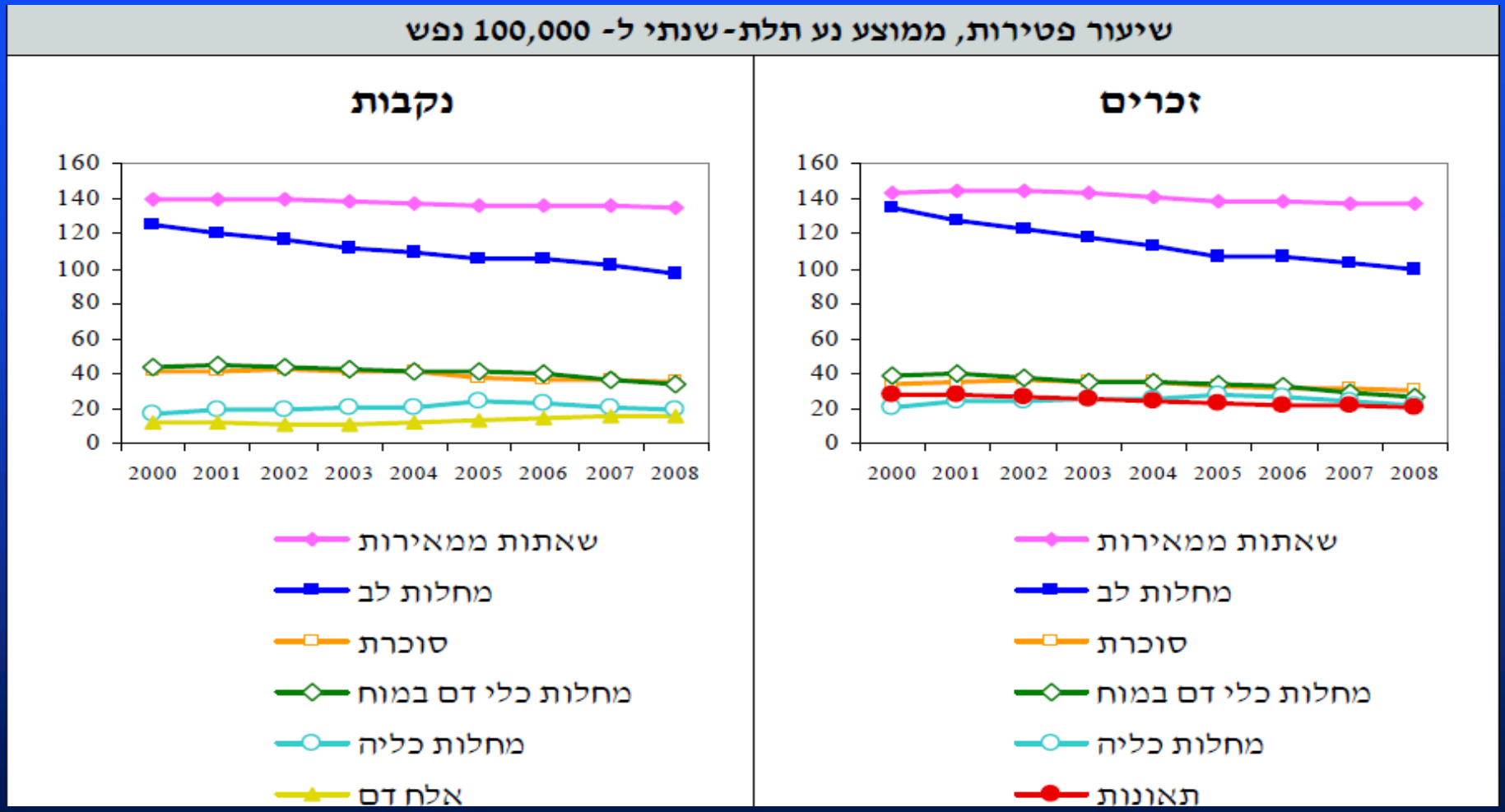
PLAC Test-The role of Lp-PLA2 in predicting increased risk for cardiovascular disease

פרופ' דרור חרץ

מרכז שטרסבורגר לליפידים

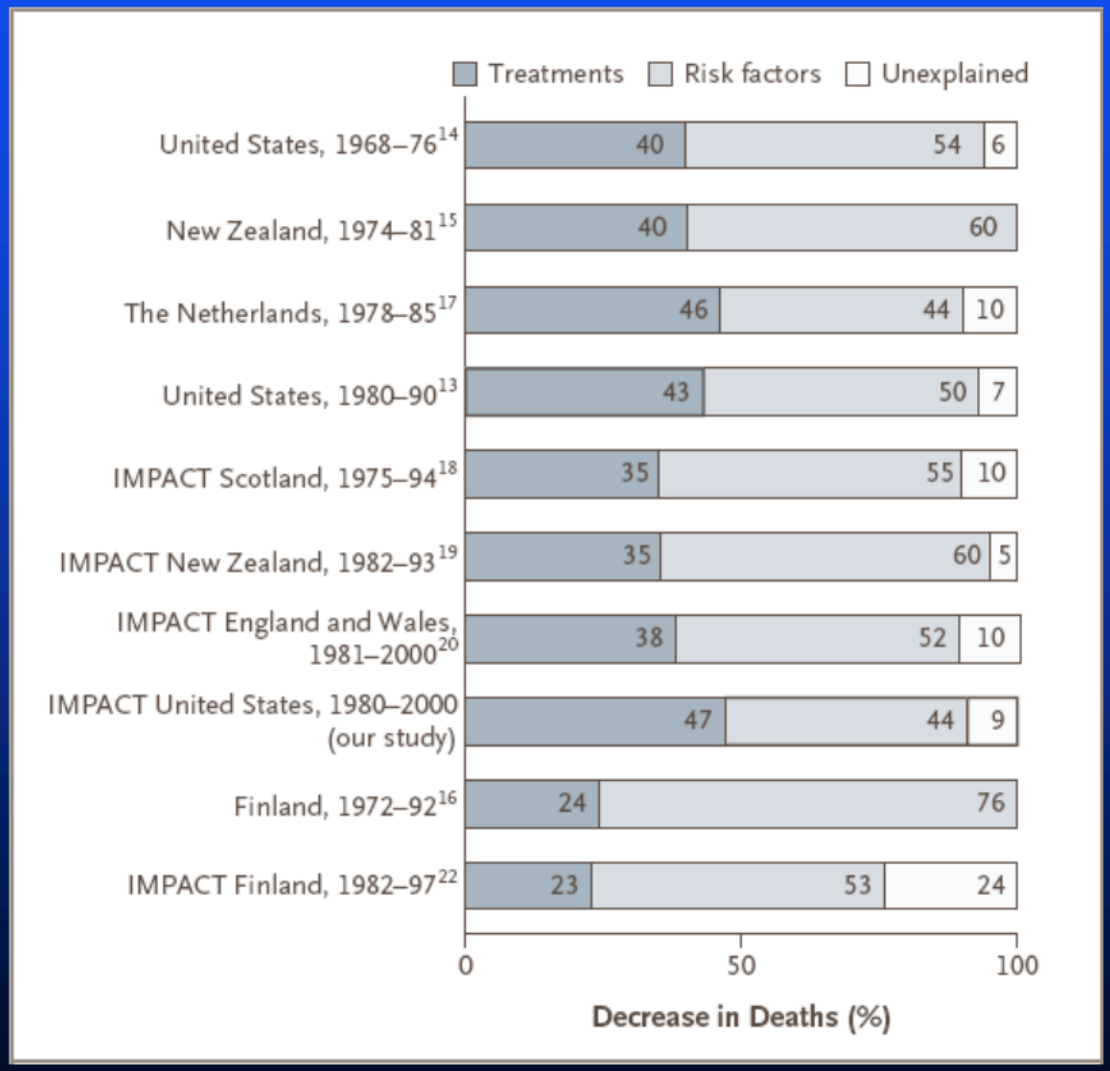
המרכז הרפואי ע"ש שיבא, תל-השומר

סיבות מוות מובילות בישראל 2000–2009



השיעור הגולמי בממוצע השנים 2007-2009 ירד בכרבע בהשוואה לממוצע השנים 1999-2001 במחלות לב (26%- לגברים, 22%- לנשים)

% of the Decrease in Deaths from CHD Attributed to Treatments and Risk-Factors



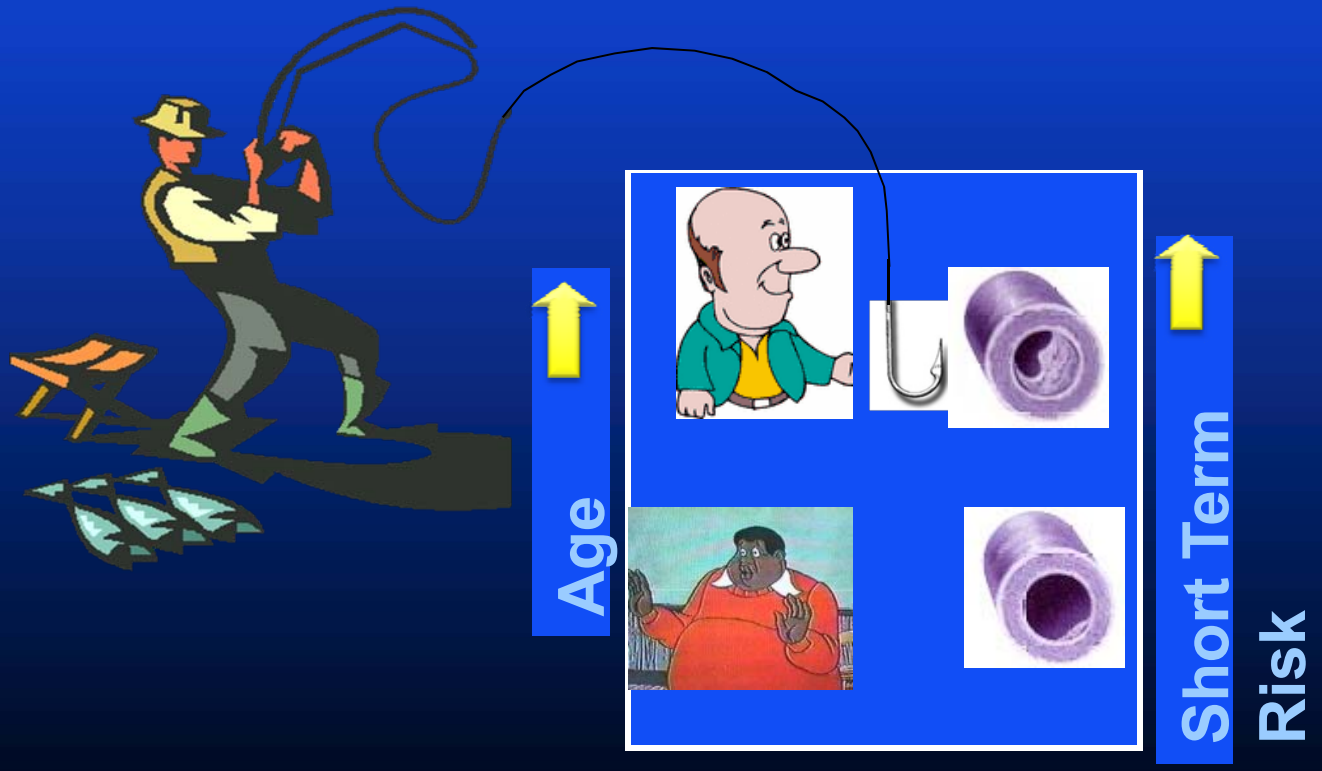
N Engl J Med

ATP III LDL-C Cutoffs for Therapy

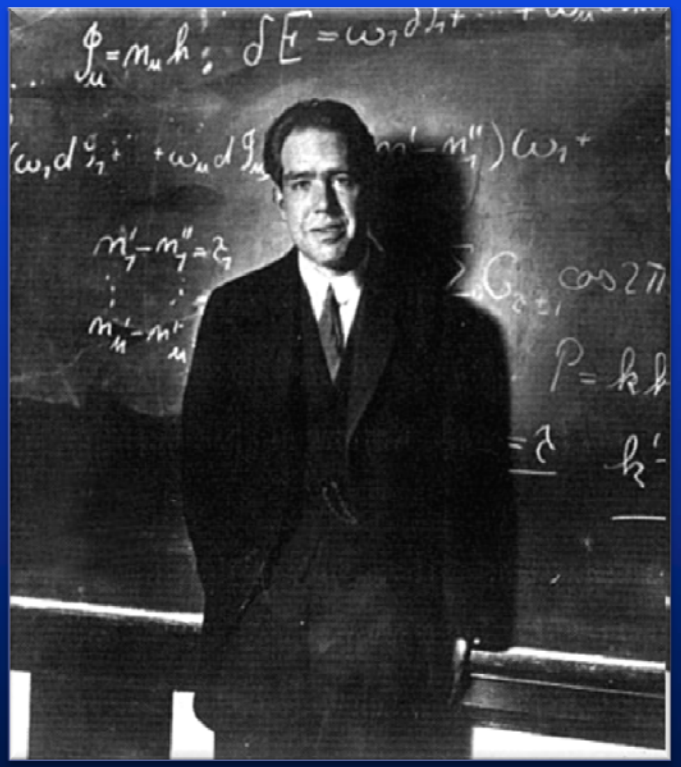
Risk category	LDL-C goal
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional <70 mg/dL)
Moderately high risk: ≥2 risk factors (10-year risk 10%-20%)	<130 mg/dL (optional <100 mg/dL)
Low risk: ≤1 risk factor	<160 mg/dL

Grundy SM et al. *Circulation*; available at

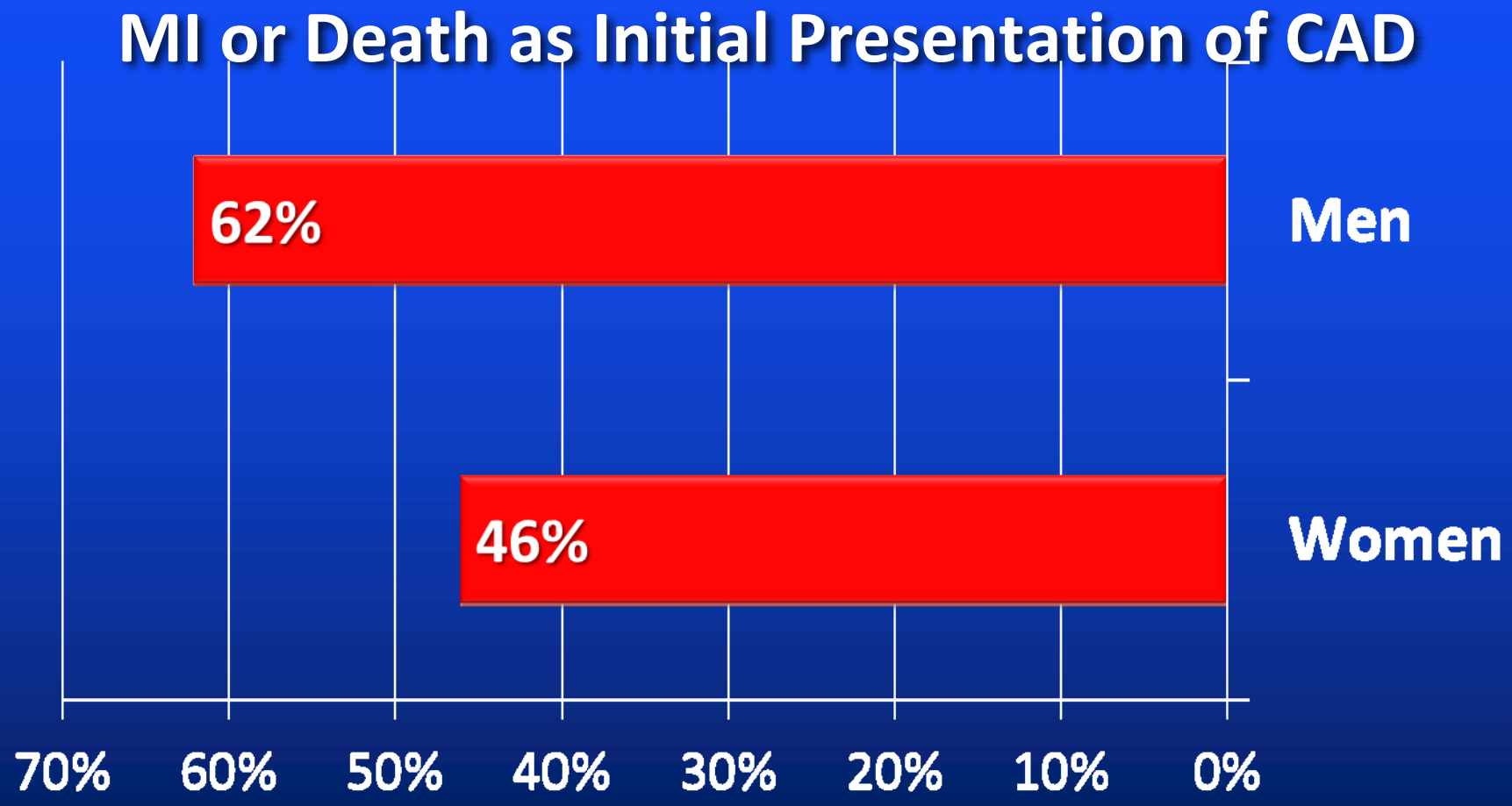
הדילמה:
איך "נדוג" את המטופלים הנמצאים בסיכון גבוה בים הגדול של מטופלים בסיכון בינוני לפי פרמינגהם?



“Prediction Is Very Difficult, Especially If It’s About The Future”



Nils Böhr

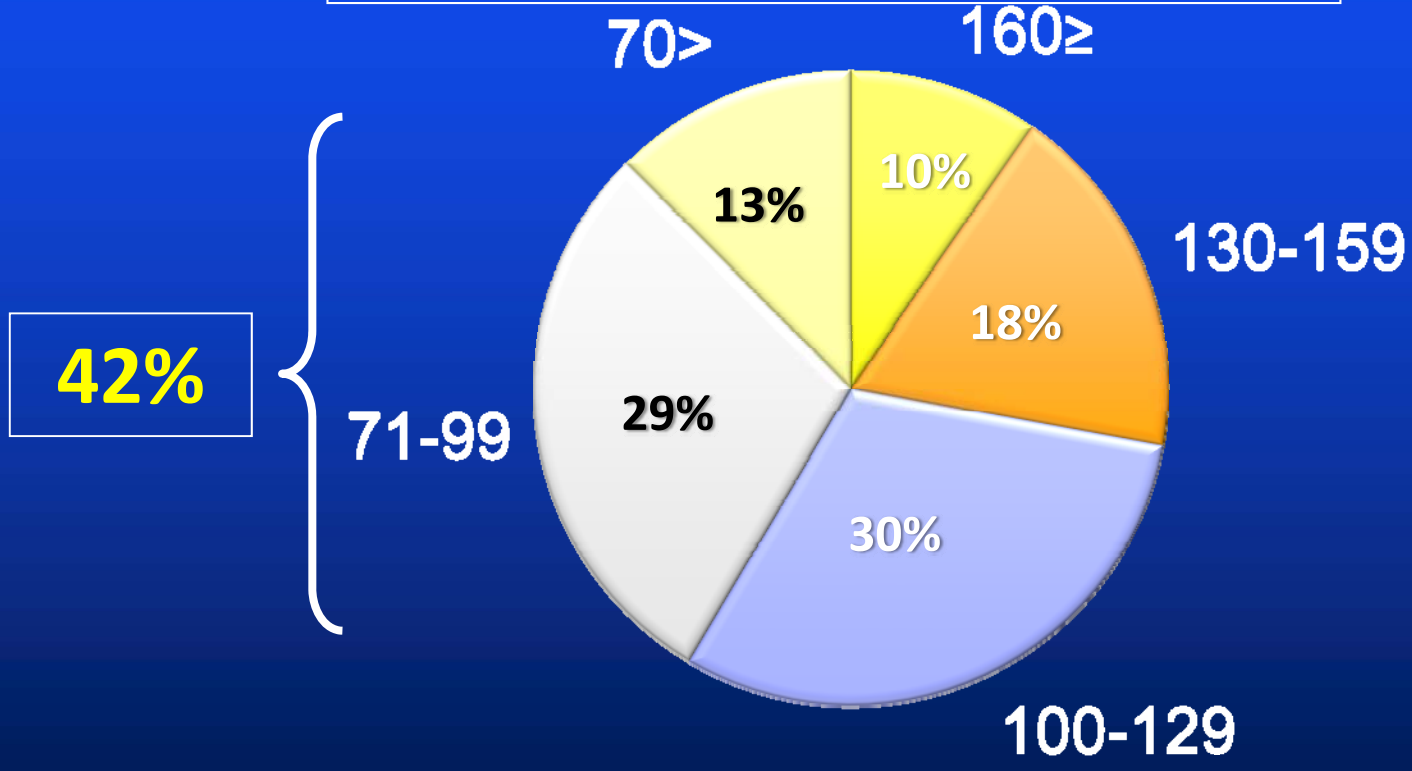


האם הערכת הסיכון עפ"י פרמינגהם מספקת?

Levy D et al in Textbook of Cardiovascular Medicine, 1998

LDL-C in Patients Hospitalized with CAD: 48,093 Patients Without History of CAD

14% on lipid lowering therapy

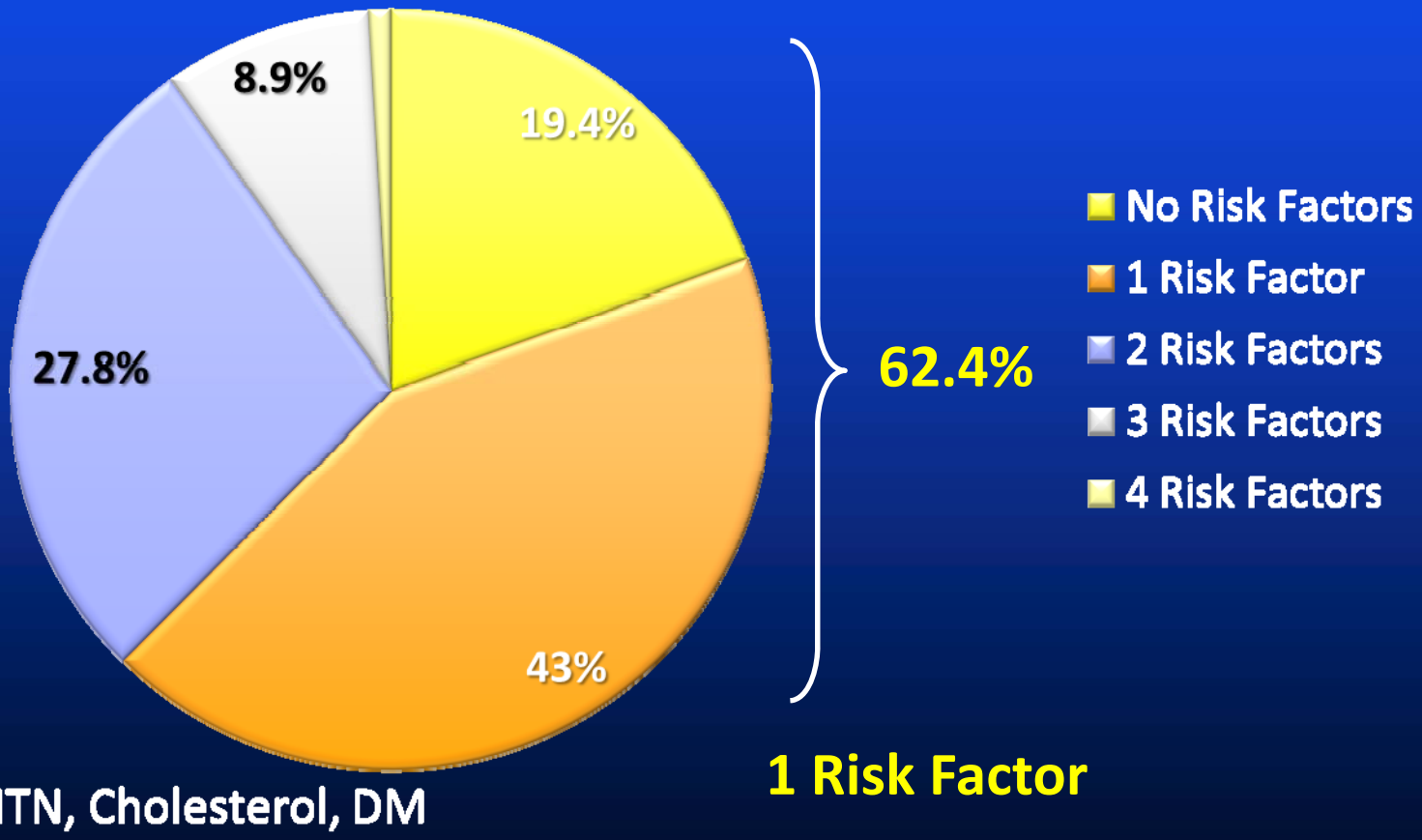


42% had LDL-C <100 mg/dl

Am Heart J

Prevalence of Conventional Risk Factors* in Men with CHD

(14 trials, N = 87,869, mean age 60)

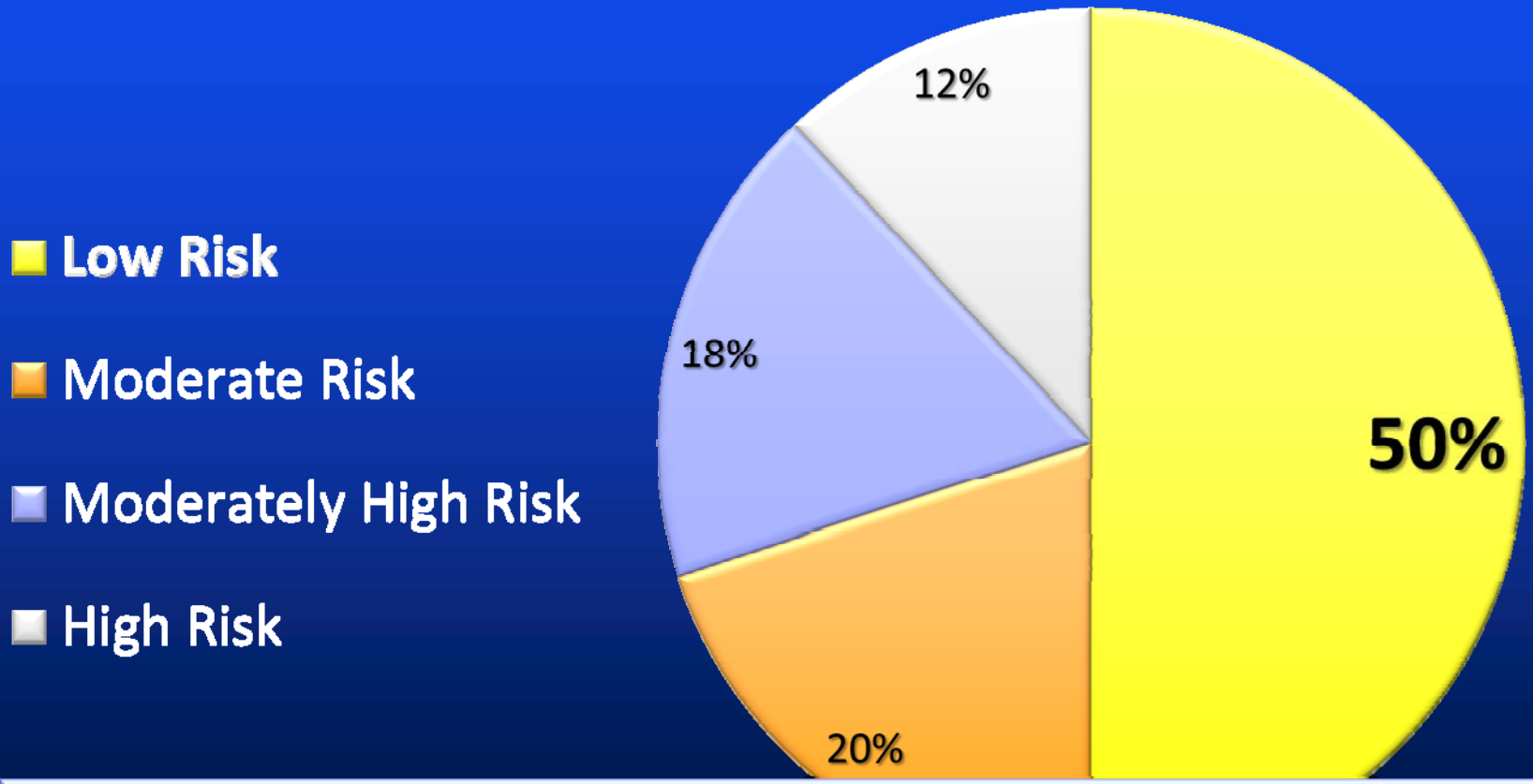


*Smoking, HTN, Cholesterol, DM

JAMA 2003;290:898

How Good Is NCEP ATP III At Predicting MI in Young People?

222 patients with 1st acute MI, no prior CAD, no DM men <55, women <65



~75% did not qualify for statins

JACC

Screening for Atherosclerosis

Risk Factors vs Disease

Numerous Risk Factors

High LDL
Low HDL
High BP
Diabetes
Smoking
CRP
Metabolic Syn
Lp(a)
Homocysteine
Dense LDL
Lp-PLA2
ApoB/ApoA
Family History
Sedentary Life
Obesity
Stress
...
?

Over 200 risk factors have been reported.

Am J Cardiol

The Forest of Biomarkers: How to choose the right biomarker

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Why should we use this test?

- The test should make a scientific sense.
- Participate in the disease process
- A marker at different disease stages
- Reflects Reversibility
- Serves as a risk factor not only as a risk marker.

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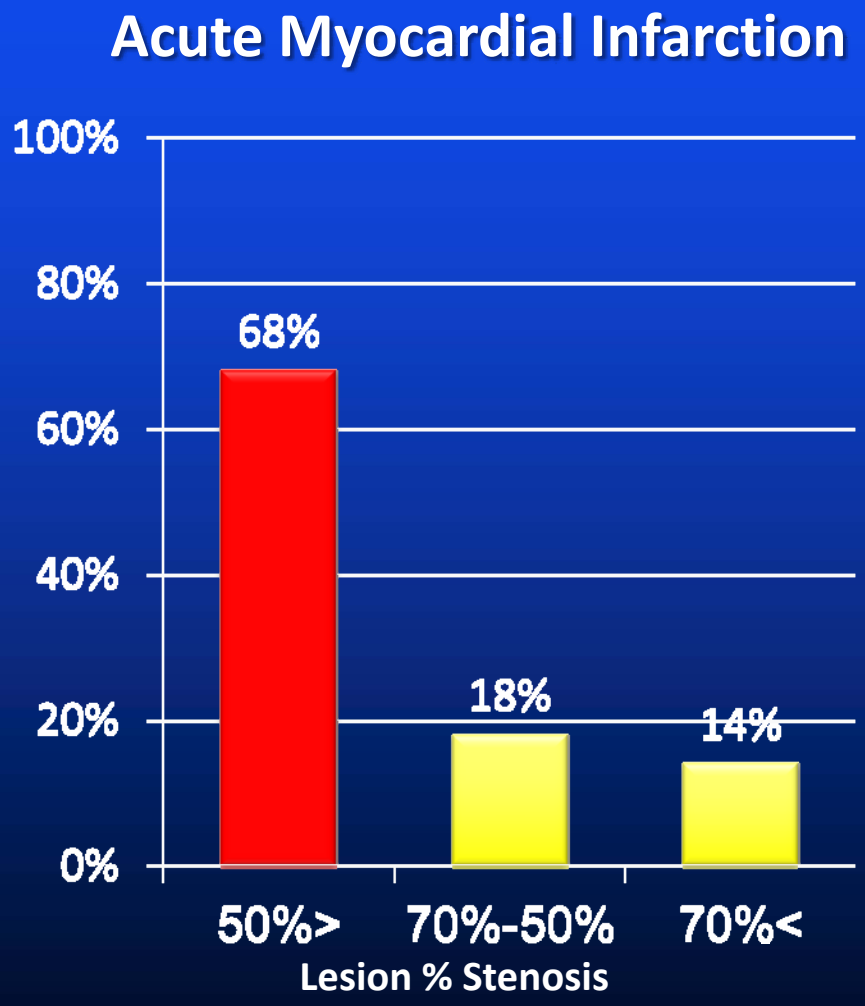
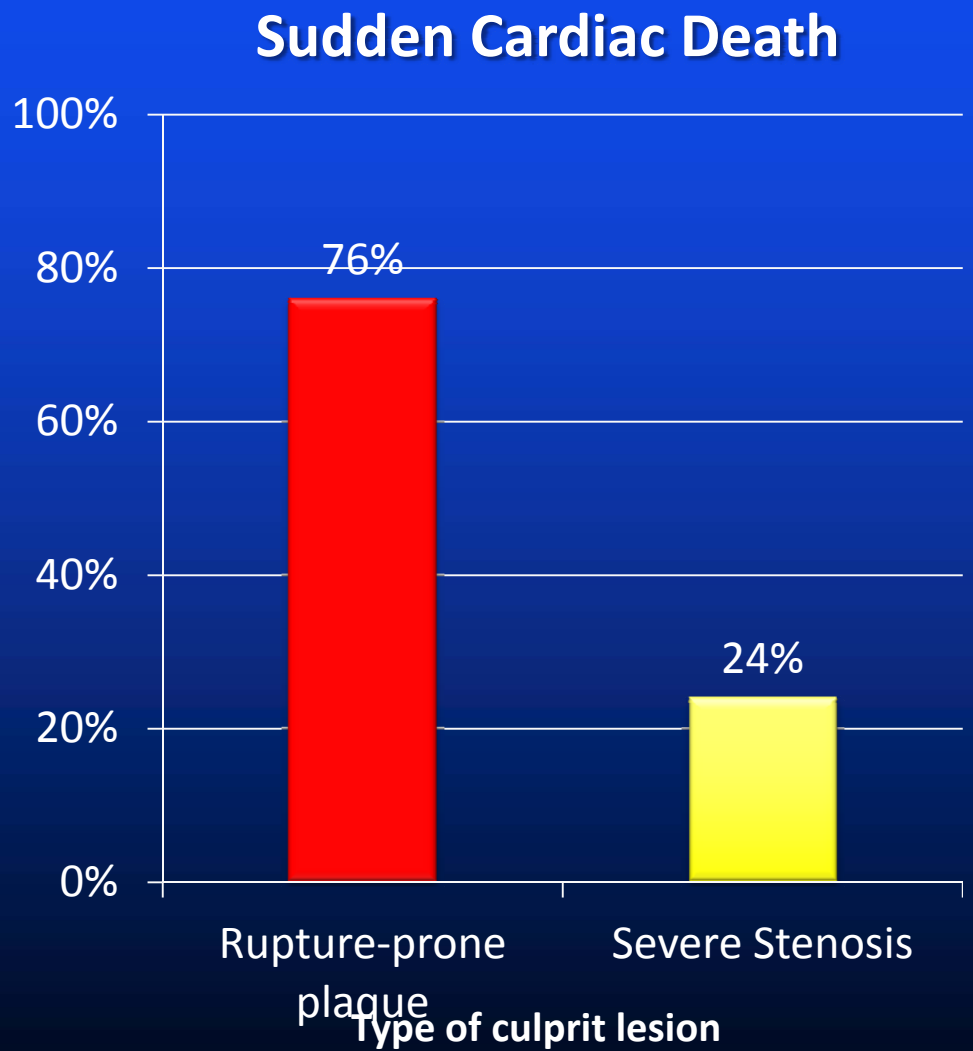
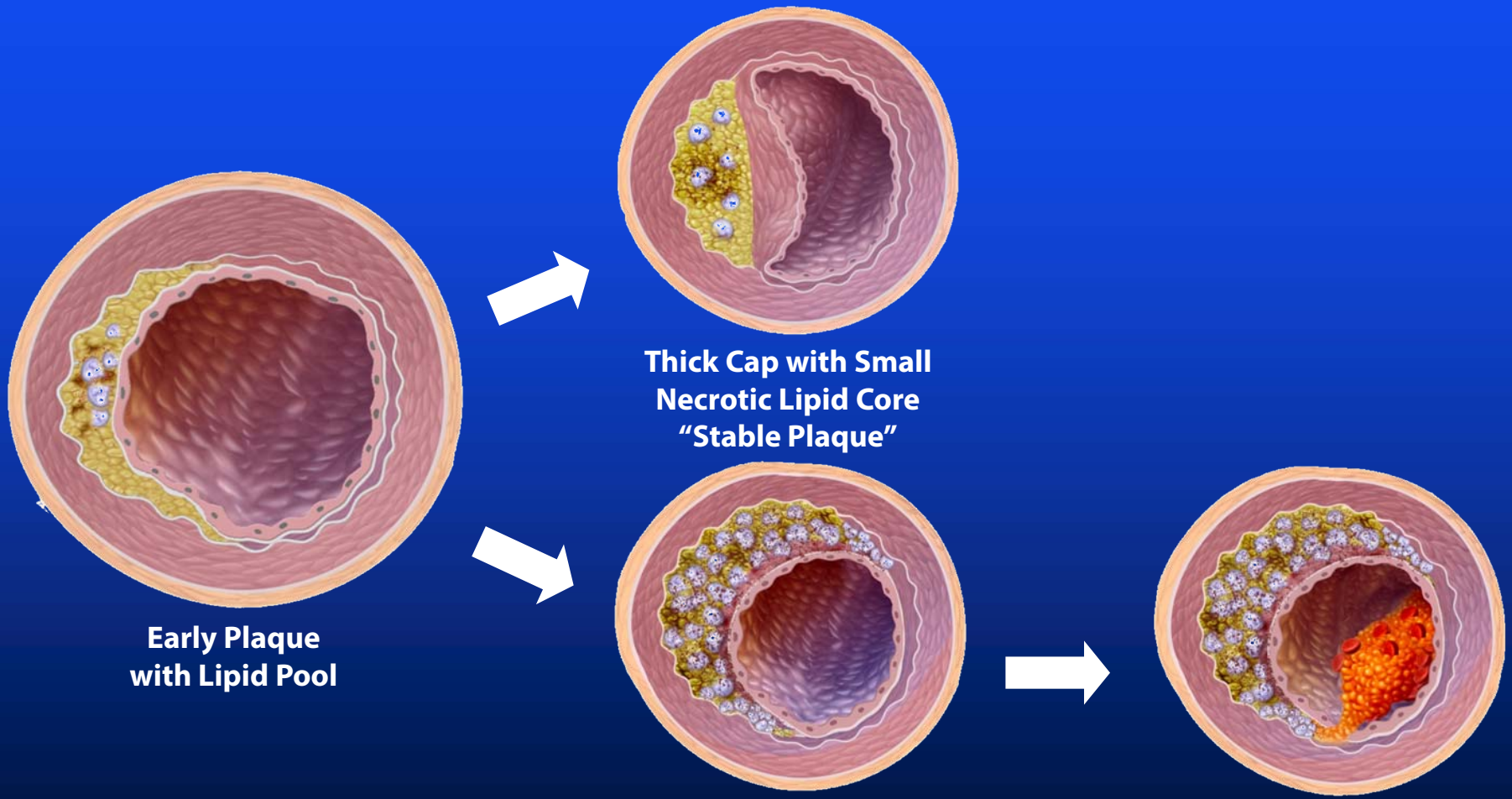
More than 2/3 of All MIs, Fatal or Non-Fatal are from Plaque Rupture





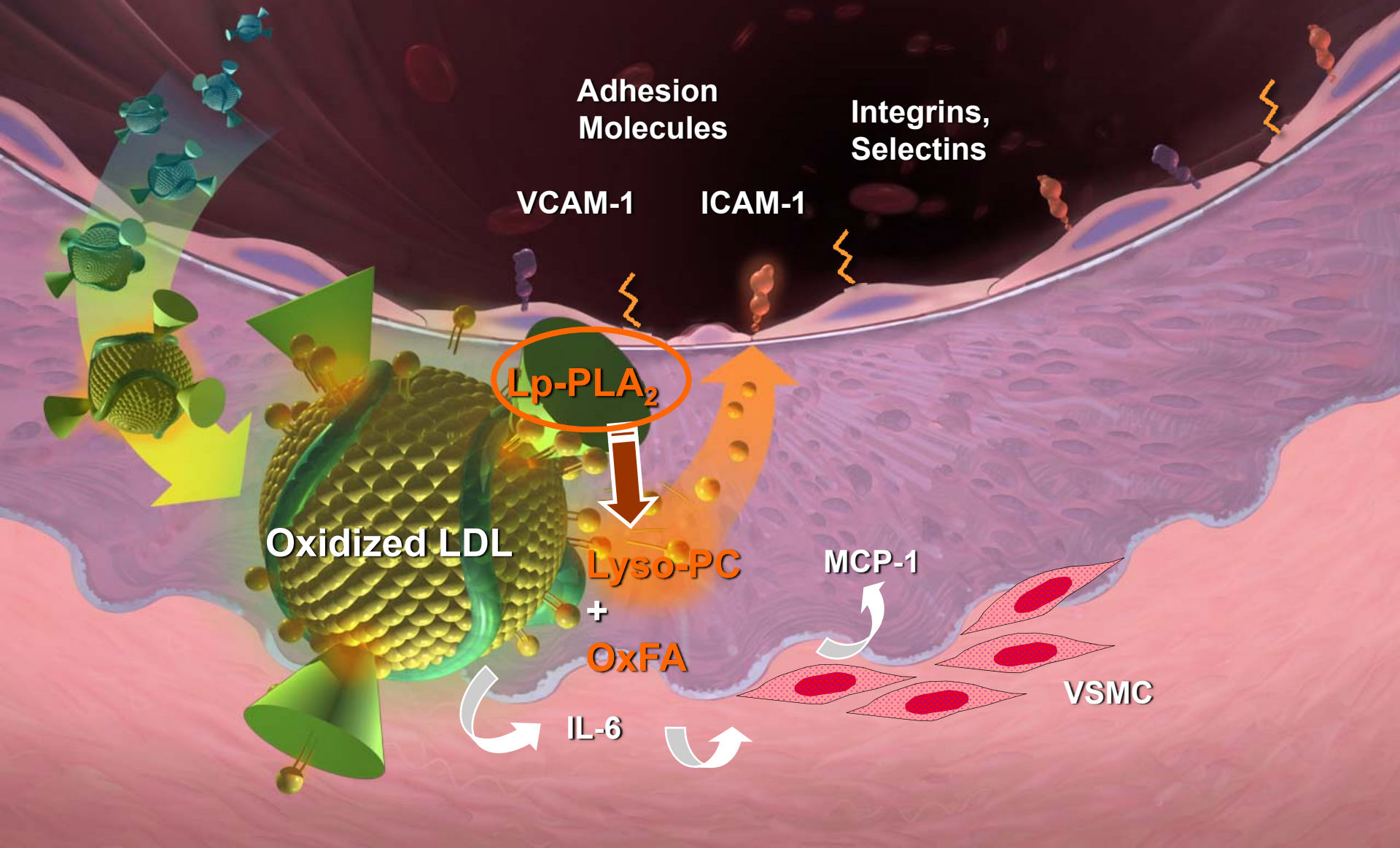
Kolodgie F, et al. *ATVB*

Rupture-Prone Plaques may not be Severely Stenosed but are Inflamed with Thin Fibrous Caps

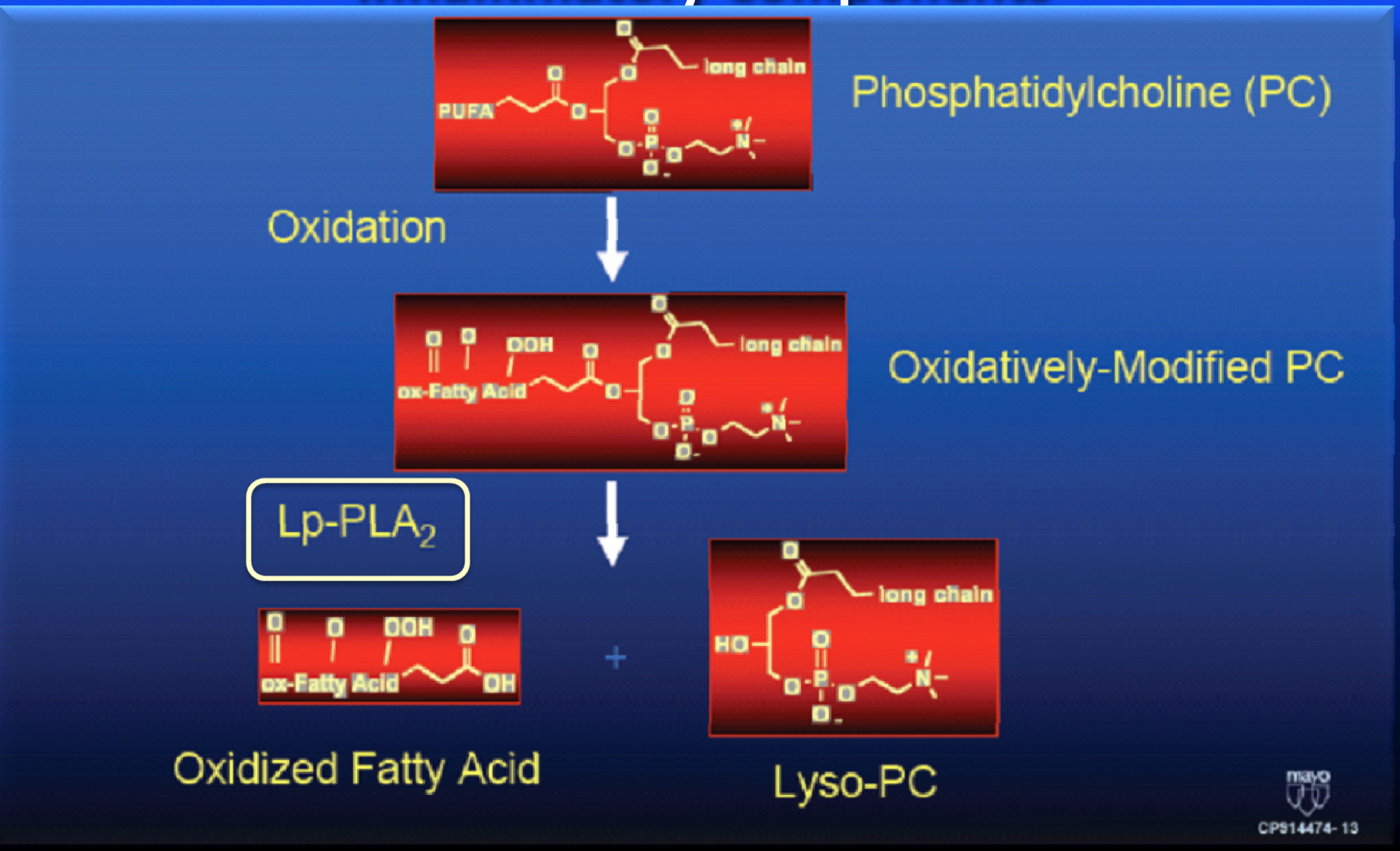


Adapted from Kolodgie F, et al. *Arterioscler Thromb Vasc Biol* 2006.

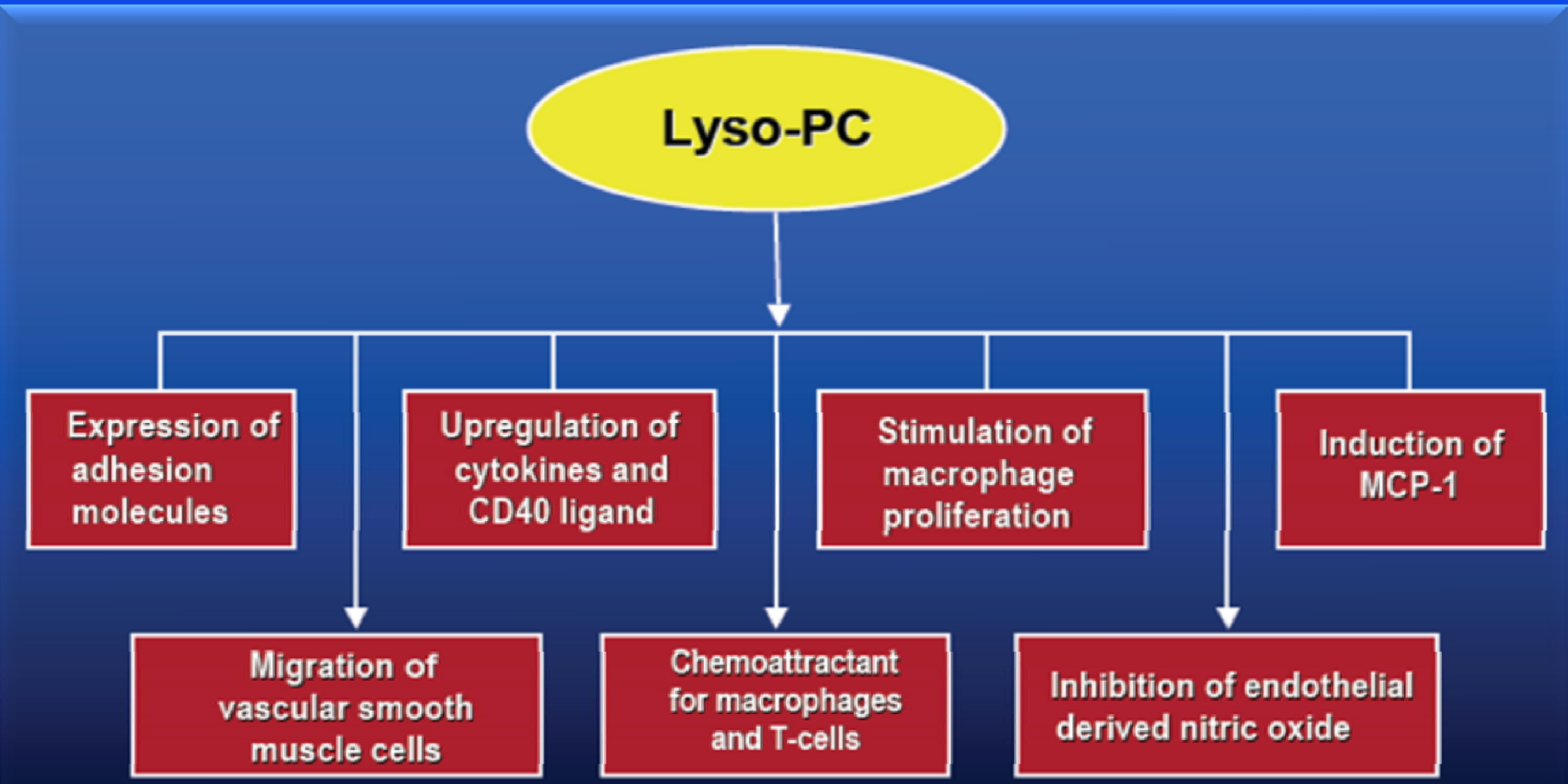
LDL is Oxidized in the Vascular Wall and its Oxidized Constituents are Released by Lp-PLA$_2$



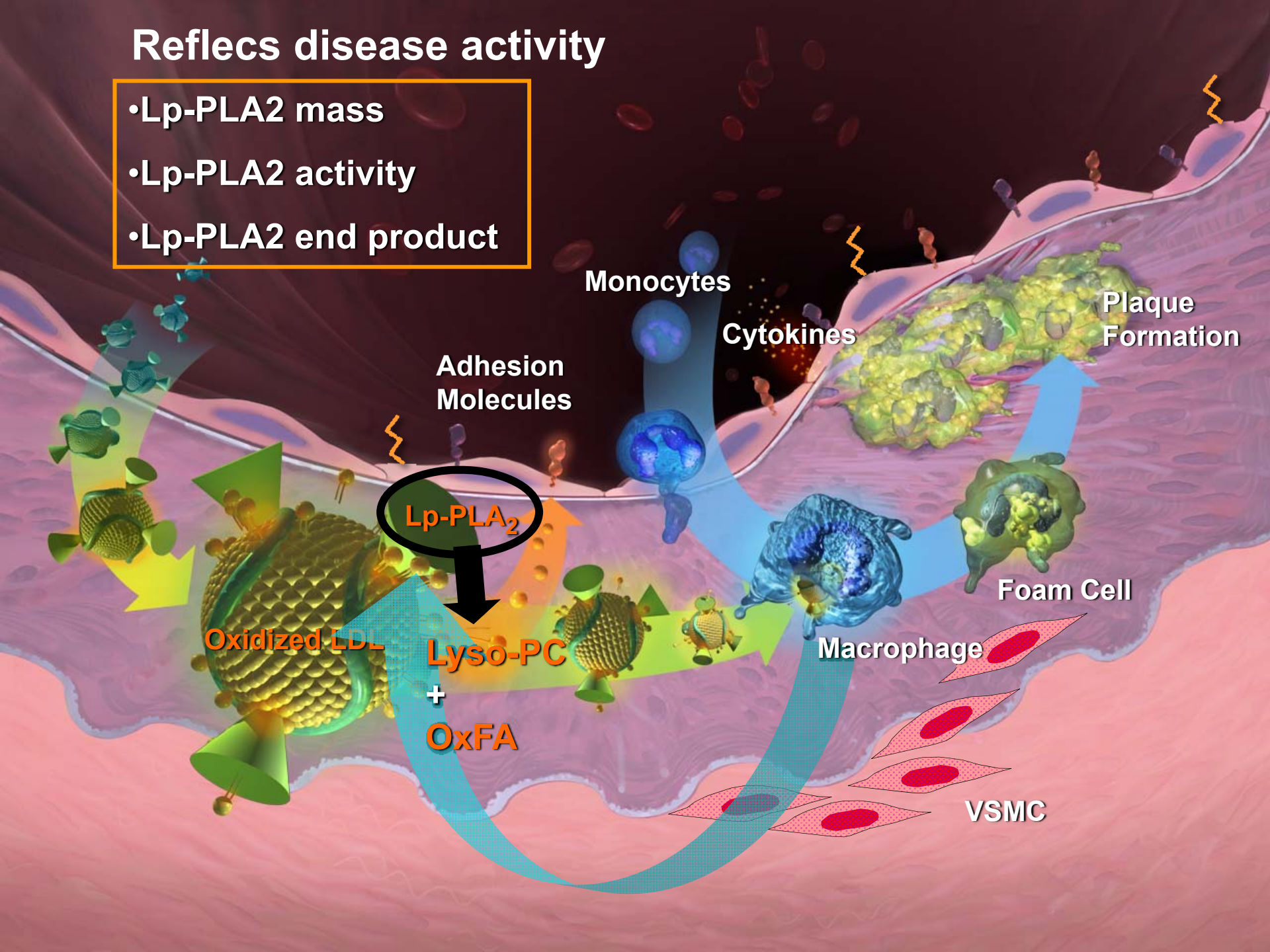
Lp-PLA2 Hydrolyzes Oxidized LDL to Release 2 Pro-Inflammatory Components



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


Reflecs disease activity
•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

Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A_2

Robert S. Rosenson[1]* and Diana M. Stafforini[†,§]

- **LpPLA2 *reduced* cellular uptake of oxidized LDL and Lp(a), and cholesterol accumulation by monocyte-derived macrophages**
- **LpPLA2 inhibited endothelial cell apoptosis induced by minimally modified LDL particles**

J. Lipid Res. 2012. 53: 1767–

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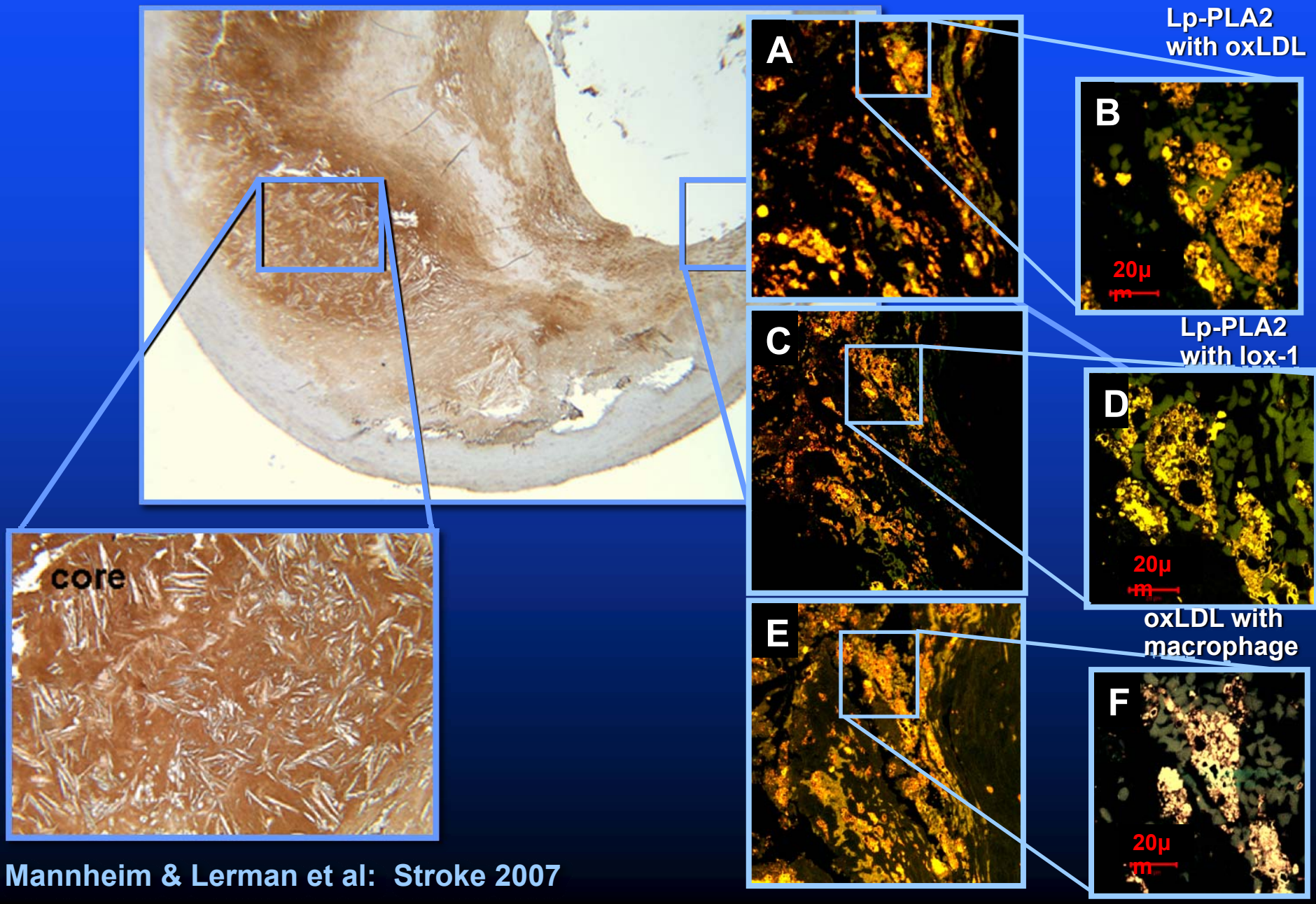
Expression of Lp-PLA2 in Atherosclerotic Carotid Plaques



Mannheim & Lerman et al: Stroke 2007

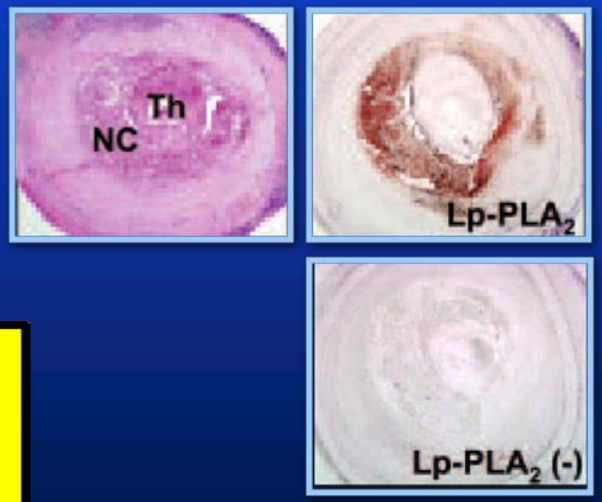
Serial Cryostat Sections Showing Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) Protein Expression in Varying Human Coronary Plaques Morphologies

Pathologic intimal thickening

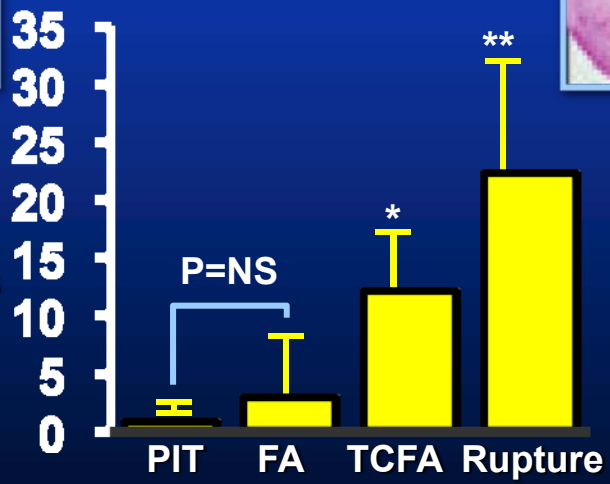
Fibroatheroma

Thin cap fibroatheroma

Plaque rupture



% Lp-PLA2 staining in varying coronary plaque morphologies

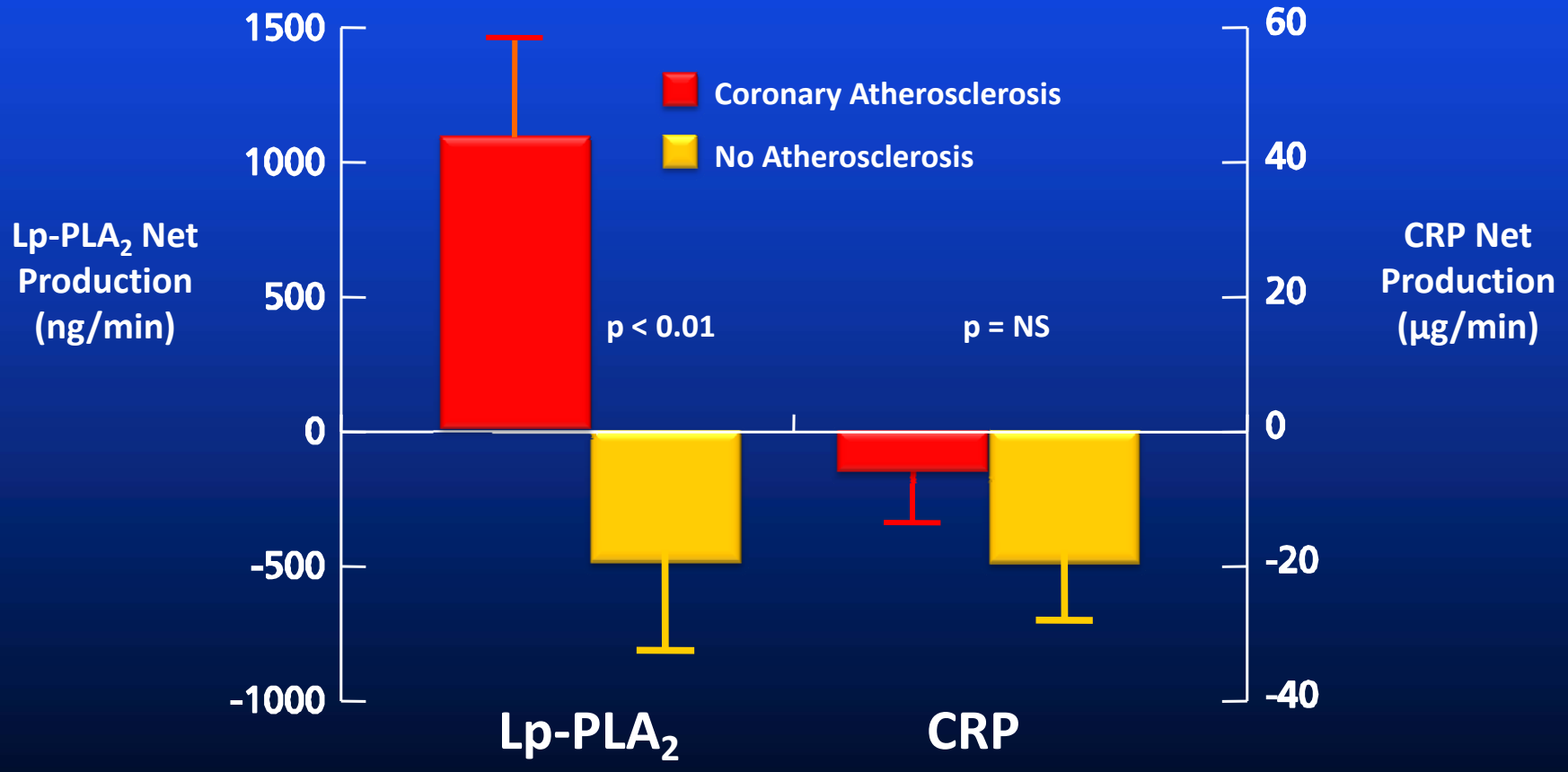


*P<0.05 vs FA or PIT; ** P<0.002 vs TCFA, FA, and PIT

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

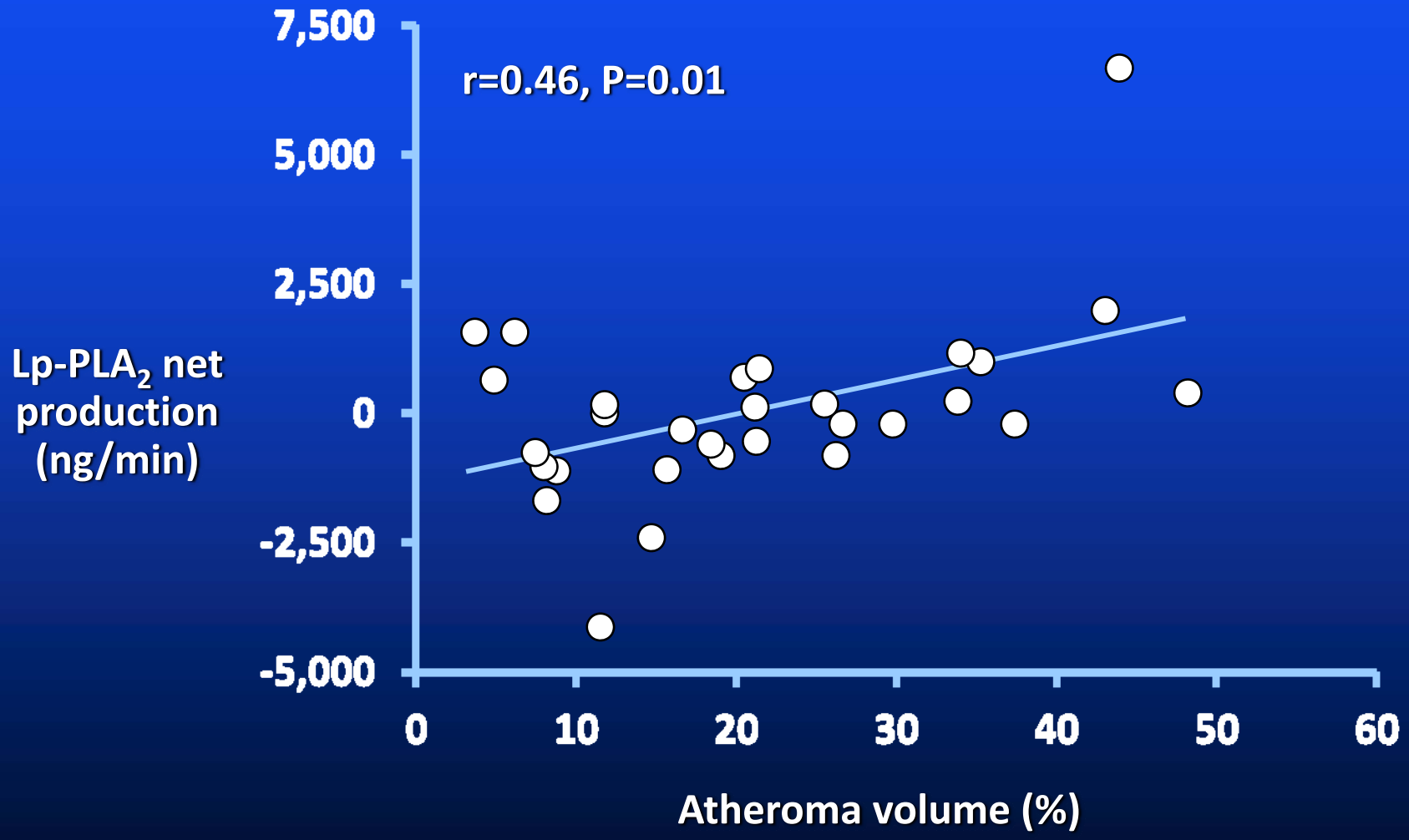
Lp-PLA$_2$ Enters Coronary Circulation When Coronary Atherosclerosis (IVUS) is Present

Net Production = Lp-PLA$_2$ concentration in coronary sinus minus the Lp-PLA$_2$ concentration in coronary os



Lavi S, et al. *Circulation 2*

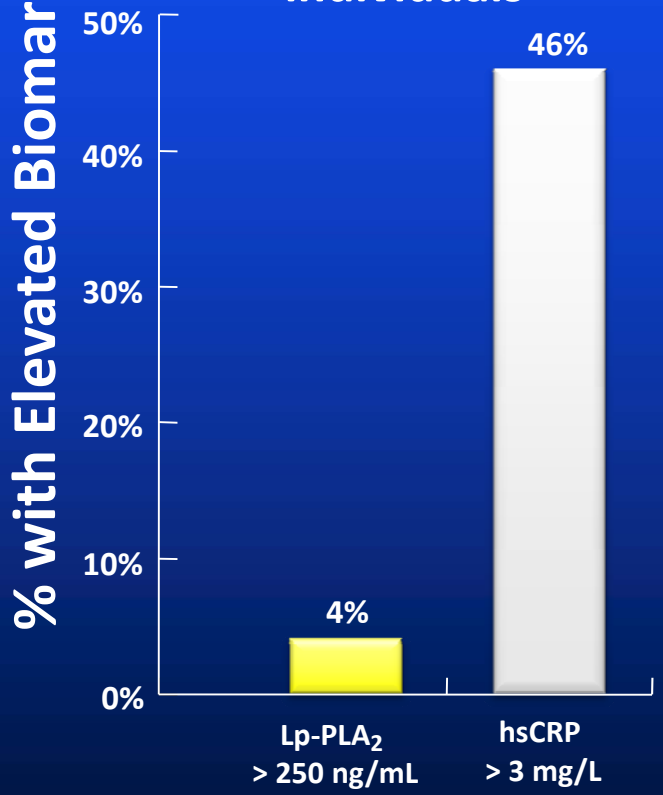
IVUS Atheroma Volume Correlates With Coronary Lp-PLA_2 Production



Lavi S, et al. Local Production of Lp-PLA_2 and LysoPC in the Coronary Circulation: Association With Early Coronary Atherosclerosis and Endothelial Dysfunction in Humans. *Circulation* 2007

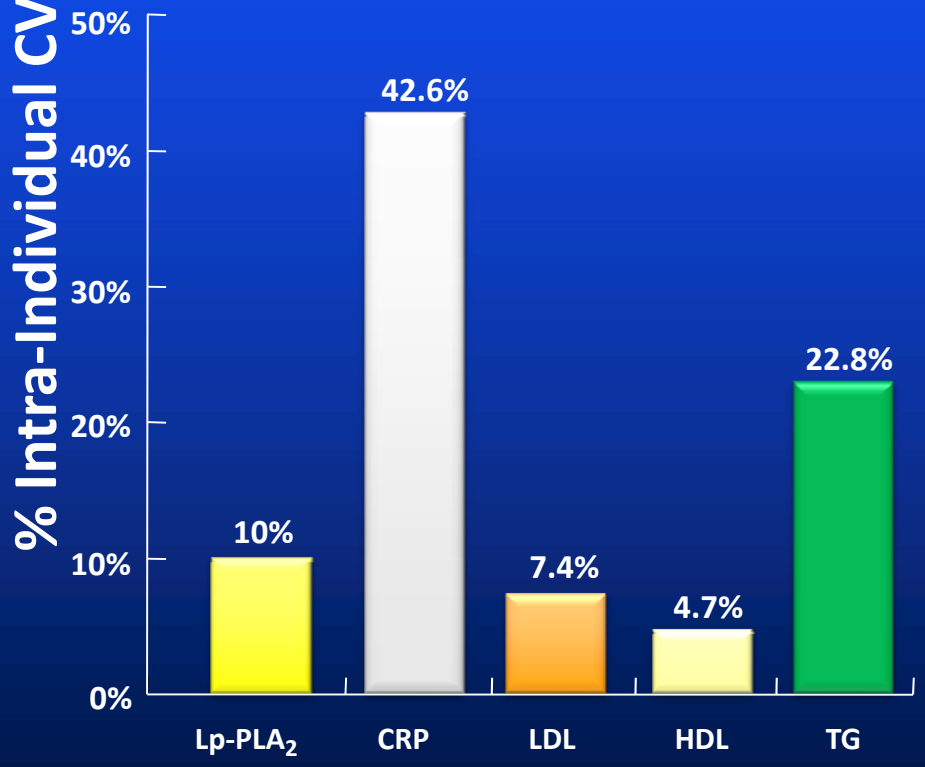
Lp-PLA$_2$ is Specific to Vascular Inflammation and has Lower Biovariability Than Other Inflammatory Markers

Lp-PLA$_2$ is not typically elevated in healthy individuals



Blood from 90 healthy heart disease free individuals

Lp-PLA$_2$ has Minimal Biovariability



Blood from 43 healthy adults each drawn 7 times over 4 weeks

Lerman A, McConnell JP. *Am J Card Supplement* 2008.

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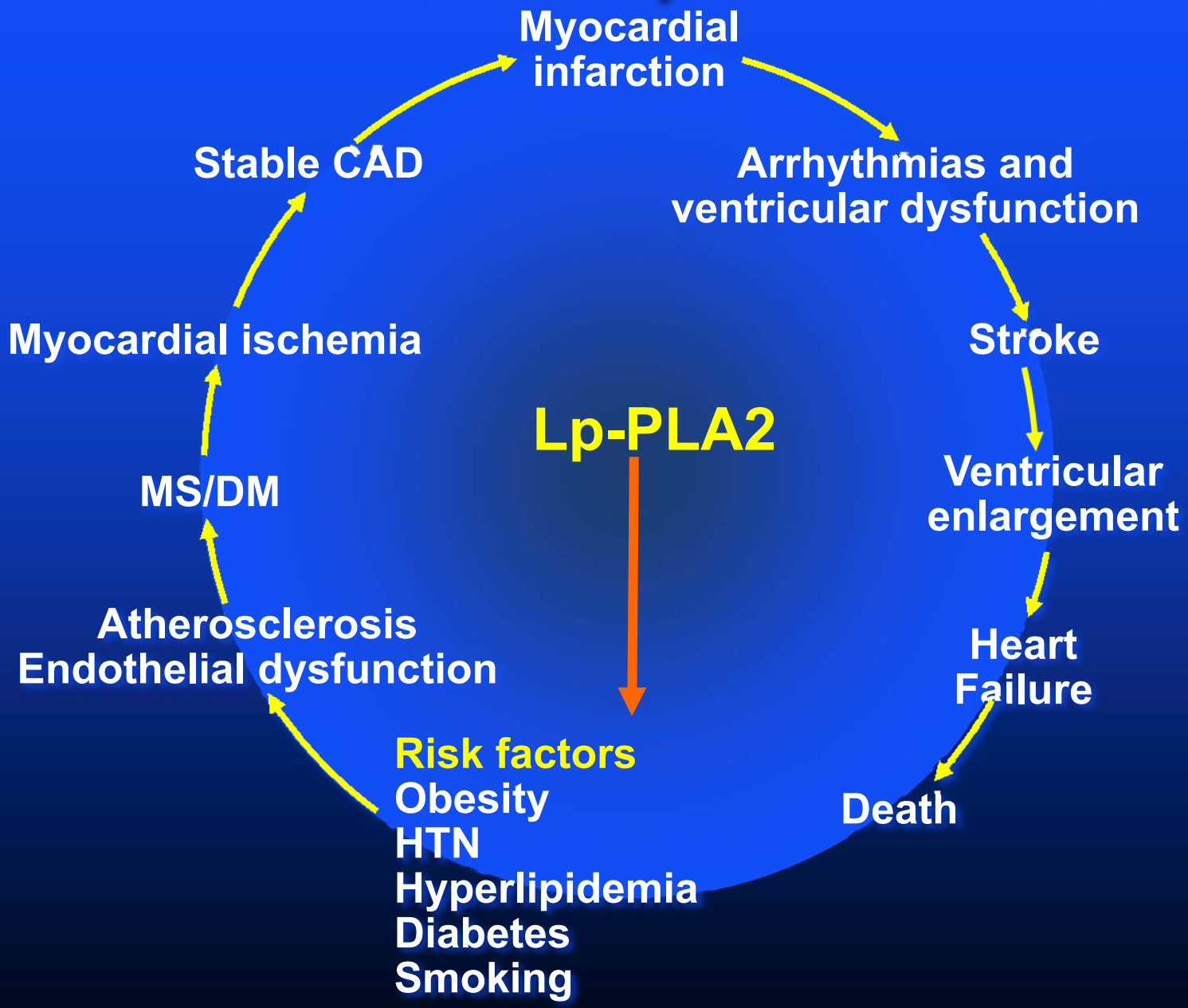
Clinical Utilization of Lp-PLA2 in CVD and Stroke



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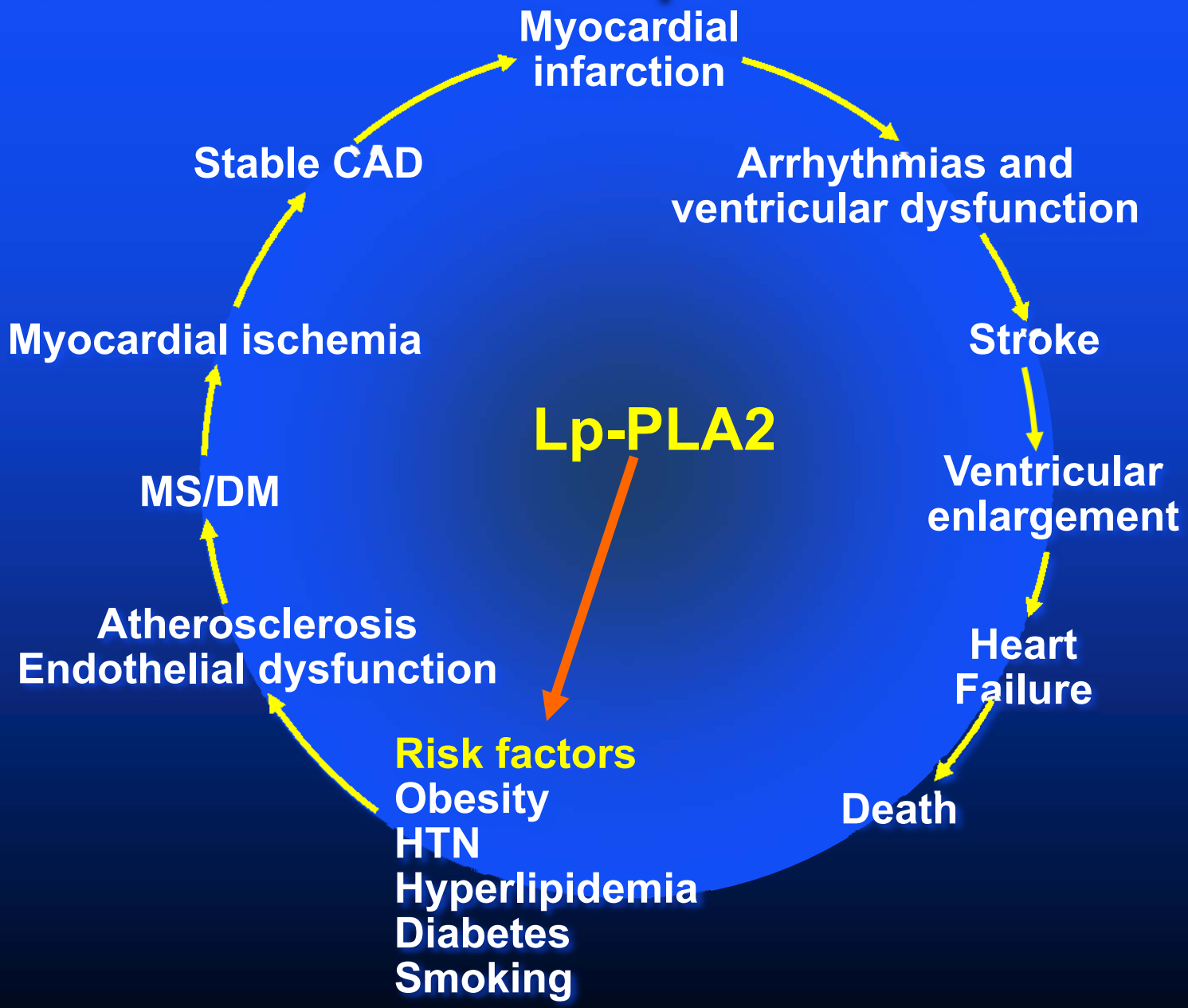


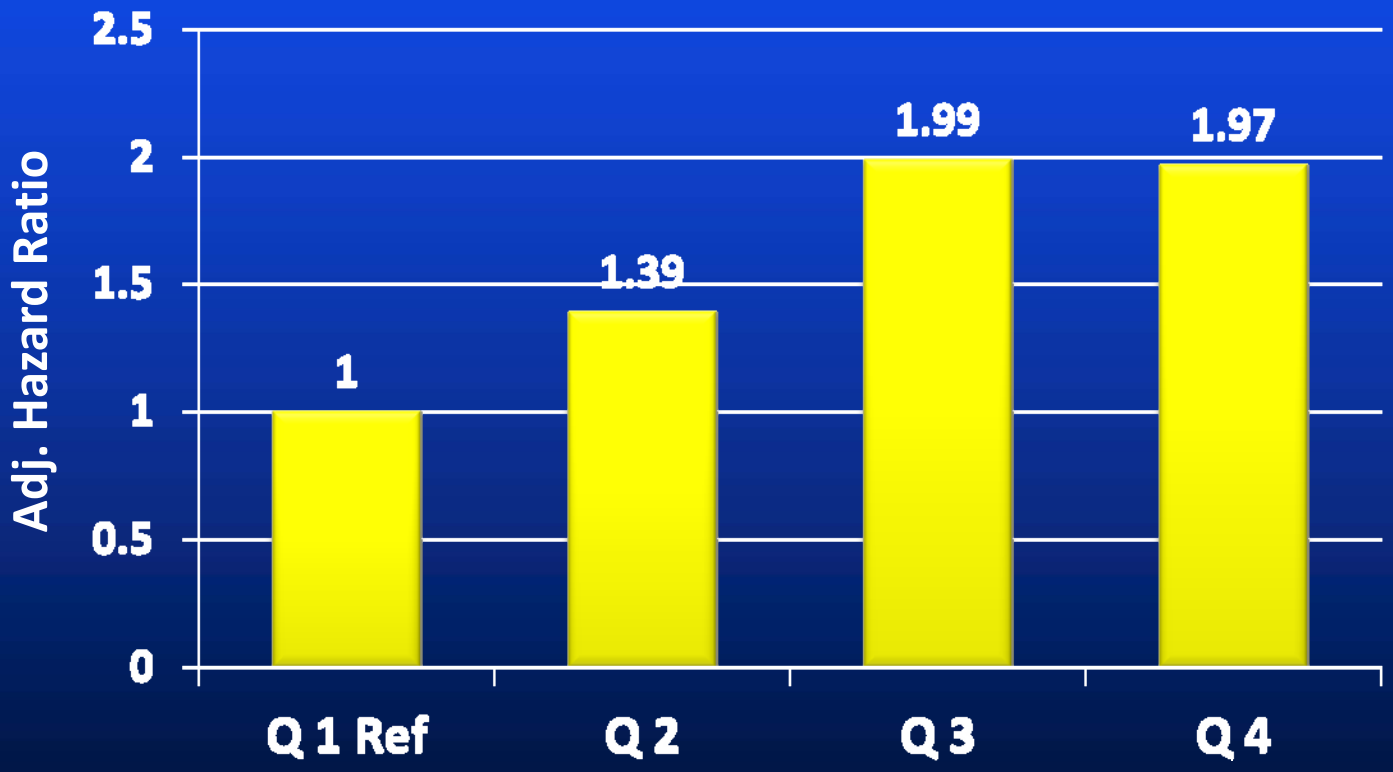
Elevated Lp-PLA$_2$ as a Predictor of Coronary and CV Events in Primary Prevention

Study - CV Endpoint	Population	Hazard/Odds Ratio (high vs. low quantiles) (95%CI)
WOSCOPS - Coronary Events	Hyperchol. Men	**1.80 (1.3-2.6)**
WHS - Coronary Events	Healthy Women	
ARIC - Coronary Events	Healthy Subjects LDL < 130	**1.15 (0.8-1.6)** **2.08 (1.2-3.6)**
Winkler Fluvastatin - Severe CAD	Type 2 Diabetics	**2.09 (1.0-4.2)**
MONICA - Coronary Events	Moderately Hyperchol. Men	
Rotterdam - Coronary Events	Healthy > 55 yrs	**1.97 (1.3-3.0)**
PROSPER - Coronary Events	Elderly Subjects	**1.25 (1.02-1.5)**
Cardiovascular Health - MI	Elderly Subjects	**1.26 (1.03-1.6)**
Malmo - MI & Stroke	Non-diabetics	**1.54 (1.1-2.2)**
Bruneck - CV events	Healthy Subjects	
Nurses' Health Study - MI	Healthy Women	**1.81 (1.3-2.6)**
Rancho Bernardo - CHD Events	Elderly Subjects	**1. 64 (1.1-2.6)**

Lp-PLA2 Multivariate-Adjusted* Hazard Ratios for CHD

Rotterdam Study: 7983 subjects >55 years of age.

P for trend = 0.01



*Adjusted for age, sex, BMI, SBP, non-HDL-C, HDL-C, DM, smoking, cholesterol-lowering medication, CRP, WBC count, and alcohol consumption.

Circulation. 2005;111:570-575

In a prospective, case cohort study in 12,819 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities study, the relation between Lp-PLA$_2$, CRP, traditional risk factors, and risk for CHD events over a period of ≈6 years was examined (ARIC study)

proinflammatory enzyme associated primarily with LDL.

Methods and Results—In a prospective, case cohort study in 12 819 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities study, the relation between Lp-PLA$_2$, CRP, traditional risk factors, and risk for CHD events over a period of ≈6 years was examined in a proportional hazards model, stratified by LDL-C. Lp-PLA$_2$ and CRP levels were higher in the 608 cases than the 740 noncases. Both Lp-PLA$_2$ and CRP were associated with incident CHD after adjustment for age, sex, and race with a hazard ratio of 1.78 for the highest tertile of Lp-PLA$_2$ and 2.53 for the highest category of CRP versus the lowest categories. Lp-PLA$_2$ correlated positively with LDL-C (r=0.36) and negatively with HDL-C (r=−0.33) but not with CRP (r=−0.05). In a model adjusted for traditional risk factors including LDL-C, the association of Lp-PLA$_2$ with CHD was attenuated and not statistically significant. For individuals with LDL-C below the median (130 mg/dL), Lp-PLA$_2$ and CRP were both significantly and independently associated with CHD in fully adjusted models. For individuals with LDL-C <130 mg/dL, those with both Lp-PLA$_2$ and CRP levels in the highest tertile were at the greatest risk for a CHD event.

Conclusions—Lp-PLA$_2$ and CRP may be complementary in identifying individuals at high CHD risk who have low LDL-C. **(*Circulation*. 2004;109:837-842.)**

Key Words: coronary disease ■ epidemiology ■ inflammation ■ risk factors

Although screening for elevated LDL cholesterol (LDL-C) remains a major component of national guidelines for the prevention of coronary heart disease (CHD), LDL-C level is insufficient to identify individuals who would develop CHD, because many CHD events occur in individuals without elevated LDL-C,[1] indicating the influence of other risk factors. Inflammation plays an important role in both atherogenesis and atherothrombotic events, and several biomarkers of inflammation, including high-sensitivity C-reactive protein (hs-CRP),[2] interleukin-6,[3] and soluble intercellular adhesion molecule-1,[4] have been associated with increased risk for CHD events. hs-CRP measurement has been recommended for some patients to refine risk assessment[5] because hs-CRP levels have been shown to provide additional predictive information beyond traditional risk factors such as LDL-C.[6] Increased hs-CRP levels may also be useful to identify patients with low LDL-C who are at increased CHD risk and may benefit from statin therapy.[7]

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is an enzyme that can hydrolyze oxidized phospholipids to generate lysophosphatidylcholine and oxidized fatty acids, which have proinflammatory properties. However, hydrolysis of platelet-activating factor and other phospholipids by Lp-PLA$_2$ could also reduce inflammation,[8] and it is not clear whether Lp-PLA$_2$ is proinflammatory or anti-inflammatory in humans.

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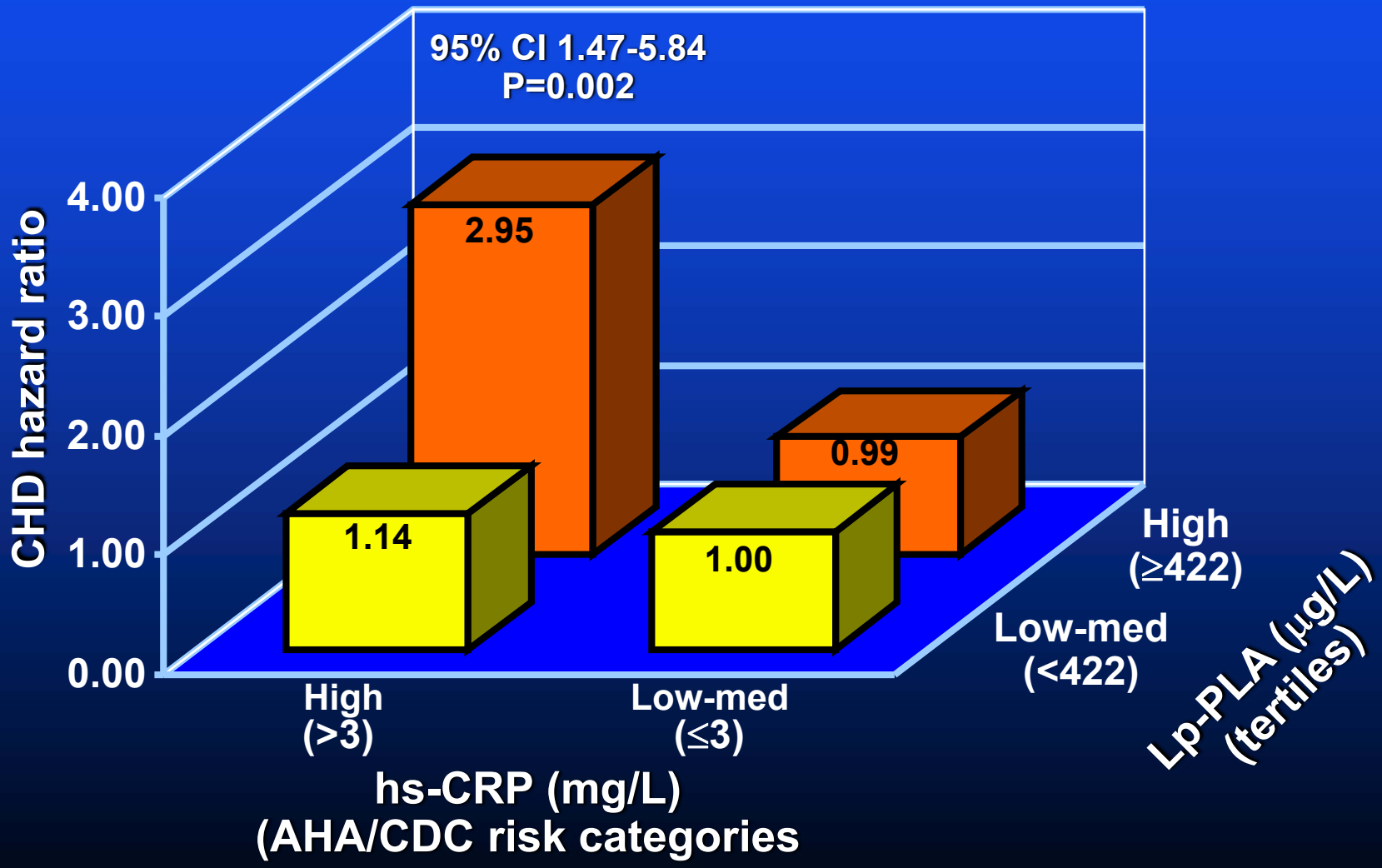
Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000116763.91992.F1

Association of Lp-PLA$_2$ and hs-CRP with Incident CHD in Patients with Low LDL-C (<130 mg/dL)



CHD HRs (95% CI) by Lp-PLA$_2$ Tertiles

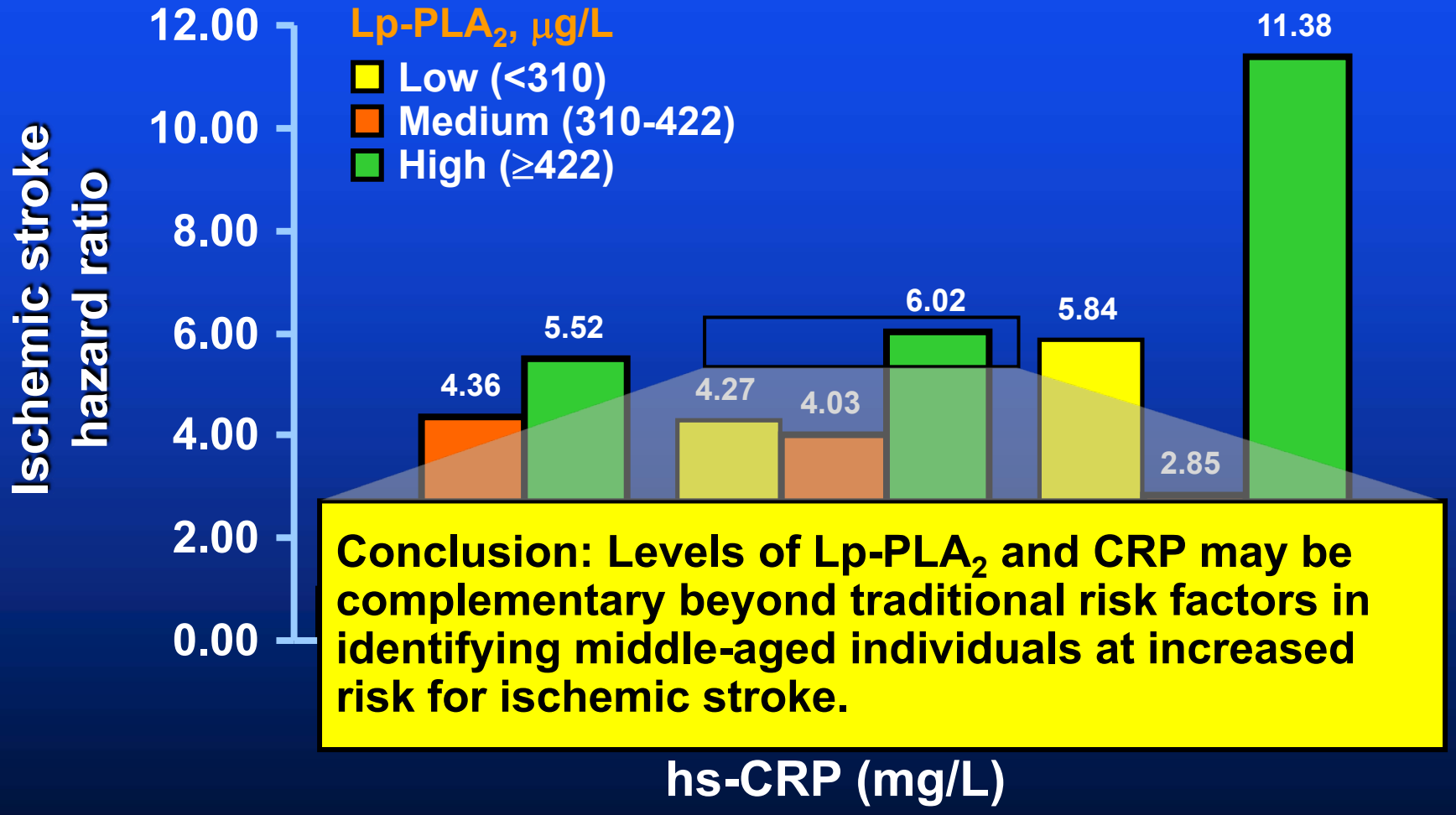
	Lp-PLA$_2$ tertiles*	
	2 (310-422 μg/L)	3 (≥422 μg/L)
Model 1†	1.26 (0.94-1.69)	1.78 (1.33-2.38)
Model 2‡	1.02 (0.73-1.43)	1.16 (0.82-1.65)
Model 2‡ LDL-C <130 mg/dL	1.83 (1.11-3.00)	1.99 (1.17-3.38)
Model 3§	1.00 (0.71-1.41)	1.15 (0.81-1.63)

Conclusions **– Lp-PLA$_2$ and CRP may be complementary in identifying individuals at high CHD risk who have low LDL-C.**

* Lowest tertile (<310 μg/L) is reference
† Adjusted for age, sex, and race
‡ Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, and diabetes
§ Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, diabetes, and hs-CRP

Ballantyne et al: Circ 109:837, 2004

Association of Lipoprotein-Associated Phospholipase ($Lp\text{-}PLA_2$) and High-Sensitivity C-Reactive Protein (hs-CRP) with Incident Ischemic Stroke

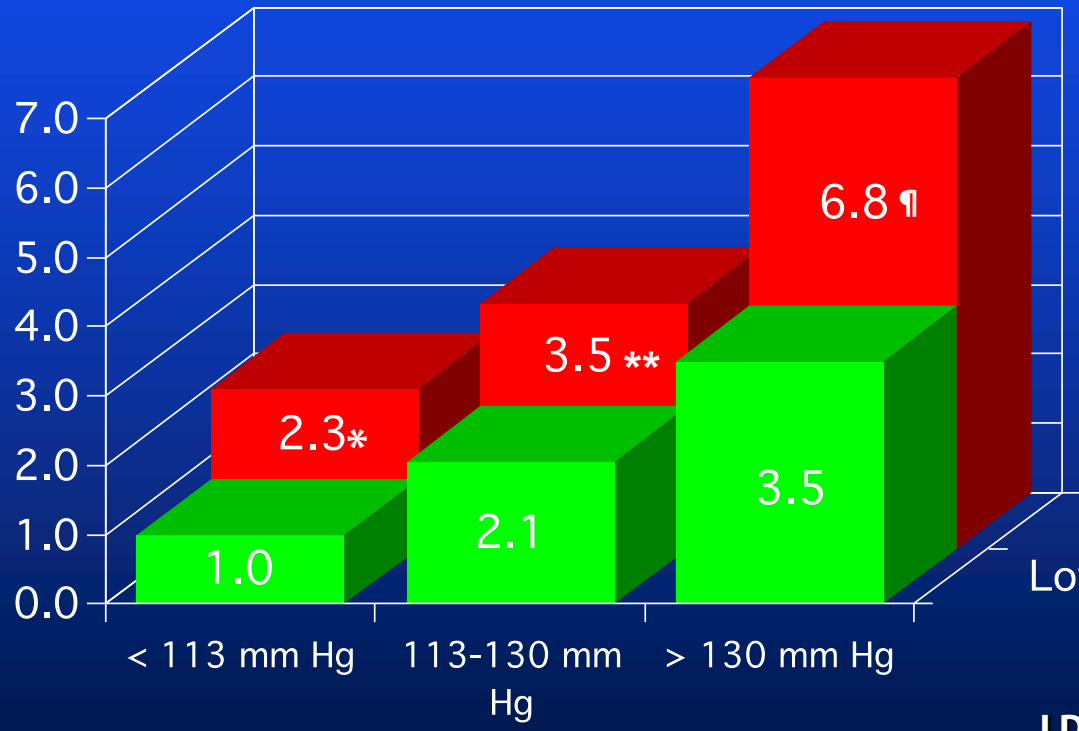


Conclusion: Levels of $Lp\text{-}PLA_2$ and CRP may be complementary beyond traditional risk factors in identifying middle-aged individuals at increased risk for ischemic stroke.

Ballantyne et al: Arch Intern Med 165:2479, 2005

ARIC Study: Lp-PLA$_2$ Increases Risk of Ischemic Stroke at All Levels of Blood Pressure

Risk Ratios for **Ischemic Stroke** Based on Lp-PLA$_2$ Level and SBP



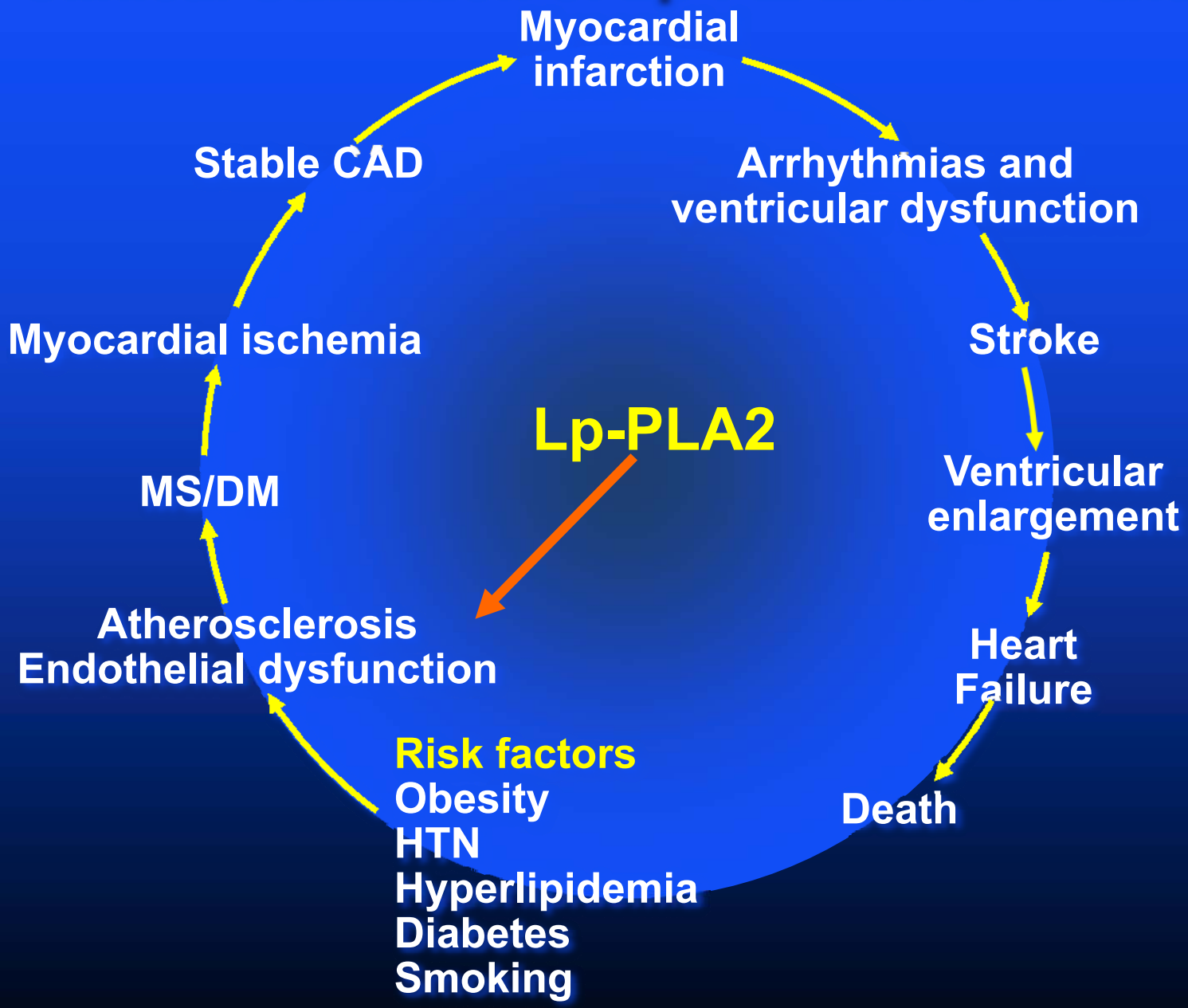
Tertile of Systolic Blood Pressure

***p=0.03, **p≤ 0.005, ¶p<0.0001 vs. Lp-PLA$_2$ below median**

LDL-C in stroke cases 136
LDL-C in matched controls 132
No significant difference.

Gorelick PM. *Am J Cardiol Supplement* 2008.

Clinical Utilization of Lp-PLA2 in CVD and Stroke



Coronary Endothelial dysfunction

Smoking | Hypertension | Hypercholesterolemia | Age | Diabetes

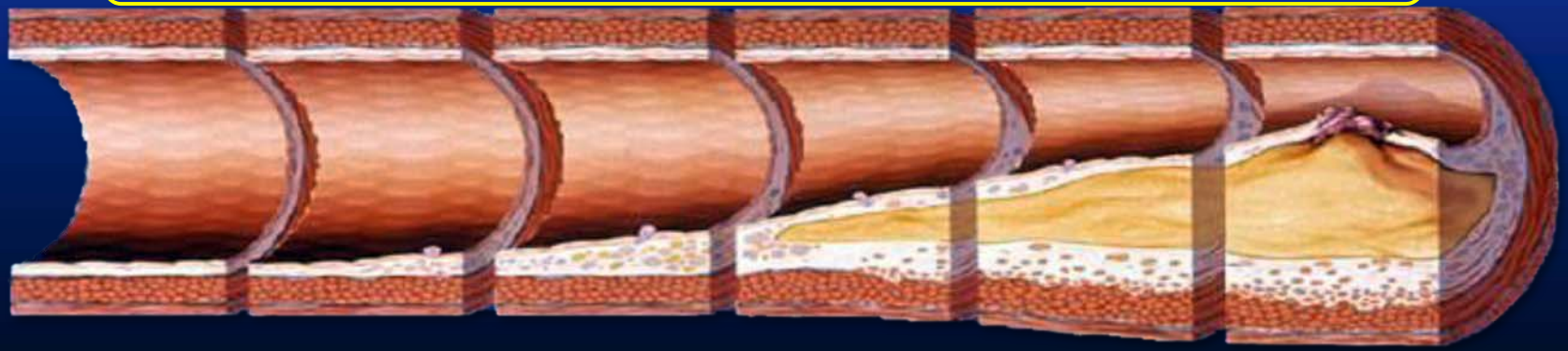
EPC s

Vasa Vasorum

DES

Inflammation & oxidative stress

Endothelial dysfunction: The risk of the risk factors



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.

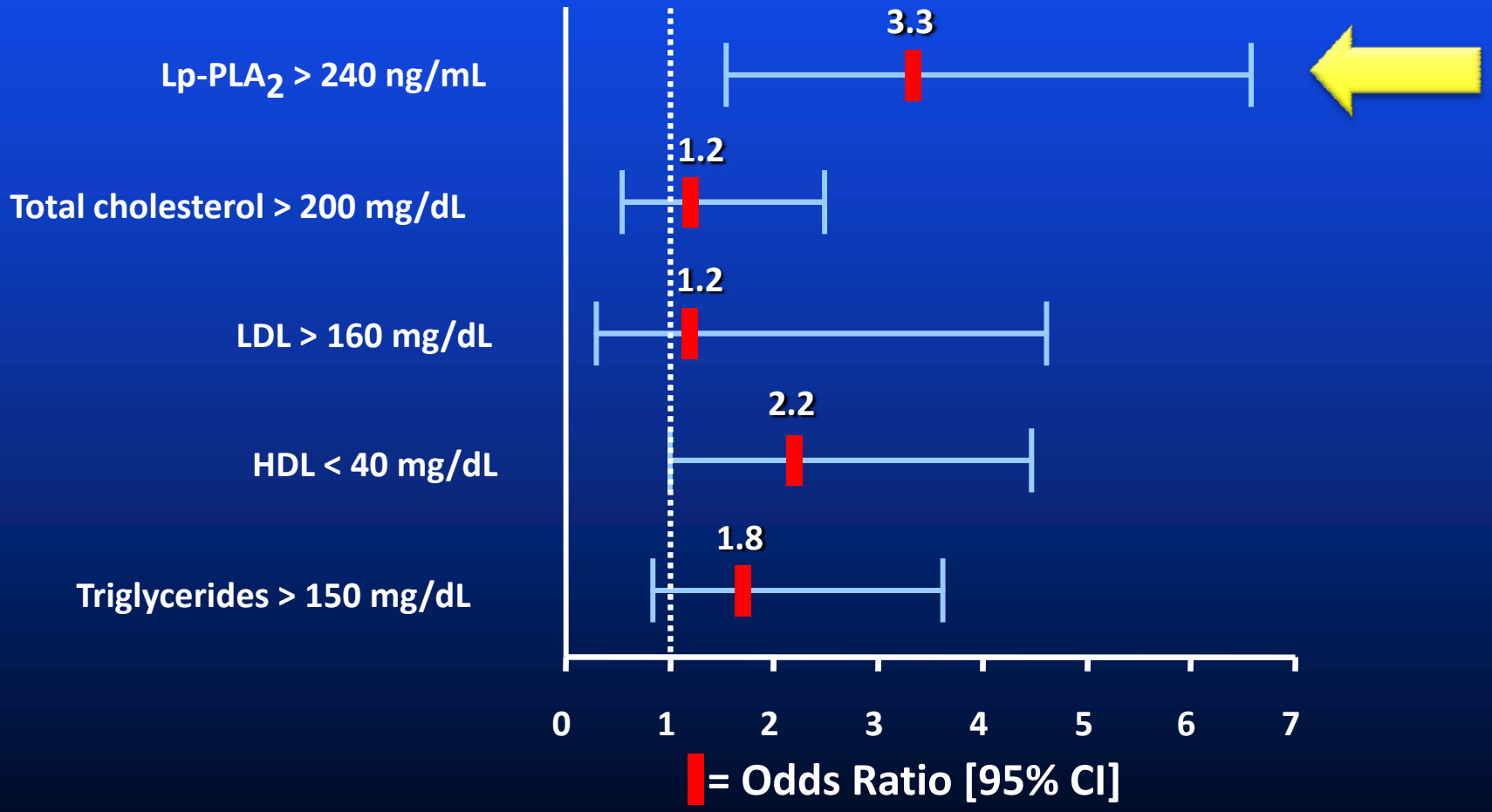
Methods and Results—Patients (172) with no significant coronary artery disease (<30% stenosis) undergoing assessment of coronary endothelial function were studied. Endothelial function was assessed by the change in coronary blood flow and coronary artery diameter in response to intracoronary acetylcholine.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

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.

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

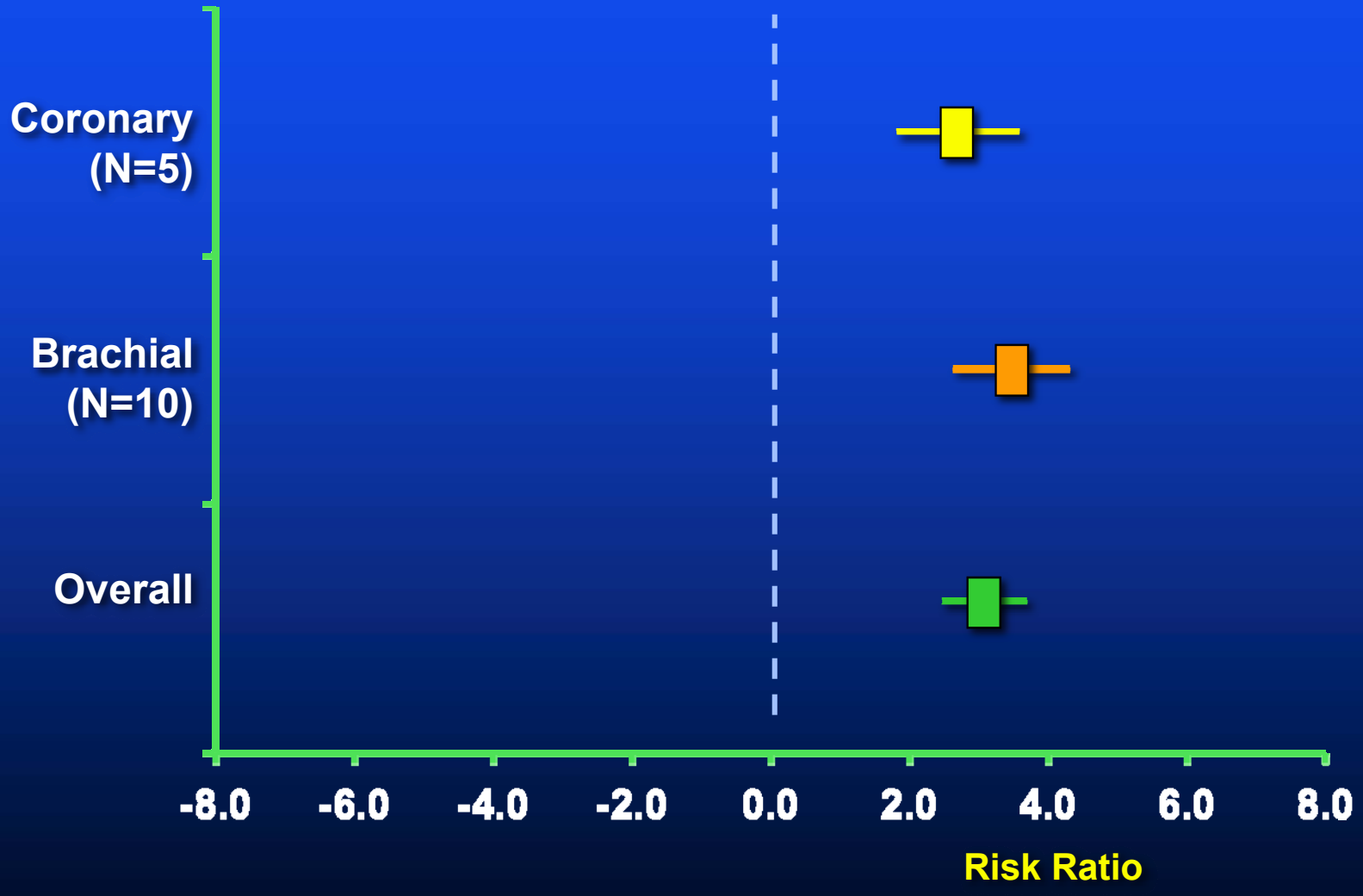
Lp-PLA$_2$ is a Strong Predictor of Coronary Endothelial Dysfunction

172 persons with no significant CAD (< 30% stenosis) assessed by response to intracoronary (LAD) acetylcholine – lipids were not predictive of endothelial dysfunction



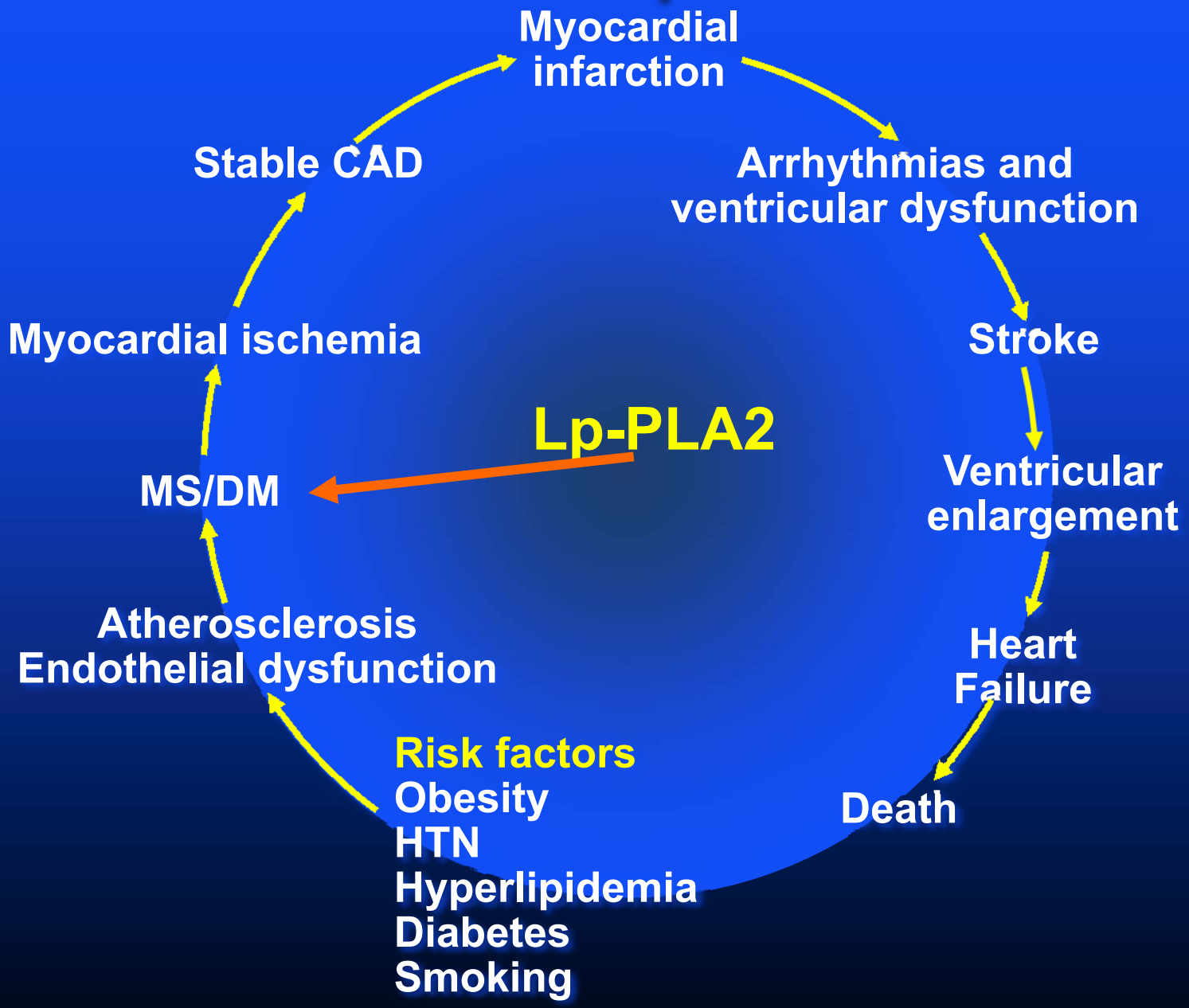
Yang EH, et al. *ATVB* 2006.

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



Lerman and Zeiher Circulation 2004

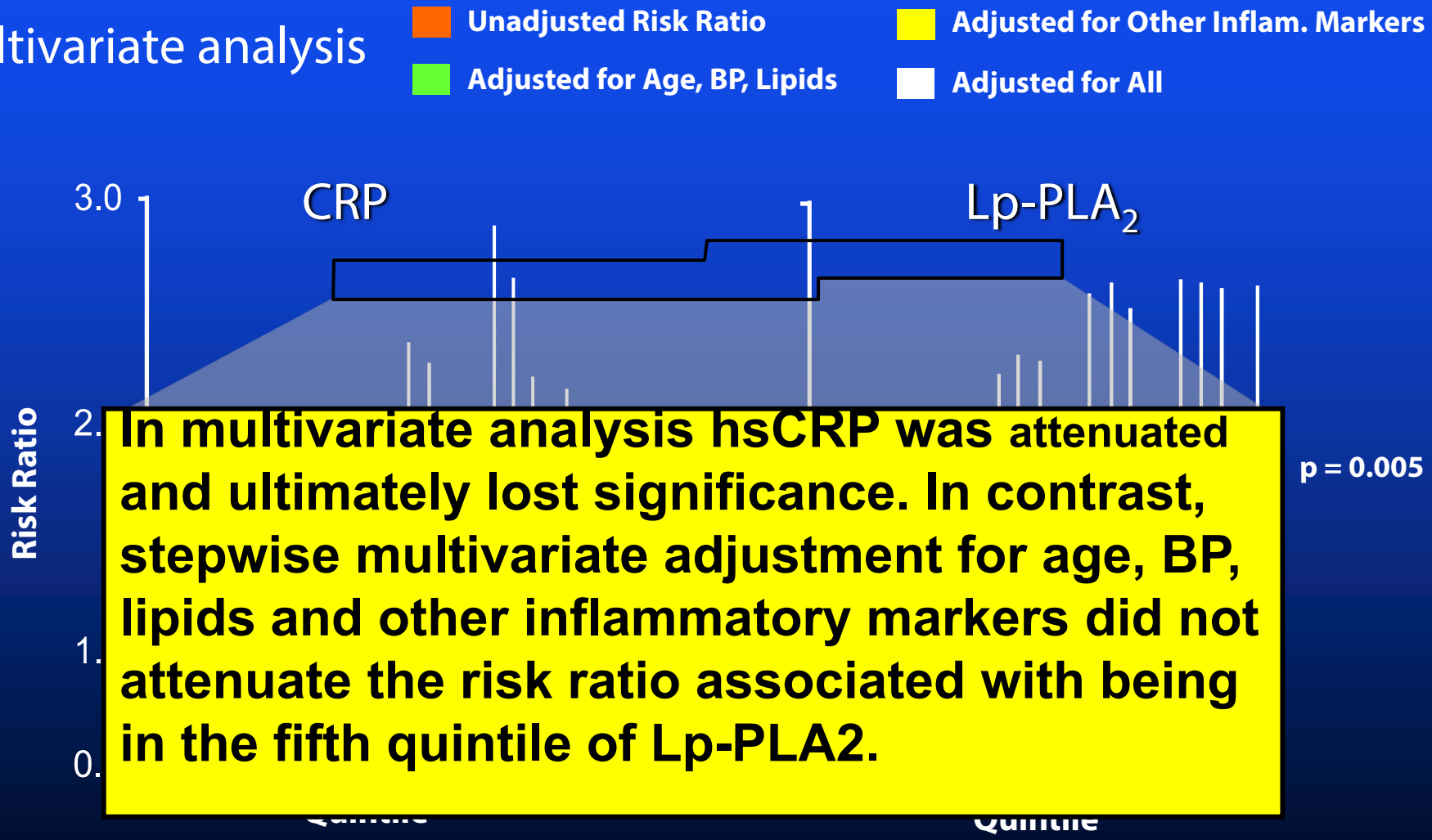
Clinical Utilization of Lp-PLA2 in CVD and Stroke



CP1053921-6

Lp-PLA$_2$ is Not Attenuated by Multivariate Adjustment As a Predictor of CHD Events in WOSCOPS

Multivariate analysis



In multivariate analysis hsCRP was attenuated and ultimately lost significance. In contrast, stepwise multivariate adjustment for age, BP, lipids and other inflammatory markers did not attenuate the risk ratio associated with being in the fifth quintile of Lp-PLA2.

Packard CJ, et al. *N Engl J Med* 2000.

Lp-PLA$_2$ Activity Levels Were Significantly Associated With Incident CHD Among Men and Women With Type 2 Diabetes

During 10y follow-up among men with 178 cases and 14y follow up among women with 146 cases of CHD

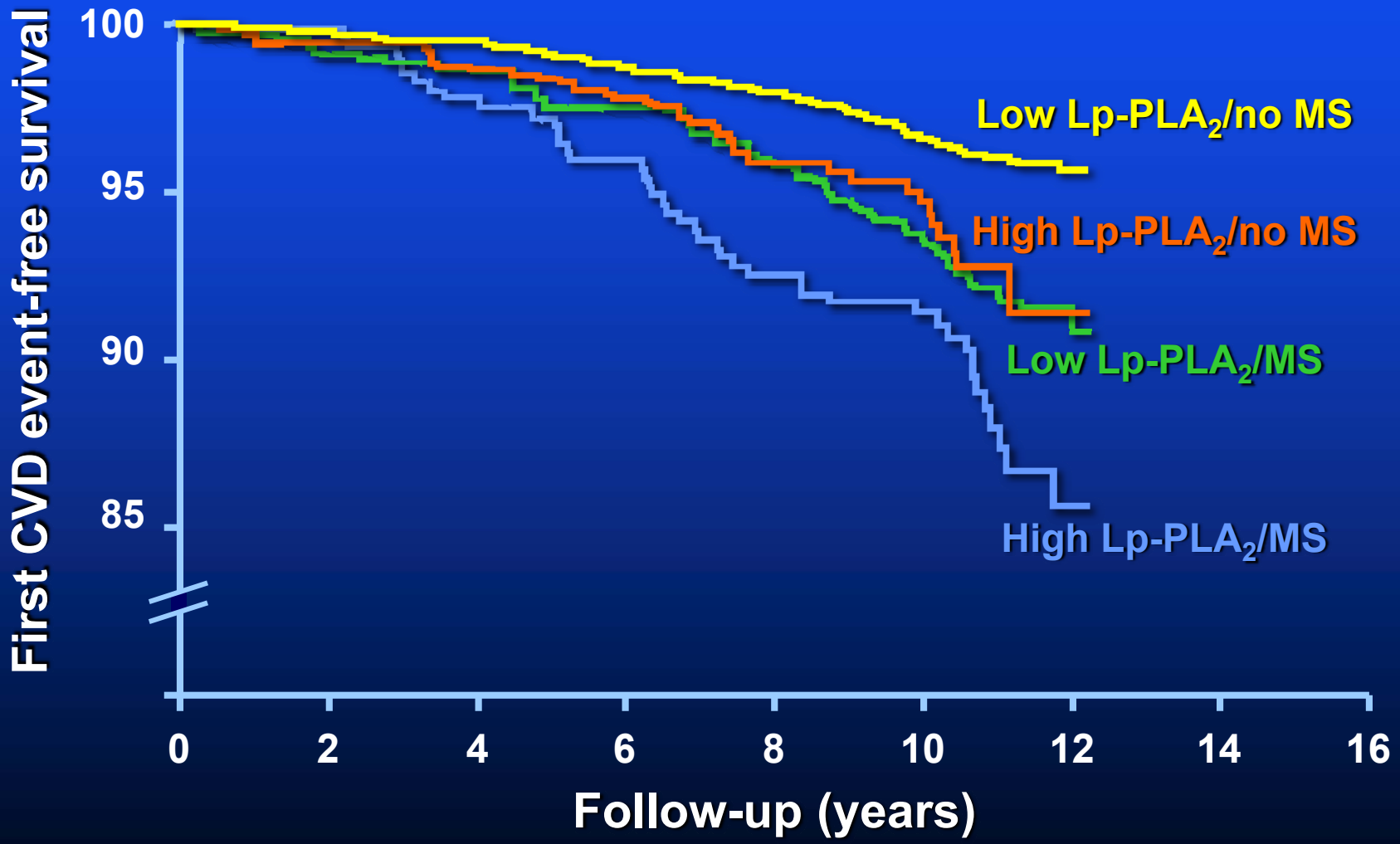
For nonfatal MI and fatal CHD, the relative risk was
1.75 (95% CI 1.05–2.92)
P = 0.001

Adjustments for
- LDL,
- HDL,
- hs-CRP ,
- hormone replacement therapy
- diabetes duration

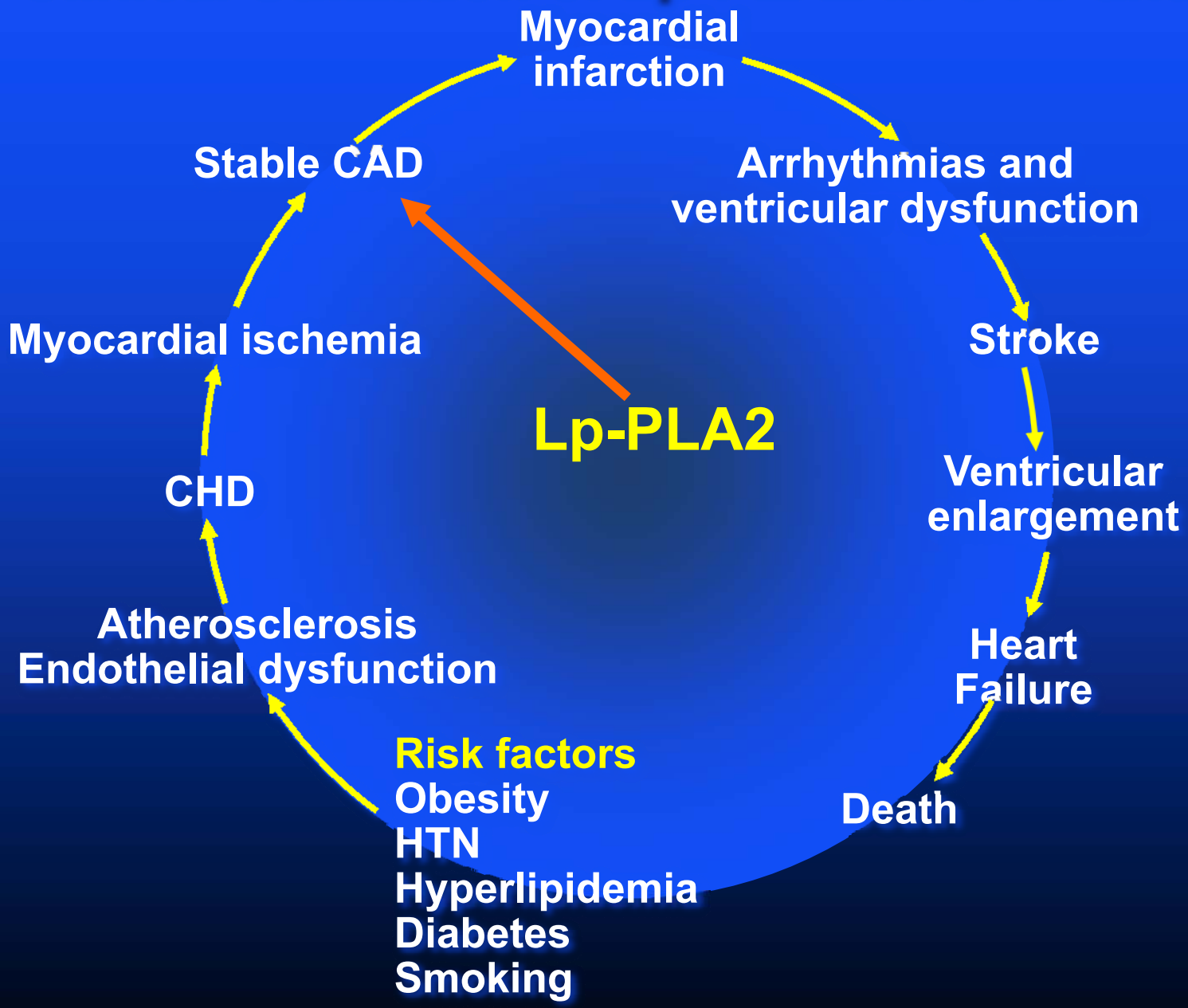
did not modify these relationships.

Hatoum, DIABETES, VOL. 59, MAY 2010

High Levels of Lipoprotein-Associated Phospholipase A_2 and Metabolic Syndrome are Independent and Additive Risk Factors in the Malmo Study



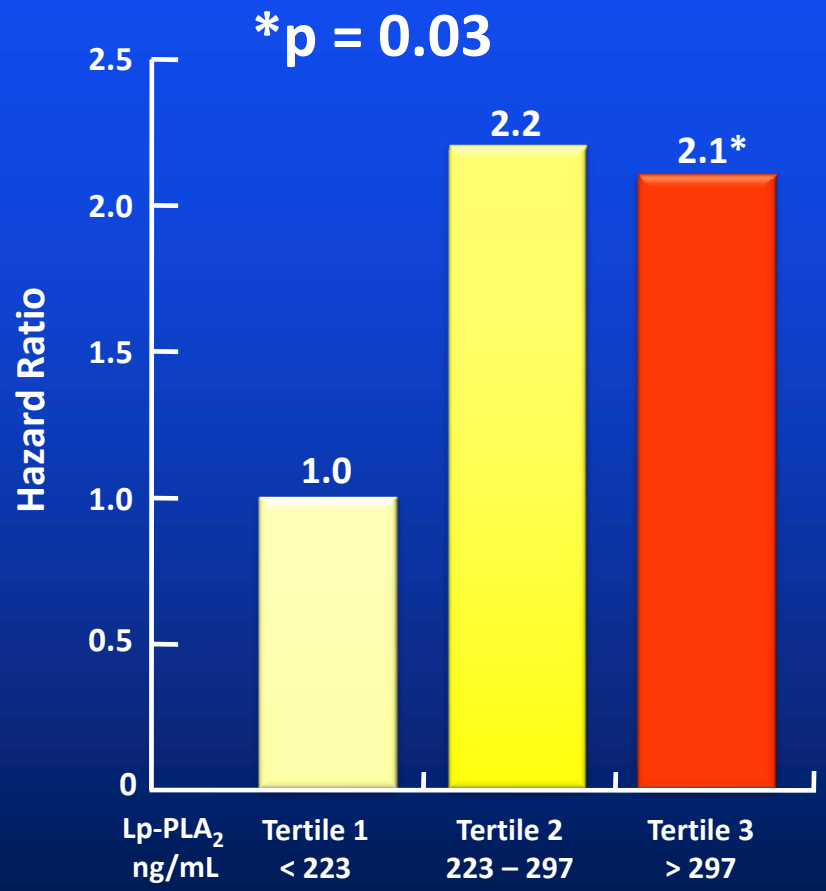
Clinical Utilization of Lp-PLA2 in CVD and Stroke



Lp-PLA2 as a Predictor of CV Events in *Secondary* Prevention

Study - CV Endpoint	Year	Population	#Cases/ #Controls	Relative Risk per SD (95%CI)	Hazard/Odds Ratio (high vs. low quantiles) (95%CI)
AtheroGENE – ACS & Angina	2003	CAD	496/477		1.80 (1.01-3.20)
Mayo Heart – Coronary Events	2005	CAD	61/466	1.30 (1.06-1.6)	2.29 (1.12-4.68)
LURIC – Severe CAD	2005	Angiography Patients	2454/694		1.85 (1.23-2.78)
HELICOR – Severe CAD	2005	Angio. Pts.	312/479		1.91 (1.12-3.28)
KAROLA – Recurrent CV events	2005	S/P ACS or revasc.	95/1051		2.09 (1.10-3.96)
Intermountain Heart – CAD	2006	Angio. Pts	475/1012		2.44 (1.58-3.79)
THROMBO – Recurrent MI	2006	Post MI	766		1.90 (1.31-2.75)
Mayo (Olmsted) – Death after MI	2006	Acute MI	42/229		4.93 (2.10-11.6)
PROVE-IT – Recurrent CV events	2006	ACS	3265		1.33 (1.01-1.74)
GUSTO & FRISC – Recurrent CV	2007	ACS	435/2266		1.40 (0.77-2.5)
NOBIS-II – Coronary events	2007	Chest pain	56/429		2.60 (1.1-6.6)
PEACE – MI & Stroke	2007	Stable CAD	1108/3766		1.41 (1.17-1.70)
VA-HIT – CV events	2008	Stable CAD	927	1.17 (1.04-1.3)	1.85 (1.38-1.50)

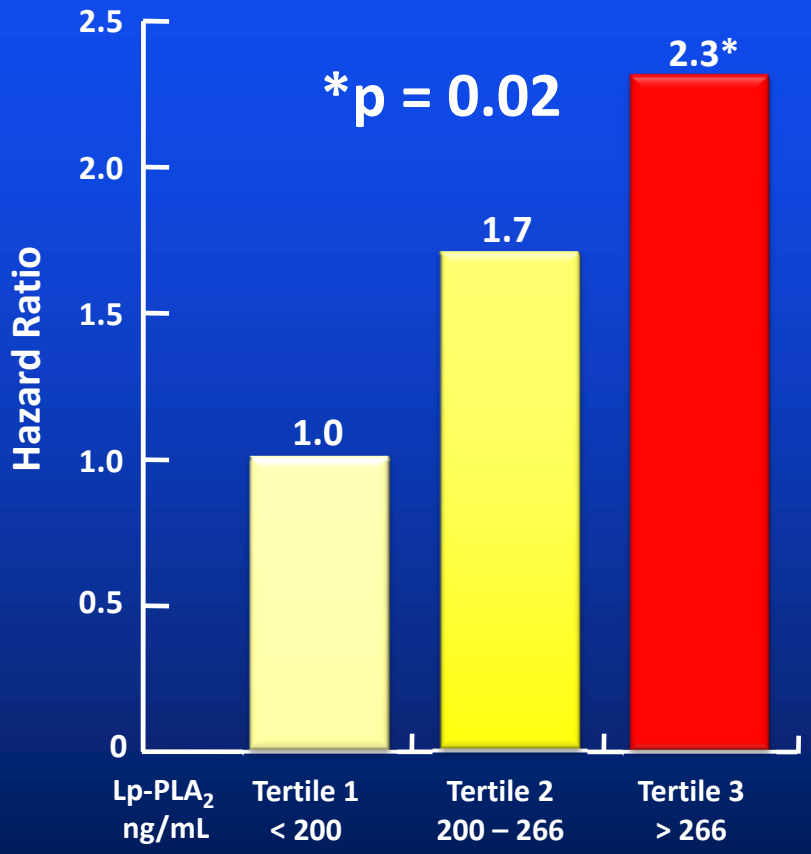
Lp-PLA$_2$ in KAROLA Study
1,051 Patients after ACS or Revascularization



Fully adjusted for traditional risk factors, LDL and HDL, statin Rx, BMI, and hsCRP

Koenig, et al. *Arterioscler Thromb Vasc Biol* 2006.

Lp-PLA$_2$ in Mayo Heart Study
504 Patients with Angiographic CAD

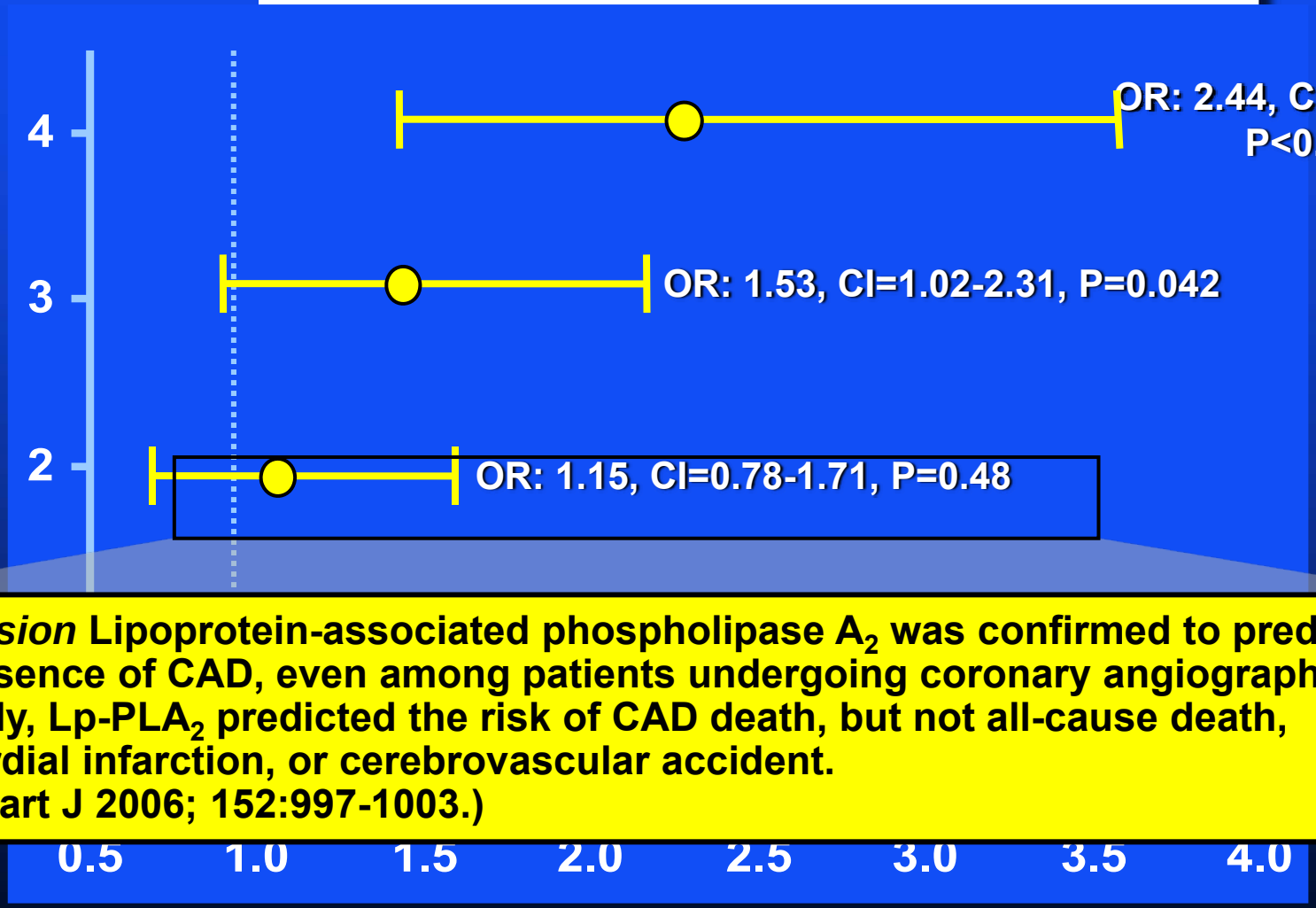


Fully adjusted for traditional risk factors, TC and HDL, triglycerides, and log-CRP

Brilakis, et al. *Euro Heart J* 2005.

Lipoprotein-associated phospholipase A_2 independently predicts the angiographic diagnosis of coronary artery disease and coronary death

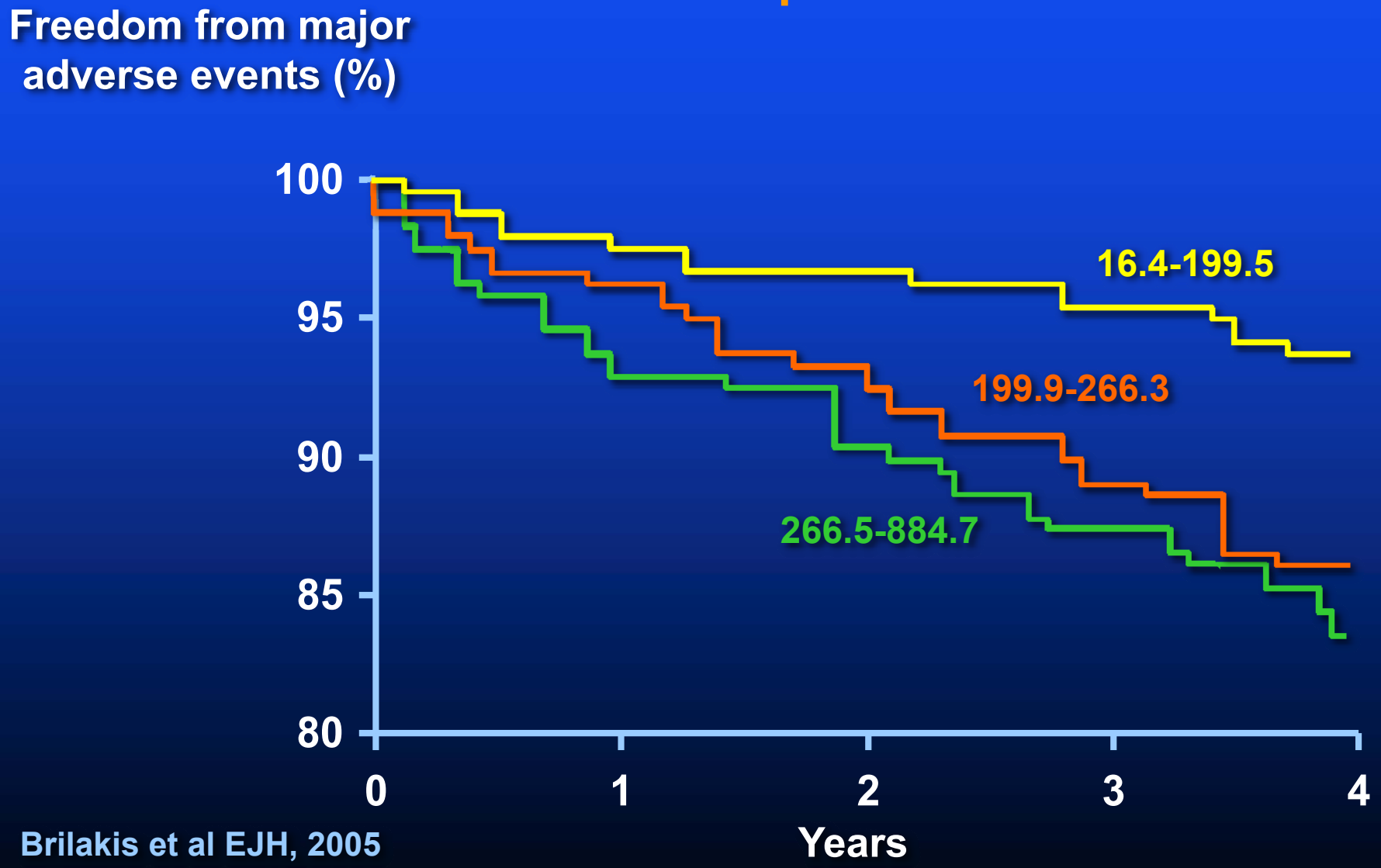
Heidi T. May, MSPH,[a] Benjamin D. Horne, PhD, MPH,[a] Jeffrey L. Anderson, MD, FACC,[a,b] Robert L. Wolfert, PhD,[c] Joseph B. Muhlestein, MD, FACC,[a,b] Dale G. Renlund, MD, FACC,[a,b] Jessica L. Clarke, BS,[a] Matthew J. Kolek, BS,[a] Tami L. Bair, BS,[a] Robert R. Pearson, BS,[a] Krishnankutty Sudhir, MD, PhD,[c] and John F. Carlquist, PhD[a,b] *Salt Lake City, UT; and San Francisco, CA*



Conclusion **Lipoprotein-associated phospholipase A_2 was confirmed to predict the presence of CAD, even among patients undergoing coronary angiography. Uniquely, Lp-PLA_2 predicted the risk of CAD death, but not all-cause death, myocardial infarction, or cerebrovascular accident.**
(Am Heart J 2006; 152:997-1003.)

Incidence of Major Adverse Events in Study Population Classified According toLp-PLA$_2$ Levels: Mayo Heart Study

What is the risk of this patient for CV events?



Brilakis et al EJH, 2005

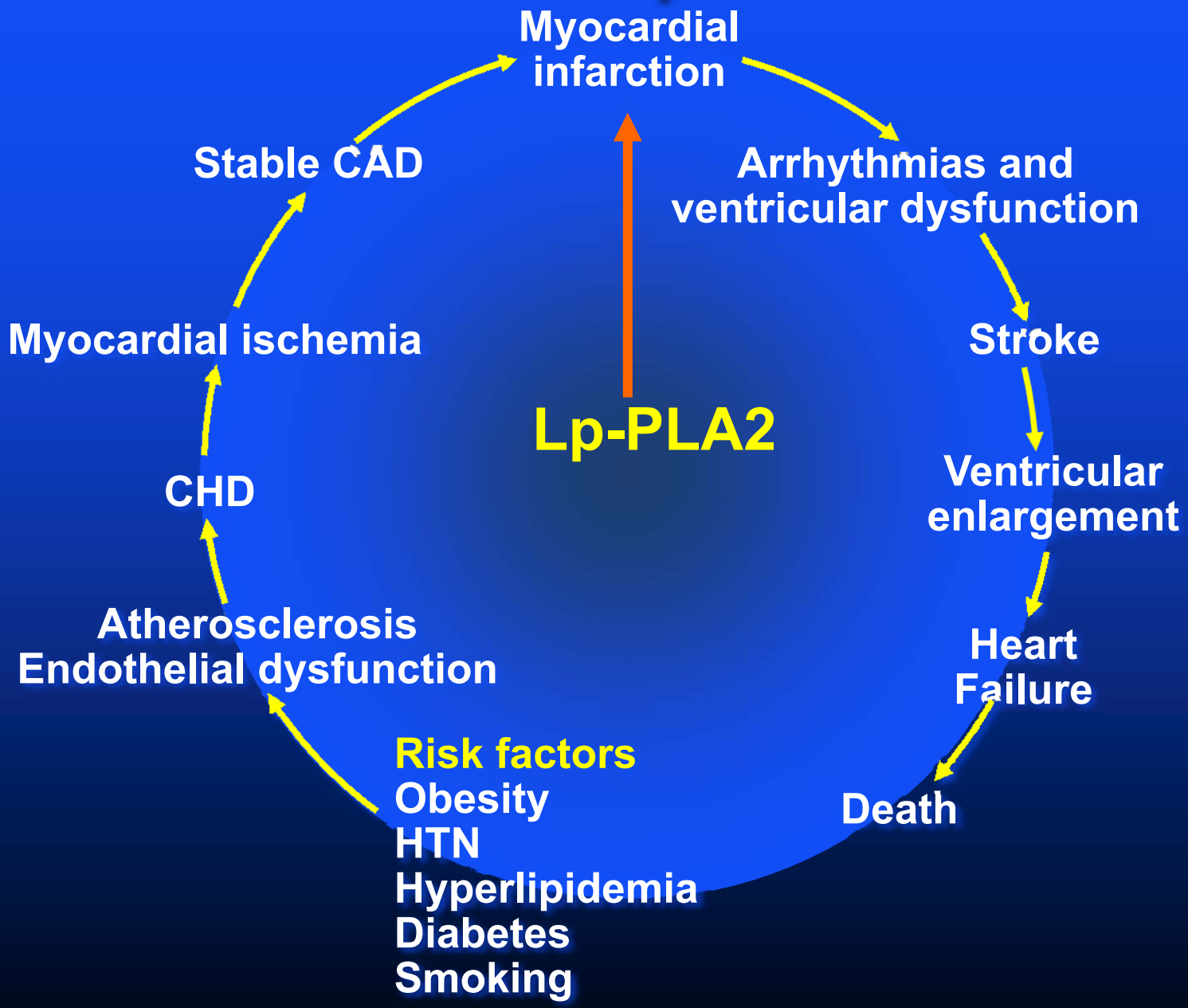
Proportion of Patients (n=1,051) w/o Secondary Fatal and Non-Fatal CVD Events During 4-Year F-U

Kaplan-Meier Survival Curves According to Tertiles of Lp-PLA$_2$ Concentrations at Baseline

Conclusions **– Increased concentrations of Lp-PLA$_2$ predict future cardiovascular events in patients with manifest CHD independent of a variety of potential risk factors including markers of inflammation, renal function, and hemodynamic stress. (Arterioscler Thromb Vasc Biol. 2006;26:1686-1693.)**

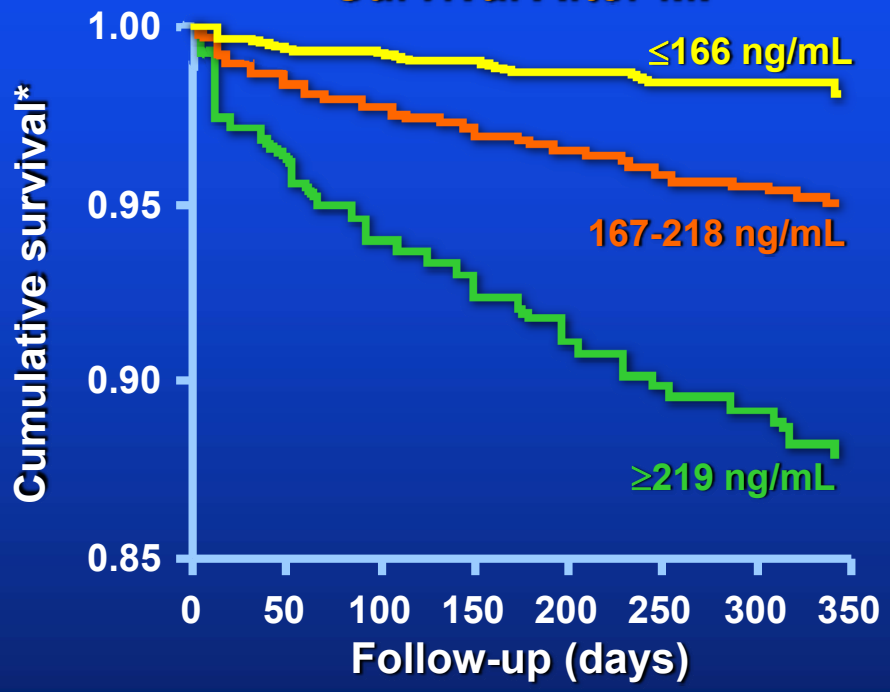
Koenig e

Clinical Utilization of Lp-PLA2 in CVD and Stroke



Lp-PLA$_2$ and Prognosis After MI: Olmsted County (n=271 MI Pt, F-U=1 yr, 42

Survival After MI



* Derived from a proportional hazards regression adjusting for age, sex, RR, diabetes, smoking, BMI, LDL-C, Killip class, EF, CRP, reperfusion or revascularization

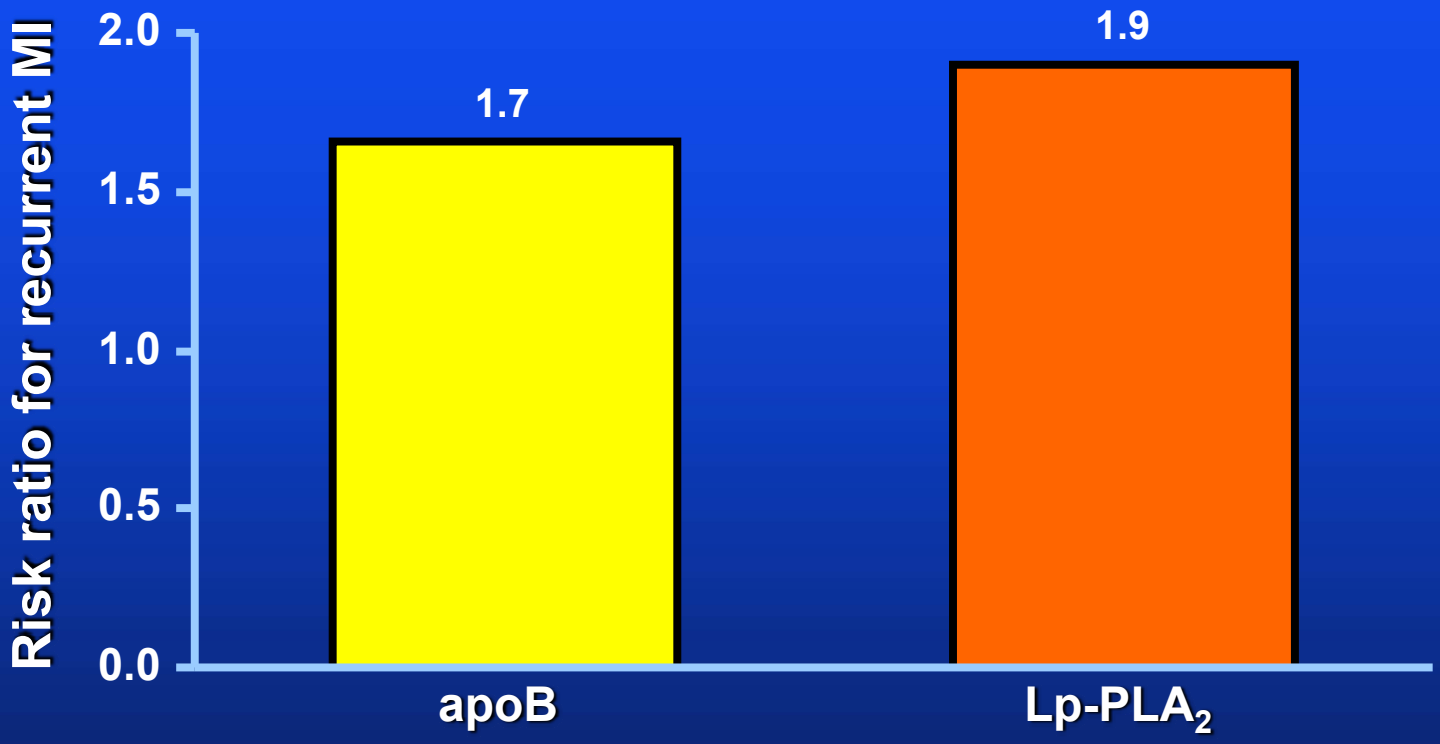
Area Under the Curve (AUC)

	Area under the curve (AUC)		
	Without Lp-PLA$_2$	With Lp-PLA$_2$	P
Model 1*	0.729	0.779	0.03
Model 2†	0.760	0.800	0.03
Model 3‡	0.823	0.852	0.05

* Includes age, sex; † includes age, sex, hypertension dyslipidemia, diabetes, smoking, and obesity; ‡ model 2 + Killip class, EF, CRP and reperfusion or revascularization

Gerber et al: ATVB 26:2517, 2006

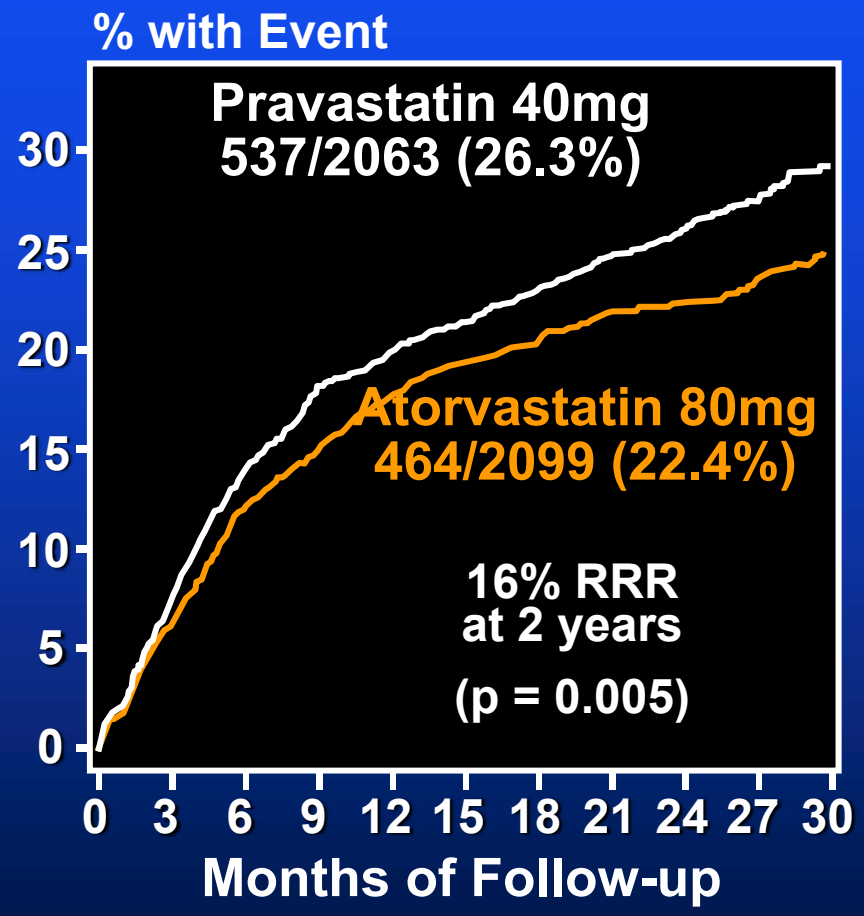
THROMBO – Lp-PLA$_2$ Activity Best Predictor* of Recurrent MI in 766 Post-MI Patients

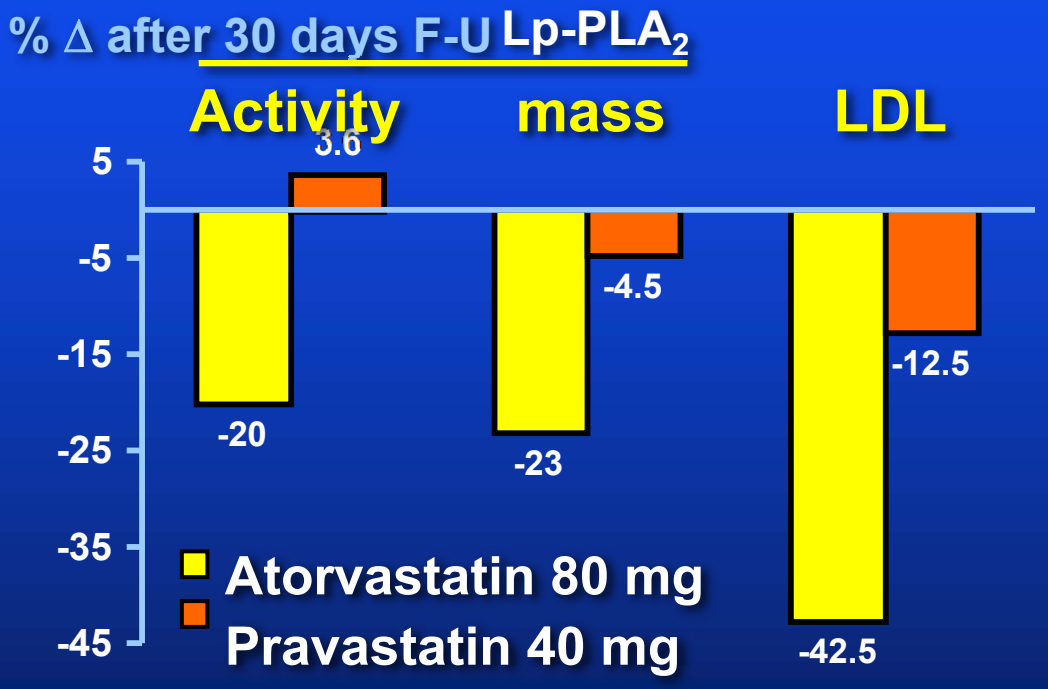


* Lp-PLA$_2$ was the only significant predictor in a fully adjusted model that included apoB, apoAI, non-HDL-C, HDL, triglycerides, LDL peak particle diameter, glucose insulin, BMI, PAI-1, Lp(a)< CRP, von WF antigen, fibrinogen, D-dimer, factor VII and factor VIIa; 26 months of follow-up; baseline Lp-PLA$_2$ were drawn 60 days after acute MI; highest quartile was compared to bottom 3 quartiles combined
Confidence interval 1.31-2.75

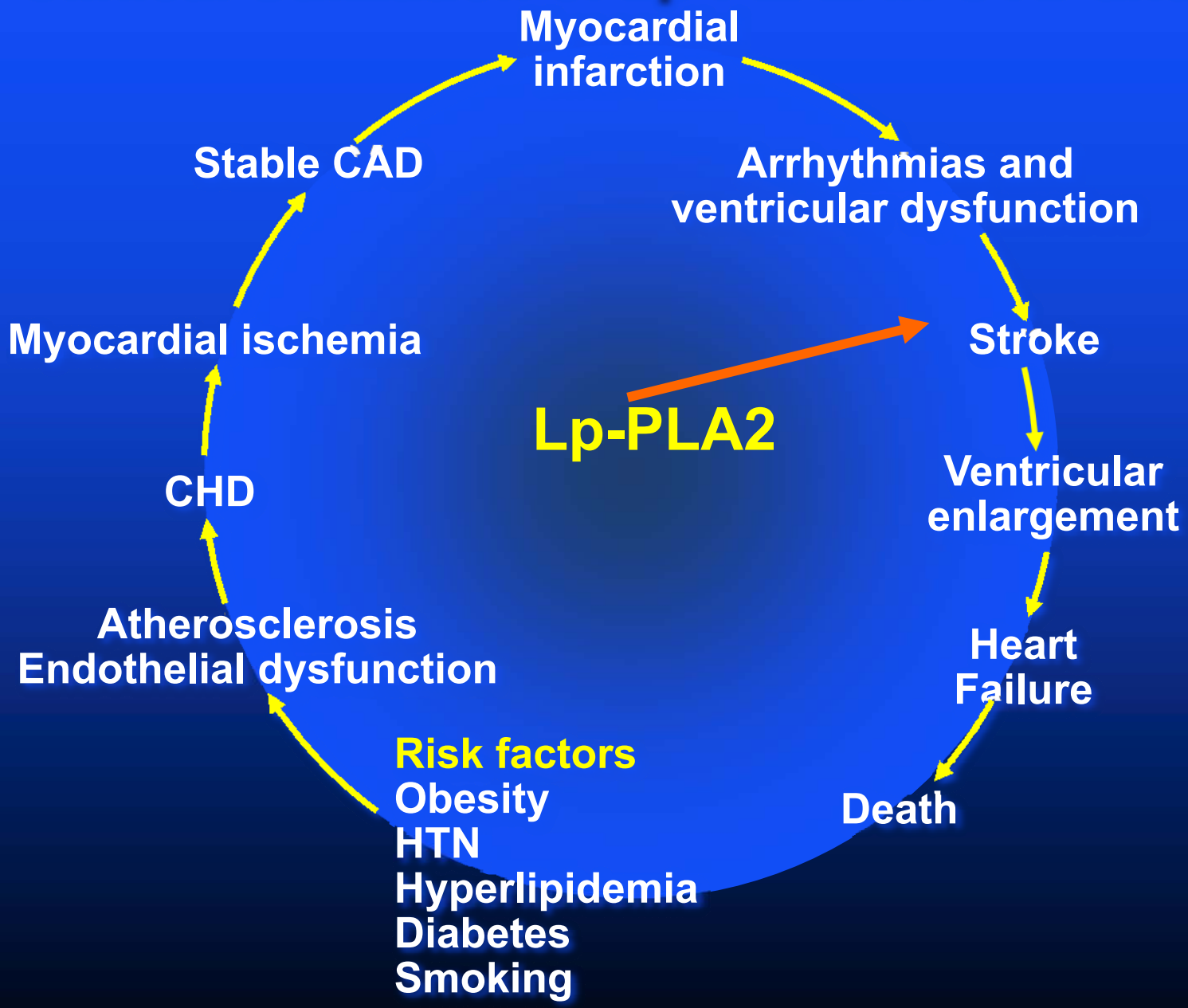
Corsetti et al: Clin Chem 52:1331, 2006

PROVE-IT: Major CV Events and PLA2

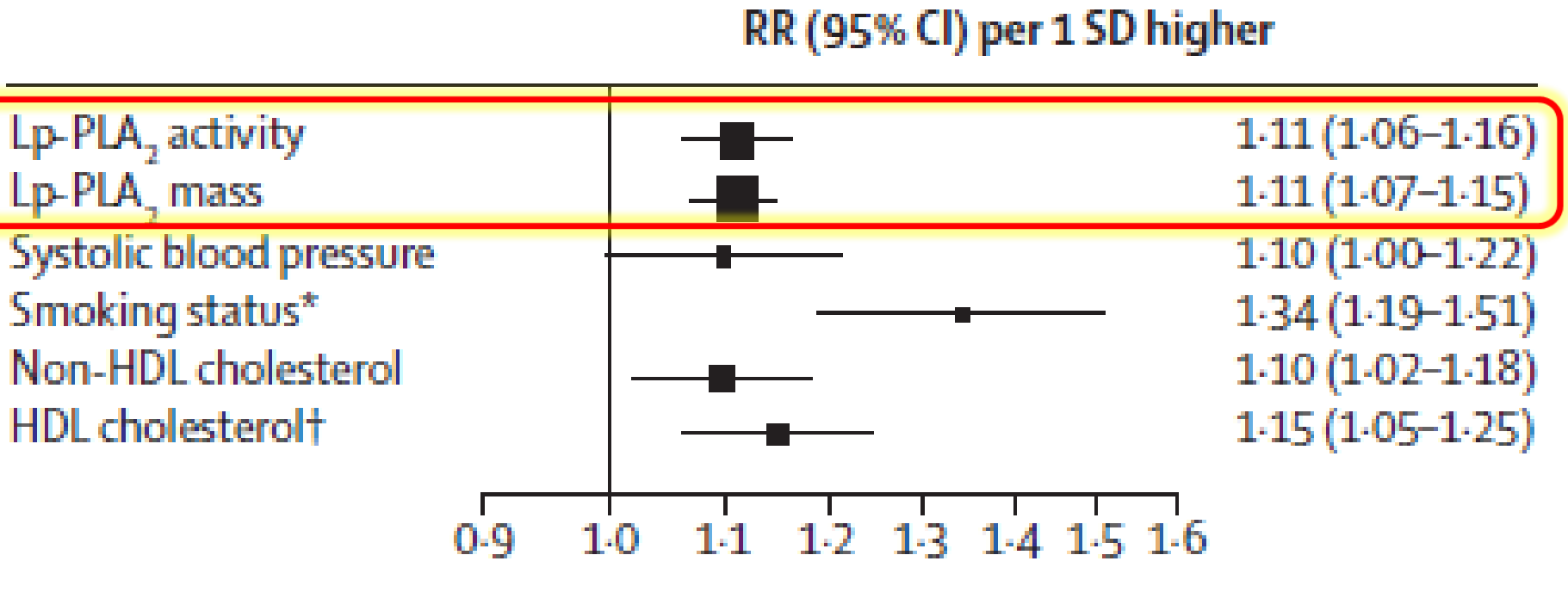




Clinical Utilization of Lp-PLA2 in CVD and Stroke



Lp-pla2 And Risk of CHD, Stroke, and Mortality: Collaborative Analysis Of 32 Prospective Studies

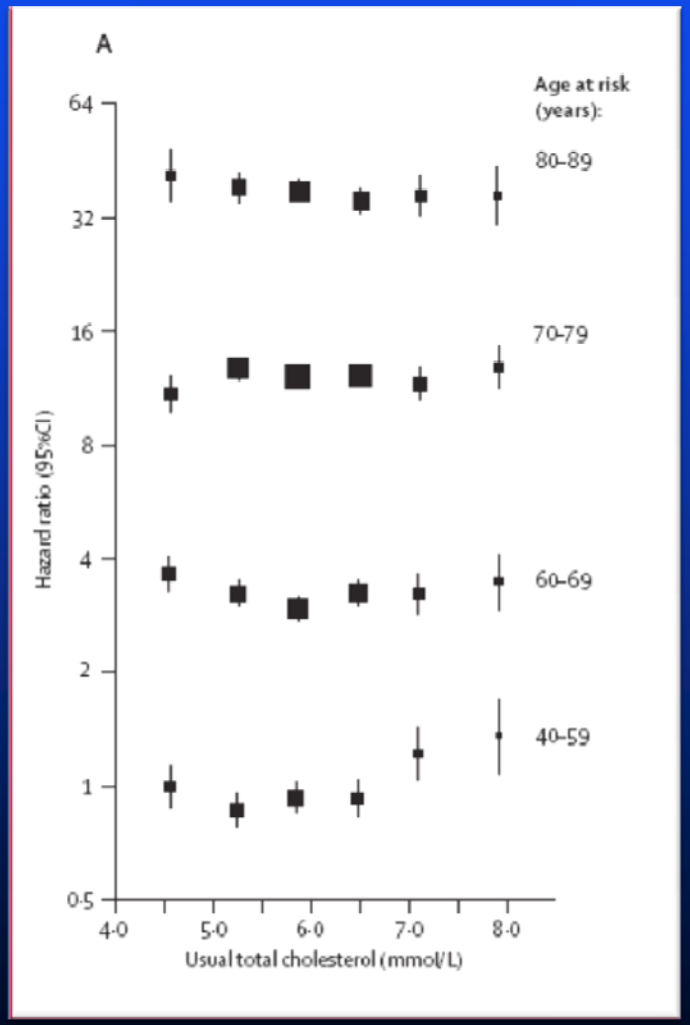


- 34,762 participants who were initially healthy or had a history of stable vascular disease.
- Adjusted for age, sex, DM, BMI, Smoking, non HDL-C, HDL-C, TG, SBP

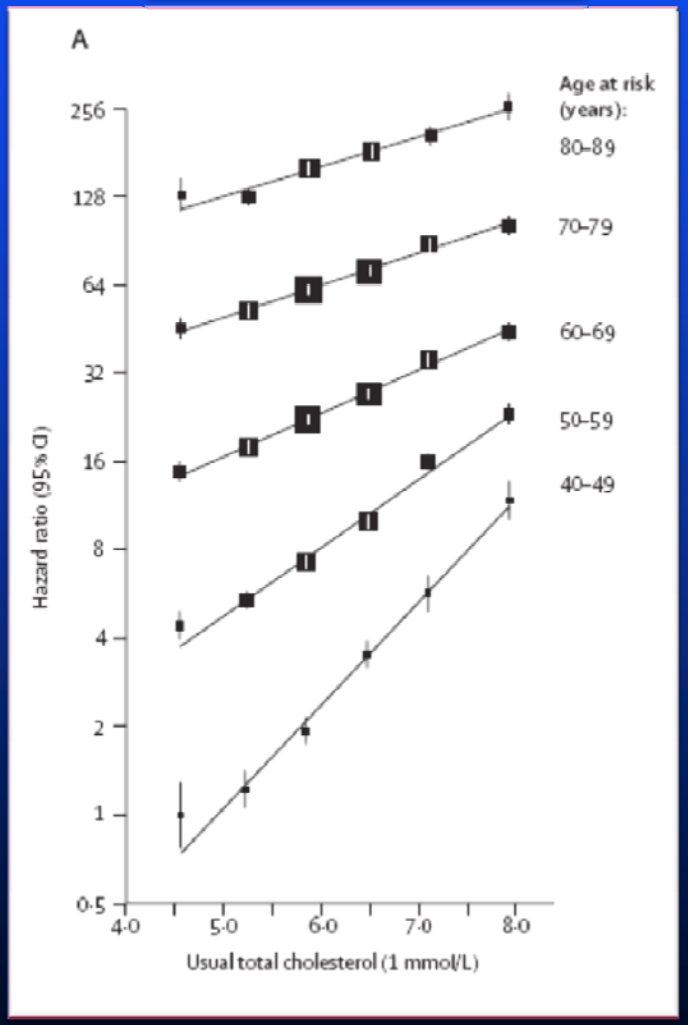
Lancet 2010; 375: 153

Cholesterol Is Not a Predictor of Stroke: a Meta-Analysis

Stroke



IHD



MAYO CLINIC

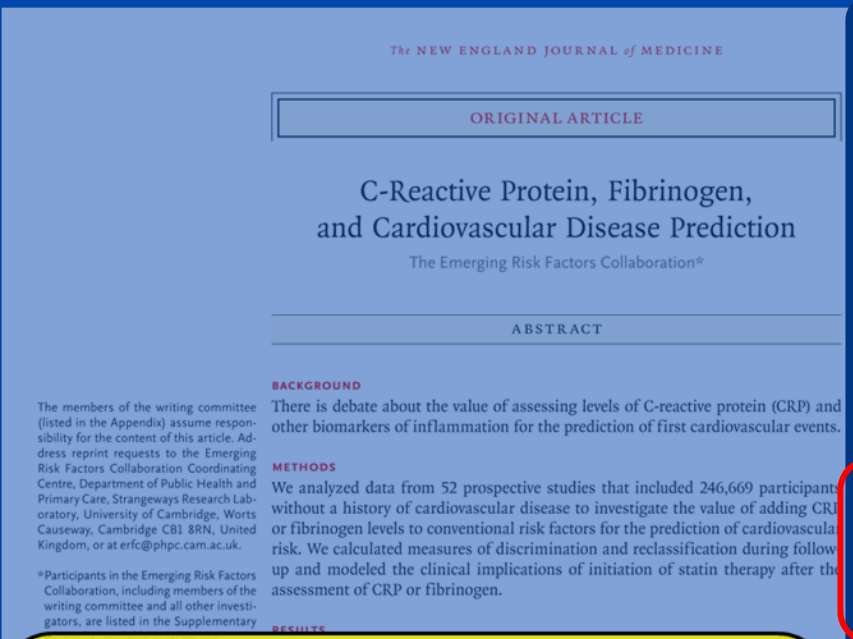
Lancet 2007; 370:1829-1839.

Meta-Analysis of Statins for Stroke Prevention

24 Trials, >165,000 Patients, >5000 Stroke Events

	RR	95% CI
Primary Prevention	**0.81**	**0.75-0.87**
Secondary Prevention	0.88	0.78-0.99
Total	0.82	0.77-0.87

***Lancet Neurol* 2009; 8: 4**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction

The Emerging Risk Factors Collaboration*

ABSTRACT

BACKGROUND

There is debate about the value of assessing levels of C-reactive protein (CRP) and other biomarkers of inflammation for the prediction of first cardiovascular events.

METHODS

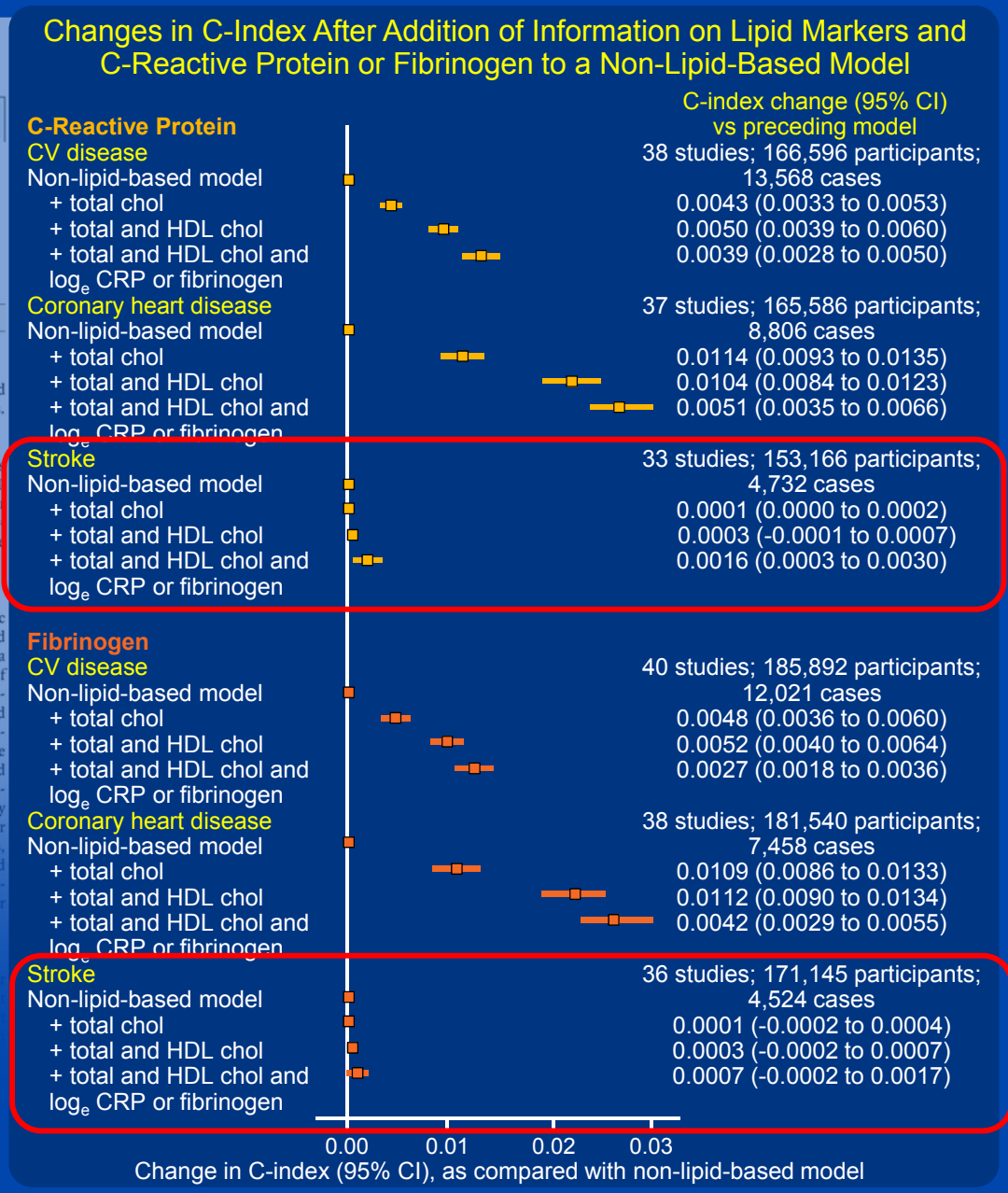
We analyzed data from 52 prospective studies that included 246,669 participants without a history of cardiovascular disease to investigate the value of adding CRP or fibrinogen levels to conventional risk factors for the prediction of cardiovascular risk. We calculated measures of discrimination and reclassification during follow-up and modeled the clinical implications of initiation of statin therapy after the assessment of CRP or fibrinogen.

RESULTS

The members of the writing committee (listed in the Appendix) assume responsibility for the content of this article. Address reprint requests to the Emerging Risk Factors Collaboration Coordinating Centre, Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Worts Causeway, Cambridge CB1 8RN, United Kingdom, or at erfc@phpc.cam.ac.uk.

*Participants in the Emerging Risk Factors Collaboration, including members of the writing committee and all other investigators, are listed in the Supplementary

Methods: We analyzed data from 52 prospective studies that included 246,669 participants without a Hx of CV disease to investigate the value of adding CRP or fibrinogen levels to conventional risk factors for the prediction of CV risk.



NEJM 367:14, 2012

Lp-PLA_2 and Risk of Stroke

- ARIC-Stroke: Lp-PLA_2 mass independently predictive of stroke in middle-aged men and women (Ballantyne et al: Arch Intern Med 165:2479, 2005)
- Similar results in the Rotterdam study with Lp-PLA_2 activity (Oei et al: Circulation 111:570, 2005)
- No significant association in the PROSPER Trial
- Significant association with recurrent stroke in NOMAS (Elkind et al: Arch Intern Med 166:2073, 2006)
- ARIC-Stroke Reclassification Study: when added to the TRF model, hs-CRP and Lp-PLA_2, reclassified 4% of low risk, 39% of intermediate risk, and 34% of the high-risk categories
  (Nambi et al: Stroke 40:376, 2009)

Enhanced Expression of Lp-PLA$_2$ and Lysophosphatidylcholine in Symptomatic Carotid Atherosclerotic Plaques

Dallit Mannheim, MD; Joerg Herrmann, MD; Daniele Versari, MD; Mario Gössl, MD; Fredric B. Meyer, MD; Joseph P. McConnell, PhD; Lilach O. Lerman, MD, PhD; Amir Lerman, MD

Background and Purpose—Circu
biomarker for cardiovascular di
oxidative stress, inflammation,
cerebrovascular disease. Theref
in symptomatic than in asympt
Methods—The expression of Lp-
staining. Plaque oxidative stress

European Heart Journal
doi:10.1093/eurheartj/ehp309

CLINICAL RESEARCH

Expression of lipoprotein-associated phospholipase A2 in carotid artery plaques predicts long-term cardiac outcome

Joerg Herrmann[1], Dallit Mannheim[1], Christine Wohlert[1], Daniele Versari[1], Fredric B. Meyer[3], Joseph P. McConnell[4], Mario Gössl[1], Lilach O. Lerman[2], and Amir Lerman[1]*

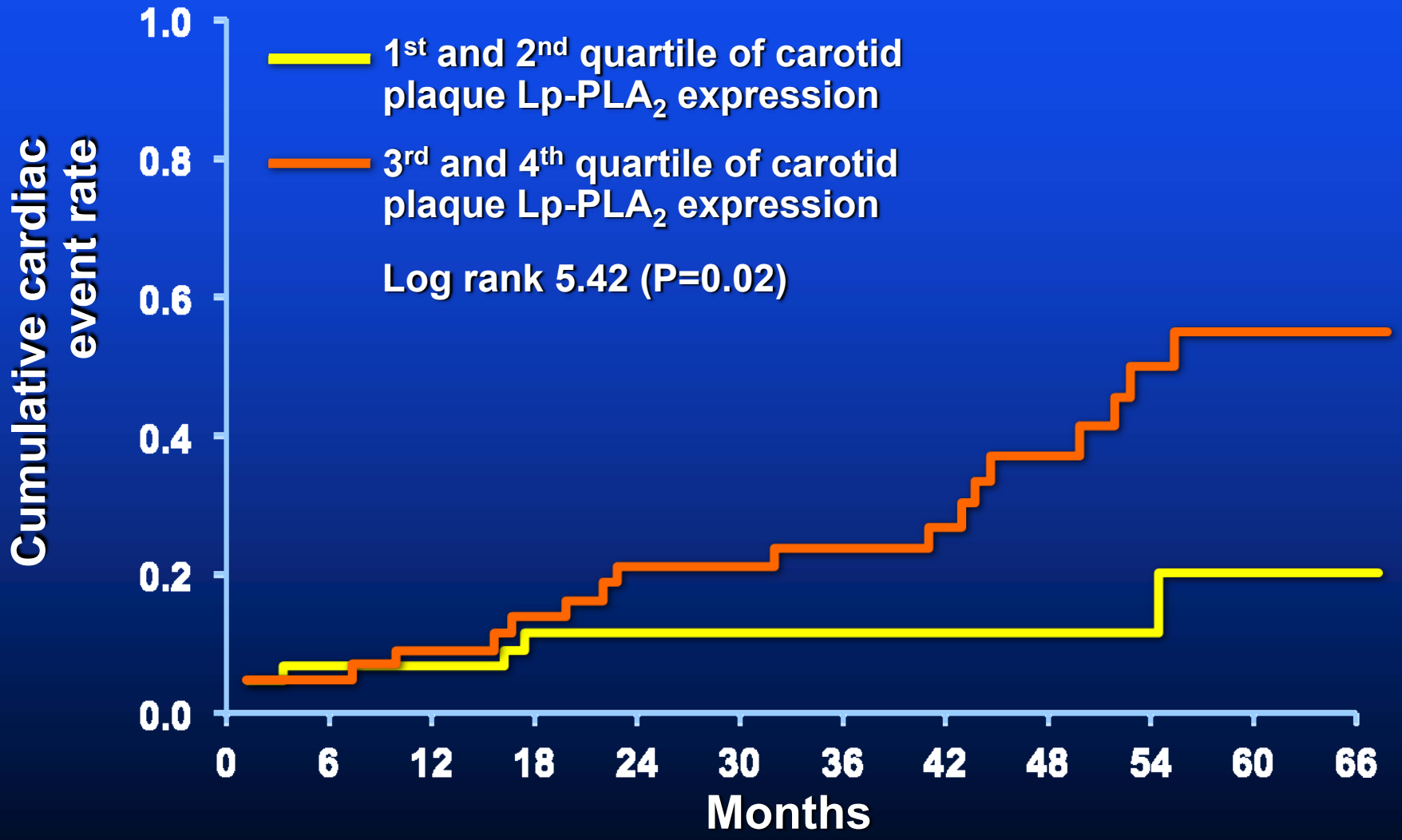
[1]Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA; [3]Department of Neurosurgery, Mayo Clinic College of Medicine, Rochester, MN, USA; and [4]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

Received 20 January 2009; revised 9 June 2009; accepted 16 July 2009

Objective –

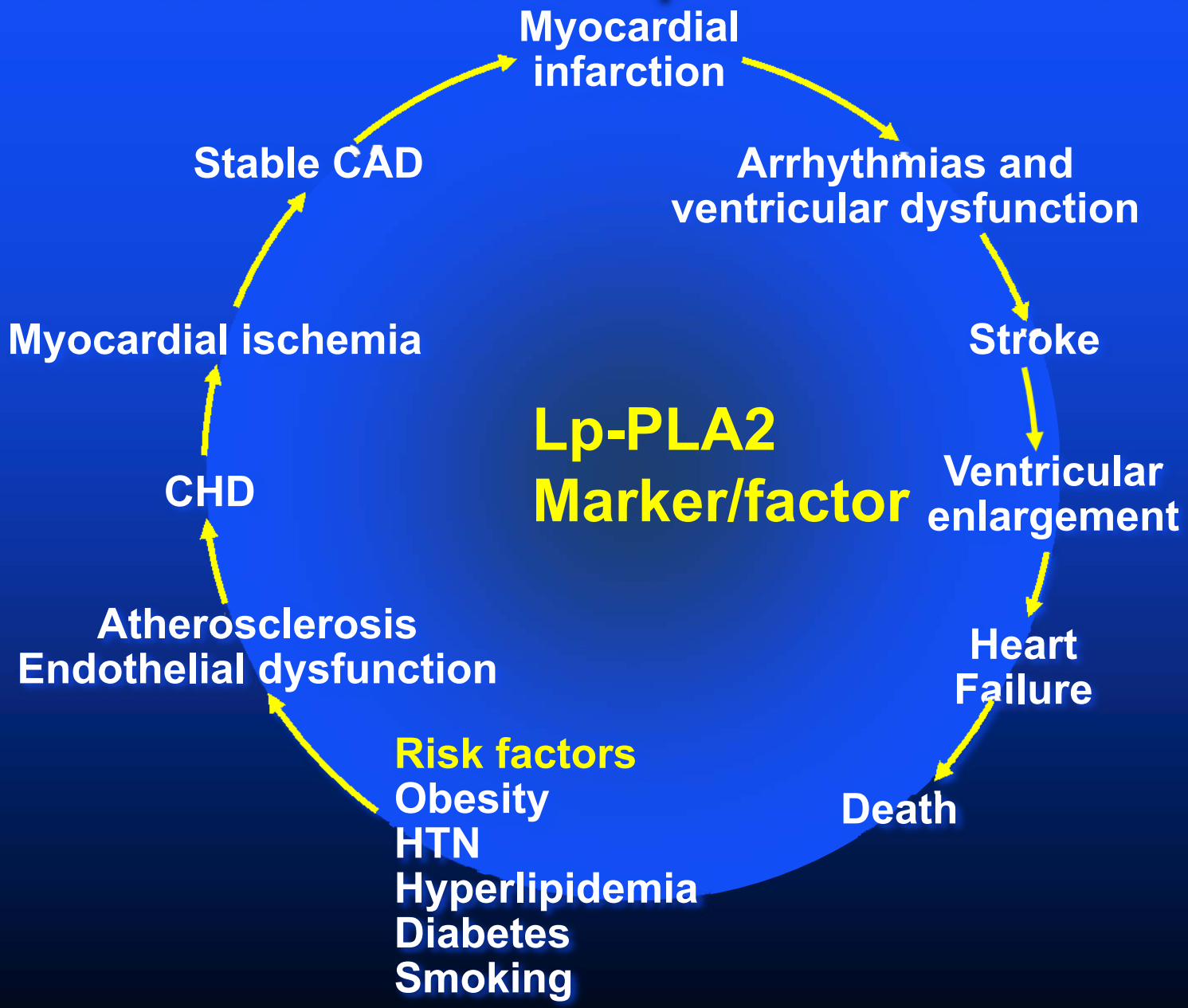
to test the hypothesis that expression of Lp-PLA$_2$ is higher in symptomatic carotid artery plaques and is predictive of CV events

Plaque Lp-PLA$_2$ and cardiac prognosis



Herrmann & Lerman: EHJ, 2009

Clinical Utilization of Lp-PLA2 in CVD and Stroke

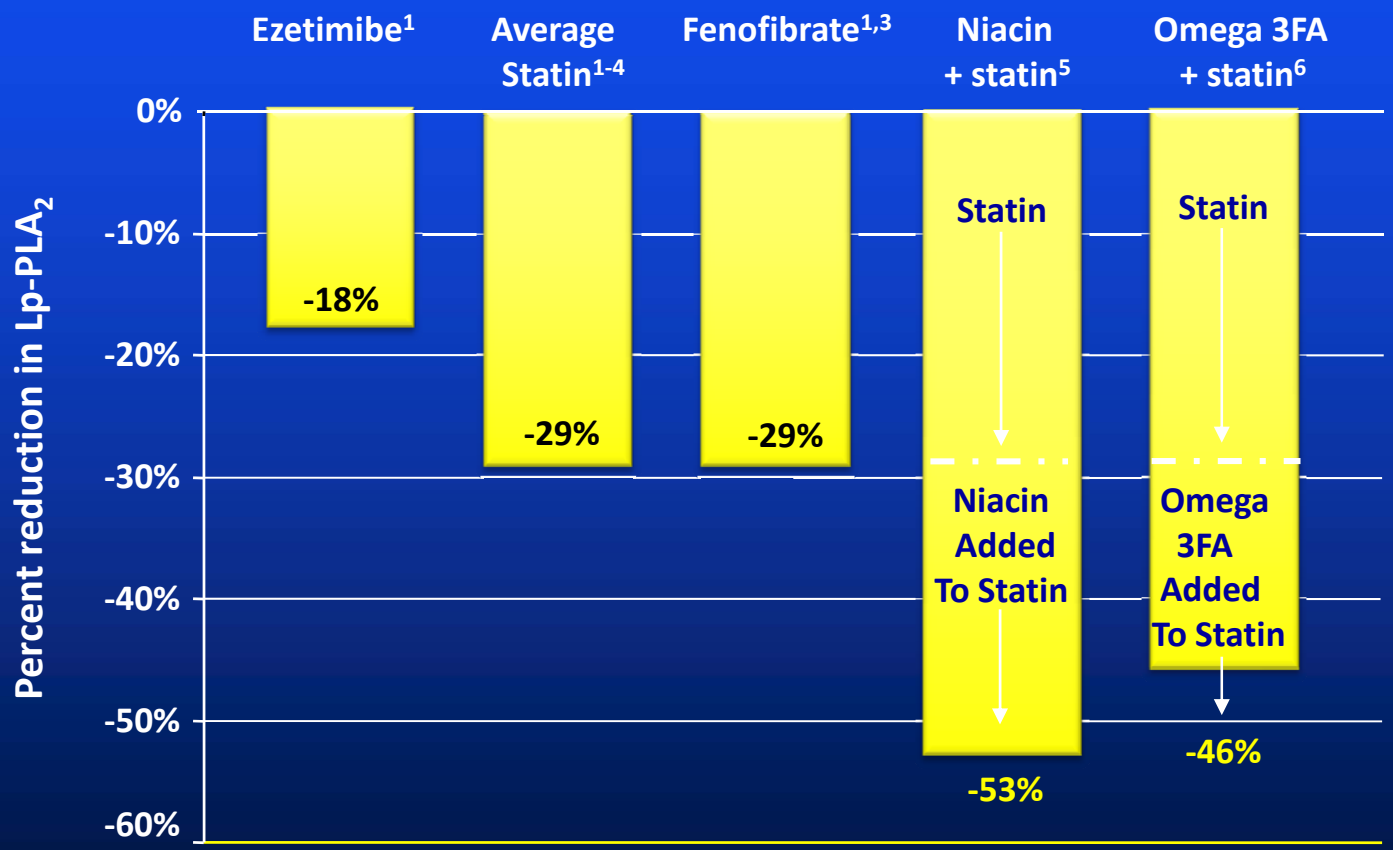


PLAC Test-The role of Lp-PLA2 in predicting increased risk for cardiovascular disease

Why should we use this test?

- The test should make a scientific sense.
- Participate in the disease process
- A marker at different disease stages
- Reflects Reversibility
- Serves as a risk factor not only as a risk marker.

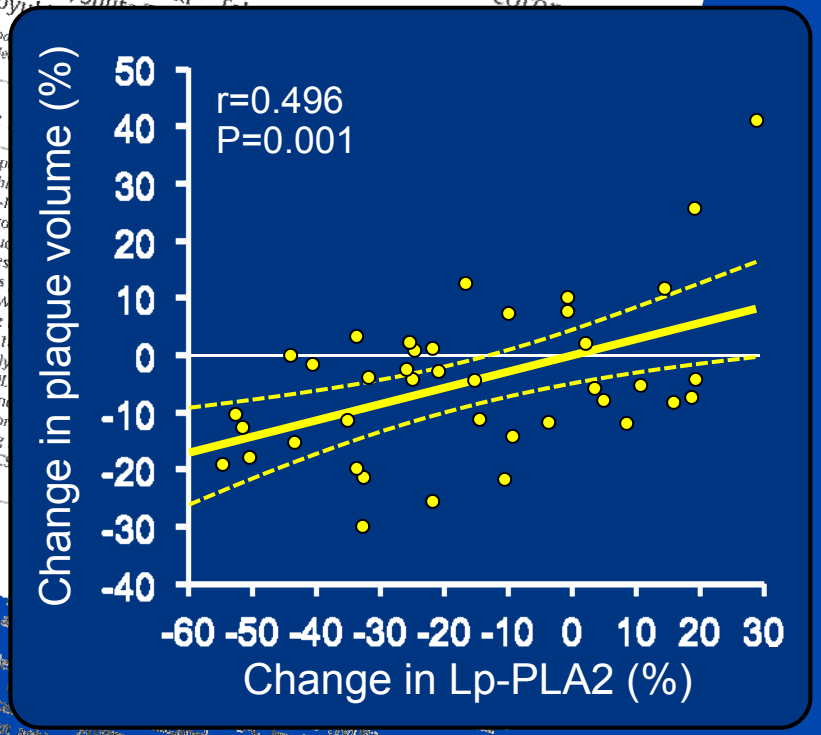
Lipid Lowering Medications Lower Lp-PLA$_2$



1. Saougos VG, et al. ATVB 2007:27.
2. Albert M, et al. *Atherosclerosis* 2005;182:193-198.
3. Schaefer EJ, et al. *Am J Cardiol.* 2005;95:1025-1032.
4. Muhlestein JB, et al. *Am H Journal*. 2006;48:396-401.
5. Kuvin J, et al. *Am J Cardiol.* 2006.
6. Schalwitz R, et al. ATVB Annual Mtg abstract 2007.

Decreased Circulating Lipoprotein-Associated Phospholipase A2 Levels are Associated with Coronary Plaque Regression in Patients with Acute Coronary Syndrome

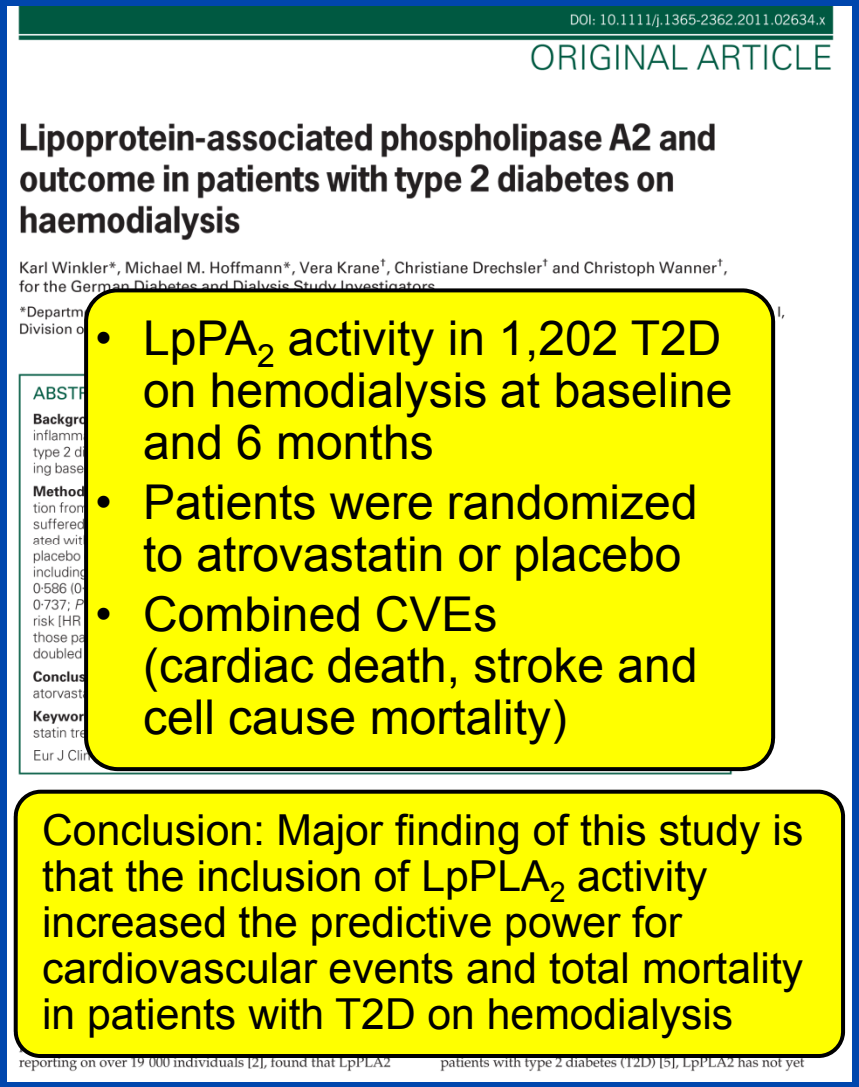
- 40 patients with ACS
- IVUS at baseline and 6 months
- Lipid levels and Lp-PLA2 levels



Conclusions

Circulating Lp-PLA2 levels are associated with changes in coronary plaque determined by IVUS in patients with ACS

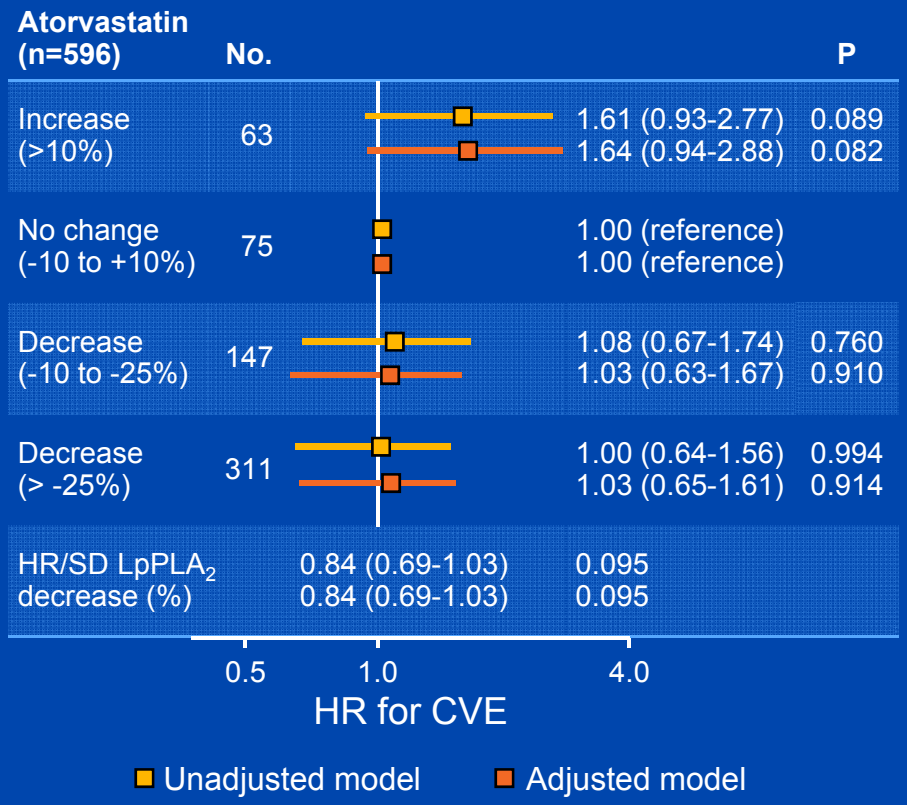
Lipoprotein-Associated Phospholipase A2 and Outcome in Patients with Type 2 Diabetes on Hemodialysis



- $LpPA_2$ activity in 1,202 T2D on hemodialysis at baseline and 6 months
- Patients were randomized to atrovastatin or placebo
- Combined CVEs (cardiac death, stroke and cell cause mortality)

Conclusion: Major finding of this study is that the inclusion of $LpPLA_2$ activity increased the predictive power for cardiovascular events and total mortality in patients with T2D on hemodialysis

In patients treated by atorvastatin, the relative reduction in $LpPLA_2$ activity demonstrated a diminished fatal risk [HR 0.74 (0.62-0.90) P=0.002]



Winkler et al: Eur J Cin Invest 42(7): 693, 2012

Outcome Study : LIPID Trial

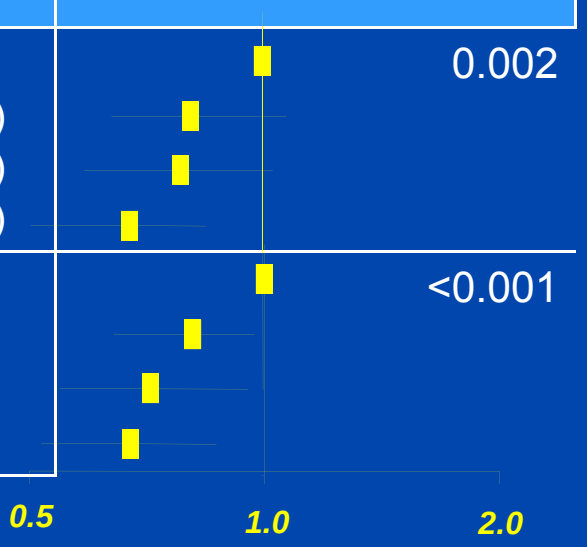
Changes in Lp-PLA$_2$ activity in secondary prevention predict coronary events and treatment effect by pravastatin in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Trial

Goal of the study

- **What is the value of Lp-PLA$_2$ activity to predict coronary events (CHD death or nonfatal MI) over 6.1 years**
- **What is the effect of pravastatin on Lp-PLA$_2$ levels**
- **What is the extent of the pravastatin treatment effect explained by changes in Lp-PLA$_2$**

Effect of changes in levels of Lp-PLA$_2$ activity on CVD outcomes adjusted for baseline Lp-PLA$_2$, 23 other factors*

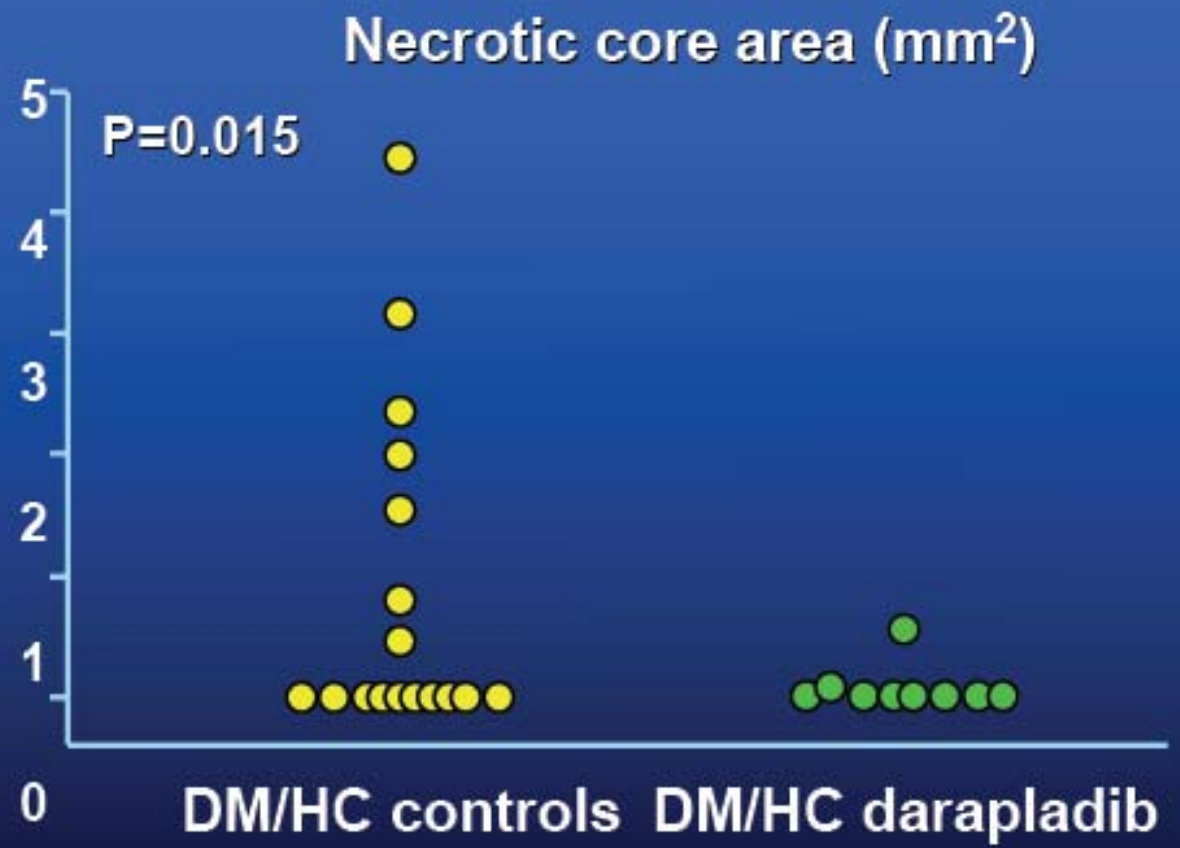
End point	Change in Lp-PLA$_2$ activity (nmol/min/mL)	HR (95% CI)	P-value (trend)
CHD death and MI	>2.8 -19.8 to 2.8 -46.6 to -19.8 ≤ -46.6	1.00 0.85 (0.67 – 1.08) 0.82 (0.63 – 1.06) 0.65 (0.50 – 0.85)	0.002
Total CVD events * **** CVD death, MI, stroke, UAP, revascularization***	>2.8 -19.8 to 2.8 -46.6 to -19.8 ≤ -46.6	1.00 0.83 (0.71, 0.95) 0.74 (0.63, 0.96) 0.70 (0.59, 0.83)	<0.001



Adjusted for age, gender, stroke, diabetes, smoker, hypertension, total-c, HDL-c, prior ACS, revascularisation, SBP, atrial fibrillation, eGFR, BMI, dyspnoea, angina, WBC, PVD, aspirin, fasting glucose, triglycerides, ApoB, ApoA1

After the additional adjustment for new biomarkers and LDL-c, baseline and change, the effect of change in Lp-PLA2 activity was essentially the same (p-trend<0.001)

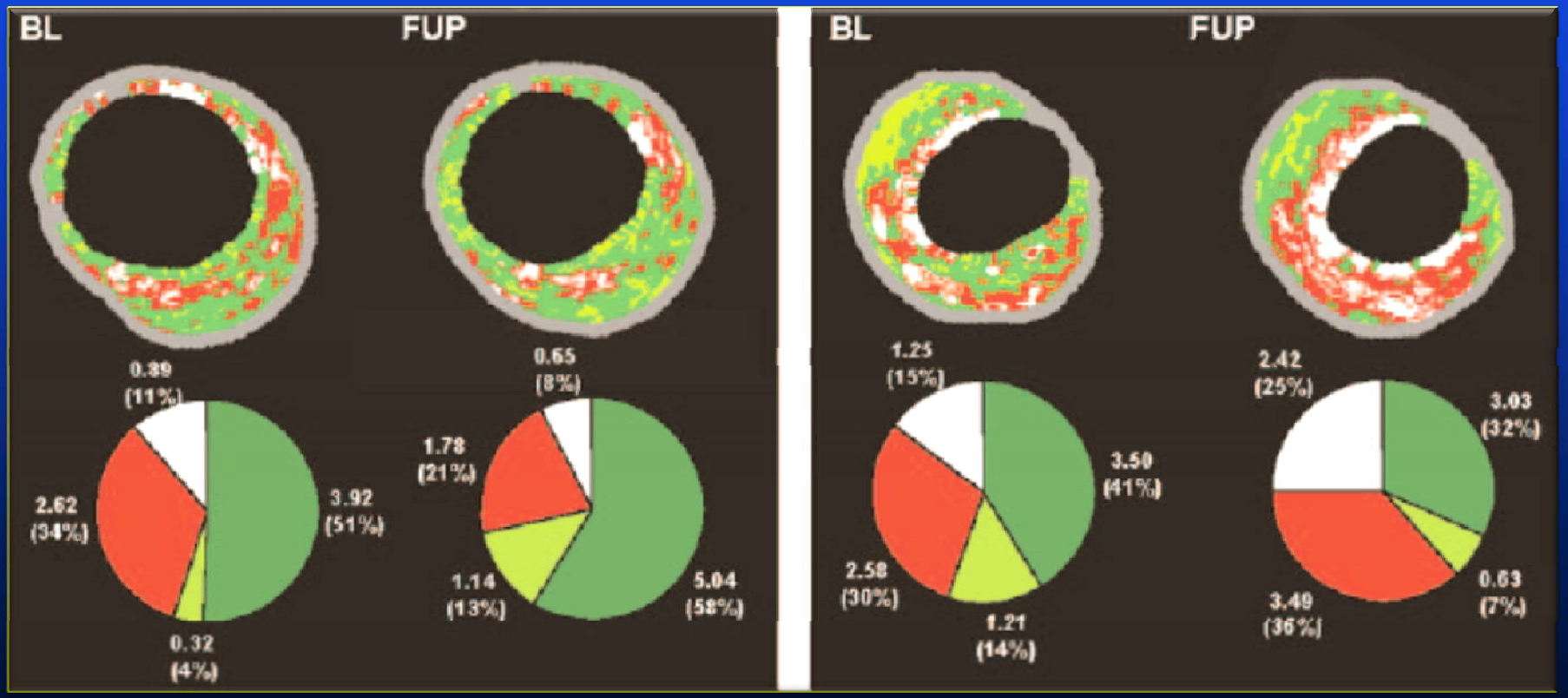
Darapladib Reduced Complex Coronary Lesion Development



Nature Medicine 2008;14: 1059 - 106

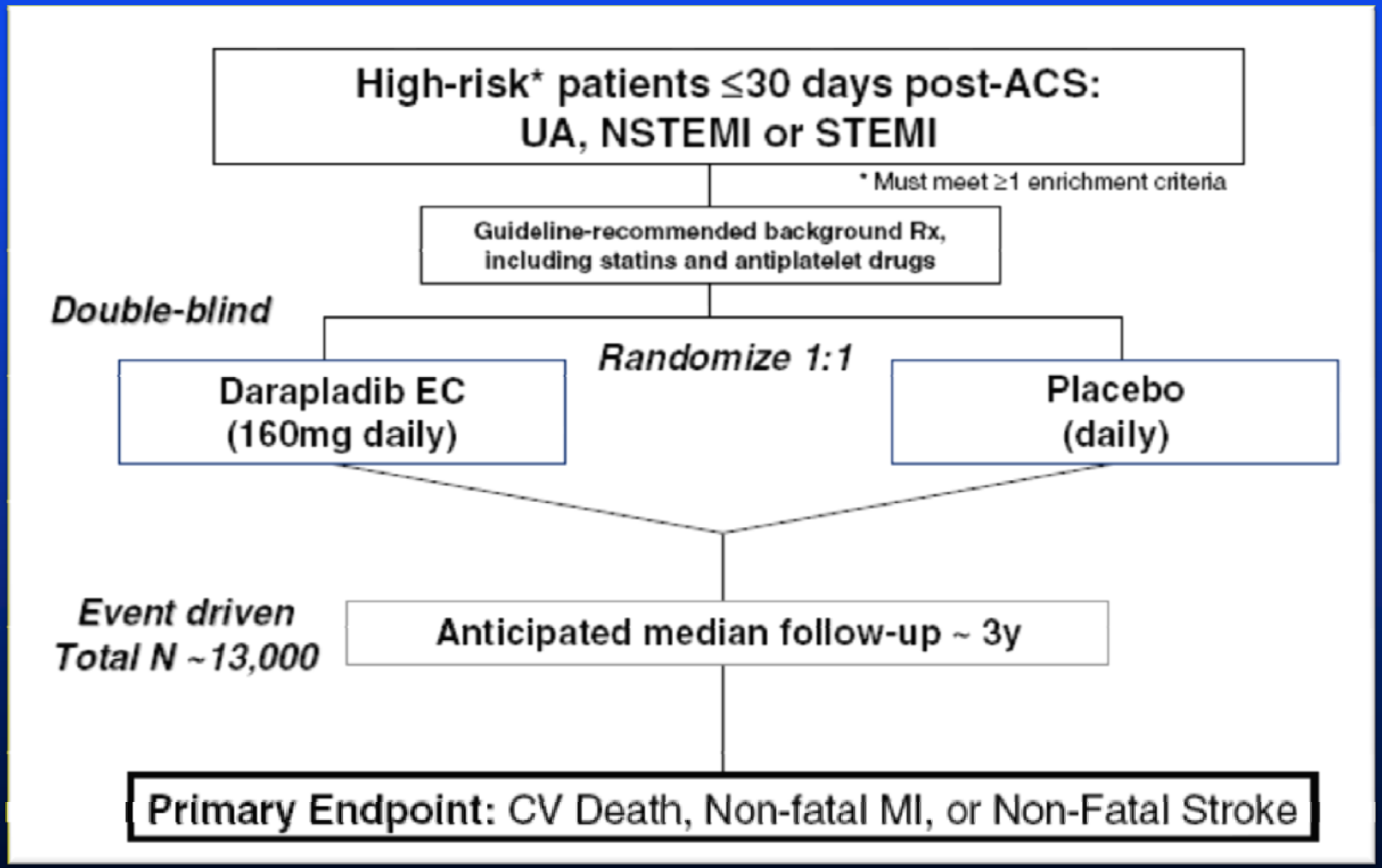
IBIS-2: Effects Darapladib on Human Coronary Atherosclerotic Plaque

Darapladib **Placebo**



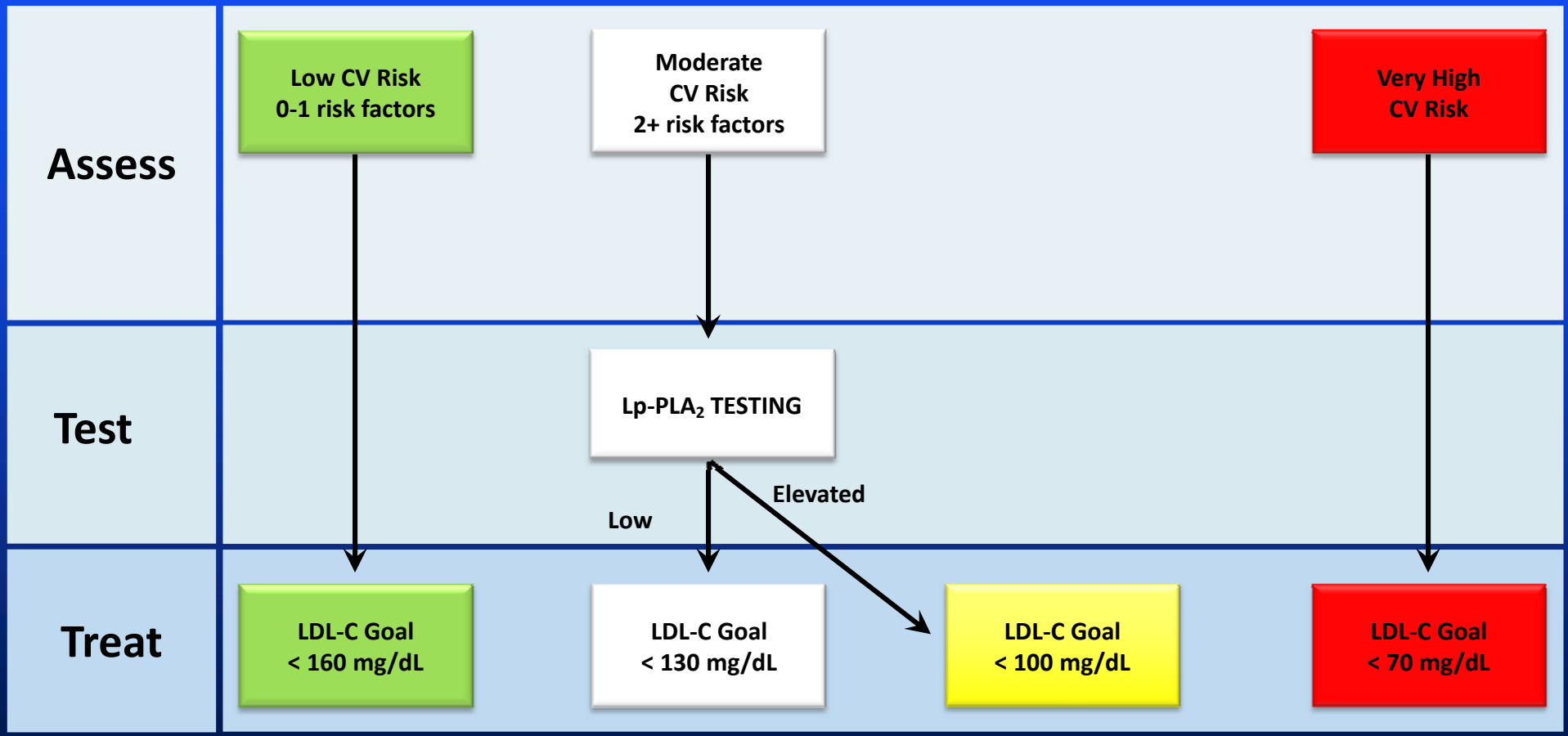
Circulation. 2008;118:1172-

SOLID-TIMI 52 Study
Estimated Study Completion Date: April 2014



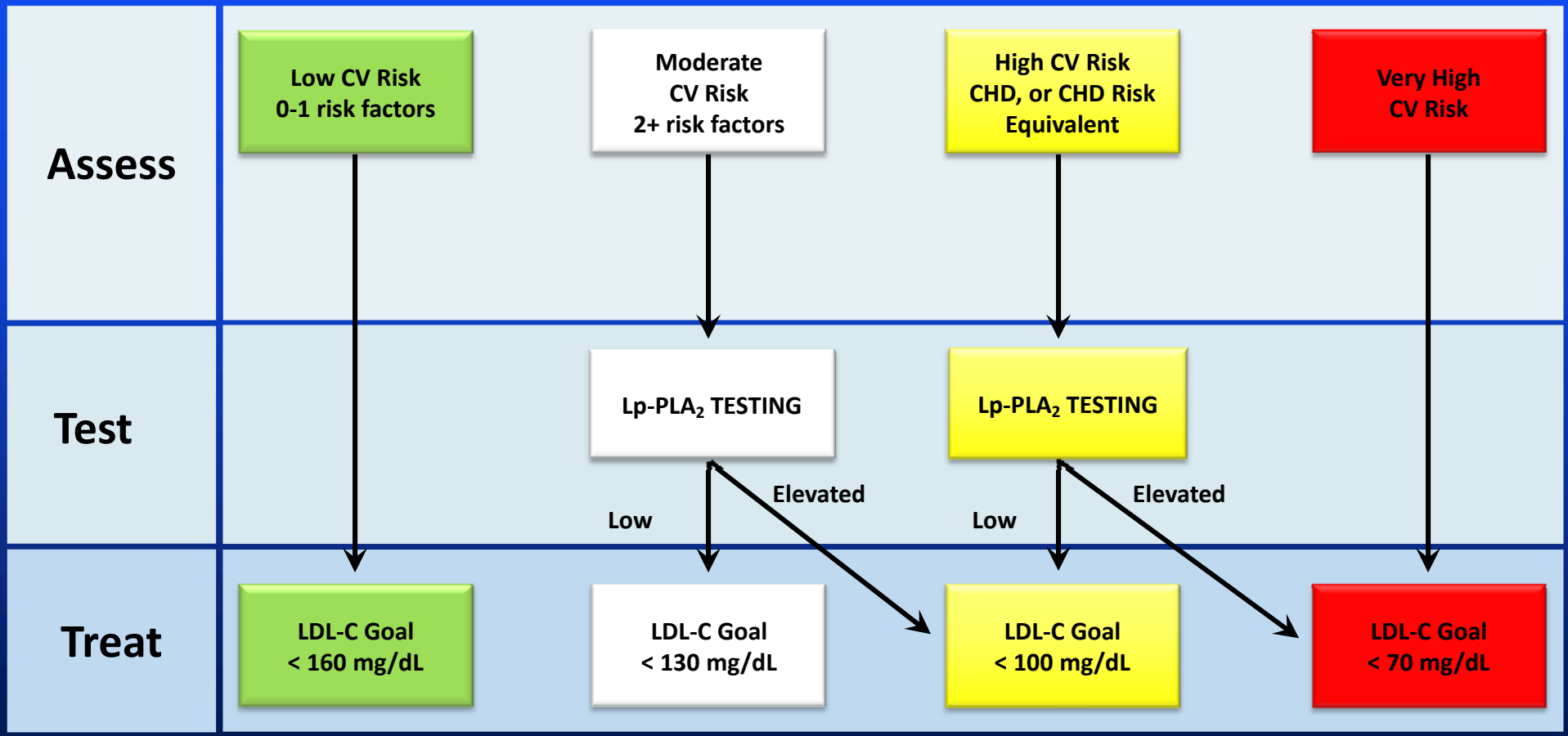
Am Heart J 2011;162:613-619.

Expert Consensus Panel Recommendation for Use of Lp-PLA$_2$ Testing



Davidson MH, et al. Am J Card S

Expert Consensus Panel Recommendation for Use of Lp-PLA$_2$ Testing



Davidson MH, et al. Am J Card S

Lp-PLA$_2$ is included in four clinical guidelines

2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

- Lp-PLA$_2$ testing may be considered in intermediate-risk asymptomatic adults.

2011 AHA/ASA Guidelines for the Primary Prevention of Stroke

- Measurement of inflammatory markers such as hs-CRP or Lp-PLA$_2$ in patients without CVD may be considered to identify patients who may be at increased risk of stroke.

2012 AACE Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis

- **Test for** Lp-PLA$_2$, which in some studies has demonstrated more specificity than highly sensitive CRP, when it is necessary to further stratify a patient's CVD risk.

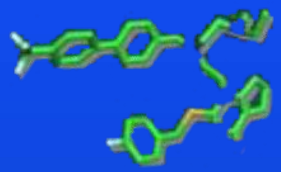
Lp-PLA$_2$: The Current Evidence

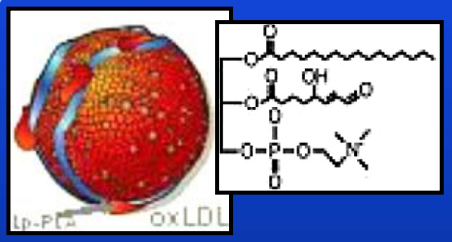
Association studies

Epidemiology
Higher plasma levels predict CV events

Pathology
Upregulation of Lp-PLA$_2$ in TCFA and ruptured VP

Functional
Higher plasma Lp-PLA$_2$ levels → coronary endothelial dysfunction





Objective
Reduction in CV events with an Lp-PLA$_2$ inhibitor

Intervention with darapladib

Preclinical
Alters coronary atherosclerosis (DM/HC pig)

Human atheroma
Downregulates plaque Lp-PLA$_2$ activity

Systemic effects
Sustained inhibition of Lp-PLA$_2$ activity on background of intensive statin therapy

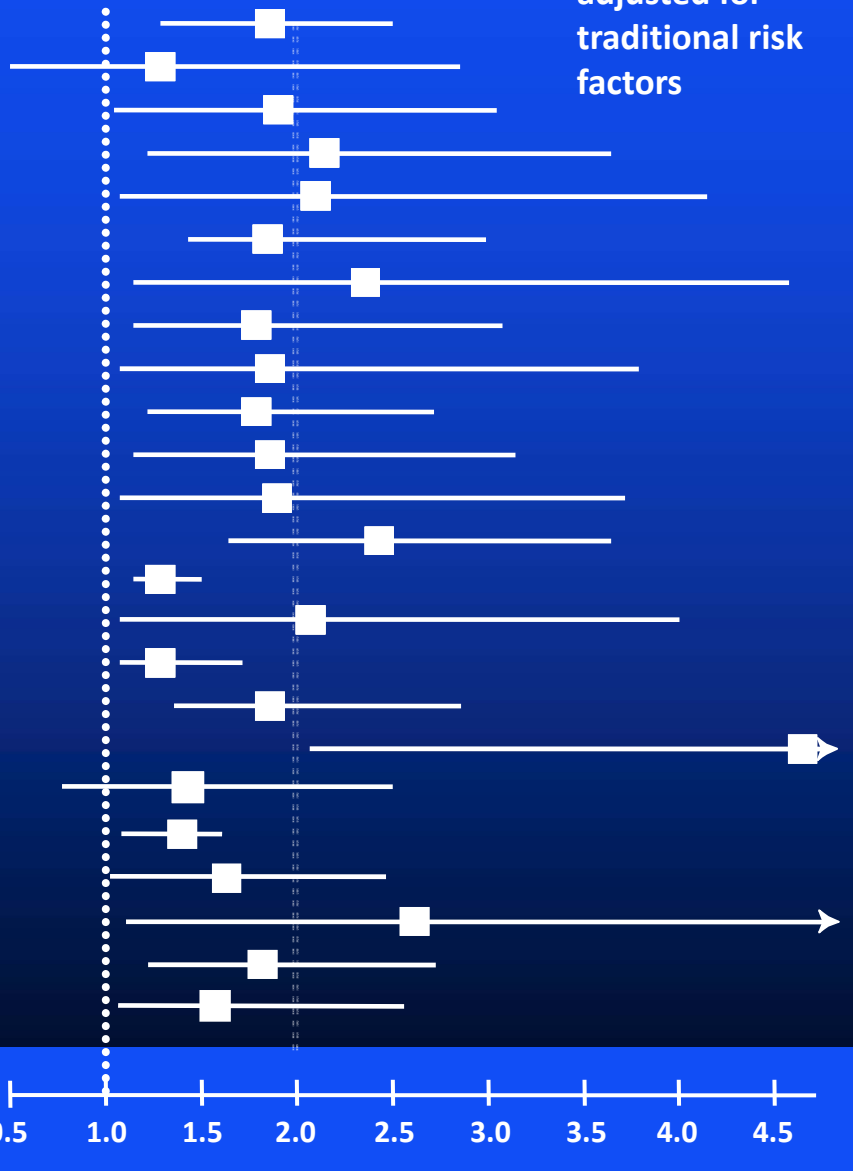
Outcomes trials
High risk 2° prevention – population, eg, stability

Coronary imaging
IBIS-2

Many Studies Show Elevated Lp-PLA$_2$ is Associated with Increased CVD Risk

- All are fully adjusted for traditional risk factors

Packard (WOSCOPS), *N Engl J Med 2000* – CHD
Blake (WHS), *J Am Coll Cardiol* 2001 – CHD
Blankenberg (AtheroGENE), *J Lipid Res* 2003 - CAD
Ballantyne (ARIC), *Circulation* 2004 - CHD LDL < 130
Winkler, *J Clin Endocrinology and Metabolism* 2004 – CHD
Oei (Rotterdam), *Circulation* 2005 – CHD
Brilakis (Mayo Heart), *Eur Heart J* 2005 – CHD
Ballantyne (ARIC), *Arch Intern Med* 2005 – Stroke
Oei (Rotterdam), *Circulation* 2005 – Stroke
Winkler (LURIC), *Circulation* 2005 – CHD
Khuseyinova (HELICOR), *Atherosclerosis* 2005 – CHD
Koenig (KAROLA), *Arterioscler Thromb Vasc Biol* 2005 – CVD
May (Intermountain Heart), *Am Heart J* - CHD
Jenny (CHS), *AHA-EPI Abstract* 2006 – MI
Elkind (NOMAS), *Arch Intern Med* 2006 – Stroke
O'Donoghue (PROVE IT), *Circulation* 2006 – CVD
Corsetti (THROMBO), *Clinical Chemistry* 2006 - CHD
Gerber (Olmsted County), *ATVB* 2006 - Death S/P MI
Oldgren (GUSTO / FRISC), *Eur Heart J* 2007 - Acute ACS
Sabatine (PEACE), *AHA-Scientific Sessions* 2006 - CVD
Persson (Malmo), *Arterioscler Thromb Vasc Biol* 2007 - CVD
Mockel (NOBIS-II), *Clin Res Cardiol* 2007 – CVD
Hatoum (Nurse's Health Study), *Circ Suppl* 2007 – MI
Daniels (Rancho Bernardo), *JACC* 2008 – CHD



Davidson MH, Jones PH. *Am J Card Suppl* 2008

Lp-PLA$_2$ Studies Collaboration
Lancet 2010

- The CVD risk due to elevated Lp-PLA2 is comparable to the elevated CVD risk associated with two other well established risk markers: non-HDL-C and blood pressure.
- Lp-PLA2 levels provide independent CVD risk assessment from other biomarkers

The *Lancet* 2010; 375: 1536–44.

“Absolute risk estimation must be viewed as an evolving science”

NCEP ATP III, 2001

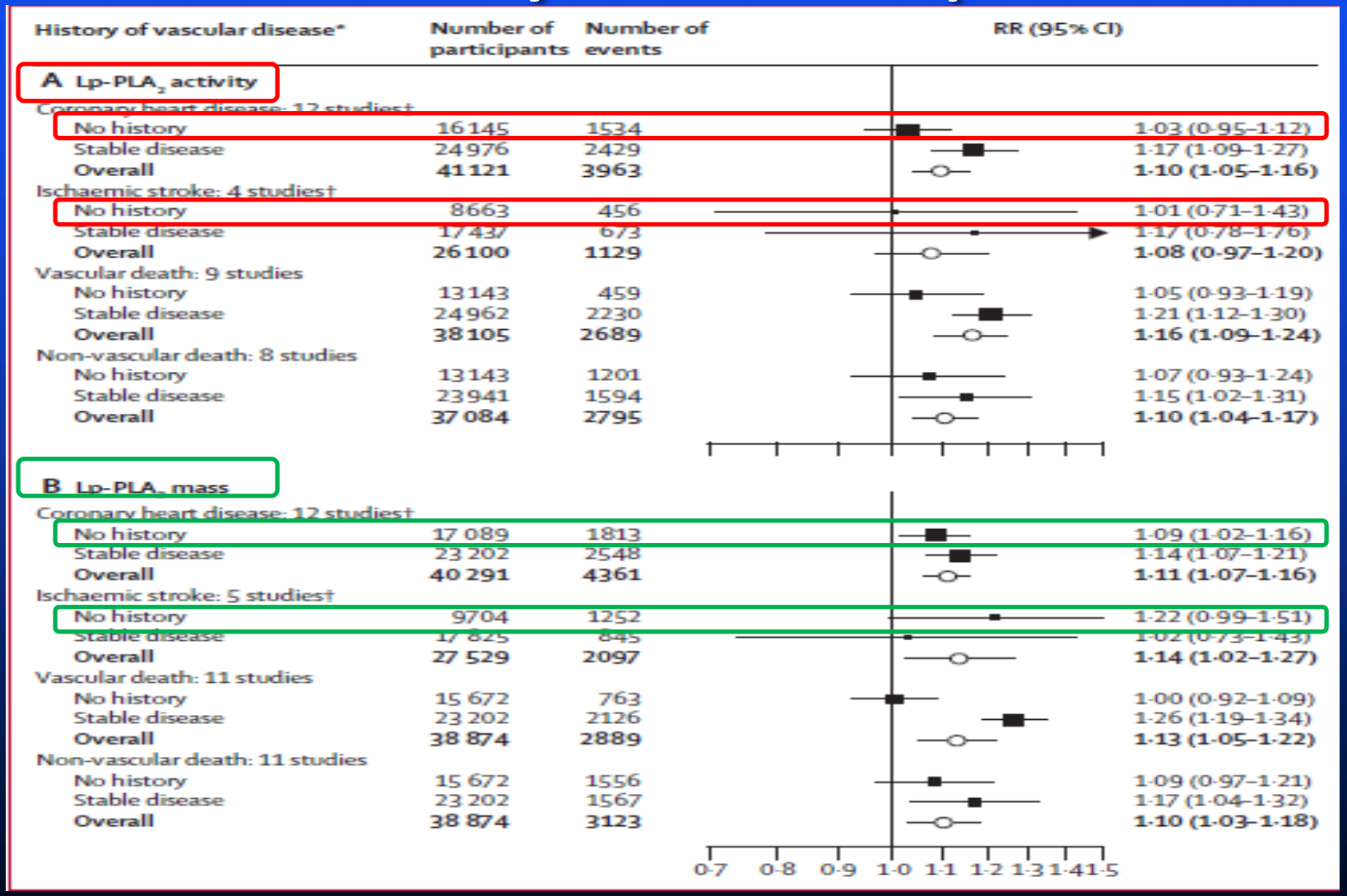
Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A_2

Robert S. Rosenson[1]* and Diana M. Stafforini[†,§]

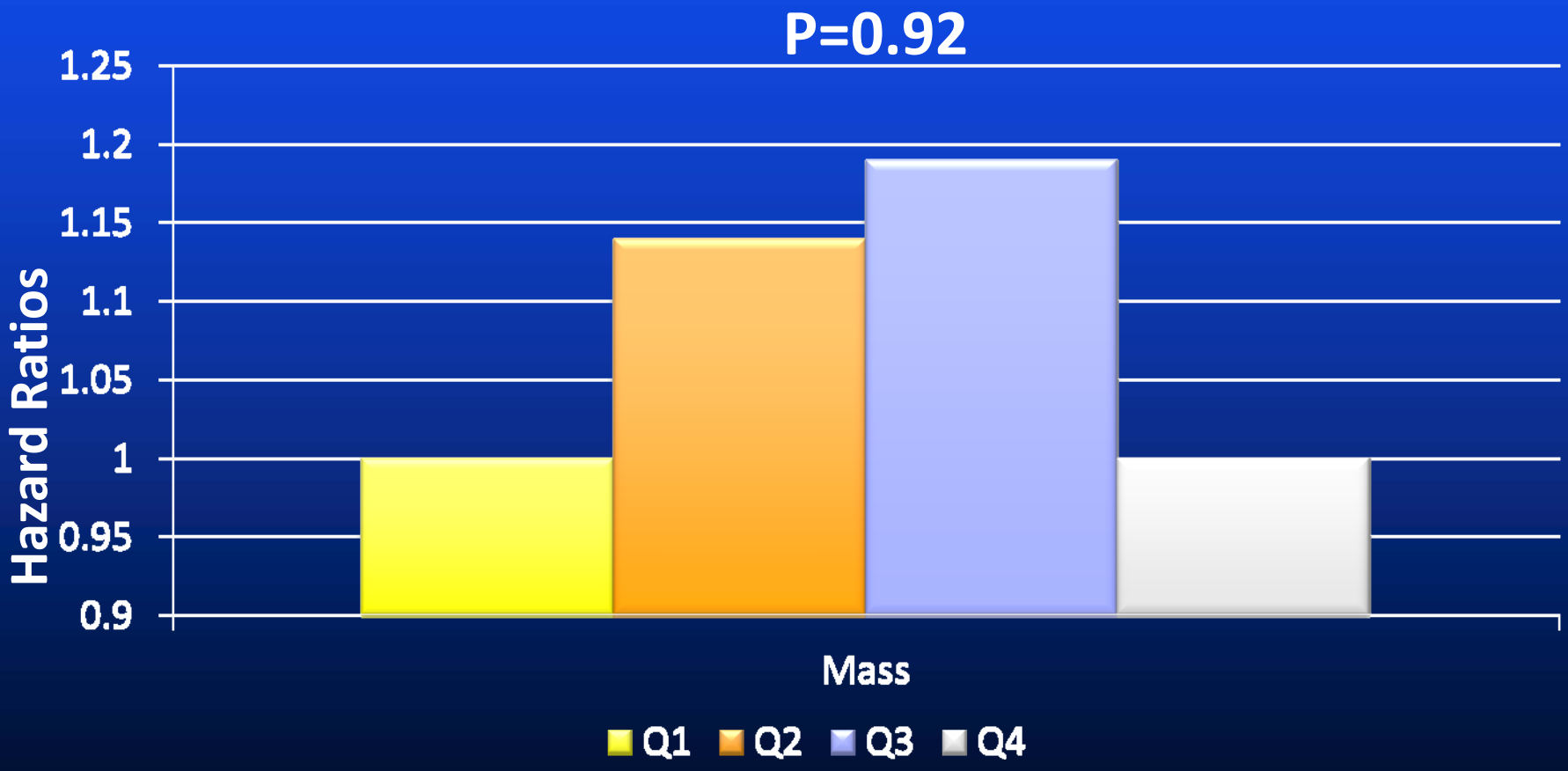
- **In individuals with no history of vascular disease at baseline no association was found between LpPLA2 activity and CHD or ischemic strokes.**

J. Lipid Res. 2012. 53: 1767–1782

Lp-pla2 And Risk of CHD, Stroke, and Mortality: Collaborative Analysis Of 32 Prospective Studies



Relationship of Lp-PLA2 Mass and Activity with Incident Vascular Events in the Placebo Group in the JUPITER Trial



Why?

- Why did baseline levels of Lp-PLA2 mass in the placebo group not predict incidence of vascular events?

  The assay used in this study was the turbidimetric assay that was under development and not released for commercial use, and not the PLAC Test (ELISA Method).