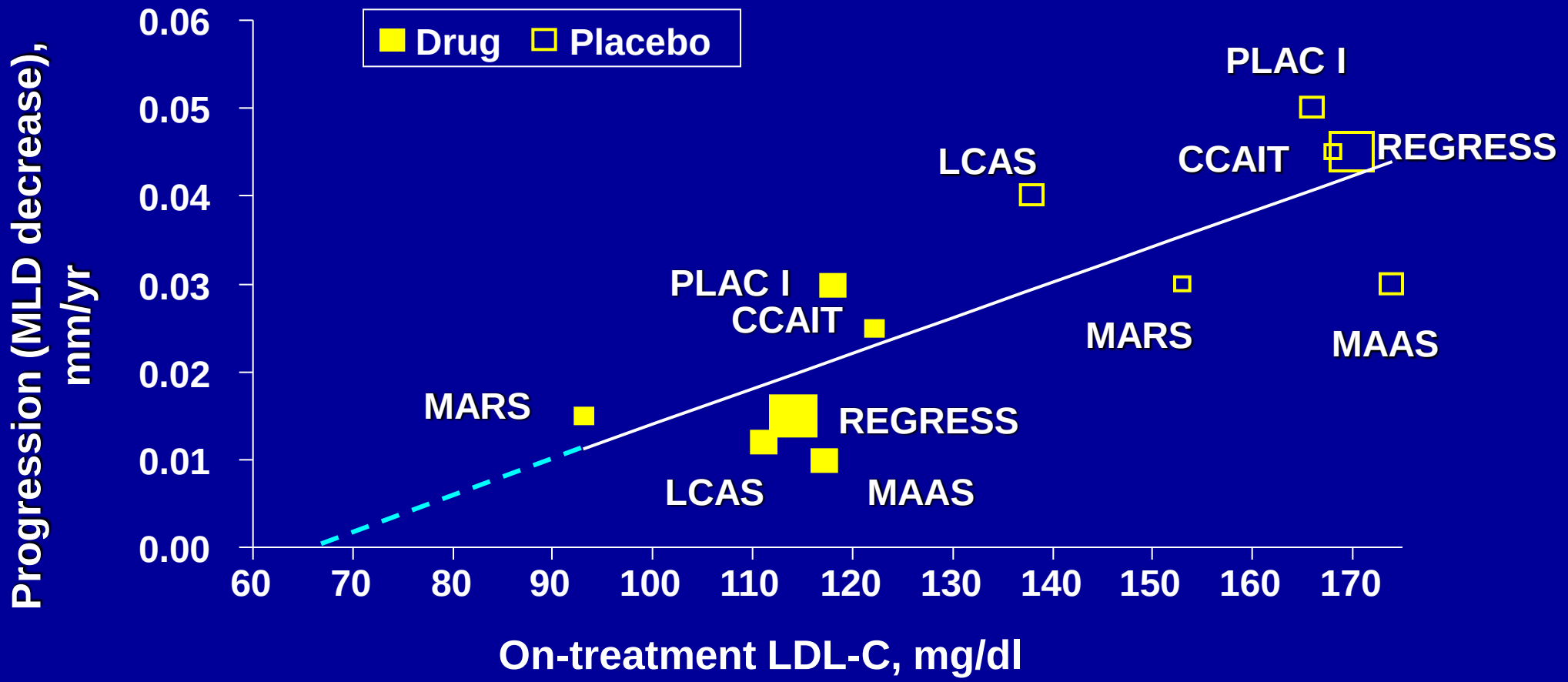
Pathophysiology of Atherosclerosis: the Mechanisms of Progression

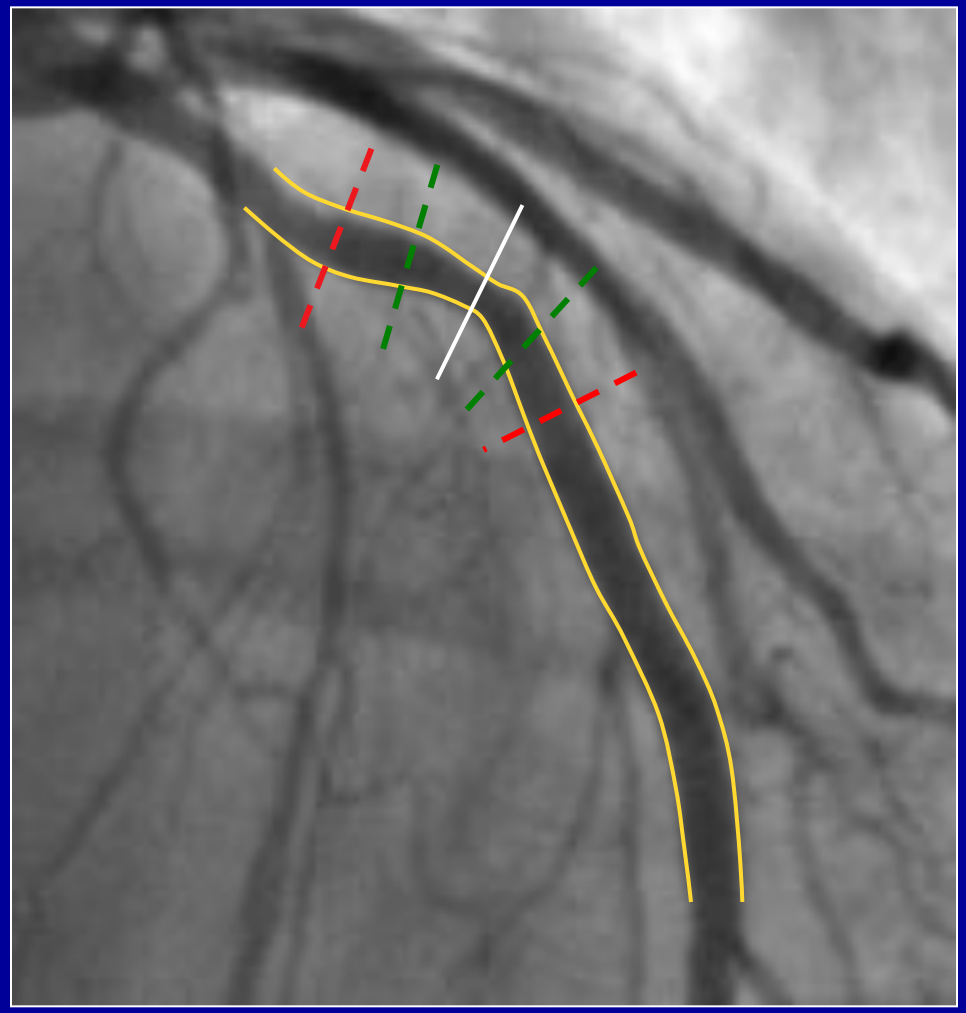
1. Lipoproteins
2. Inflammation and progression of atherosclerosis
3. Lipoproteins and inflammation

Angiographic Progression Rate by LDL-C Achieved in Statin Trials

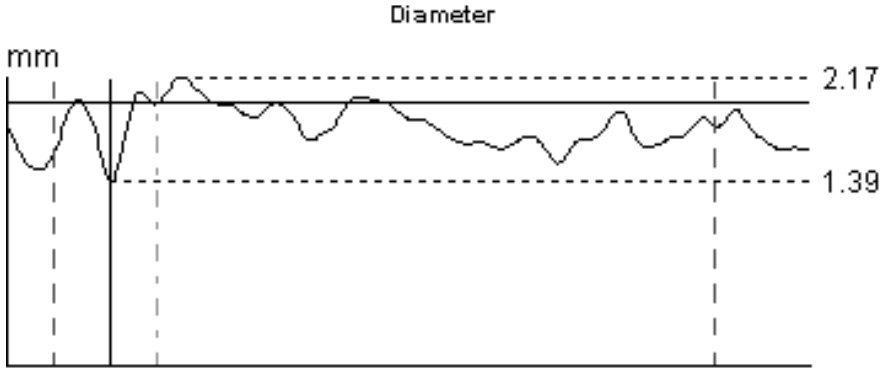


Ballantyne CM et al. *Curr Opin Lipidol* 1997;8:354–361.

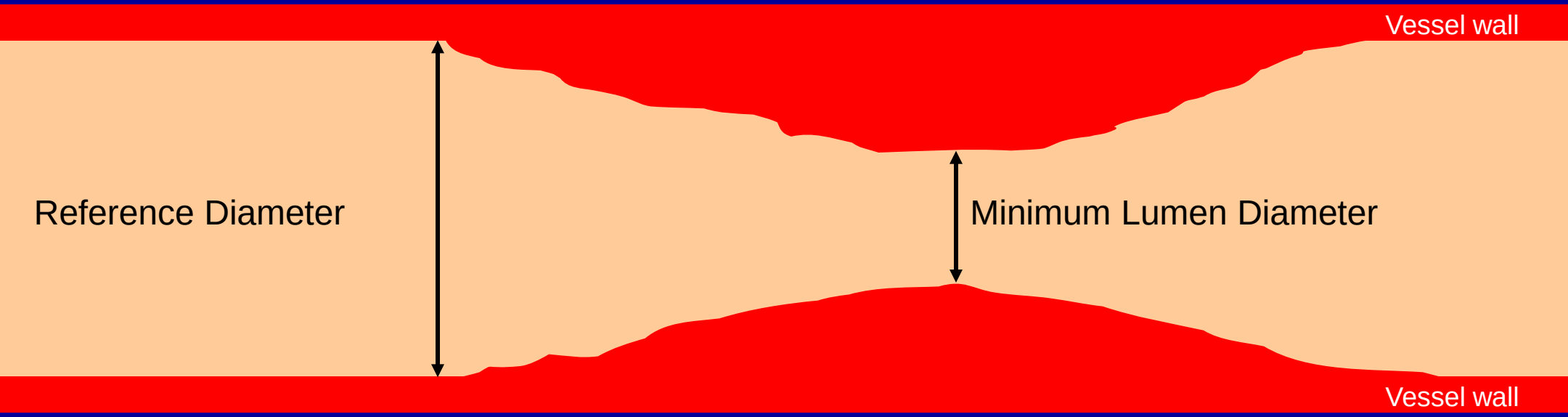
QCA of the mid LAD



MLD	:	**1.39**	mm
% diameter stenosis	:	**30**	%
Reference diameter	:	**1.99**	mm
Position reference diameter	:	13.38	mm
Length stenotic segment	:	**53.01**	mm
Position of proximal border	:	4.53	mm
Position of distal border	:	57.72	mm
Minimum area absolute	:	0.33	mm2
MLA densitometry	:	1.97	mm2
MLA circular	:	1.52	mm2
% area stenosis densitometry	:	**37**	%
% area stenosis circular	:	**51**	%
Reference area	:	3.10	mm2



QCA Measurements



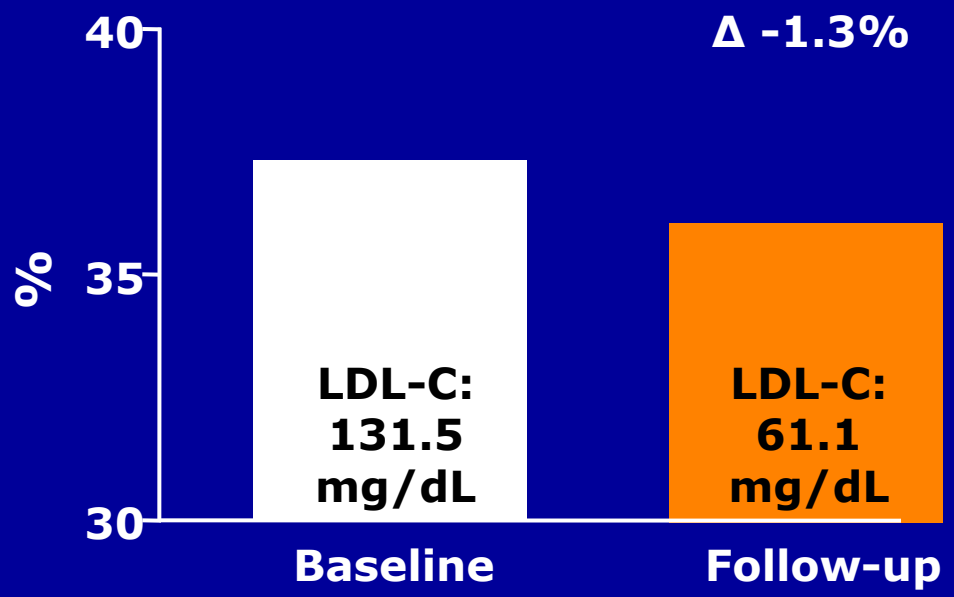
Outcome variable: change in percent diameter stenosis
for all stenoses > 25% at baseline

$$\text{Percent diameter stenosis} = \frac{\text{Reference Diameter} - \text{Minimum Lumen Diameter}}{\text{Reference Diameter}} \times 100$$

ASTEROID: Angiographic Regression

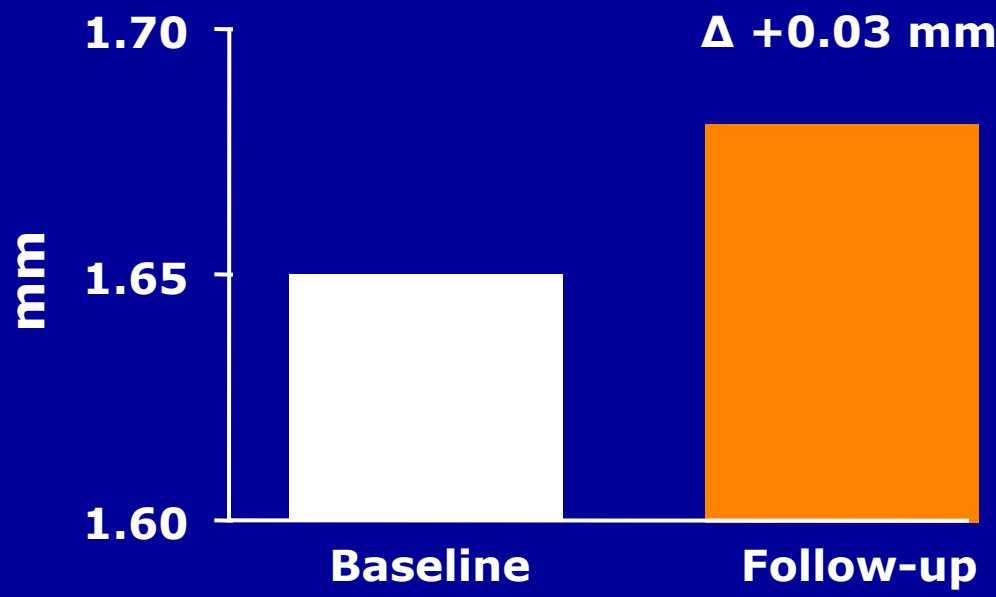
292 patients with at least 1 segment containing >25% stenosis

Mean Δ Percent Diameter Stenosis



Median Δ %DS: –0.50% (–4.00, 2.00)
p <0.001

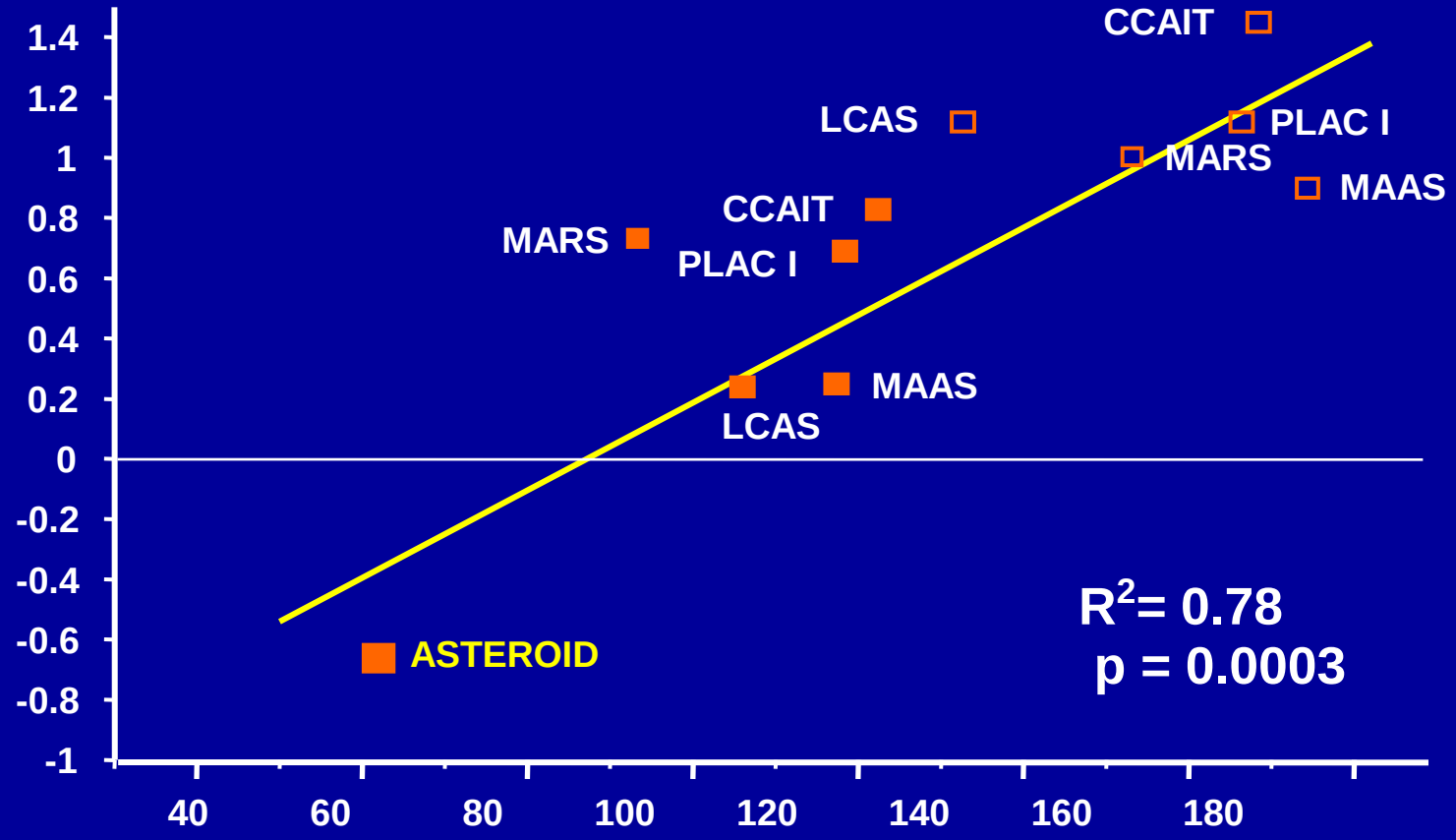
Mean Δ Minimum Lumen Diameter



Median Δ MLD: +0.02 (–0.04, 0.11) mm
p <0.001

Ballantyne CM et al. *Circulation* 2008;117:2458–2466.

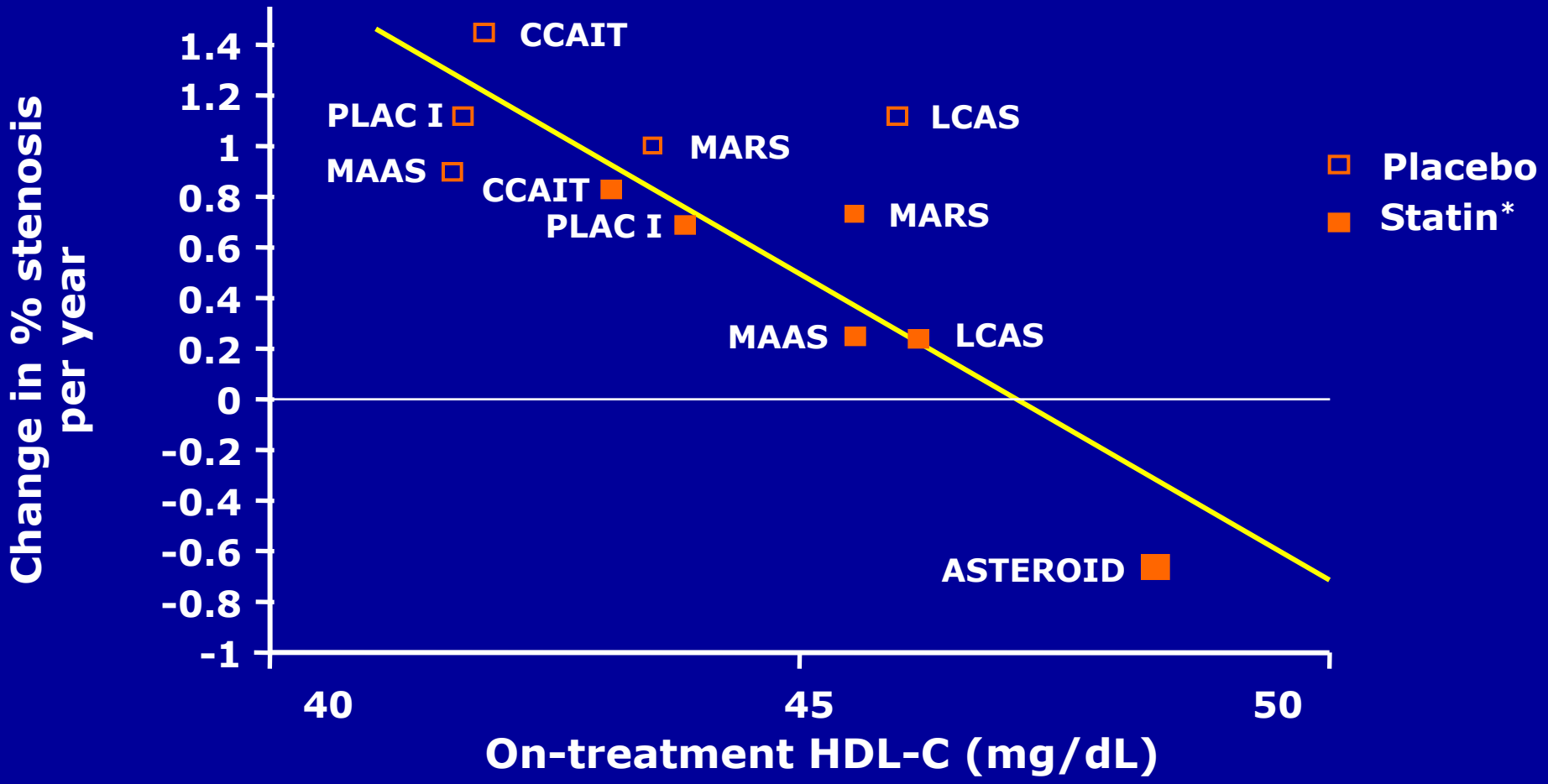
Change in Percent Diameter Stenosis vs On-Treatment LDL-C in QCA Trials



* ASTEROID rosuvastatin
CCAIT lovastatin
LCAS fluvastatin
MAAS simvastatin
MARS lovastatin
PLAC I pravastatin

Ballantyne CM et al. *Circulation* 2008;117:2458–2466.

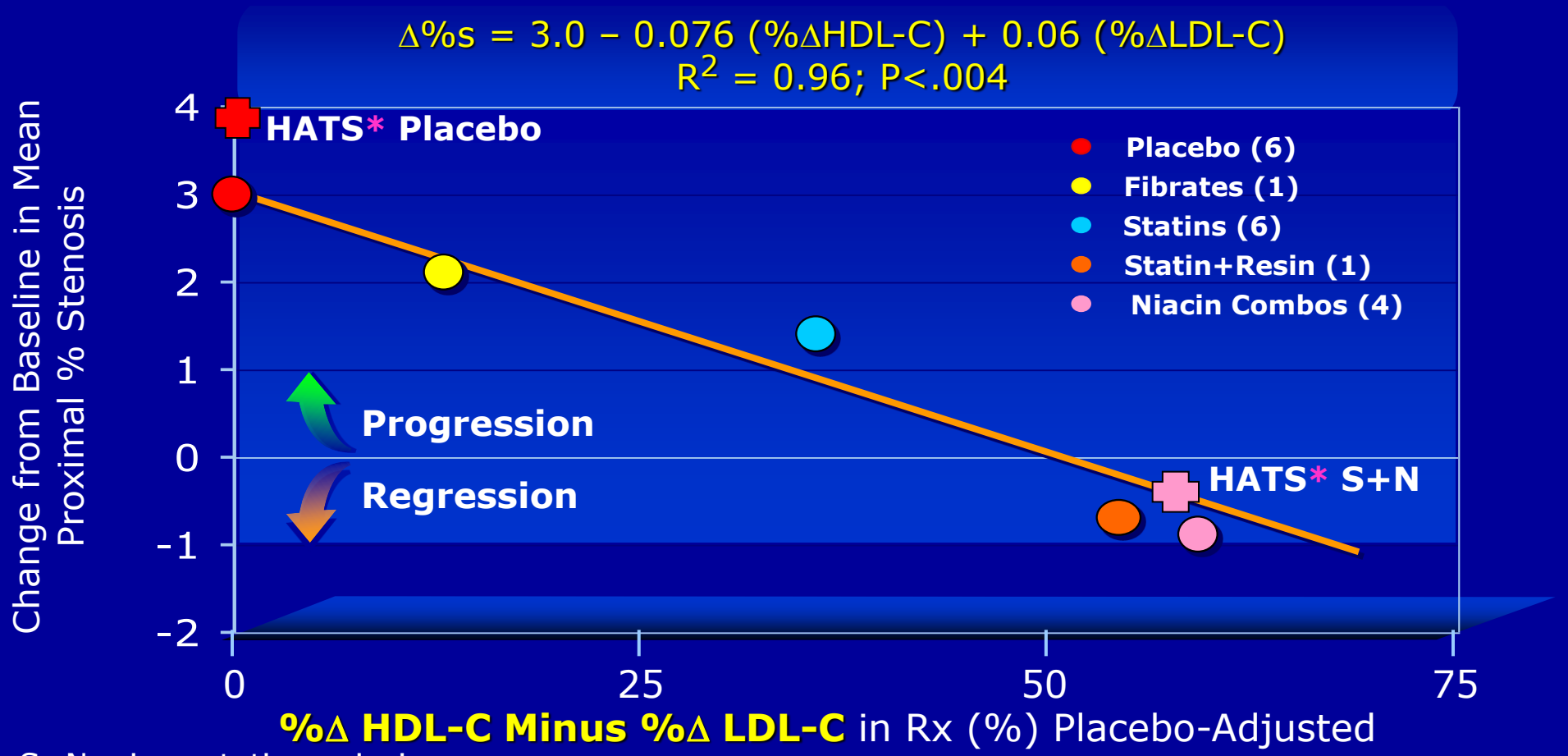
Change in Percent Diameter Stenosis vs On-treatment HDL-C in QCA Trials



*ASTEROID rosuvastatin MAAS simvastatin CCAIT lovastatin
MARS lovastatin LCAS fluvastatin PLAC I pravastatin

Ballantyne CM et al. *Circulation* 2008;117:2458–2466.

Angiographic Effects of Lipid Drug Classes Meta-Analysis, 12 Trials

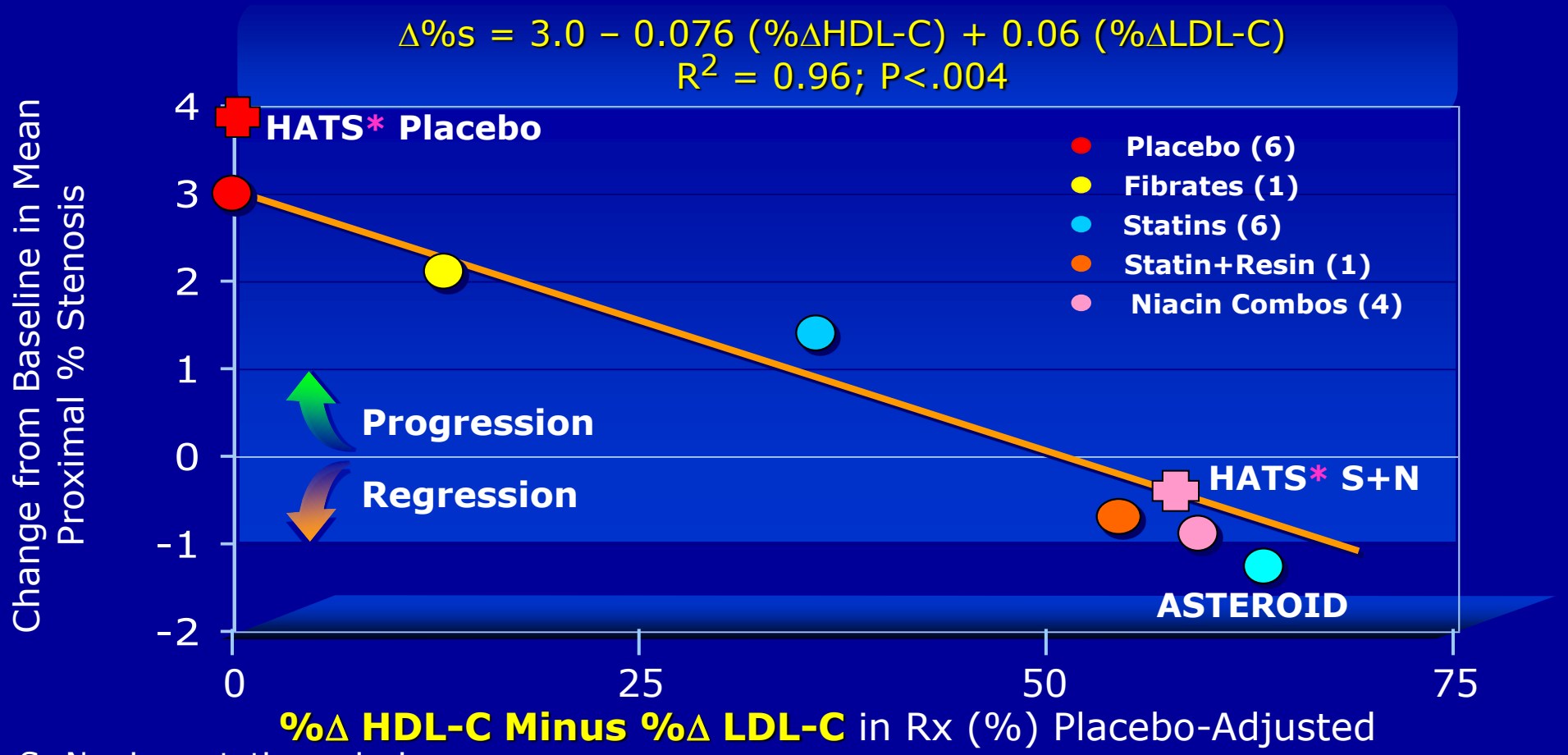


S+N=simvastatin + niacin

* HATS (HDL-atherosclerosis treatment study) data not shown in original study

Brown BG et al. *Curr Opin Lipidol* 2006;17:631–636.

Angiographic Effects of Lipid Drug Classes Meta-Analysis, 12 Trials

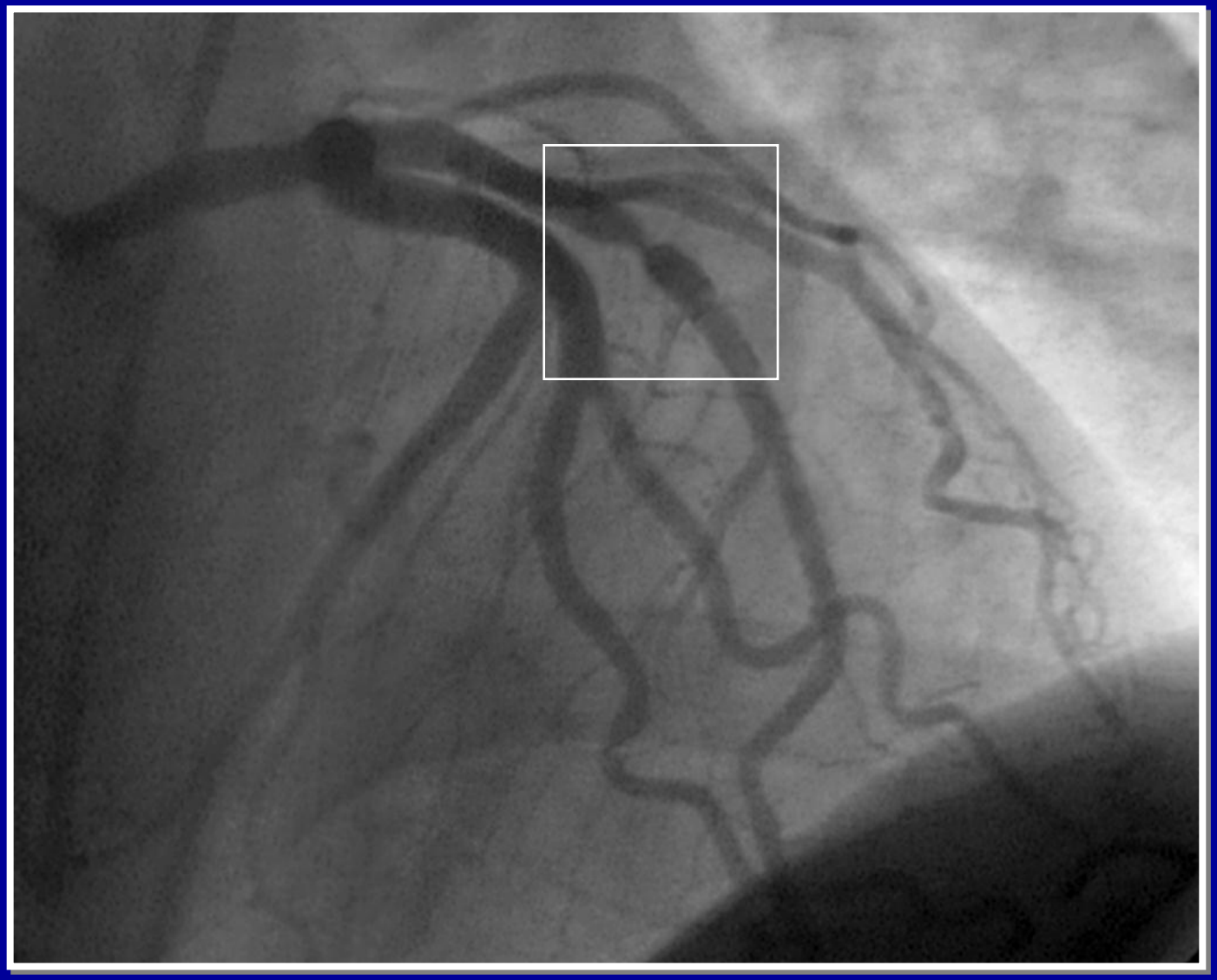


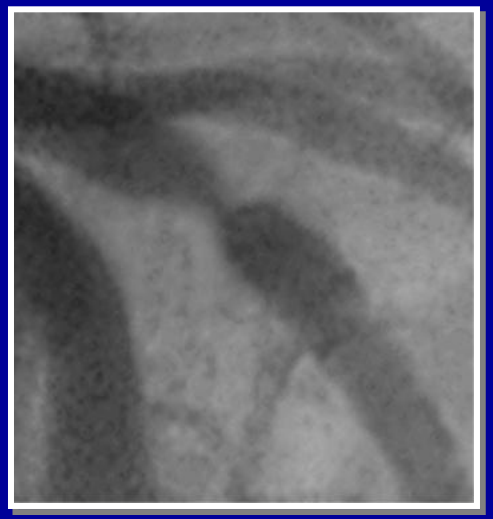
S+N=simvastatin + niacin

* HATS (HDL-atherosclerosis treatment study) data not shown in original study

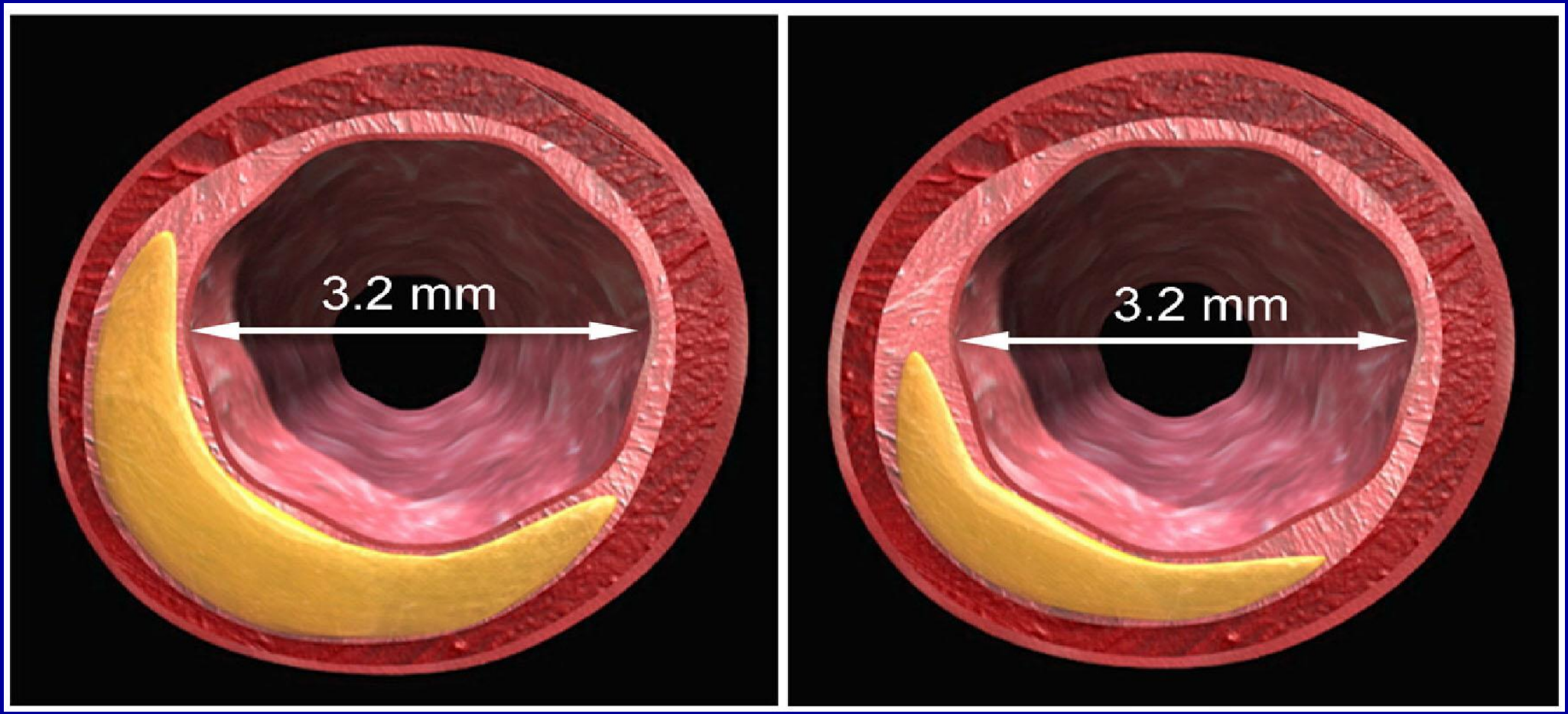
Brown BG et al. *Curr Opin Lipidol* 2006;17:631–636.

Angiography Does Not Image Plaque

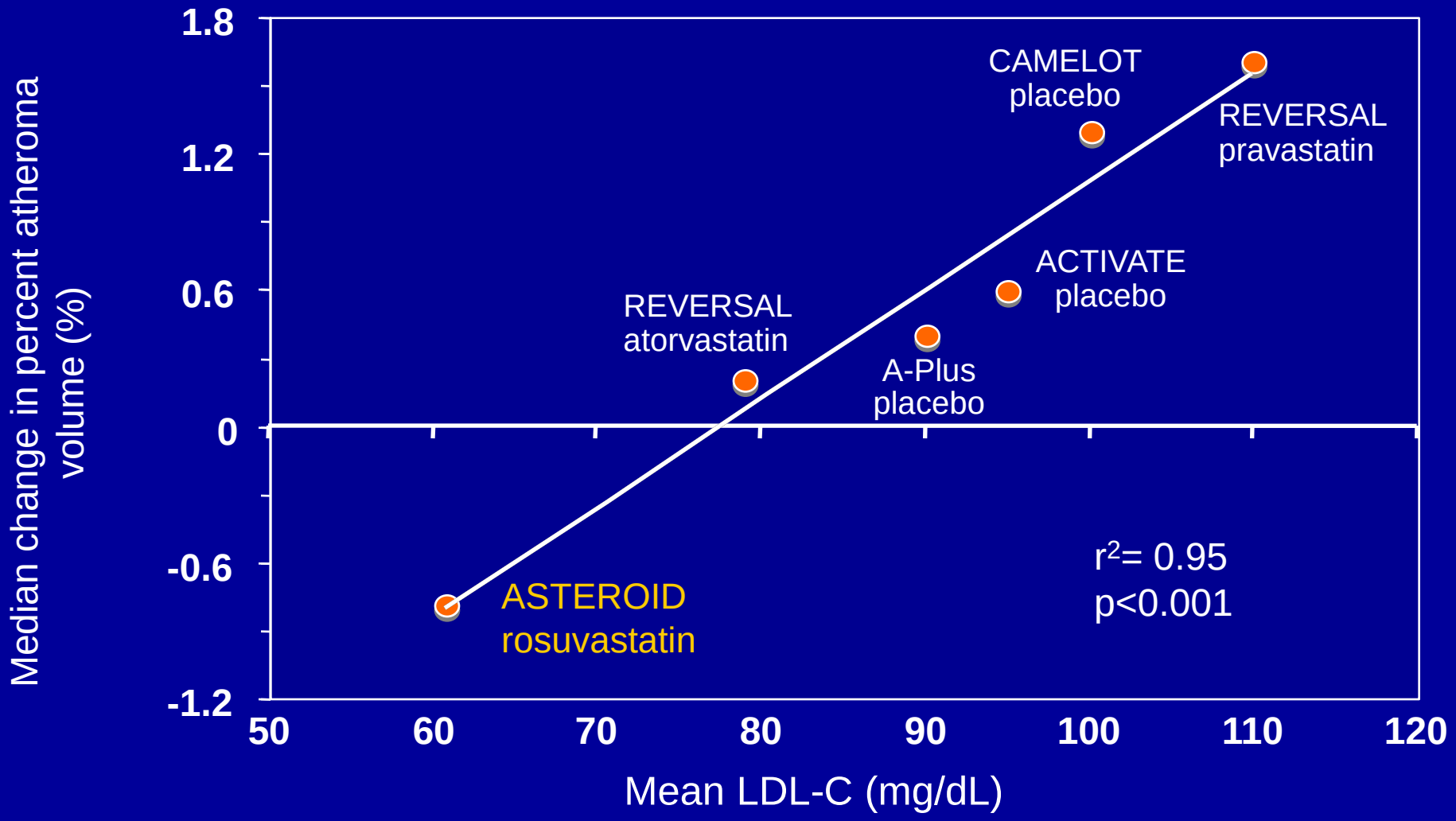




Discord between Lumen and Atherosclerosis

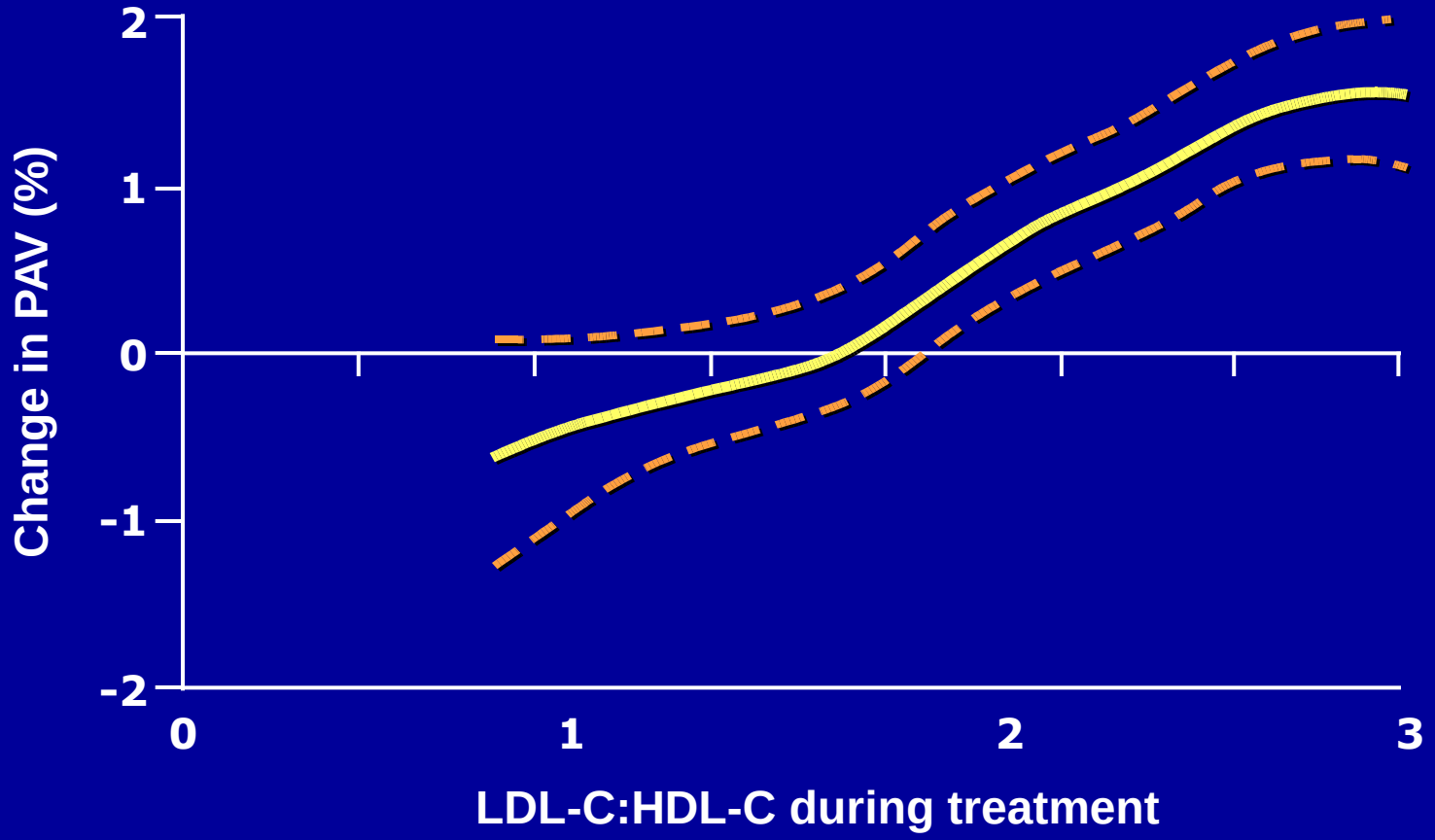


Recent Coronary IVUS Progression Trials: Relation between LDL-C and Progression Rate



Nissen SE et al. *JAMA* 2006;295:1556-1565.

Beneficial Impact of Lowering LDL-C:HDL-C Ratio on Atherosclerosis



Nicholls S et al. *JAMA* 2007;297:499–508

What is the significance of progression as measured by QCA (i.e., luminal narrowing)?

- Patients with the most progression have the highest rate of CAD
- Progression of CAD as measured by QCA has been shown to predict clinical CV events such MI, CAD mortality, and need for revascularization in the following studies:
  - Program for the Surgical Control of the Hyperlipidemias
  - Montreal Heart Institute study of nicardipine
  - Cholesterol Lowering Atherosclerosis Study

Changes in lumen dimension over time correlated weakly with IVUS parameters

- Relationship between QCA and IVUS at single time points (n=525) and changes over time (n=432)
- Statistically significant correlations were observed between QCA coronary artery score and IVUS-derived lumen volume ($r=0.65$, $P<0.0001$) and total vessel volume ($r=0.55$, $P<0.0001$)
- Statistically significant but weak correlations between changes over time in lumen dimesions on QCA and IVUS ($r=0.14$, $P<0.01$)
- Nevertheless, pts with and without angiographic progression had changes in plaque volume on IVUS of 9.13 and 0.20 mm^3 ($P=0.08$)

Berry et al. Circulation 2007;115:1851-1857.

IVUS vs. QCA

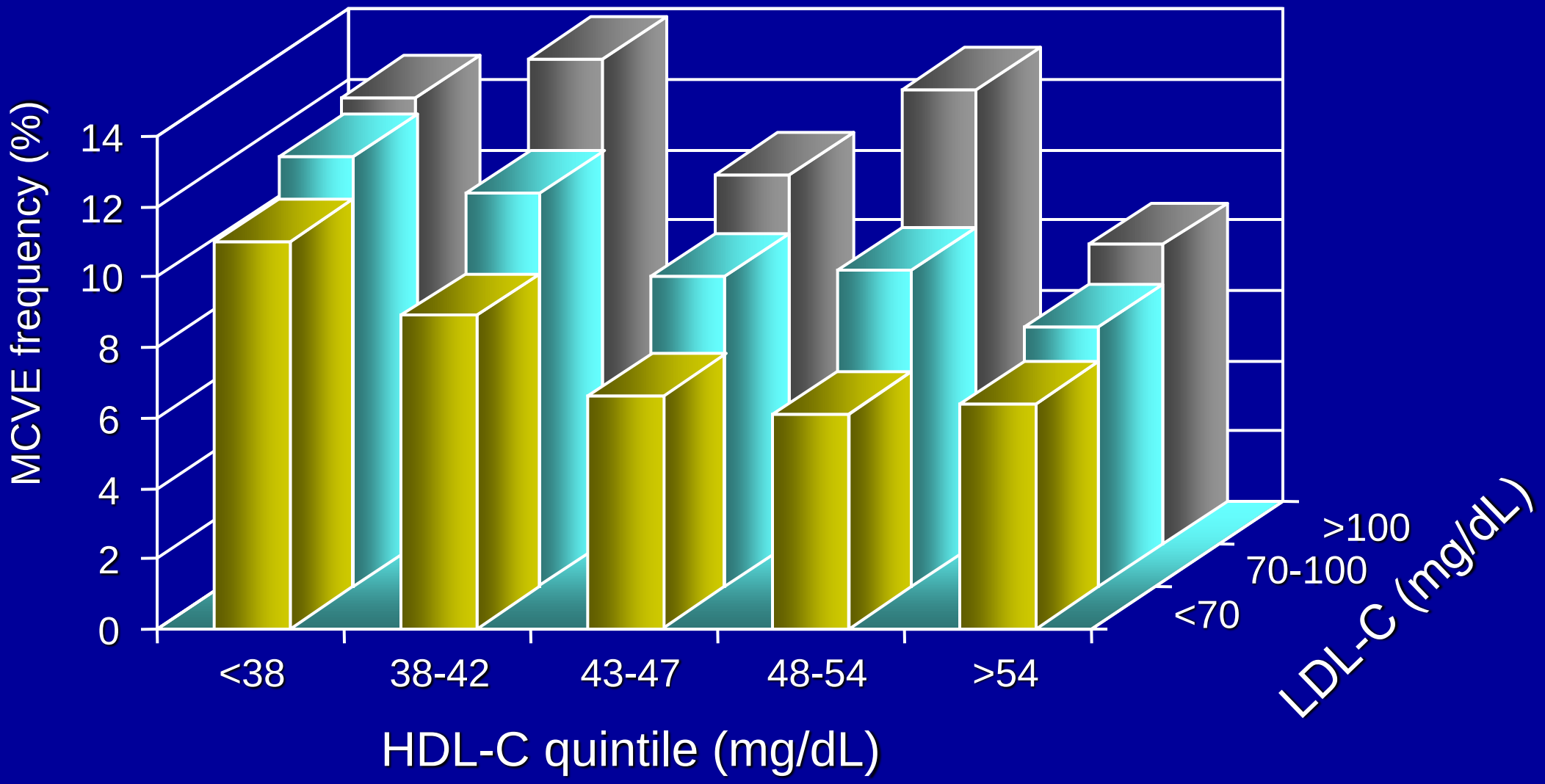
IVUS

- Measures wall precisely (not atheroma)
- Measures disease in a single proximal artery without critical disease, ie focuses on the portion with the LEAST luminal narrowing
- More precise method to measure changes in vessel wall and lumen size for CAD
- Clinical significance of progression and regression?

QCA

- Measures lumen dimension
- Examines the entire coronary bed including branches
- Focuses on the portion with the GREATEST luminal narrowing
- More sensitive to picking of thrombotic luminal narrowing due to atherothrombotic events anywhere in coronary bed
- Progression as defined by QCA predicts clinical events
- Significance of regression in regards to clinical events unclear

MCVE Frequency by LDL and HDL levels in TNT

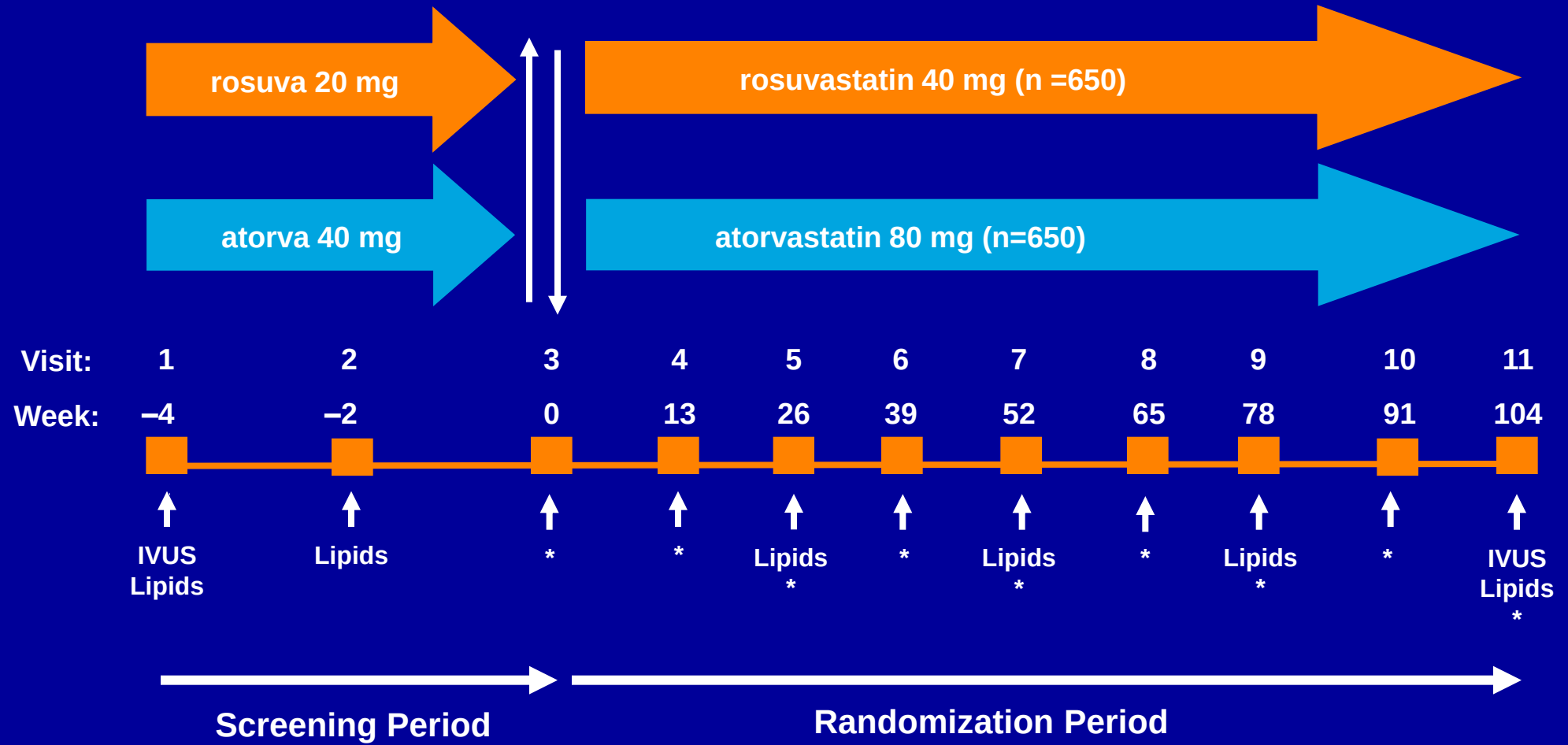


Barter et al, NEJM 2007, 357; 13, 1301-1310

SATURN

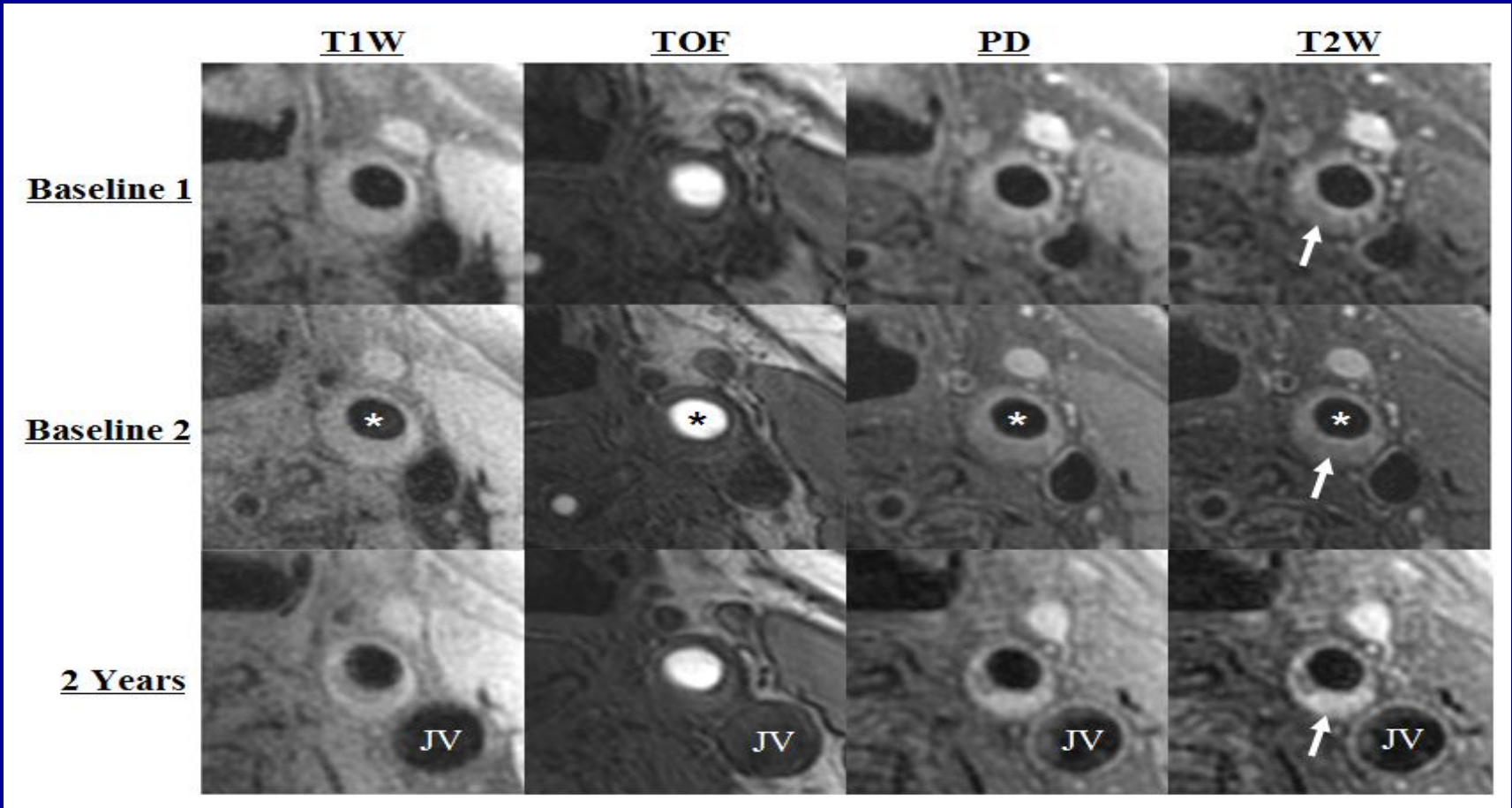
1300 patients with symptomatic CAD (angiographic stenosis >20%)

LDL-C with (>80 mg/dL) or without (>100 mg/dL) statin use last 4 weeks



* Safety assessments

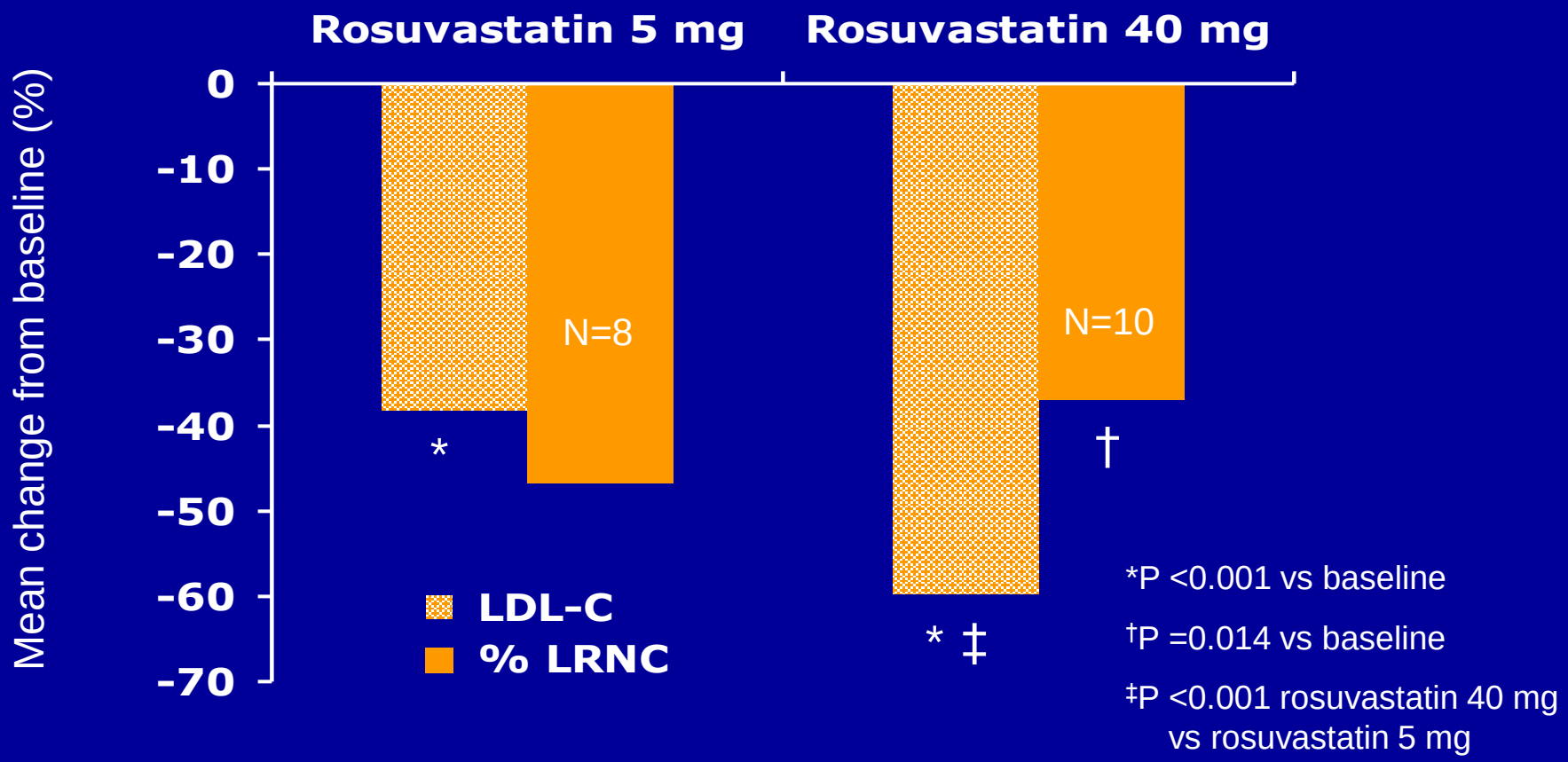
ORION: Example of Change in Plaque Composition over 2 Years with Rosuvastatin Treatment



T1W=T1-weighted; TOF=time-of-flight; PD=proton density; T2W=T2-weighted; *=lumen; JV=jugular vein

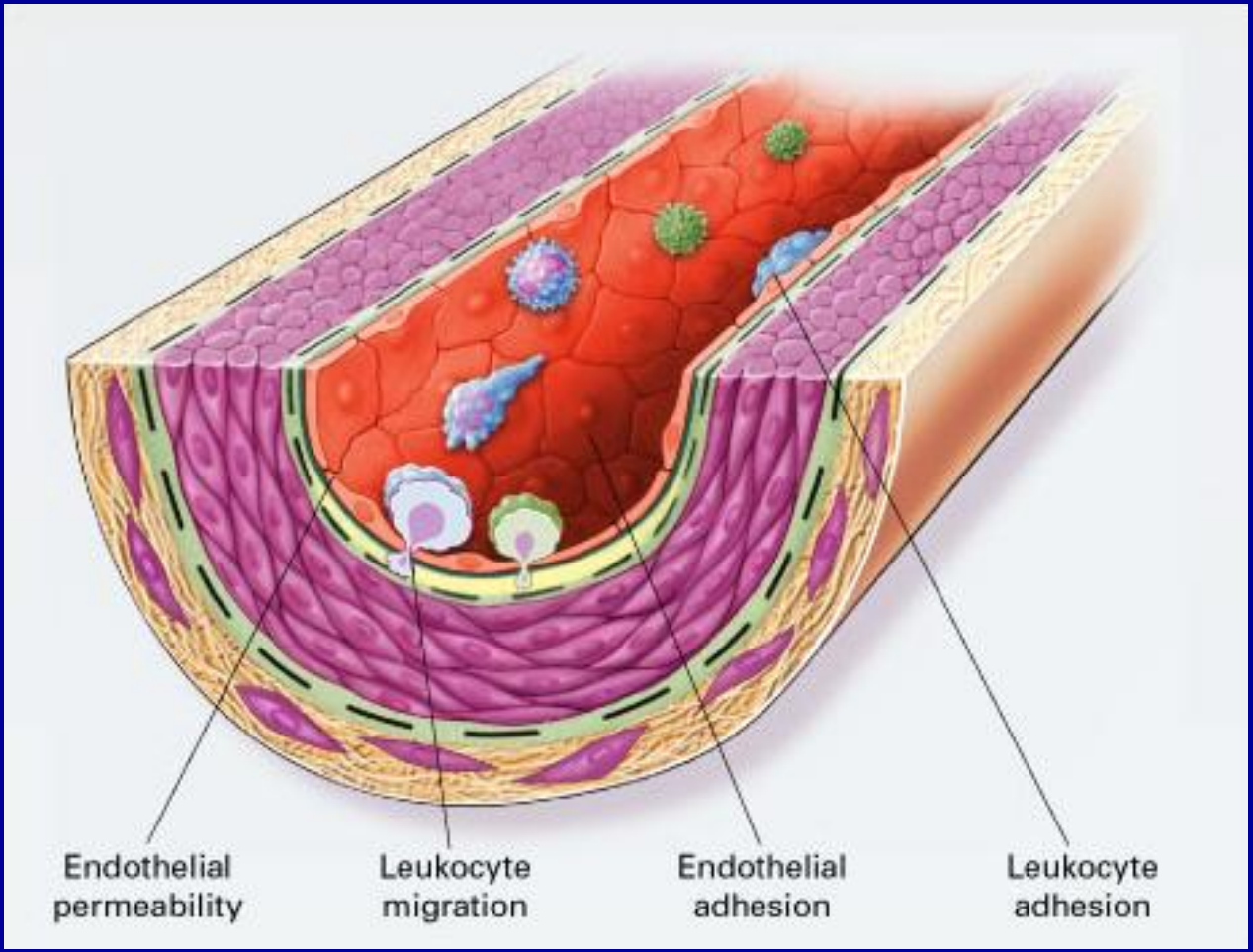
Underhill HR et al. Am Heart J 2008; 155: 584.e1–e8

ORION: Reduction in LDL-C and Lipid-Rich Necrotic Core with Rosuvastatin



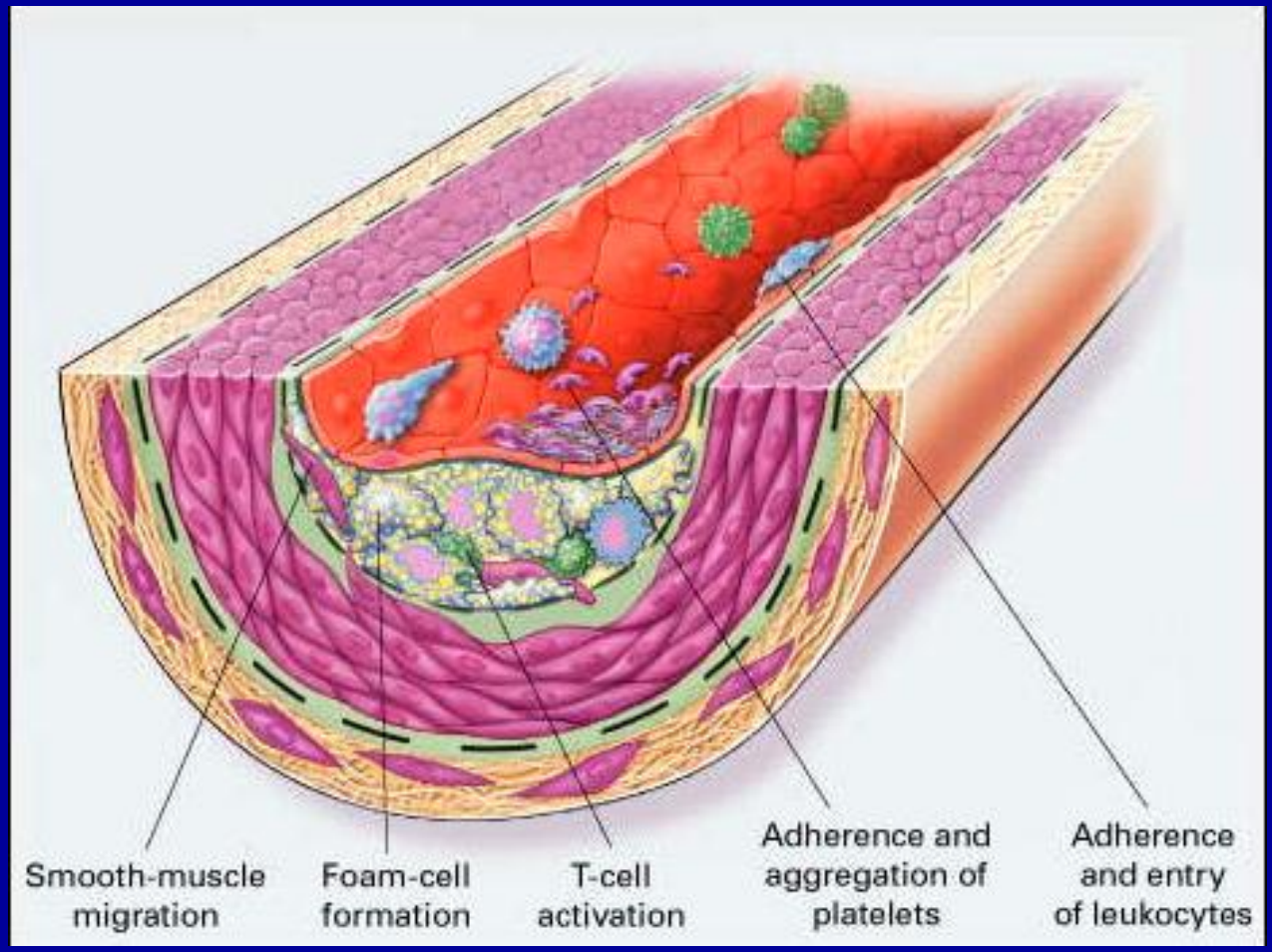
Underhill HR, et al. Am Heart J. 2008;155:584e1–584e8

Endothelial Dysfunction in Atherosclerosis



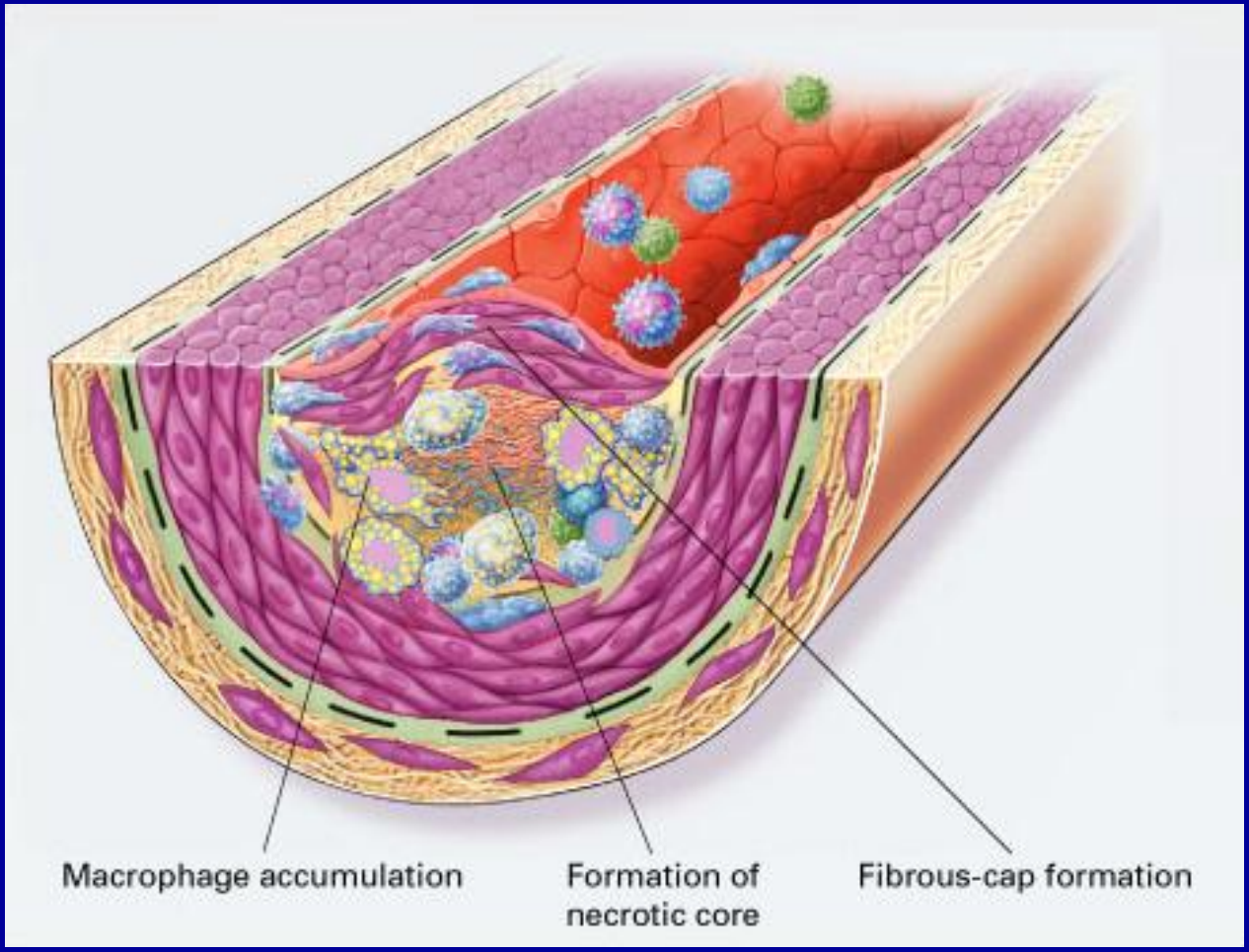
Ross R. *N Engl J Med* 1999; 340:115–126.

Fatty-Streak Formation in Atherosclerosis



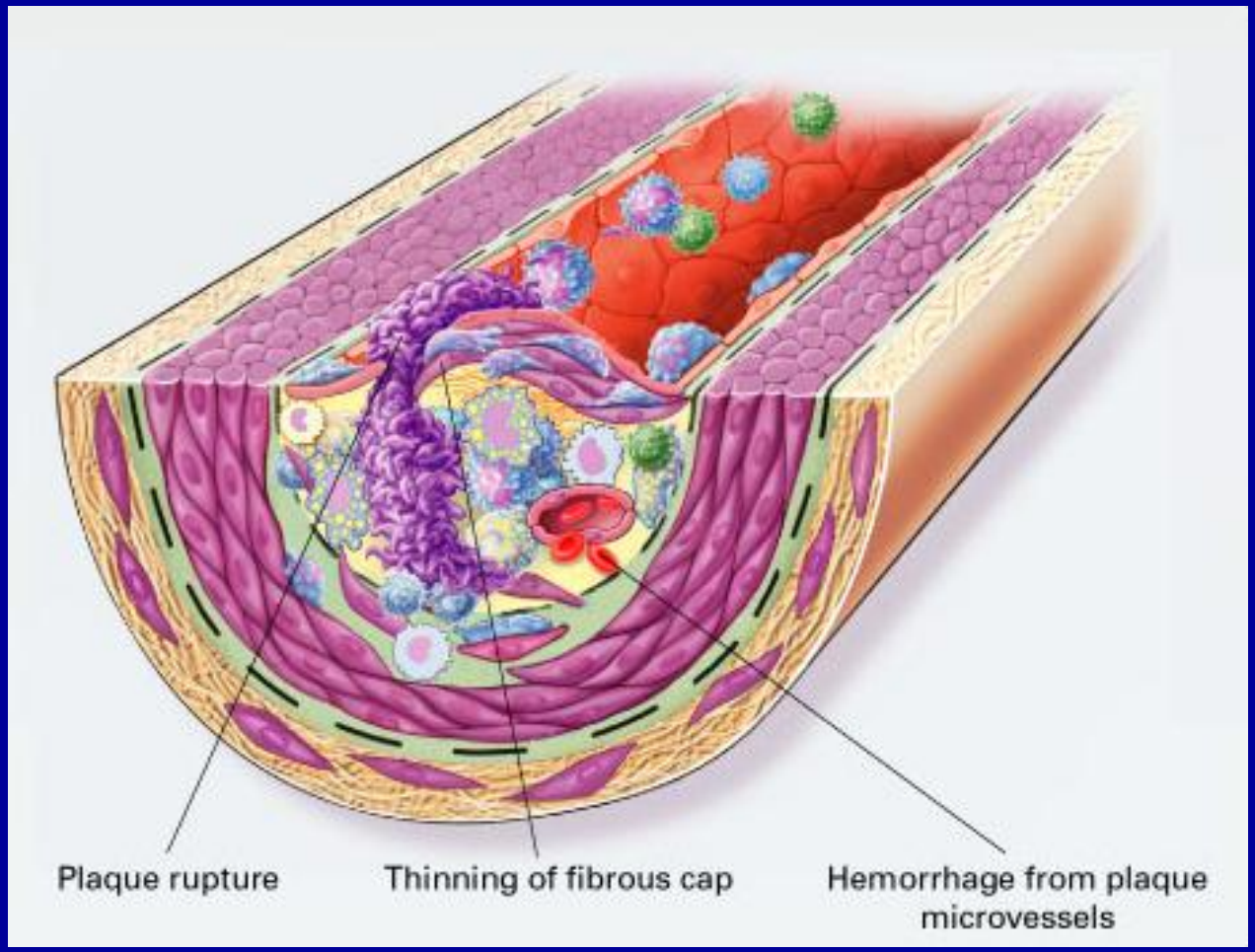
Ross R. *N Engl J Med* 1999; 340:115–126.

Formation of an Advanced, Complicated Lesion in Atherosclerosis



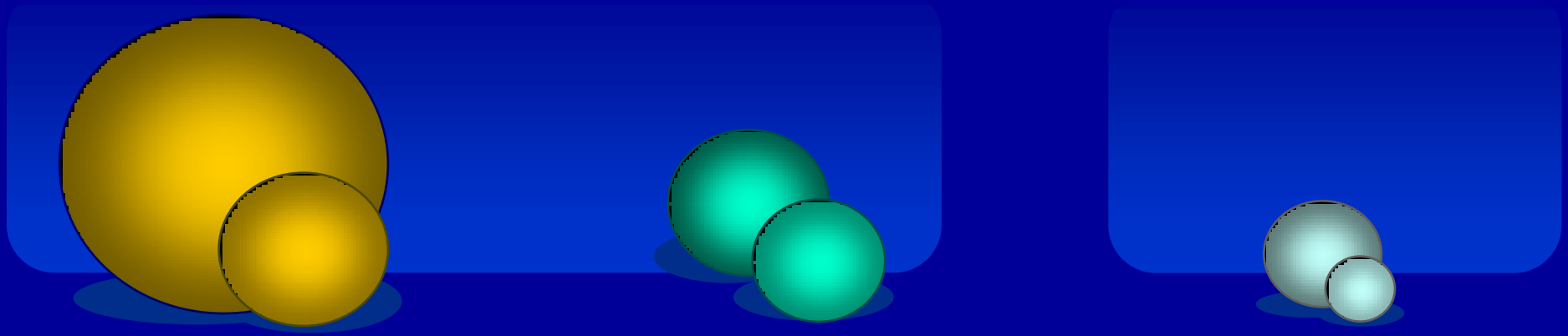
Ross R. *N Engl J Med* 1999; 340:115–126.

Unstable Fibrous Plaques in Atherosclerosis



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

Lipoprotein Classes and Inflammation



Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

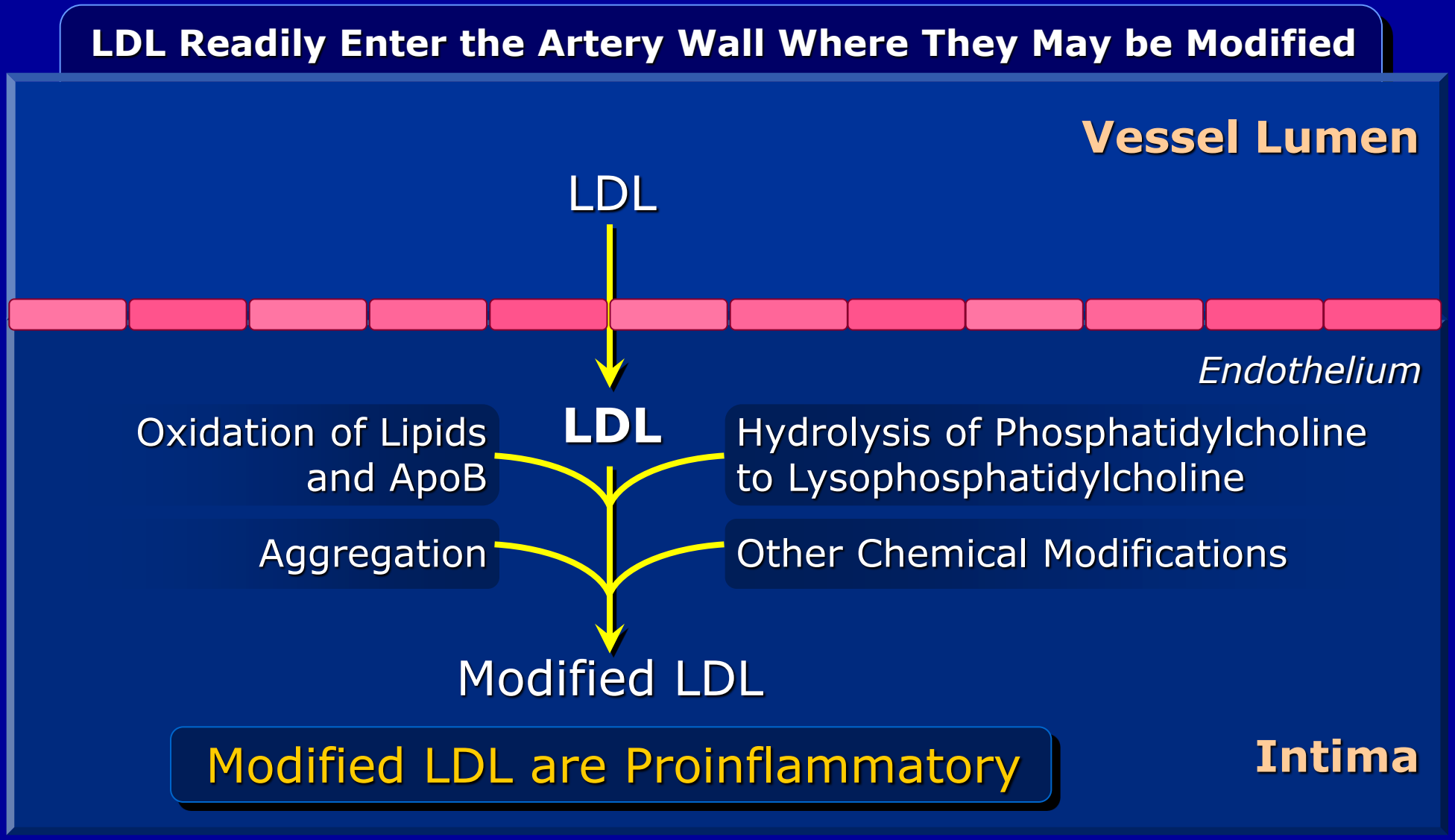
> 30 nm *20–22 nm* *9–15 nm*

Potentially proinflammatory

Potentially anti-inflammatory

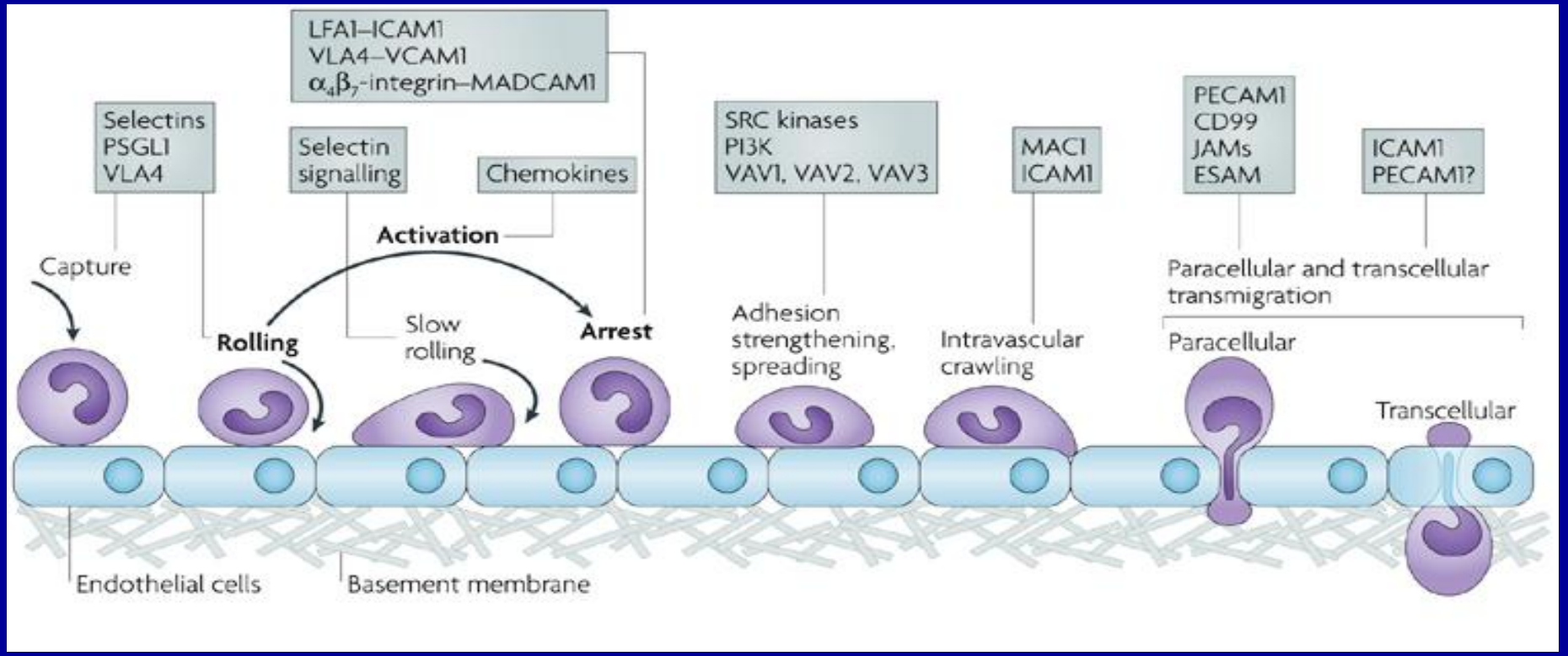
Doi H et al. *Circulation* 2000;102:670-676; Colome C et al. *Atherosclerosis* 2000; 149:295-302; Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.

Role of LDL in Inflammation



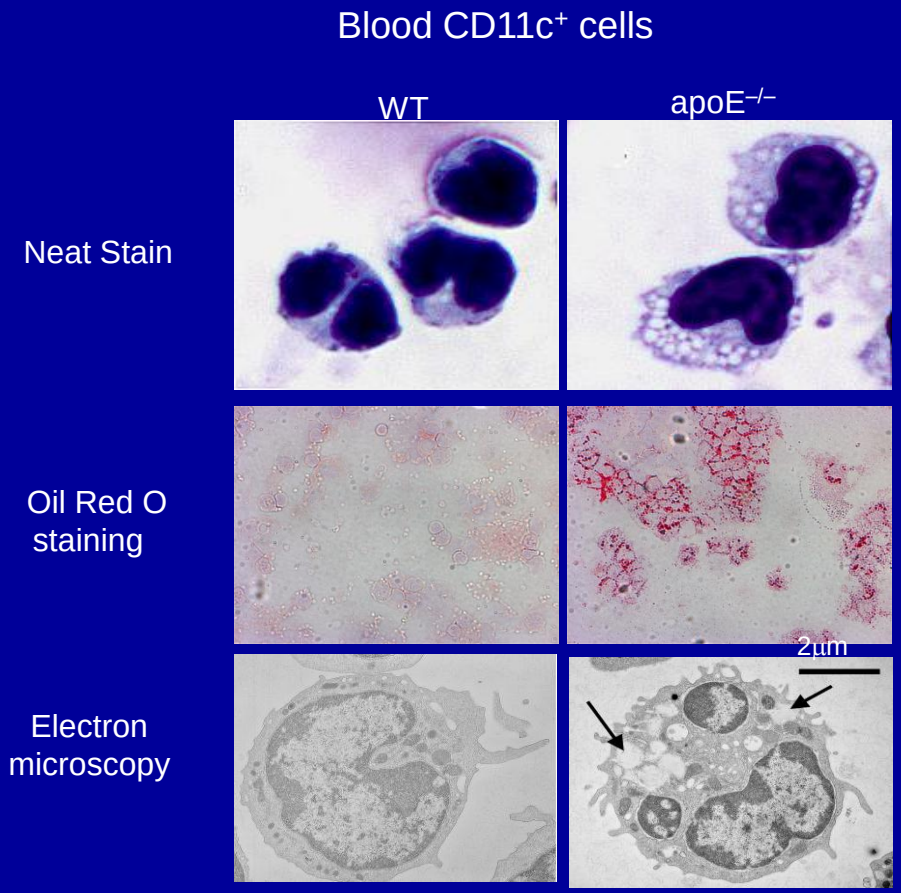
Steinberg D et al. *N Engl J Med* 1989;320:915-924.

Adhesion molecules mediate leukocyte migration



Ley K, et al. Nat Rev Immunol. 2007;7:678-89

Characteristics of Monocytes from Blood of ApoE$^{-/-}$ Mice on High-Fat Diet

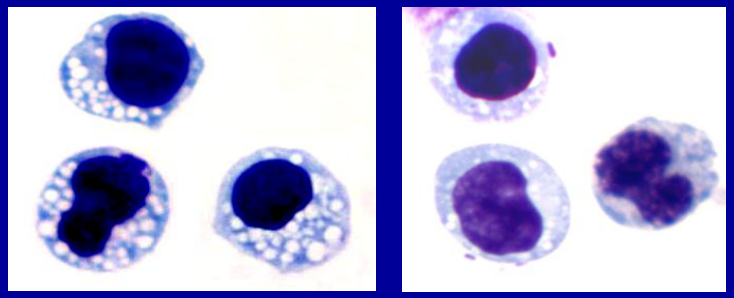


Wu H et al. *Circulation* 2009;119:2708–2717.

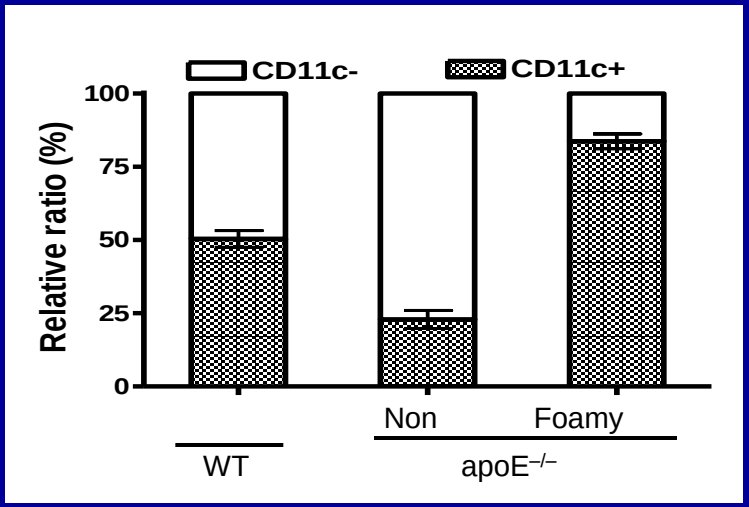
The majority of foamy monocytes were CD11c^{+} in blood of apoE$^{-/-}$ mice on HFD

Neat Stain of monocytes from apoE$^{-/-}$

CD11c^{+} CD11c^{-}



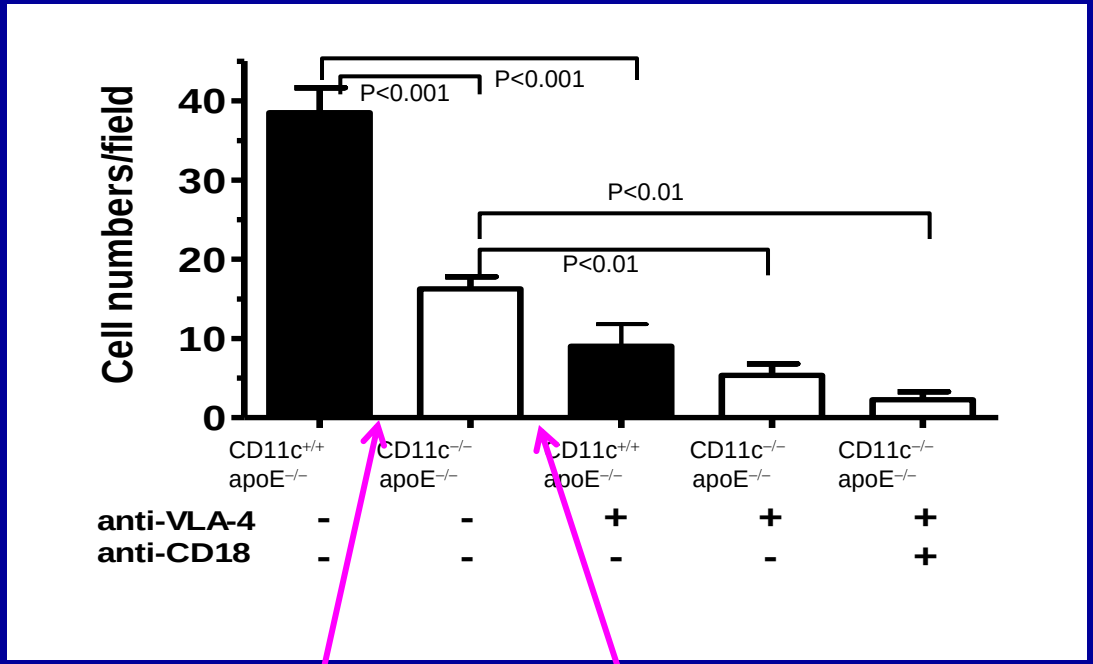
Relative ratio of CD11c^{+} to CD11c- monocytes



Wu H, et al. Circulation. 2009 May 26;119(20):2708-17.

CD11c and VLA-4 cooperate in monocyte capture and firm arrest

MNCs arrested at 2 dyne/cm^2



60% decrease

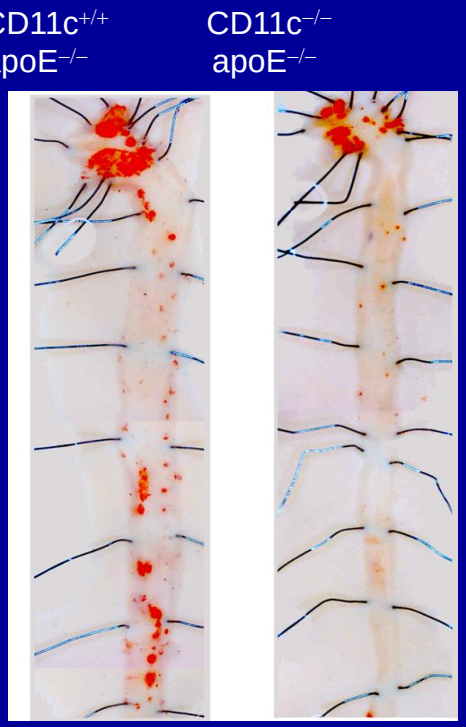
75% decrease

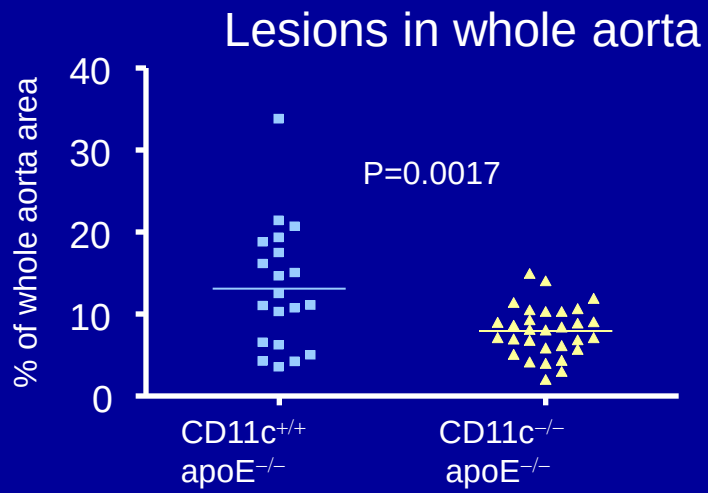
CD11c and VLA-4 contributions are not additive.
They cooperate to mediate efficient monocyte arrest on VCAM-1

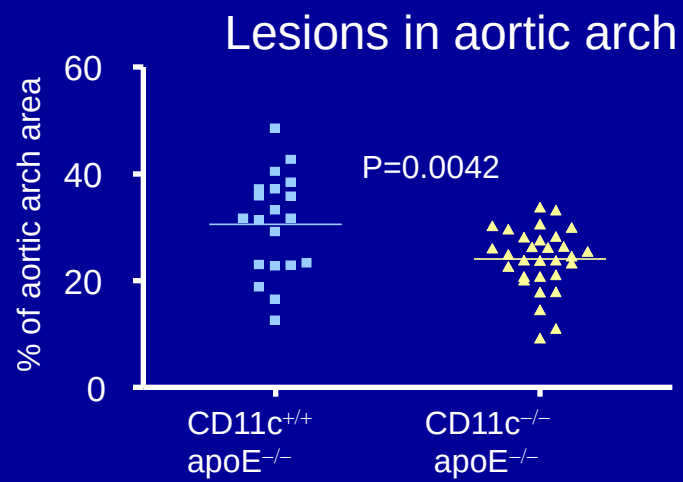
Wu H, et al. Circulation. 2009 May 26;119(20):2708-17.

CD11c and Atherosclerosis in ApoE$^{-/-}$ Mice

Sudan IV staining of mouse aortas

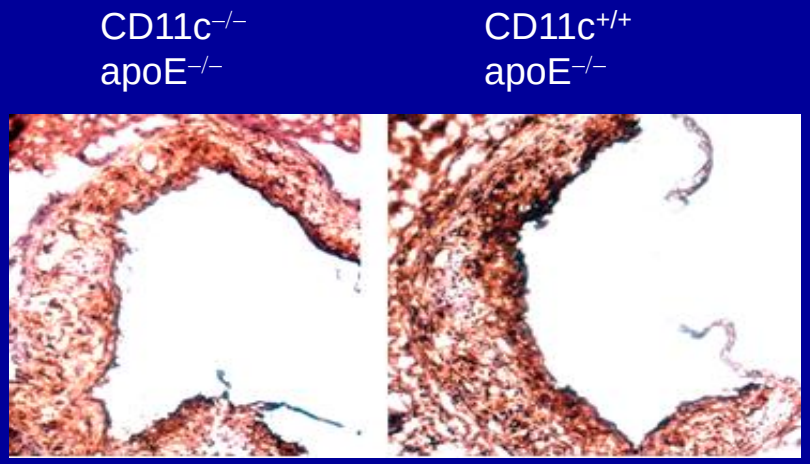


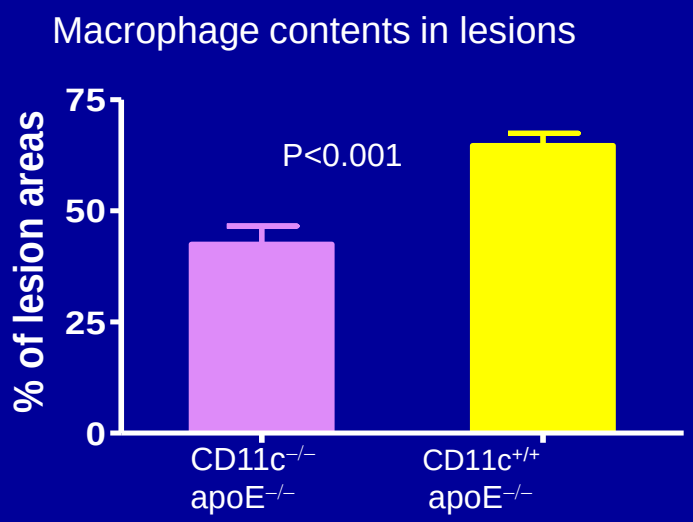




Wu H et al. *Circulation* 2009;119:2708–2717.

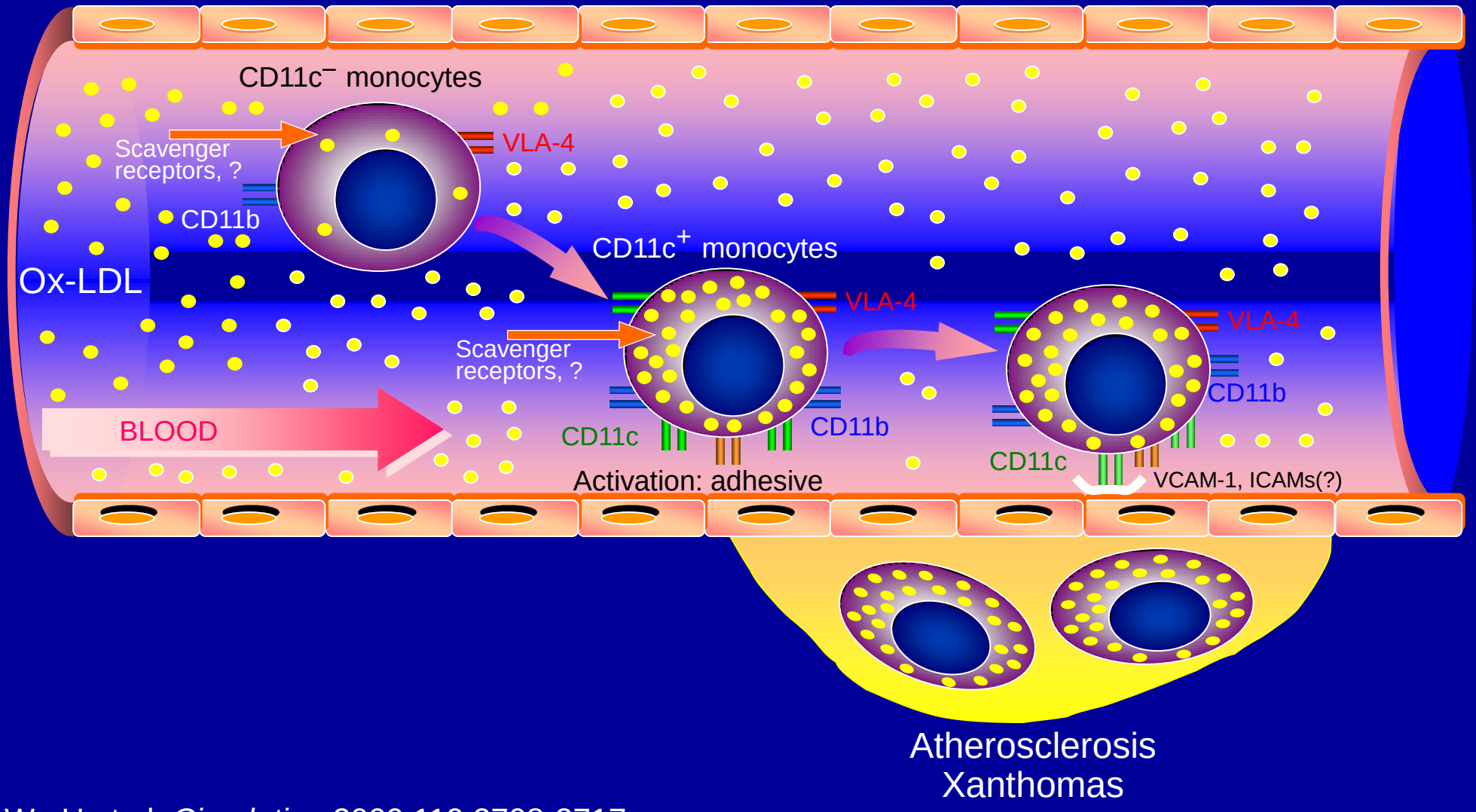
Deficiency of CD11c decreases macrophage contents in atherosclerotic lesions of apoE$^{-/-}$ mice





Wu H, et al. Circulation. 2009 May 26;119(20):2708-17.

A Model for Involvement of CD11c in Atherogenesis in Hypercholesterolemia



Wu H et al. *Circulation* 2009;119:2708-2717.

CD11c/CD18 Expression Is Upregulated on Blood Monocytes During Hypertriglyceridemia and Enhances Adhesion to Vascular Cell Adhesion Molecule-1

R. Michael Gower, Huaizhu Wu, Greg A. Foster, Sridevi Devaraj, Ishwarlal Jialal, Christie M. Ballantyne, Anne A. Knowlton, Scott I. Simon

Objective—Atherosclerosis is associated with monocyte adhesion to the arterial wall that involves integrin activation and emigration across inflamed endothelium. Involvement of β_2-integrin CD11c/CD18 in atherogenesis was recently shown in dyslipidemic mice, which motivates our study of its inflammatory function during hypertriglyceridemia in humans.

Methods and Results—Flow cytometry of blood from healthy subjects fed a standardized high-fat meal revealed that at 3.5 hours postprandial, monocyte CD11c surface expression was elevated, and the extent of upregulation correlated with blood triglycerides. Monocytes from postprandial blood exhibited an increased light scatter profile, which correlated with elevated CD11c expression and uptake of lipid particles. Purified monocytes internalized triglyceride-rich lipoproteins isolated from postprandial blood through low-density lipoprotein–receptor–related protein-1, and this also elicited CD11c upregulation. Laboratory-on-a-chip analysis of whole blood showed that monocyte arrest on a vascular cell adhesion molecule-1 (VCAM-1) substrate under shear flow was elevated at 3.5 hours and correlated with blood triglyceride and CD11c expression. At 7 hours postprandial, blood triglycerides decreased and monocyte CD11c expression and arrest on VCAM-1 returned to fasting levels.

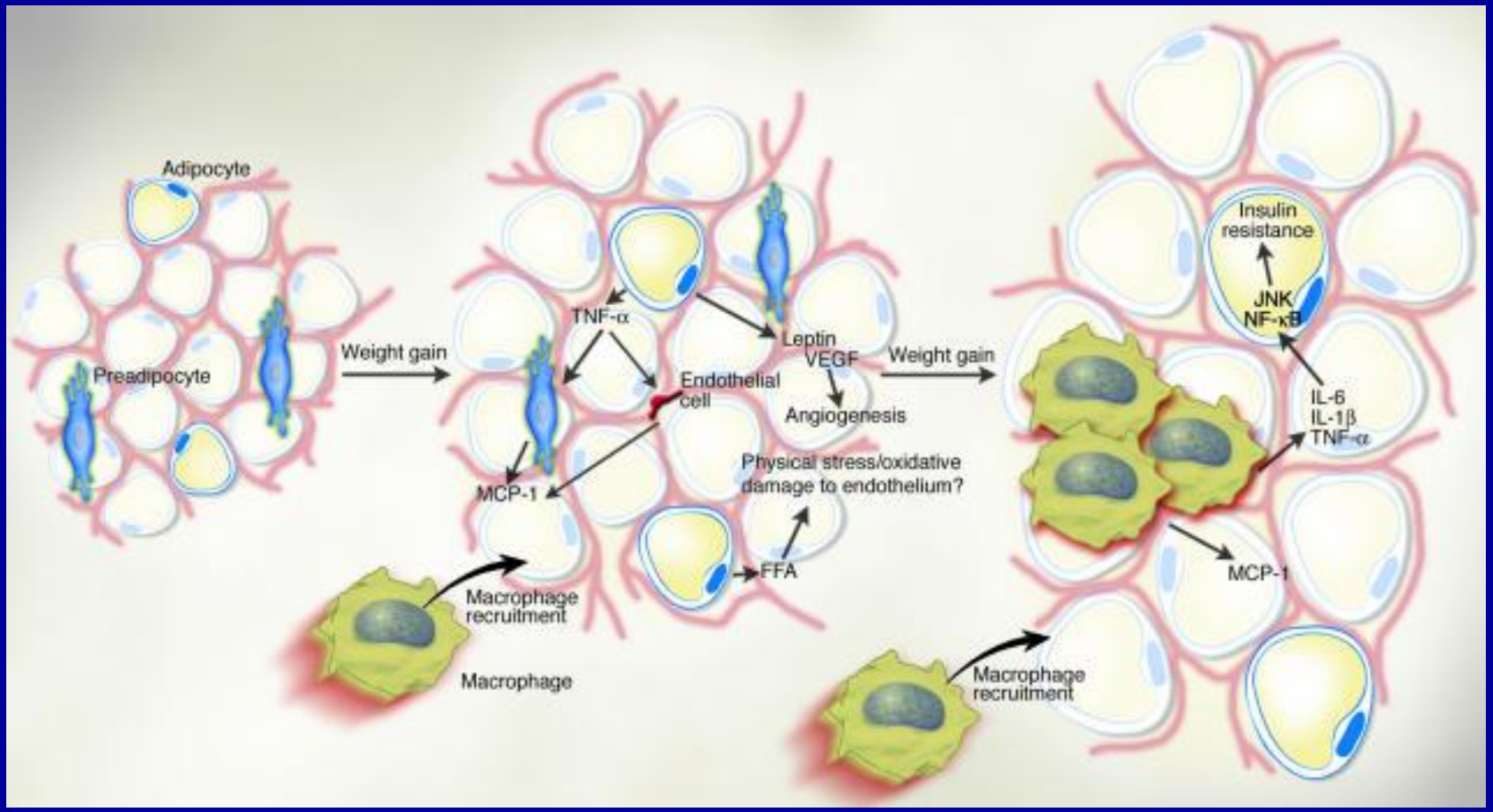
Conclusion—During hypertriglyceridemia, monocytes internalize lipids, upregulate CD11c, and increase adhesion to VCAM-1. These data suggest that analysis of monocyte inflammation may provide an additional framework for evaluating individual susceptibility to cardiovascular disease. (*Arterioscler Thromb Vasc Biol*. 2011;31:00-00.)

Inflammation in Adipose Tissue is Present with Obesity and Plays a Crucial Role in Obesity Related Insulin Resistance

- Increased expression of inflammatory genes in white adipose tissue of mice with obesity due to genetic causes, greatest increase in obesity induced by very high fat diet
- Macrophages present in adipose tissue and reduced by treatment with rosiglitazone
- Positive correlation between macrophage markers, BMI, and adipocyte size in both mouse and man
- Bone marrow transplants and macrophage deficient mice show most are CSF-1 dependent, bone marrow derived
- Most TNF alpha in adipose tissue derived from macrophages

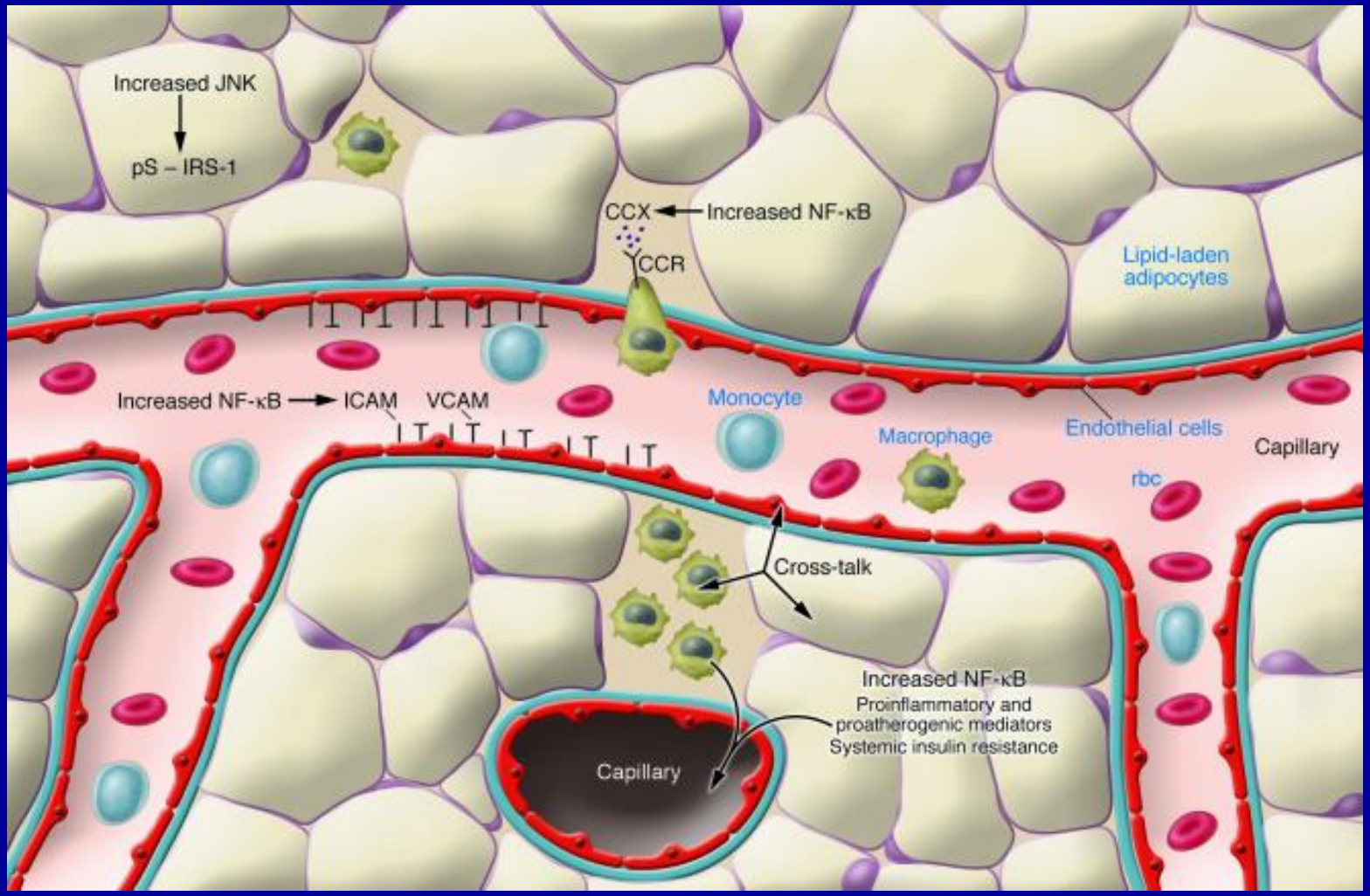
Weisberg SP et al. *J Clin Invest* 2003;112:1796-1808.
Xu H et al. *J Clin Invest* 2003;112:1821-1830.

Obese Adipose Tissue is Characterized by Inflammation and Progressive Infiltration by Macrophages as Obesity Develops



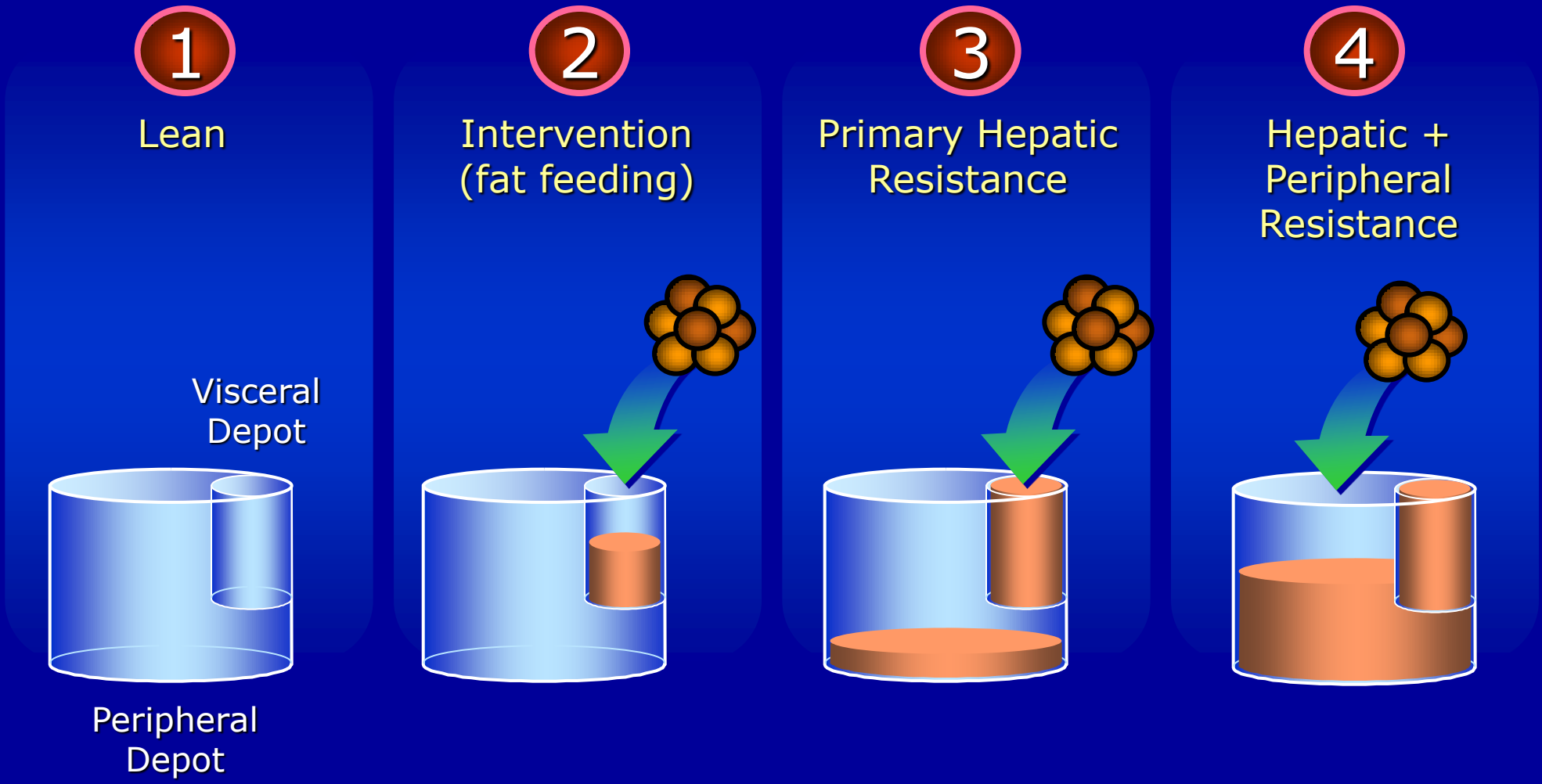
Wellen KE et al. *J Clin Invest* 2006;116:1785–1788.

Potential Mechanisms for Activation of Inflammation in Adipose Tissue

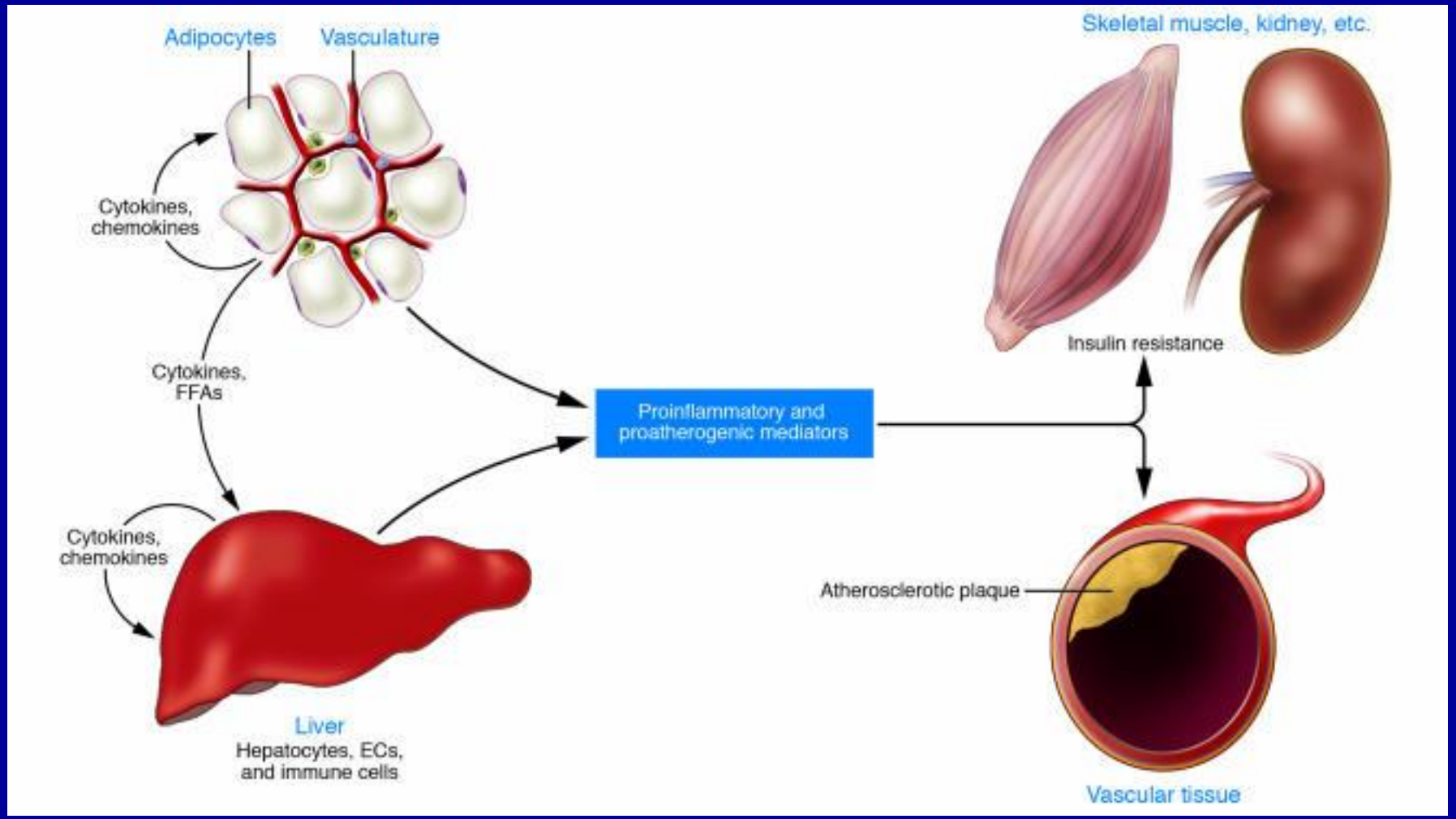


Shoelson SE et al. *J Clin Invest* 2006;116:1793–1801.

Overflow Hypothesis



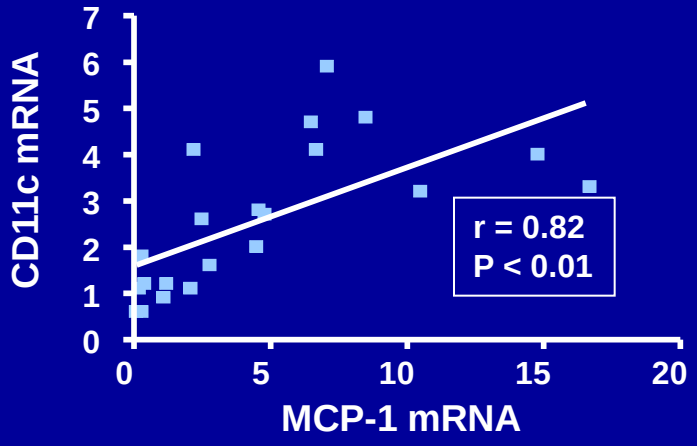
Local, Portal, and Systemic Effects of Inflammation in Insulin Resistance and Atherogenesis



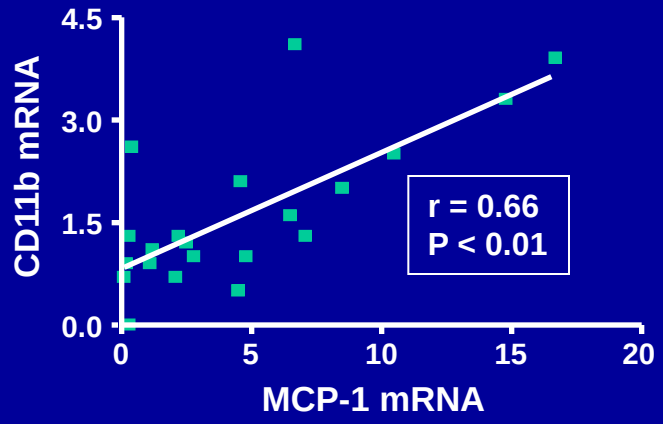
Shoelson SE et al. *J Clin Invest* 2006;116:1793–1801.

CD11c, CD11b, and MCP-1 in Human AT or Blood

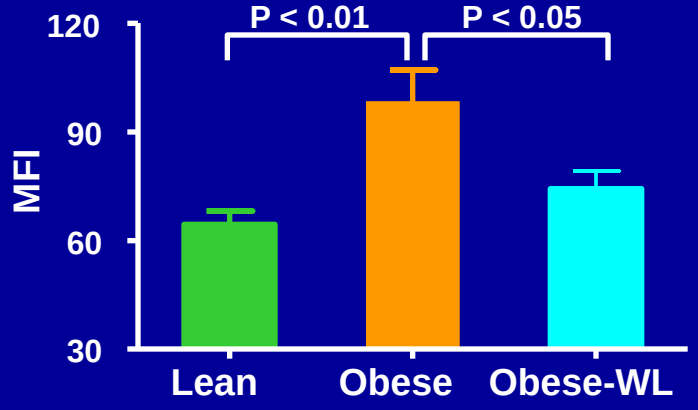
Relationship of MCP-1 with CD11c in human VAT



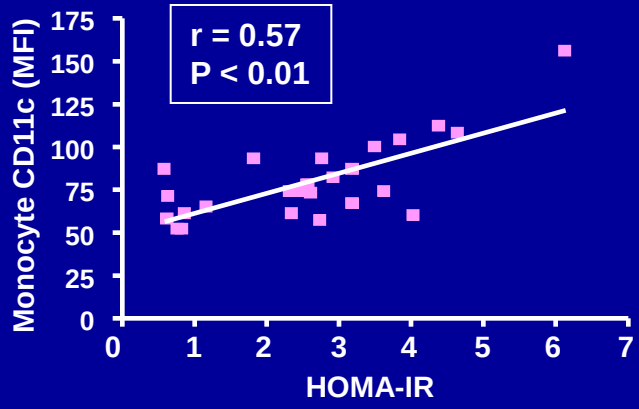
Relationship of MCP-1 with CD11b in human VAT



CD11c level on human monocytes



Relationship of monocyte CD11c with HOMA-IR in humans



Wu H et al. *Arterioscler Thromb Vasc Biol.* 2010;30:186-192.

Can Anti-Inflammatory Therapy Reduce Cardiometabolic Risk?

- High-dose sodium salicylate shown to reduce glycosuria[1,2]
- Small studies showed reduction in fasting glucose with high-dose ASA[3,4]
- Effects of ASA on IKK/NF-κB axis[5,6]
- May explain some benefits seen with TZD and ACE on diabetes prevention

1. Ebstein W. *Berliner Klinische Wochenschrift* 1876;13:337
2. Williamson RT. *BMJ* 1901;1:760
3. Reid et al. *BMJ* 1957;2:1071
4. Hecht A et al. *Metabolism* 1959;8:418
5. Yuan M et al. *Science* 2001;293:1673
6. Hundal RS et al. *J Clin Invest* 2002;109:1321

Can Anti-Inflammatory Therapy Reduce Cardiometabolic Risk?

- MCP-1 and CCR2 are increased in adipose tissue with obesity
- CCR2 deficient mice had modest reduction in adipose inflammation, increased adiponectin, reduced hepatic steatosis and improved systemic glucose homeostasis
- Short term rx with CCR2 antagonist in mice with diet induced obesity did not alter weight, modest reduction in macrophages in adipose tissue with improved HOMA-IR

Weisberg SP et al. *J Clin Invest* 2006;116:115-124.

The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY)

- 15,828 men and women with CHD and ≥1 of the following:
  - age ≥60 years
  - Diabetes requiring medication
  - Low HDL-C
  - Current or recent smoking
  - Mildly or moderately reduced kidney function
  - Cerebrovascular disease or PAD
- Randomized to darapladib 160 mg/d or placebo; each in addition to standard therapy
- **Primary endpoint:** Time to the first MACE: CV death, nonfatal myocardial infarction, nonfatal stroke
- Anticipated study duration: 2.75 years (median)

White H et al. *Am Heart J* 2010;160:655-661.

Summary

1. LDL and HDL are associated with progression of atherosclerosis and atherothrombotic events
2. LDL contributes to vascular inflammation; HDL may inhibit this process
3. Chronic inflammation promotes vascular inflammation and may increase atherogenicity of lipoproteins
4. Obesity, metabolic syndrome, and diabetes are associated with chronic inflammation, leukocyte activation, and dyslipidemia