Statine ad alto dosaggio nell'IMA: quale, quando e per quanto tempo?

dott. Francesco Abbadessa
Azienda Ospedaliera Universitaria "San Martino" Genova

Congresso congiunto ANMCO – SIC - ANCE

Archivio di Stato di Genova, 12 marzo 2011

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3, NO. 3, 20
© 2010 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 1936-8798/10/$36.
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2009.11.0

Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction

The STATIN STEMI Trial

Pre treatment in emergency room:

- ASA 200 mg
- Clopidogrel 600 mg
- Atorvastatina 80 mg or 10 mg

171 patients

ELSEVIER

International Journal of Cardiology 137 (2009) 246–251

International Journal of Cardiology

www.elsevier.com/locate/ijcard

The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome ☆

K.H. Yun et al. / International Journal of Cardiology 137 (2009) 246–251

- ASA 300 mg
- Clopidogrel 300 mg
- 5000 UI UFH iv
- Rosuvastatin 40 mg or no statin

445 patients

Perché somministrare un carico di statine prima di una procedura di PCI ?

statine ad alto dosaggio,
prima della coronarografia,
nelle sindromi coronariche acute

Razionale fisiopatologico

- Danno miocardico associato a PCI
- Aterosclerosi:
  - stabile
  - instabile
- Statine:
  - effetti lipidici
  - effetti non lipidici

EDITORIAL COMMENT

Recapturing the Magic

Revisiting the Pleiotropic Effects of Statins in Percutaneous Coronary Revascularization*

Stephen G. Ellis, MD, Saif Anwaruddin, MD

Cleveland, Ohio

Danno miocardico associato a PCI

Attenuation of injury and inflammation associated with percutaneous coronary intervention (PCI) is an important concept in cardiovascular medicine

JACC Vol. 54, No. 6, 2009
August 4, 2009:566–8

The NEW ENGLAND JOURNAL of MEDICINE

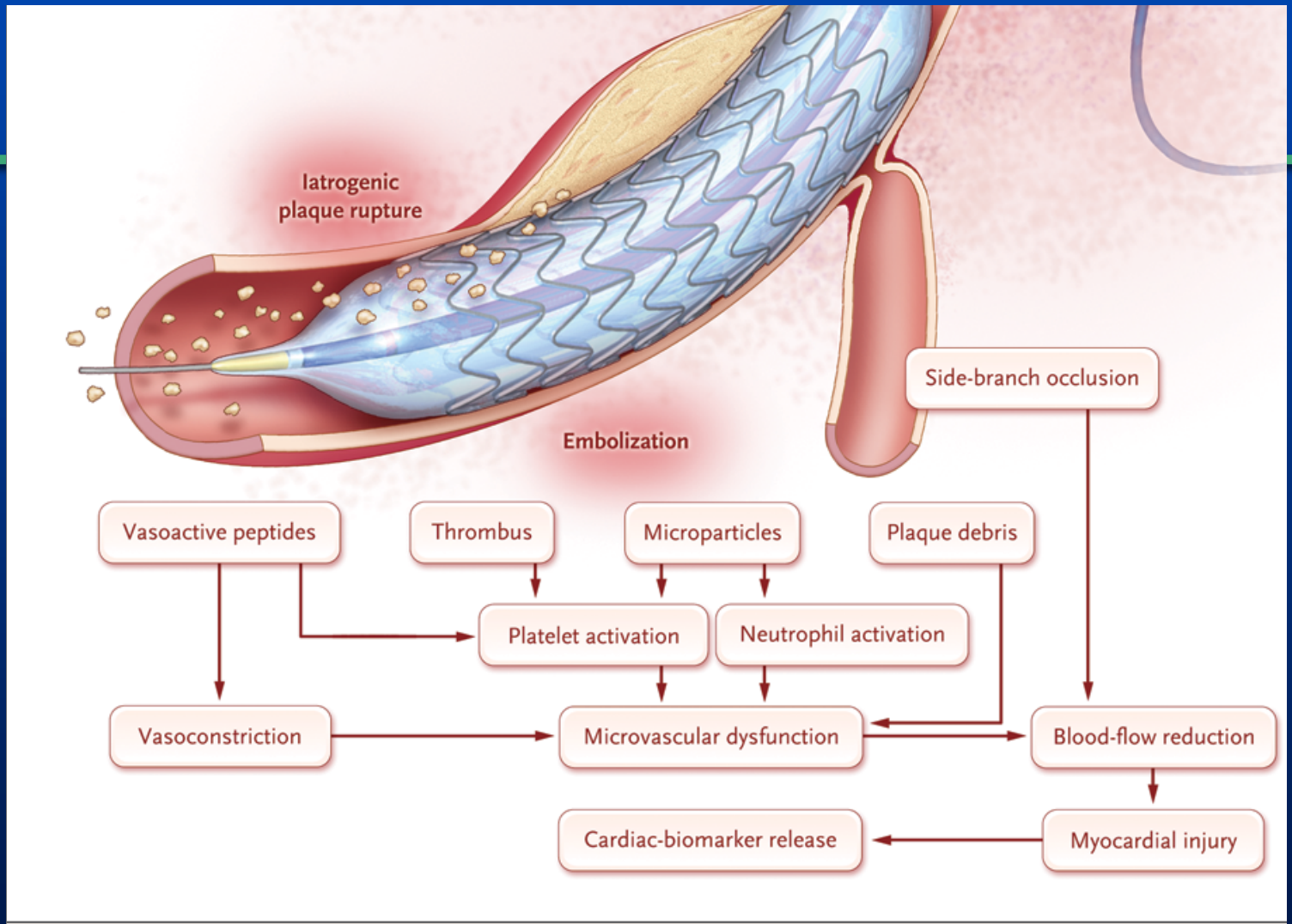


Figure 1. Mechanisms Underlying Periprocedural Myocardial Infarction.

Universal Definition of Myocardial Infarction

Kristian Thygesen; Joseph S. Alpert; Harvey D. White;
on behalf of the Joint ESC/ACCF/AHA/WHF Task Force
for the Redefinition of Myocardial Infarction

Table 1 Clinical classification of different types of myocardial infarction

Type 1
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension

Type 3
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a
Myocardial infarction associated with PCI

Type 4b
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5
Myocardial infarction associated with CABG

There is currently no solid scientific basis for defining a biomarker threshold for the diagnosis of peri-procedural myocardial infarction. Pending further data, and by arbitrary convention, it is suggested to designate increases **more than three times** the 99th percentile URL as **PCI-related myocardial infarction** (type 4a).

Troponin

Circulation **November 27, 2007**

With the "Universal Definition," Measurement of Creatine Kinase-Myocardial Band Rather Than Troponin Allows More Accurate Diagnosis of Periprocedural Necrosis and Infarction After Coronary Intervention

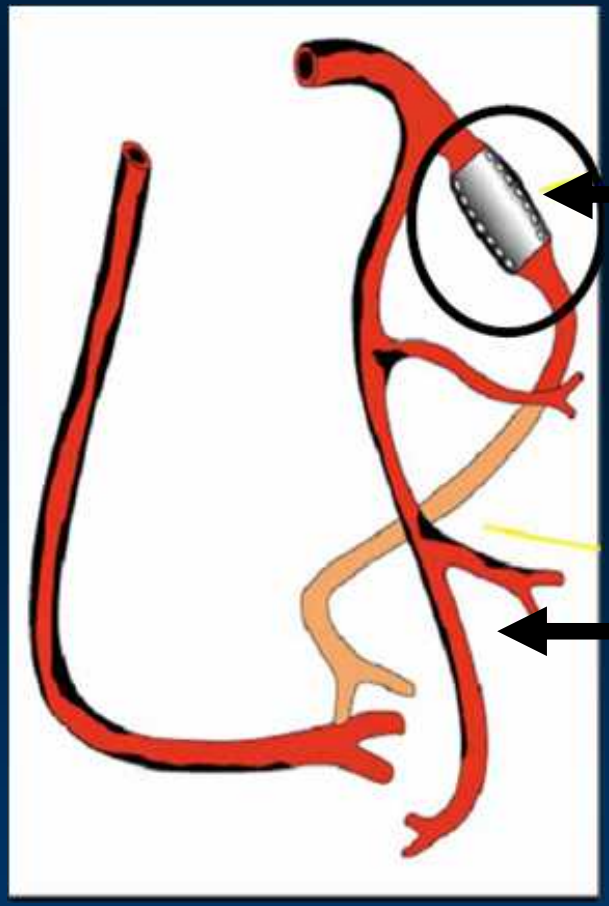
Chris C. S. Lim, MBBS,*†‡ William J. van Gaal, MBBS, MSc, MD,†‡ Luca Testa, MD,‖

a **CK-MB** level that is **more than 5 times** the upper reference limit

N Engl J Med February 3, 2011

JACC February 8, 2011

Treatment Strategy to Stabilize Patients with Acute Coronary Syndrome



1

PCI - stent
- Culprit / culprits

Focal treatment

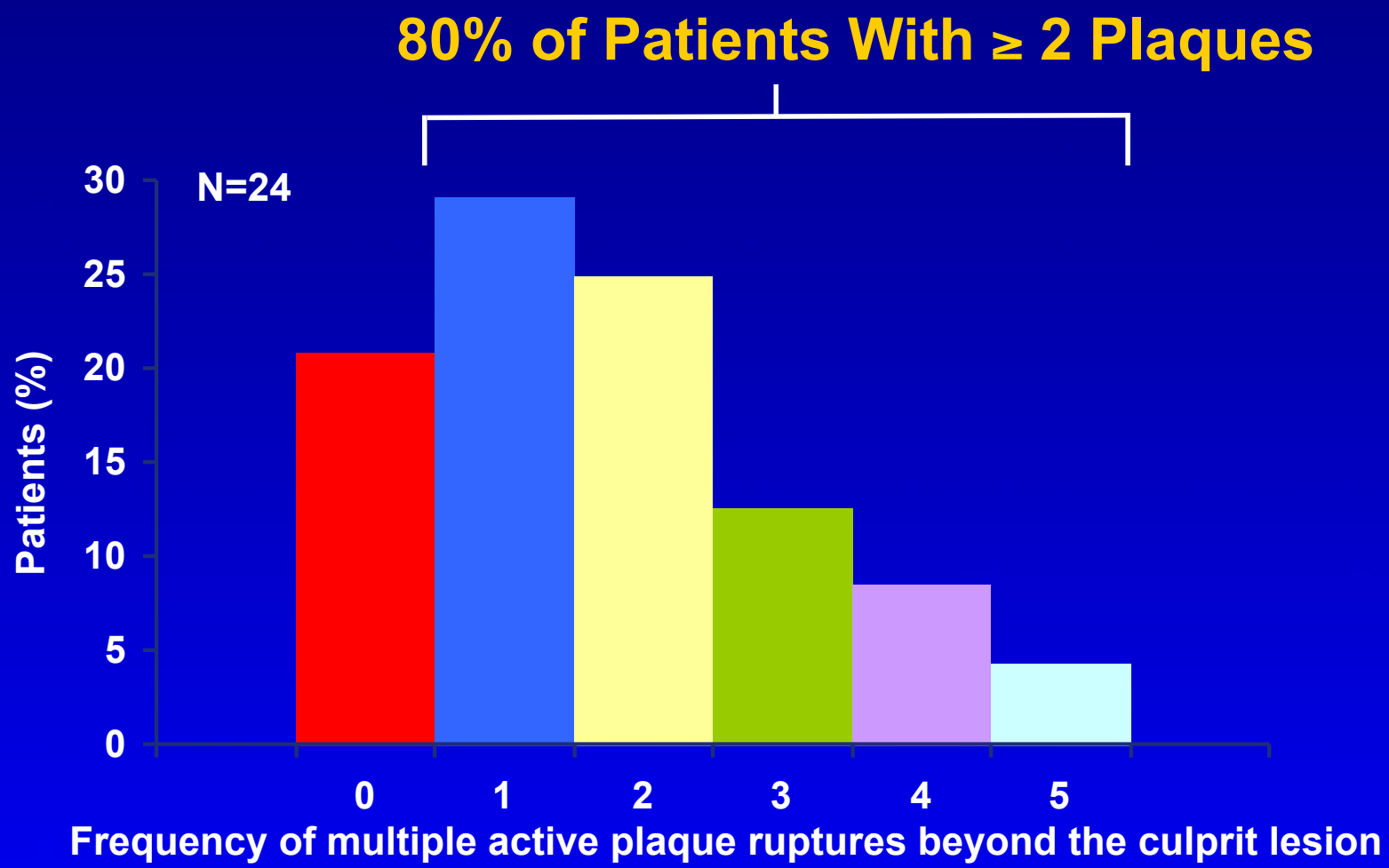
2

Intensive statin
- Vulnerable, stable
- Time to benefit
  - weeks

Additional systemic treatment

Yoseph Rozenman, E. Wolfson Medical Center, Holon, Israel

Frequency of Multiple "Active" Plaques in Patients With ACS



ACS, acute coronary syndrome.

Rioufol G, et al. *Circulation* 2002;106:804-808. (with permission)

Aterosclerosi coronarica

Concezioni attuali

- Coronaropatia ostruttiva stabile
- Atero-trombosi ➔ ACS

Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 23, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.09.009

STATE-OF-THE-ART PAPER

Inflammation in Atherosclerosis

From Pathophysiology to Practice

Peter Libby, MD,* Paul M Ridker, MD, MPH,*† Göran K. Hansson, MD, PHD,‡
for the Leducq Transatlantic Network on Atherothrombosis

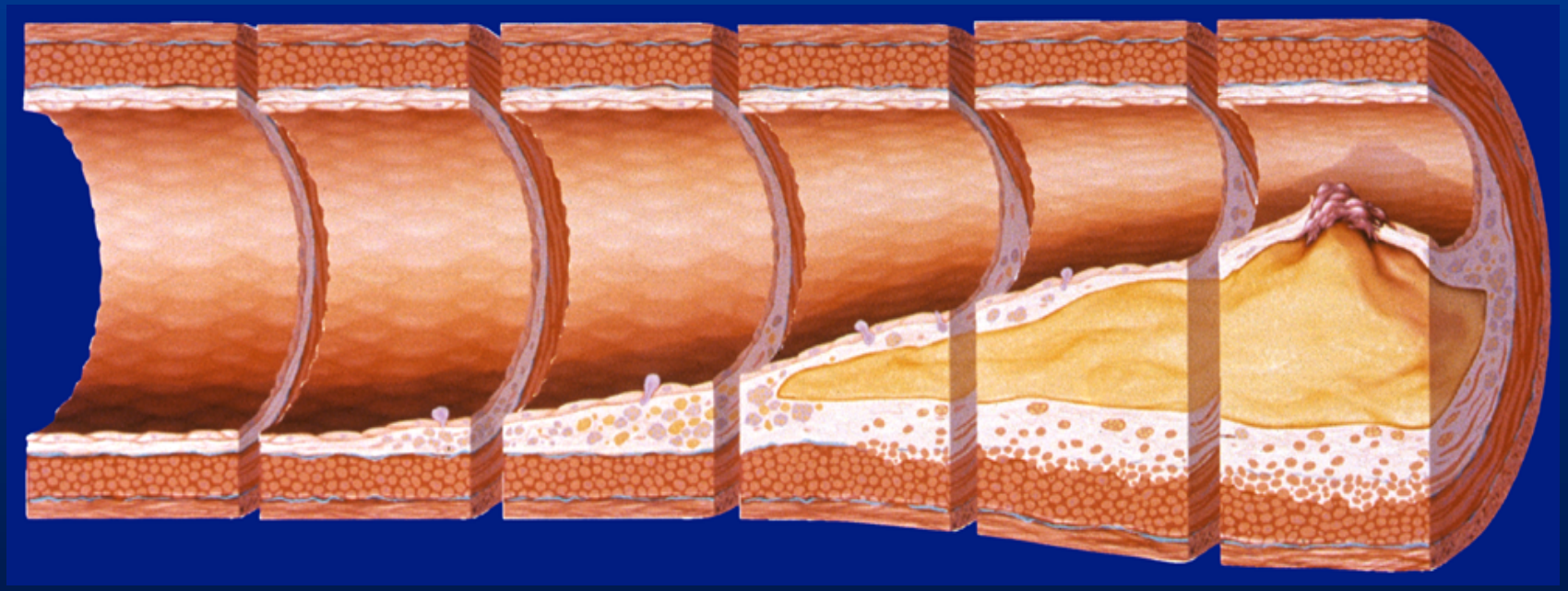
Boston, Massachusetts; and Stockholm, Sweden

The advent of the cell biological era of atherosclerosis supplanted the simplistic concept of the atheroma as a passive deposition of lipid debris on the artery wall.

This revolution in our thinking about the pathophysiology of atherosclerosis has begun to provide clinical insight and practical tools that may aid patient management.

Atherosclerosis: traditional model

Atheroma accumulation leads to luminal narrowing from the onset of the disease process



Gradual luminal narrowing

The Origins of Atherosclerosis

Peter Libby
Brigham & Women's Hospital
Harvard Medical School

Lessons from the Lipid Legends

www.theheart.org 2004

" like rust in a pipe"

The Traditional View of Atherosclerosis

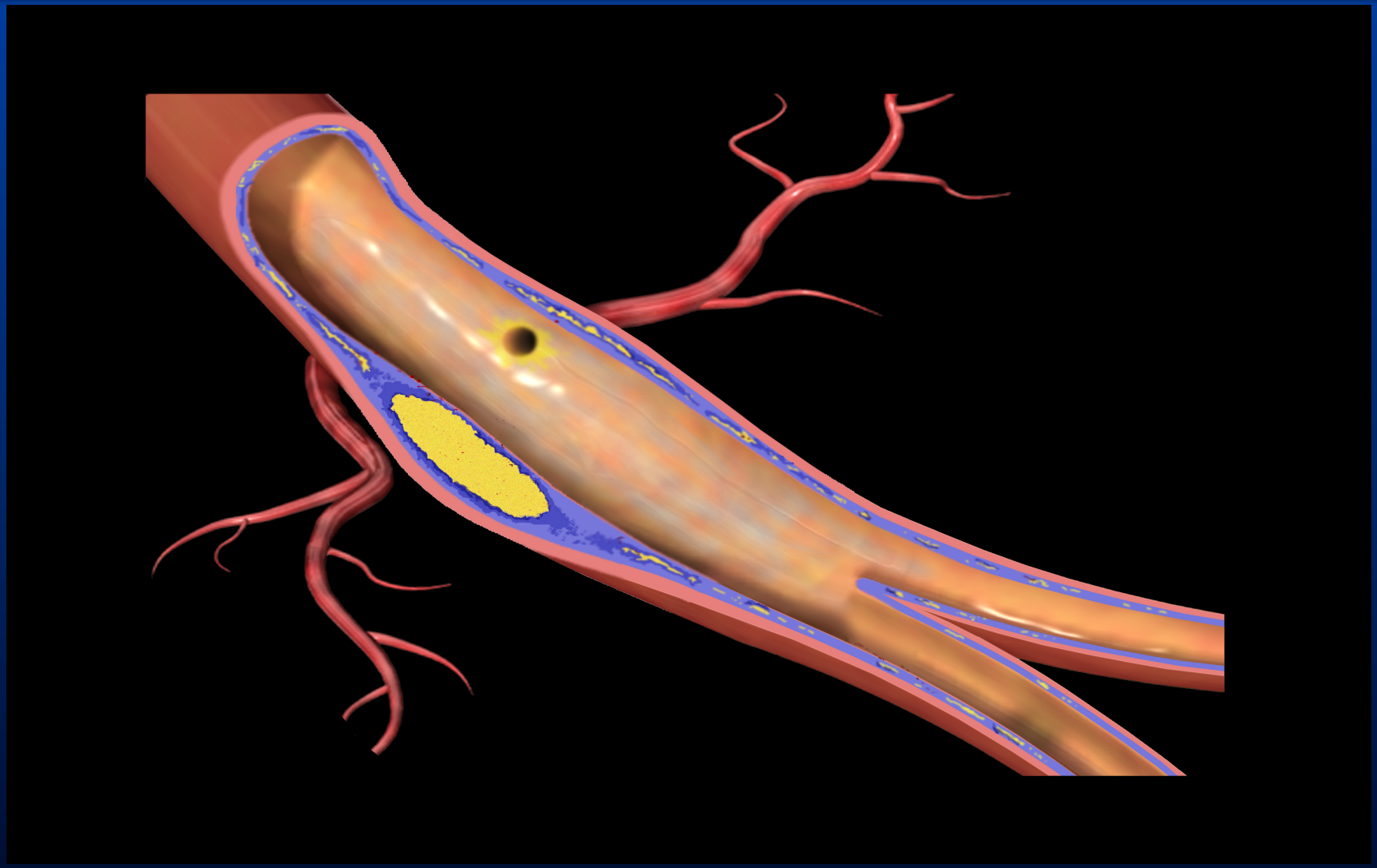
Atherosclerosis is more than luminal narrowing

- 99% of atherosclerotic disease is in vessel wall
- Does not narrow the lumen
- Hidden from angiographic view

Steven Nissen

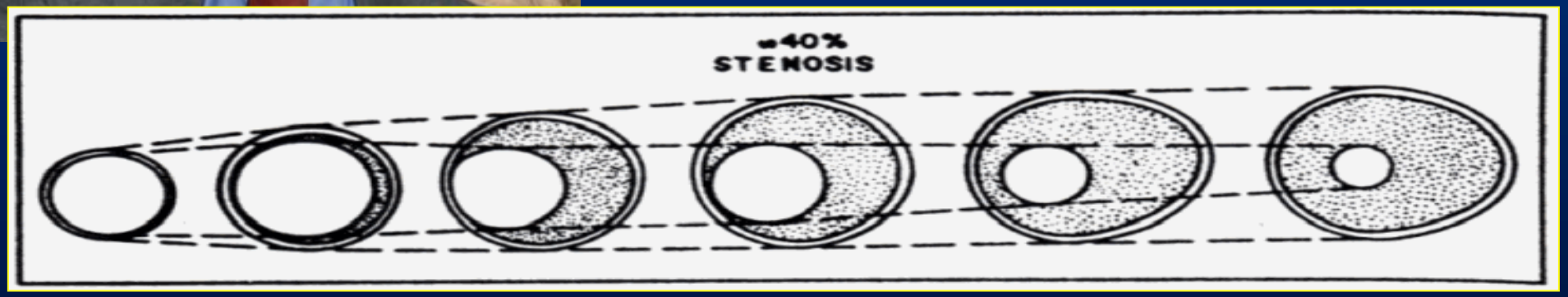
European Atherosclerosis Society april 2004 meeting, Seville, Spain

Vulnerable plaque



Sviluppo strutturale della placca: Rimodellamento

Seymour Glagov
pathologist
Chicago



"Compensatory enlargement of human atherosclerotic coronary artery"

Seymour Glagov et al, N Engl J Med 1987; 316:1371-5.

Angiographic limits

Our preoccupation with coronary luminology.

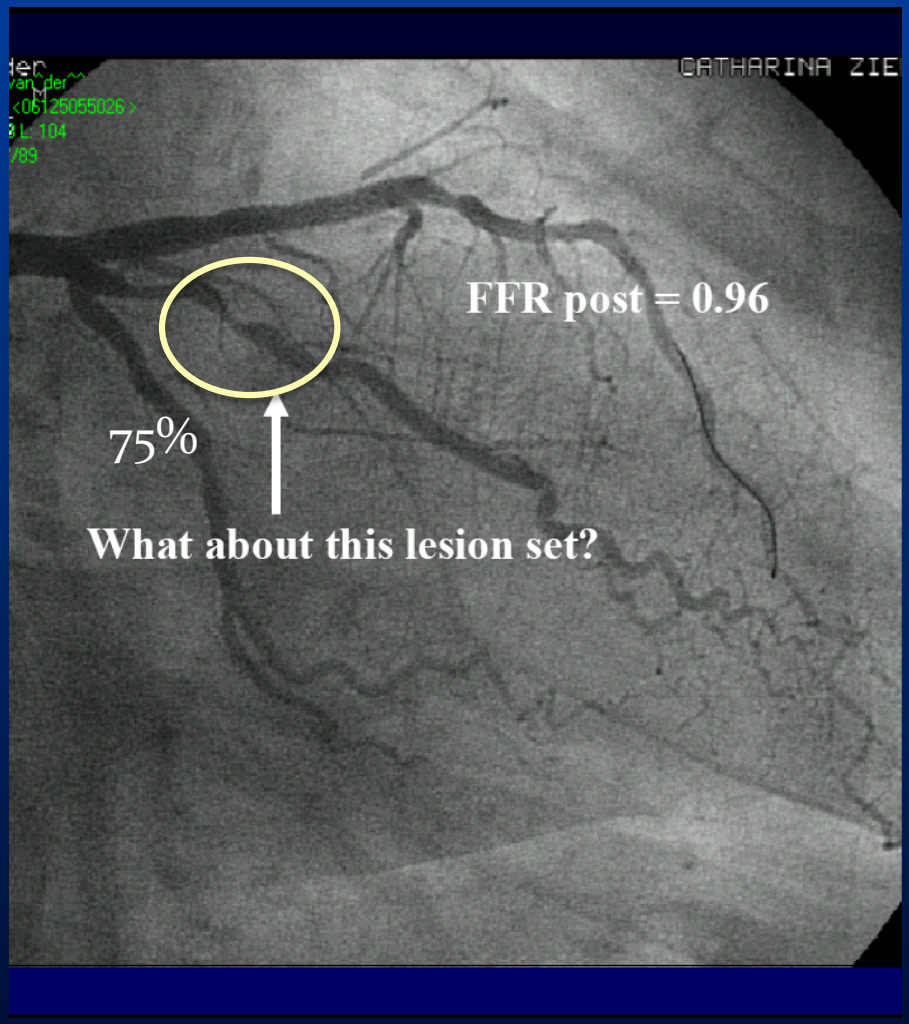
The dissociation between clinical and angiographic findings in ischemic heart disease.

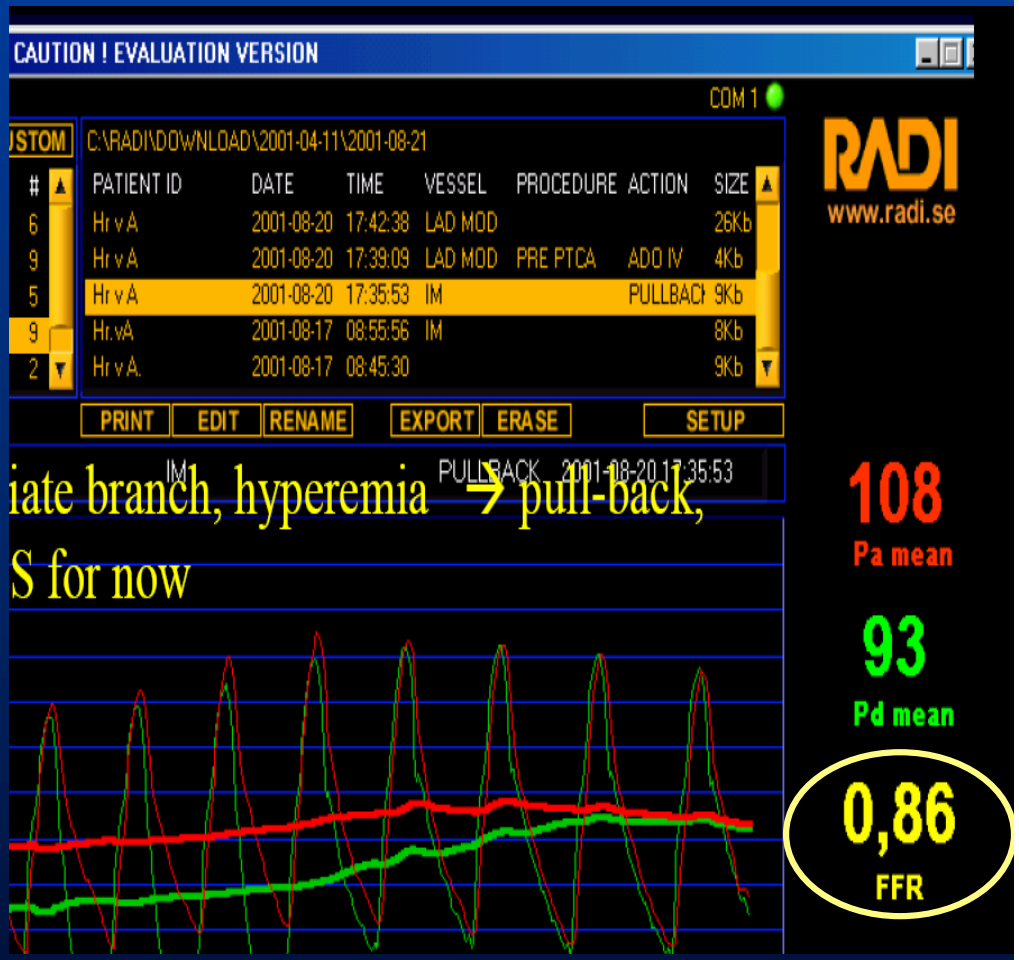
Eric J. Topol, Steven E.Nissen

Circulation. 1995; 92:2333-2342.

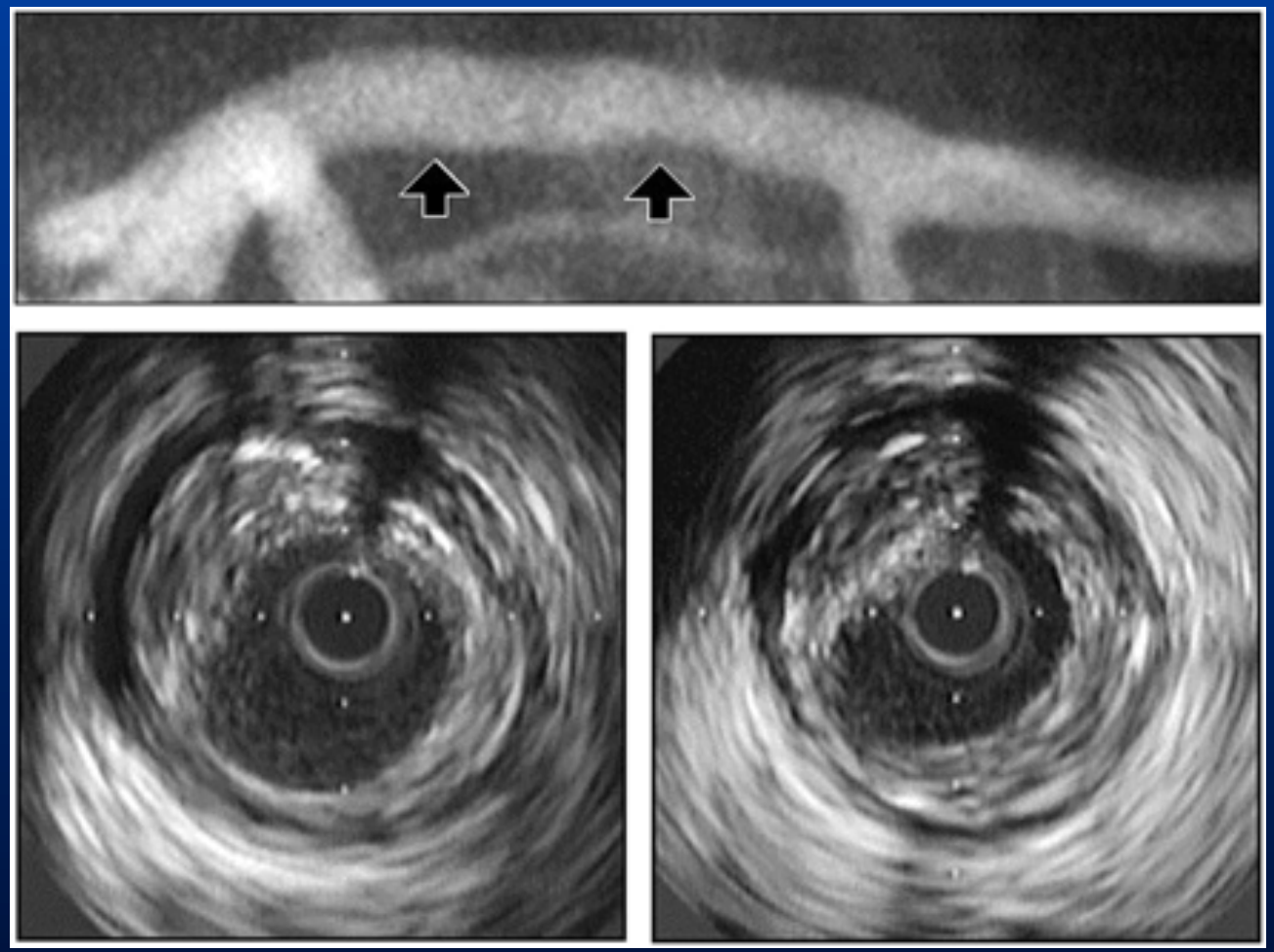
- **Luminology:** % diameter stenosis
- **oculo-stenotic reflex**
- **Coronary cosmetology**

Valutazione funzionale
FFR





Angiographic underestimation of disease



Steven E. Nissen, MD; Paul Yock, MD. *Circulation.* 2001;103:604

Anatomical treatment in stable obstruttive CAD

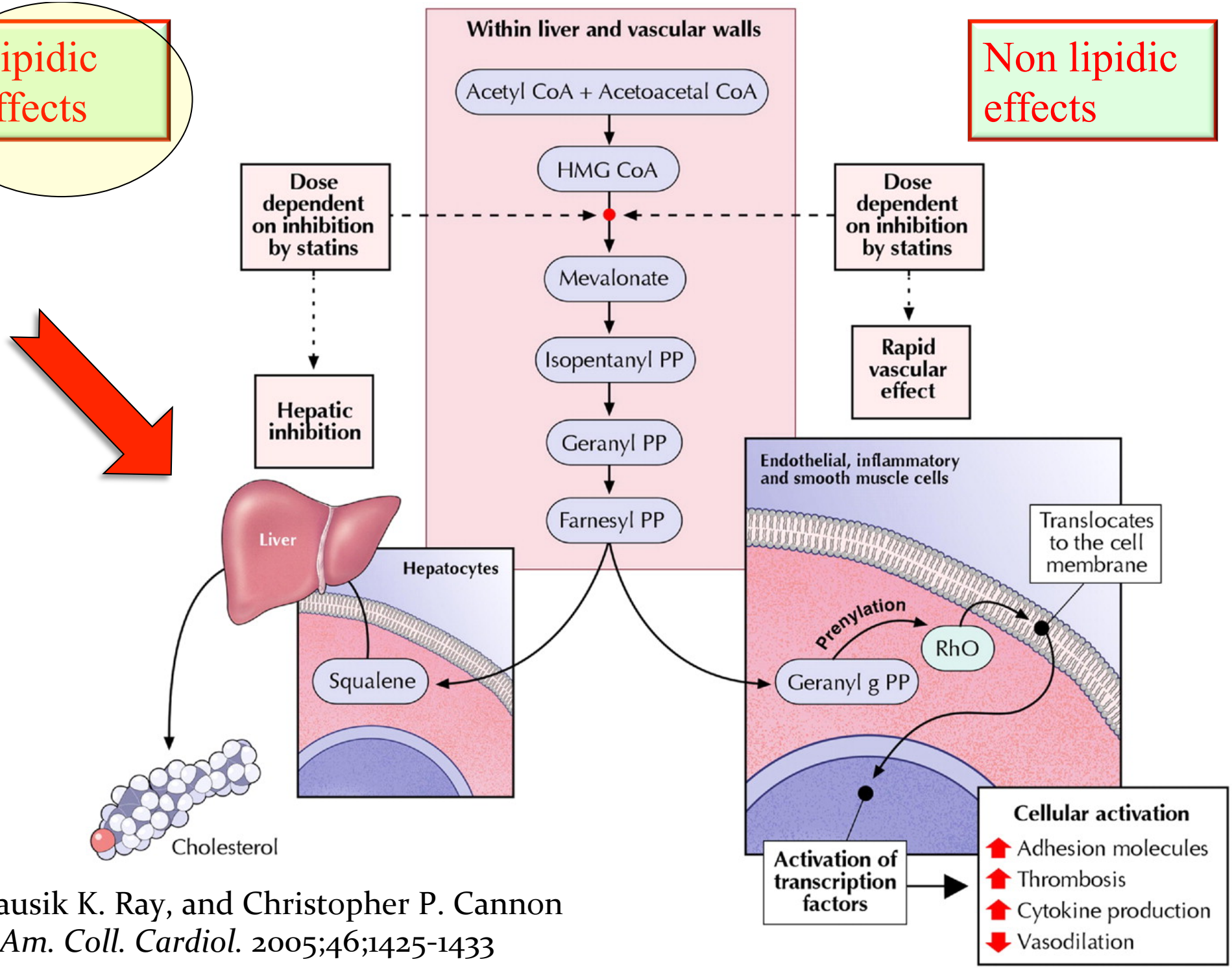
- 1957 - M. Sones: coronary angiography

- 1968 - R. Favaloro: bypass surgery

- 1977 - A. Gruentzig: PTCA

Lipidic effects

Non lipidic effects



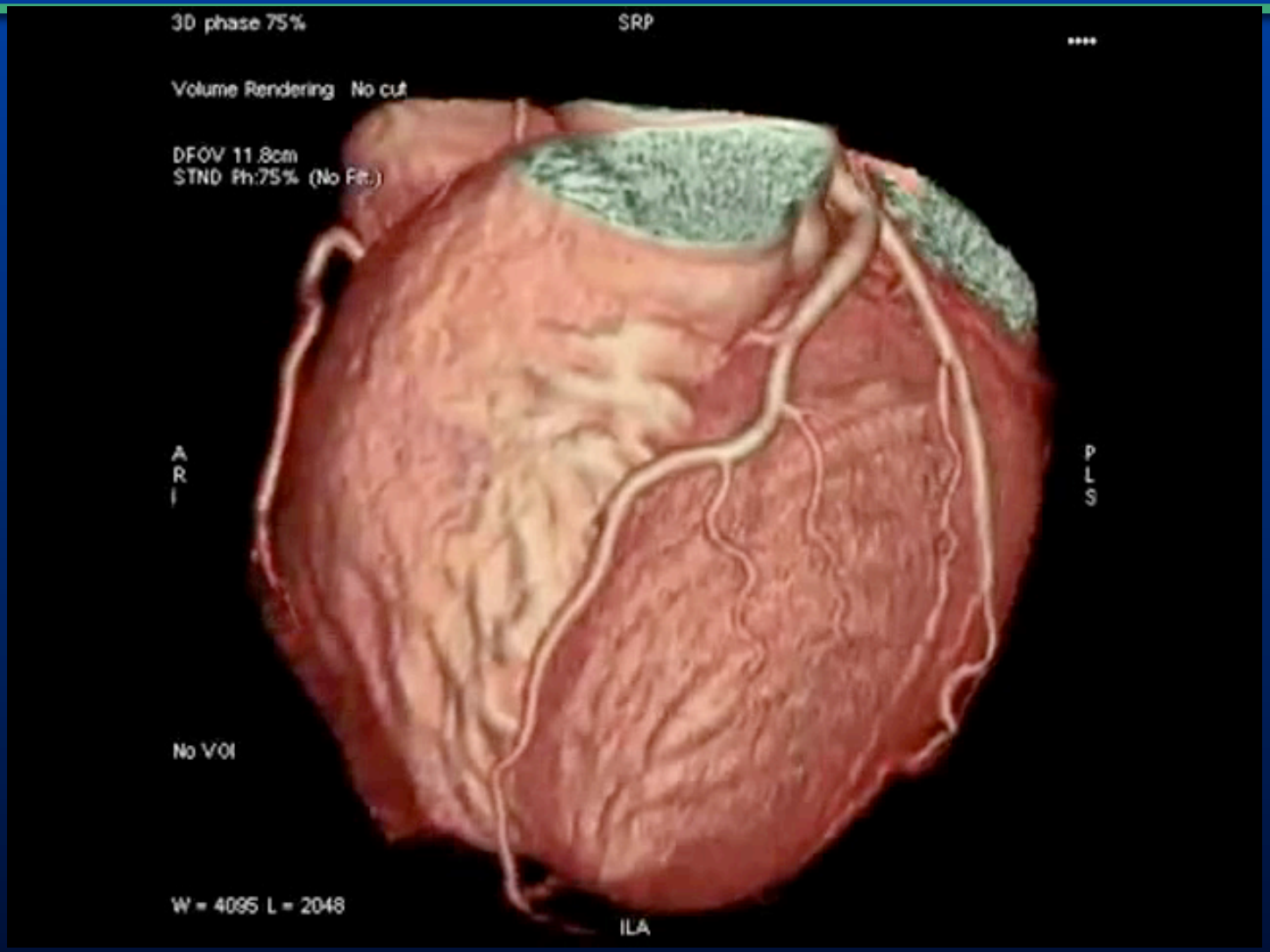
Kausik K. Ray, and Christopher P. Cannon
J. Am. Coll. Cardiol. 2005;46;1425-1433

Nobel Medicina 1985

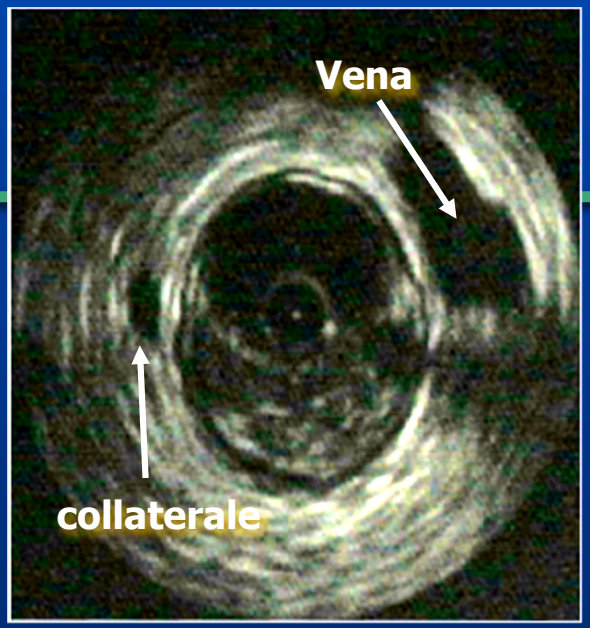
Richard Goldstein and Michael Brown

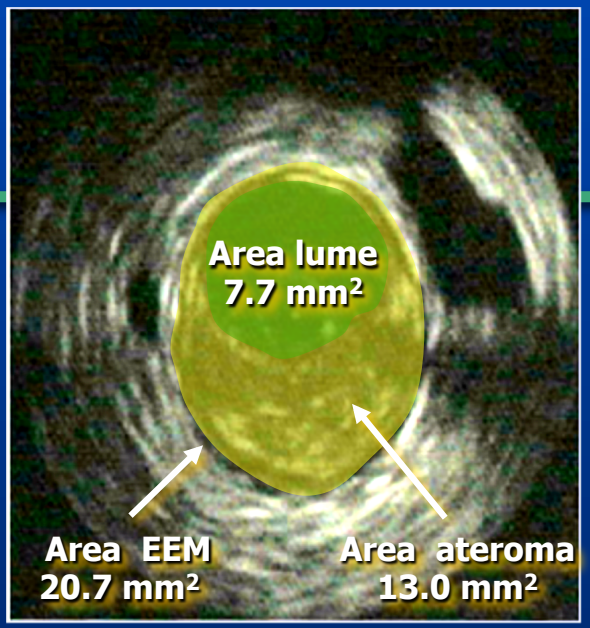
14 ottobre 1985, MIT Cambridge, Massachusetts, USA

Imaging

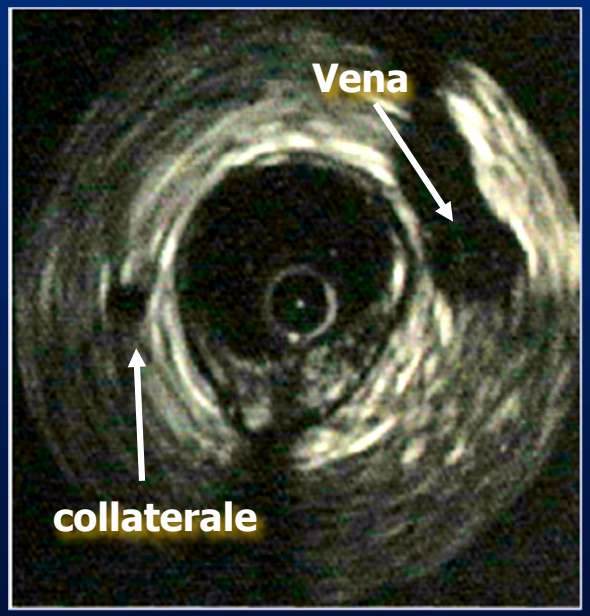


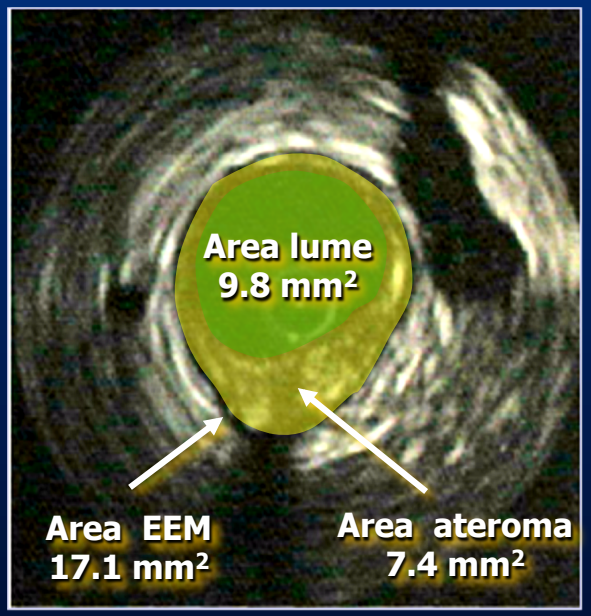
Reversal trial





Basale

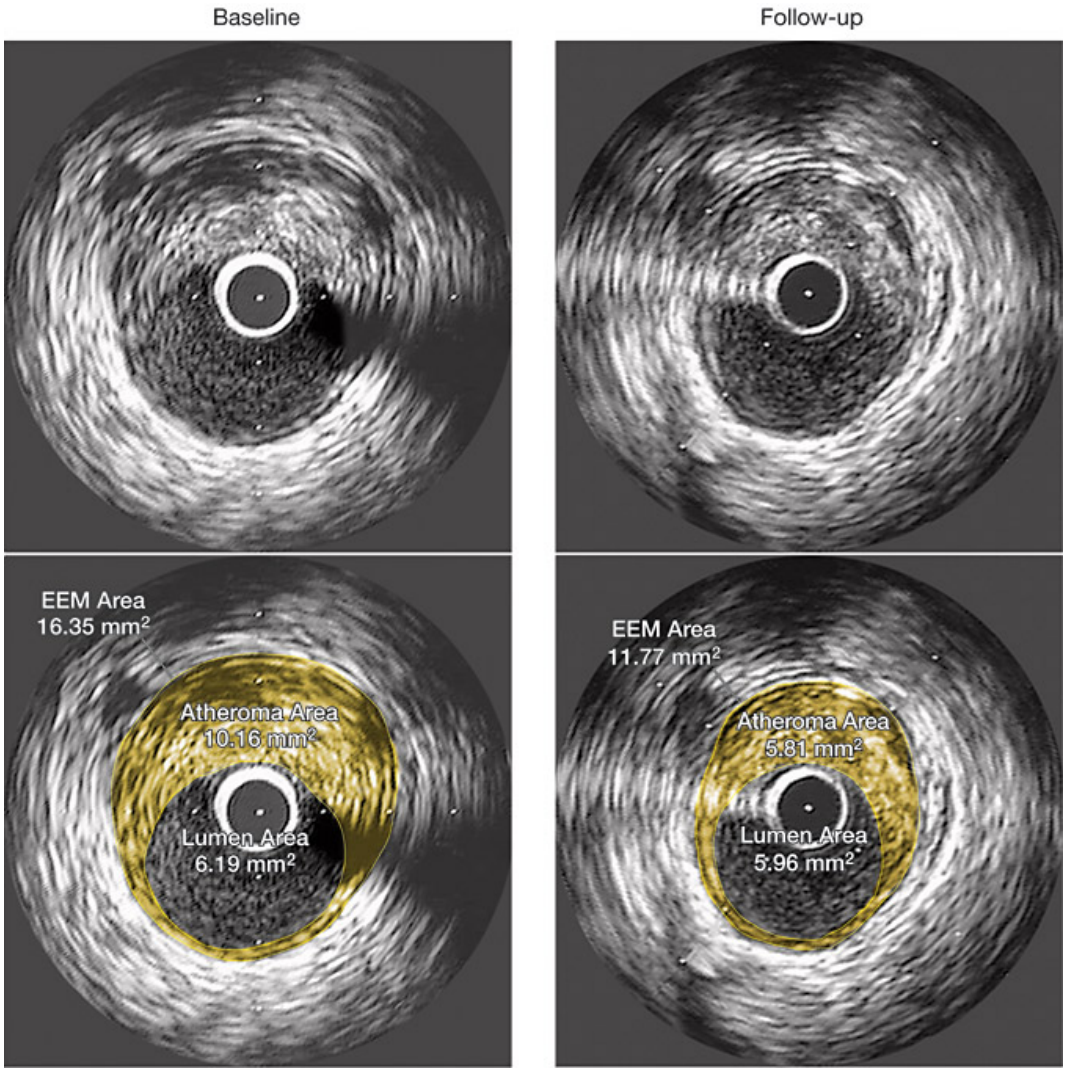




Dopo 18 mesi di trattamento

American Heart Association, Scientific sessions, Orlando; Nov. 2003
Nissen SE et al. JAMA 2004;291:1071-1080

Asteroid trial



Nissen, S. E. et al. JAMA 2006;295:1556-1565

JAMA

Table 2 **Intravascular ultrasound progression/regression studies**

Study	Design	Year	Treatment	*n*	FU	Primary endpoint	Results (mean ± SD)
Statin trials							
GAIN[58]	RCT	2001	Atorvastatin	48	12 months	Plaque volume	2.5 ± 24.9 mm^3
			Control	51			11.8 ± 31 mm^3
ESTABLISH[84]	RCT	2004	Atorvastatin	24	6 months	% Change in plaque volume	13.1 ± 12.8%
			Control	24			8.7 ± 14.9%
REVERSAL[59]	RCT	2004	Atorvastatin	253	18 months	% Change in plaque volume	4.1 ± 29.6%
			Pravastatin	249			5.4 ± 20.1%
Jensen *et al.*[85]	Non-RCT	2004	Simvastatin	40	12 months	% Change in plaque volume	6.30%
Petronio *et al.*[86]	RCT	2005	Simvastatin	36	12 months	Plaque volume	−2.5 ± 3.0 mm^3/mm
			Control	35			1.0 ± 3.0 mm^3/mm
Nishioka *et al.*[87]	Non-RCT	2004	Pravastatin, atorvastatin, simvastatin, and fluvastatin	22	6 months	Plaque Volume	30.9 ± 15.6 mm^3
			Control	26			35.5 ± 12.7 mm^3
Tani *et al.*[88]	RCT	2005	Pravastatin	52	6 months	% Change in plaque volume	−14.4 ± 23%
			Control	23			1.1 ± 4.6%
ASTEROID[89]	Non-RCT	2006	Rosuvastatin	349	24 months	Change in PAV	−0.98 ± 3.15%
Takashima *et al.*[90]	Non-RCT	2007	Pitavastatin	41	6 months	% Change in plaque volume	−10.6 ± 9.4%
			Control	41			8.1 ± 14.0%
COSMOS[91]	Non-RCT	2009	Rosuvastatin	126	18 months	Change in PAV	−5.1 ± 14.1%
JAPAN-ACS[92]	RCT	2009	Atorvastatin	127	8–12 months	% Change in plaque volume	−18.1 ± 14.2%
			Pitavastatin	125			−16.9 ± 13.9%
Hirayama	Non-RCT	2009	Atorvastatin	28	28 weeks	% Change in plaque volume	−9.4 ± 10.3%
					80 weeks		−18.9 ± 14.1%
ACAT (acyl-coenzyme A:cholesterol acyltransferase) inhibitor trials							
A-PLUS[93]	RCT	2004	Avasimibe 50 mg	108	24 months	Change in PAV	0.7 ± 0.4%
			Avasimibe 250 mg	98			0.8 ± 0.4%
			Avasimibe 750 mg	117			1.0 ± 0.3%
			Placebo	109			0.4 ± 0.4%
ACTIVATE[64]	RCT	2006	pactimibe	206	18 months	Change in PAV	0.69 ± 0.25%
			Placebo	202			−0.59 ± 0.25%
Increasing high-density lipoprotein therapies							
ApoA-I Milano[94]	RCT	2003	ApoA-I Milano 15 mg/kg	21	5 weeks	Change in PAV	−1.29 ± 3.5%
			ApoA-I Milano 45 mg/kg	15			−0.73 ± 2.8%
			Placebo	11			0.14 ± 3.09%
ERASE[62]	RCT	2007	CSL-111 (reconstituted HDL infusion)	89	4 weeks	% change in plaque volume	−3.41 (IQR, −6.55 to 2.25)
			Placebo	47			−1.62 (IQR, −5.95 to 1.94)
CART-2[95]	RCT	2008	Succinobucol (AGI-1067)	183	12 months	Absolute change in plaque volume	−3.4 ± 14.5 mm^3
			Placebo	49			−0.6 ± 13.4 mm^3

JACC 1988

High-Risk Disease Evolving into Acute Myocardial Infarction

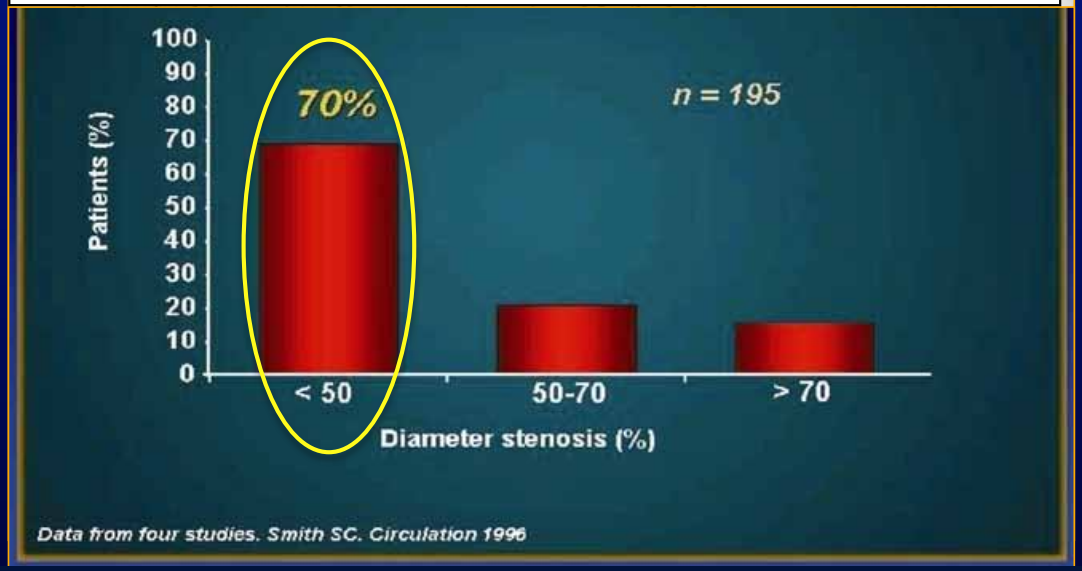
John A. Ambrose, MD

Valentin Fuster, MD, PhD

Angiographic Progression of Coronary Artery Disease and the Development of Myocardial Infarction

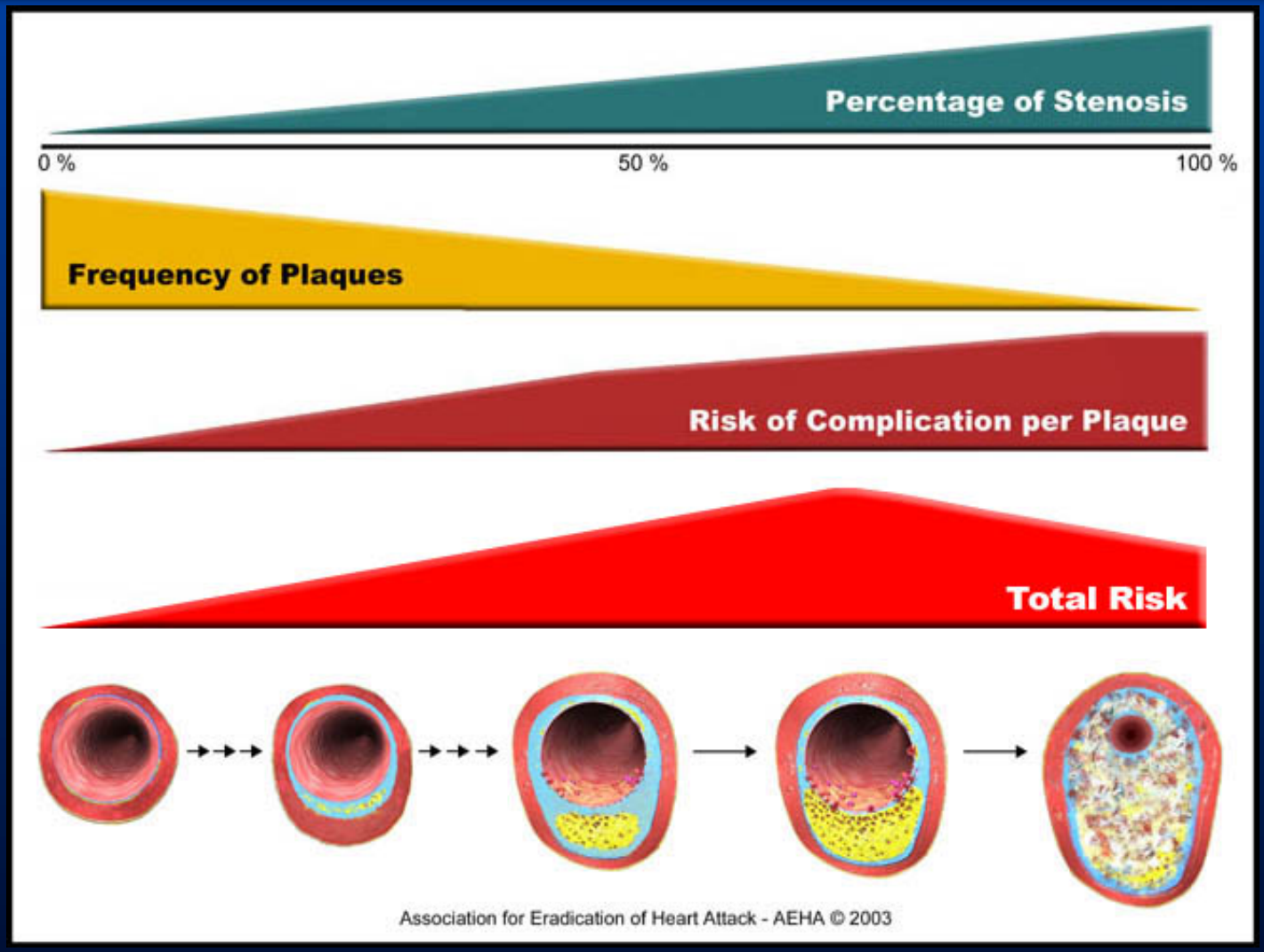
JOHN A. AMBROSE, MD, FACC, MARK A. TANNENBAUM, MD, DIMITRIOS ALEXOPOULOS, MD, CRAIG E. HJEMDAHL-MONSEN, MD,* JEFFREY LEAVY, MD, MELVIN WEISS, MD, FACC,* SUSAN BORRICO, BS, RICHARD GORLIN, MD, FACC, VALENTIN FUSTER, MD, FACC

The only **independent predictor** for progression to MI was a **proximal location** in the coronary artery



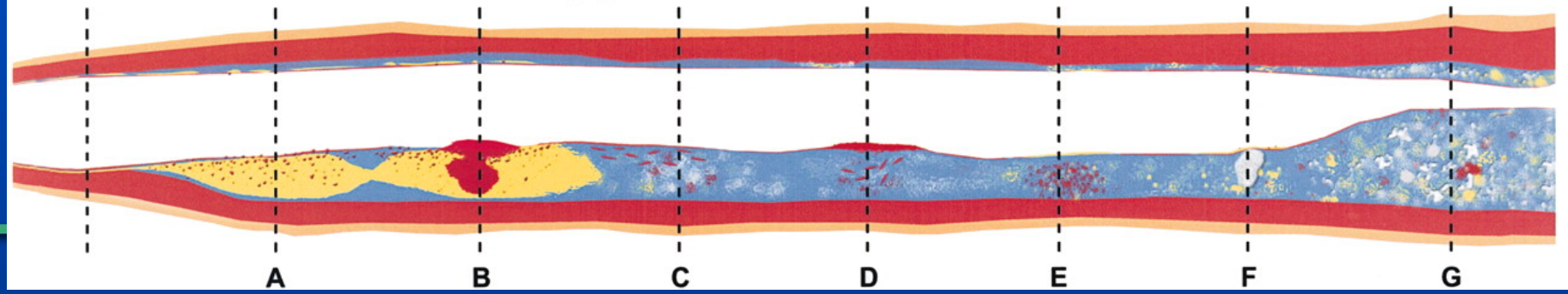
Pedro R. Moreno, Mount Sinai Medical Center, New York. ISET 2011

Non-Stenotic Vulnerable Plaques overall are More Dangerous Since they are far More Frequent than Stenotic Ones



Naghavi et al. *Circulation*. 2003;108:1664

Different Types of Vulnerable Plaque



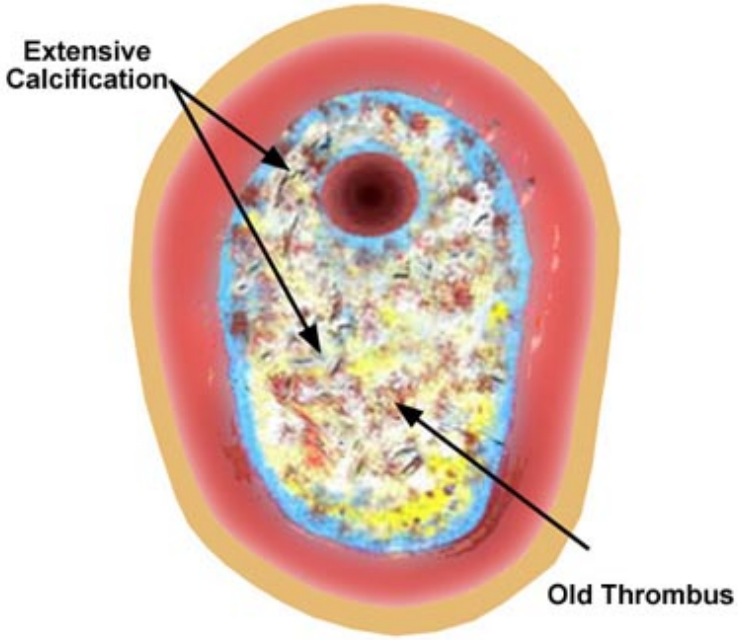
A. Rupture-prone

B. Ruptured

C. Erosion-prone

D. Eroded

The most common type



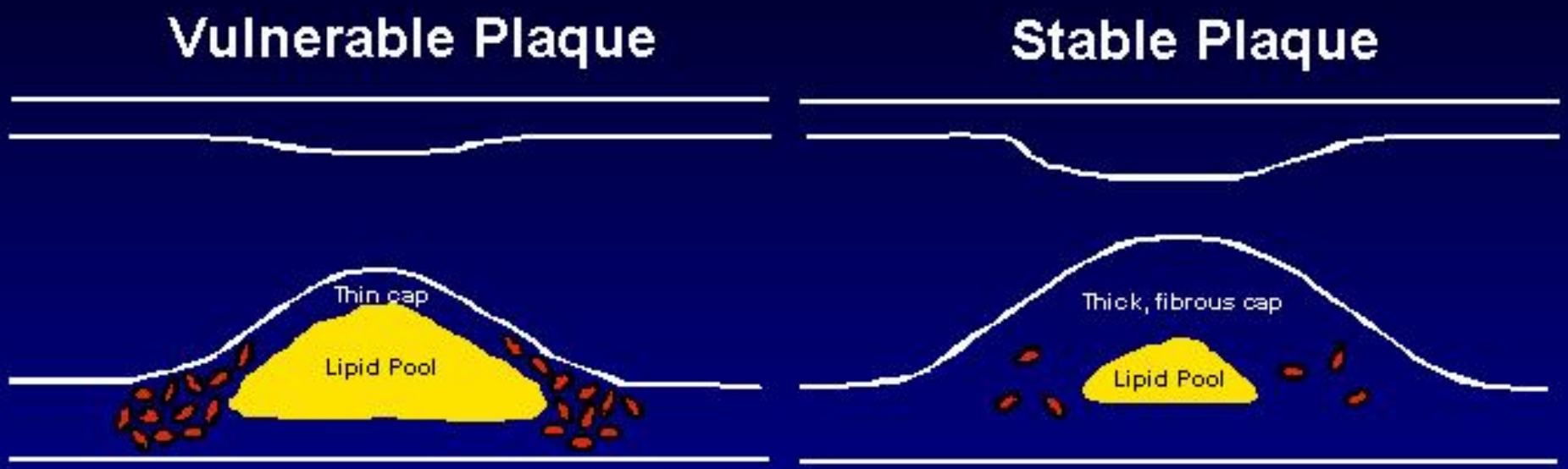
E. Ip-Hemorrhage

F. Calcified nodule

G. stenotic

Naghavi et al. *Circulation.* 2003;108:1664

Vulnerable Plaque



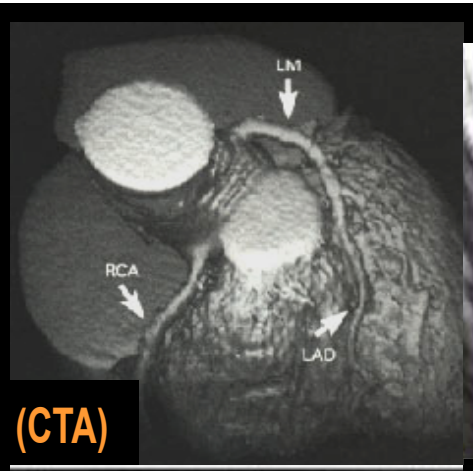
High — **Lipid conc.** — Low

Thin — **Cap** — Thick

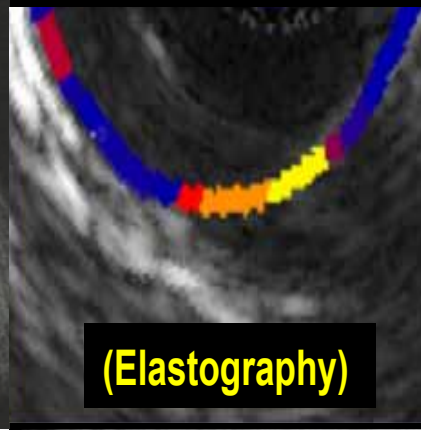
Abundant — **Macrophages** — Few

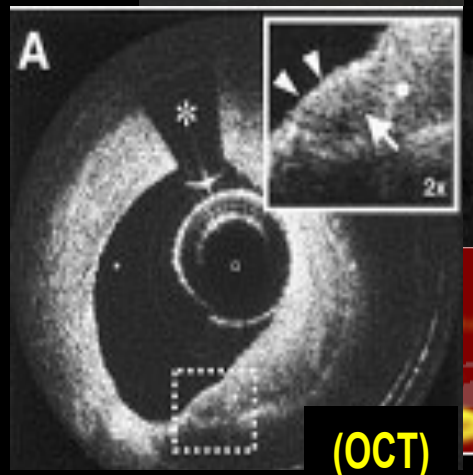
Vulnerable Plaque Imaging Detection in 2011

- 64 slice-CT Angiography (CTA)
- Optical Coherence Tomography
- Virtual Histology
- Palpography
- Near Infrared & Raman Spectroscopy
- Intravascular MRI

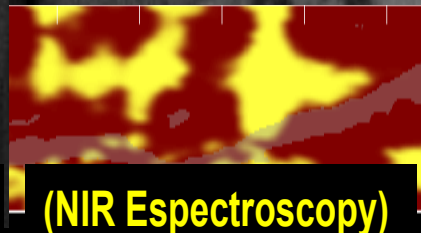


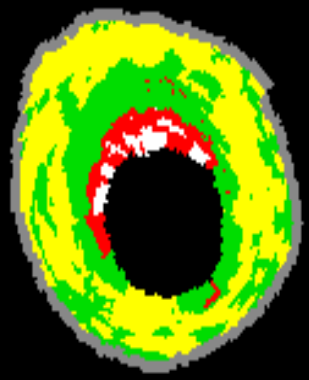
(CTA)

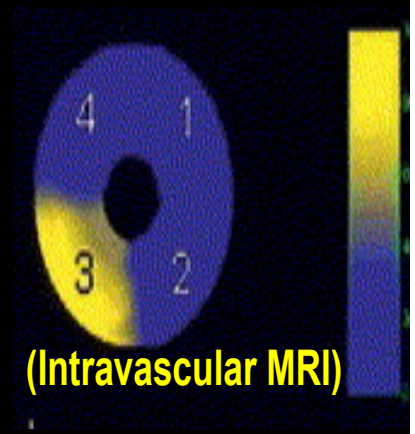

(Elastography)



(OCT)


(NIR Espectroscopy)


(VH: Virtual Histology)



(Intravascular MRI)

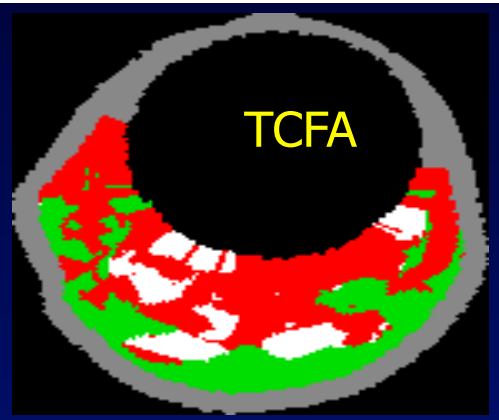
Pedro R. Moreno, Mount Sinai Medical Center, New York. At TCT 2010

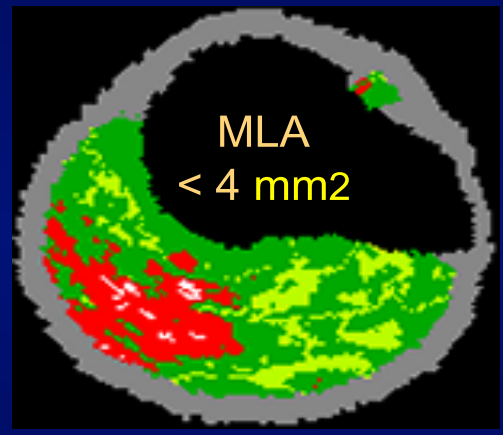
The PROSPECT trial

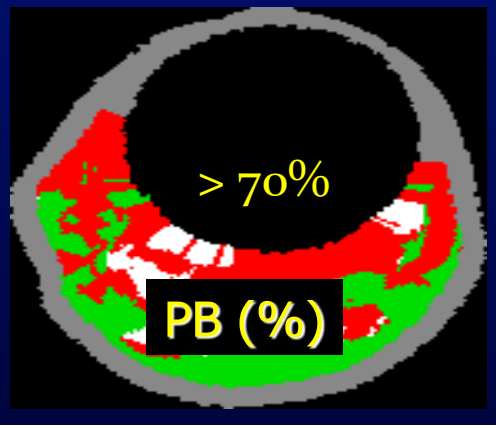
1. Thin Cap FibroAtheroma TCFA

2. Minimal Luminal Area (MLA mm^2)

3. Plaque Burden (PB-percent)

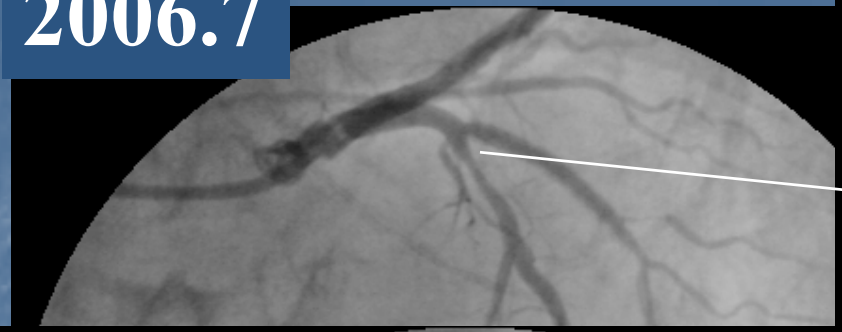


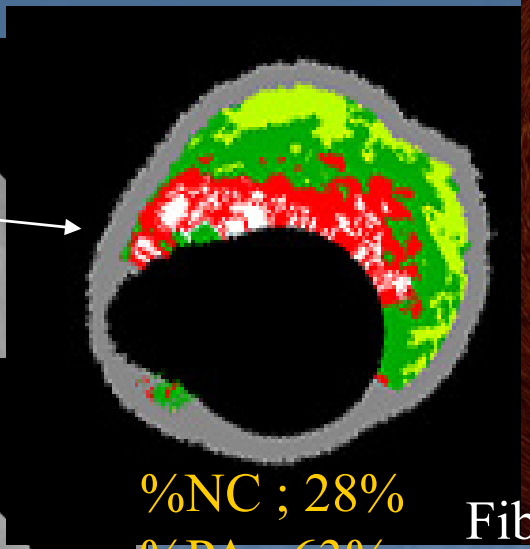




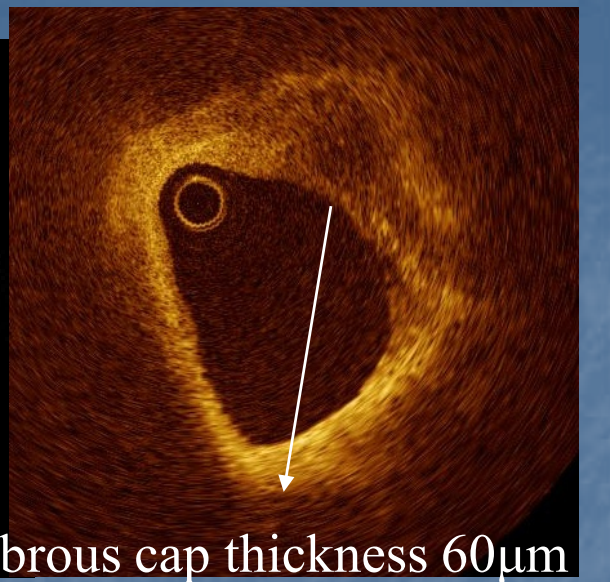
Example of TCFA caused ACS later

2006.7



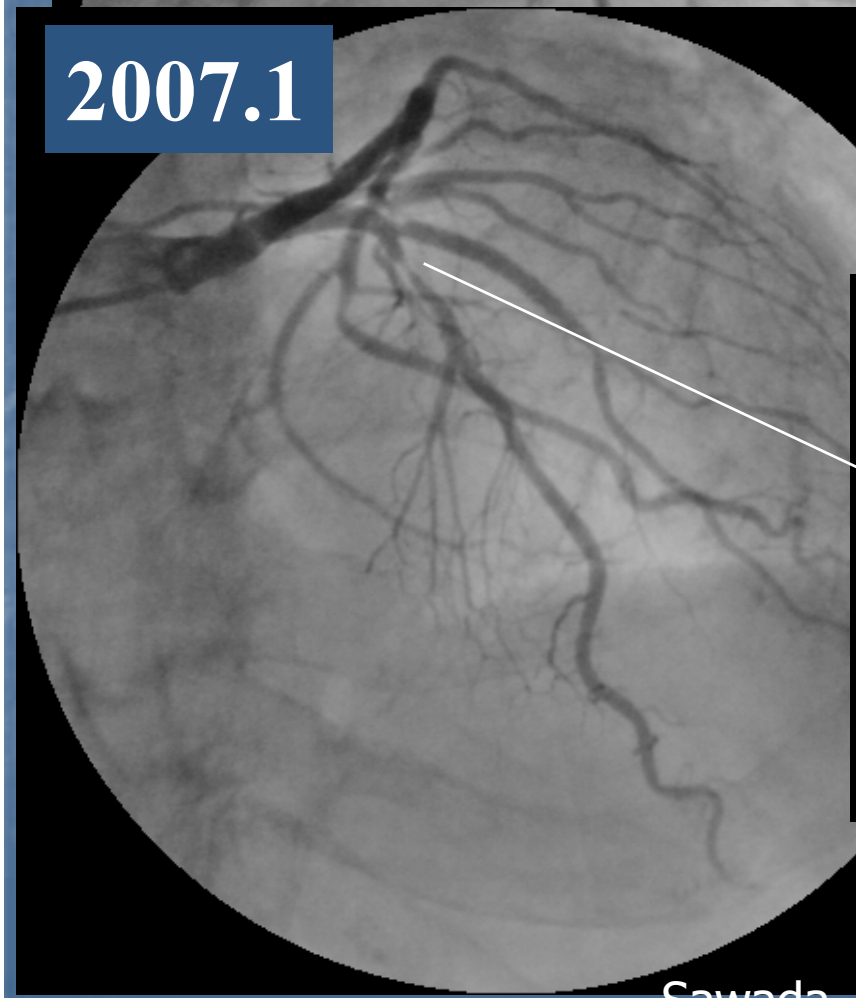


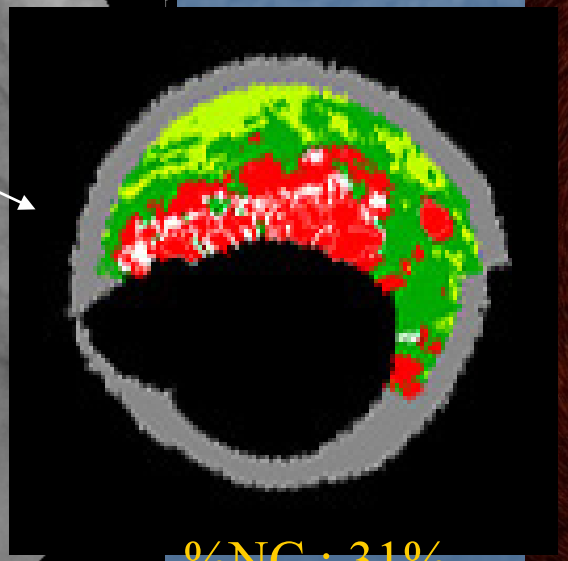
%NC ; 28%
%PA ; 63%



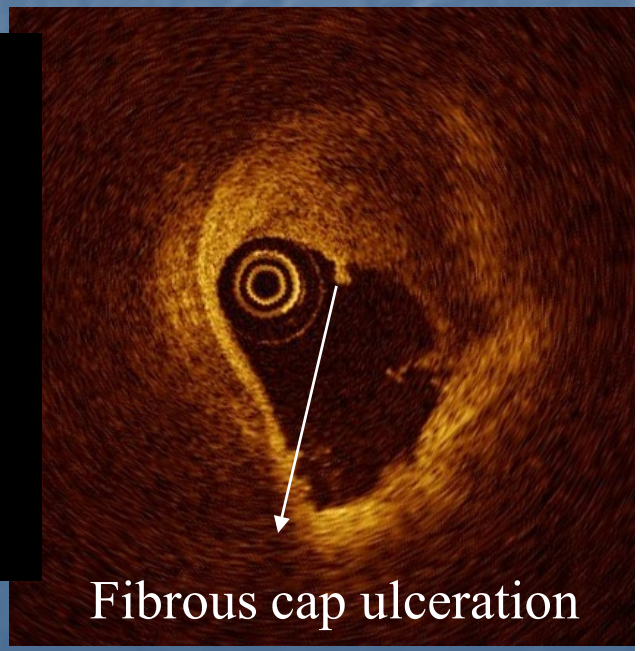
Fibrous cap thickness 60μm

2007.1





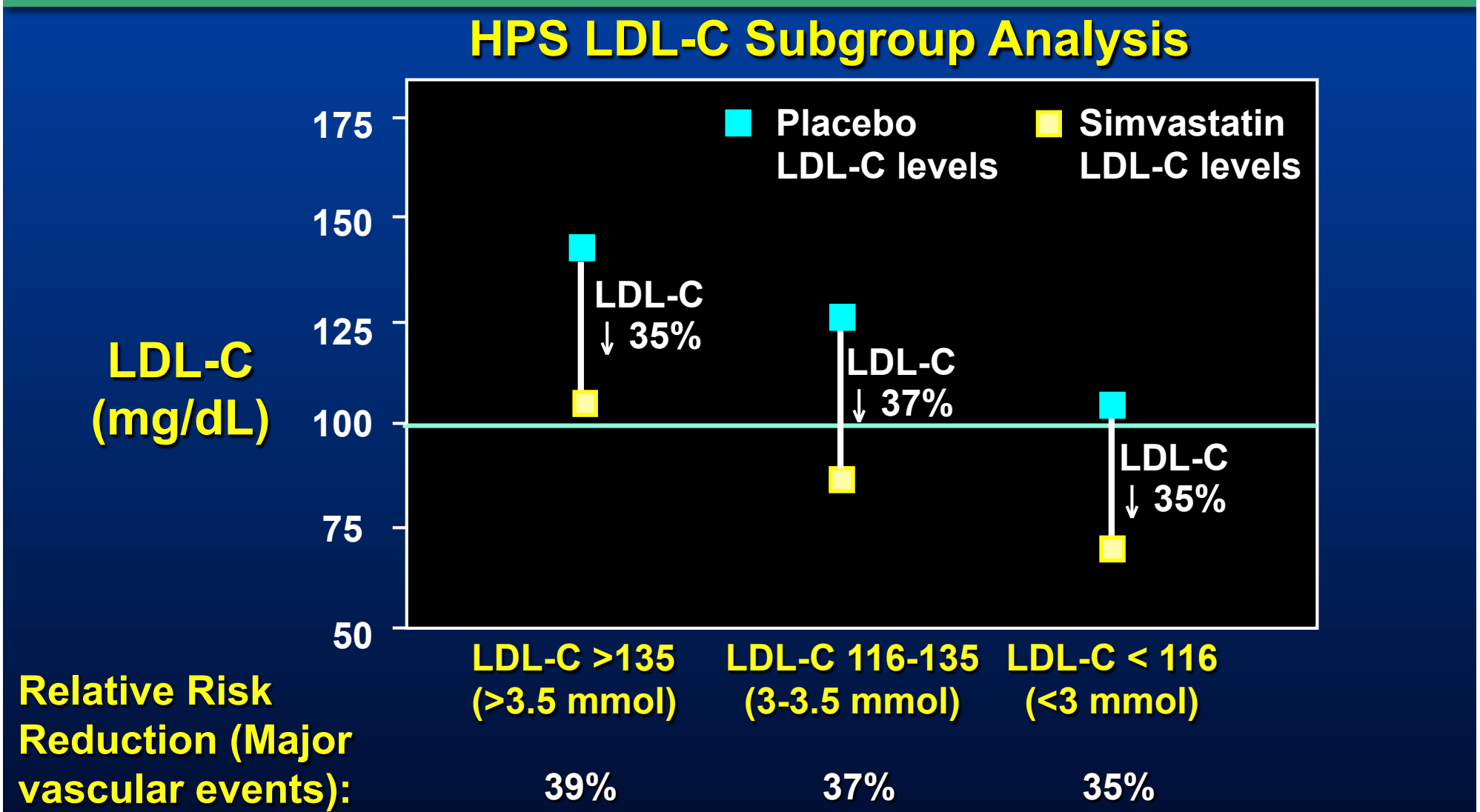
%NC ; 31%
%PA ; 74%

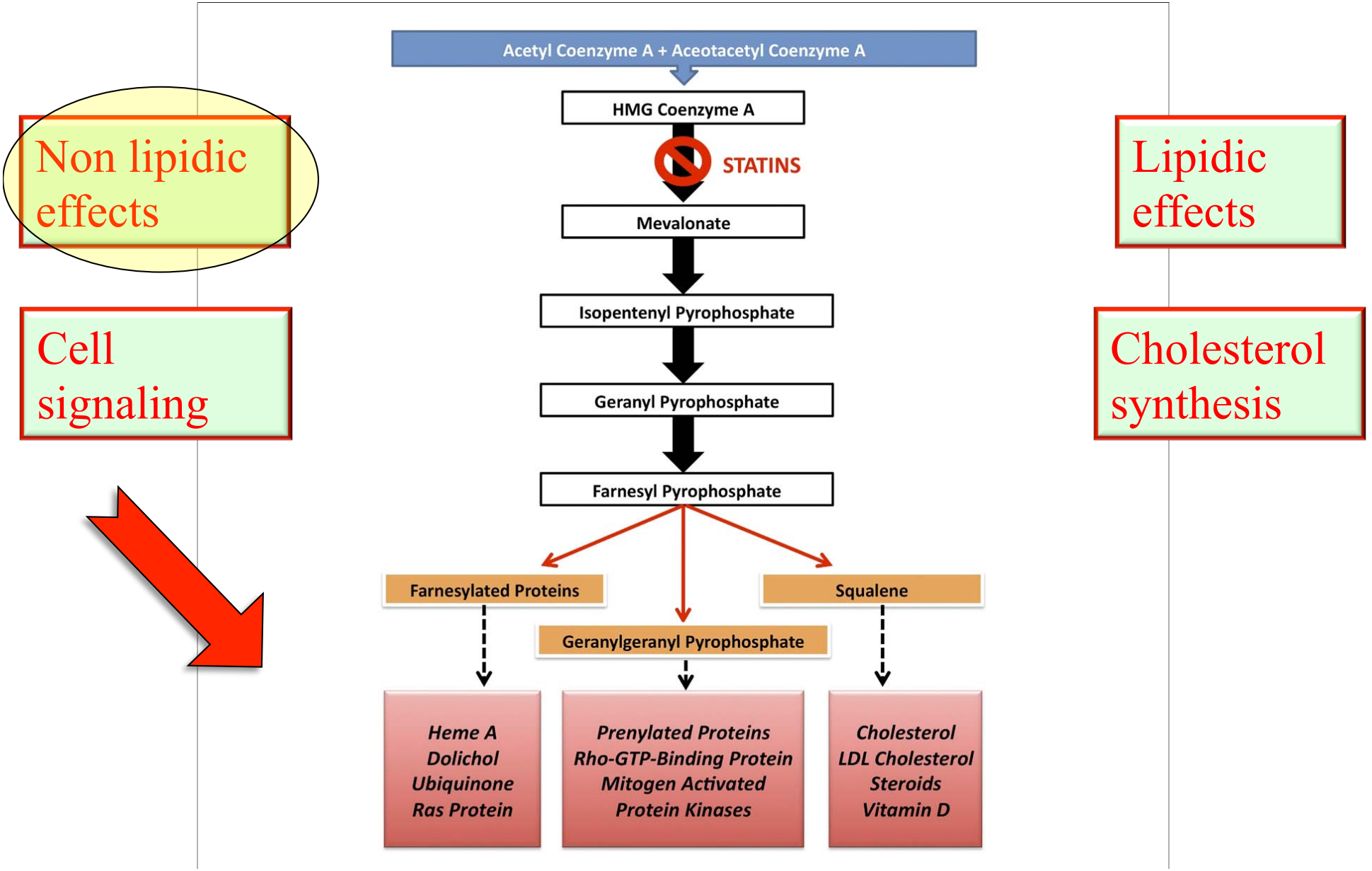


Fibrous cap ulceration

Sawada, Shite et al.European Heart J 2008; 29:1136-1146

HPS: Effects of Statin indipendent by baseline LDL-C





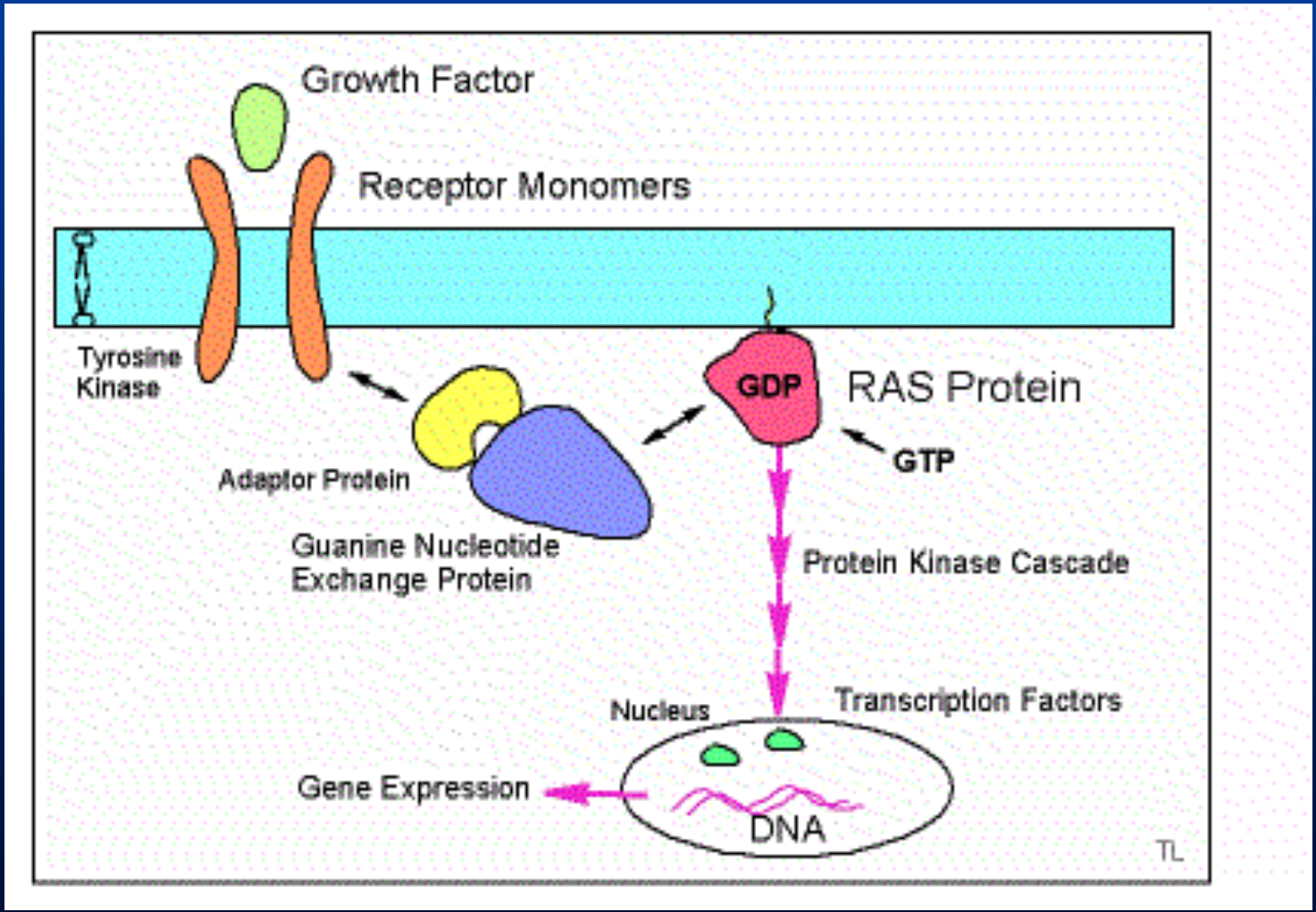
Eagle and Chopra : Statins Before Coronary Procedures

JACC, 2010 September 28, 2010:1110–2

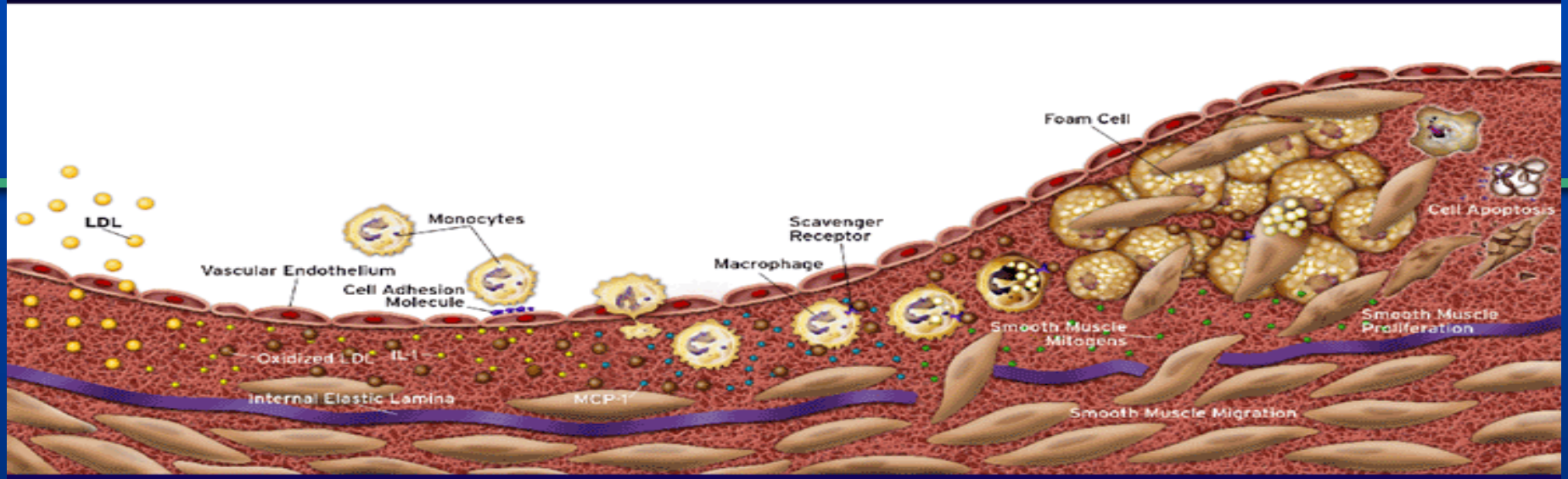
G protein: RAS

Ras acts as a molecular switch

Activation of Ras protein



Atherosclerosis is an Inflammatory Disease



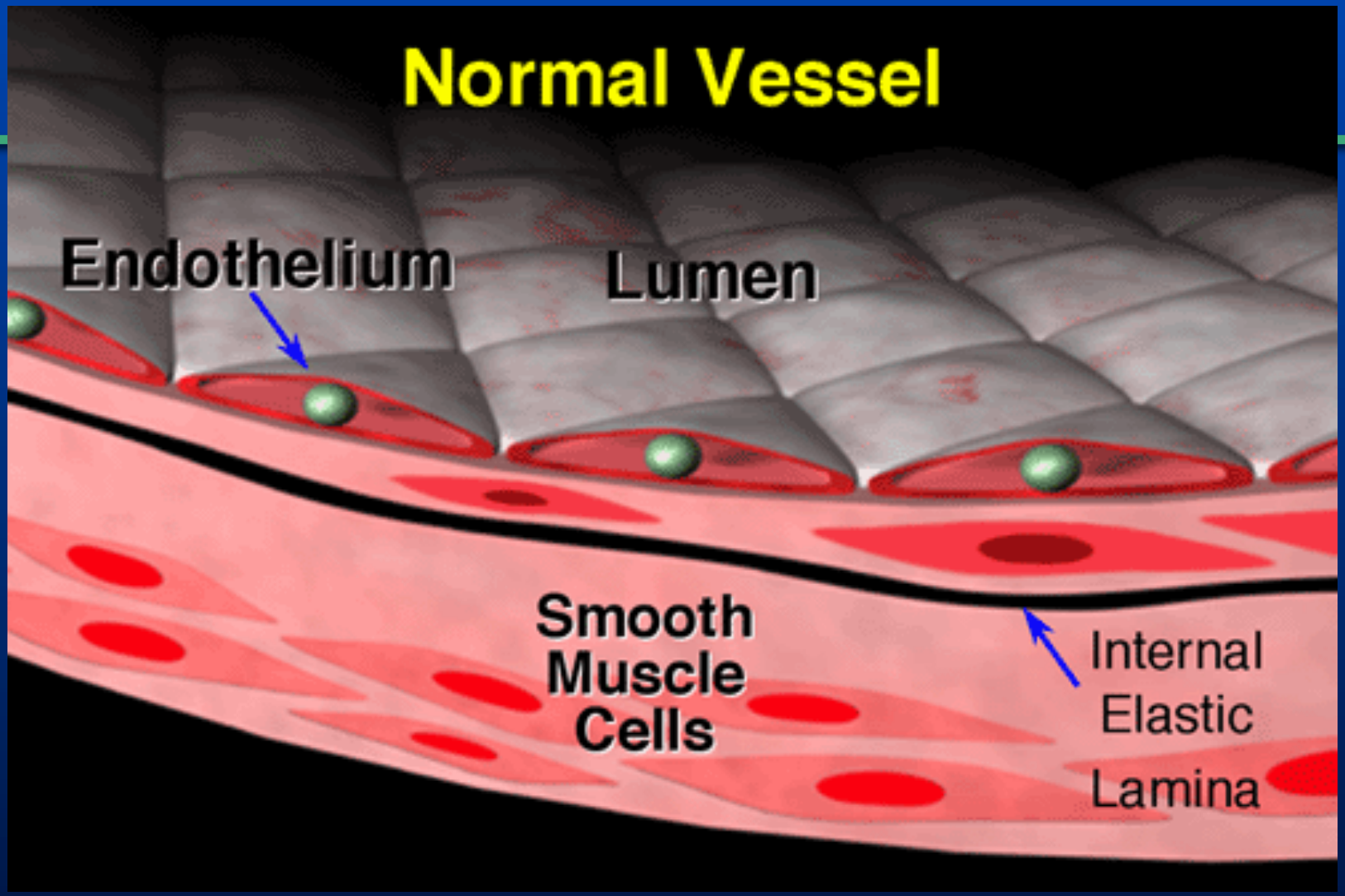
Libby, P. The Vascular Biology of Atherosclerosis.
Heart Disease (Braunwald, Zipes & Libby Eds.) 2001

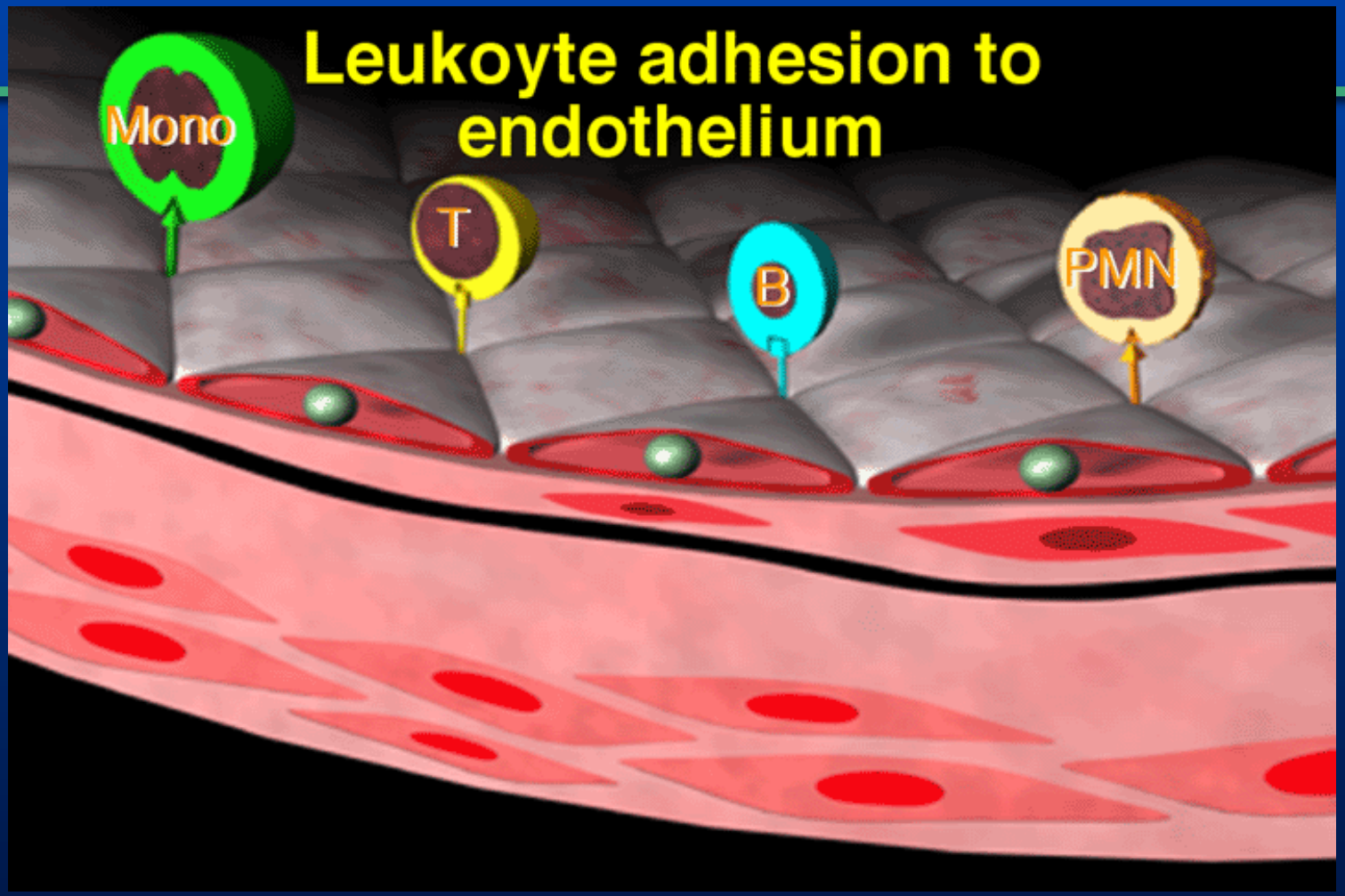
The Origins of Atherosclerosis

Peter Libby
Brigham & Women's Hospital
Harvard Medical School

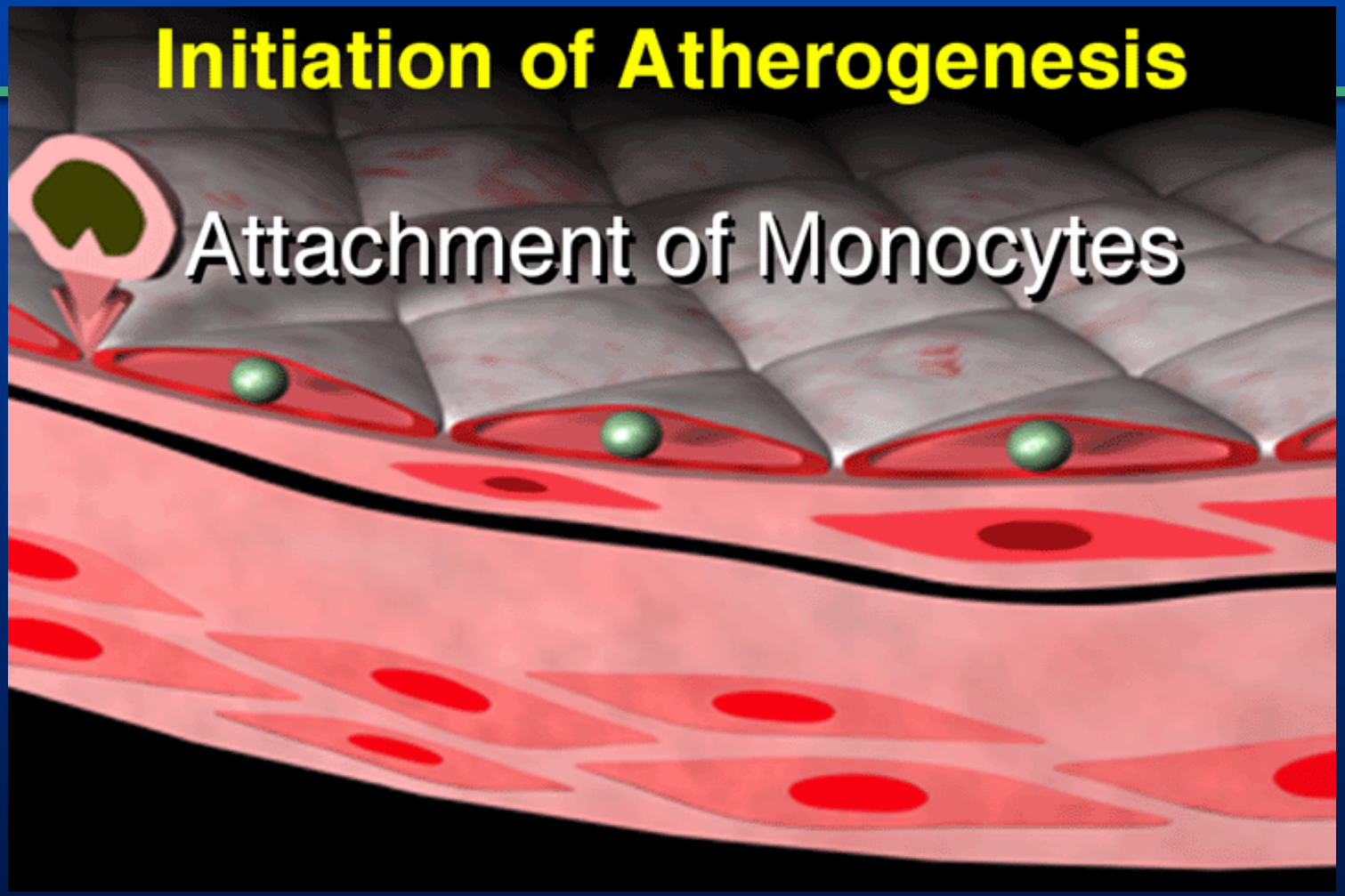
Lessons from the Lipid Legends

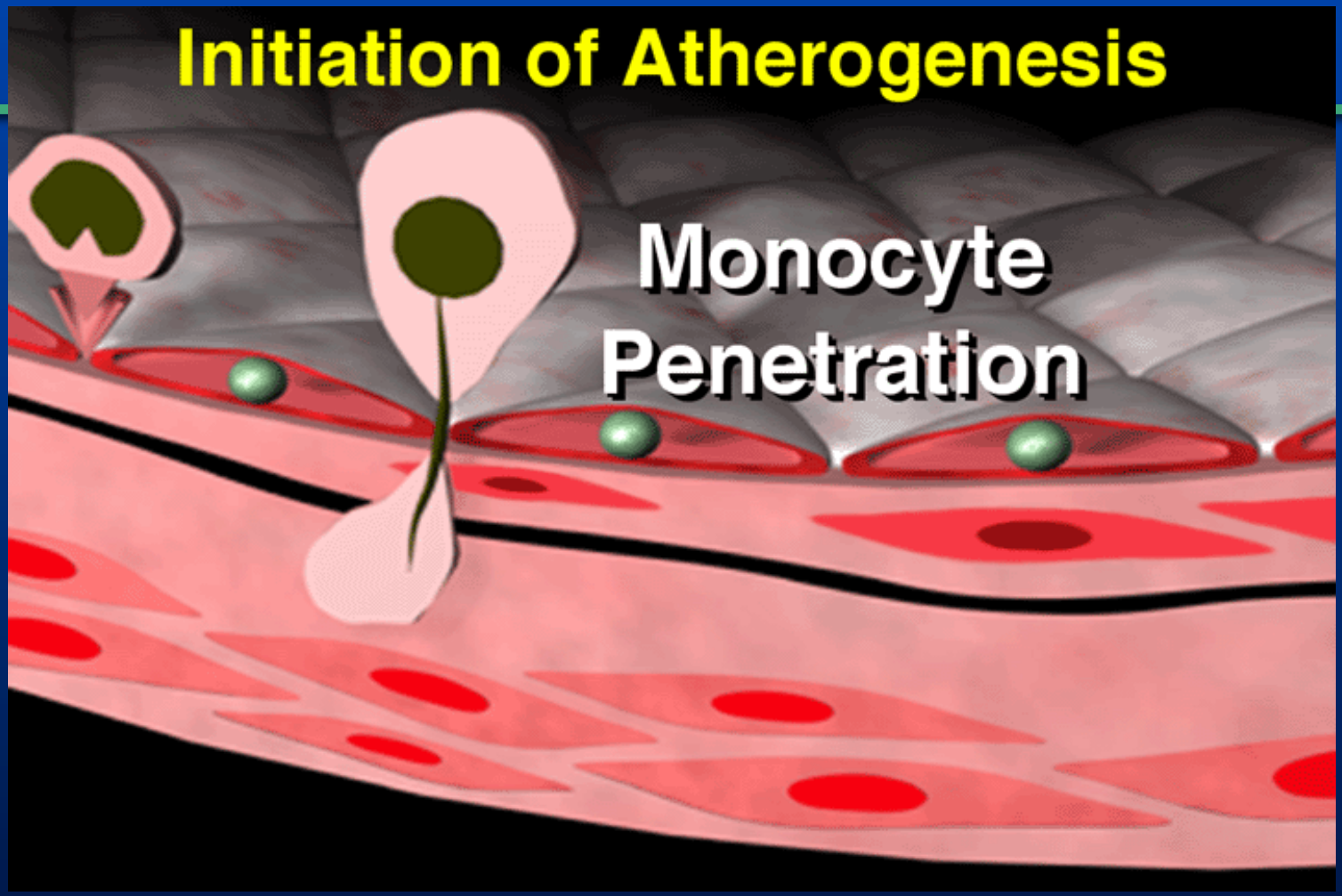
www.theheart.org 2004

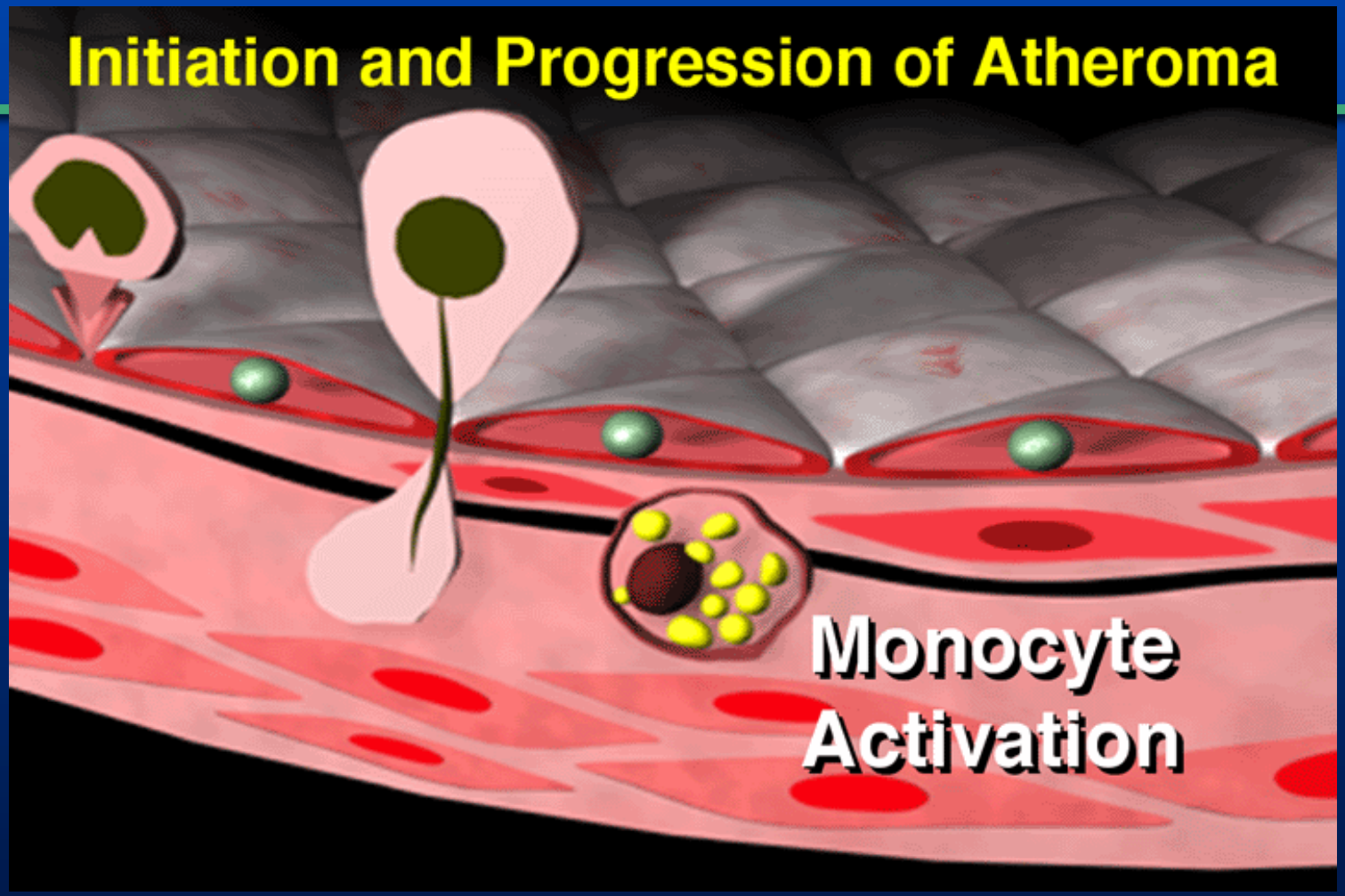


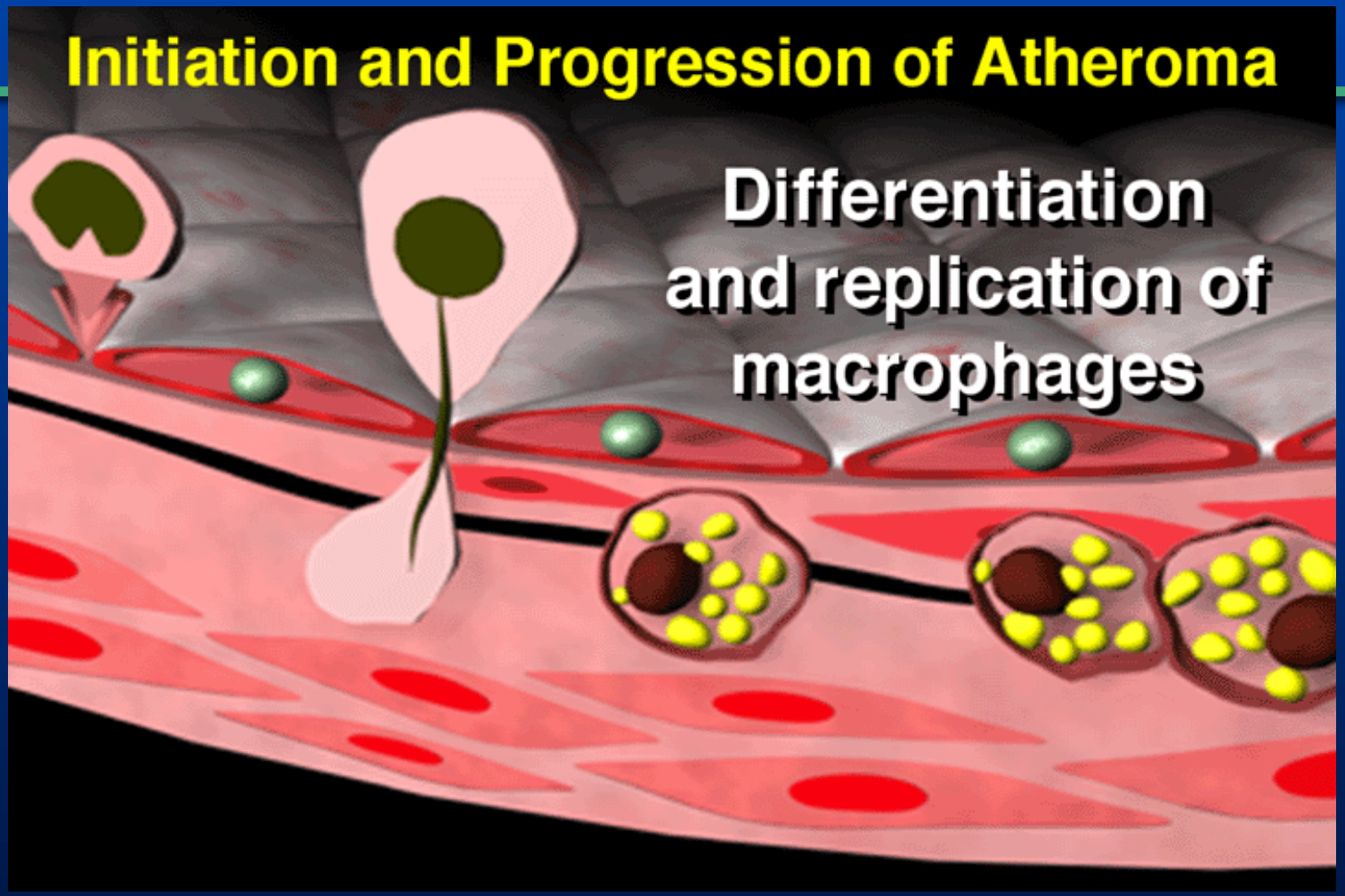


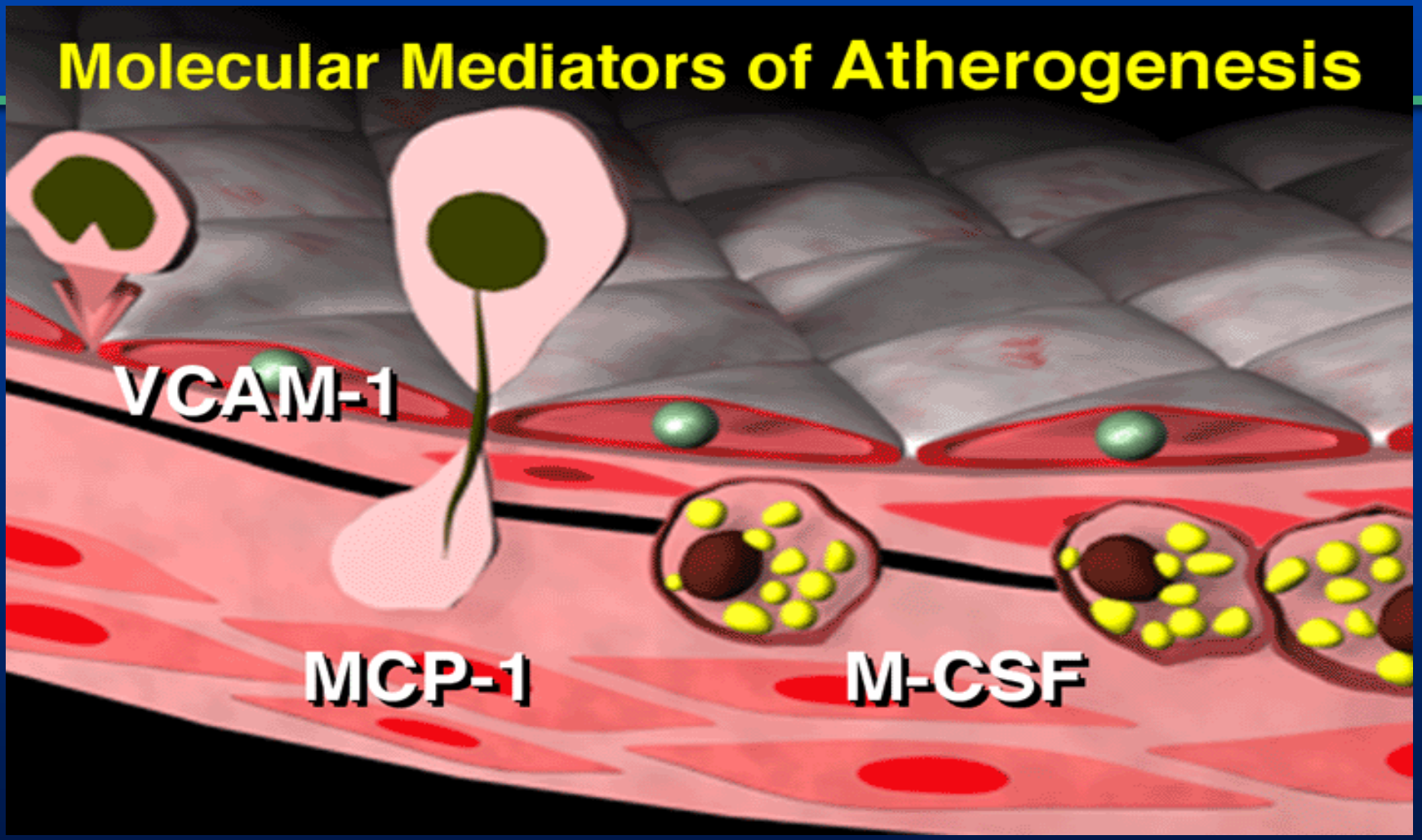
Initiation of Atherogenesis











Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 8, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.05.086

FOCUS ISSUE: PROVE IT-TIMI 22 State-of-the-Art Paper

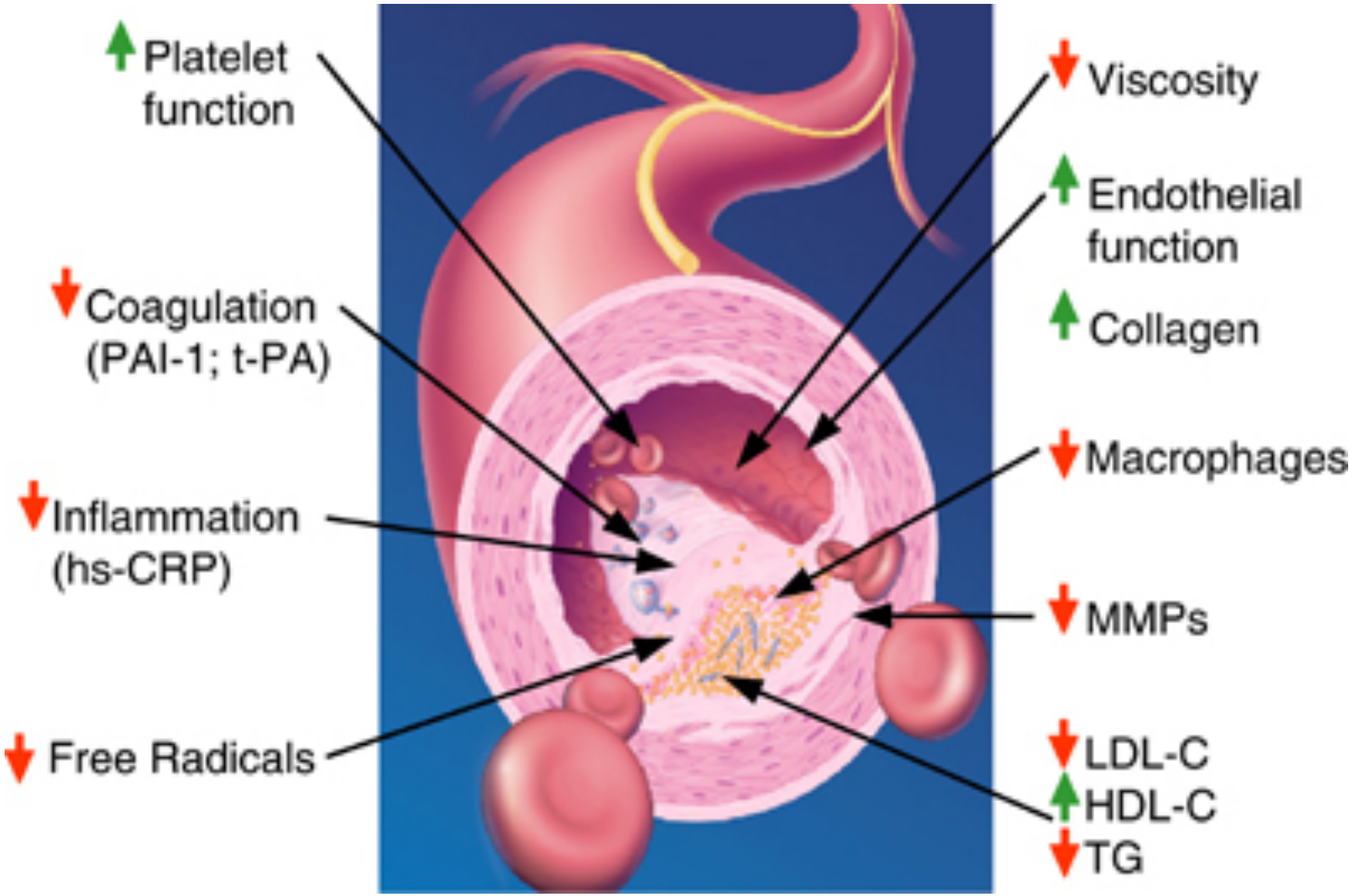
The Potential Relevance of the Multiple Lipid-Independent (Pleiotropic) Effects of Statins in the Management of Acute Coronary Syndromes

Kausik K. Ray, MRCP, MD, Christopher P. Cannon, MD, FACC
Boston, Massachusetts

Although a culprit thrombotic lesion may be treated effectively by antithrombotic therapy and revascularization, this will have little effect on the global processes that determine recurrent events at non-culprit sites.

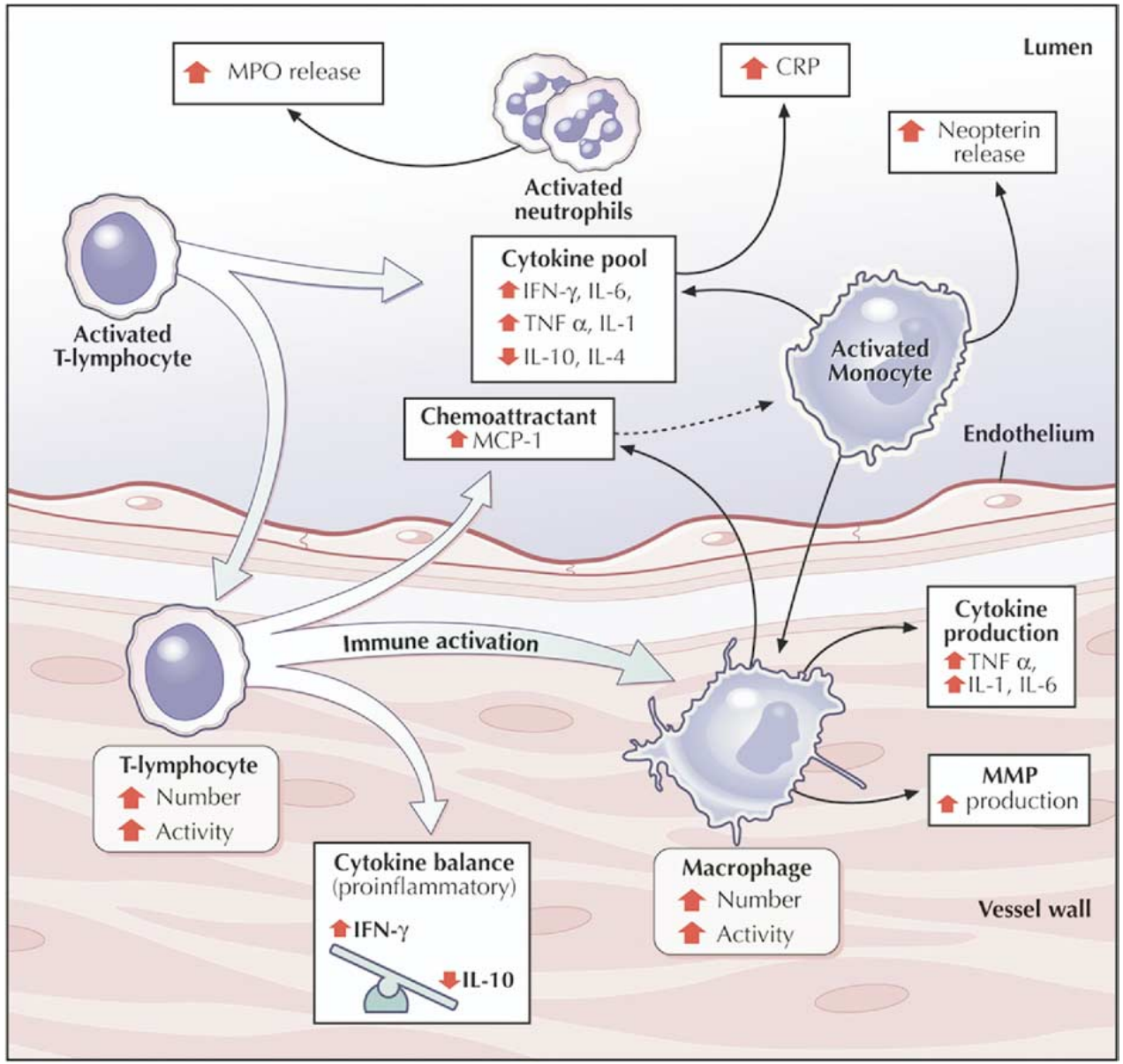
Thus, additional systemic treatment is required

Statins possess multiple beneficial effects that are independent of low-density-lipoprotein cholesterol (LDL-C) lowering and that have favorable effects on **inflammation**, the **endothelium**, and the **coagulation cascade**.



Davignon J. (2004) Beneficial cardiovascular pleiotropic effects of statins. *Circulation* **109** (Suppl III) III–39-III-43.

JACC Vol. 46, No. 8, 2005
October 18, 2005:1425–33

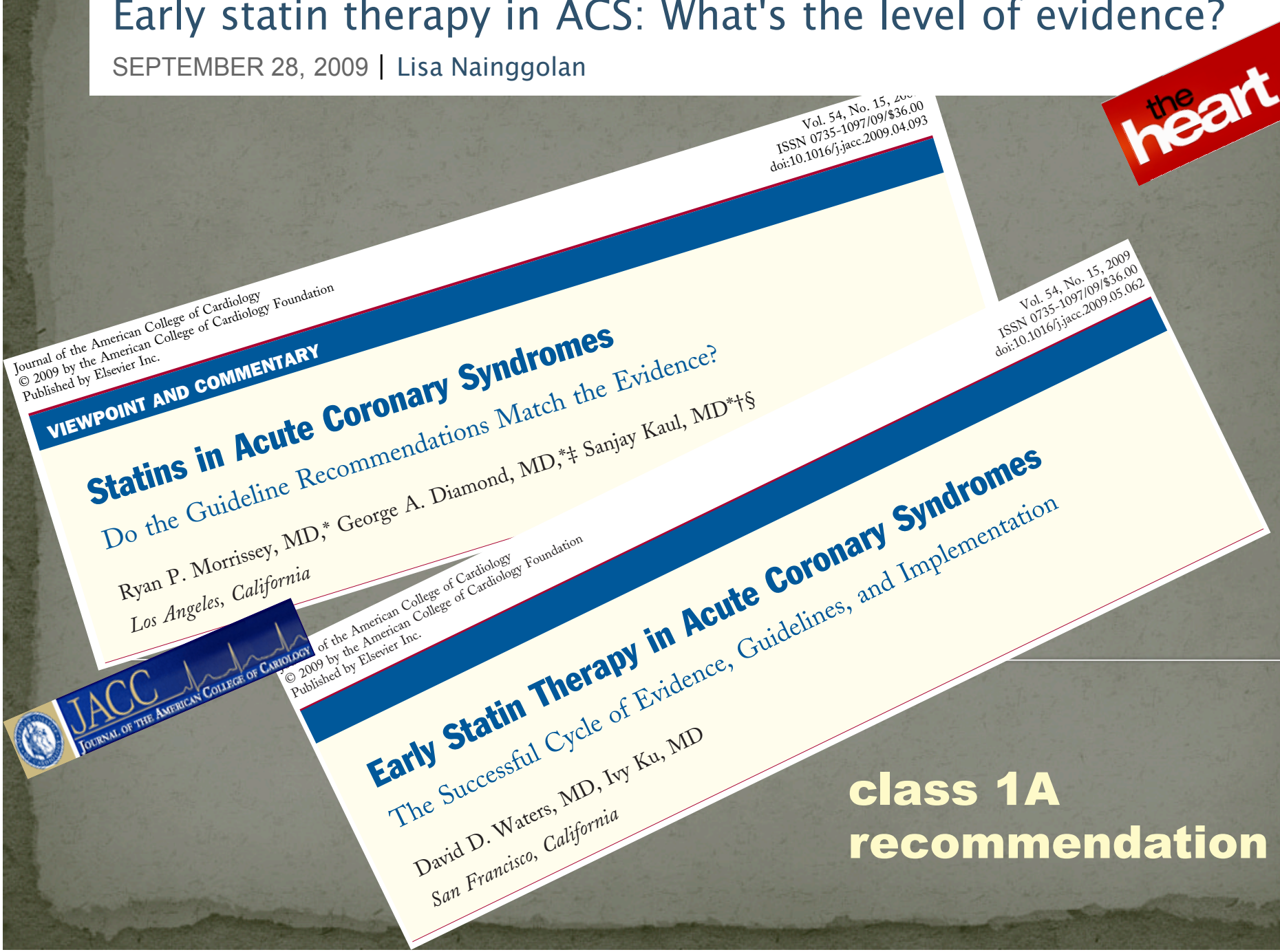


Evidenze cliniche

- Trial clinici randomizzati
- Metanalisi

Early statin therapy in ACS: What's the level of evidence?

SEPTEMBER 28, 2009 | Lisa Nainggolan



Statins early in ACS should not be a class IA recommendation

> Here we have two professional societies looking at the same evidence and coming up with different recommendations.

As substance for his argument, he points out that the European guidelines on this "are somewhat more faithful to the evidence. They say to start early, within one to four days of ACS admission, but this is given a class IB rather than a class IA recommendation, and they put their target treatment level at <100 mg/dL. For the more aggressive treatment target of 70 mg/dL, they have a class IIA, level B recommendation," he notes, adding, "This is more in line with the evidence than the American guidelines. So here we have two professional societies looking at the same evidence and coming up with different recommendations—it's open to interpretation and it becomes more of an opinion."

***Dr Sanjay Kaul**, Cedars Sinai Medical Center, Los Angeles, CA*

Their choice, to attack this recommendation from among so many easier targets, seems quixotic.

David D. Waters, MD, Ivy Ku, MD
San Francisco, California

Armyda

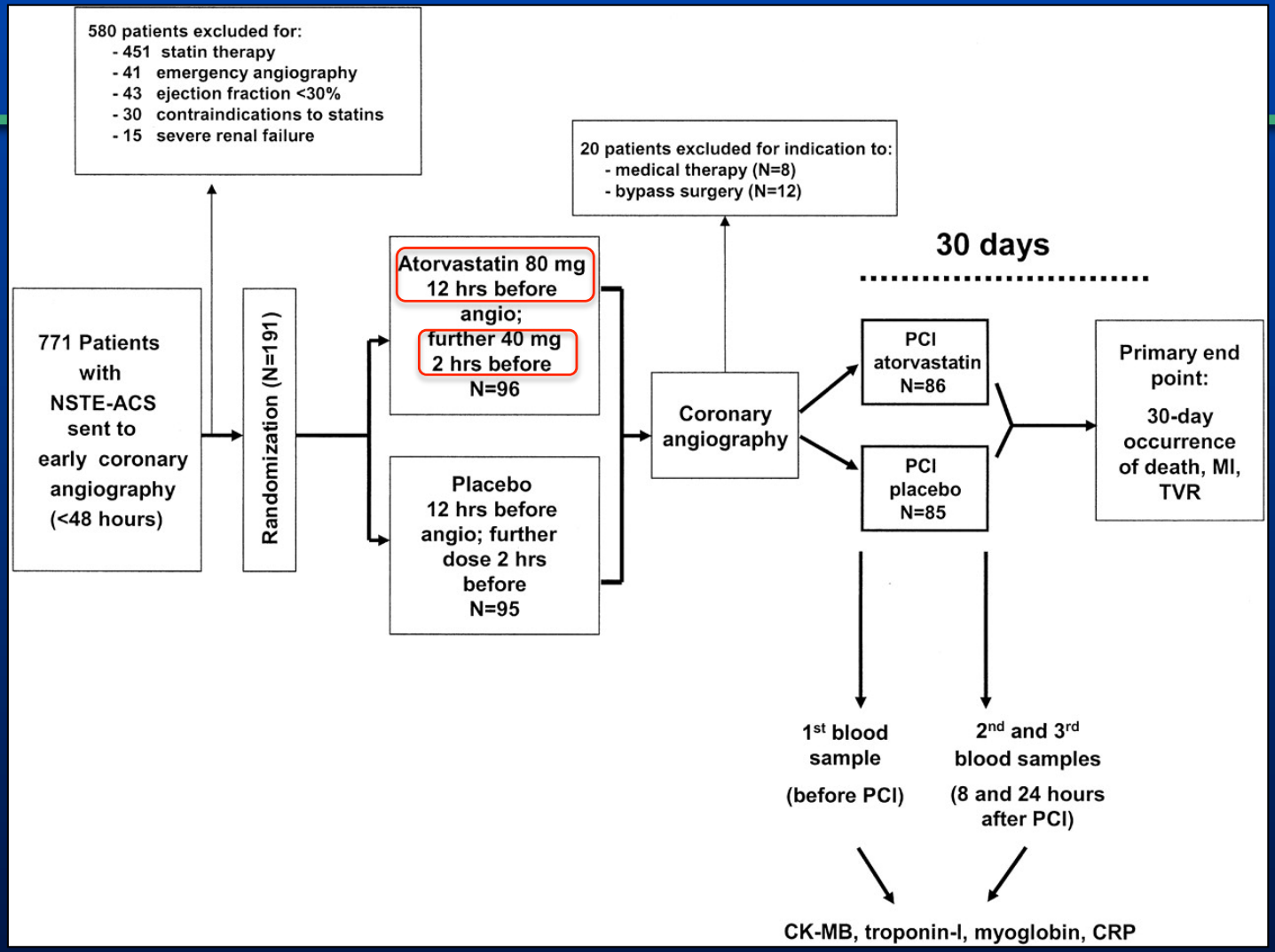
Anthony Van Dyck "Rinaldo e Armida" 1628-1629

Olio su tela, 236.5x224 cm. (particolare) Museum of Art. Baltimore, U.S.A.

Armyda

RCT	year	n° pts	Pts population	atorvastatin
Armyda	2004	153	Stable angina	40
Armyda-ACS	2007	171	NSTE ACS	80 + 40
Armyda Recapture	2009	383	Stable + NSTE ACS	80 + 40

Study Design of the ARMYDA-ACS Trial



Patti, G. et al. J Am Coll Cardiol 2007;49:1272-1278

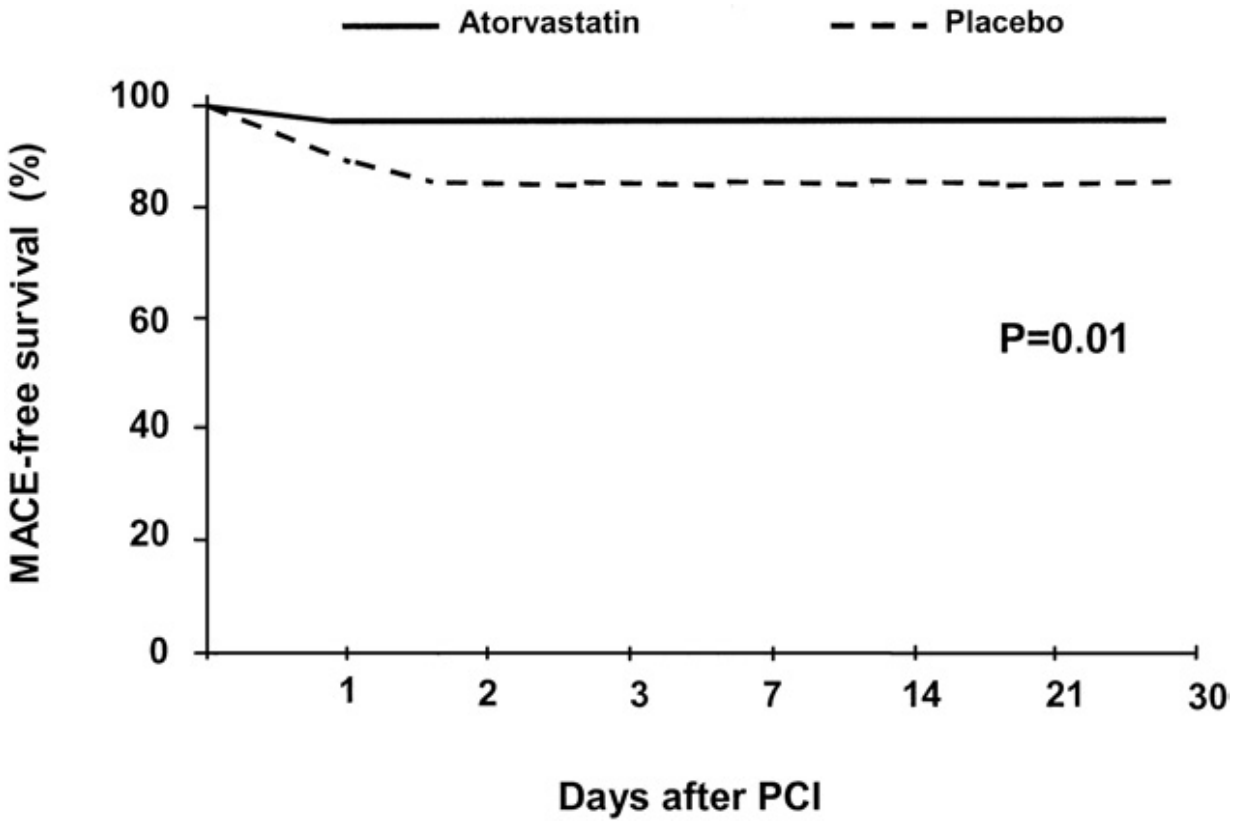
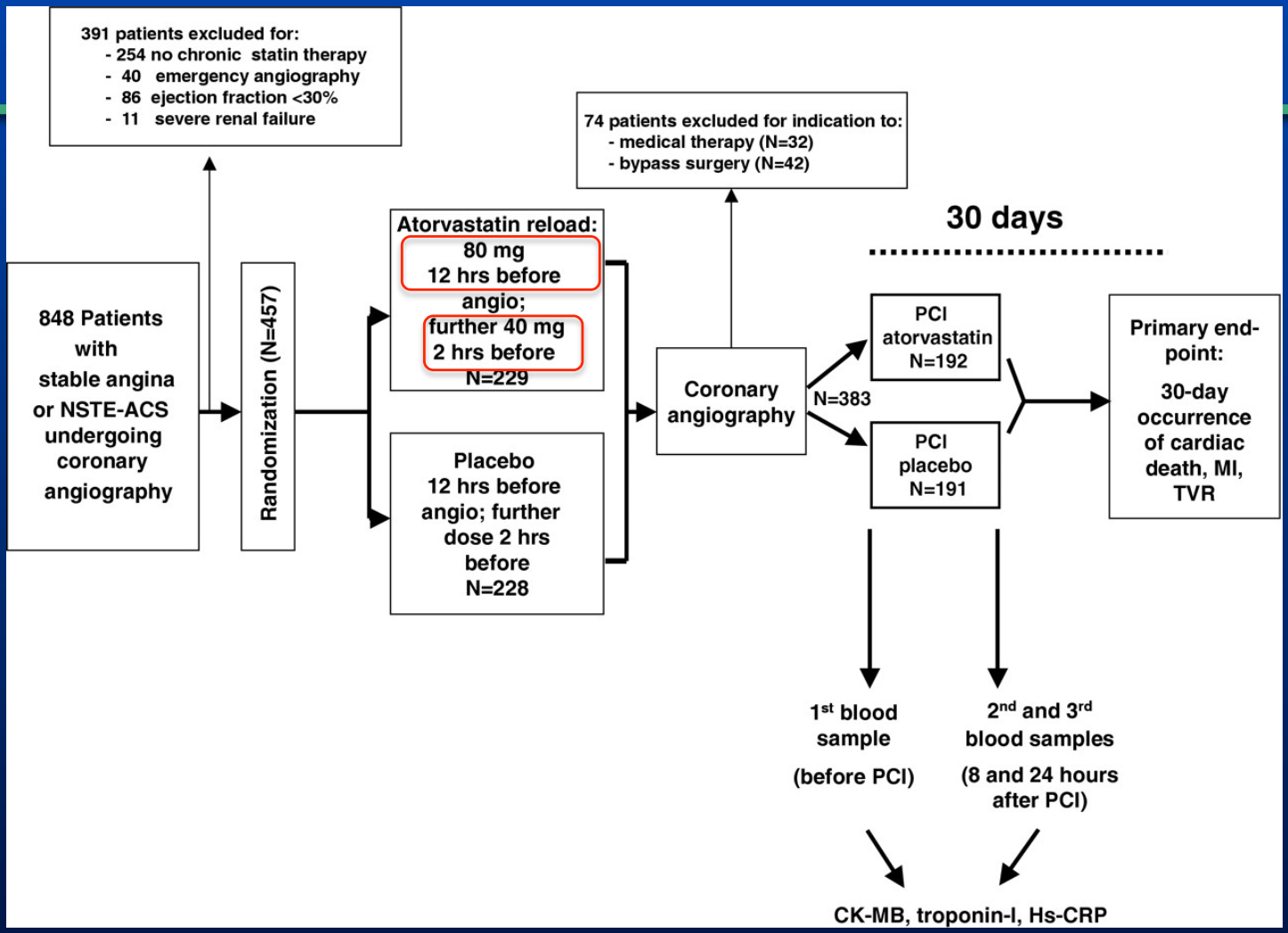


Figure 2 **ARMYDA-ACS Survival Curves**

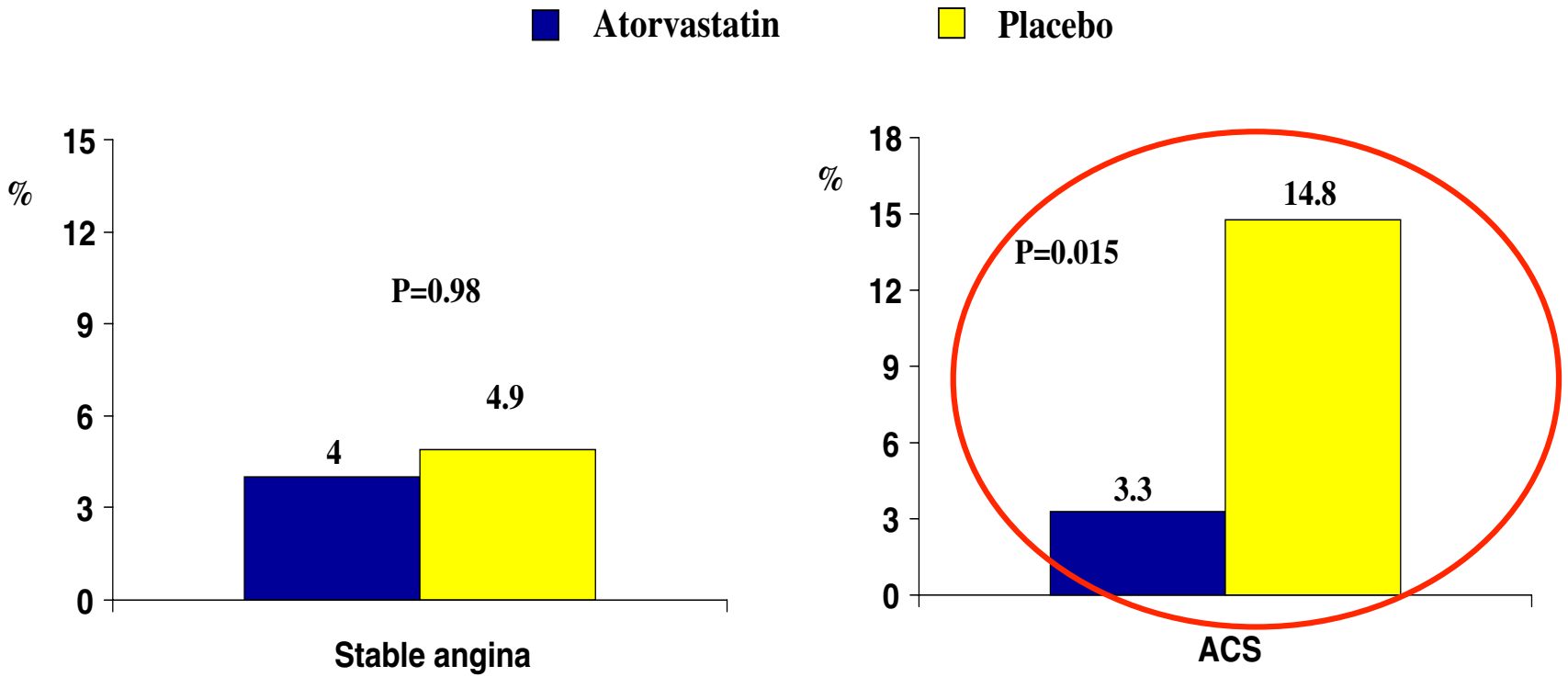
Actuarial curves of 30-day major adverse cardiac event (MACE)-free survival in the 2 arms. PCI = percutaneous coronary intervention.

Study Design of the ARMYDA-RECAPTURE Trial



Di Sciascio, G. et al. J Am Coll Cardiol 2009;54:558-565

Armyda Recapture



Conclusions The ARMYDA-RECAPTURE trial suggests that reloading with high-dose atorvastatin improves the clinical outcome of patients on chronic statin therapy undergoing PCI. These findings may support a strategy of routine reload with high-dose atorvastatin early before intervention even in the background of chronic therapy. (J Am Coll Cardiol 2009;54:558–65) © 2009 by the American College of Cardiology Foundation

ROsuvastatin Pretreatment in PatientsUndergoing Elective Pci To Reduce The Incidence of MyocArdial Periprocedural Necrosis -ROMA trial- *(NCT01007279)*

G. SARDELLA MD,FACC,FESC

O.U.of Invasive Cardiology
Department of Cardiovascular and Pulmonary Sciences
Policlinico Umberto I
"Sapienza" University of Rome

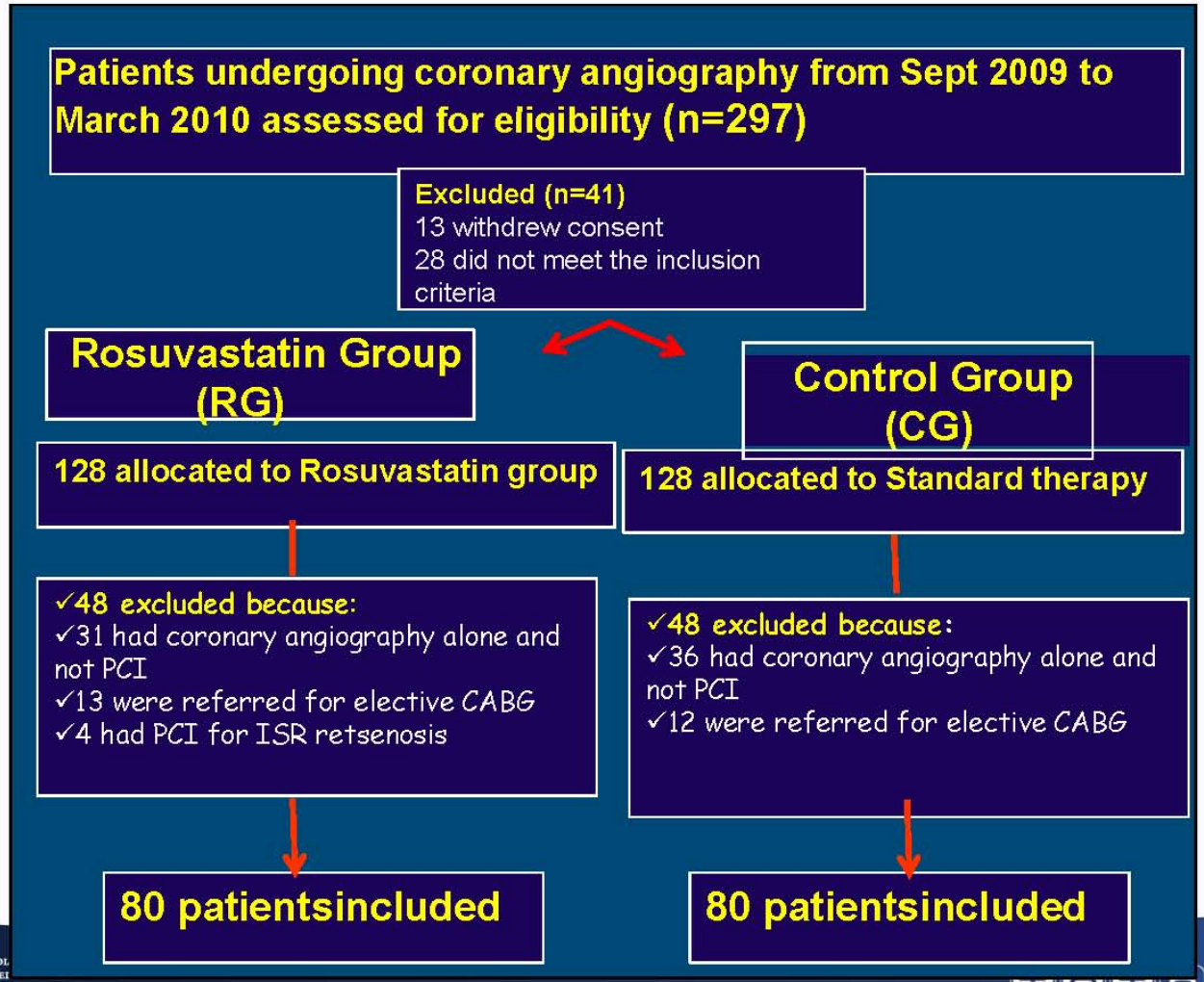
rino.sardella@uniroma1.it

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

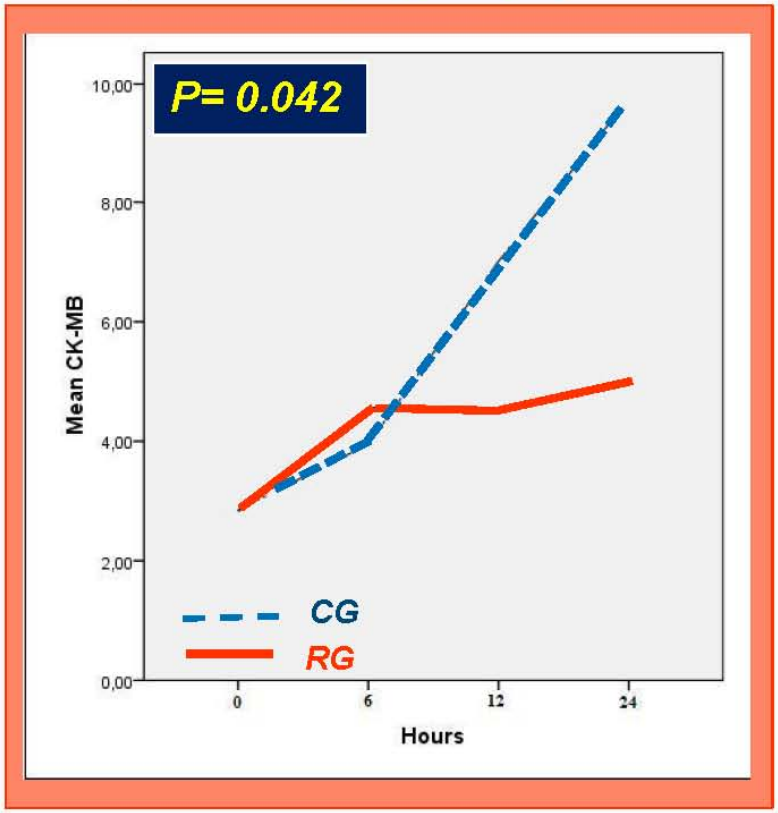
TCT2010

ROMA Trial

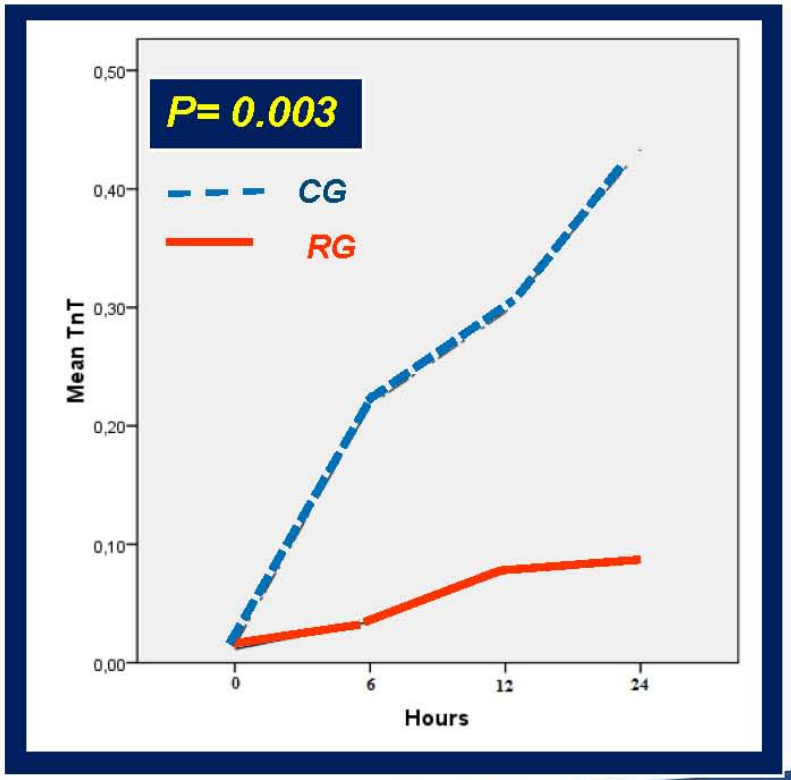


ENZYMATIC TREND UP TO 24 HOURS

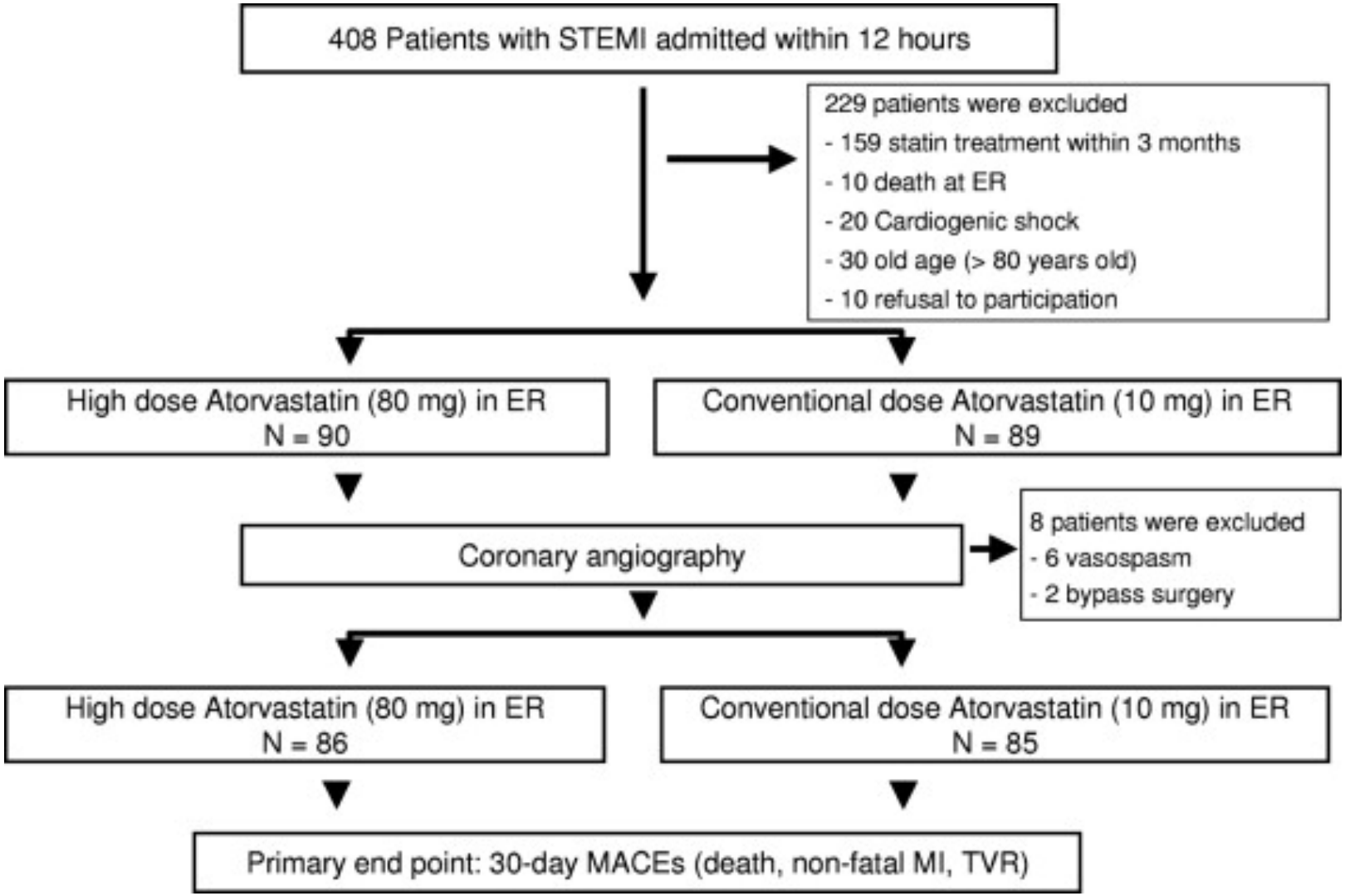
CK-MB(ng/ml)



TnT (ng/ml)

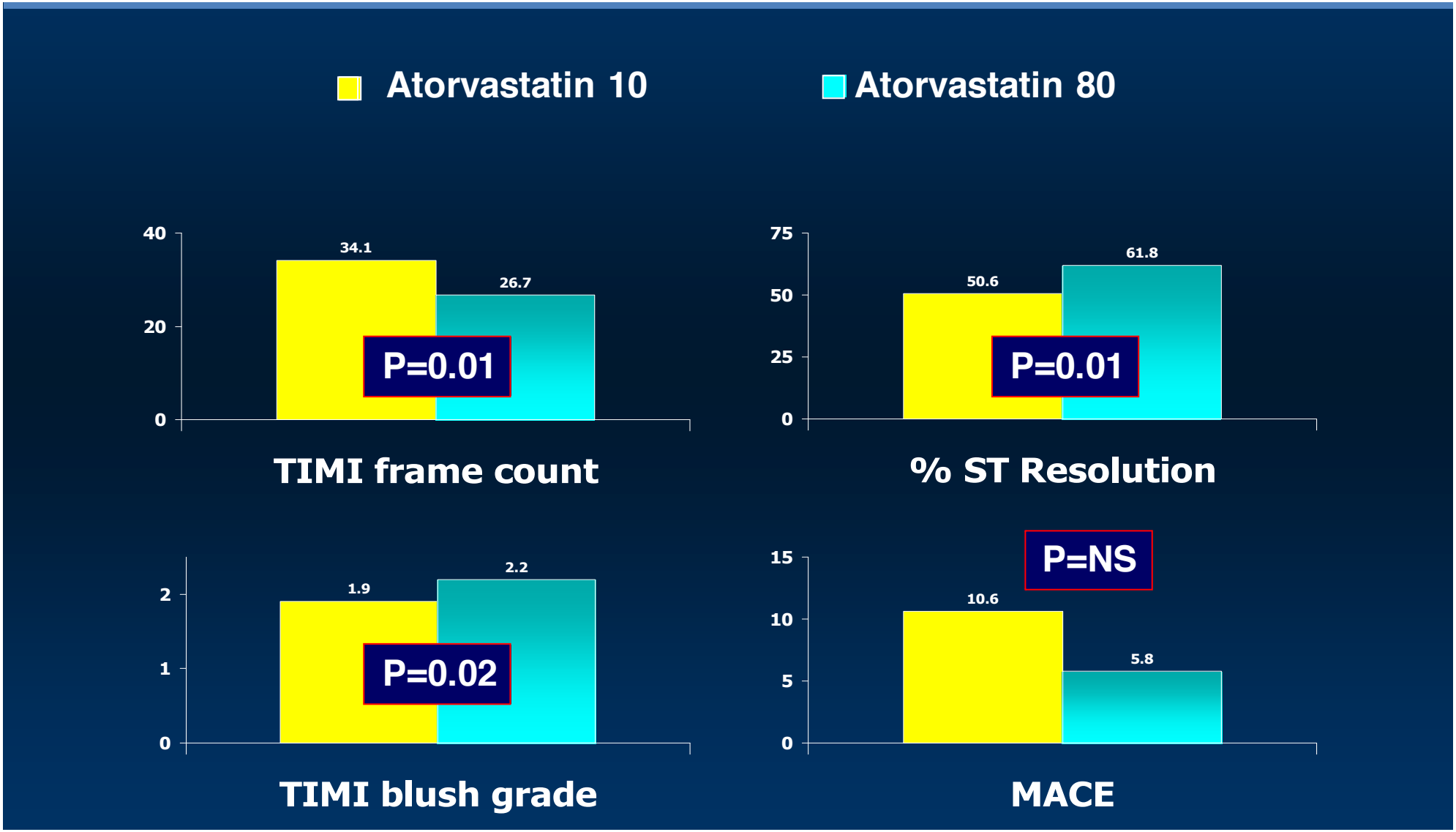


STATIN STEMI



J.S. KIM et al. JACC Intv: vol. 3, n° 3, 2010 MARCH 2010:332–9

STATIN STEMI



J.S. KIM et al. JACC Intv: vol. 3, n° 3, 2010 MARCH 2010:332–9

Yun

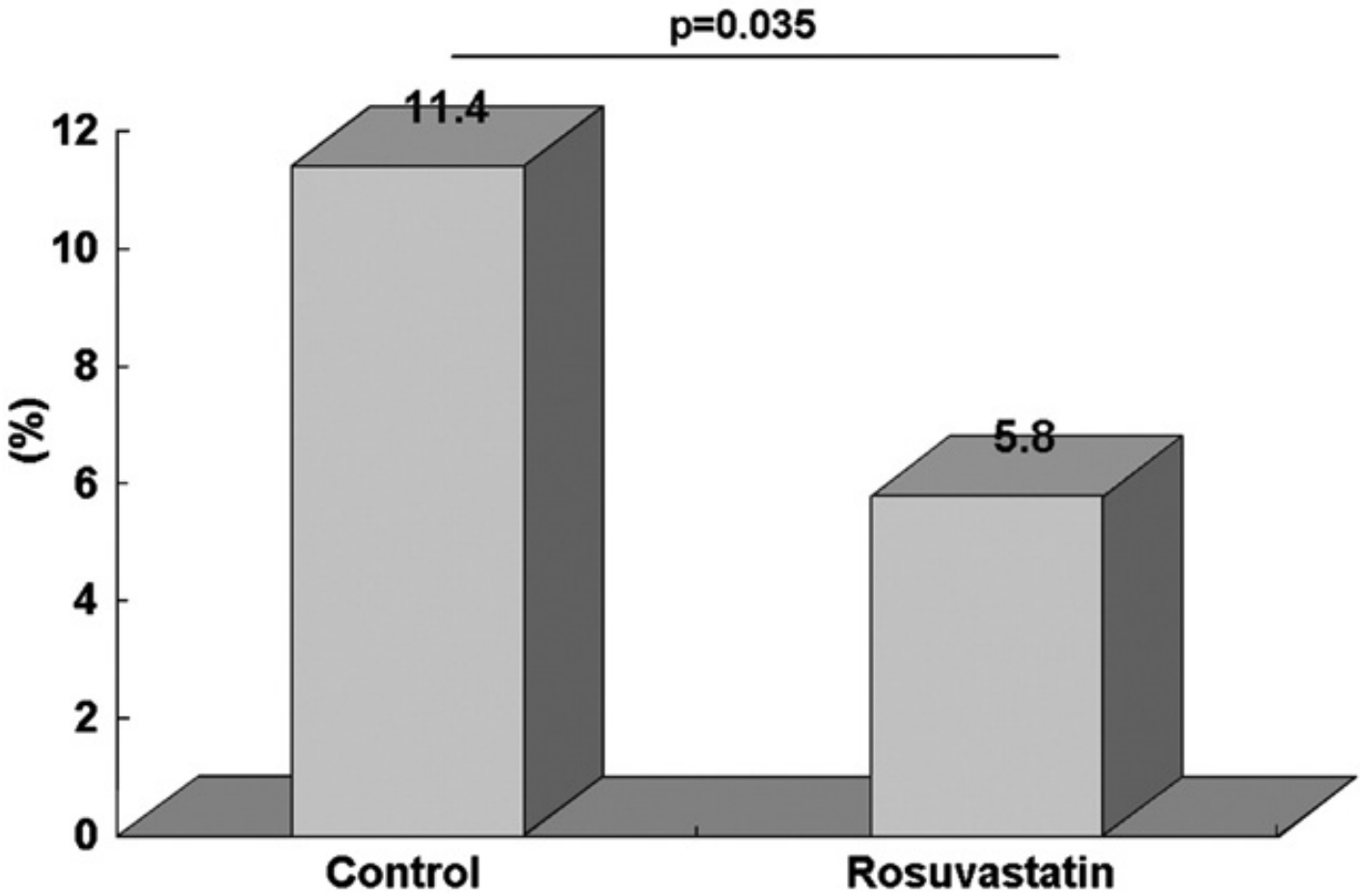
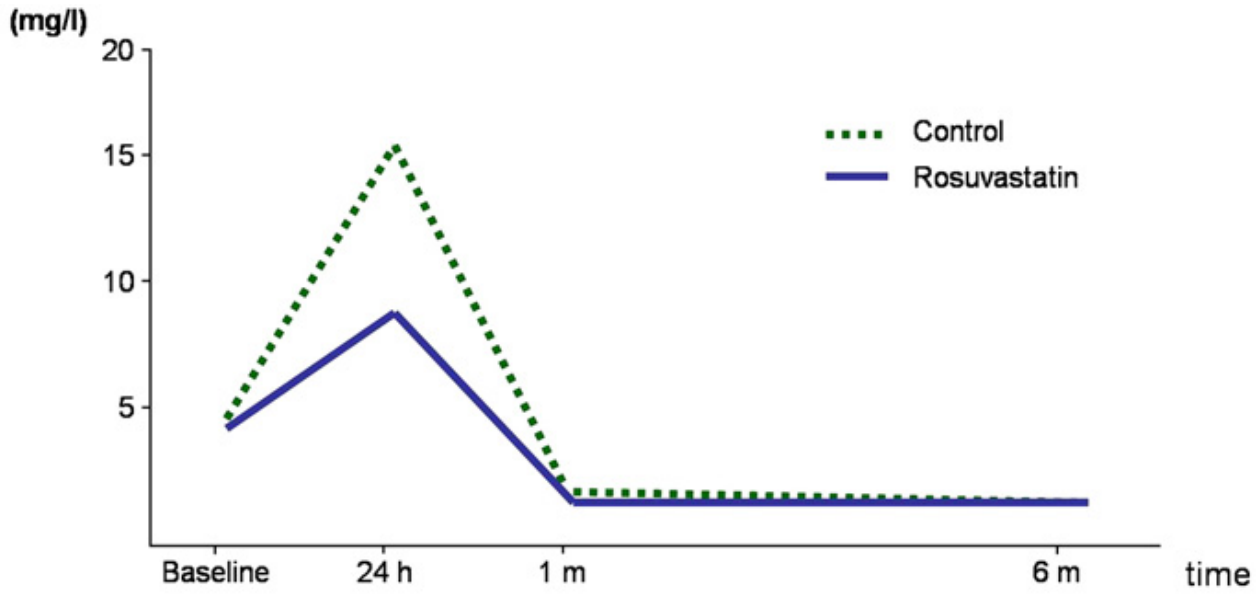


Fig. 2. Incidence of periprocedural myocardial injury, defined by post-procedural increase of creatine kinase-MB > 2 times above the upper limit of normal, in the control group and high dose rosuvastatin loading group.

K.H. Yun et al. / International Journal of Cardiology 137 (2009) 246–251

Yun



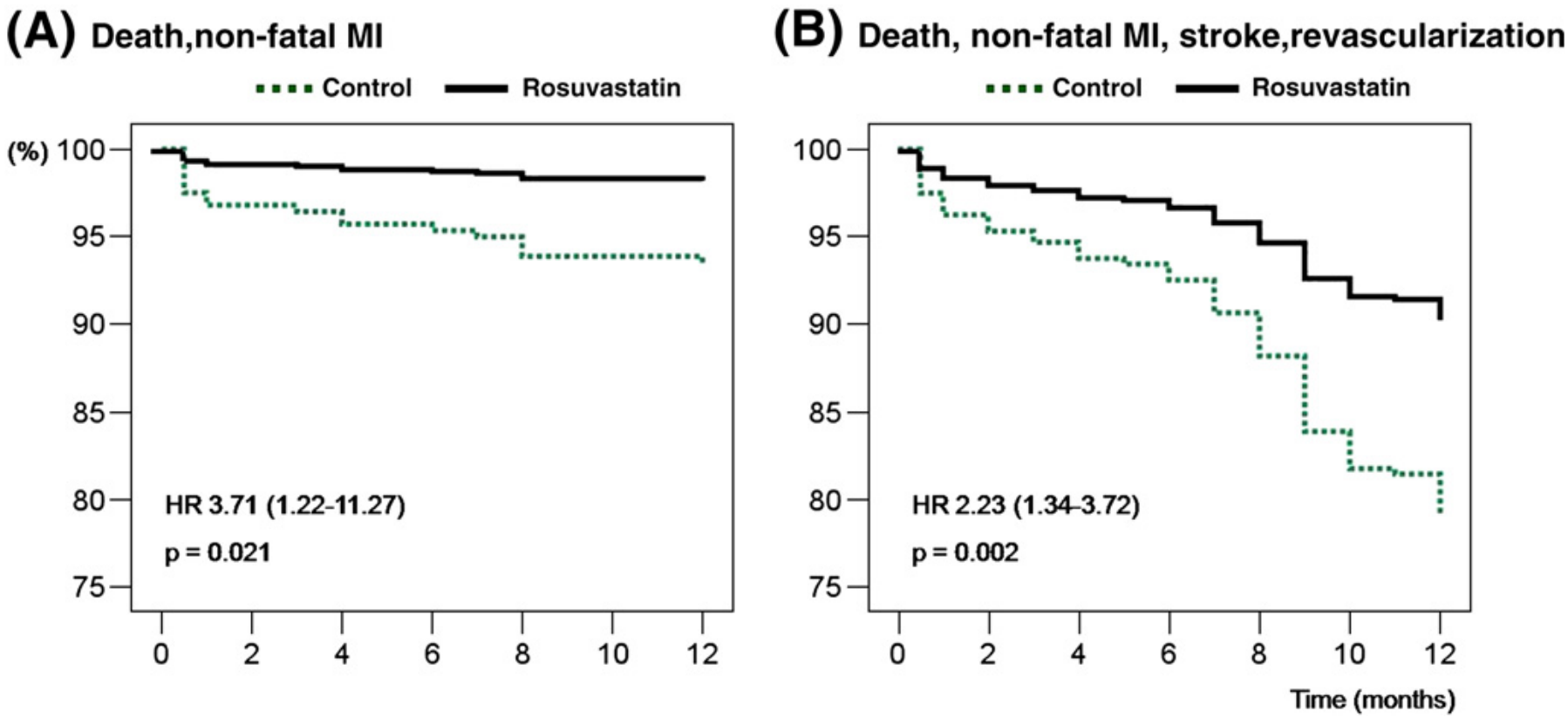
	Baseline	24h after PCI	1 month	6 months
No. of patients	445	434	355	308
Control group (mg/l)	4.9 ± 8.7	15.9 ± 27.7	1.7 ± 2.8	1.4 ± 2.1
Rosuvastatin group (mg/l)	4.6 ± 8.7	9.2 ± 12.5	1.9 ± 3.9	1.7 ± 2.1
p value	0.656	<0.001	0.366	0.133

Fig. 4. The change in high-sensitivity C-reactive protein level over time in patients with acute coronary syndrome who received no rosuvastatin treatment (control group) or high dose (40 mg) rosuvastatin loading (rosuvastatin group) before percutaneous coronary intervention (PCI).

K.H. Yun et al. / International Journal of Cardiology 146 (2011) 68–72

Yun

K.H. Yun et al. / International Journal of Cardiology 146 (2011) 68–72



Evidence of Pre-Procedural Statin Therapy

JACC Vol. 56, No. 14, 2010
September 28, 2010:1099–109

A Meta-Analysis of Randomized Trials

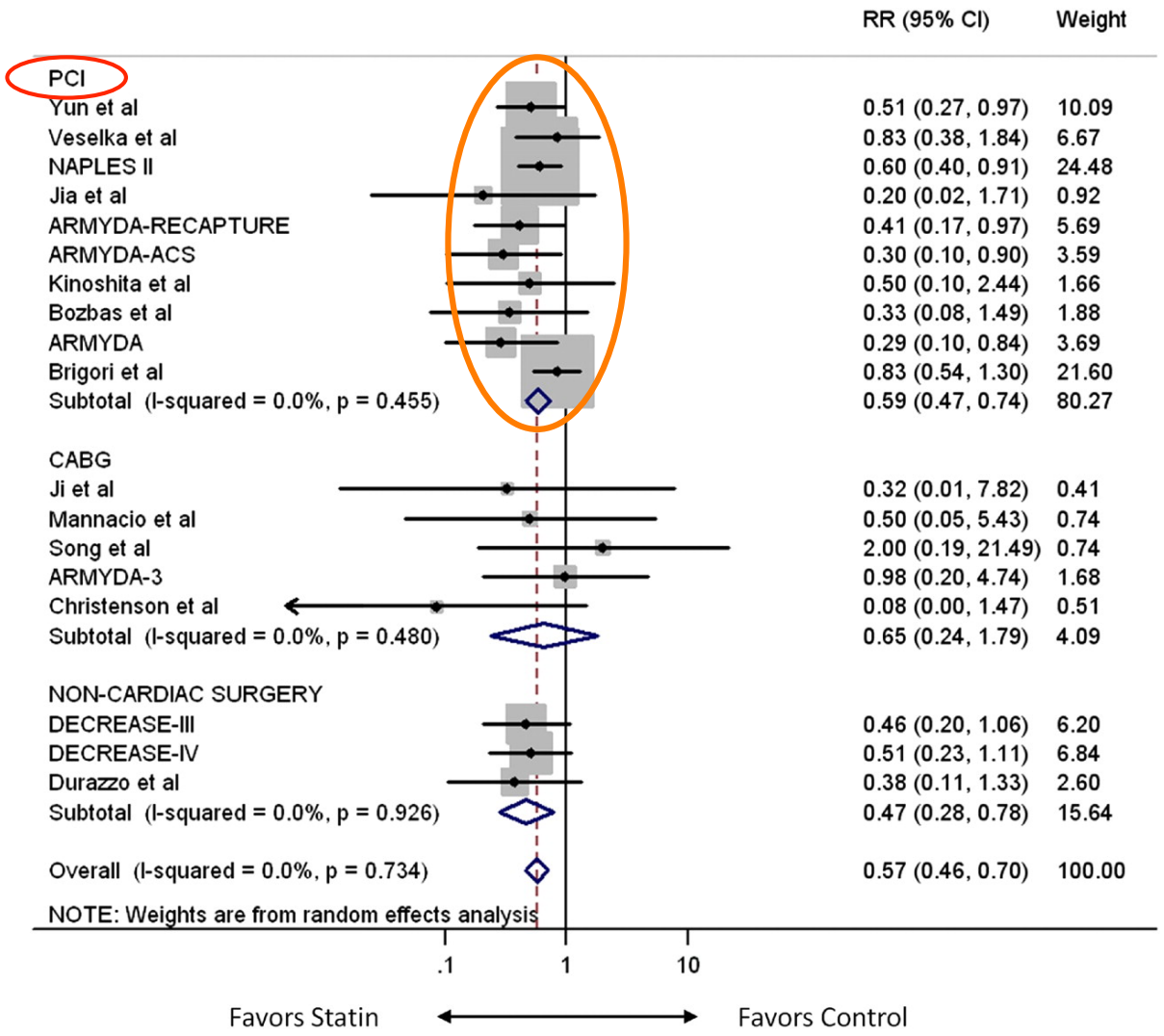
David E. Winchester, MD,* Xuerong Wen, MPH,† Lola Xie, BS,‡ Anthony A. Bavry, MD, MPH*
Gainesville, Florida

- 21 trials
- 4805 patients
- Elective PCI or urgent PCI for NSTE ACS

Significant reduction of post procedural MI

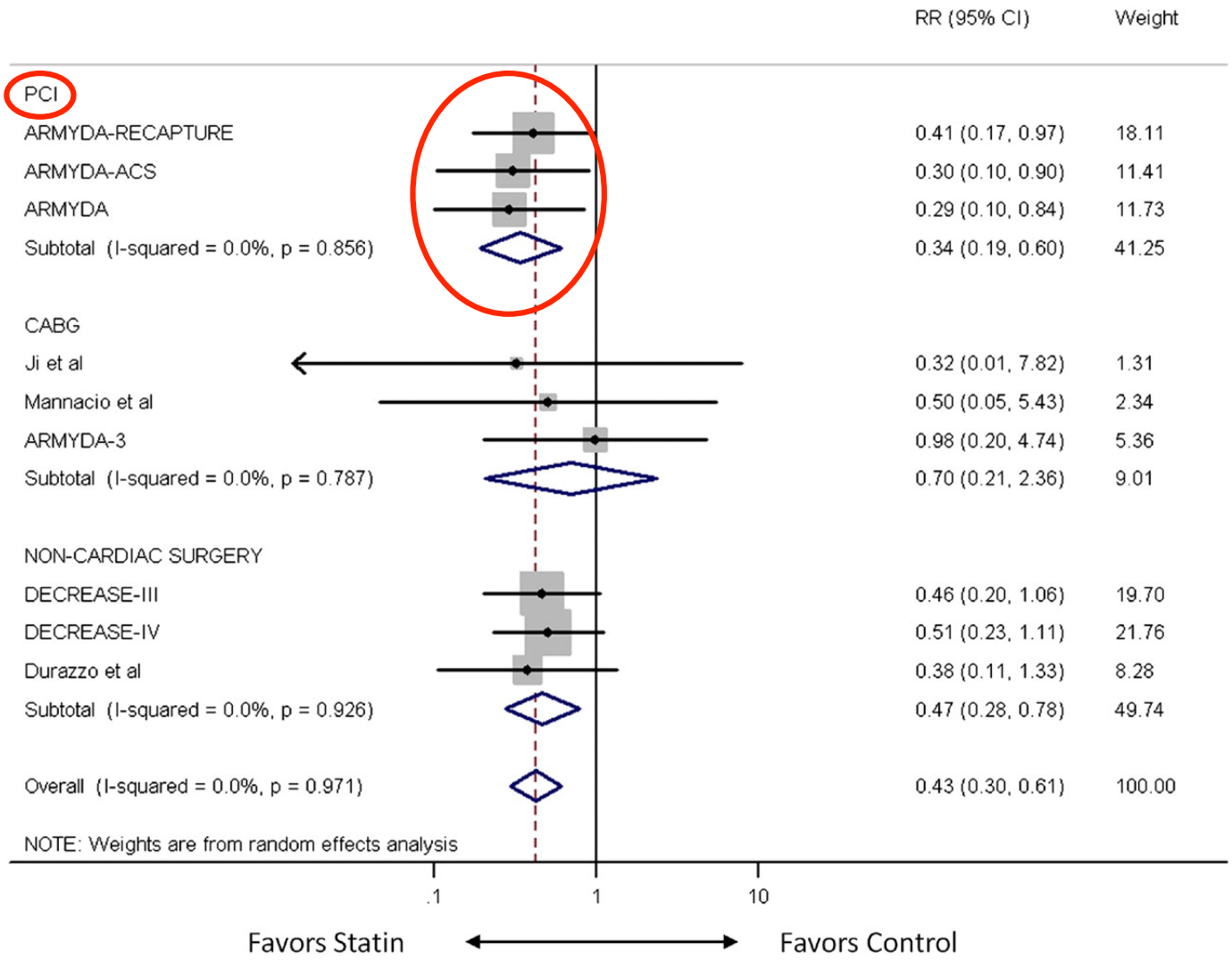
JACC Vol. 56, No. 14, 2010 September 28, 2010:1099–109

RRs for Post-Procedural Myocardial Infarction



Winchester, D. E. et al. J Am Coll Cardiol 2010;56:1099-1109

RRs for Post-Procedural Myocardial Infarction in Placebo-Controlled Trials



Winchester, D. E. et al. J Am Coll Cardiol 2010;56:1099-1109

Conclusioni

La somministrazione di statine pre procedurali in ACS produce:

NSTE

Riduzione dei markers di necrosi post procedurali

STE

Miglioramento dei marker di perfusione miocardica
(TFC, blush, ST resolution)

QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES Editorial Comment

Statins Before Coronary Procedures

A New Indication for an Old Friend*

Kim A. Eagle, MD,† Vineet Chopra, MD‡

Ann Arbor, Michigan

JACC Vol. 56, No. 14, 2010 September 28, 2010:1110–2

Given the strong biological rationale and the sum of the clinical data,
no patient should undergo coronary procedures without statin therapy
unless clear contraindications exist.

Statine up-stream

Un carico di statina ad alto dosaggio

- Atorvastatina 80 mg
- Rosuvastatina 40 mg

Dovrebbe essere somministato pre-PCI

Come avviene per :

- ASA
- Tienopidinici (clopidiogrel/prasugrel)
- Eparina (UFH/Enoxaparin)

Il trattamento sistemico nelle ACS non può essere solo antitrombotico

Questa presentazione è disponibile sul WEB

Gli eventuali interessati possono richiedere il collegamento inviando una mail al seguente indirizzo:

francesco.abbadessa@hsanmartino.it

Grazie per l'attenzione