TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION IV:

THE NEW CARDIAC INTENSIVE CARE UNIT—NO LONGER THE CCU?

A. Lerman (Rochester—MN—USA)

When does a risk marker become a risk factor?

When does a Risk Marker becomes a Risk Factor?

Amir Lerman, MD
Professor of Medicine
Cardiovascular Division
Mayo Clinic, Rochester, MN

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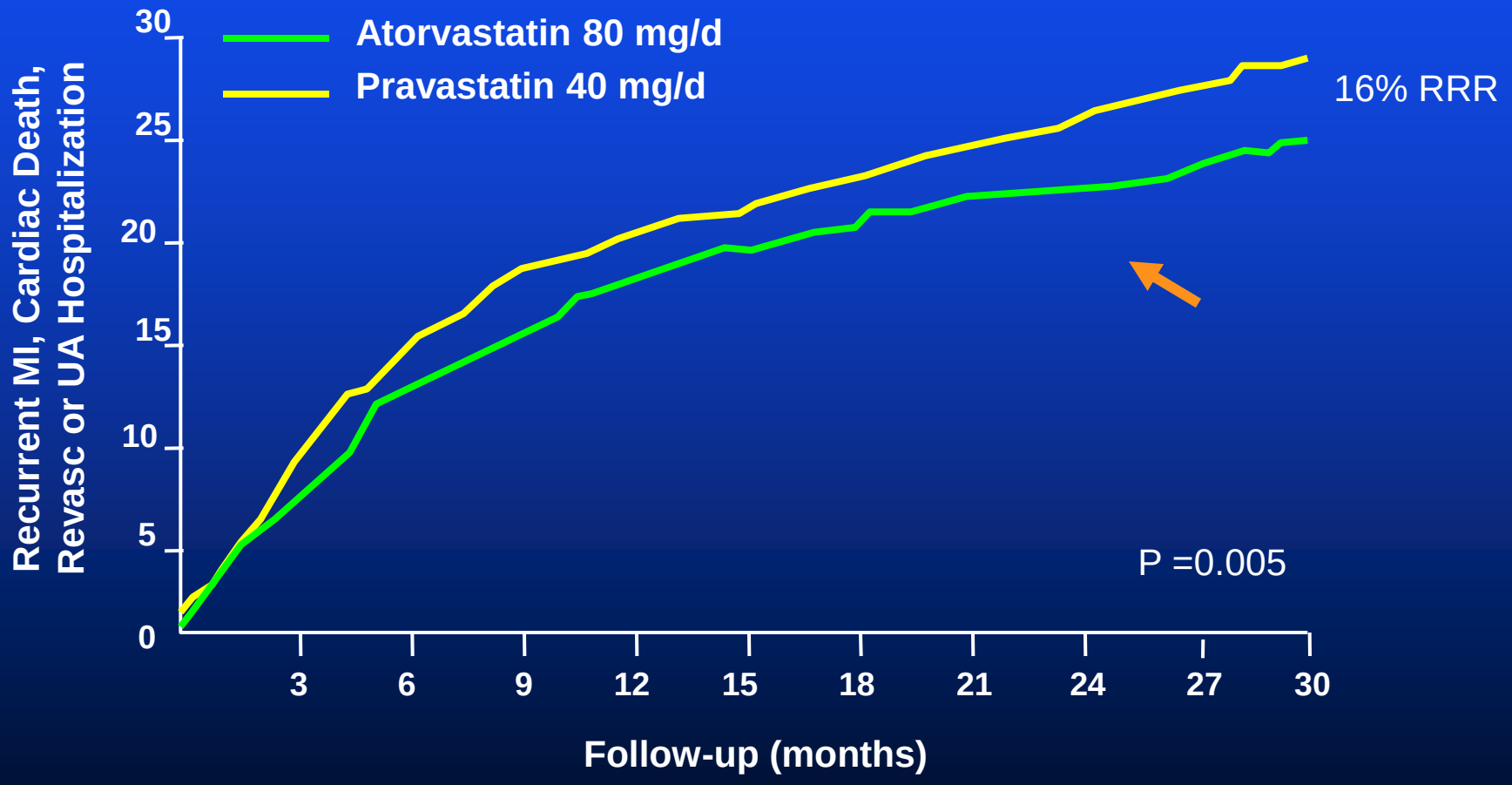
Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—TIMI 22 Study

- 4,162 patients with an ACS randomized to atorvastatin 80mg or pravastatin 40mg for 2 yrs.



Baseline LDL 106 and Baseline HDL 38-39

Cannon CP et al. *NEJM* 2004;350:1495-1504

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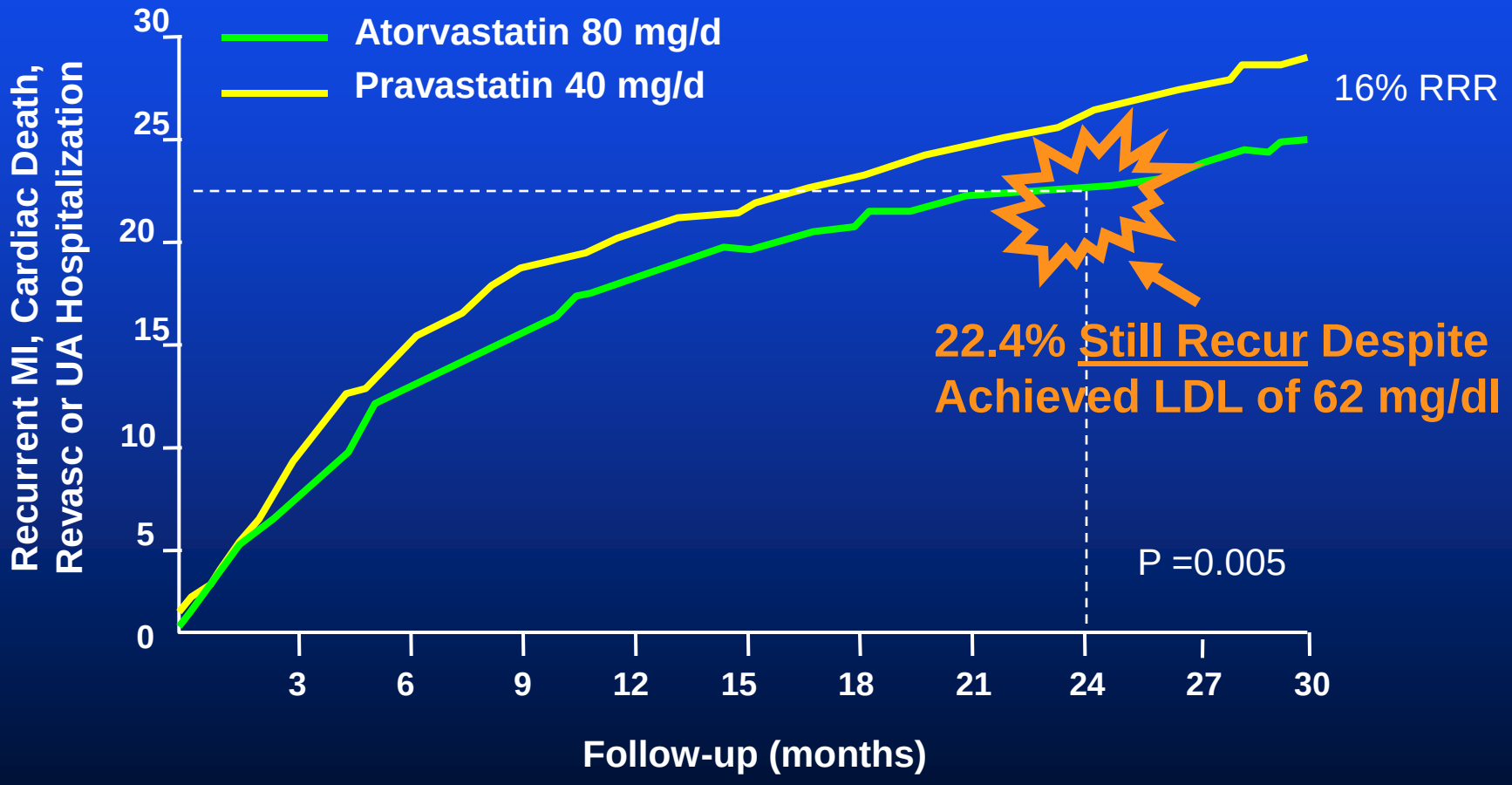

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Risk Marker or a Risk Factor

Molecular and basic mechanism

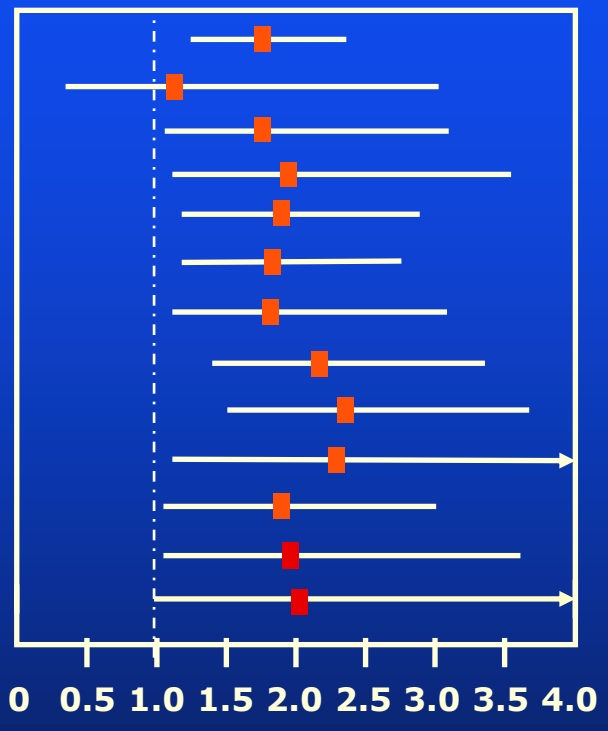
Plaque
- LDL
- ox LDL
- CRP
- IL-6
- IL-10
- IL-18
- Fbg
- TNF-

Unstable plaque
- MMP-9
- MPO
- ICAM
- VCAM
- LpPLA2

Plaque rupture
- sCD40L
- PIGF
- PAPP-A
- VCAM

Thrombosis
- PAI-1
- sCD40L
- VwF
- D-dimer

Epidemiology



Translation from basic mechanism to CV events in humans

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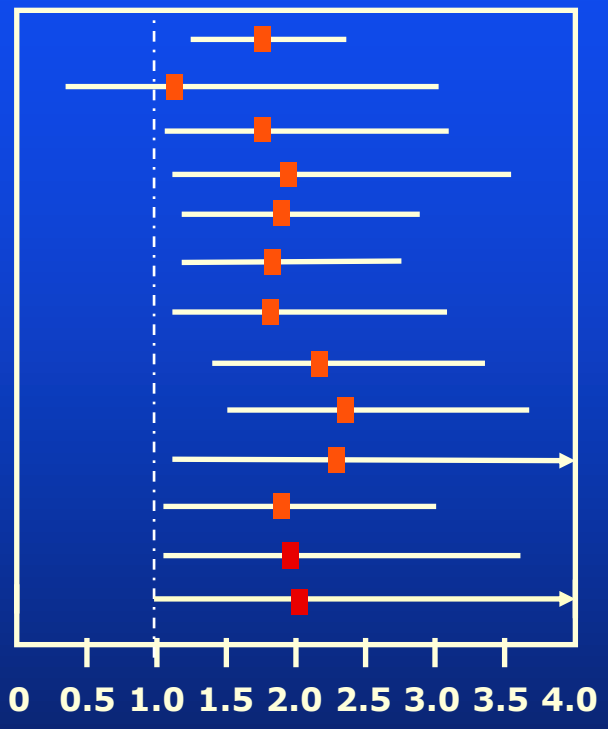
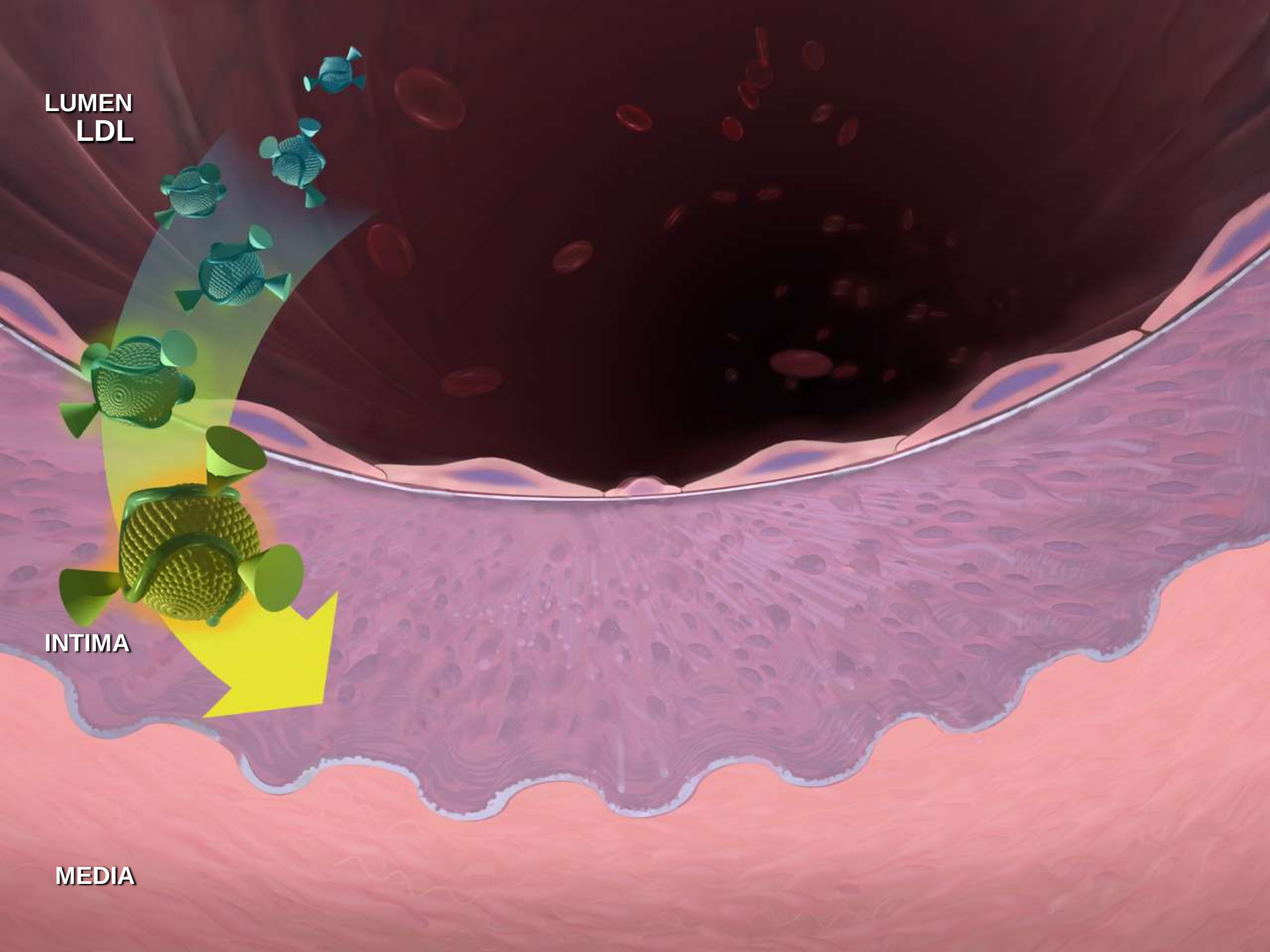
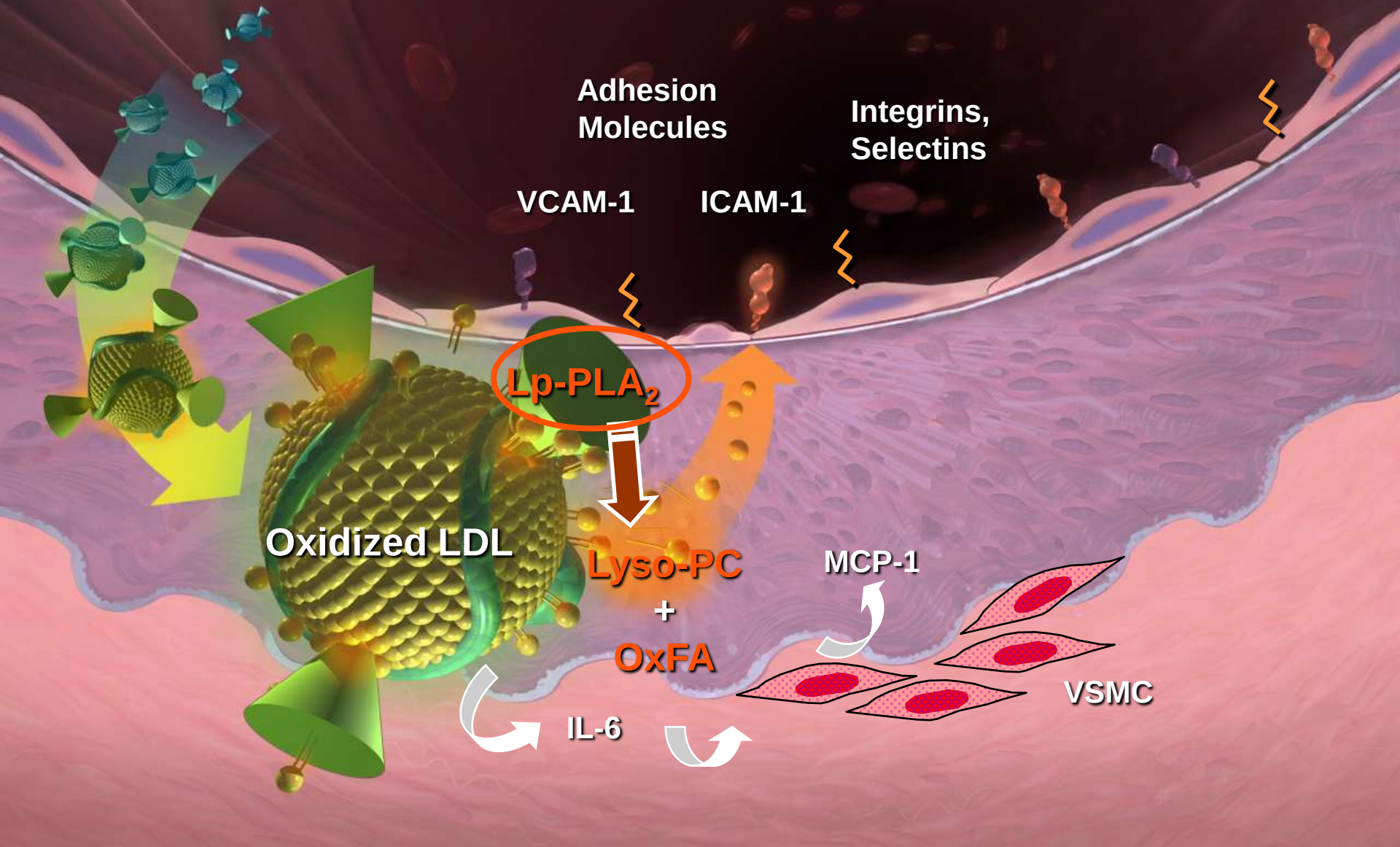


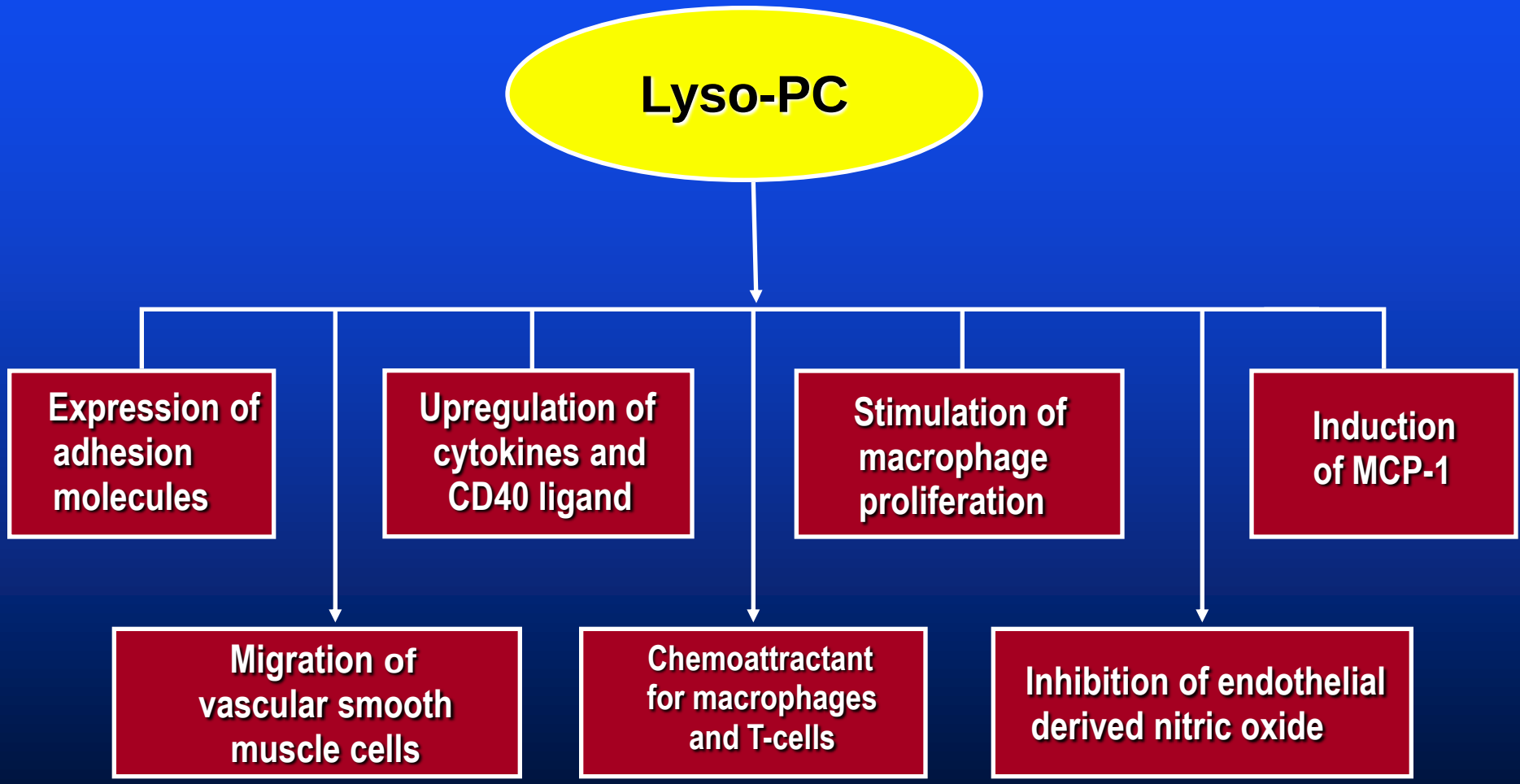
Lp-PLA$_2$ in early and advanced atherosclerosis in humans


LUMEN
LDL
INTIMA
MEDIA

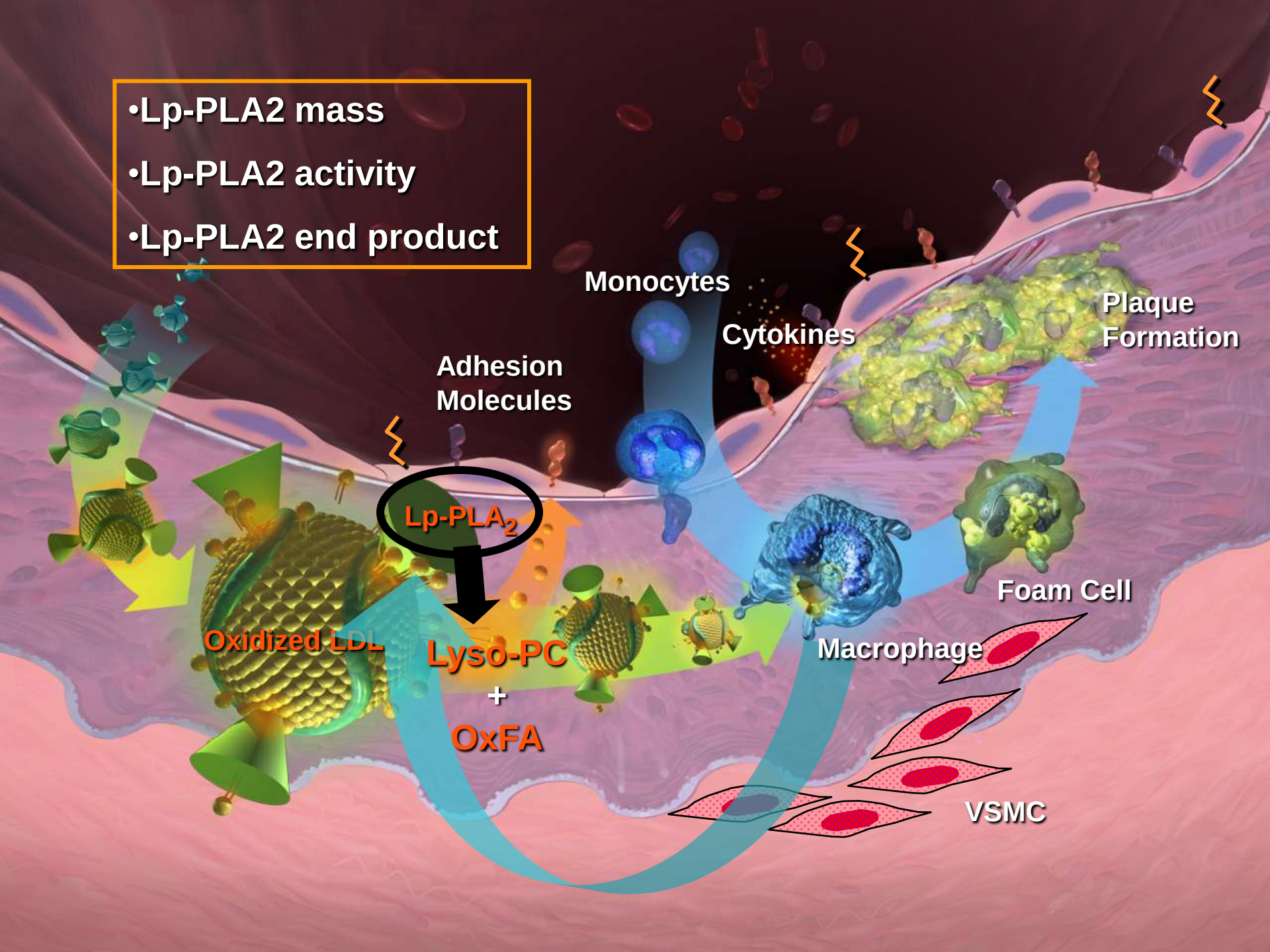
LDL is Oxidized in the Vascular Wall and its Oxidized Constituents are Released by Lp-PLA$_2$



Lysophosphatidylcholine (Lyso-PC) Exhibits Multiple Pro-Atherogenic Activities



1. Dada et al. *Expert Rev Mol Diagn*. 2002;2(1):89-94
2. Quinn et al. *Proc Natl Acad Sci USA*. 1988;85:2805-2809
3. MacPhee et al. *Biochem J*. 1999;338:479-487
4. Carpenter et al. *FEBS Lett*. 2001;505:357-363


•Lp-PLA2 mass
•Lp-PLA2 activity
•Lp-PLA2 end product
Monocytes
Cytokines
Plaque Formation
Adhesion Molecules
Lp-PLA2
Oxidized LDL
Lyso-PC
+
OxFA
Foam Cell
Macrophage
VSMC

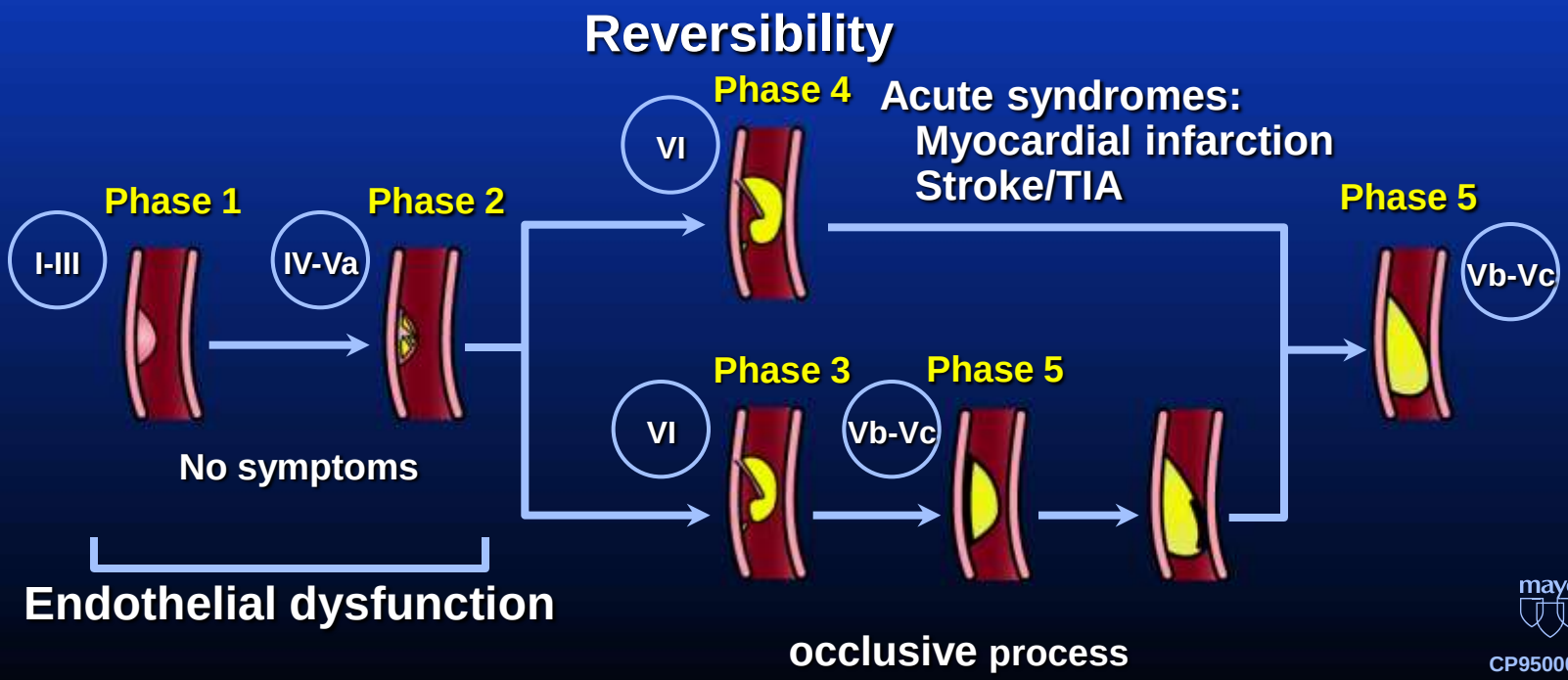
Risk Marker or a Risk Factor

Circulating and regional Levels

- Increase in early stage of the disease
- Correlates with the disease process
- Correlates with functional and structural abnormalities

Tissue Levels

- Increase in the plaque
- Associated with other known markers of disease.
- Correlates with functional abnormalities



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CP950001- 1

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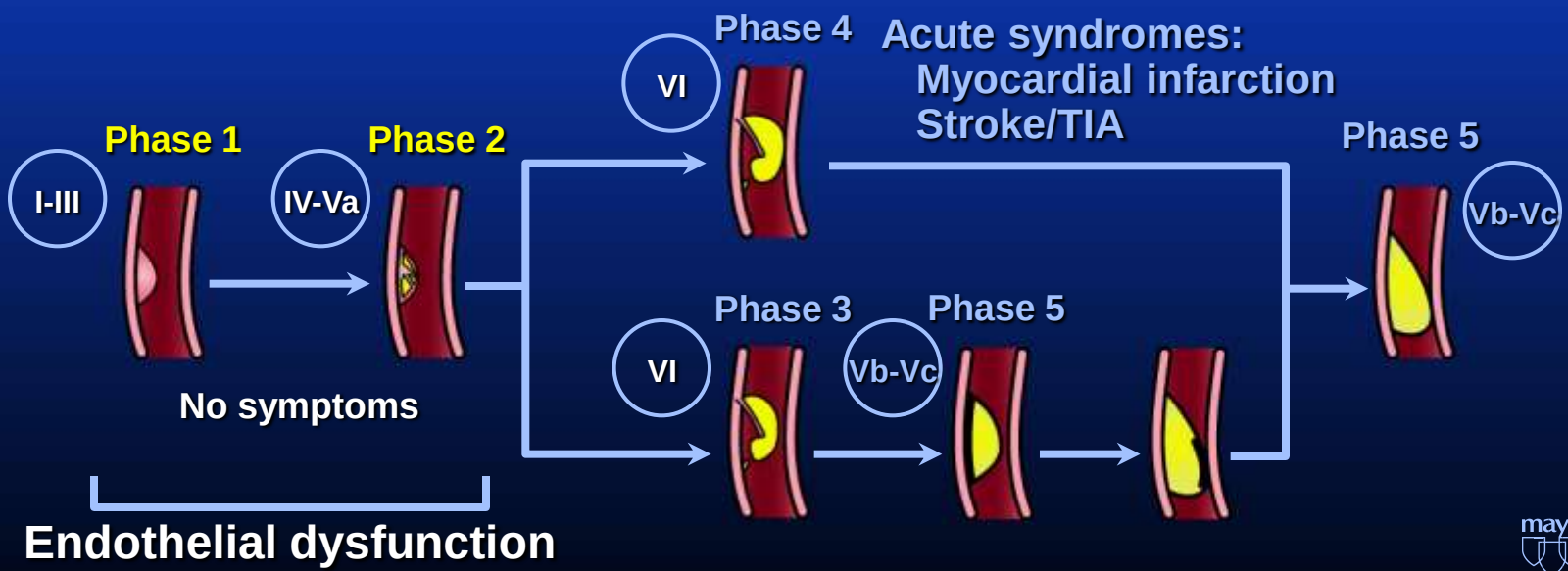
Reversibility



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Early Atherosclerosis and endothelial dysfunction

Smoking

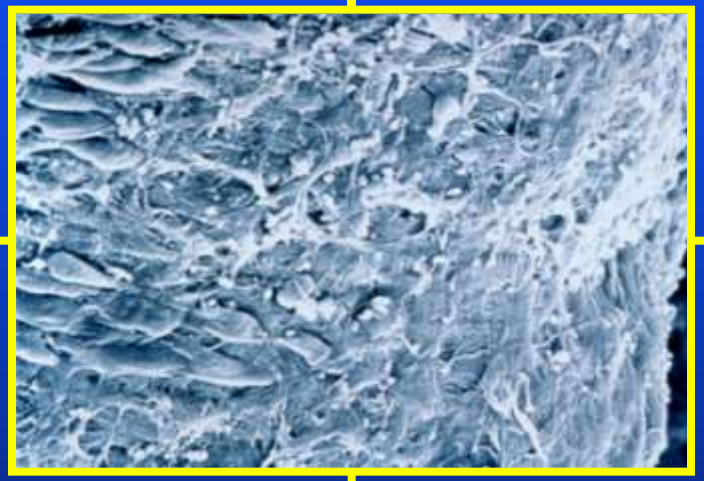
Hypertension

Hypercholesterolemia

Obesity

Diabetes

New risk factors



Genomic predisposition

Endothelial dysfunction: The risk of the risk factors

Vascular lesion and remodeling

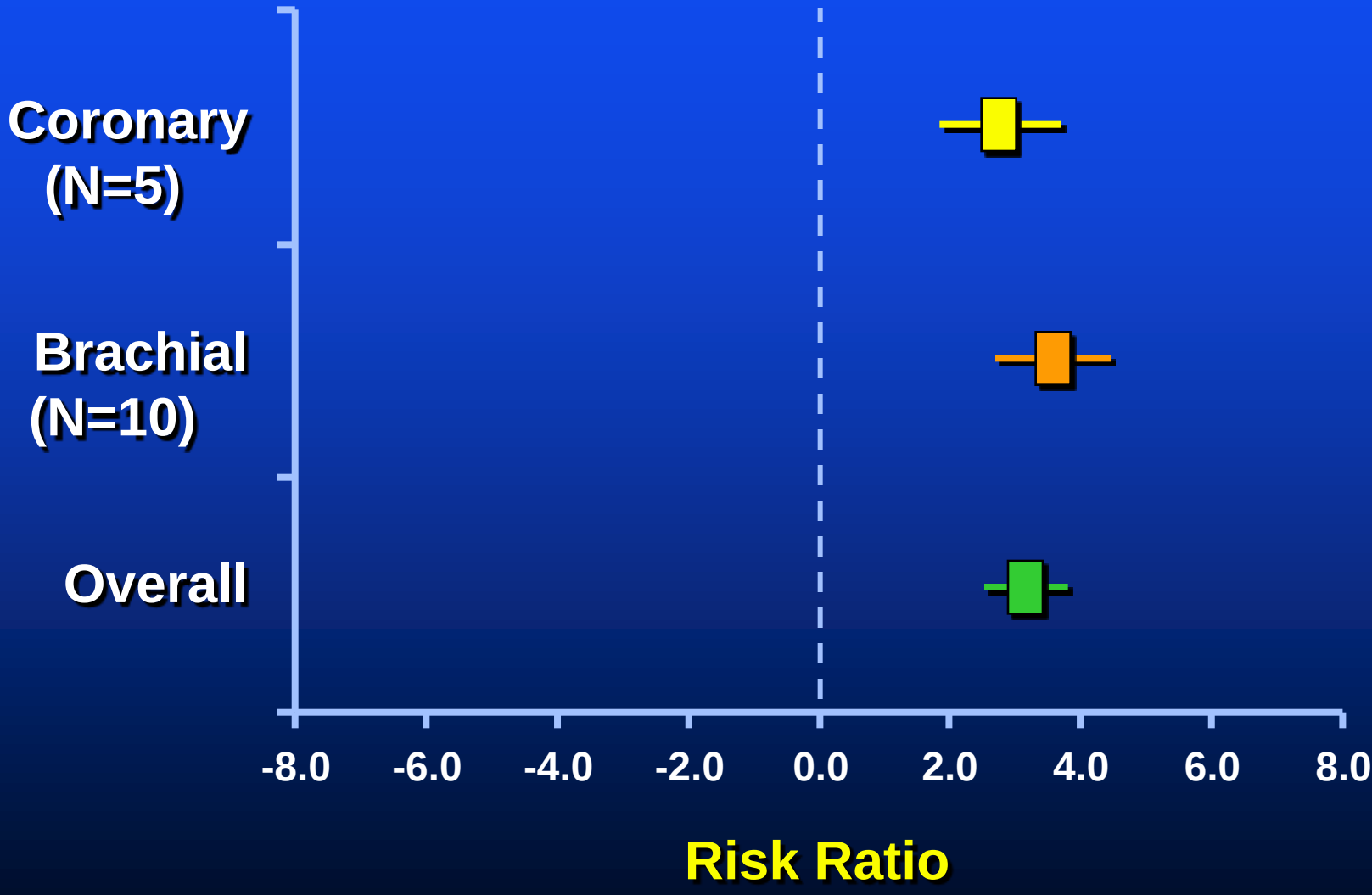
Thrombosis

Inflammation

Impaired relaxation

Plaque rupture/ erosion

Endothelial Dysfunction and CV Events: Meta-analysis of 15 studies



Lerman and Zeiher Circulation 2004

Coronary Endothelial Function Protocol

Diagnostic angiography

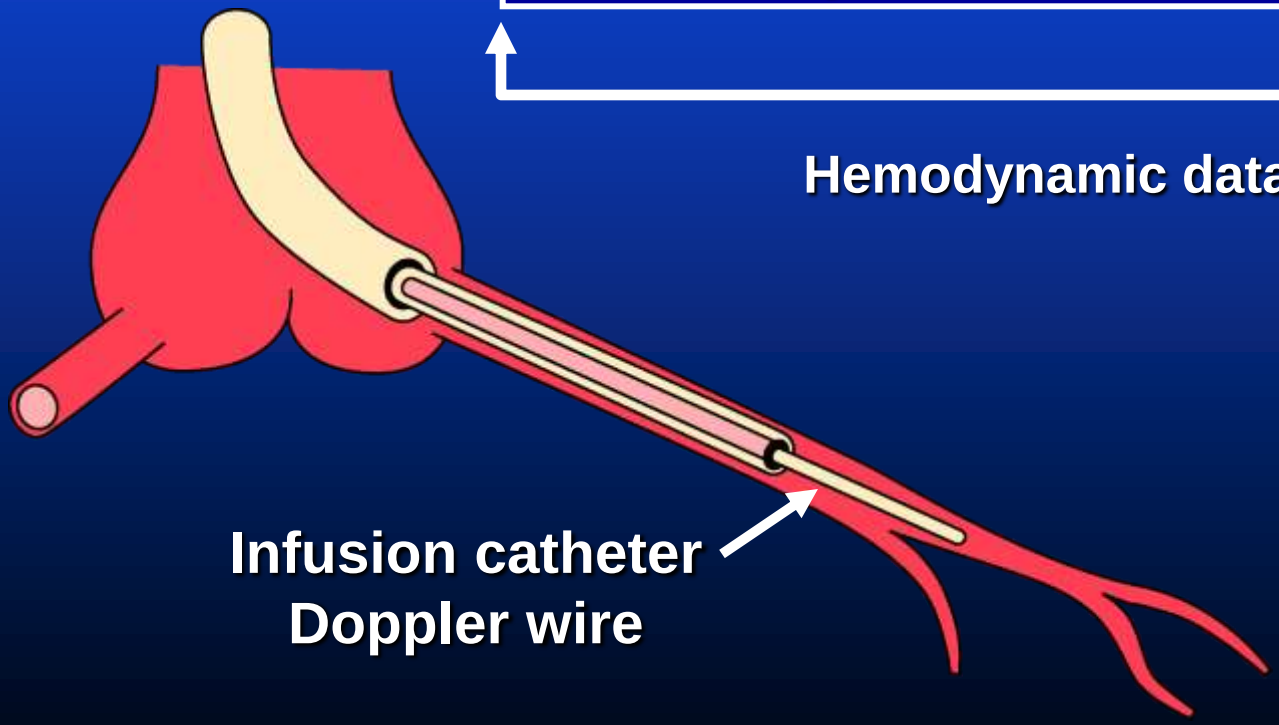
Adenosine IC

Acetylcholine

NTG

Hemodynamic data

3D/IVUS



Infusion catheter
Doppler wire

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CH-981247/98-22

- Potential mechanisms of Lp-PLA2 in early atherosclerosis and endothelial dysfunction.

Lipoprotein-Associated Phospholipase A_2 Is an Independent Marker for Coronary Endothelial Dysfunction in Humans

Eric H. Yang, Joseph P. McConnell, Ryan J. Lennon, Gregory W. Barsness, Geralyn Pumper, Stacy J. Hartman, Charanjit S. Rihal, Lilach O. Lerman, Amir Lerman

Objective—The purpose of the current study was to determine whether lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is associated with coronary endothelial dysfunction and is a predictor of endothelial dysfunction in humans.

Methods and Results—Patients (172) with no significant coronary artery disease (<30% stenosis) undergoing assessment of coronary endothelial function were studied. Endothelial function was assessed by the change in coronary blood flow and coronary artery diameter in response to intracoronary acetylcholine. Plasma concentrations of Lp-PLA_2 were

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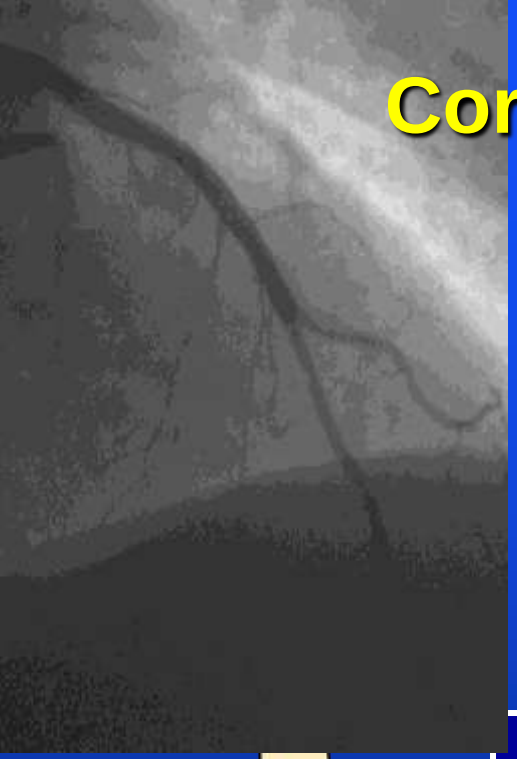
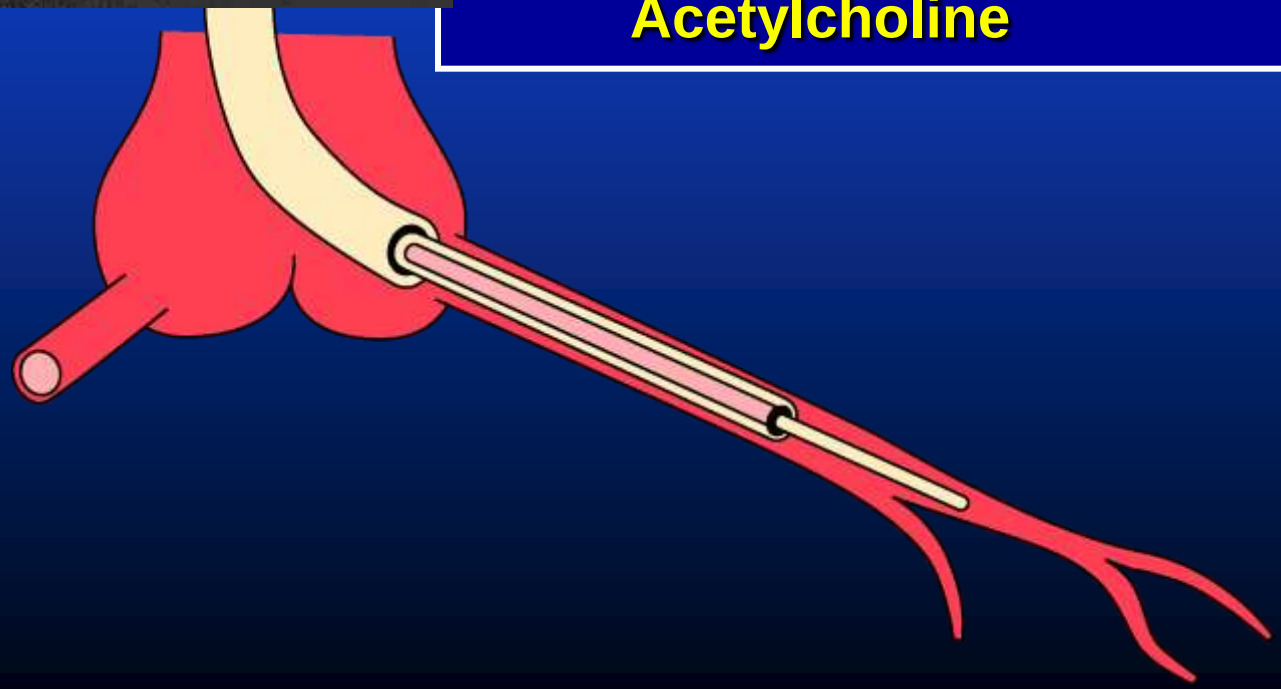
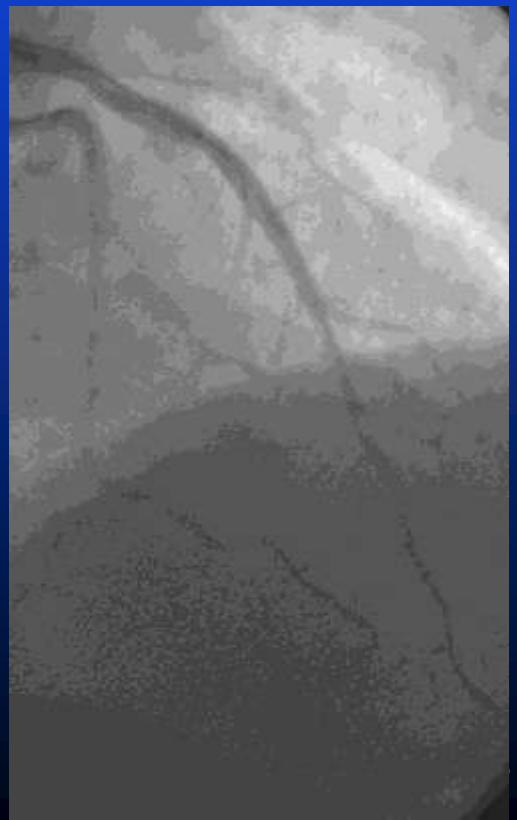
Key Words: lipoprotein-associated phospholipase A_2 ■ endothelial function ■ inflammatory markers

Coronary Endothelial Function Protocol



Acetylcholine



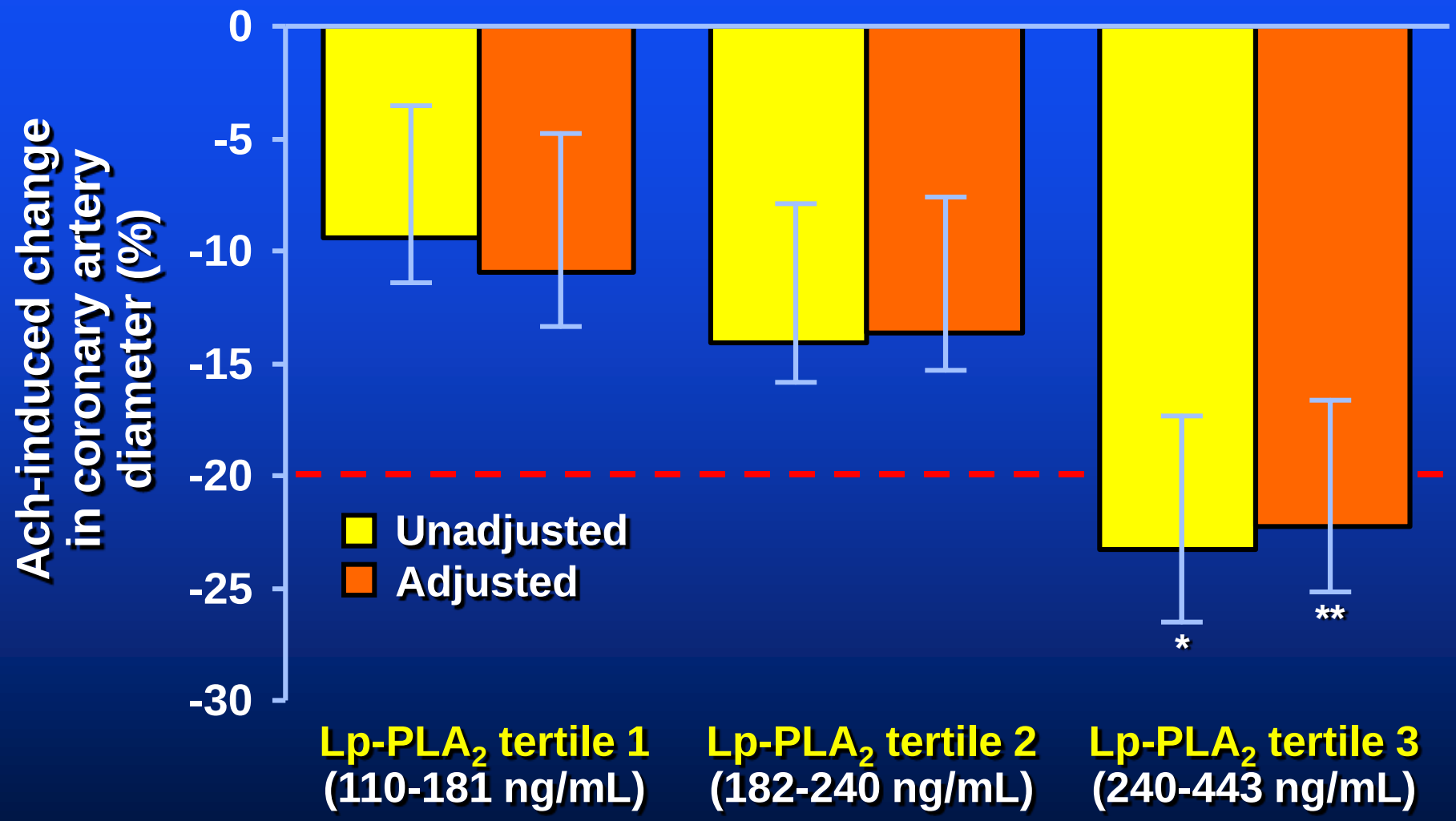


Patient Characteristics

Variable	Tertile 1 110-181.4 ng/mL n=57	Tertile 2 181.48-239.6 ng/mL n=58	Tertile 3 240-443 ng/mL n=57	P
Age	50.1±13.2	48.1±12.0	48.3±10.7	0.41
Hypertension, no. (%)	26 (45)	21 (37)	29 (51)	0.57
Diabetes, no. (%)	3 (5)	5 (9)	7 (12)	0.18
Hyperlipidemia, no. (%)	86 (64)	33 (57)	35 (61)	0.76
History of smoking, no. (%)	21 (37)	21 (36)	24 (42)	0.58
Body mass index, kg/m^2	27.6±5.8	28.6±5.6	29.4±5.9	0.10
Mean arterial pressure (mm Hg), median (IQR)	95.0 (89.0 to 103.0)	97.5 (87.0 to 107.0)	94.0 (85.0 to 109.0)	0.94
C-reactive protein (mg/dL), median (IQR)	0.2 (0.1 to 0.7)	0.2 (0.1 to 0.6)	0.3 (0.1 to 0.6)	0.89
Total cholesterol, mg/dL	169.2±36.0	181.3±43.4	193.3±37.1	0.001

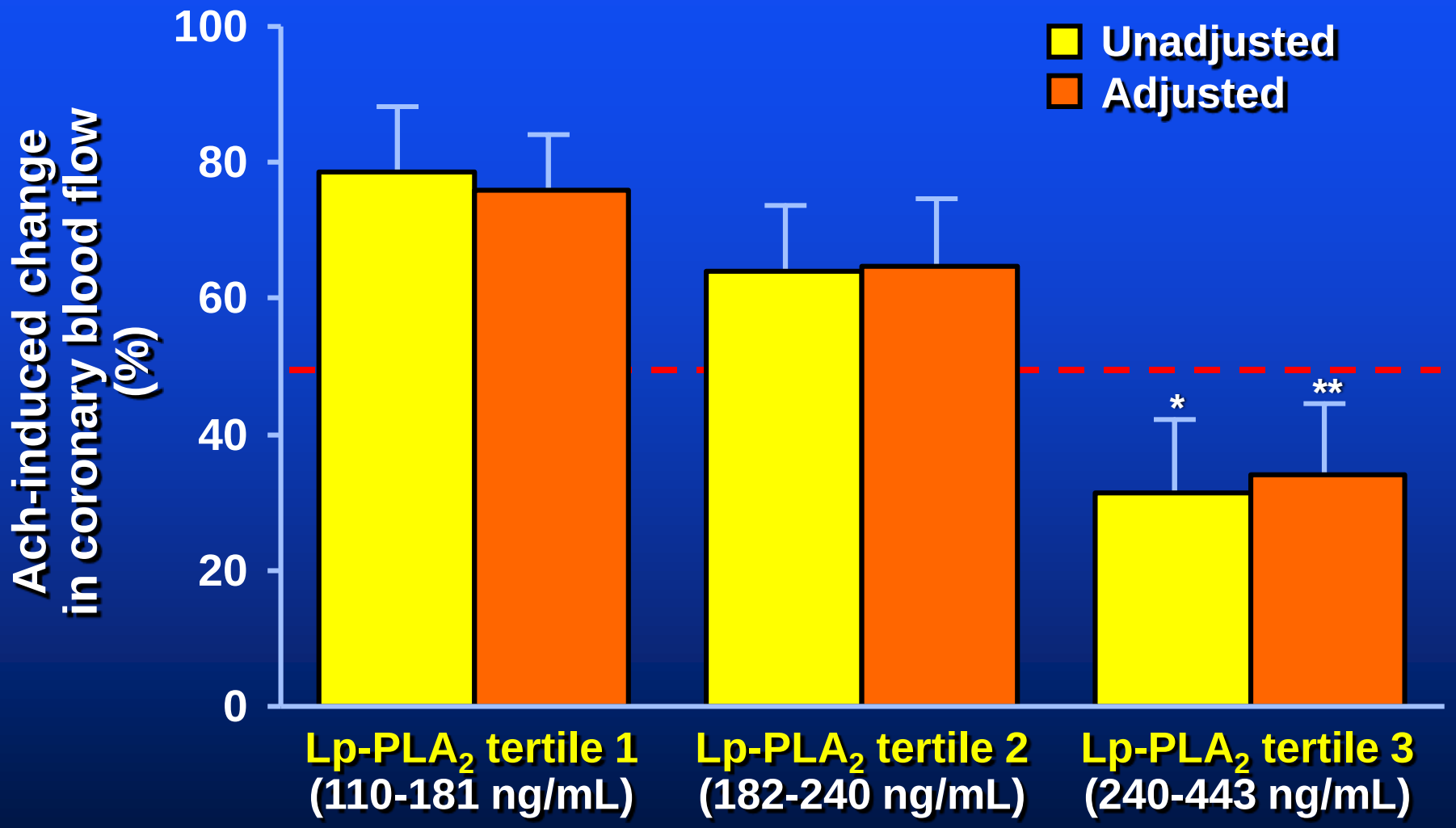
Yang & Lerman et al: ATVB, 2006

Lp-PLA$_2$ - Epicardial endothelial function



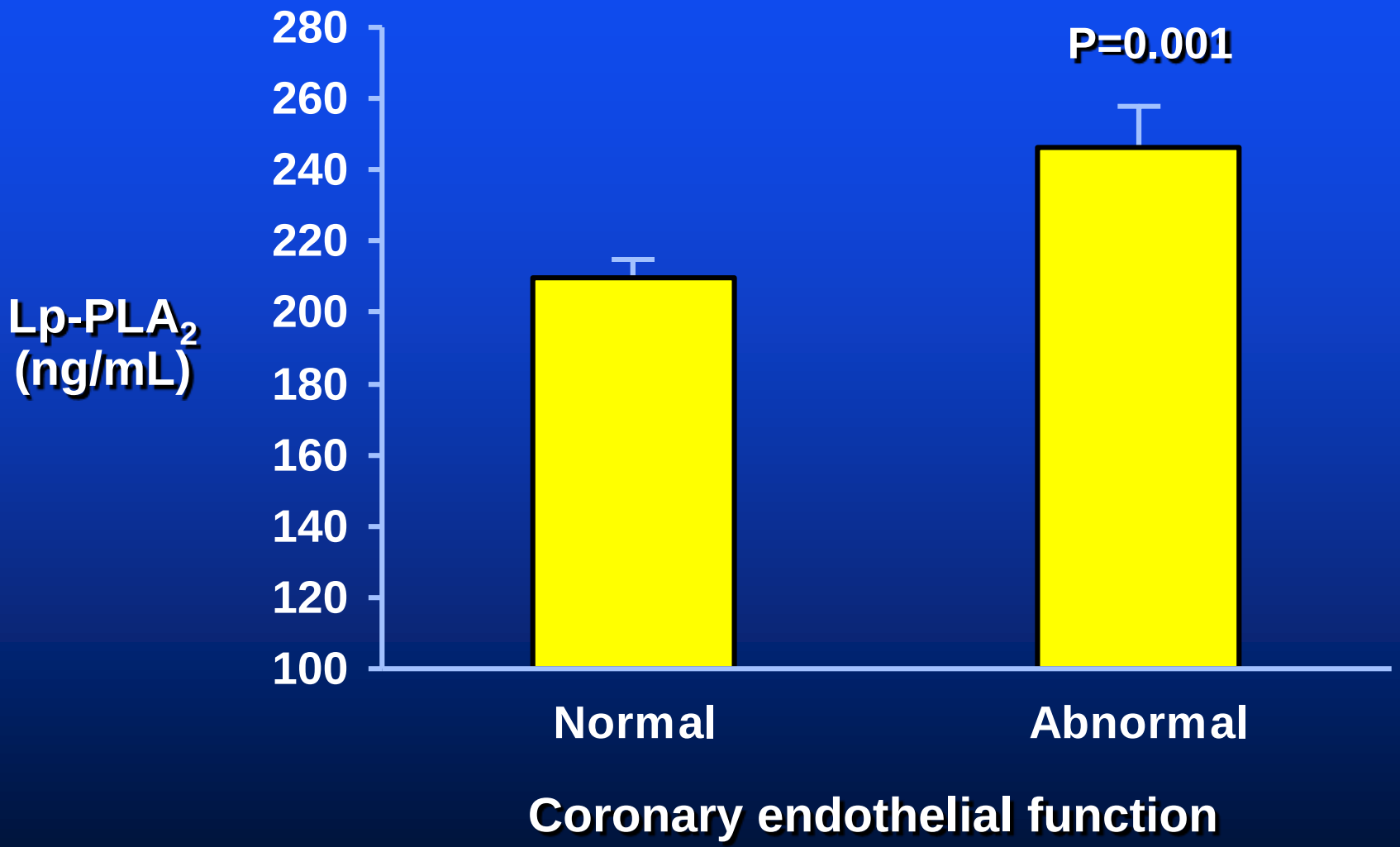
*P<0.001, **P=0.006 for trend

Lp-PLA$_2$ – Microvasc. endothelial function



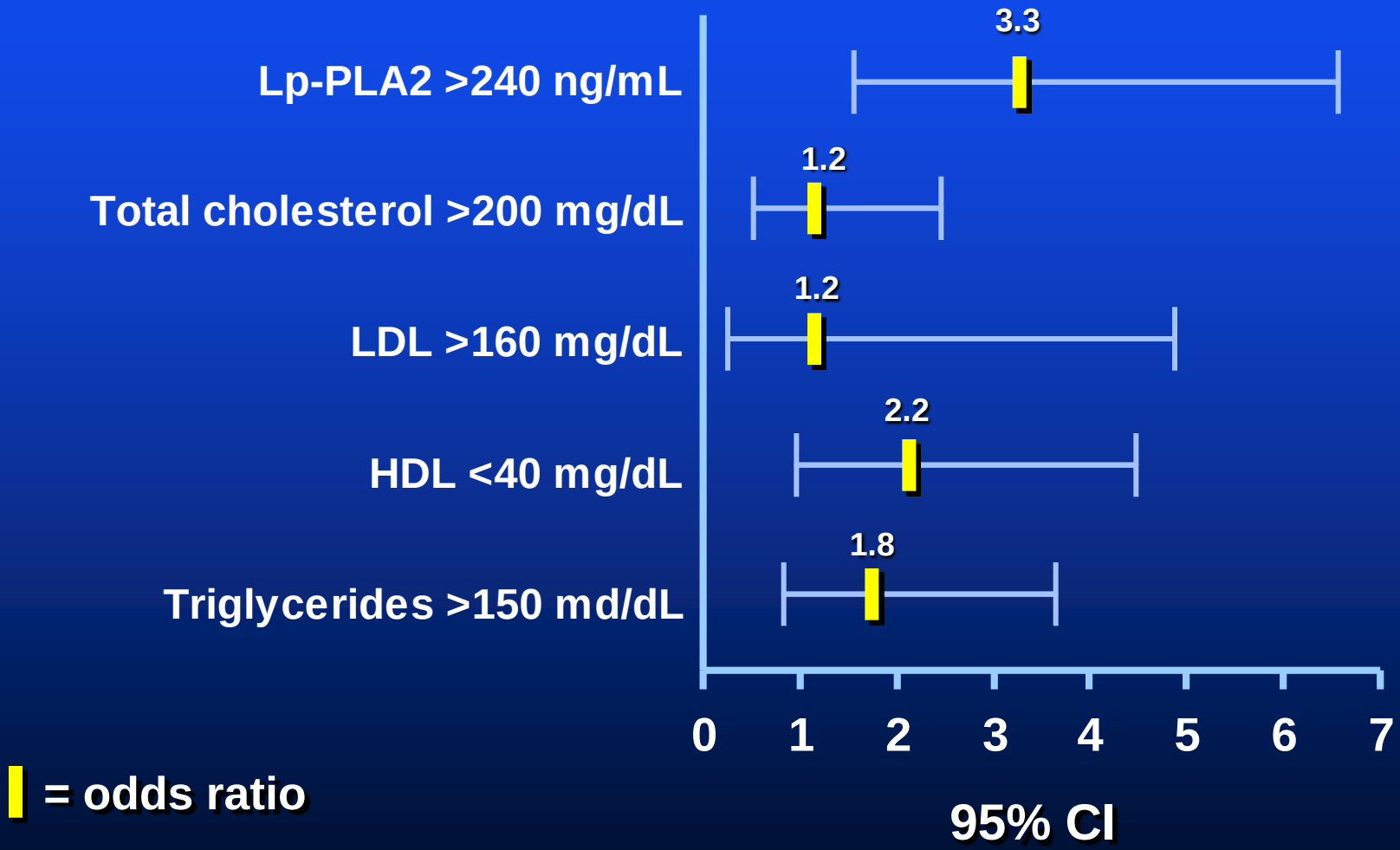
*P<0.001, **P=0.008 for trend

Lp-PLA2 levels and coronary endothelial function



Yang & Lerman et al ATVB 2006

Odds Ratio for Coronary Endothelial Dysfunction



Yang & Lerman et al ATVB 2006

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Conclusions—Lp-PLA_2 is independently associated with coronary artery endothelial dysfunction and is a strong predictor of endothelial dysfunction in humans. (***Arterioscler Thromb Vasc Biol.* 2006;26:106-111.**)

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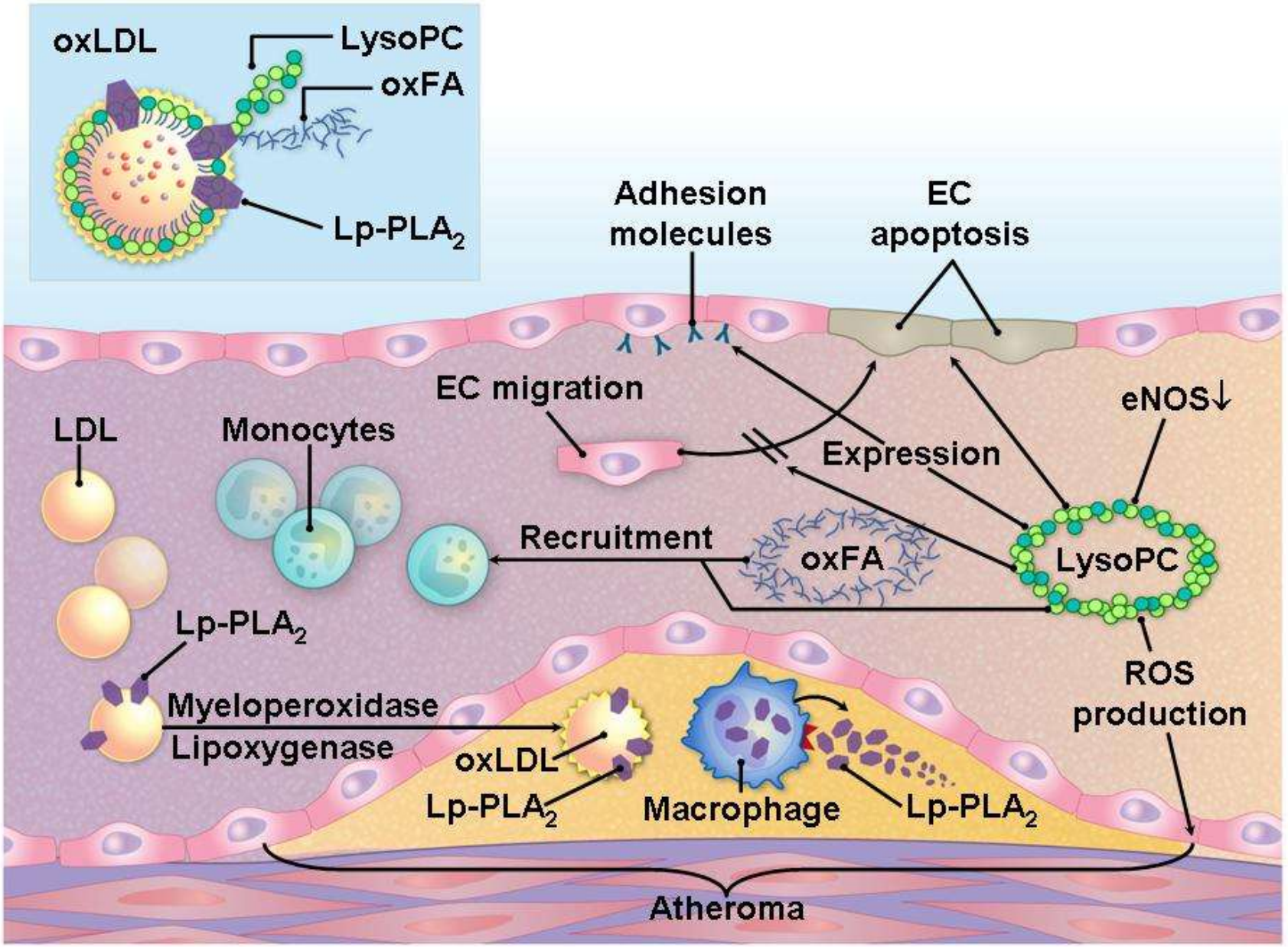
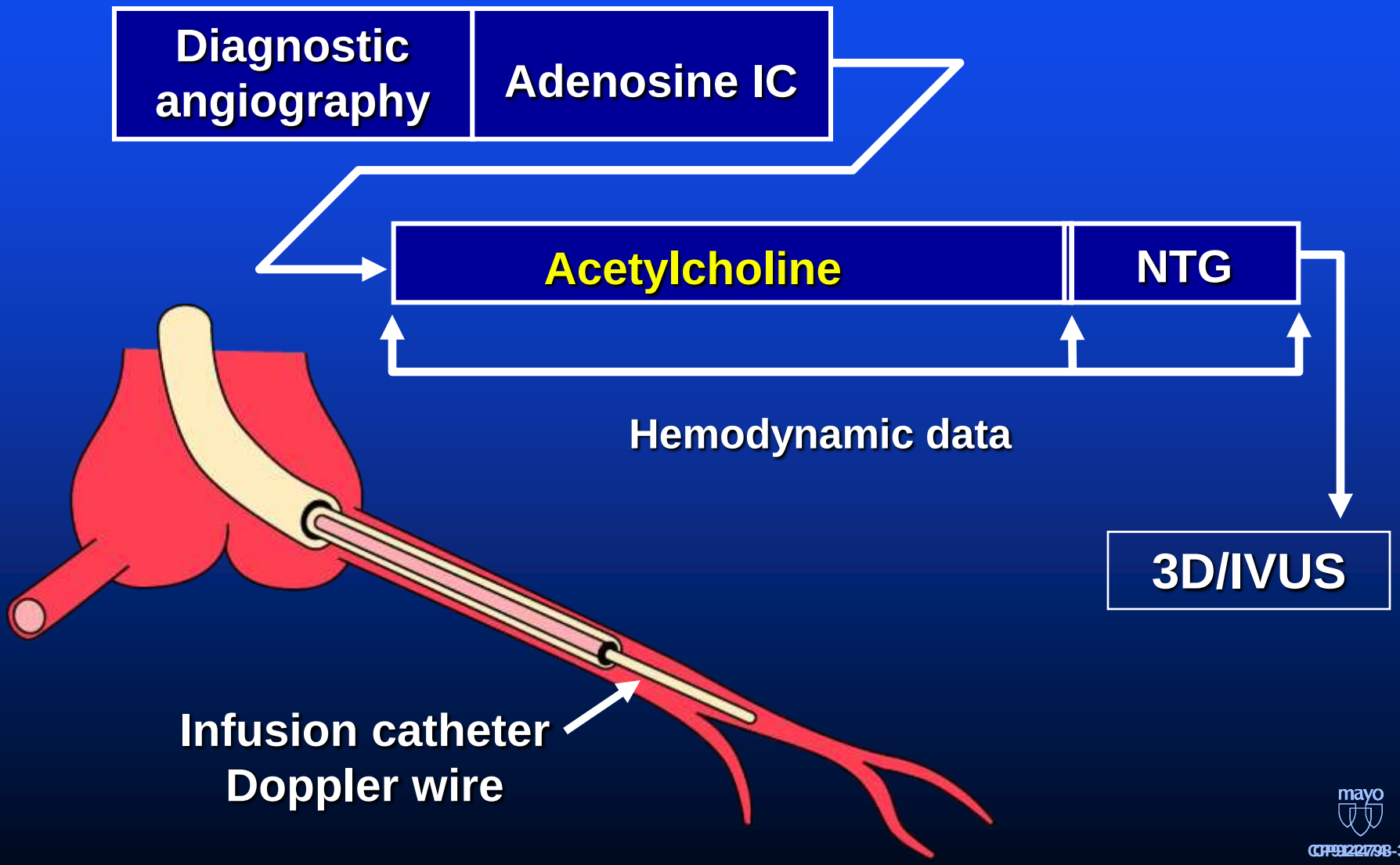


Coronary Endothelial Function Protocol

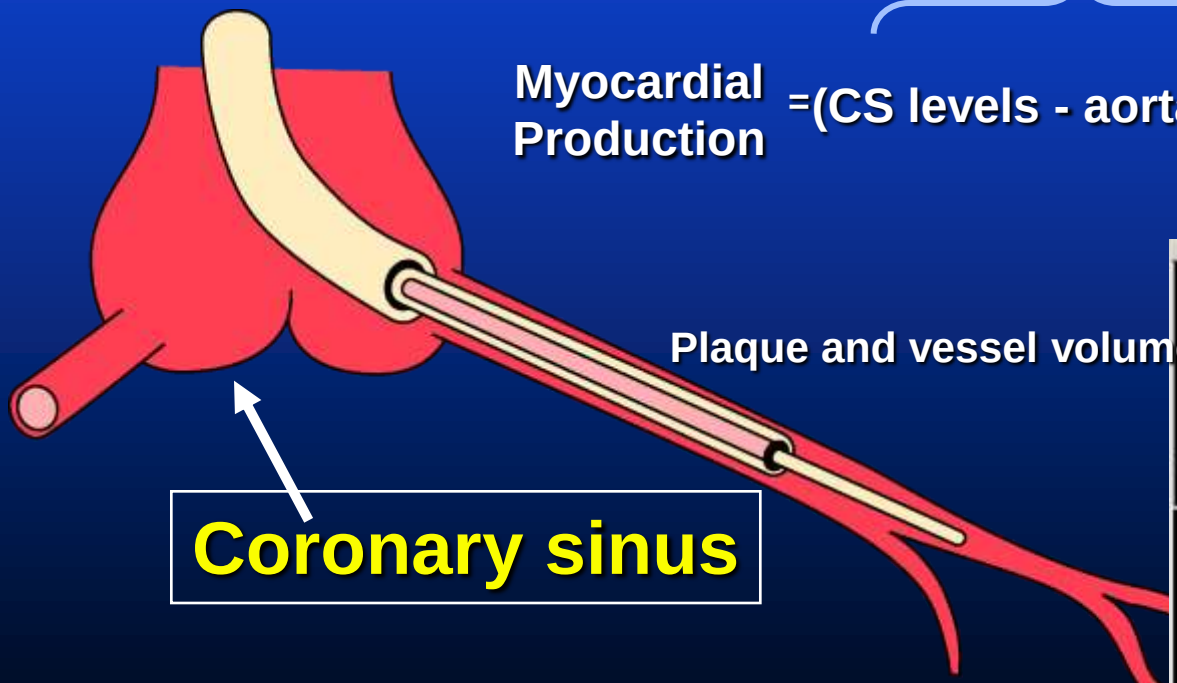


Coronary Endothelial Function Protocol

Diagnostic angiography	Lp-PLA2, lyso PC, CRP, F2 Isoprostane

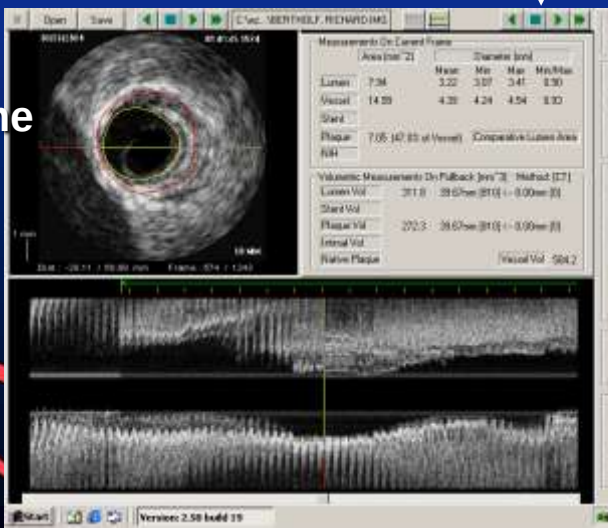
Coronary gradient

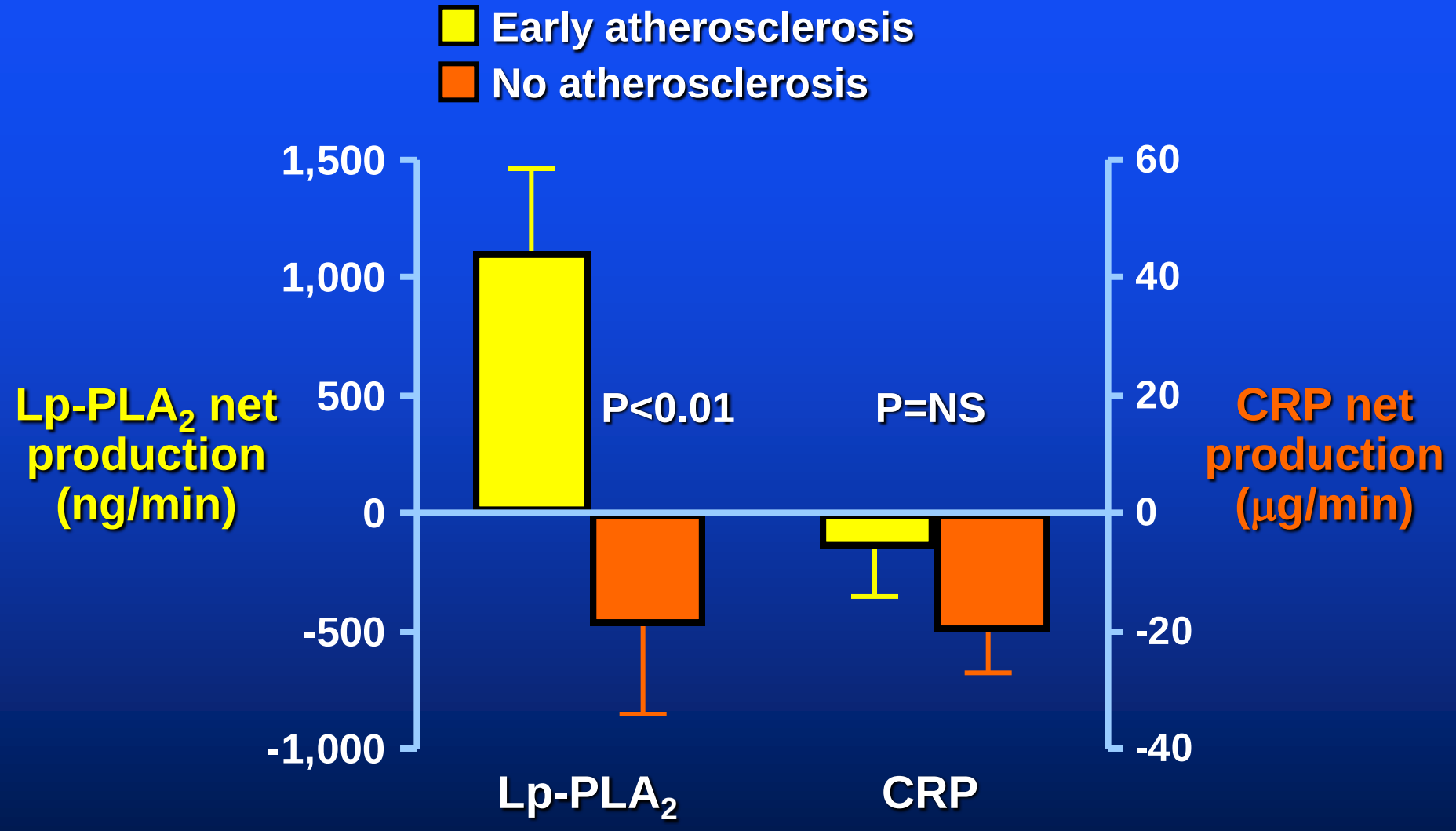
Myocardial Production =(CS levels - aorta levels) X CBF



Plaque and vessel volume

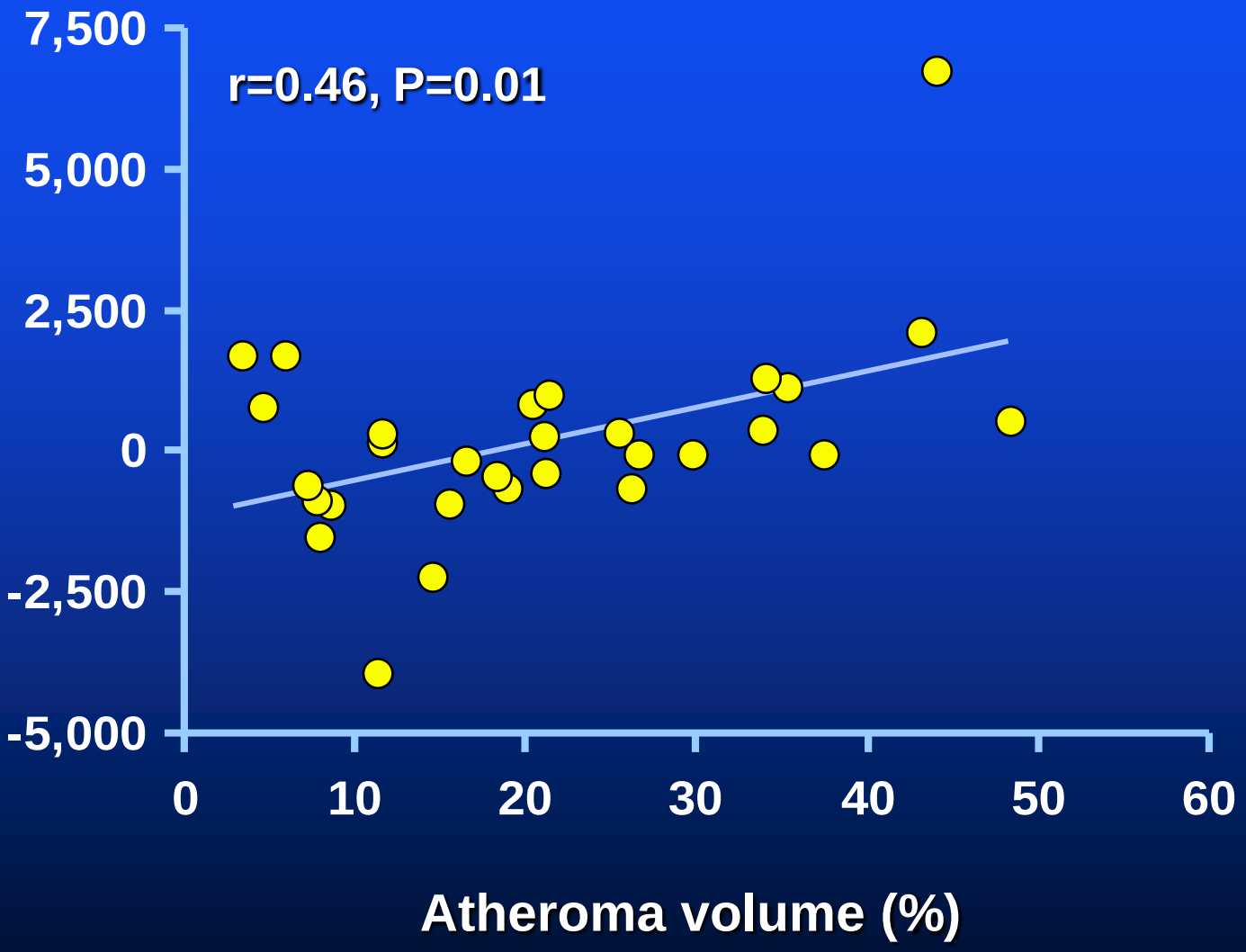
Coronary sinus





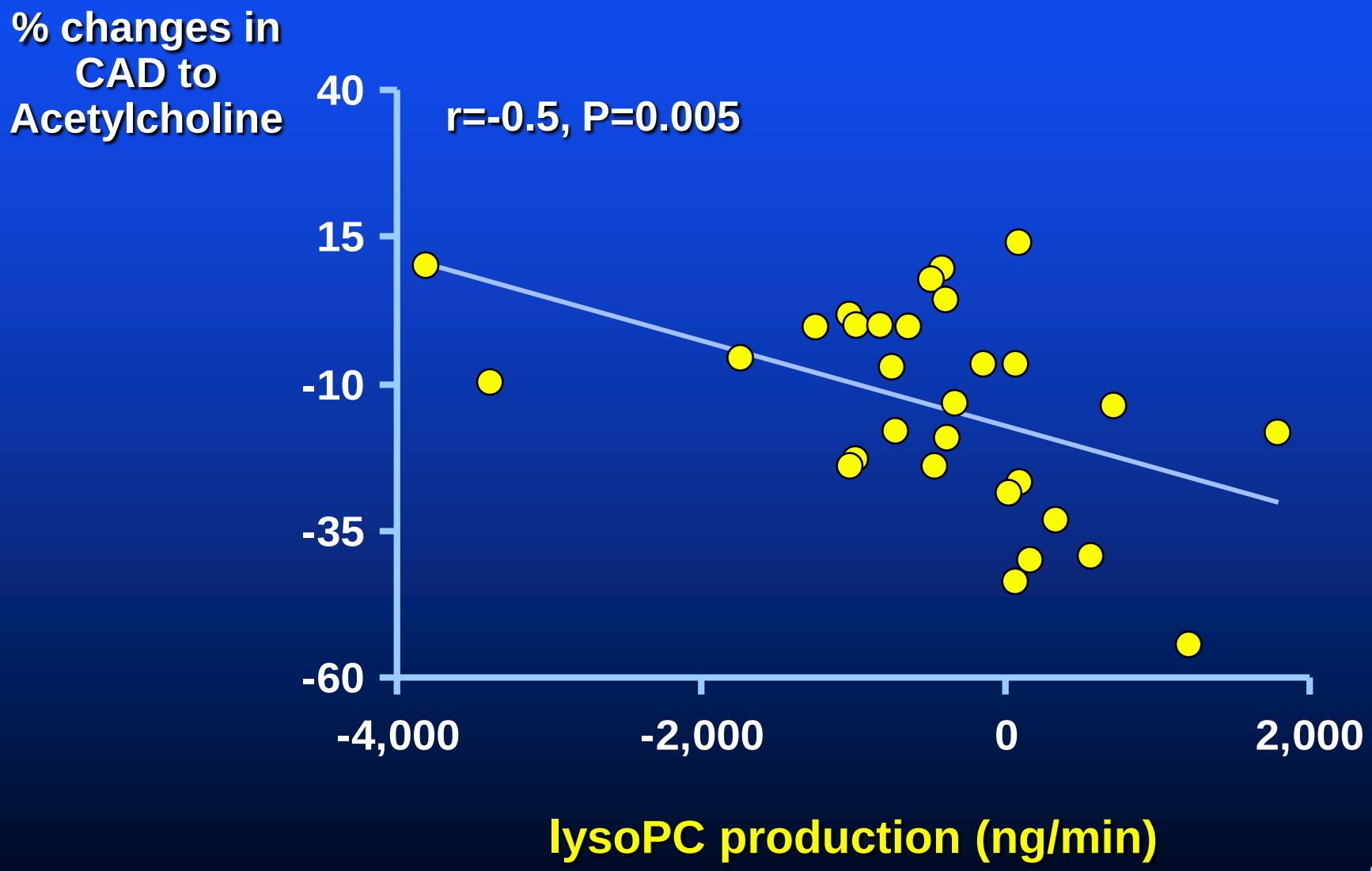
Lavi & Lerman et al: Circulation 2007

Correlation between coronary atherosclerosis and coronary Lp-PLA2



Lavi & Lerman et al: Circulation 2007

Correlation between Coronary endothelial function and coronary Lyso PC



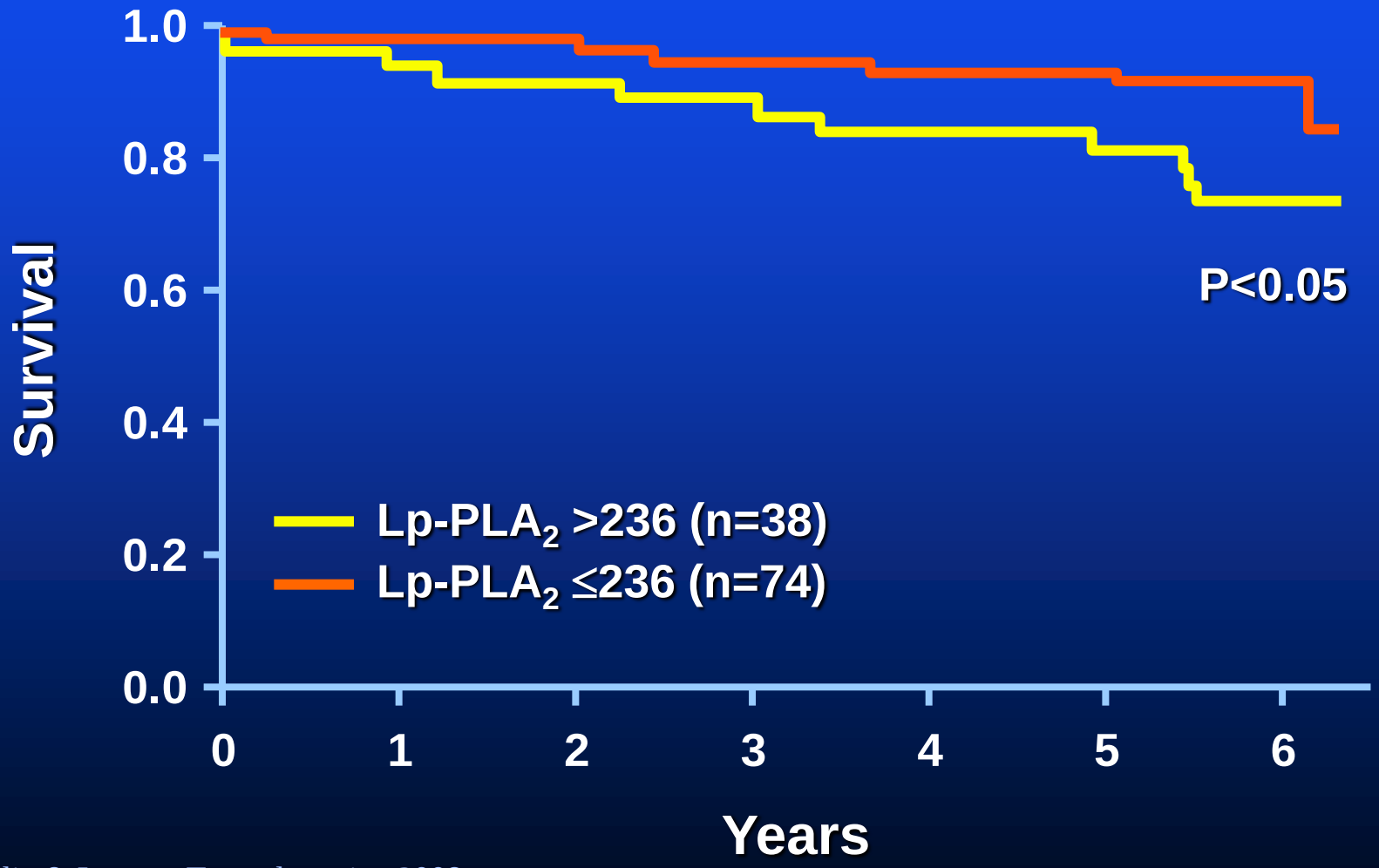
Lavi & Leman et al: Circulation 2007

Conclusions

- The coronary production of Lp-PLA2 correlates with the degree of the coronary atherosclerotic plaque.
- Furthermore, coronary Lyso PC , the active product of the enzyme and oxidative stress correlate with the degree of coronary endothelial function.

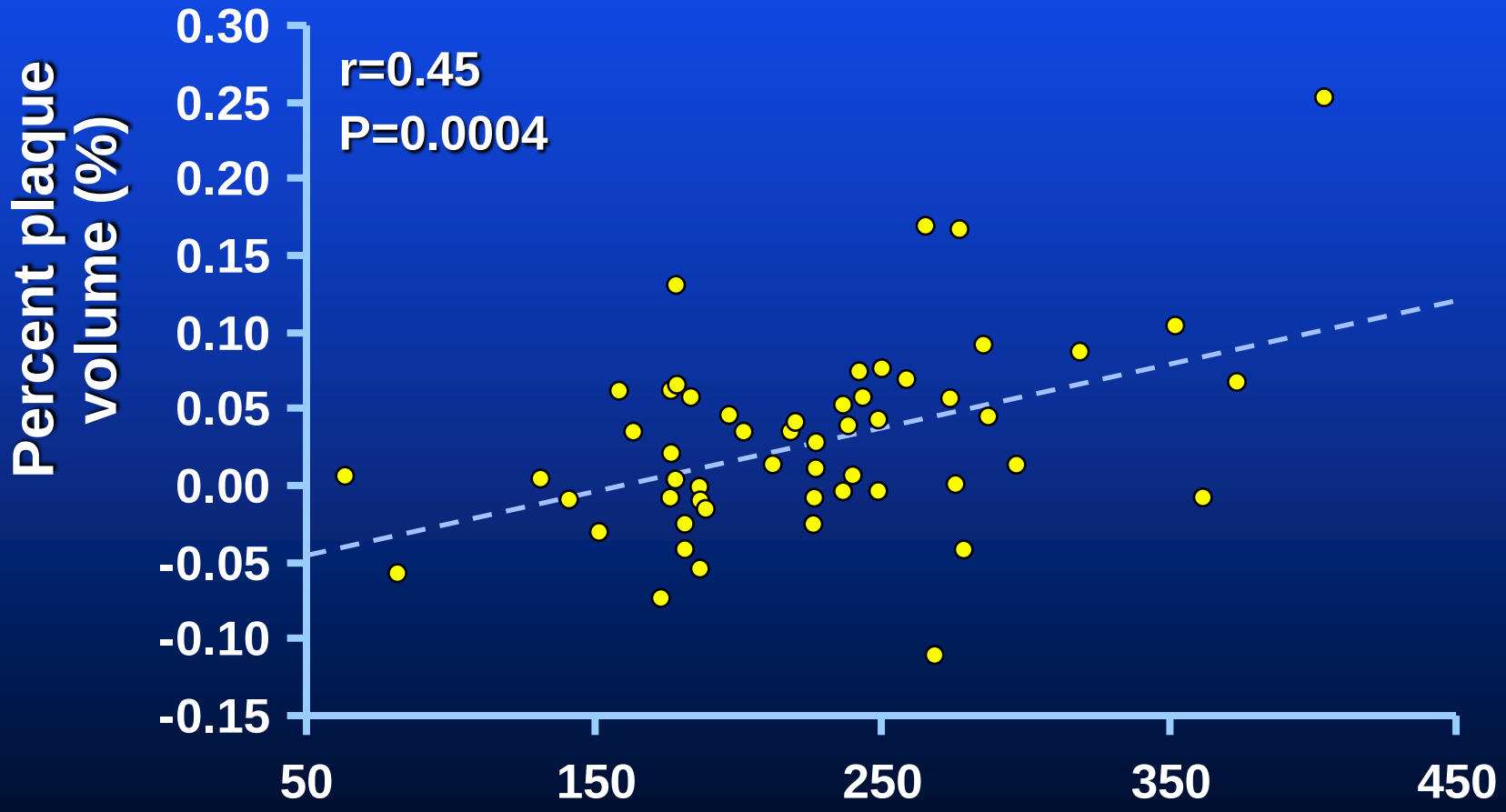
- Potential role of Lp-PLA2 in early cardiac transplant vasculopathy.

Cardiovascular Event-Free Survival in Cardiac Transplant Population According to Lp-PLA$_2$ Levels



Rachlin & Lerman Transplantation 2008.

Correlation Between Lp-PLA$_2$ and Changes in Percent Coronary Plaque Volume by IVUS in Patients post Heart Transplant



Rachlin & Lerman Transplantation 2008.

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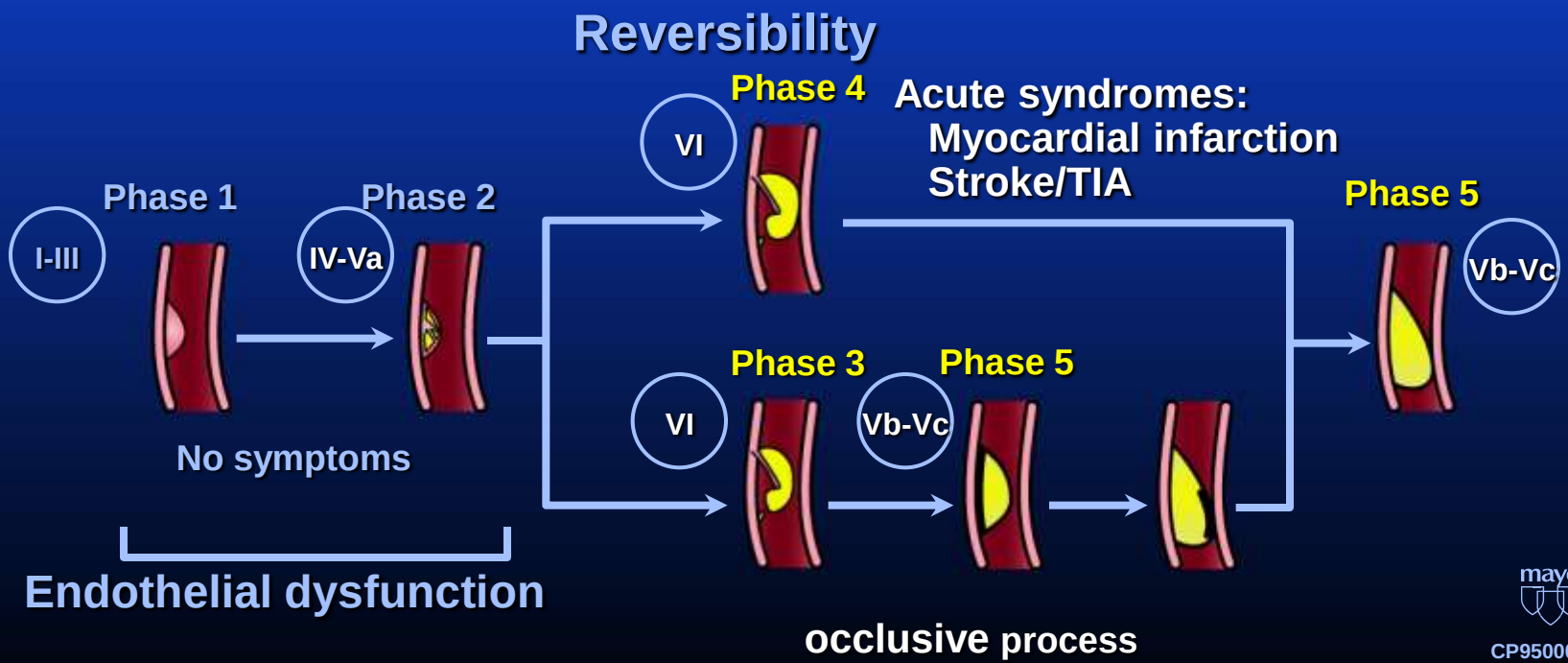


Lipoprotein-Associated Phospholipase A_2 Protein Expression in the Natural Progression of Human Coronary Atherosclerosis

Frank D. Kolodgie, Allen P. Burke, Kristi S. Skorija, Elena Ladich, Robert Kutys, Addisalem Taye Makuria, Renu Virmani

Objective— Although lipoprotein-associated phospholipase A_2 (Lp-PLA_2) has received recent attention as a biomarker of inflammation and risk for acute coronary events, its relative expression in coronary plaque phenotypes, including unstable lesions, has not been established.

Methods and Results— Coronary segments (n=30) were prospectively collected from 25 sudden coronary death patients for immunolocalization of Lp-PLA_2. Lesion morphologies were classified as pathologic intimal thickening, fibroatheromas, thin-cap fibroatheromas (fibrous cap thicknesses <65 μm), and rupture. The expression of Lp-PLA_2 was detected using a specific monoclonal antibody. Apoptosis was identified by DNA end-labeling using terminal deoxynucleotidyl transferase (TdT). Lp-PLA_2 staining in early plaques was absent or minimally detected. In contrast, thin-cap fibroatheromas and ruptured plaques showed intense Lp-PLA_2 expression within necrotic cores and surrounding macrophages including those in the fibrous cap. The degree of macrophage apoptosis was greater in thin-cap fibroatheroma and ruptures compared with less advanced plaques with additional double labeling studies showing Lp-PLA_2 present in apoptotic cells in regions of high macrophage density.

Conclusions—Lp-PLA_2 is strongly expressed within the necrotic core and surrounding macrophages of vulnerable and ruptured plaques, with relatively weak staining in less advanced lesions. These findings together with the association of Lp-PLA_2 in apoptotic macrophages suggest a potential role in promoting plaque instability. (***Arterioscler Thromb Vasc Biol.* 2006;26:2523-2529.**)

Key Words: lipoprotein-associated phospholipase A_2 ■ sudden coronary death ■ plaque rupture ■ apoptosis ■ cardiovascular risk

The natural history of atherosclerosis in humans is a dynamic process involving the progression of early lesions to more complex plaques that are responsible for the majority of acute ischemic coronary and stroke events. Throughout lesion progression, there are transitional plaque phenotypes ranging from early lipid pools to those characterized by a dense fibrous cap of connective tissue and a strong collagen matrix overlying a core of lipids and necrotic debris, and ultimately, to plaques with large necrotic cores and thin fibrous caps invaded by macrophages, referred to as thin-cap necrotic cores, and greater macrophage infiltrates compared with TCFAs.[2] In this context a better understanding of the biology of rupture-prone plaques has the potential to reduce the morbidity and mortality associated with atherothrombotic disease.

See page 2417 and cover

Inflammation plays a primary role in the progression of human atheroma based on the local and systemic inflammatory responses observed throughout the spectrum of athero-

Kolodgie et al:
Arterioscler Thromb Vasc Biol 26:2523, 2006

Serial Cryostat Sections Showing Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) Protein Expression in Varying Human Coronary Plaques Morphologies

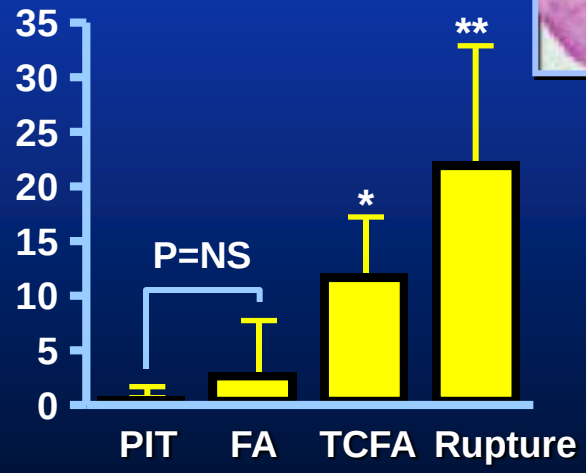
Pathologic intimal thickening

Fibroatheroma

Thin cap fibroatheroma

Plaque rupture

% Lp-PLA2 staining in varying coronary plaque morphologies

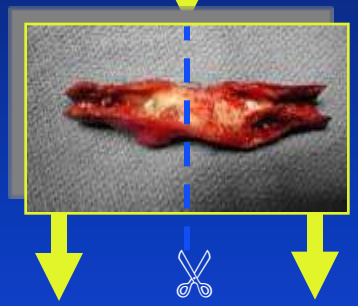


*P<0.05 vs FA or PIT; ** P<0.002 vs TCFA, FA, and PIT

Kolodgie et al: Arterioscler Thromb Vasc Biol 26:2523, 2006

Role of PLA2 in human carotid plaque stability

Carotid endarterectomy



Frozen (-80°C)

Formalin

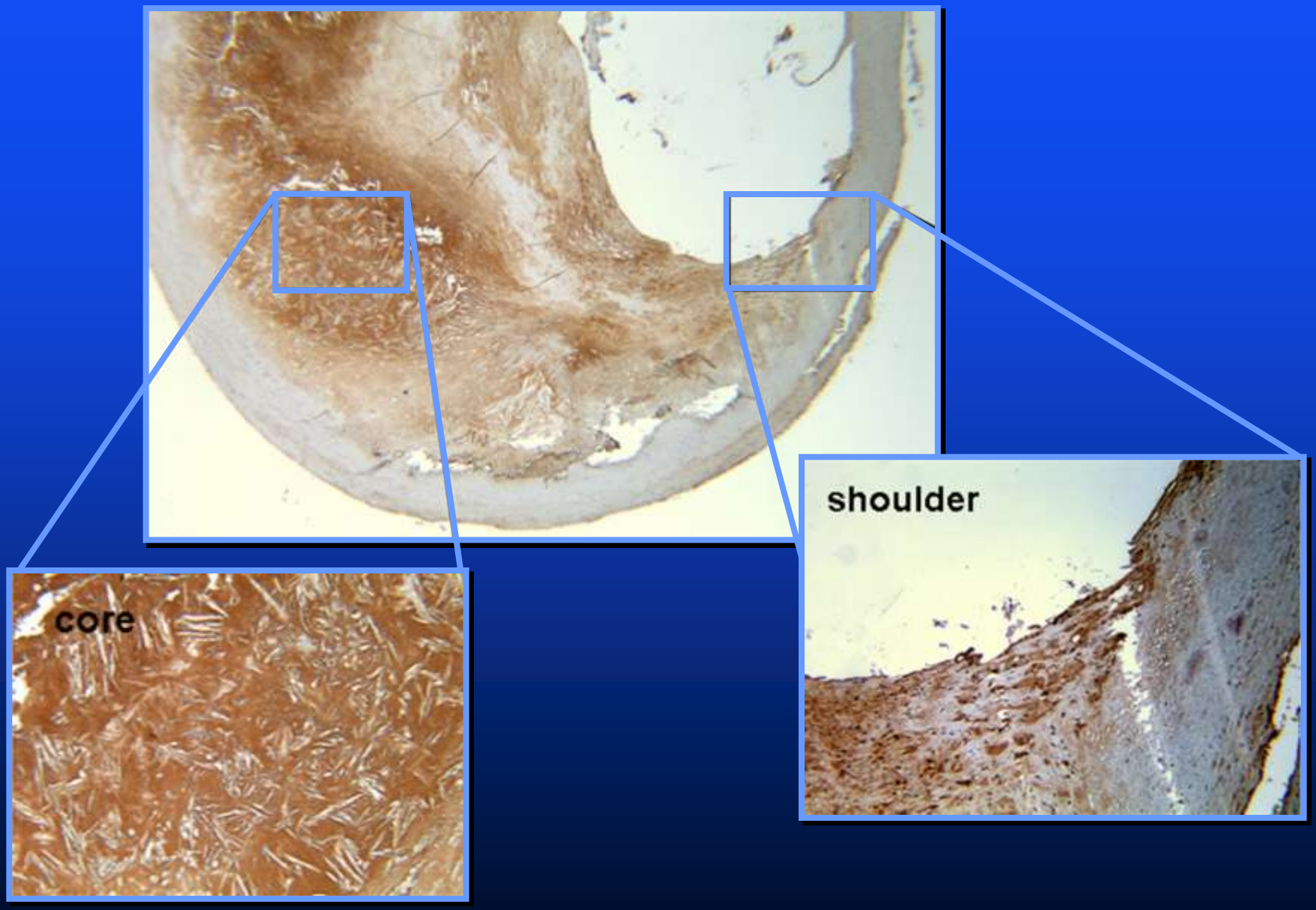
PLA2 and LysoPC expression

Immunoperoxidase:PLA2, nitrotyrosine, NADPH-oxidase

Immunofluorescence: ubiquitin, SMC, macrophage

Mannheim & Lerman et al: Stroke 2007

Expression of Lp-PLA2 in Atherosclerotic Carotid Plaques



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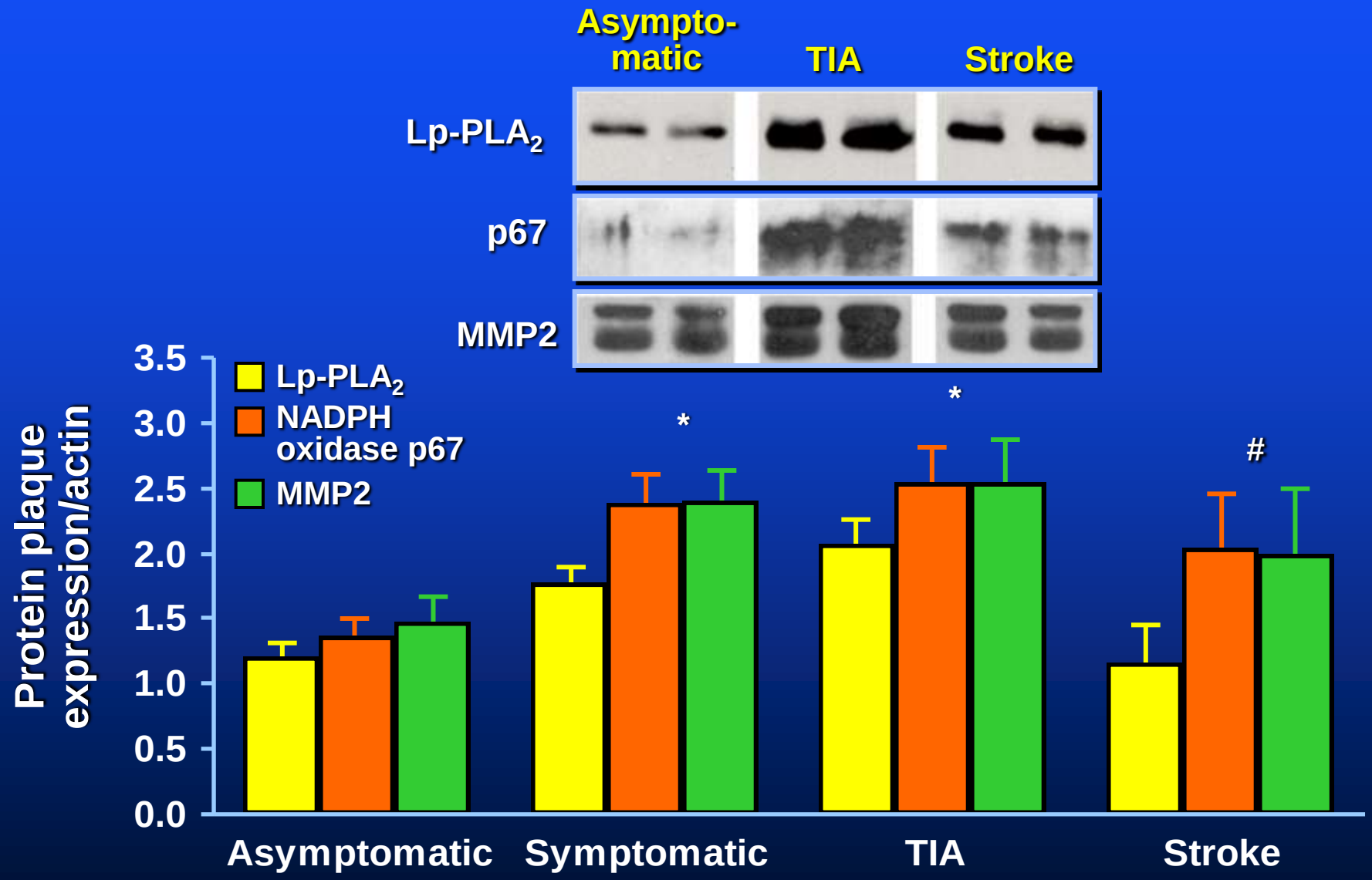
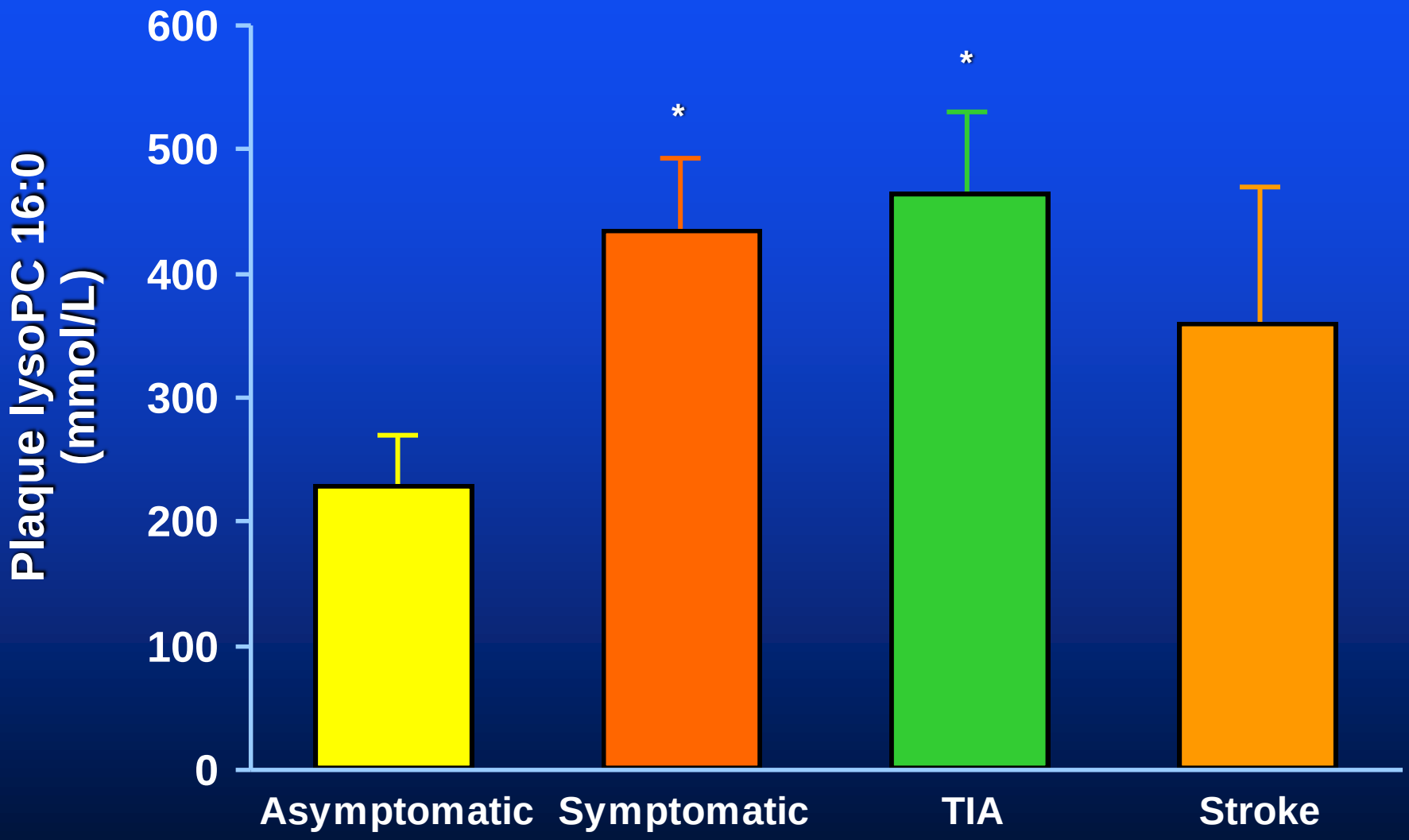


Mannheim & Lerman et al: Stroke 2007

Expression of LysoPC in Atherosclerotic Carotid Plaques



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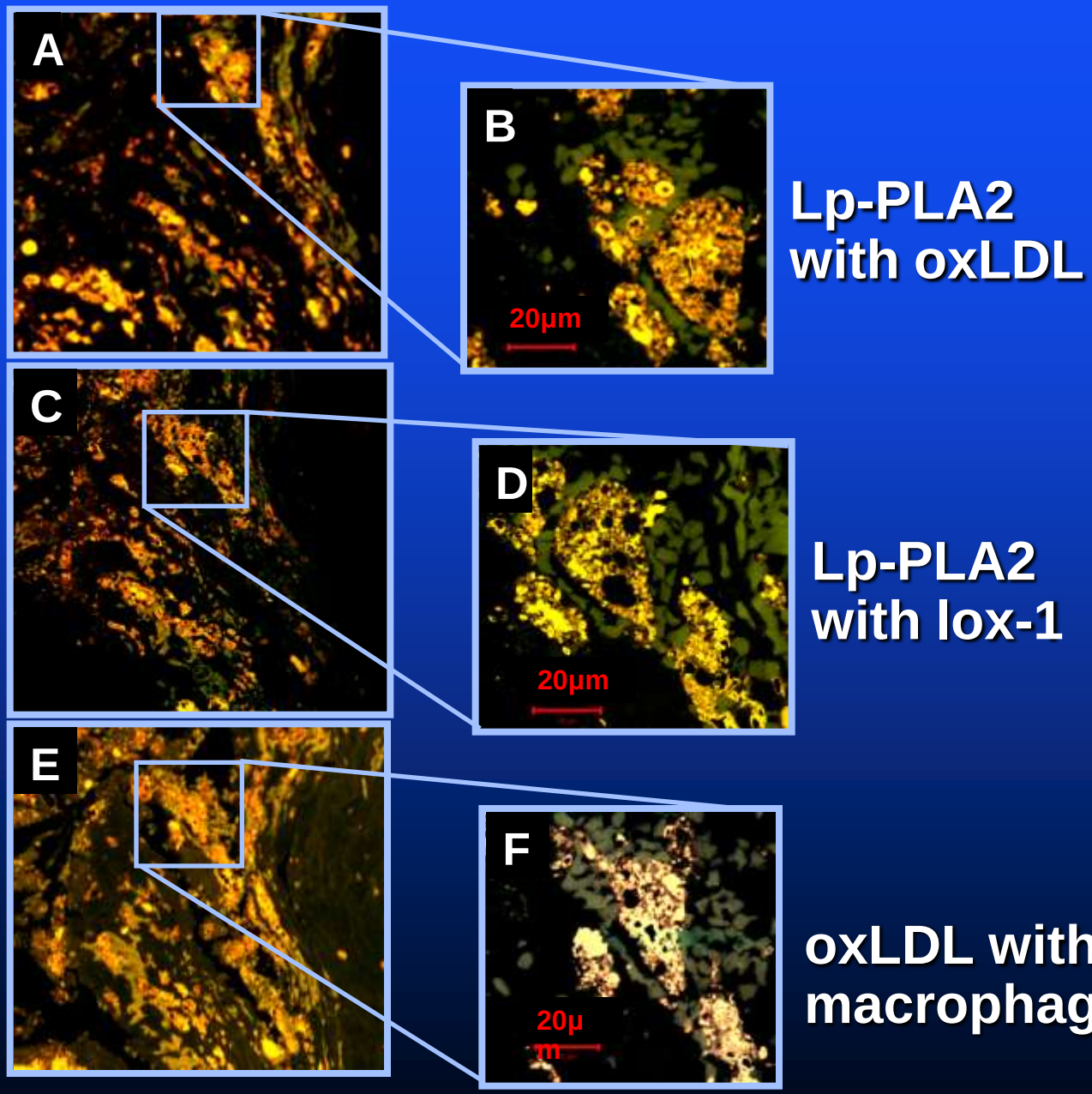
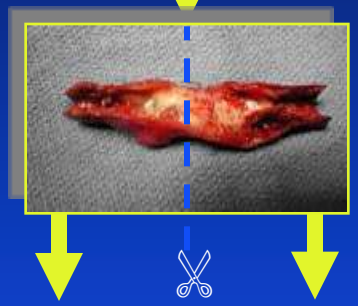
Co localization of Lp-PLA2 with Oxidative stress and Inflammation



Role of PLA2 in human carotid plaque stability

Carotid endarterectomy



Frozen (-80°C)

Formalin

PLA2 and LysoPC expression

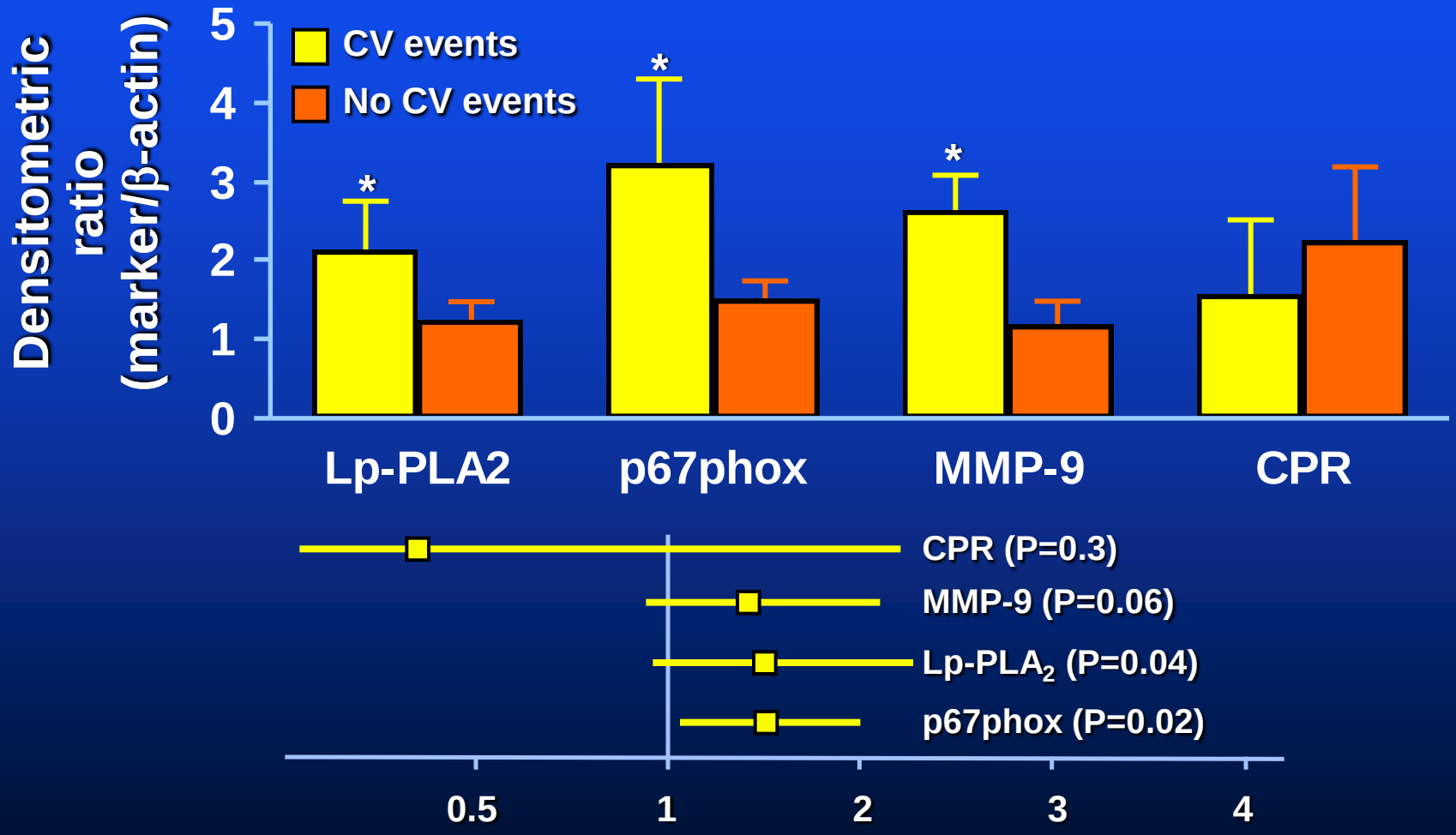
Immunoperoxidase:PLA2, nitrotyrosine, NADPH-oxidase

Immunofluorescence: ubiquitin, SMC, macrophage

Follow up for CV events

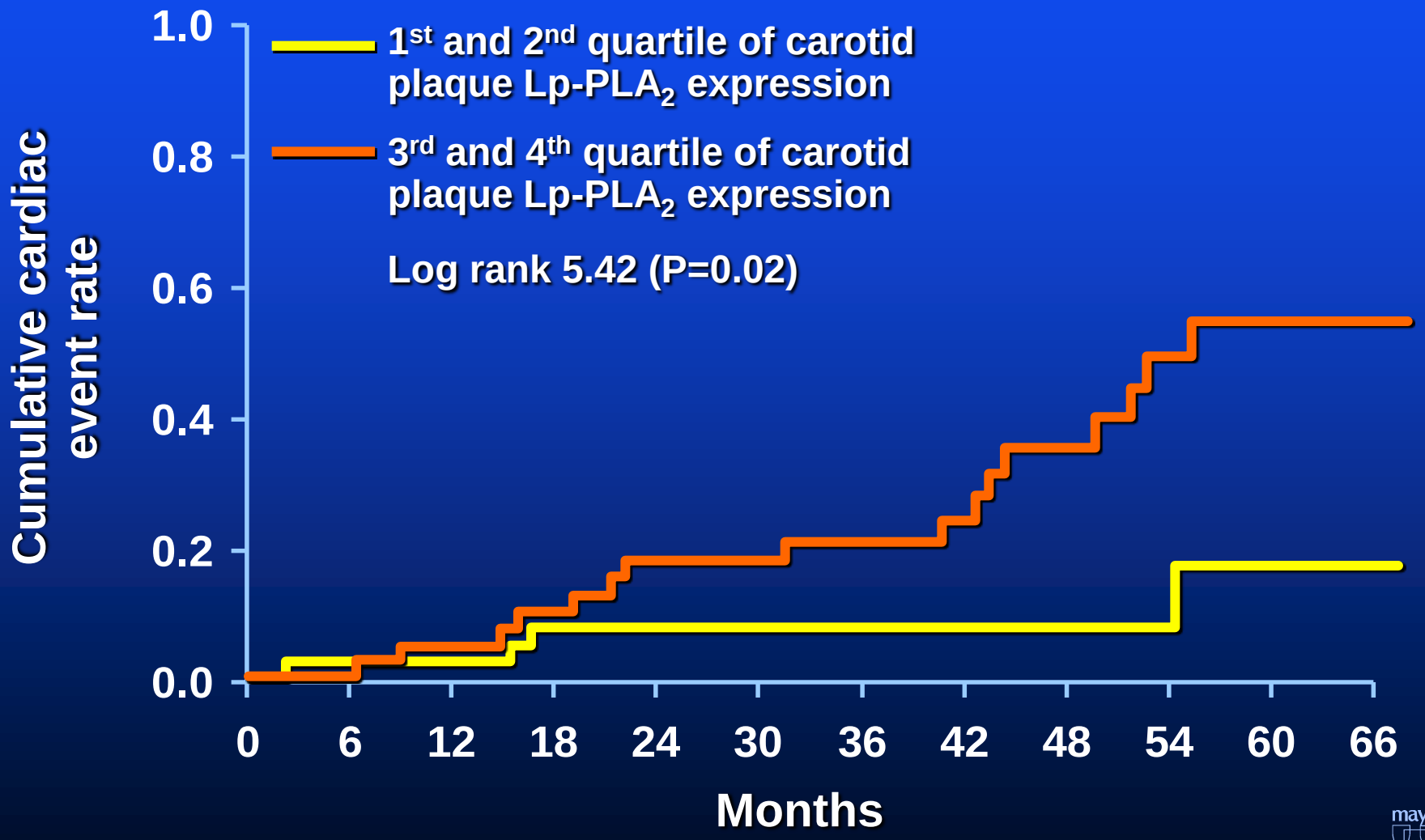
Carotid Plaque Biomarkers and CV Events (Fatal and Nonfatal MI and Stroke)

Univariate Analyses



*P<0.05 for group comparison

Plaque Lp-PLA$_2$ and cardiac prognosis



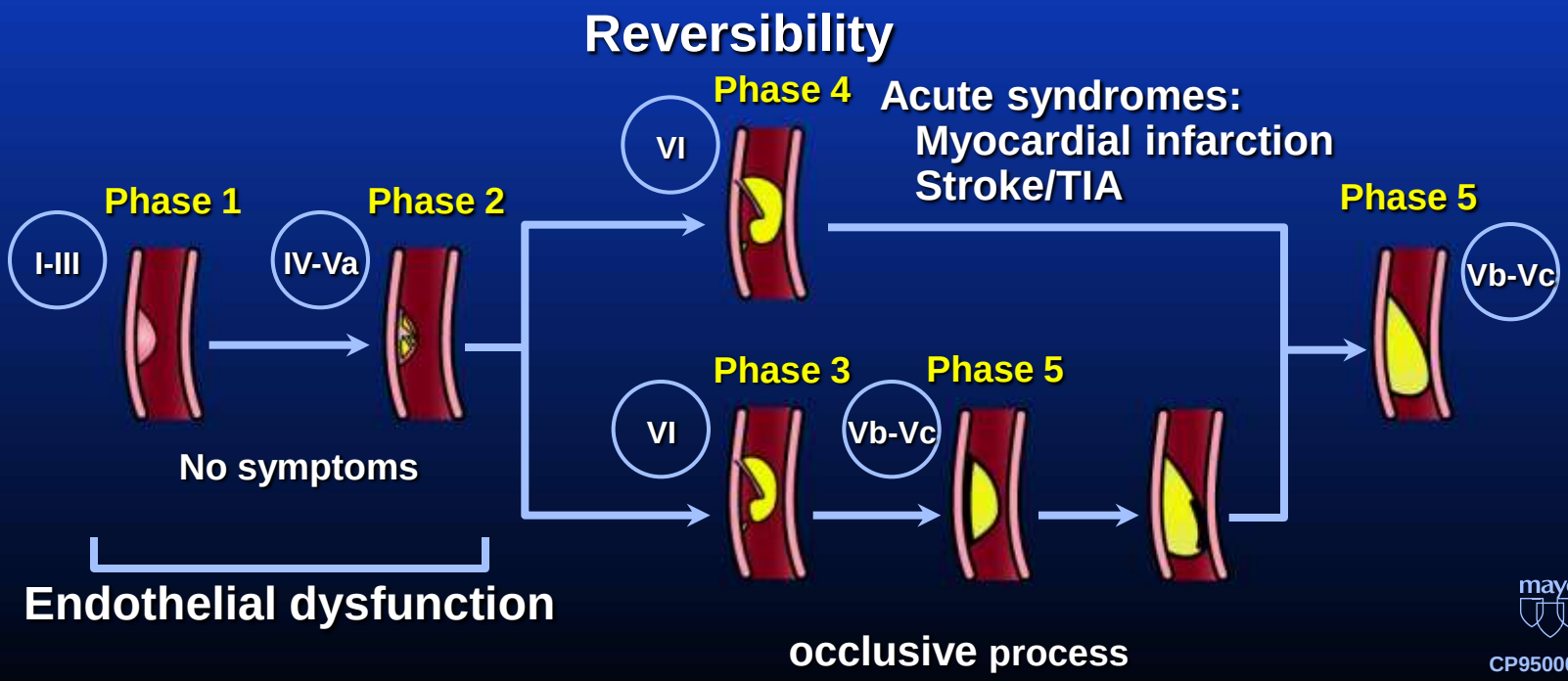
Risk Marker or a Risk Factor

Circulating and regional Levels

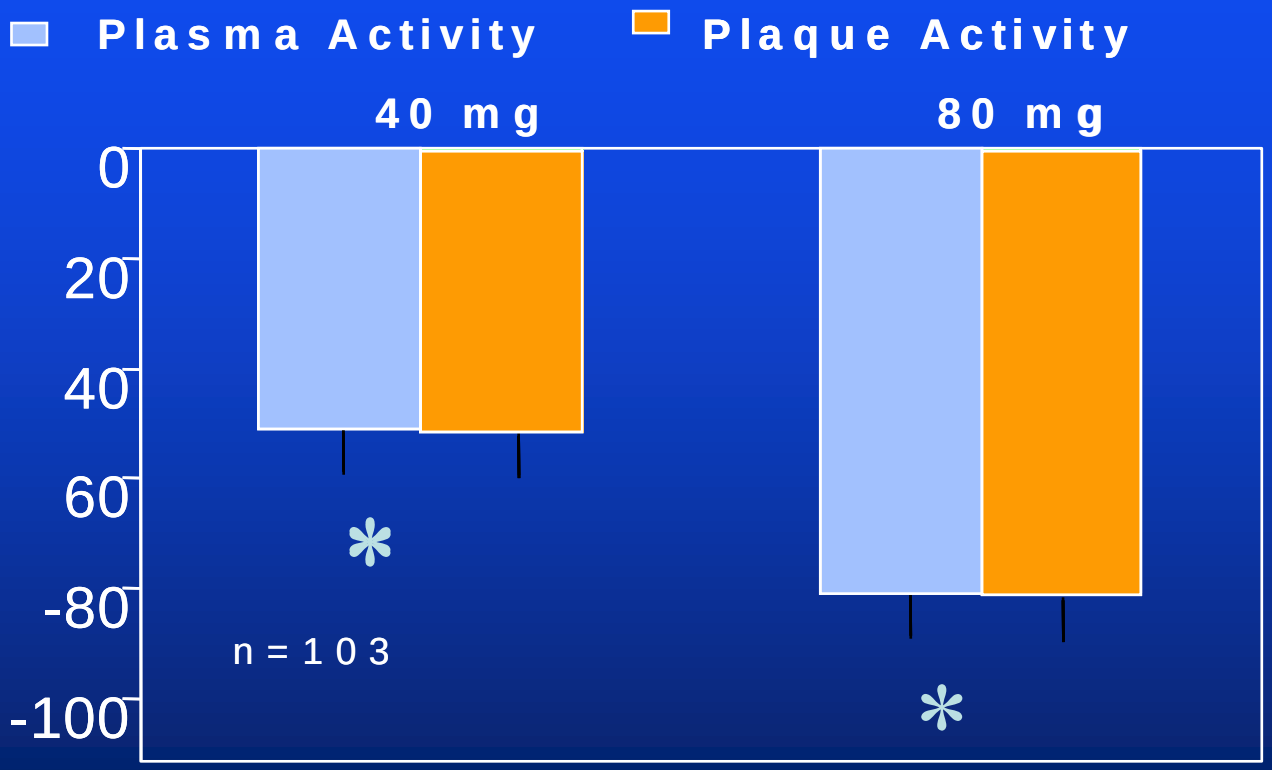
- Increase in early stage of the disease
- Correlates with the disease process
- Correlates with functional and structural abnormalities

Tissue Levels

- Increase in the plaque
- Associated with other known markers of disease.
- Correlates with functional abnormalities



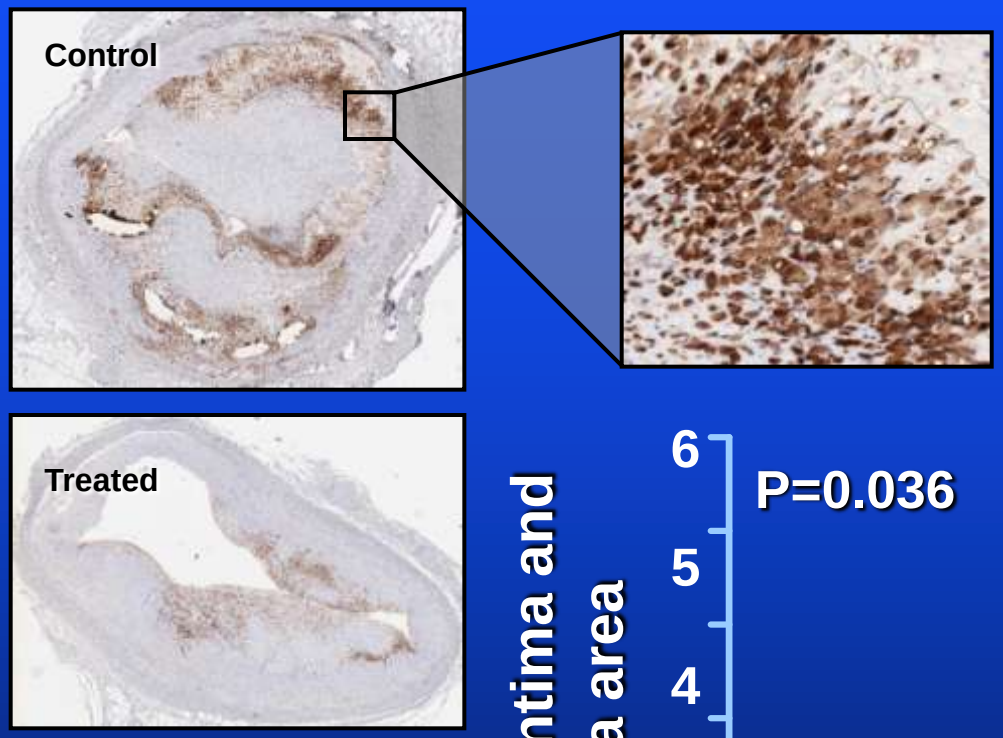
Pre-surgical dosing in patients undergoing carotid endarterectomy



Effects of treatment (14 days) with darapladib on Lp-PLA_2 activity in plasma and in carotid plaques. A statistically significant dose-dependent reduction in Lp-PLA_2 activity was achieved in plasma and in plaques

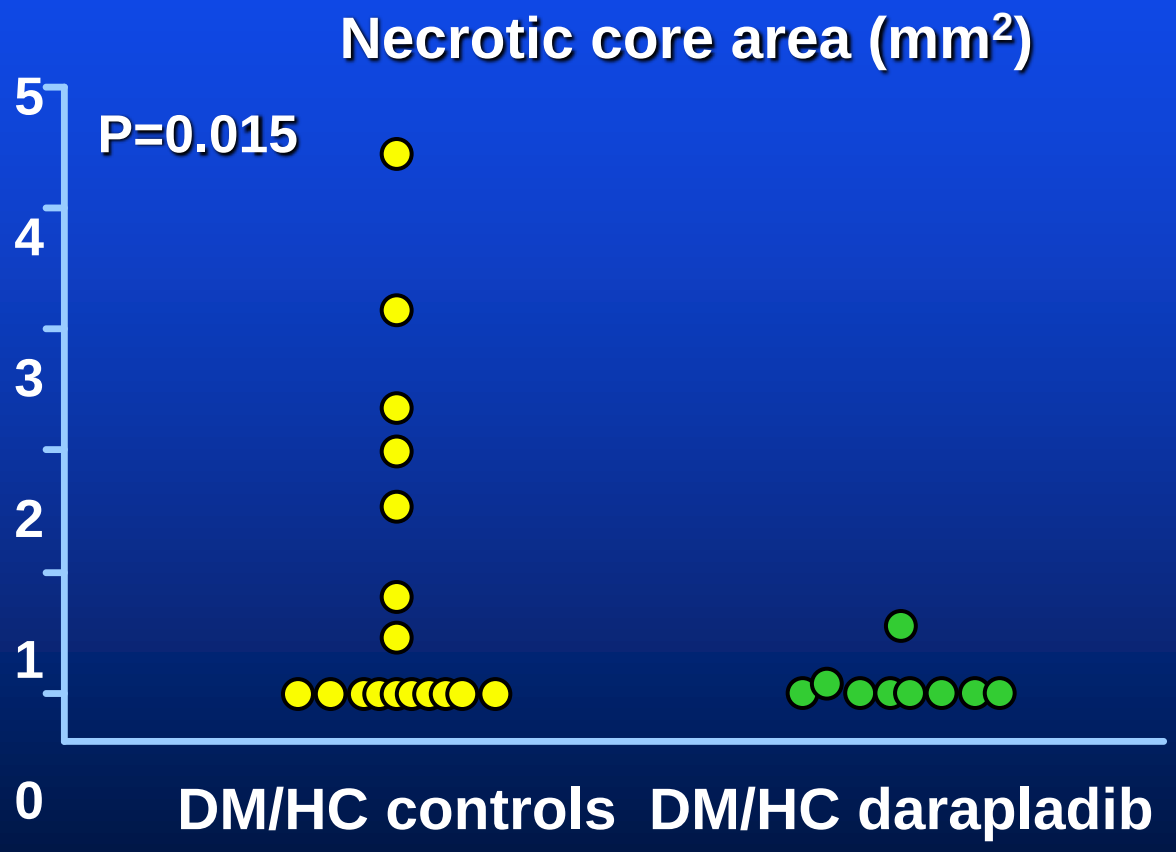
Johnson AG, Zalewski A, Janmohamed S, et al. AHA 2004.

Darapladib Reduced Macrophage Content



Wilensky et al: Nat Med (in press)

Coronary Artery Lesion Complexity and necrotic core were Reduced in Treatment Group



Wilensky et al: Nat Med (in press)

CLINICAL RESEARCH | Clinical Trial

The Effect of Darapladib on Plasma Lipoprotein-Associated Phospholipase A_2 Activity and Cardiovascular Biomarkers in Patients With Stable Coronary Heart Disease or Coronary Heart Disease Risk Equivalent

The Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

Emile R. Mohler III, MD, FACC,* Christie M. Ballantyne, MD
Michael H. Davidson, MD, FACC,‡ Markolf Hanefeld, MD, P
Joel L. Johnson, PHARMD,¶ Andrew Zalewski, MD,¶# for the D

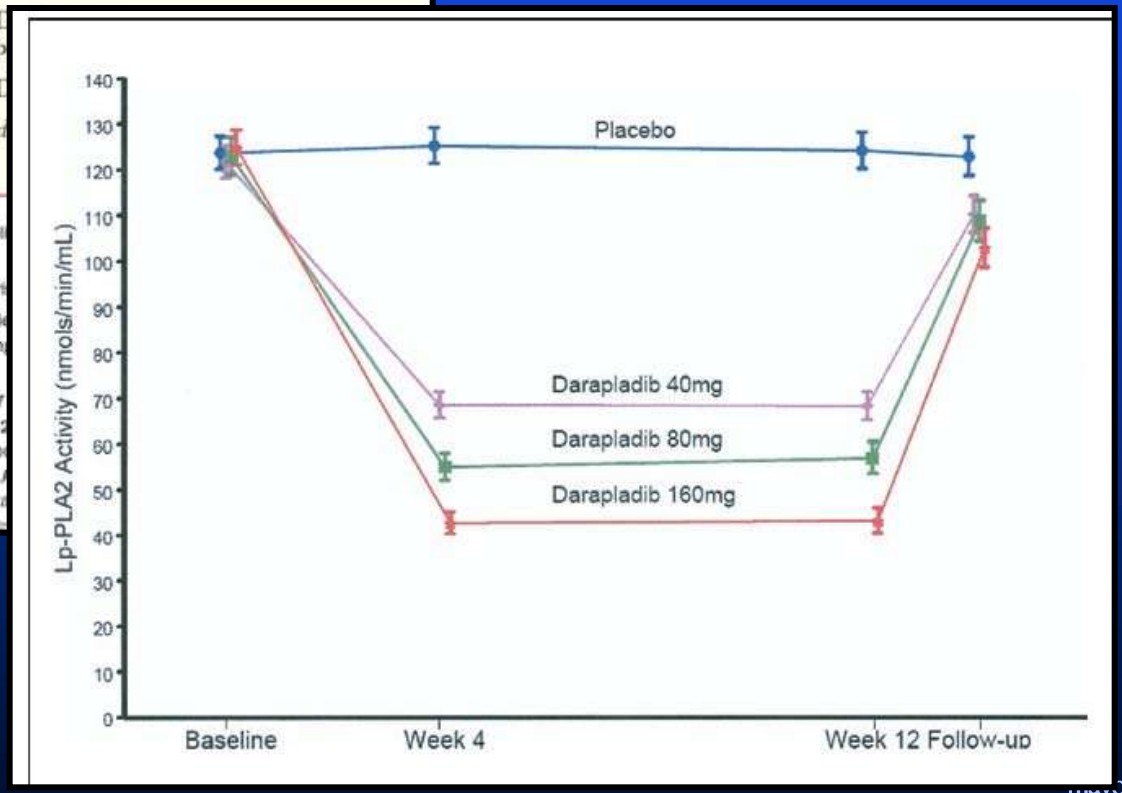
Philadelphia, Pennsylvania; Houston, Texas; Chicago, Illinois; Dresd and Research Triangle Park, North Carolina

Objectives This study examined the effects of darapladib, a selective l inhibitor, on biomarkers of cardiovascular (CV) risk.

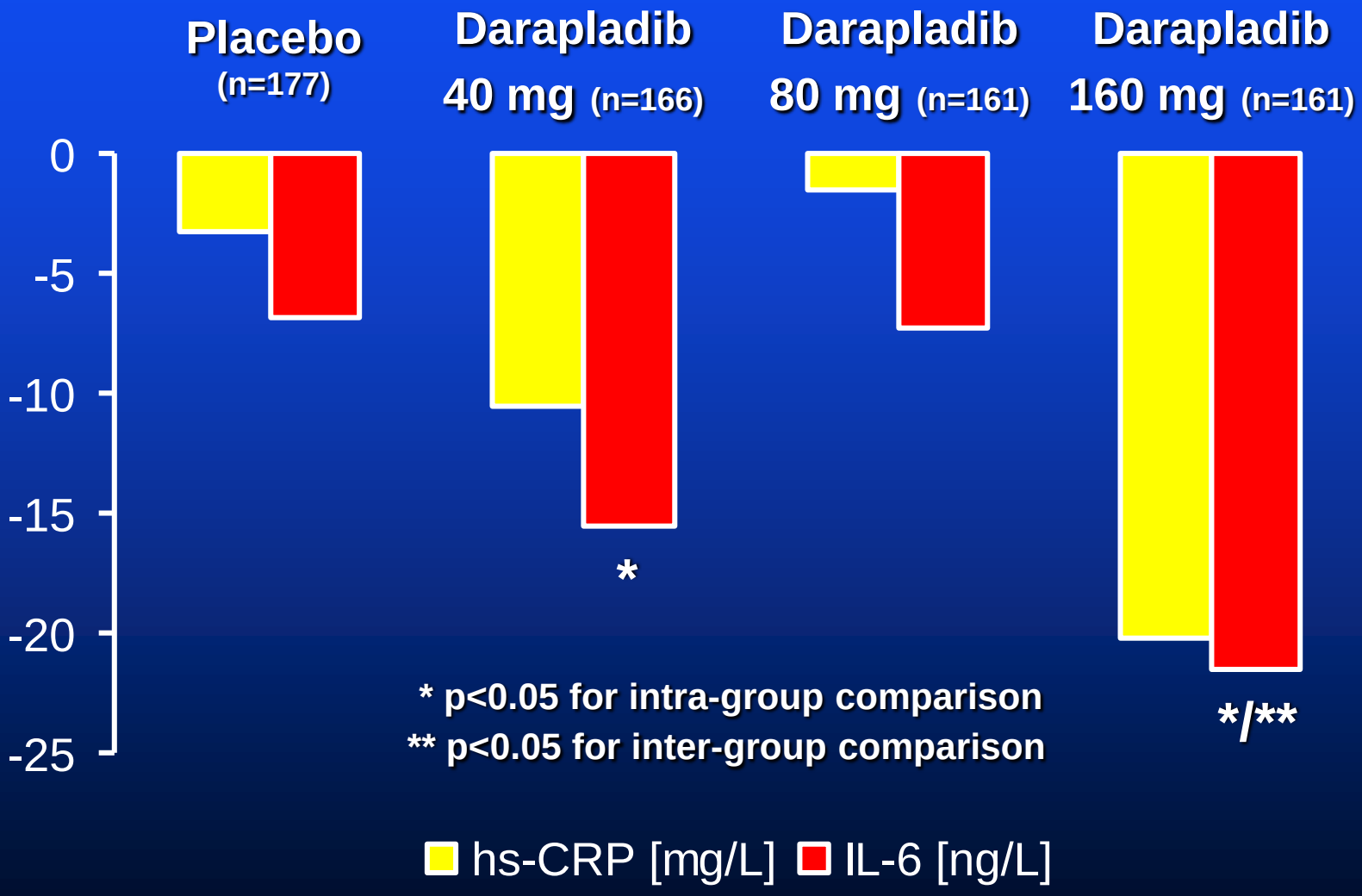
Background Elevated Lp-PLA_2 levels are associated with an increased ri

Methods Coronary heart disease (CHD) and CHD-risk equivalent patie were randomized to oral darapladib 40 mg, 80 mg, 160 mg were analyzed for Lp-PLA_2 activity and other biomarkers.

Results Baseline low-density lipoprotein cholesterol (LDL-C) was 67 patients (≥75 years), in men, in those taking atorvastatin 2 protein cholesterol (HDL-C) <40 mg/dl, or in those with do $p < 0.01$). Darapladib 40, 80, and 160 mg inhibited Lp-PLA compared with placebo ($p < 0.001$ weeks 4 and 12). Susta both atorvastatin groups and at different baseline LDL-C (



Lp-PLA$_2$ inhibitors



Mohler ER et al. **J Am Coll Cardiol 2008;51:1632-41**

Effects of the Direct Lipoprotein-Associated Phospholipase A_2 Inhibitor Darapladib on Human Coronary Atherosclerotic Plaque

Patrick W. Serruys, MD, PhD; Héctor M. García-García, MD, MSc; Pawel Buszman, MD, PhD; Paul Erne, MD, PhD; Stefan Verheye, MD, PhD; Michael Aschermann, MD; Henrikus Duckers, MD, PhD; Oyvind Bleie, MD; Dariusz Dudek, MD; Hans Erik Bøtker, MD; Clemens von Birgelen, MD, PhD; Don D'Amico, MA; Tammy Hutchinson, MSc; Andrew Zambanini, MD; Frits Mastik; Gerrit-Anne van Es, PhD; Antonius F.W. van der Steen, PhD; D. Geoffrey Vince, PhD; Peter Ganz, MD; Christian W. Hamm, MD; William Wijns, MD, PhD; Andrew Zalewski, MD, PhD; for the Integrated Biomarker and Imaging Study-2 Investigators

Background—Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is expressed abundantly in the necrotic core of coronary lesions, and products of its enzymatic activity may contribute to inflammation and cell death, rendering plaque vulnerable to rupture.

Methods and Results—This study compared the effects of 12 months of treatment with darapladib (an oral Lp-PLA_2 inhibitor, 160 mg daily) or placebo on coronary atheroma deformability (intravascular ultrasound palpography) and plasma high-sensitivity C-reactive protein in 330 patients with angiographically documented coronary disease. Secondary end points included changes in necrotic core size (intravascular ultrasound radiofrequency), atheroma size (intravascular ultrasound gray scale), and blood biomarkers. Background therapy was comparable between groups, with no difference in low-density lipoprotein cholesterol at 12 months (placebo, 88±34 mg/dL; darapladib, 84±31 mg/dL; P=0.37). In contrast, Lp-PLA_2 activity was inhibited by 59% with darapladib (P<0.001 versus placebo). After 12 months, there were no significant differences between groups in plaque deformability (P=0.22) or plasma high-sensitivity C-reactive protein (P=0.35). In the placebo-treated group, however, necrotic core volume increased significantly (4.5±17.9 mm^3; P=0.009), whereas darapladib halted this increase (−0.5±13.9 mm^3; P=0.71), resulting in a significant treatment difference of −5.2 mm^3 (P=0.012). These intraplaque compositional changes occurred without a significant treatment difference in total atheroma volume (P=0.95).

Conclusions—Despite adherence to a high level of standard-of-care treatment, the necrotic core continued to expand among patients receiving placebo. In contrast, Lp-PLA_2 inhibition with darapladib prevented necrotic core expansion, a key determinant of plaque vulnerability. These findings suggest that Lp-PLA_2 inhibition may represent a novel therapeutic approach. **(*Circulation*. 2008;118:1172-1182.)**

Key Words: atherosclerosis ■ drugs ■ imaging ■ lipoprotein-associated phospholipase A_2

Despite intensive management of conventional risk factors, many patients continue to experience recurrent coronary events.[1] Most acute coronary events arise from initially non–flow-limiting stenoses that often are underestimated by angiography.[2,3] The salient features of culprit lesions resulting in fatal myocardial infarction include the

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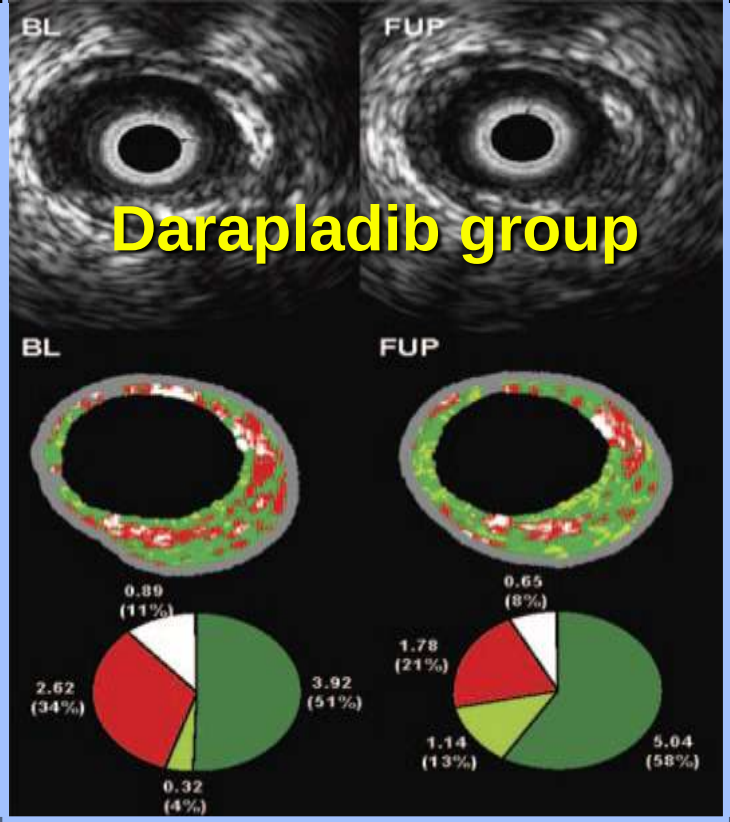

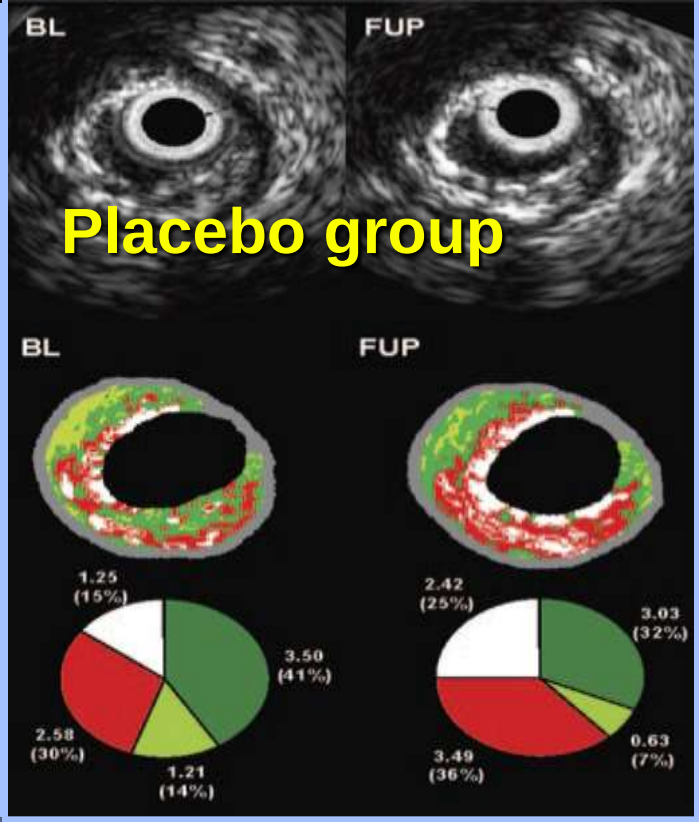

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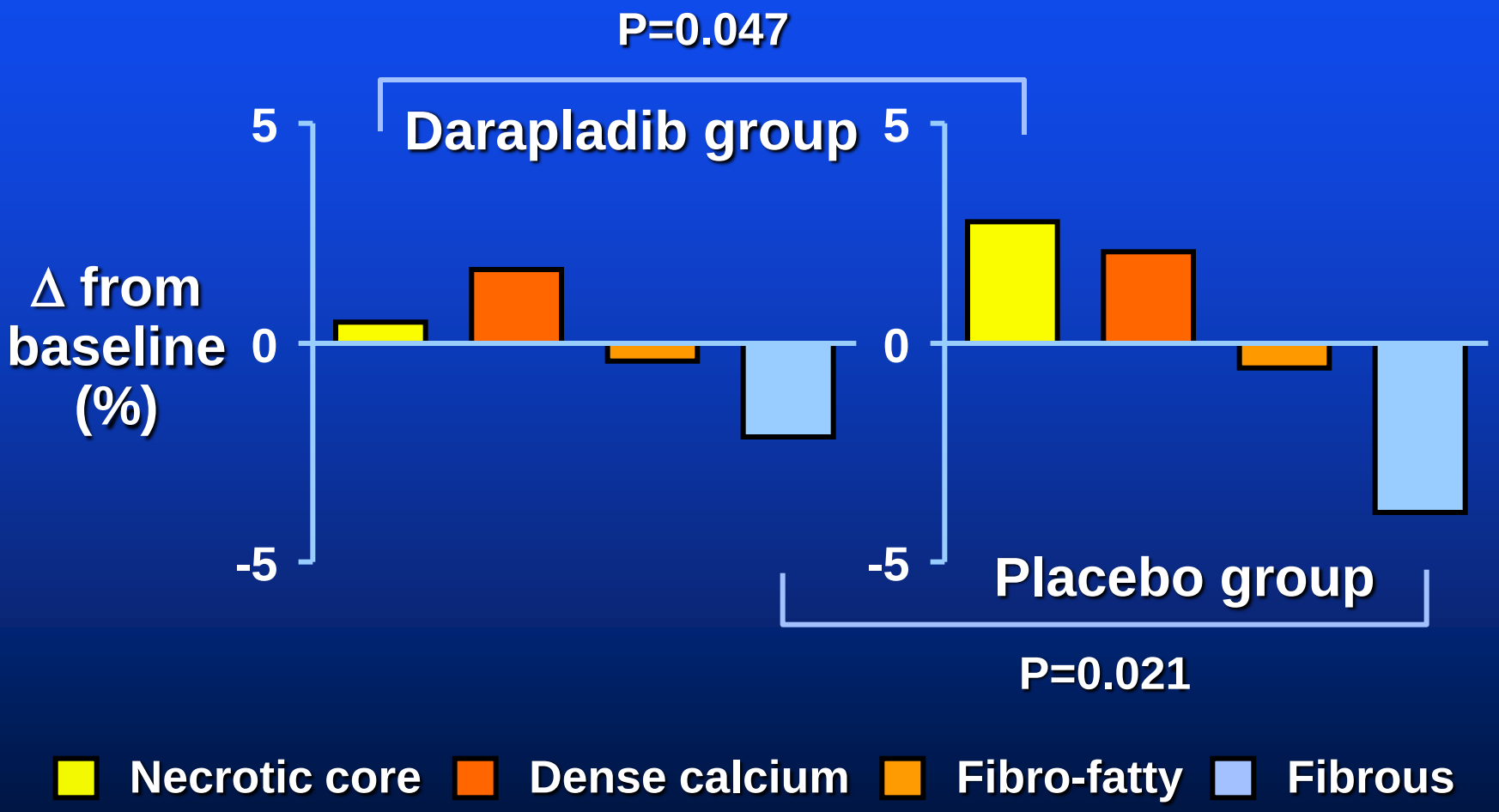
Differential Changes in Plaque Components from IVUS RF Analysis in the Overall Placebo and Darapladib Groups



Serruys et al: Circ 118:1172, 2008

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Spectrum and Consequences of Elevated Risk Identified by Biomarkers

Molecular and basic mechanism

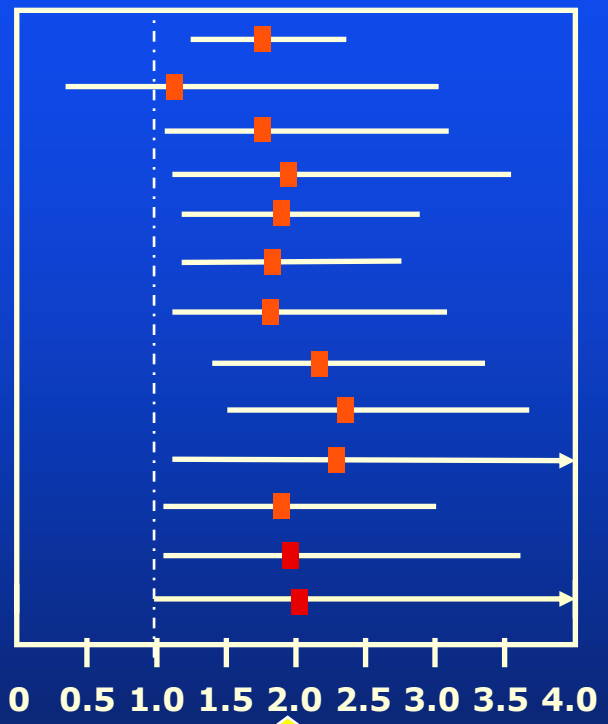
Plaque
- LDL
- ox LDL
- CRP
- IL-6
- IL-10
- IL-18
- Fbg
- TNF-

Unstable plaque
- MMP-9
- MPO
- ICAM
- VCAM
- LpPLA2

Plaque rupture
- sCD40L
- PIGF
- PAPP-A
- VCAM

Thrombosis
- PAI-1
- sCD40L
- VwF
- D-dimer

Epidemiology



A risk factor & a risk marker

Translation from basic mechanism to CV events in humans