REALABILITY - CORSO TEORICO – PRATICO DI TECNICHE DI RIVASCOLARIZZAZIONE MEDIANTE CHIRUGIA VIRTUALE

Genova 7- 9 giugno 2004

La placca aterosclerotica ed il ruolo del trattamento ipolipemizzante nel pz. sottoposto a procedure di rivascolarizzazione

dott. Francesco Abbadessa

Ospedale San Martino Genova

Early and Sustained Survival Benefit Associated With Statin Therapy at the Time of Percutaneous Coronary Intervention

Albert W. Chan, MD, MS; Deepak L. Bhatt, MD; Derek P. Chew, MBBS; Martin J. Quinn, MD, PhD;David J. Moliterno, MD; Eric J. Topol, MD; Stephen G. Ellis, MD

Observational study

5000 patients after PCI and statin therapy

Significant mortality benefit with statin (30 d & 6 m)

Independent of lipid lowering

Circulation. 2002; 105:691- 696

Relation of Inflammation and Benefit of Statins After Percutaneous Coronary Interventions

Albert W. Chan, MD, MSc; Deepak L. Bhatt, MD; Derek P. Chew, MBBS, MPH; Joel Reginelli, MD;Jakob P. Schneider, RN; Eric J. Topol, MD; Stephen G. Ellis, MD

1552 pts, follow-up 1 year

Statin therapy, before PCI

Marked reduction in mortality among patients with statin and high hs-CRP levels,

Independent of the baseline cholesterol levels

Circulation. 2003;107;1750-1756.

Beyond lowering lipids

Vascular injury from PCI, like ACS, induces

platelet activation,

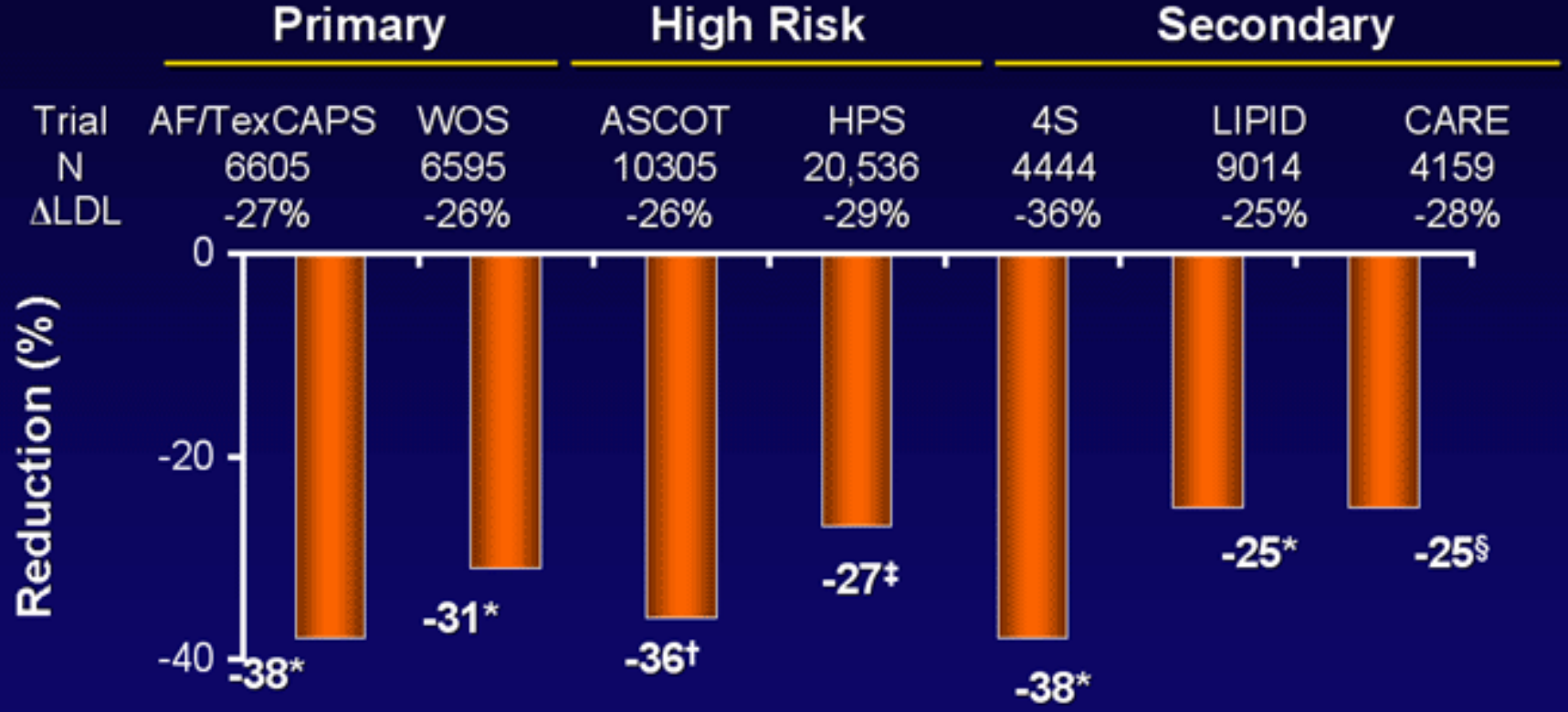
thrombosis

inflammation

within the vessel wall and the distal microvasculature.

Statin therapy play a beneficial role early after PCI

Statins Prevent Major Coronary Events



*P<0.001; †P=0.0005; ‡P<0.0001; §P=0.002.

HPS Collaborative Group. *Lancet*. 2002;360:7-22; LaRosa et al. *JAMA*. 1999;282:2340-2346; Sever et al. *Lancet*. 2003;361:1149-1158.

Clinical Trials of Statins

Chronic atherosclerosis

- 4S
- CARE
- LIPID
- AVERT
- HPS
- PROSPER
- ASCOT

Acute Coronary Syndrome

- L-CAD
- MIRACL
- FLORIDA
- PACT
- PROVE-IT

Primary prevention

- WOSCOP
- AF/TEX-CAPS

Rilevant recent trials

Apo A-I Milano

Reversal

PROVE-IT

Apo A-I Milano trial

Effect of recombinant Apo A-I Milano on coronary atherosclerosis in patients with acute coronary syndromes. A randomized controlled trial

Steven E. Nissen et al.

Cleveland Clinic

JAMA , November 5, 2003.

Apo A-I Milano trial

Rilevant issues

- First compelling evidence of atherosclerosis regression in humans
- HDL therapy
- Role of IVUS

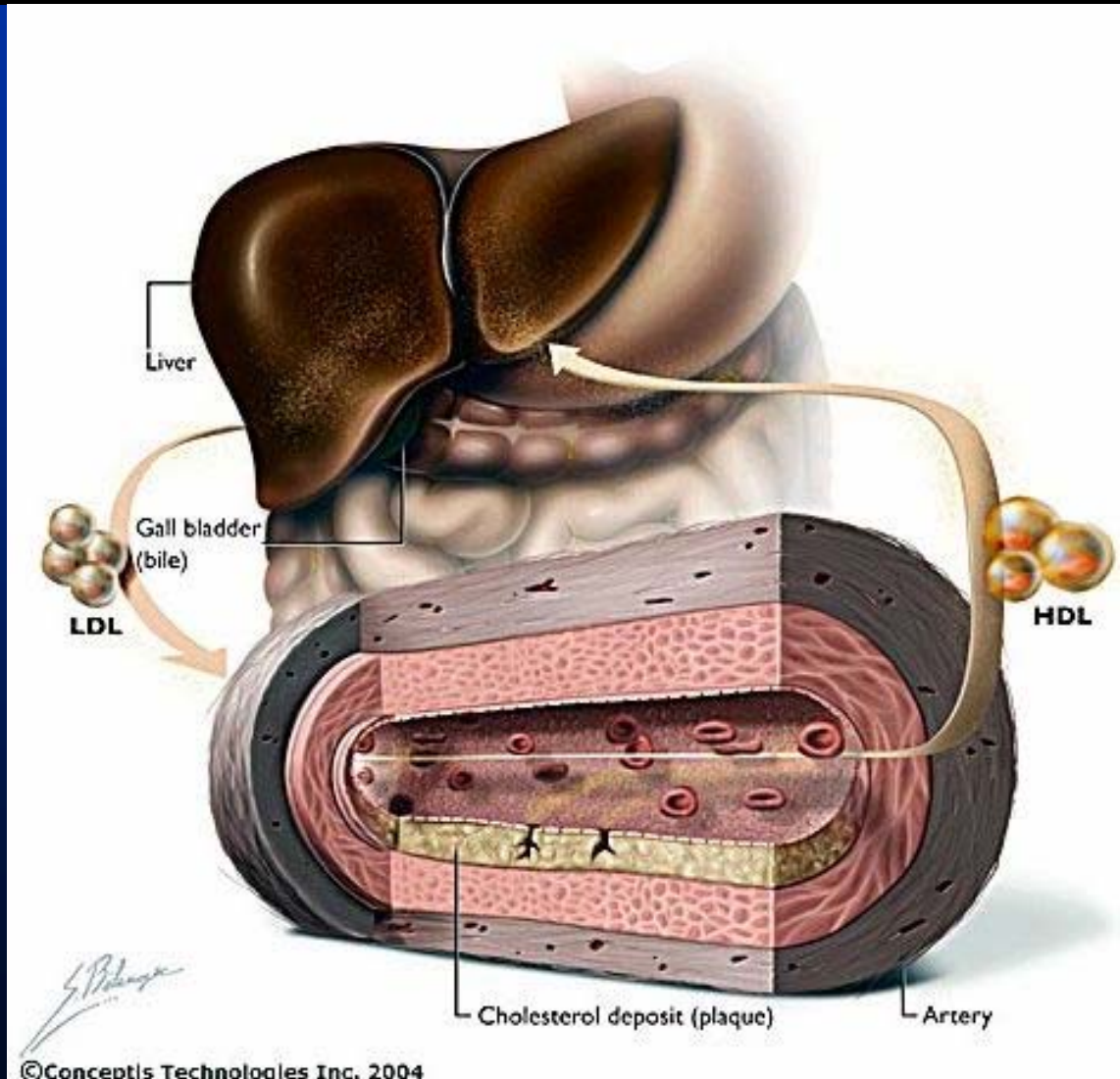
Apo A-I Milano

Limone sul Garda

1980

- Variant of Apo A I
- 40 carriers
- Very low HDL
- longevity

Reverse cholesterol transport

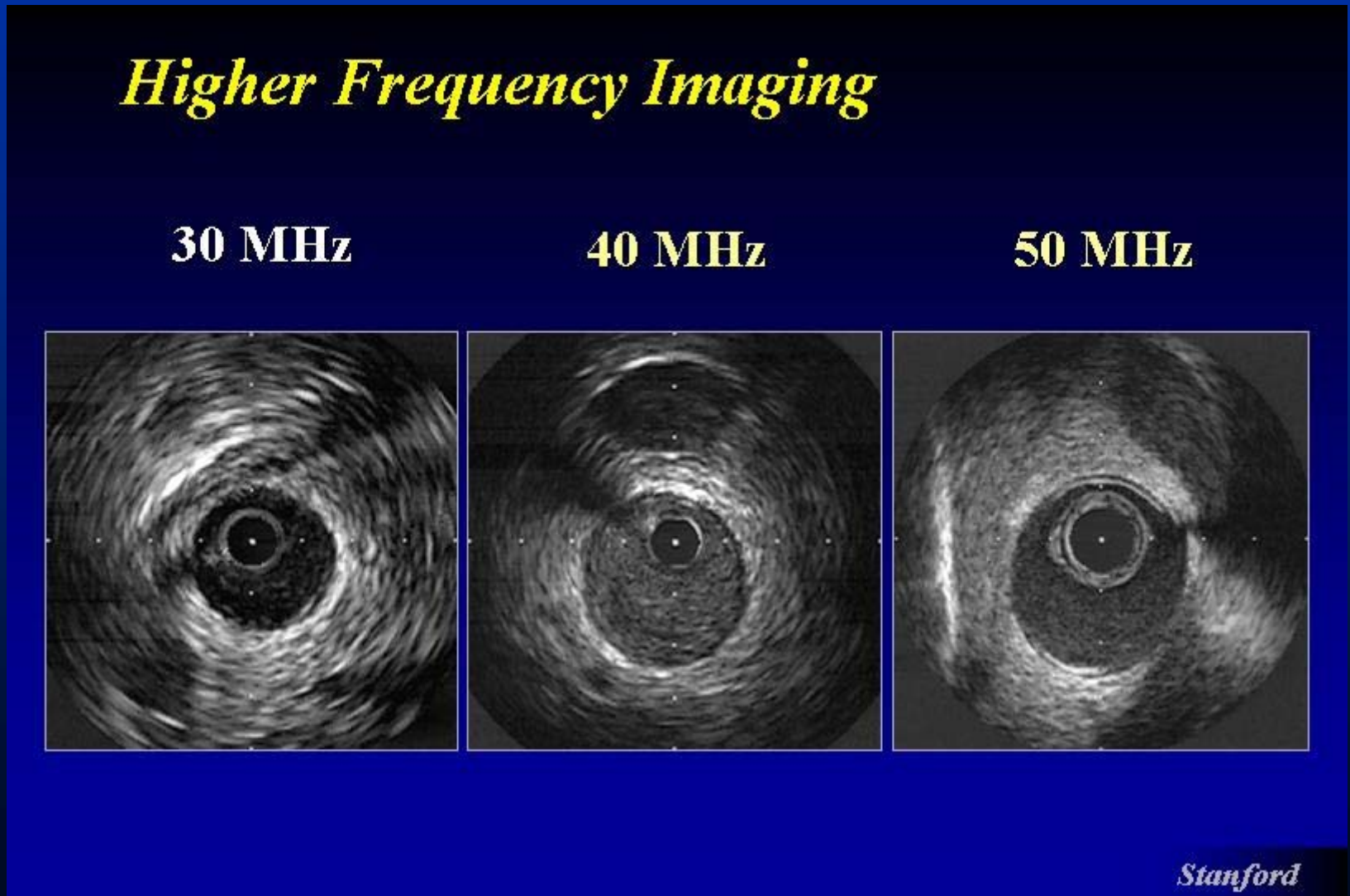


Apo A-I Milano trial

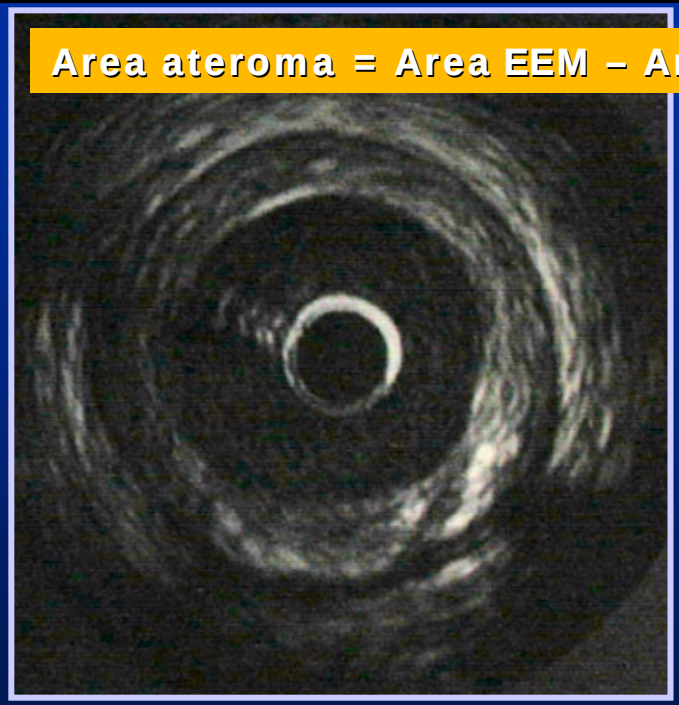
- ACS pts within 14 days
- Lesions > 20% > 50% at angiography
- 5 weekly recombinant Apo A-I Milano intravenous infusions
- IVUS at baseline and after treatment

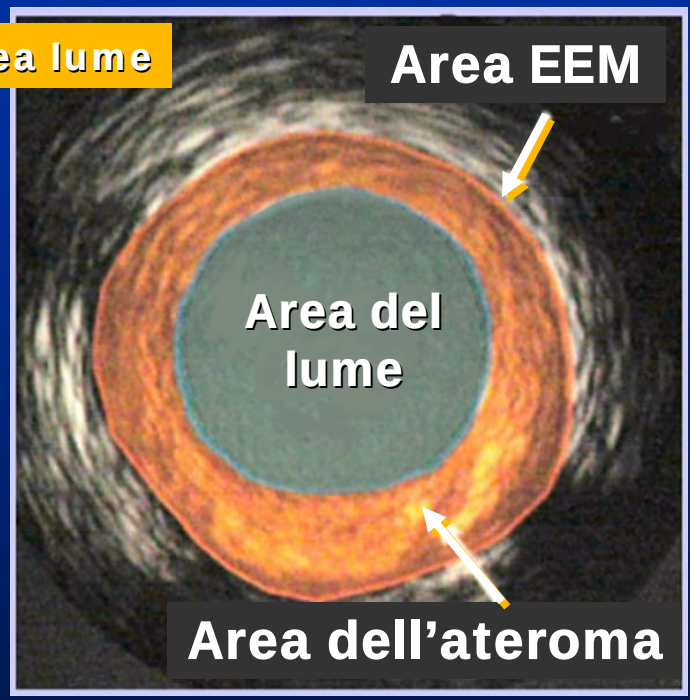
SE Nissen et al. JAMA 2003;290:2292-2300

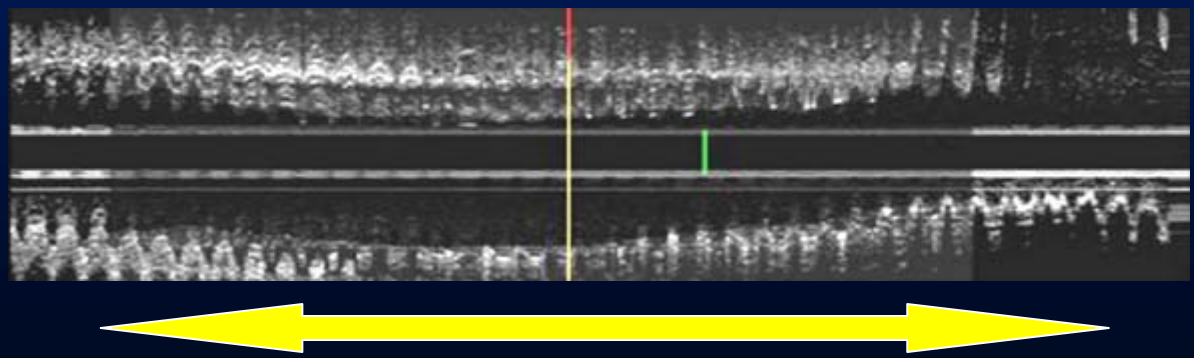
IVUS emerges as the "gold standard" in the study of atherosclerosis progression-regression



Determinazione IVUS dell'area dell'ateroma







Apo A-I Milano trial

Results

The absolute reduction in atheroma volume was:

-14.1 mm^3 or

4.2% decrease from baseline (p<.001)

In five weeks

40 000 $ / treatment

SE Nissen et al. JAMA 2003;290:2292-2300

Focus on new HDL therapy

- HDL mimetics: APO-A1 Mi, oral peptides
- CETP inhibitors: torcetrapib, JTT-705
- CETP vaccine
- PPARs agonist: glitazones, 10 drugs
- SR-BI HDL receptor
- Gene therapy

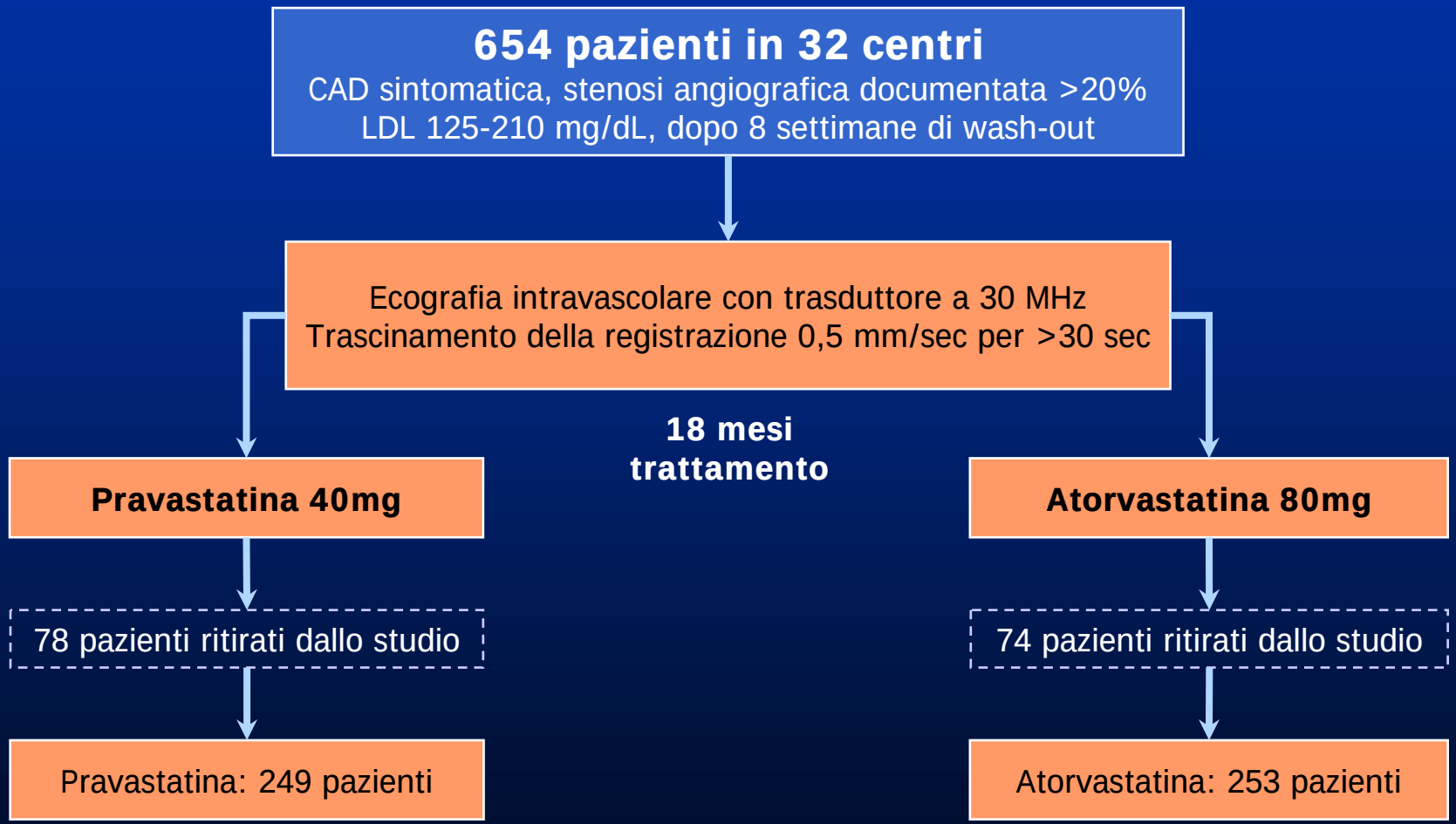
REVERSAL trial

Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial.

Nissen SE, Tsunoda T, Tuzcu EM, et al.

JAMA , March 3, 2004.

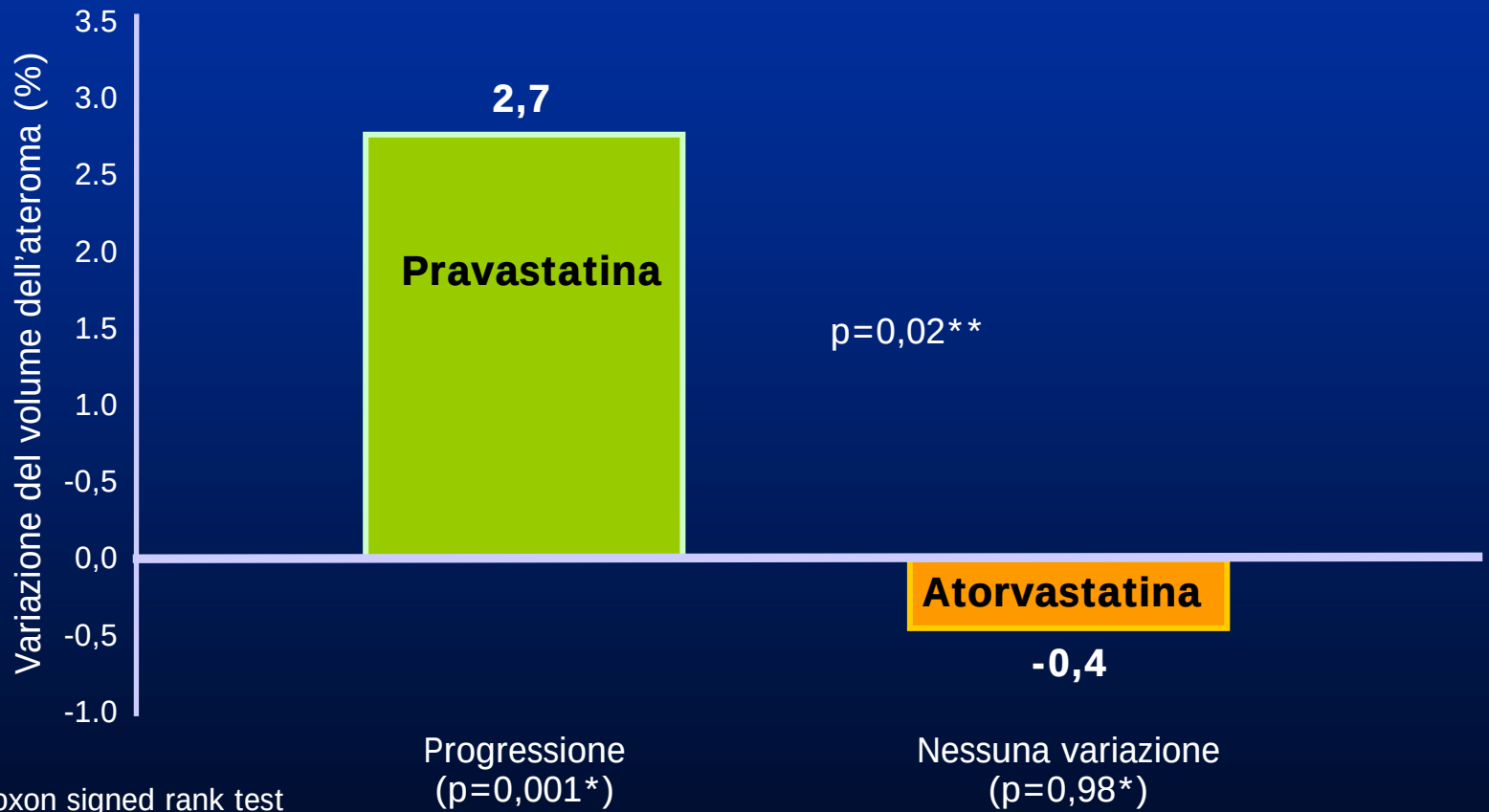
Disegno dello Studio REVERSAL



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

Endpoint primario

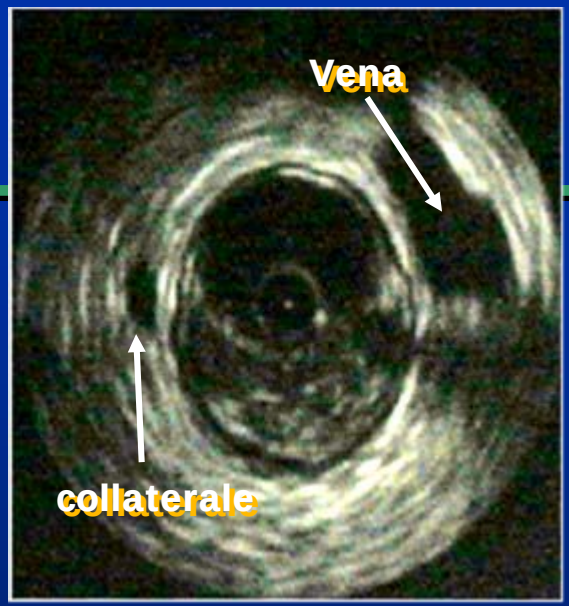
Variazione percentuale del volume dell'ateroma

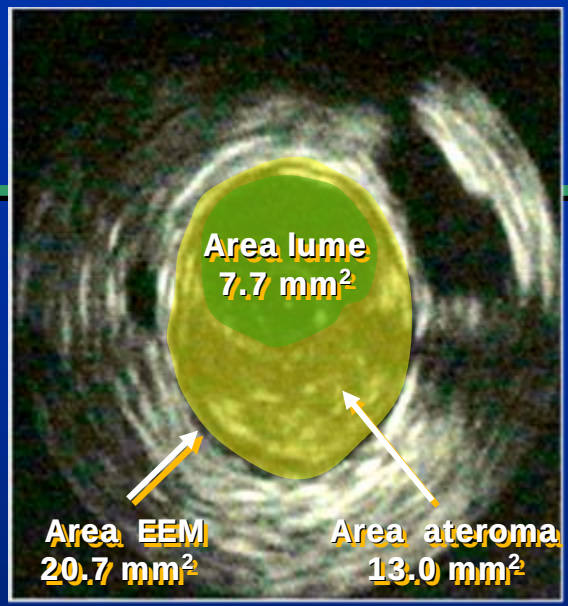


* Wilcoxon signed rank test
** Wilcoxon rank sum test

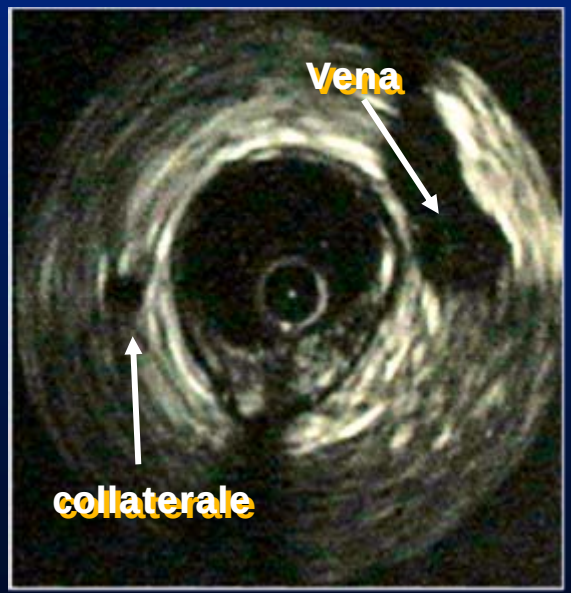
American Heart Association, Scientific sessions, Orlando; Nov. 2003
Nissen SE et al. JAMA 2004;291:1071-1080

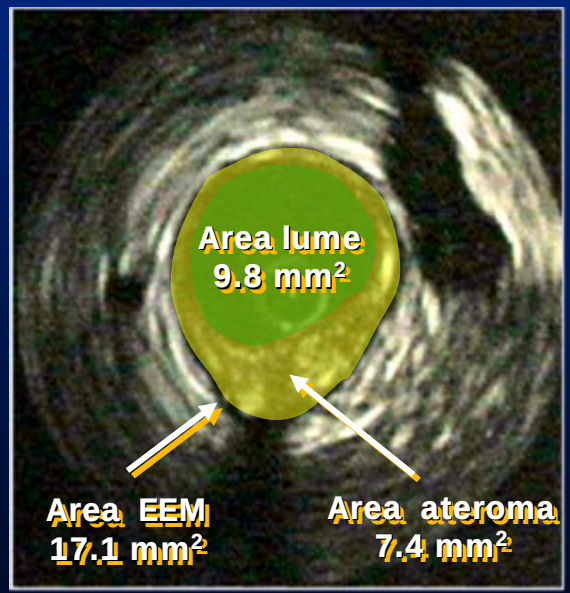
Variazioni IVUS





Basale

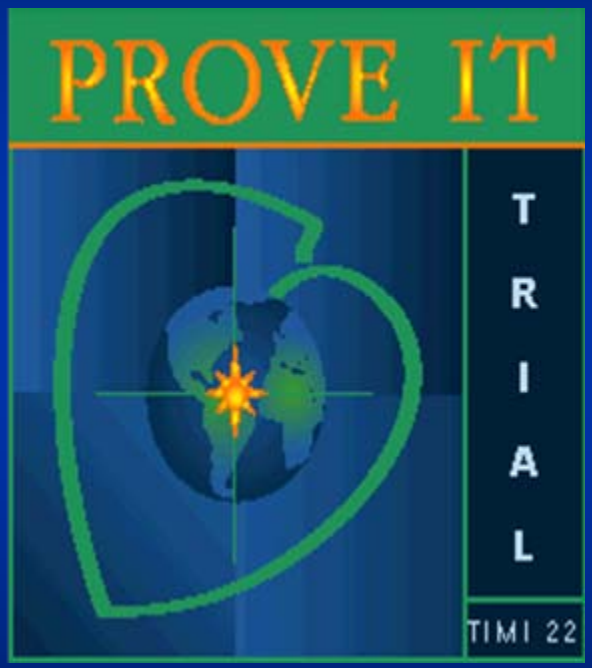




Dopo 18 mesi di trattamento

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

PROVE - IT

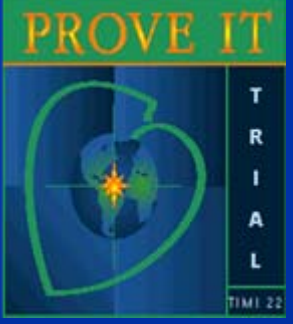


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 26, 2004 VOL. 350 NO. 9

PRavastatin Or atorVastatin Evaluation and Infection Therapy (TIMI 22)

Cannon CP, Braunwald E, McCabe CH, et al. *N Engl J Med* 2004;350:15



PROVE IT (TIMI 22): Study Design

Double-blind, randomized trial in 4,162 patients with ACS <10 days and Total Cholesterol ≤ 240 mg/dL

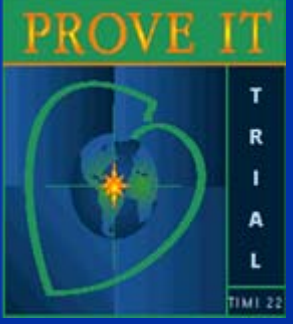
ASA + Standard Medical Therapy

- **Pravastatin 40 mg**
- **Atorvastatin 80 mg**

Duration: Mean 2 year follow-up (925 events)

Primary Endpoint: Death, MI, Stroke, UA requiring hosp., or revascularization (> 30 days after randomization)

Cannon et al. Am J Card 2002;89:860–861.

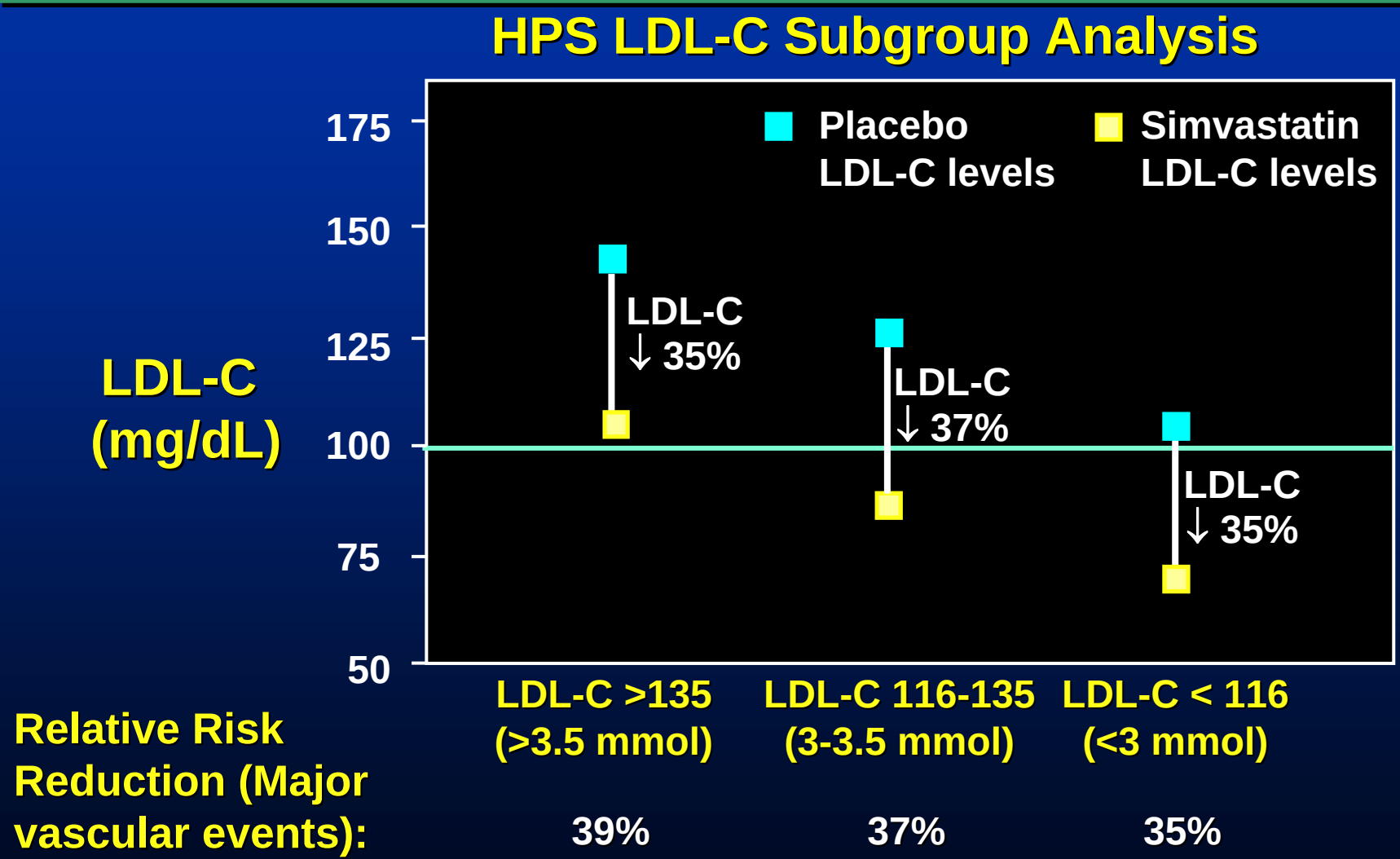


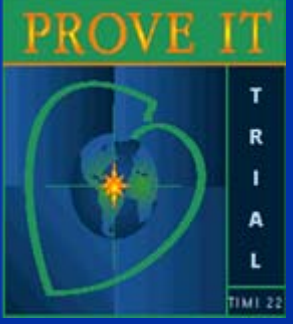
Background

Statin therapy is highly effective vs. placebo in long-term treatment of CHD

- **Are statins effective in reducing events in patients with an ACS ?**
- **Does "intensive" LDL-C lowering to an average of 65 mg/dL achieve a greater reduction in clinical events than "standard" LDL-C lowering to an average of 95 mg/dL?**

HPS: Effects of Fixed Dose Statin by LDL-C Subgroups

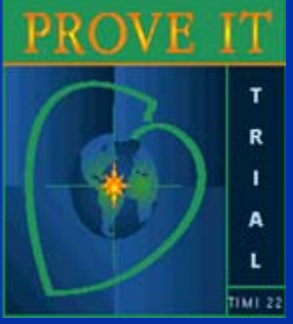




Results

In patients recently hospitalized within 10 days for ACS:

- **"Intensive" high-dose LDL-C lowering (median LDL-C 62 mg/dL) compared to "moderate" standard-dose lipid-lowering therapy (median LDL-C 95 mg/dL) reduced the risk of all cause mortality or major cardiac events by 16% (p=0.005)**
- **Benefits emerged within 30 days post ACS with continued benefit observed throughout the 2.5 years of follow-up**



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2004 VOL. 350 NO. 9

PROVE-IT conclusions

Our findings indicate that patients recently hospitalized for an ACS benefit from early and continued lowering of LDL-C to levels substantially below current target levels.

Cannon CP, Braunwald E, McCabe CH, et al. *N Engl J Med* 2004;350:15
www.nejm.org

Rilevant recent trials

- ✓ Apo A-I Milano
- ✓ Reversal
- ✓ PROVE-IT

Atherosclerosis: Progression- Regression

Brown BG, Zhao XQ, Sacco DE, Albers JJ.

Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease.

Circulation. **1993;87:1781-1790.**

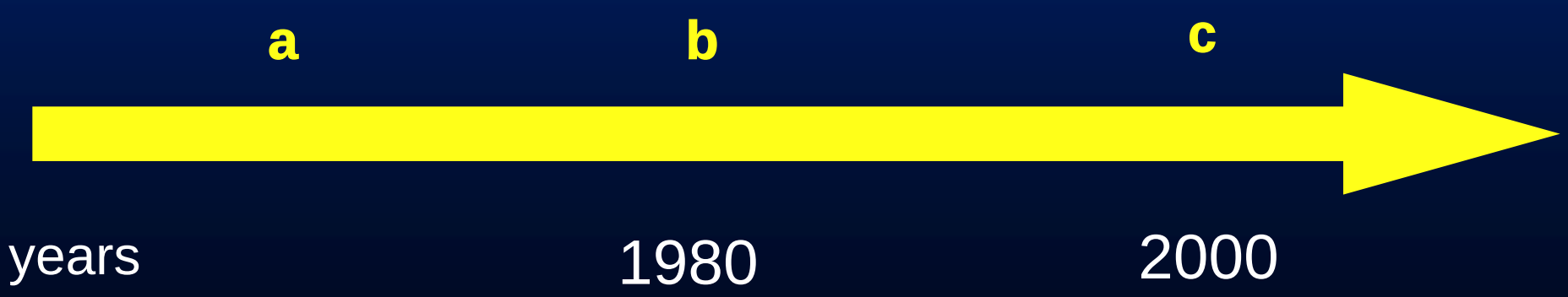
- **Dissociation between angiography and clinical outcomes.**
- **Negligible improvement of luminal caliber: 1-3 %**

Evolution of Atherosclerosis model

a **Gradual luminal narrowing**

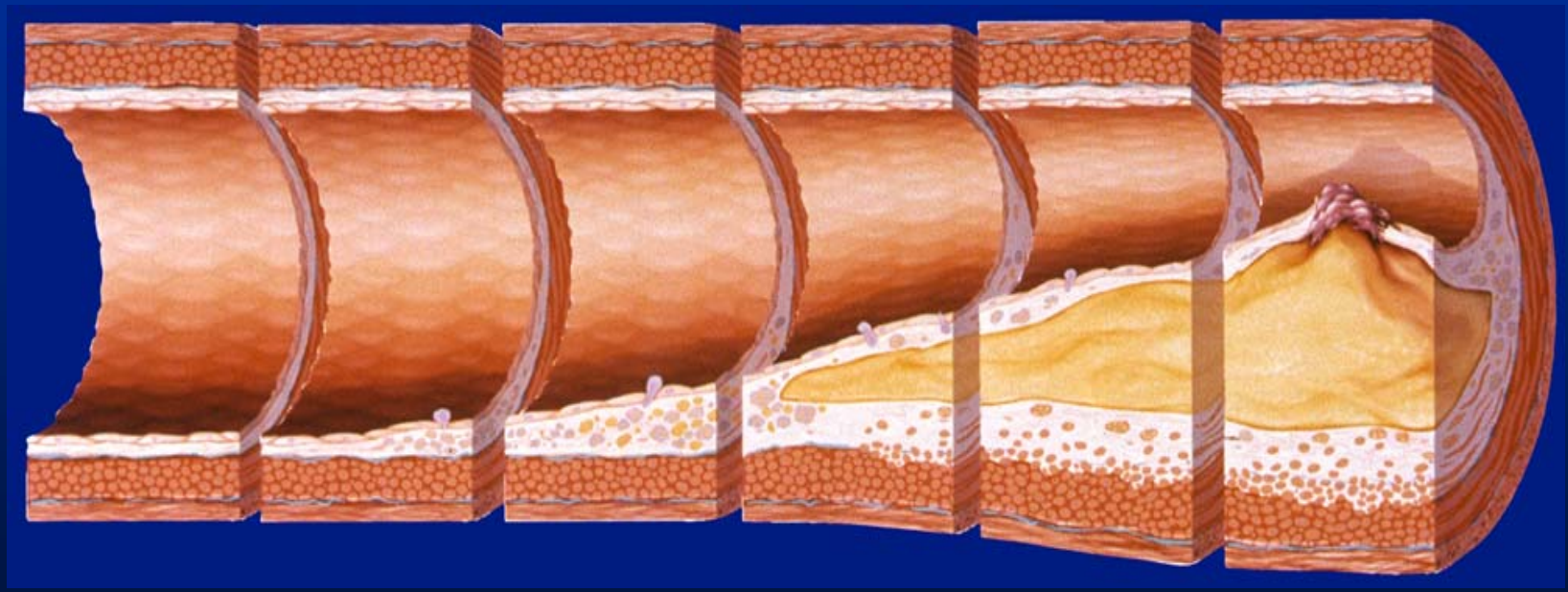
b **Plaque rupture**

c **Inflammation**



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

Relationship Plaque/Lumen

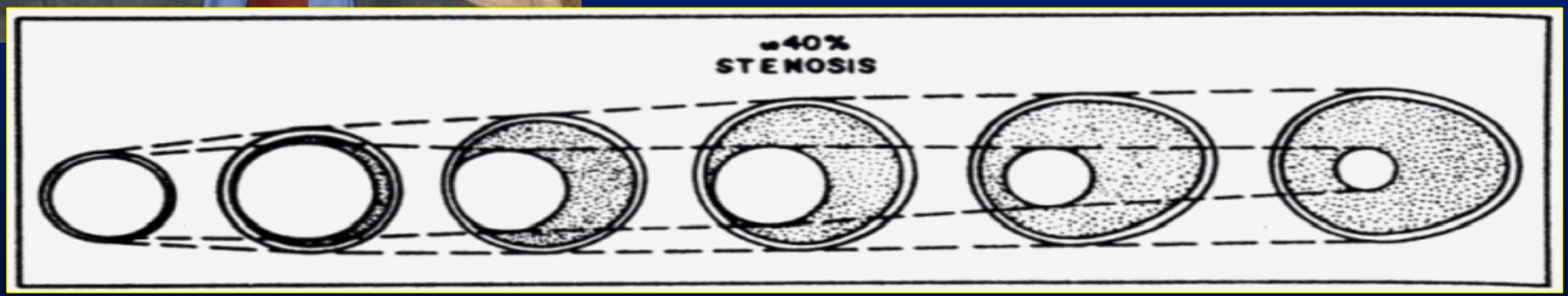
- Plaque size in itself is not the sole predictor of luminal narrowing:
- Marked compensatory enlargment of the coronary artery with plaque progression
- Lumen size is not correlated with plaque size

Renu Virmani

Armed Forces Institute of Pathology,
Washington, DC

Interazione placca-parete: Rimodellamento

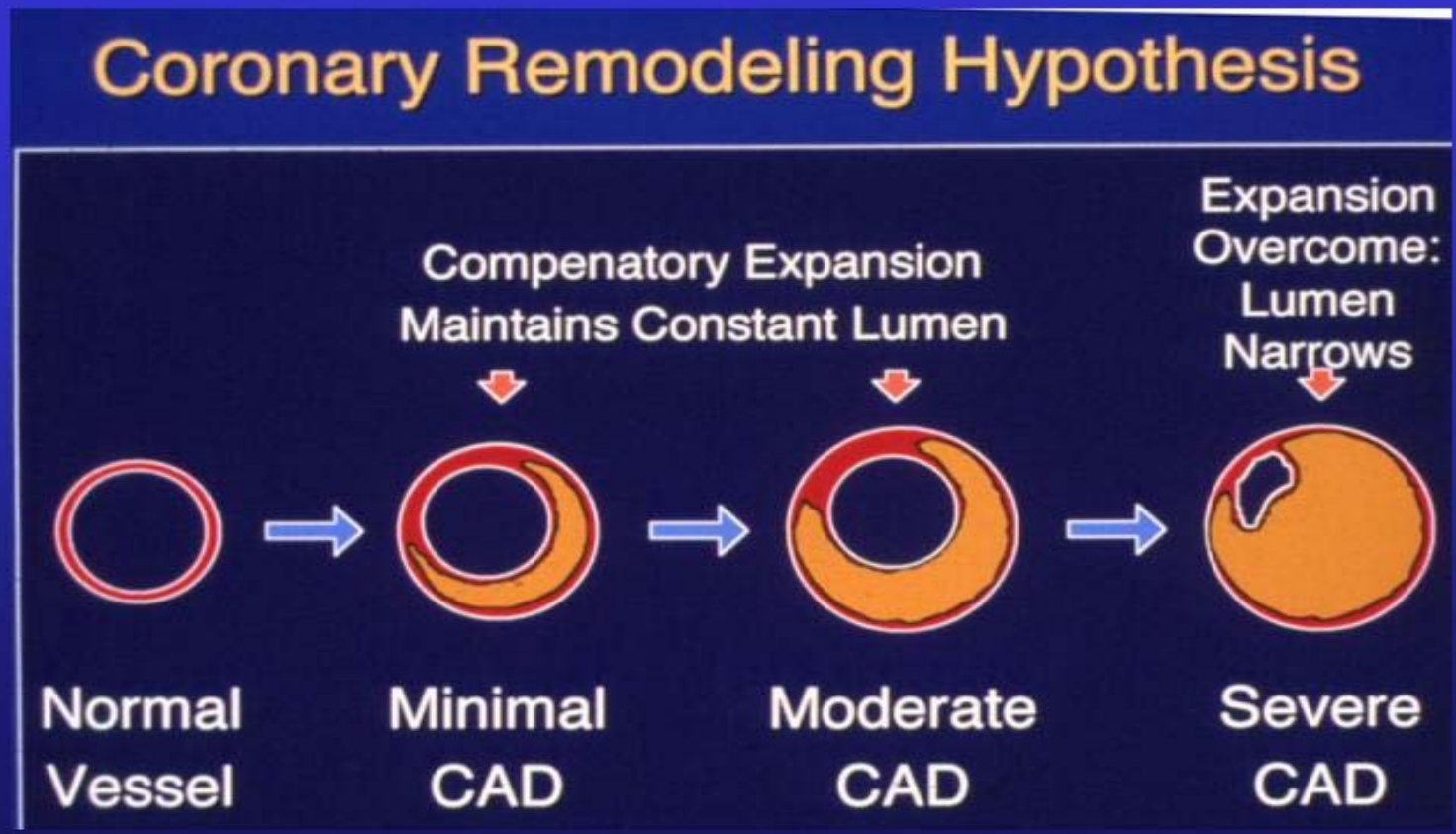
Seymour Glagov
pathologist
Chicago



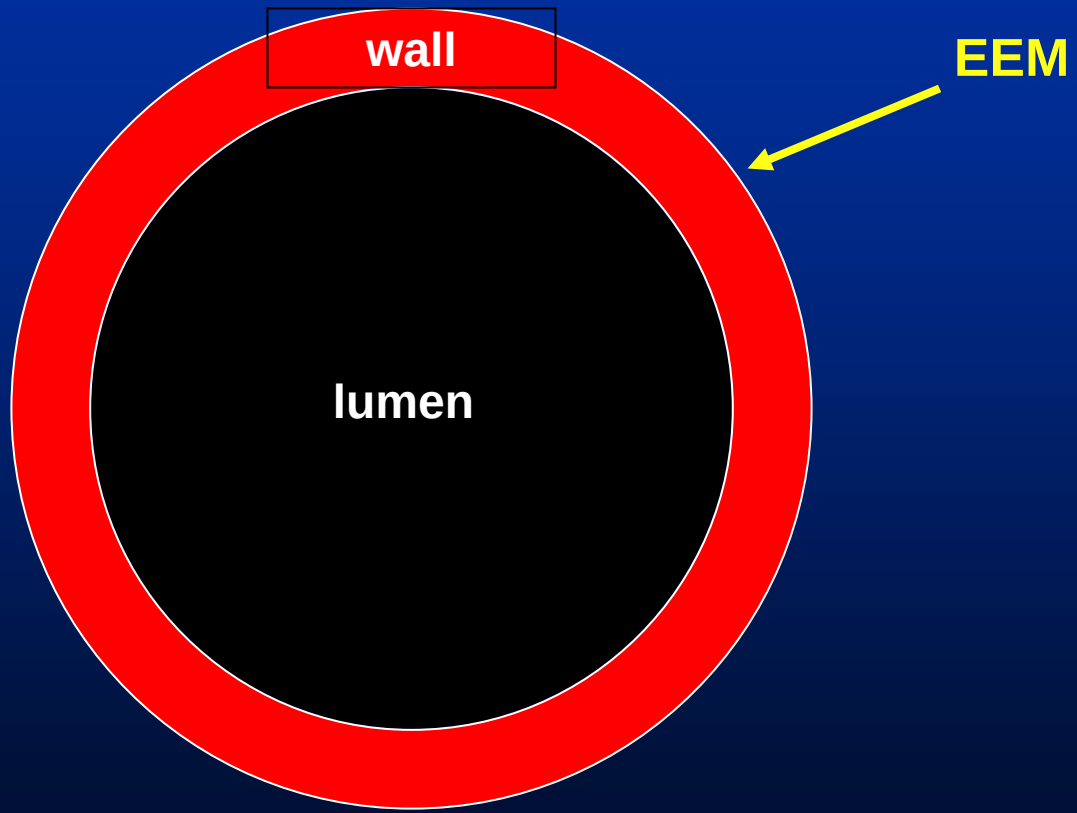
"Compensatory enlargement of human atherosclerotic coronary artery"

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

Glagov hypothesis

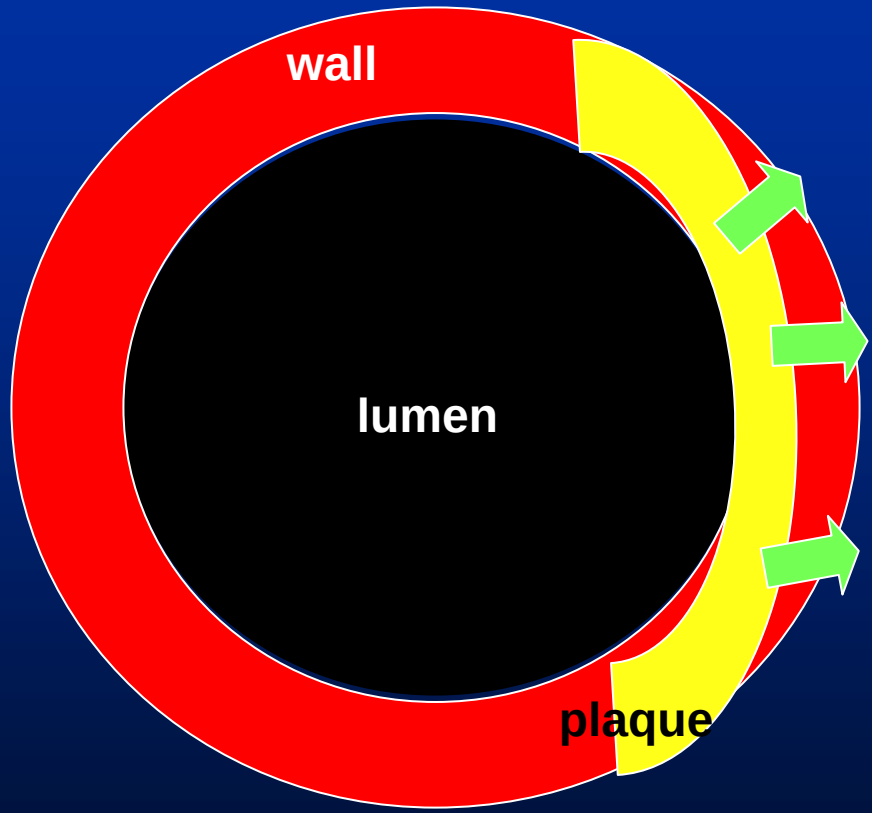


Normal



Remodeling: compensatory enlargement

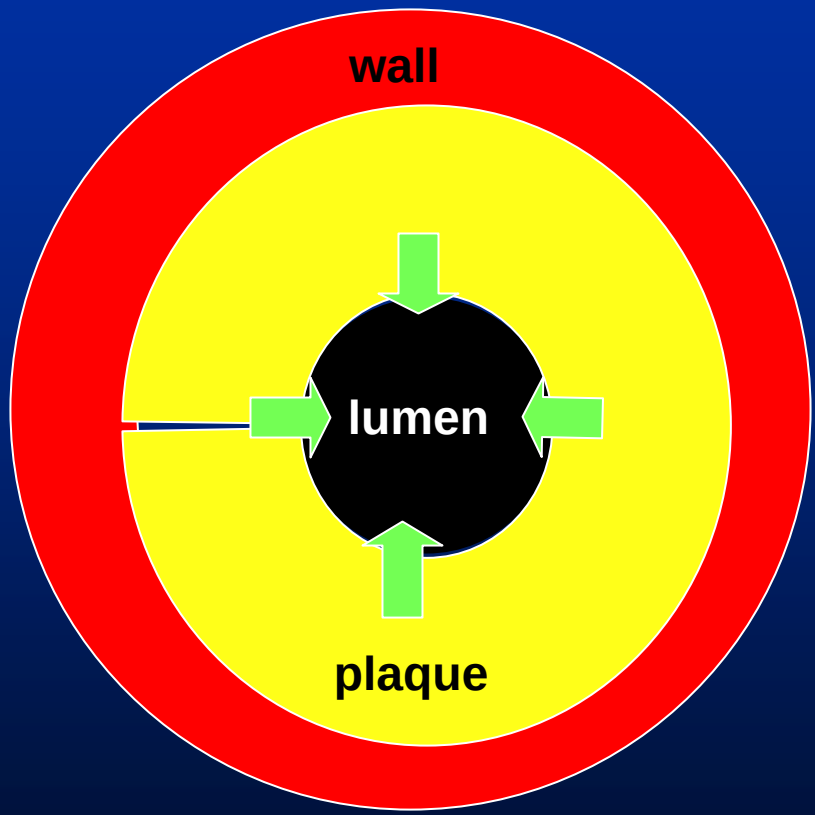
Lumen is normal



Plaque grows in outward fashion

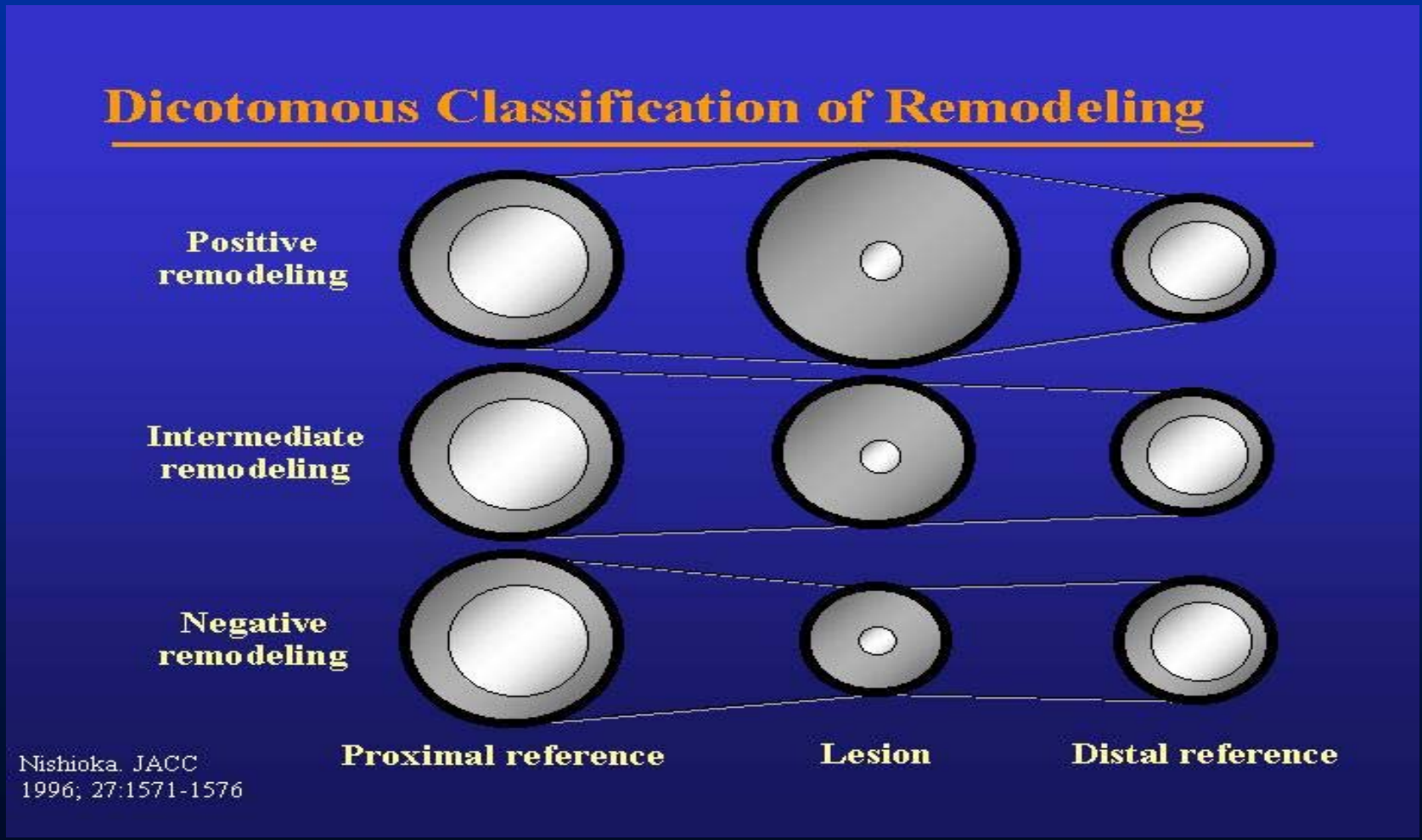
Remodeling permits large accumulation before lumen narrowing

Stenosis

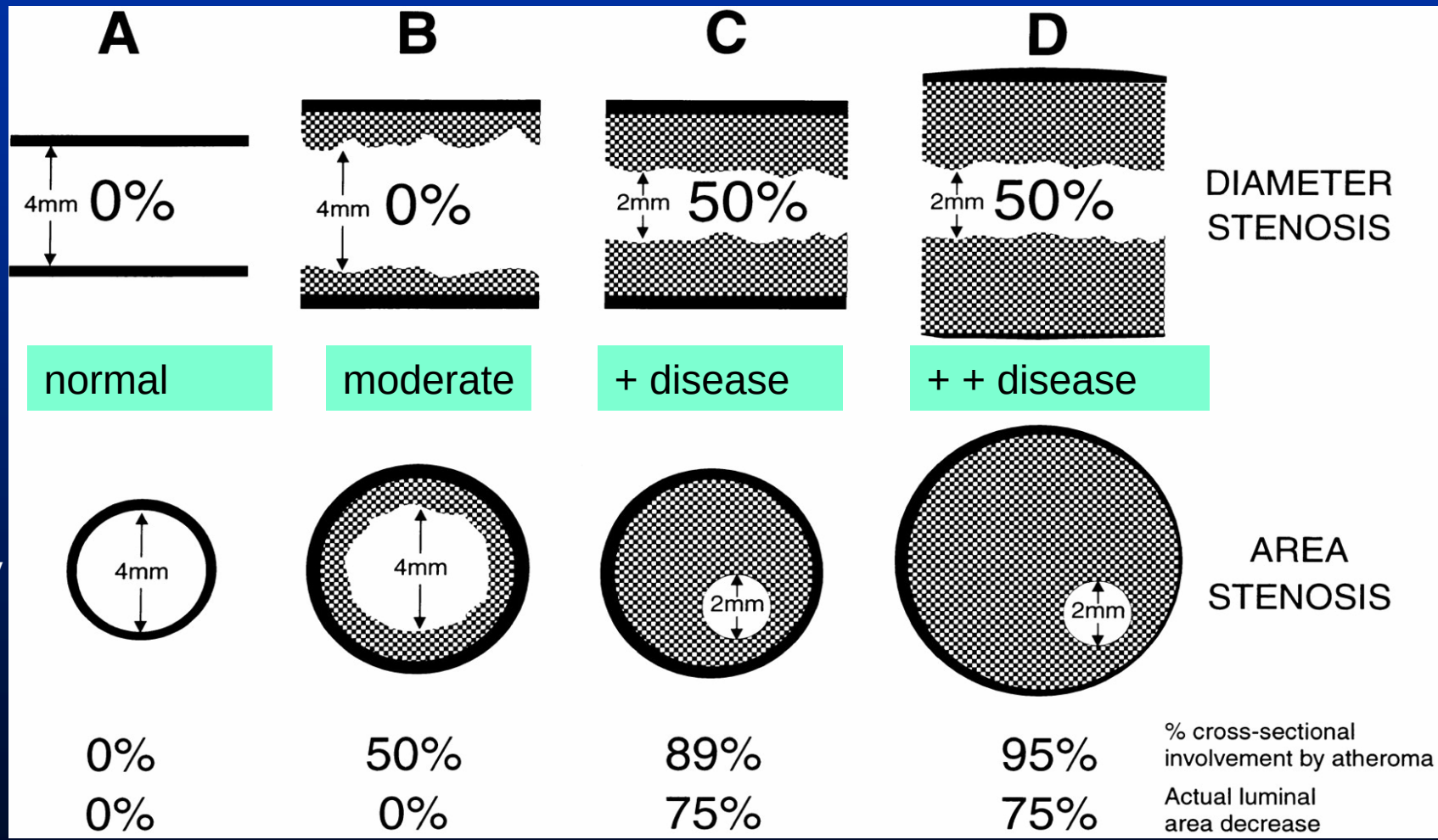


Lumen stenosis is delayed until the lesion occupies 40% of the potential lumen area

Remodeling classification

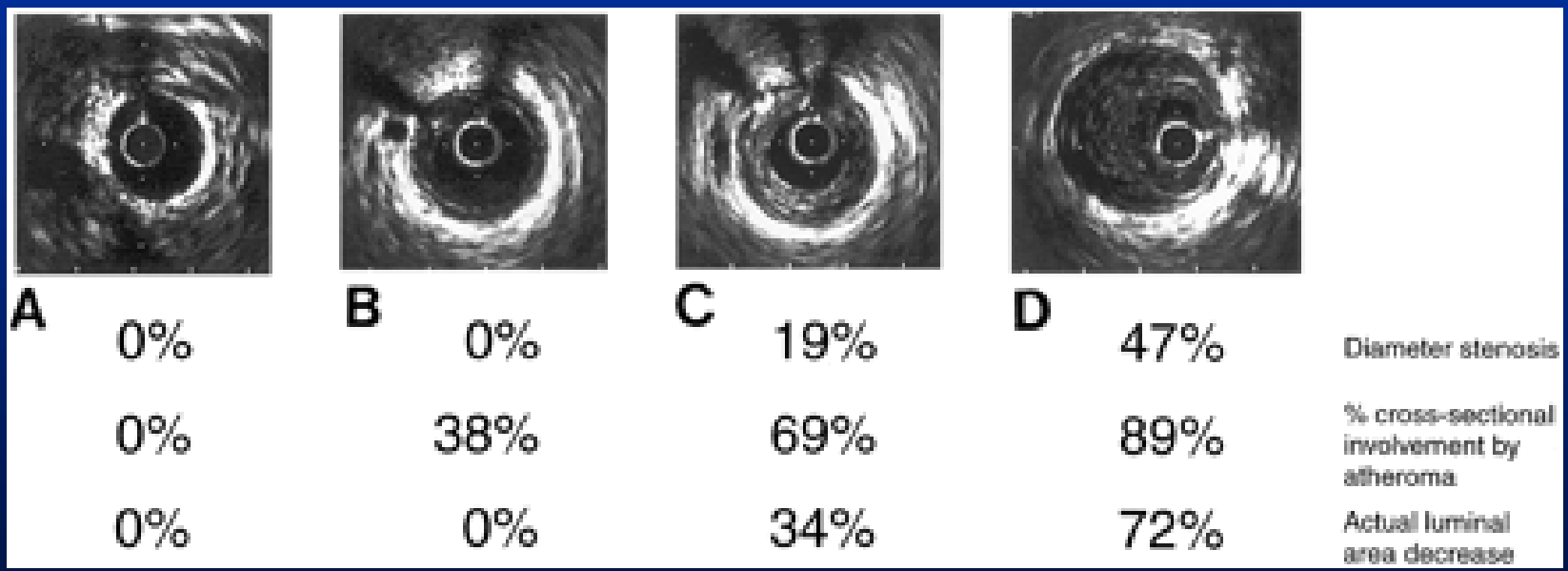


Atherosclerosis and vascular remodeling



M.C. Fishbein & R.J. Siegel, Circulation. 1996;94:2662-2666

Atherosclerosis & coronary remodeling IVUS views



M.C. Fishbein & R.J. Siegel, Circulation. 1996;94:2662-2666

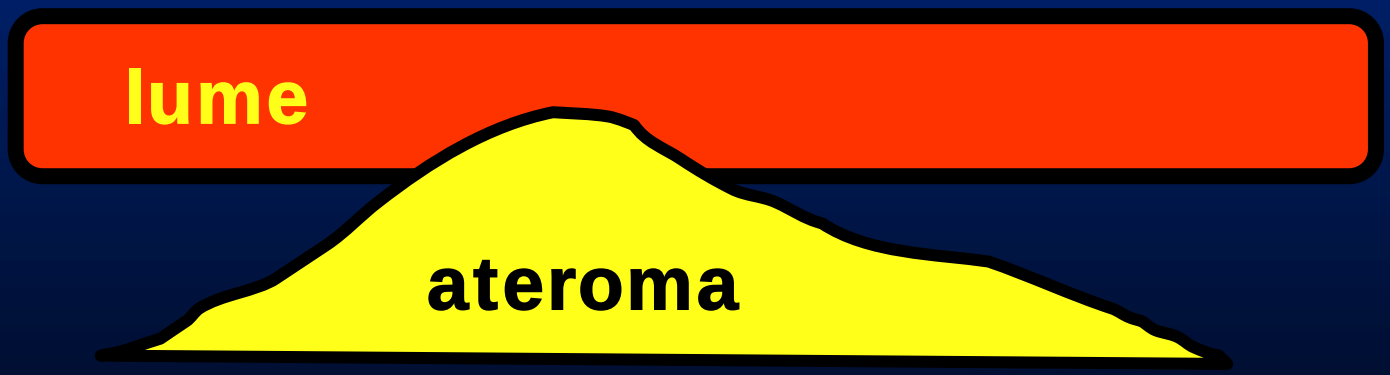
Irregolarità luminali: significato patologico

Il riscontro angiografico di alterazioni del lume indica quindi un'estensione della placca di almeno il 40% dell'area del vaso.

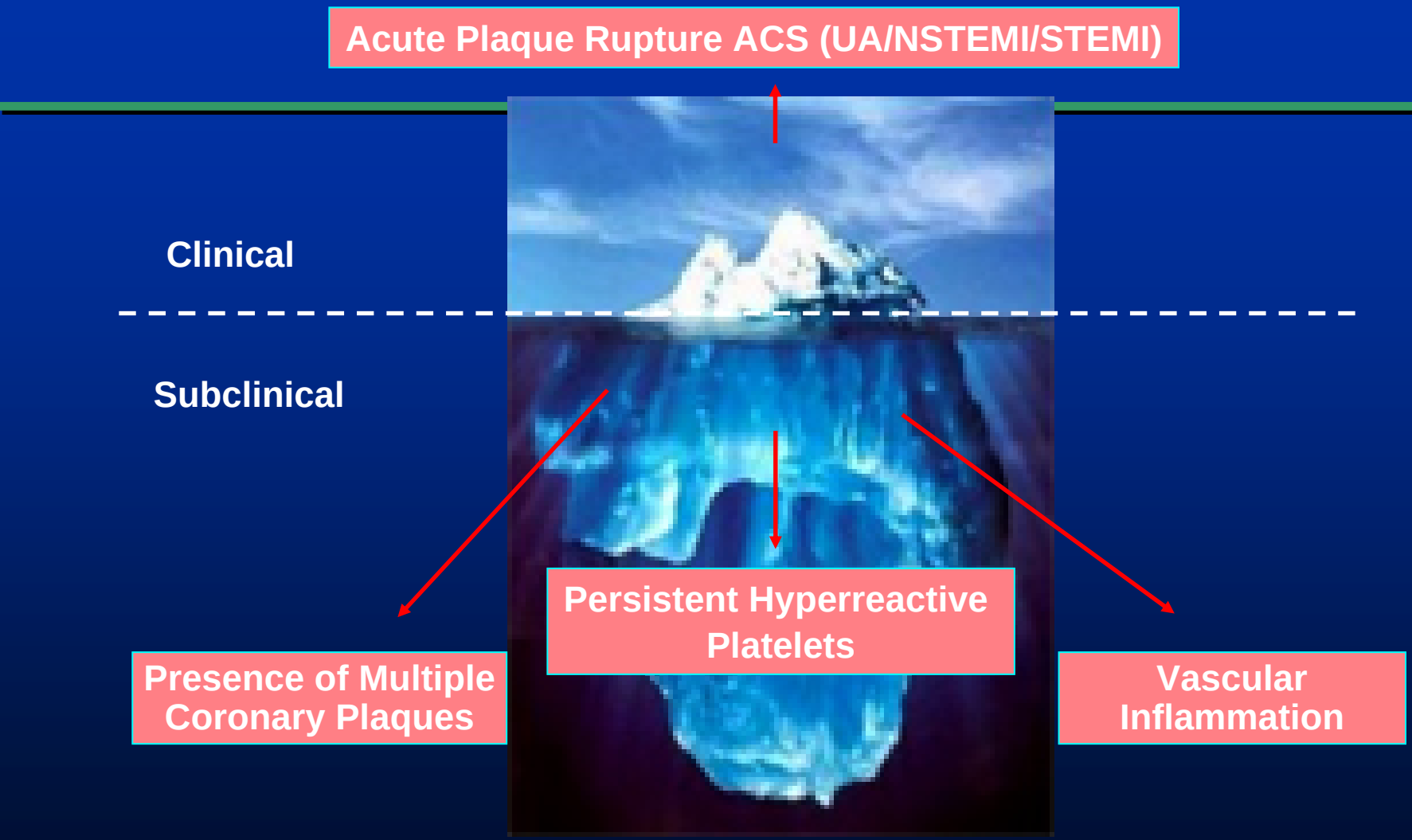
In questo caso la maggior parte dell'intero albero coronarico è già interessata dall'aterosclerosi

Placca/stenosi patologia/angiografia

- La stenosi visibile all'angiografia è un'impronta nella proiezione del lume
- punta affiorante dell'ateroma parietale
- falsa impressione di interessamento focale



ACS: Tip of the Atherothrombotic "Iceberg"



ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Adapted from Goldstein JA. *J Am Coll Cardiol.* 2002;39:1464-1467.

Angiographic limits: luminology

Our preoccupation with coronary luminology.

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

Eric J. Topol, Steven E.Nissen

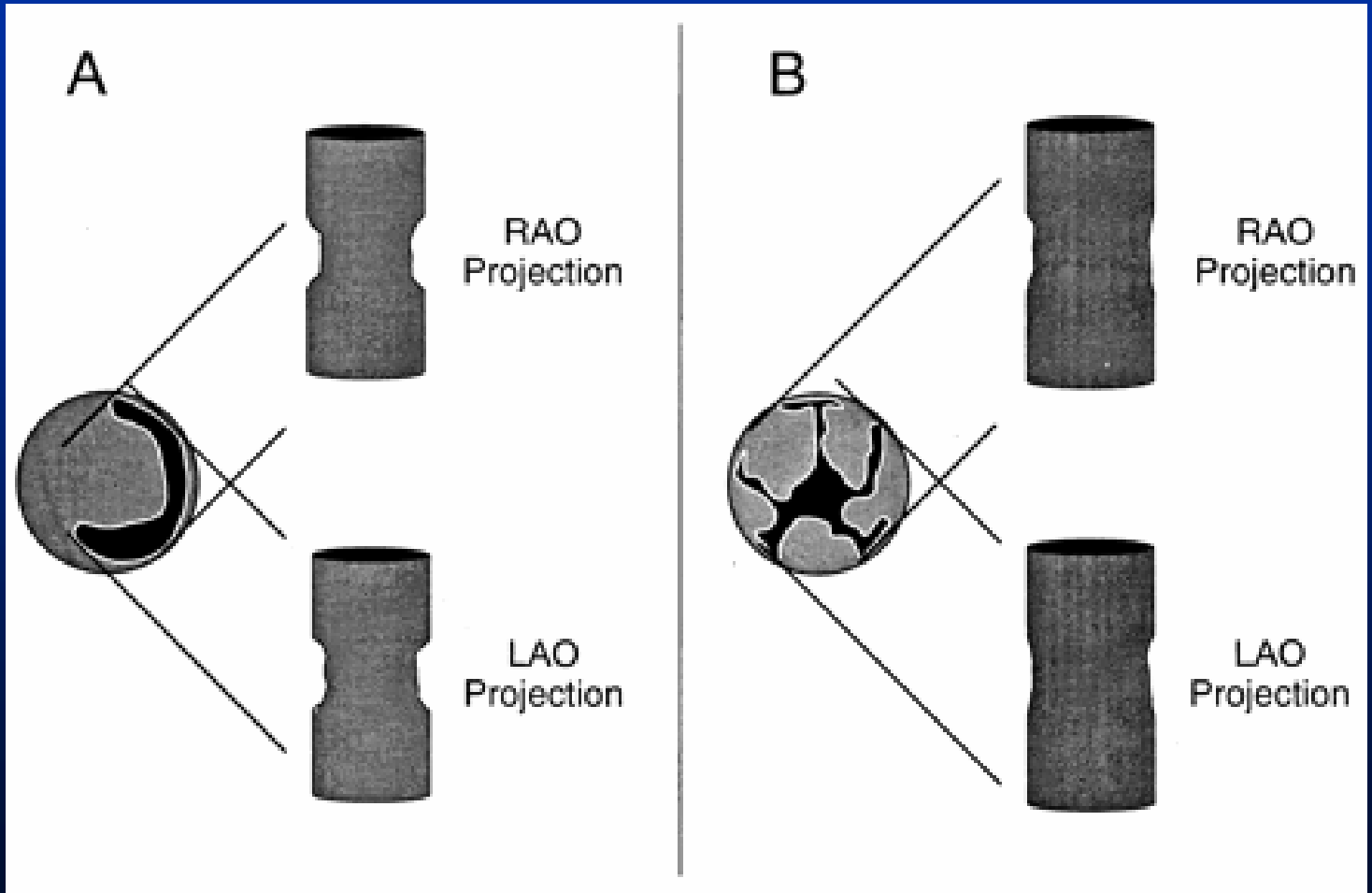
Circulation. 1995; 92:2333-2342.

After 50 years coronary angiography is still considered as “gold standard”

Coronary angiography: simple two-dimensional projection of the lumen (stenosis)

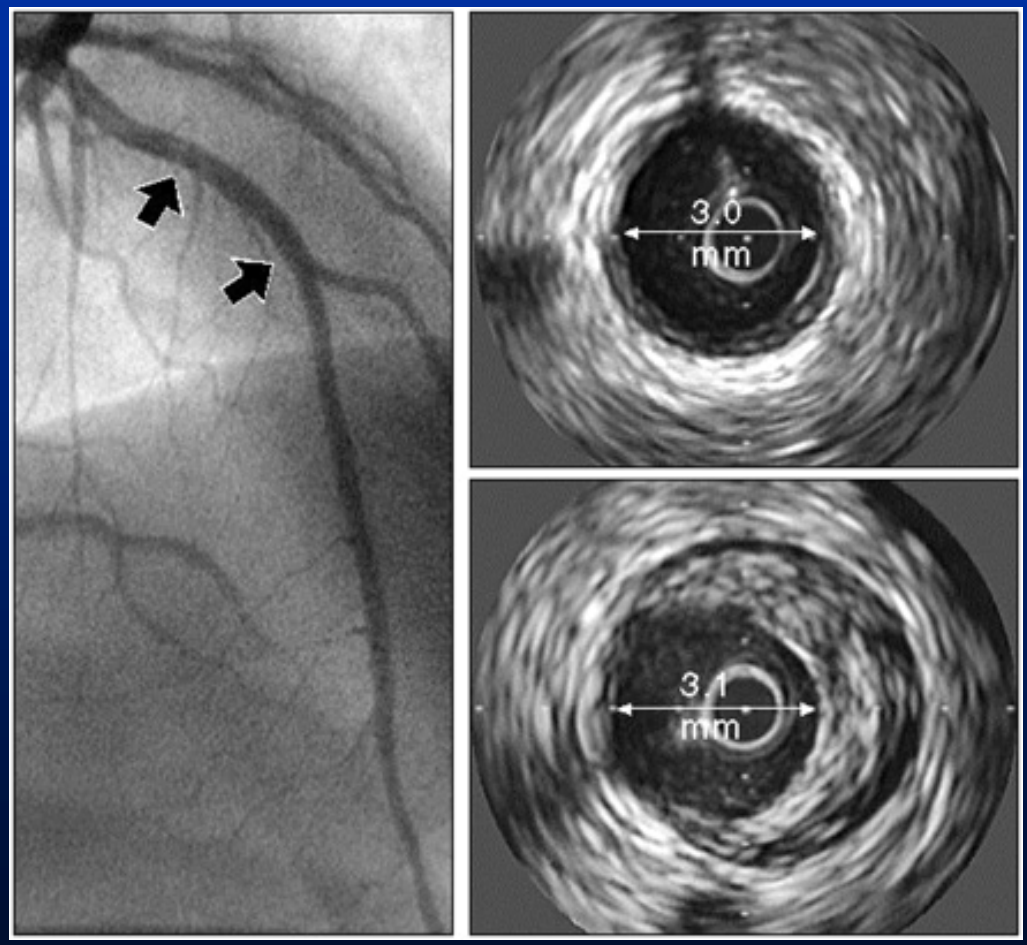
Atherosclerosis: disease of the arterial wall (plaque)

Limitation of angiographic projection



Eric J. Topol, Steven E.Nissen Circulation. 1995; 92:2333-2342

False-negative angiogram
Coronary remodeling

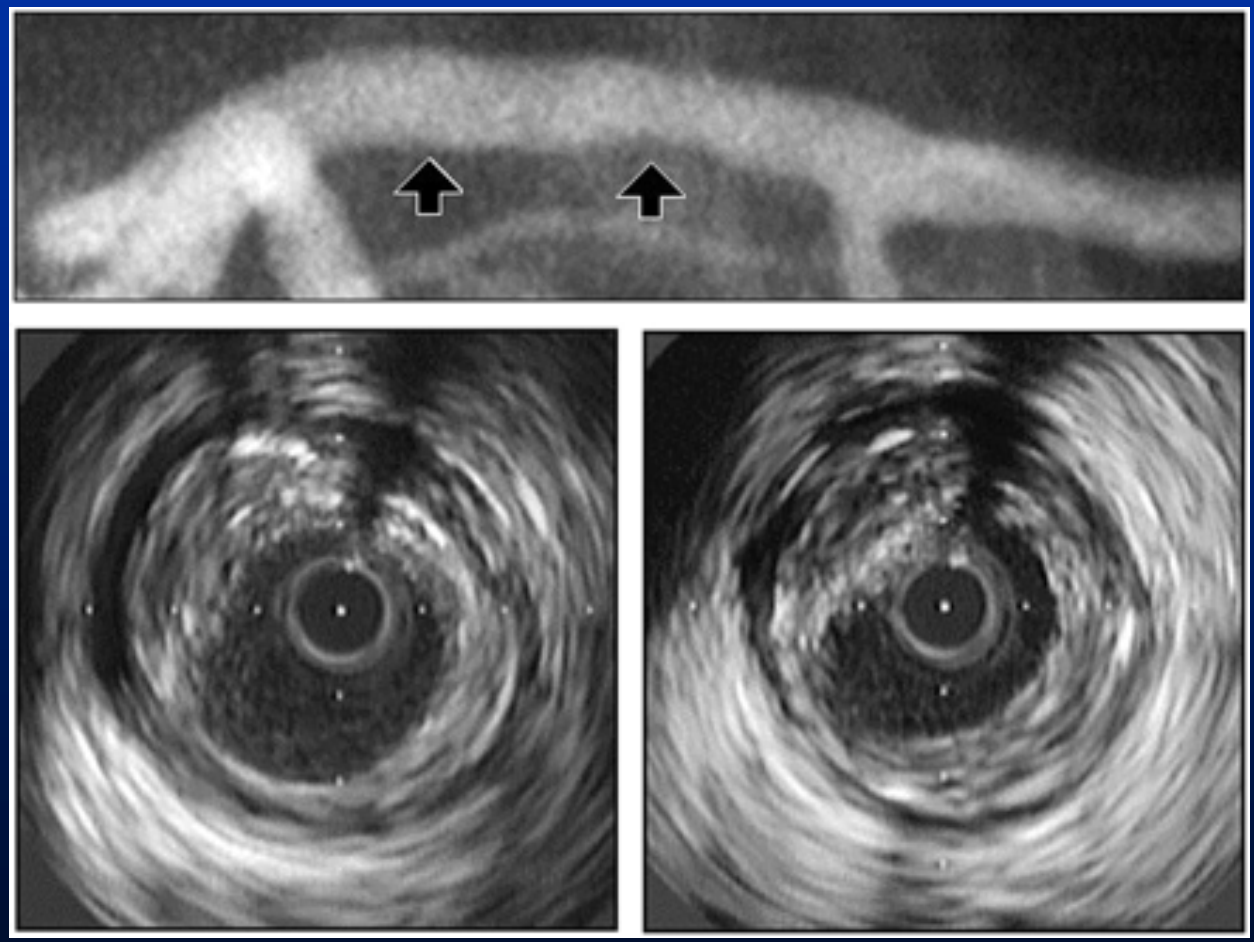


distal

proximal

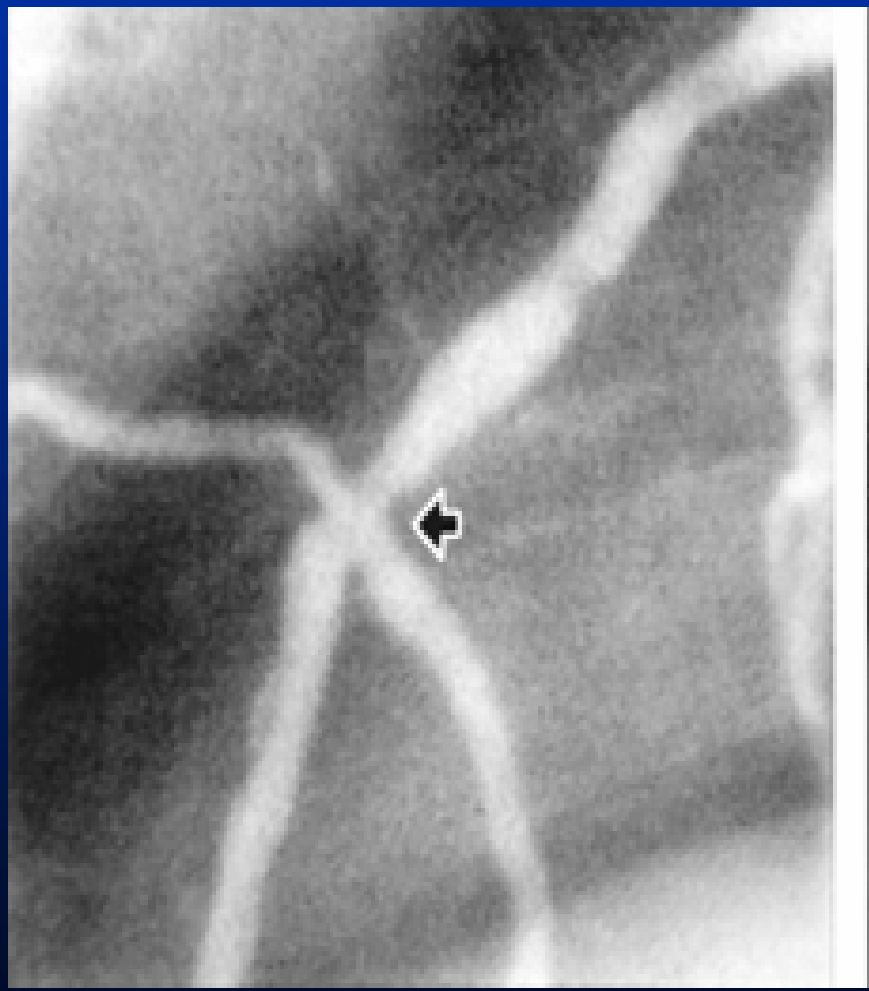
Steven E. Nissen, MD; Paul Yock, MD. *Circulation.* 2001;103:604

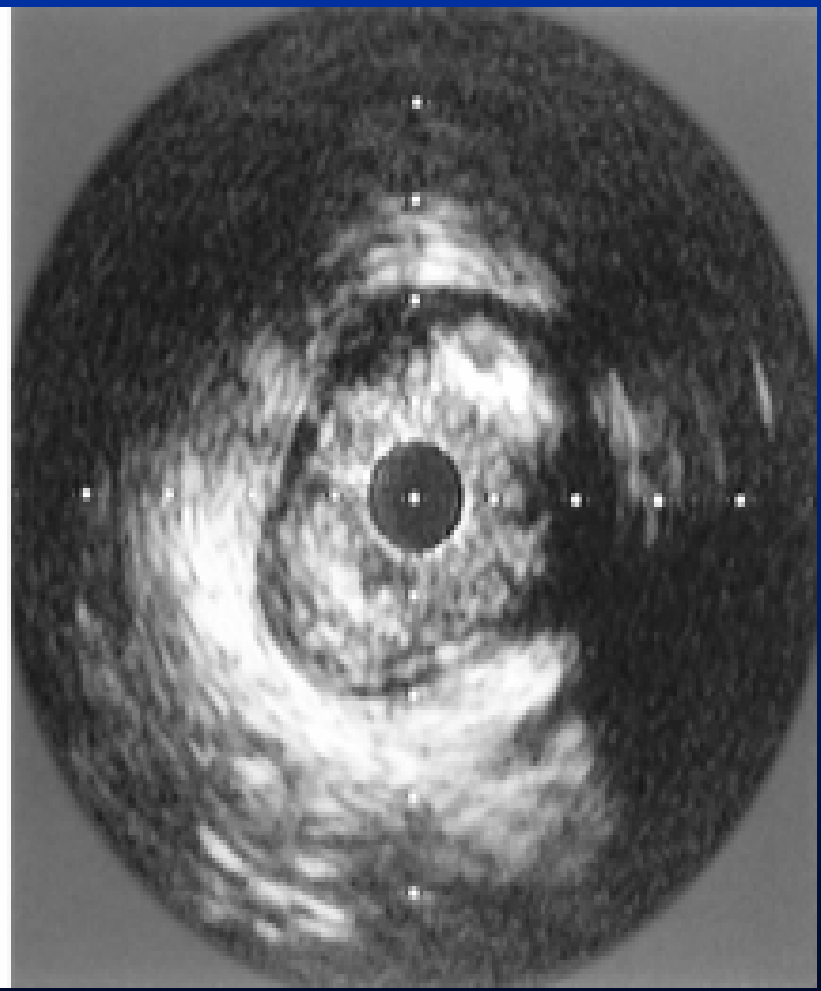
Angiographic underestimation of disease



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

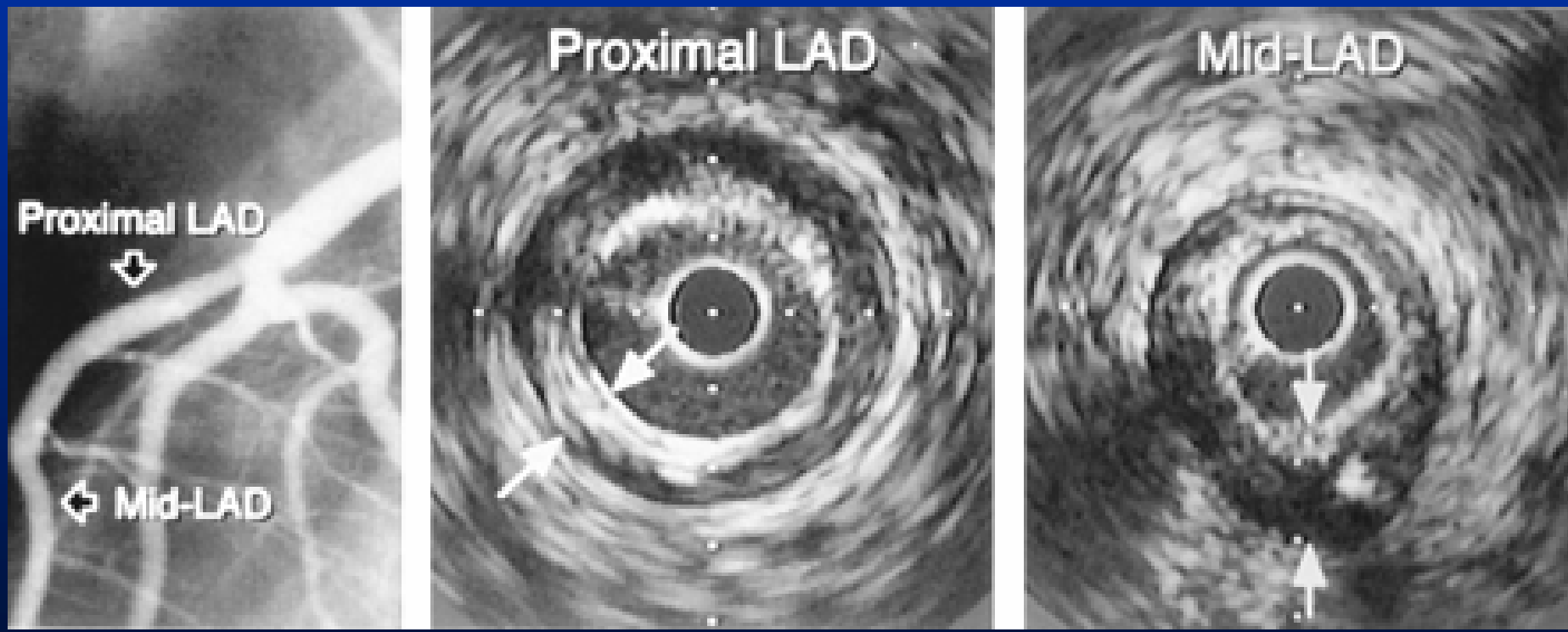
False-negative angiogram: bifurcation





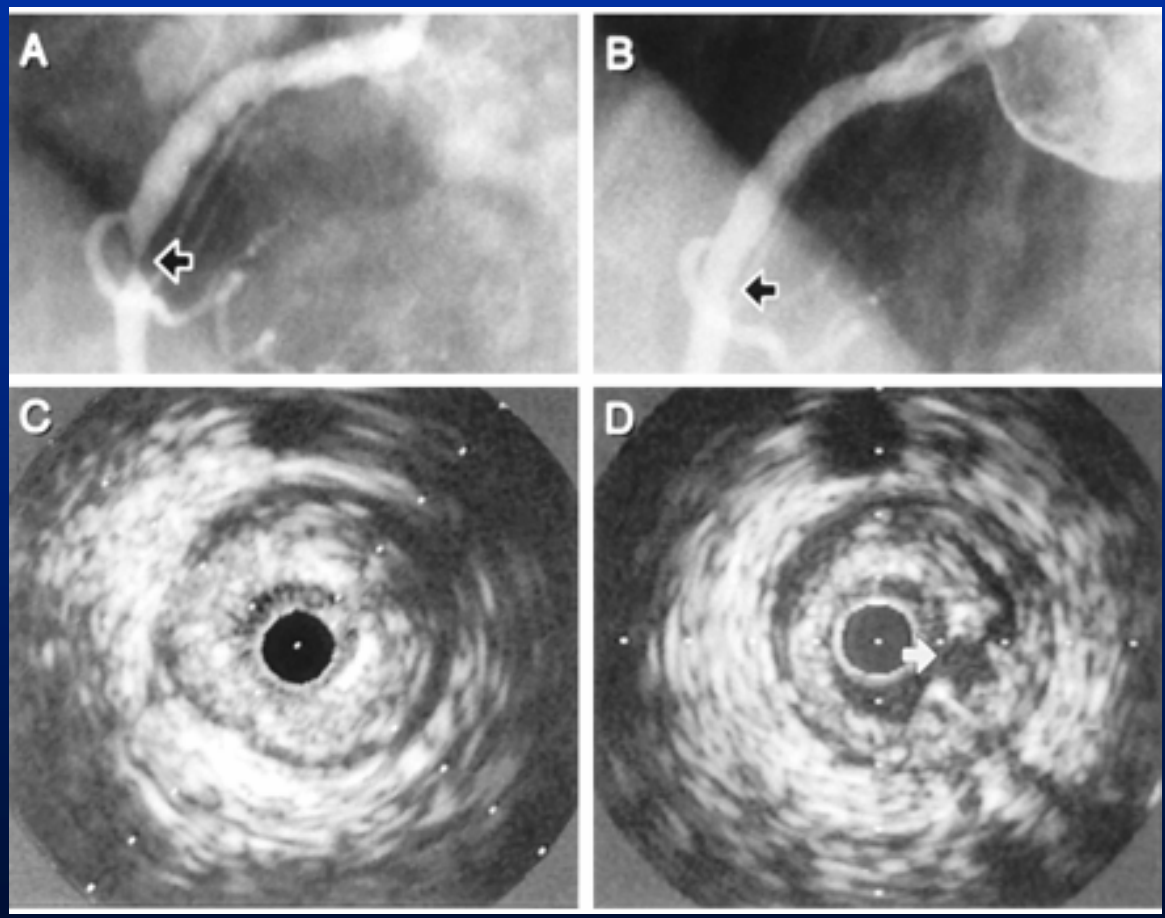
Eric J. Topol, Steven E.Nissen Circulation. 1995; 92:2333-2342

False-negative angiogram: severe concentric disease



Eric J. Topol, Steven E.Nissen Circulation. 1995; 92:2333-2342

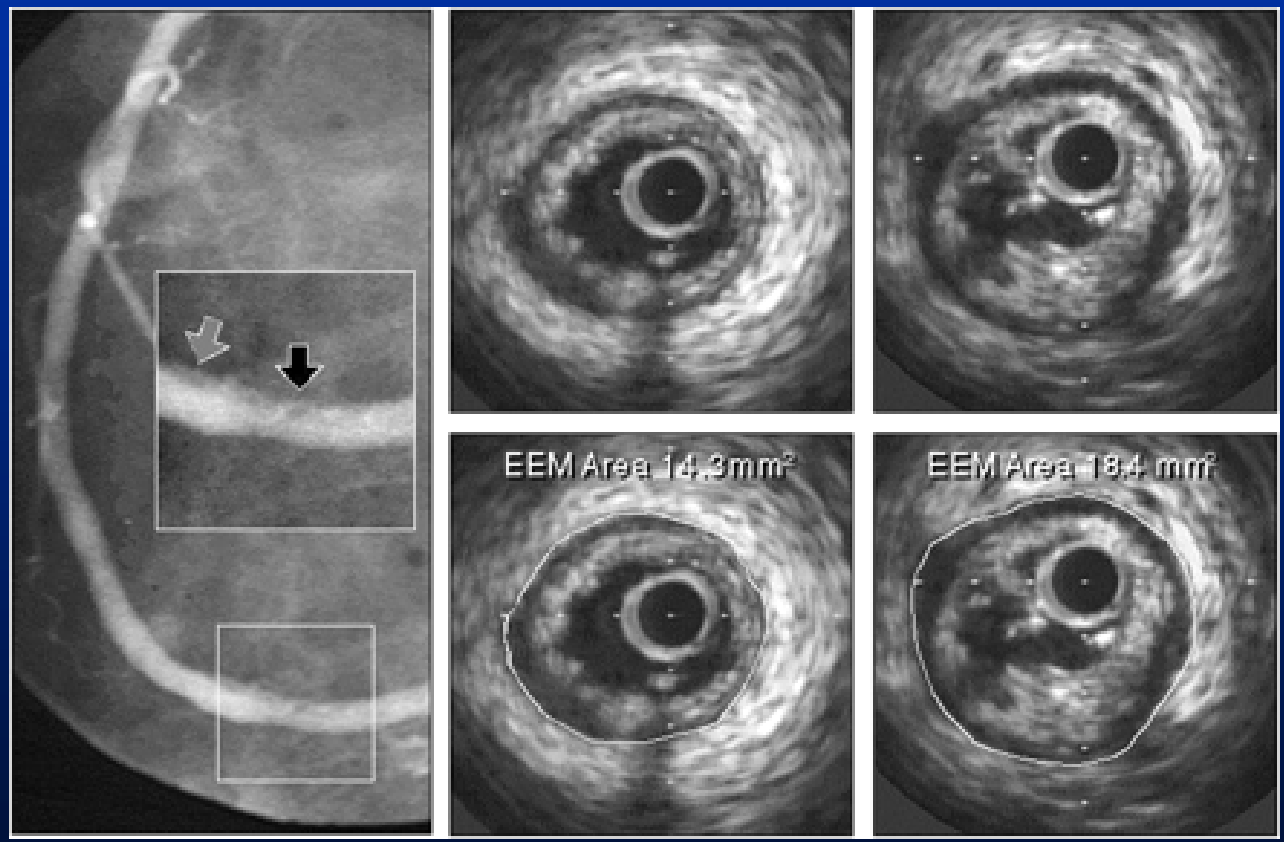
Overestimation of lumen gain by angiography after PTCA



Eric J. Topol, Steven E.Nissen Circulation. 1995; 92:2333-2342

Positive remodeling

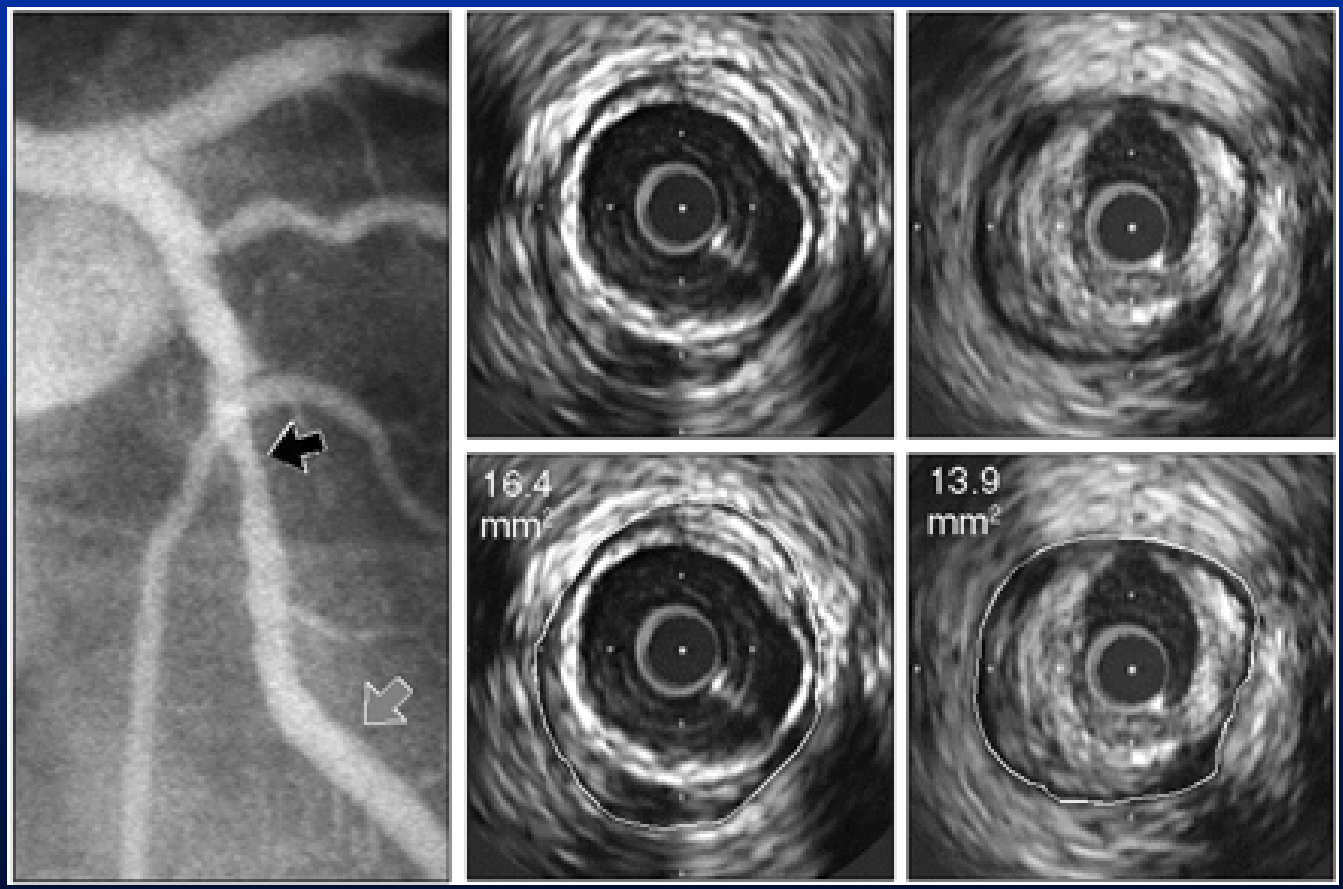
AMI after lysis



proximal distal

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

Negative remodeling



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

Early Atherosclerosis

Enos WF et al.

Coronary disease among soldiers killed in action in Korea: preliminary report.

JAMA.1953;152:1090-1093.

Mc Namara JJ et al.

Coronary artery disease in combat casualties in Vietnam

JAMA. 1971; 216:1185-1187

Early Atherosclerosis

E. Murat Tuzcu et al.

High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults

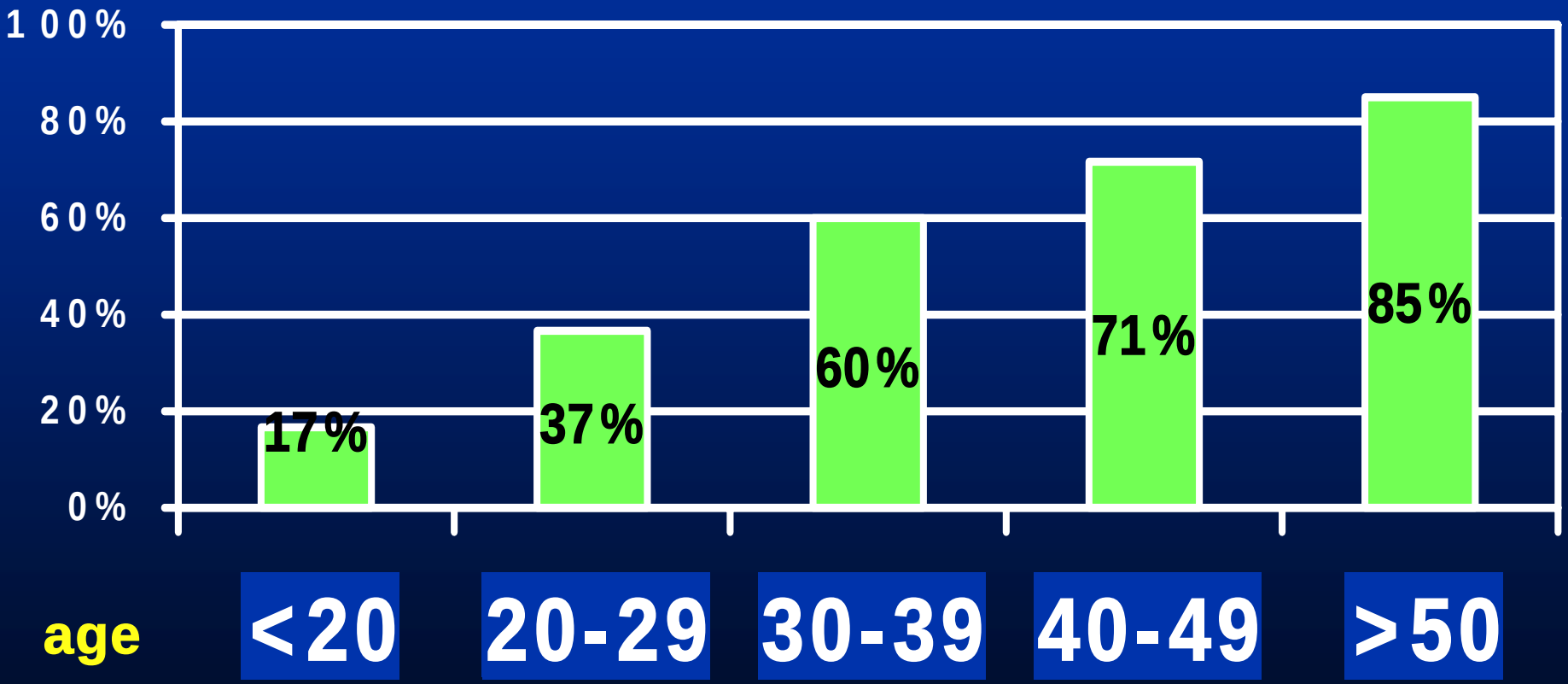
Evidence from intravascular ultrasound

Circulation. 2001; 103: 2705-2710.

Prevalence of atherosclerosis: (heart transplant donor population)

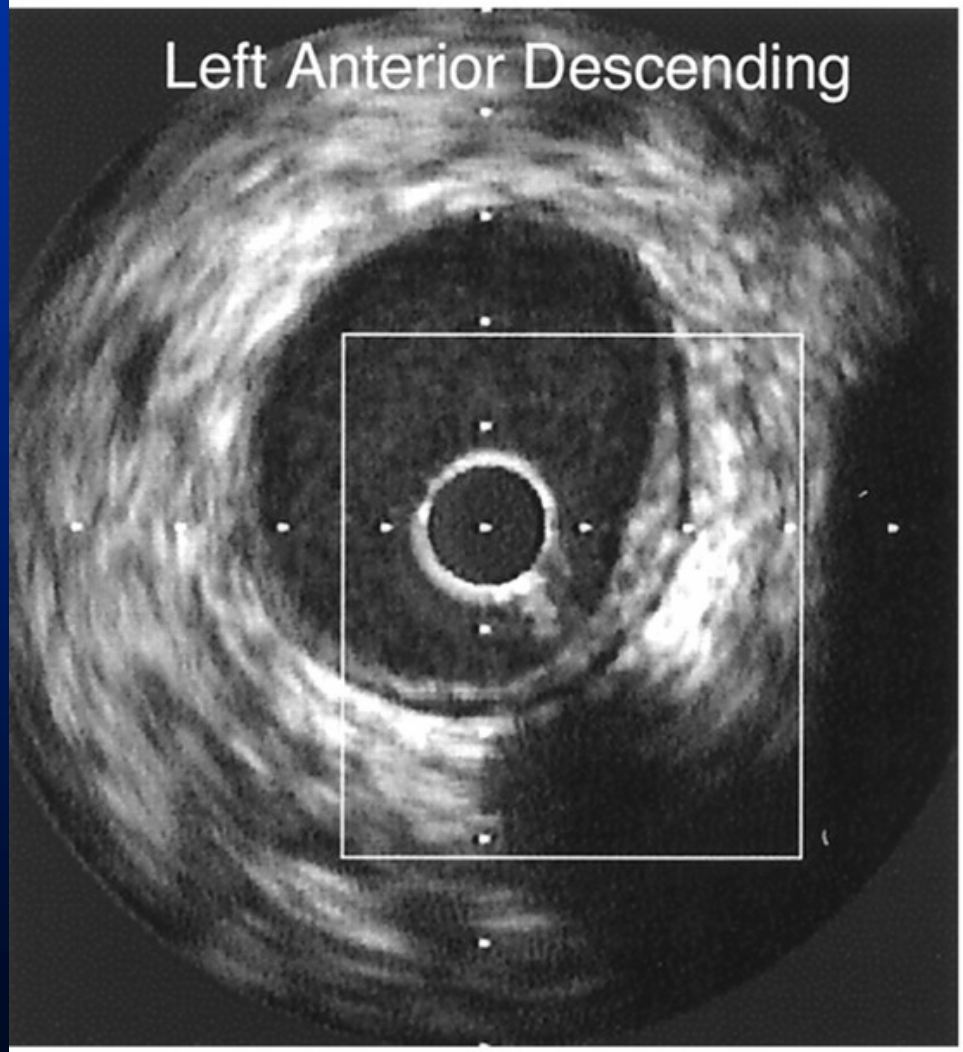
- **17% < 20 years old**
- **85% ≥ 50 years old**
- **Angiography completely normal in 92 %, irregularity in 8 %**

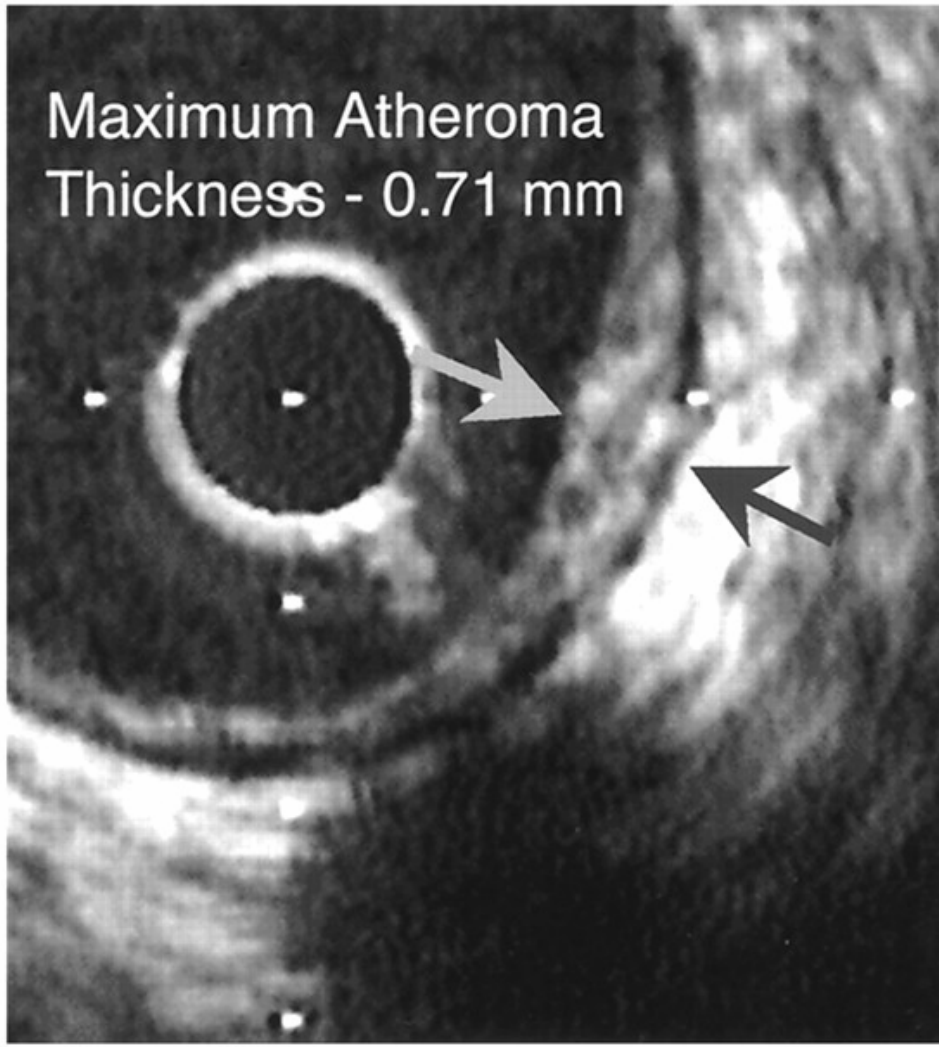
Coronary Atherosclerosis in 262 Heart Transplant donors



Circulation. 2001; 103: 2705-2710.

Early Atherosclerosis





Evolution of Atherosclerosis model

a **Gradual luminal narrowing**

b **Plaque rupture**

c **Inflammation**

Davies, MJ and Thomas A.C.

Plaque fissuring:

The cause of acute myocardial infarction, sudden ischemic death and crescendo angina.

Br. Heart J. 53:363, 1985.

Falk, E.

Unstable angina with fatal outcome:

Dynamic coronary thrombosis leading to infarction and/or sudden death: Autopsy evidence of recurrent mural thrombosis with periferal embolization culminating in total vascular occlusion.

Circulation 71:699, 1985

DeWood MA, Spores J , Notske R. et al.

Prevalence of coronary occlusion during the early hours of transmural myocardial infarction.

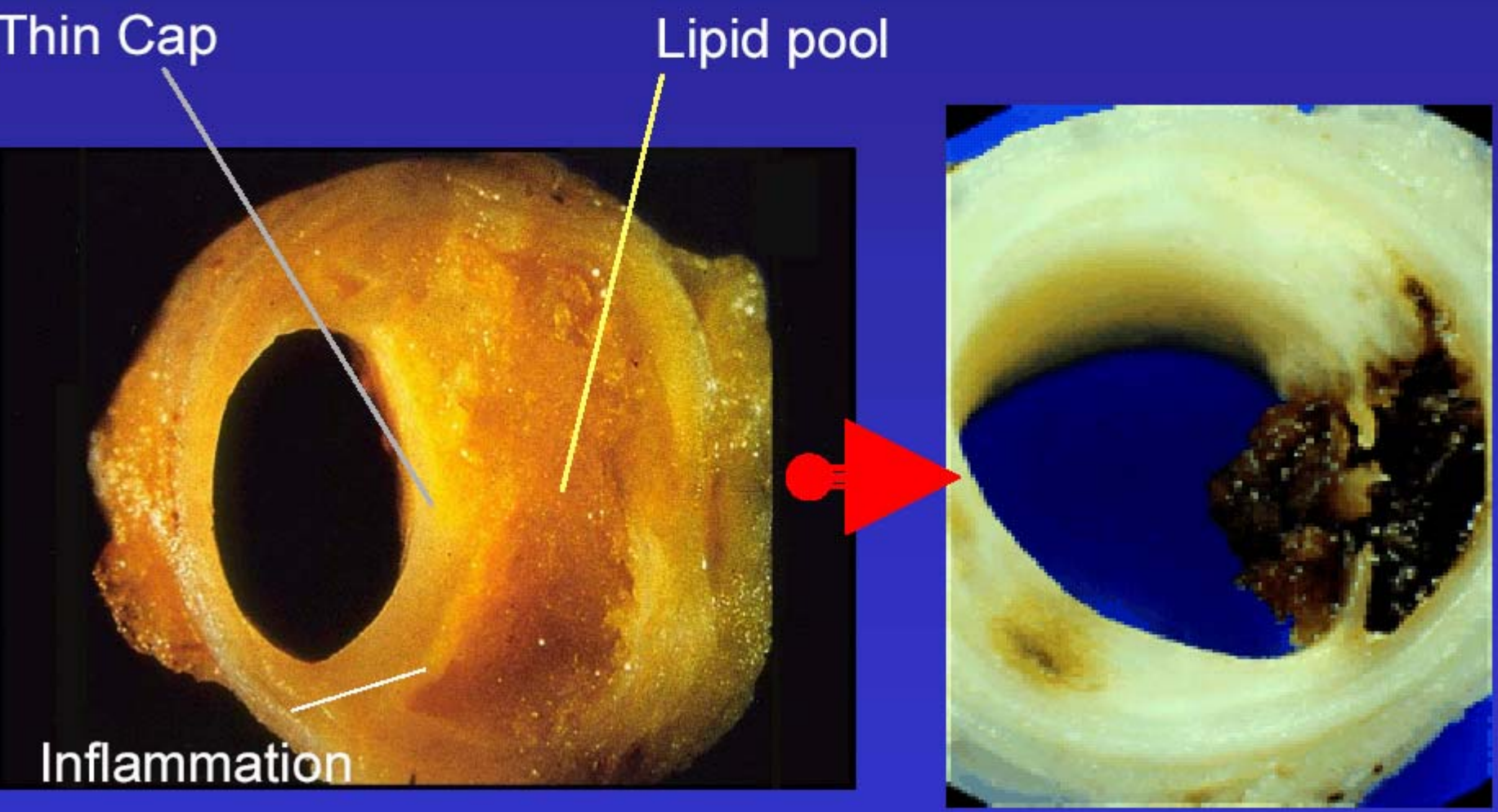
New Engl J Med. 1980; 303:897-902.

Costantinides P.

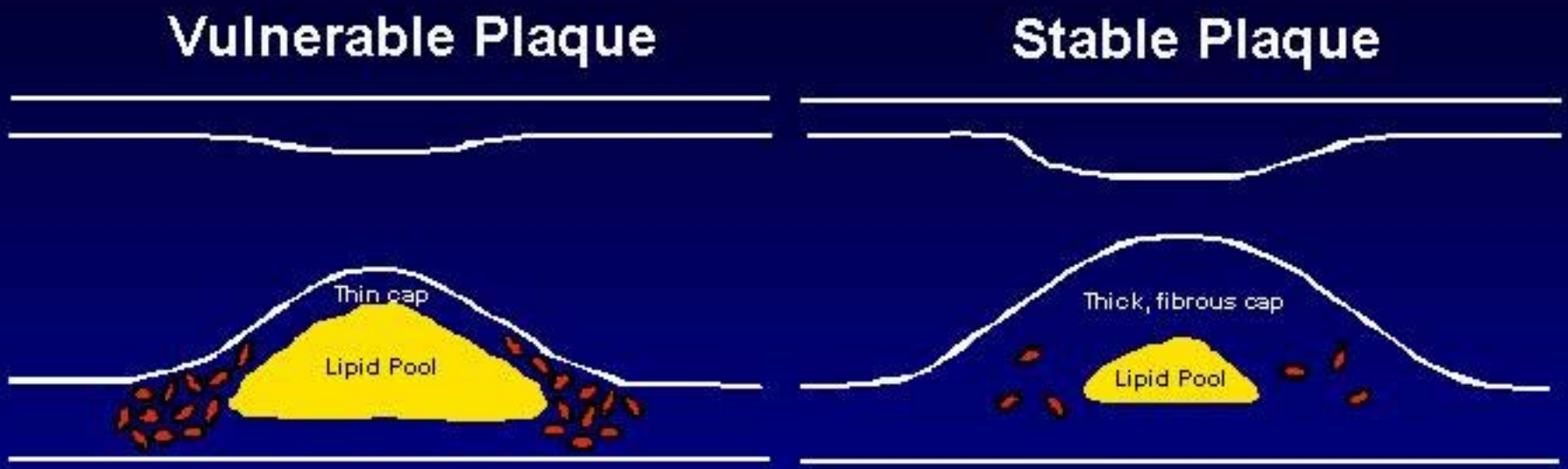
Plaque fissuring in human coronary artery thrombosis.

J. Atherosclerosis Res. 1966; 6: 1-17.

The vulnerable plaque mantra



Vulnerable Plaque



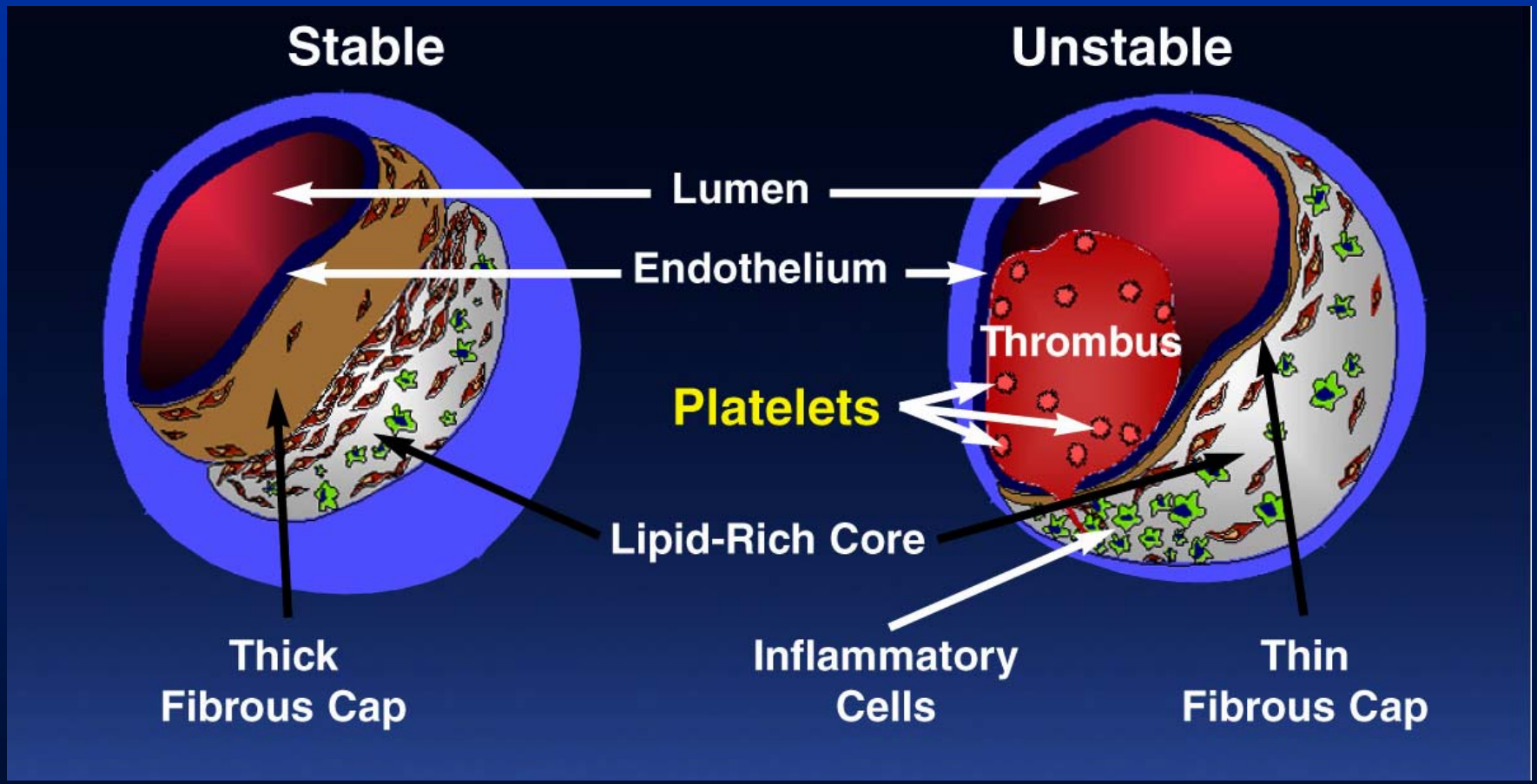
High	**Lipid conc.**	Low
Thin	**Cap**	Thick
Abundant	**Macrophages**	Few

Cappuccio fibroso: struttura dinamica

Bilanciamento

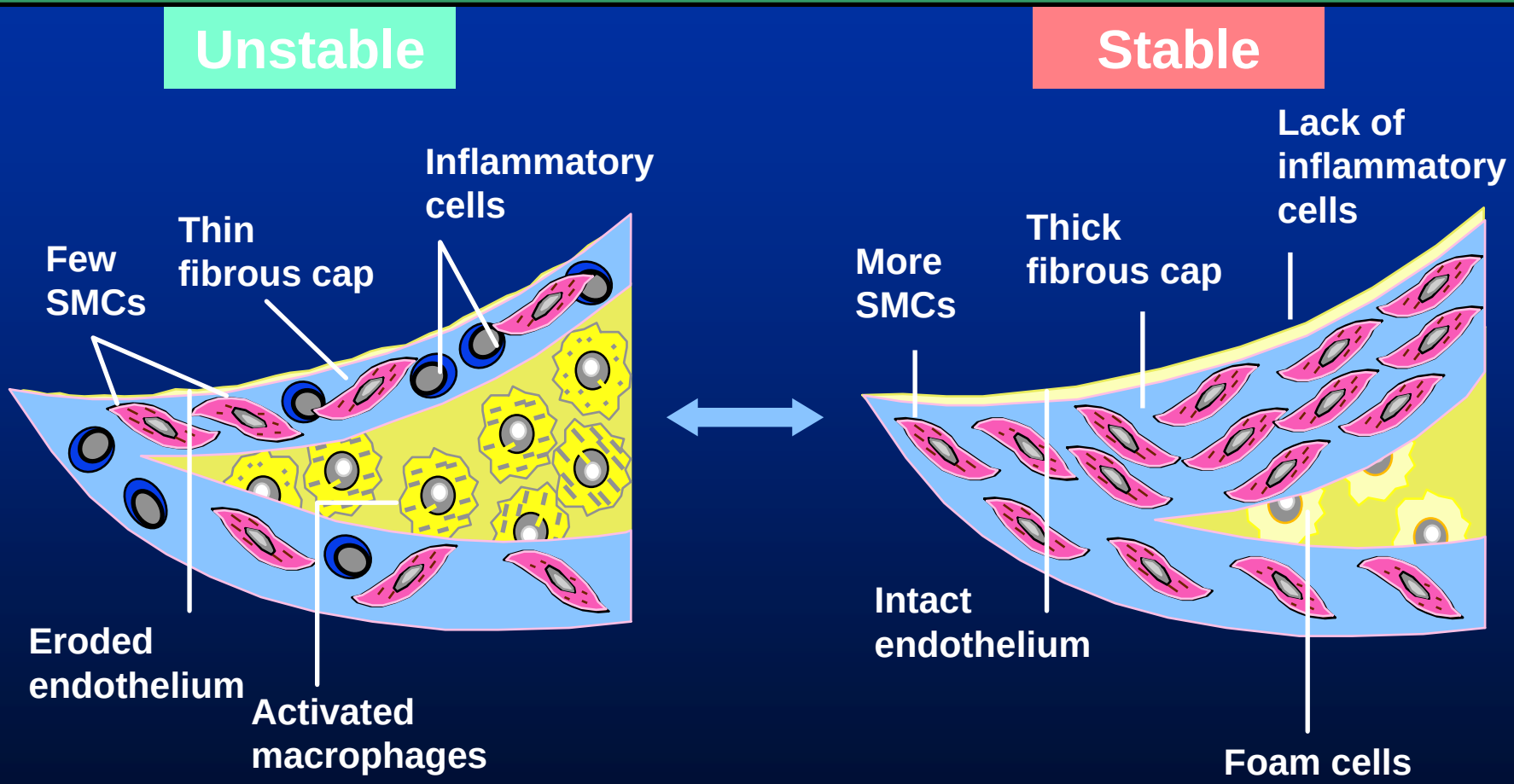
- **Sintesi: cellule muscolari lisce e matrice proteo-glicanica**
- **Degradazione : cellule infiammatorie→peptidasi**

Atherothrombosis: Thrombus Superimposed on Atherosclerotic Plaque



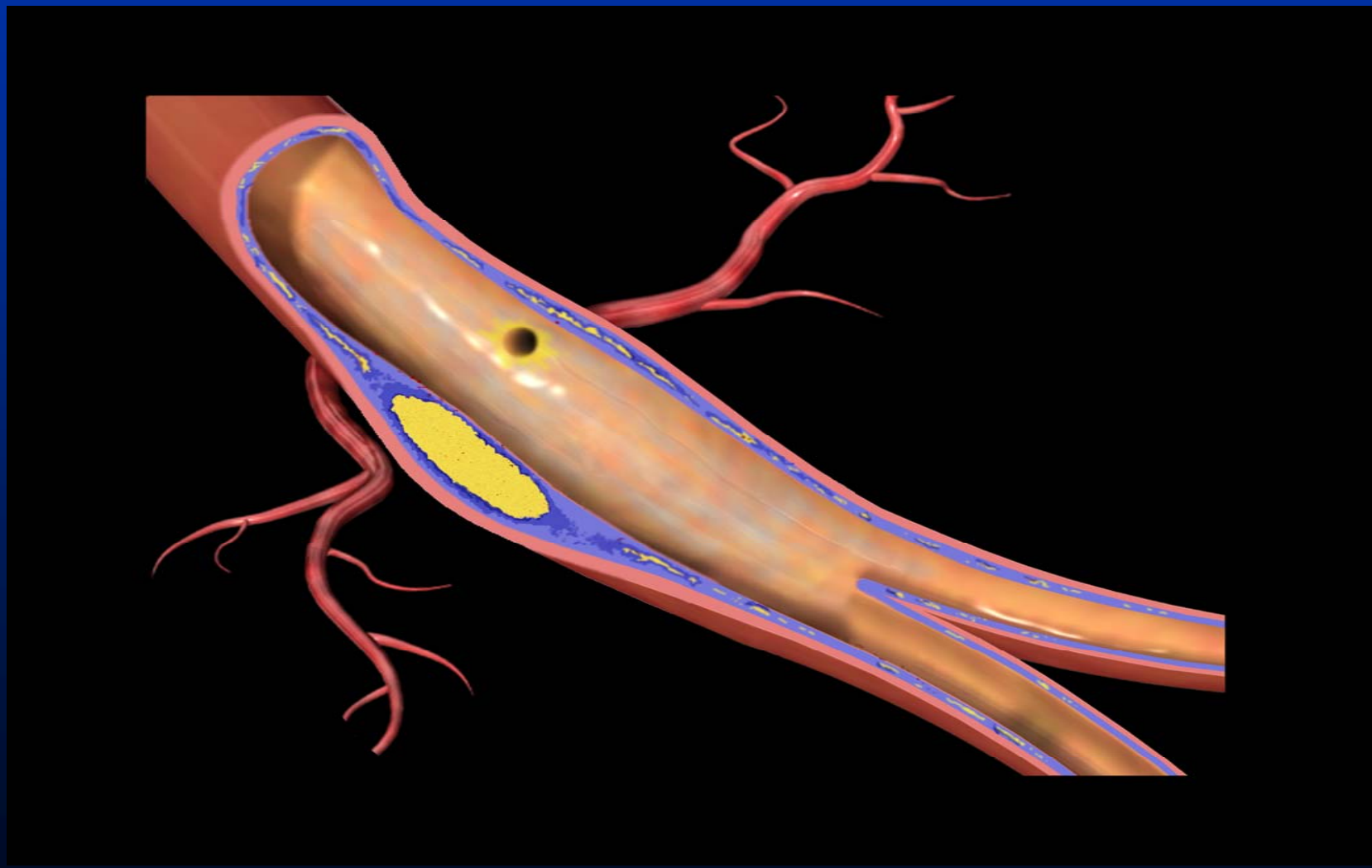
Adapted from Falk E, et al. *Circulation.* 1995;92:657-671.

Characteristics of Unstable and Stable Plaque



Libby P. *Circulation*. 1995;91:2844-2850.

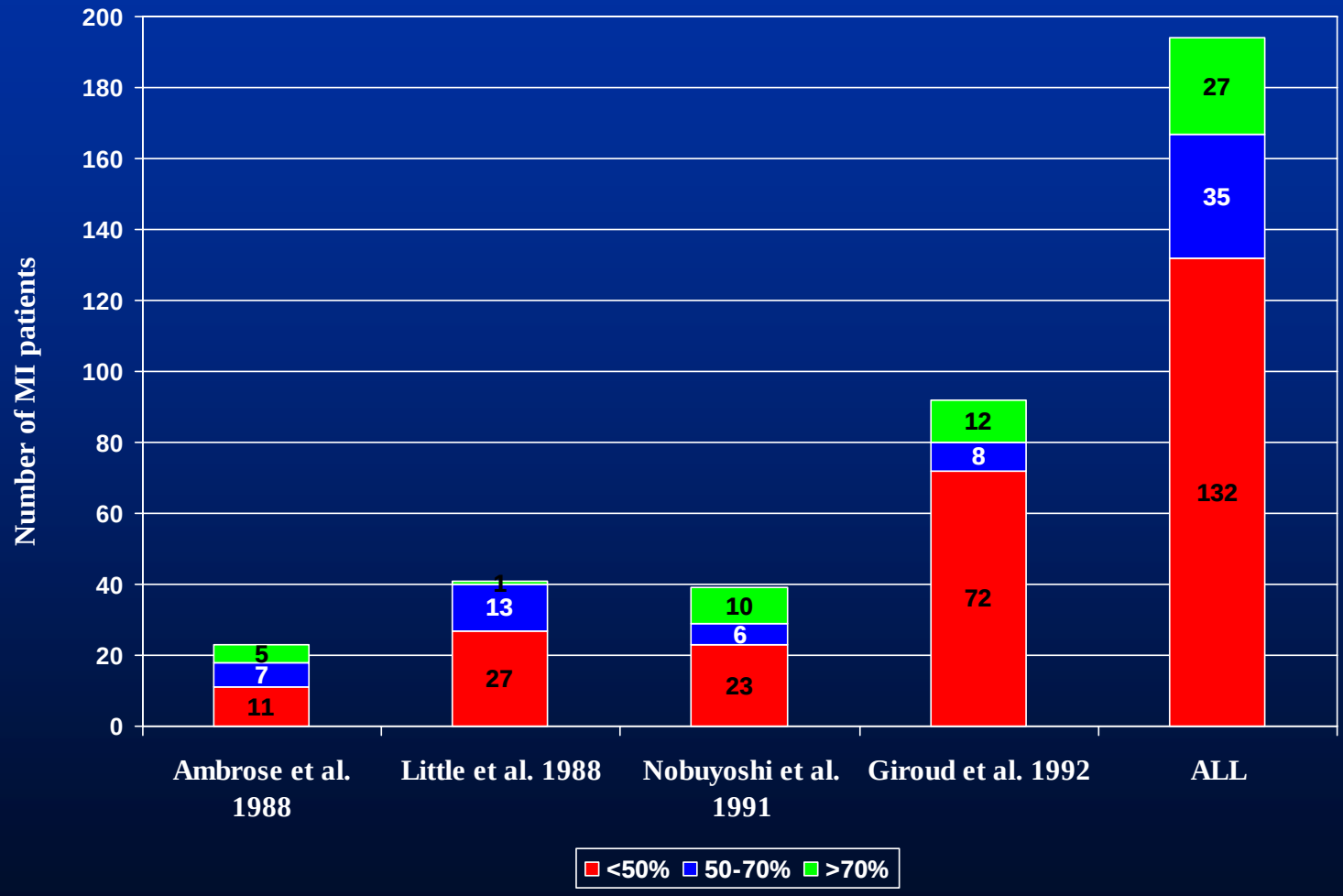
Vulnerable plaque



The propensity for plaques to rupture is independent of plaque size

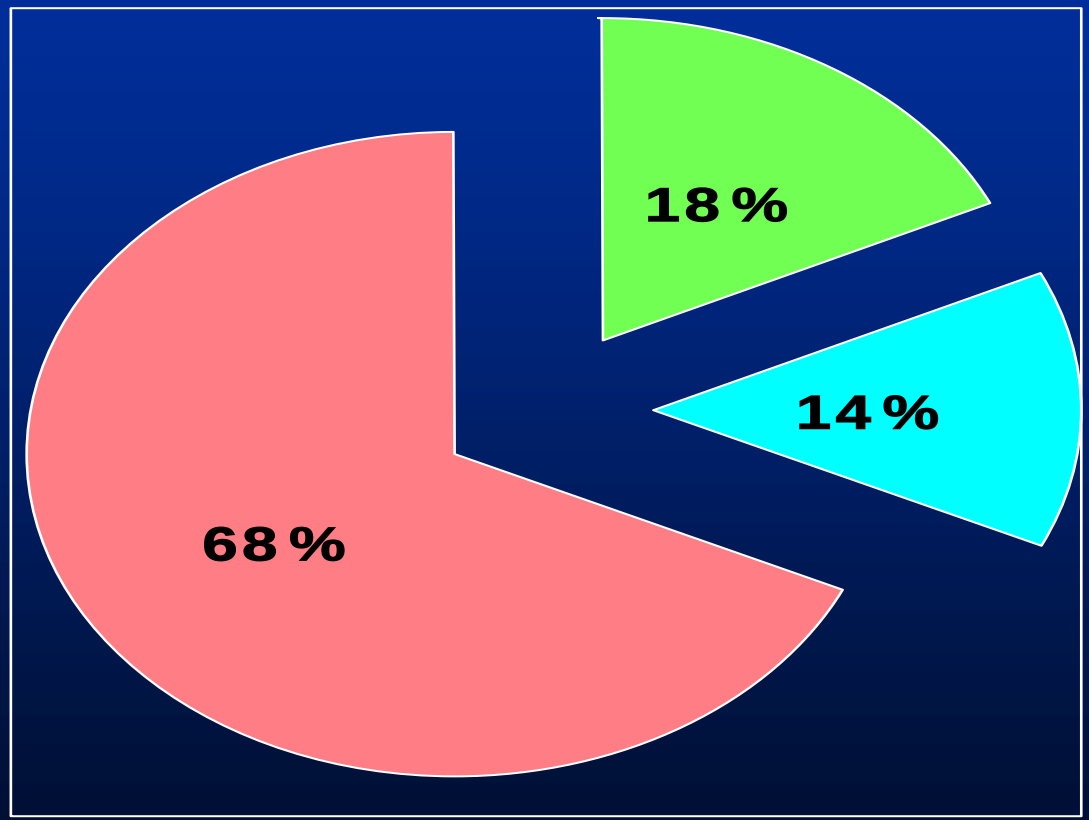
Michael C. Fishbein, MD; Robert J. Siegel, MD
How Big Are Coronary Atherosclerotic Plaques That Rupture?
Circulation. 1996;94:2662-2666.

AMI Evolve Most Frequently From Plaques With Mild to Moderate Obstruction



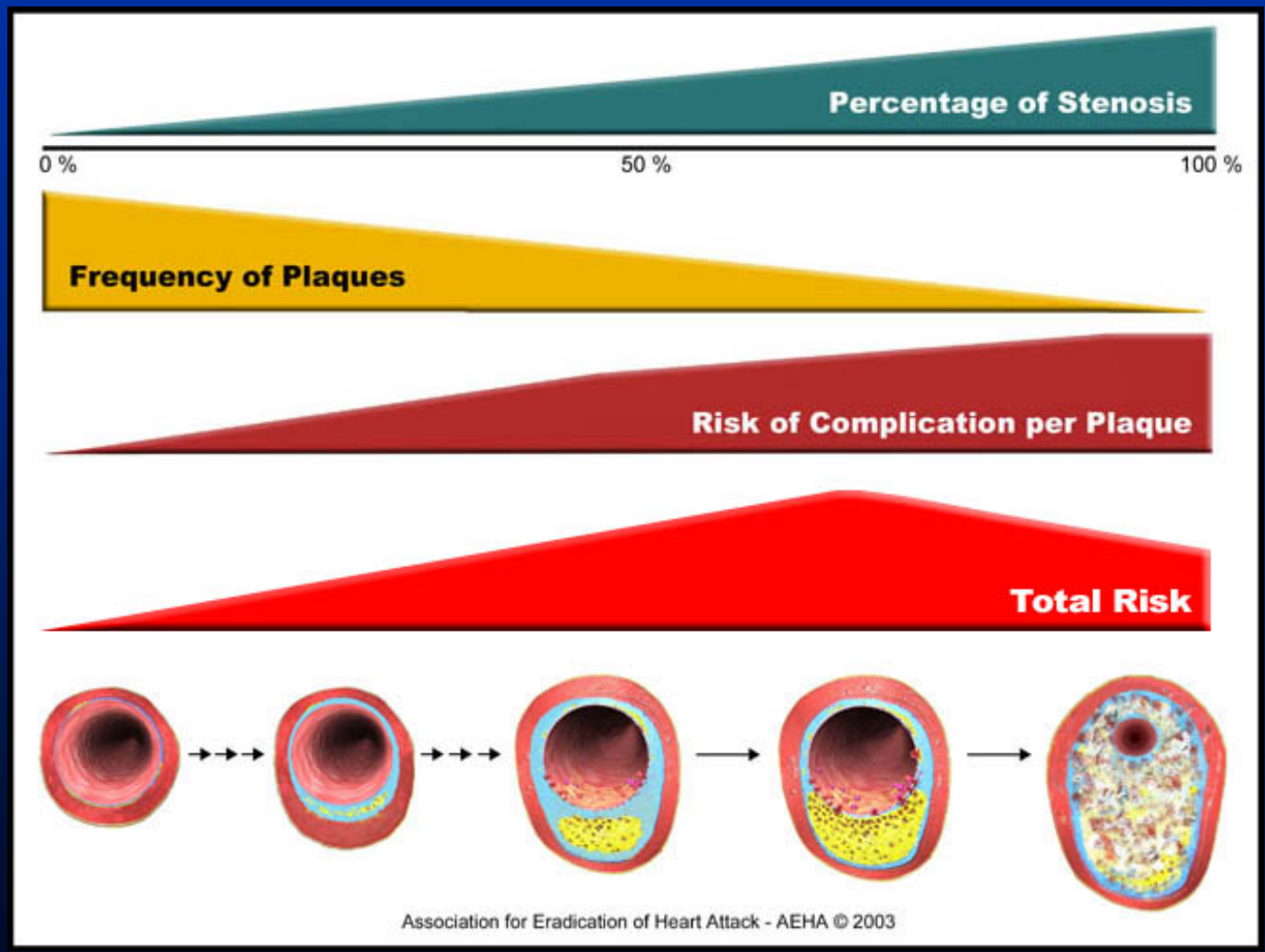
E Falk, PK Shah, V Fuster. Circulation 1995;92:657

Coronary stenosis severity prior to AMI

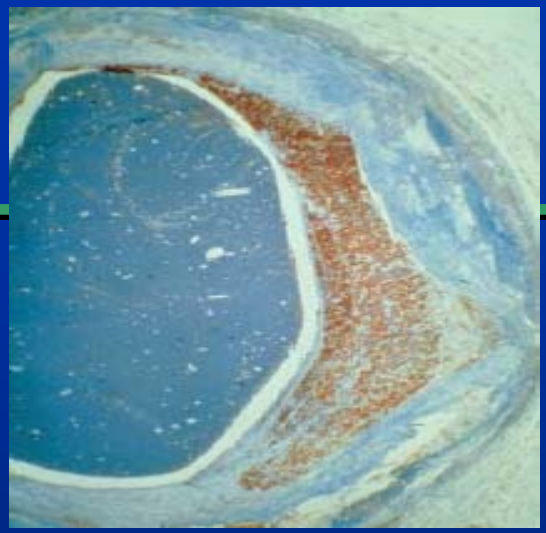


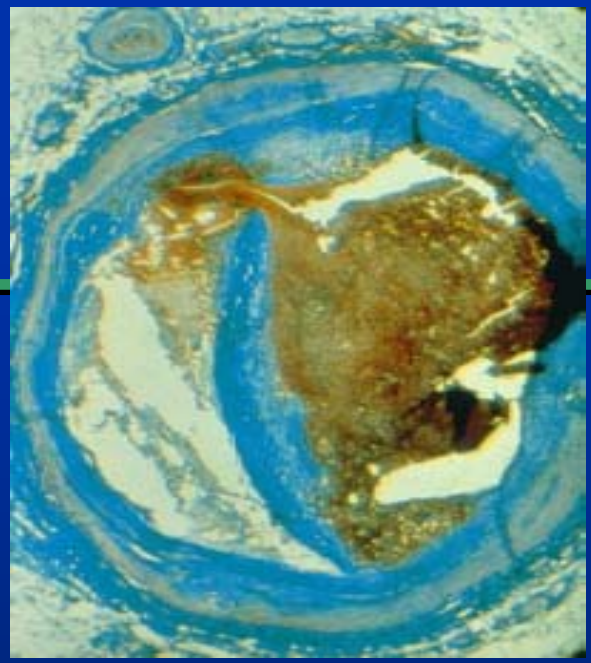
E Falk, PK Shah, V Fuster. Circulation 1995;92:657

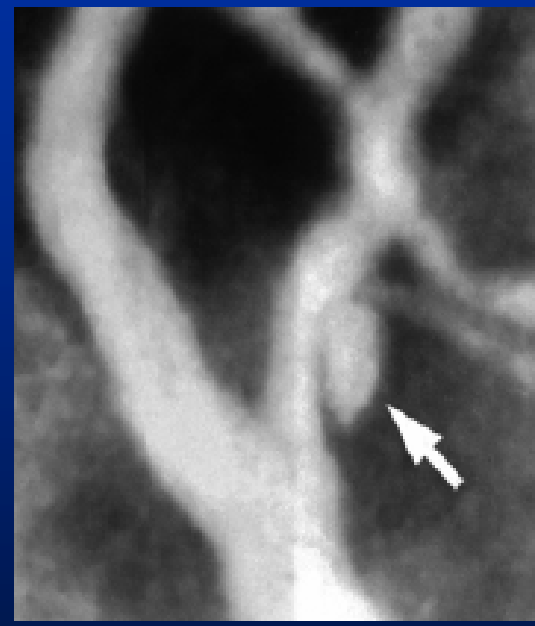
Non-Stenotic Vulnerable Plaques overall are More Dangerous Since they are far More Frequent than Stenotic Ones

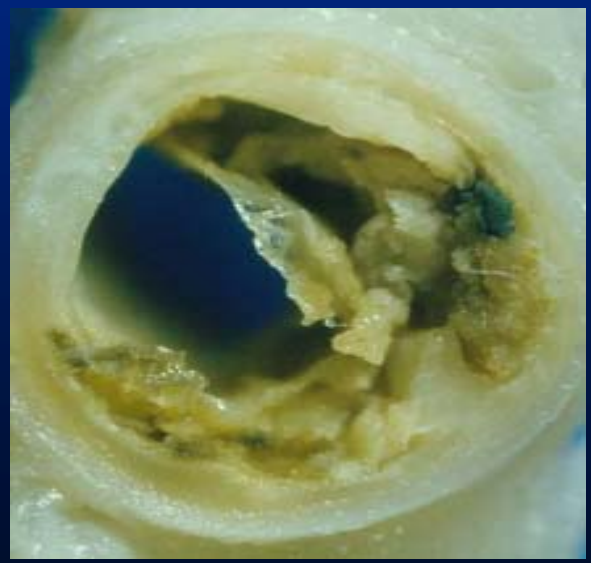


Naghavi et al. *Circulation.* 2003;108:1664

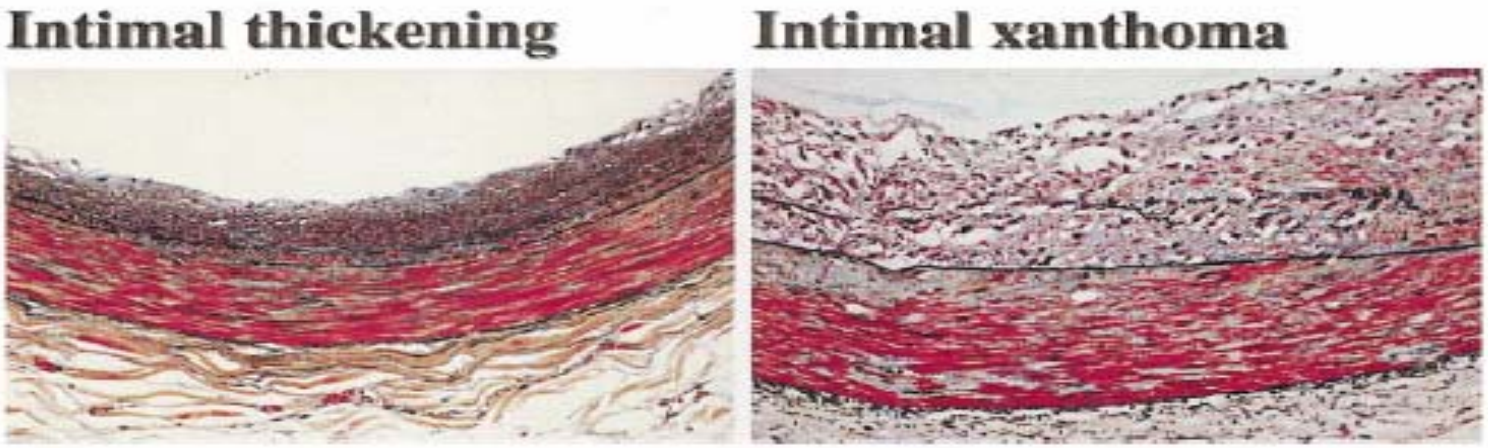


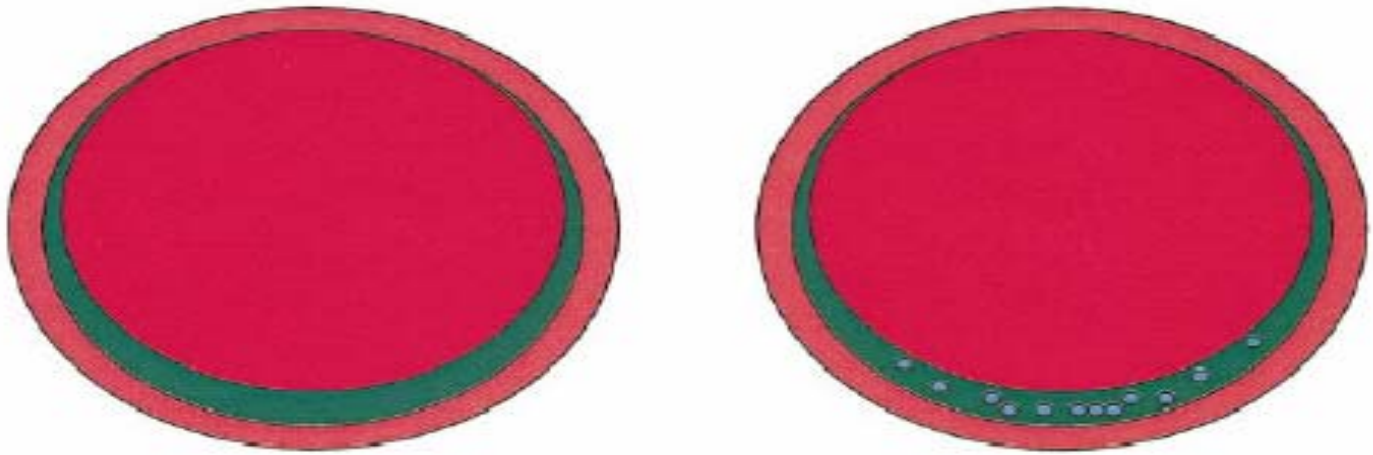






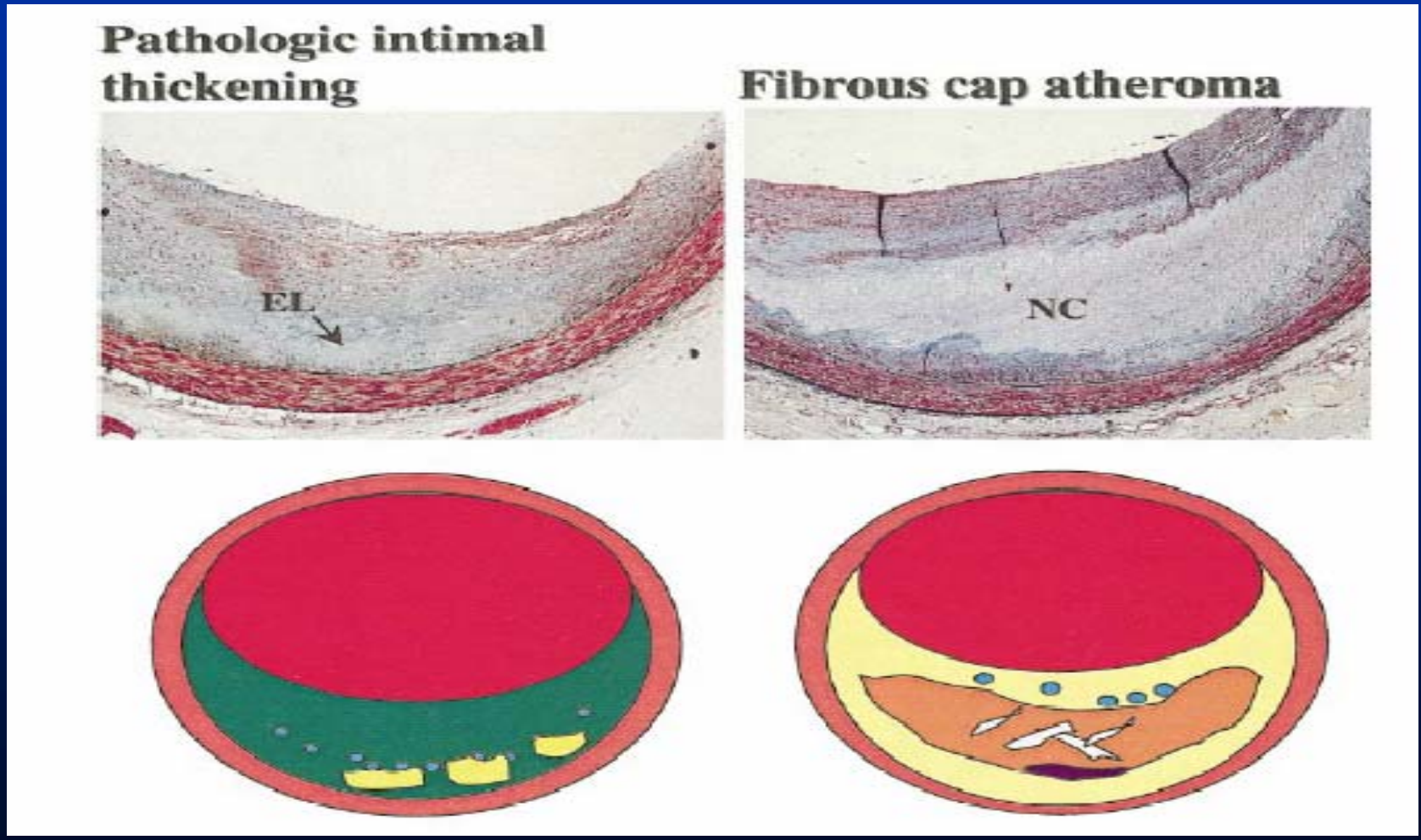
Pre-atherosclerotic coronary lesions





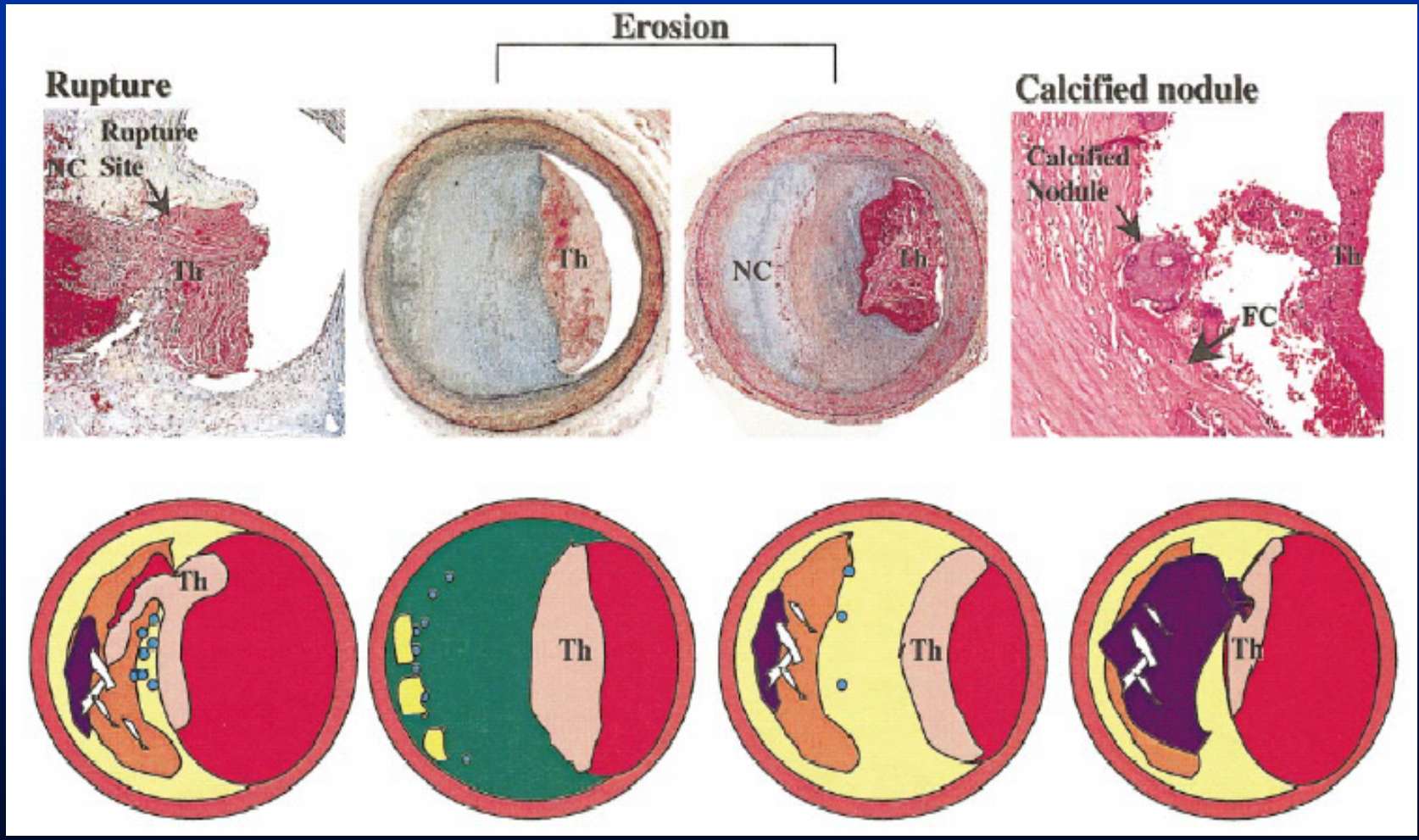
Virmani et al *Arterioscler Thromb Vasc Biol.* May 2000

Intermediate lesion



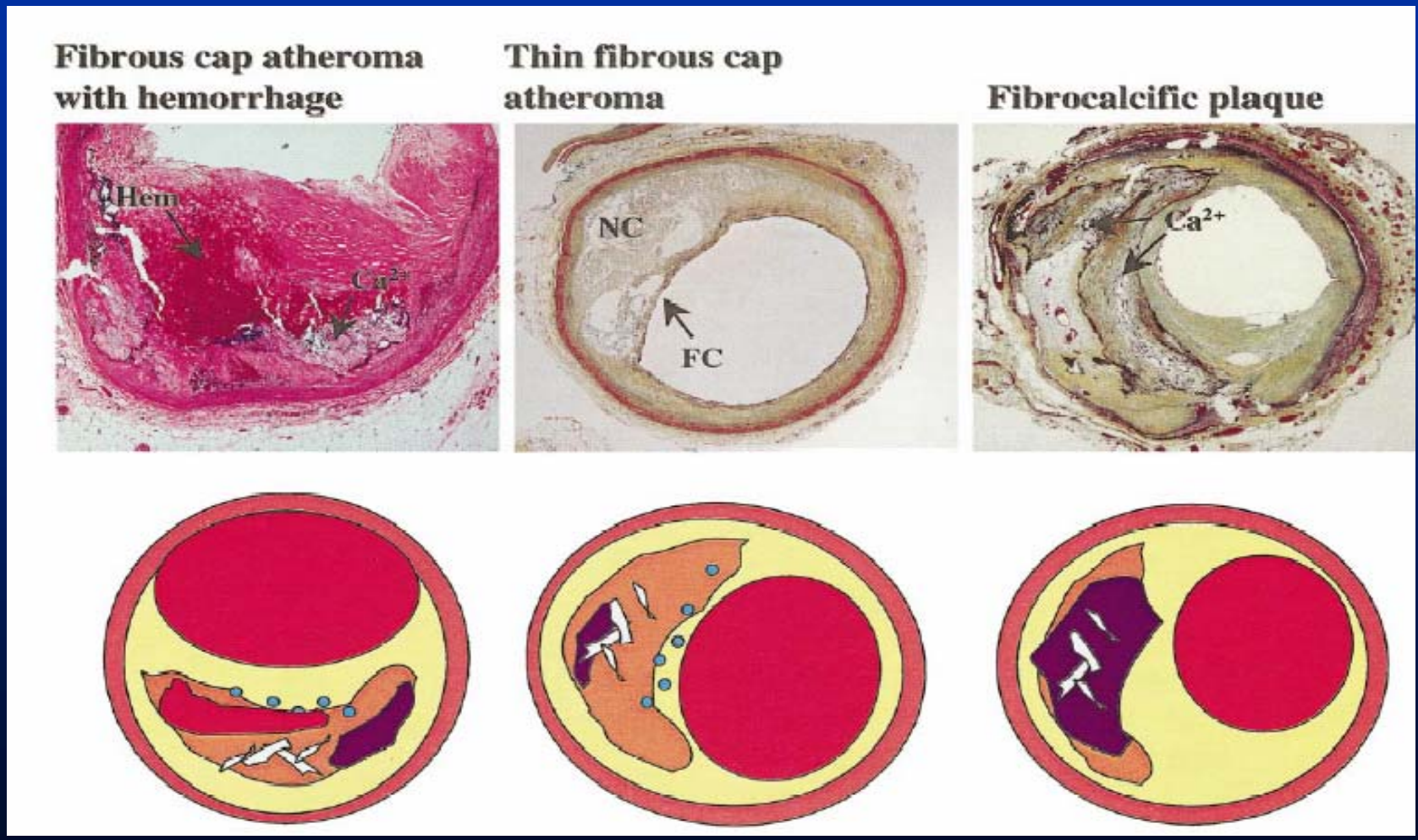
Virmani et al *Arterioscler Thromb Vasc Biol.* May 2000

Atherothrombosis



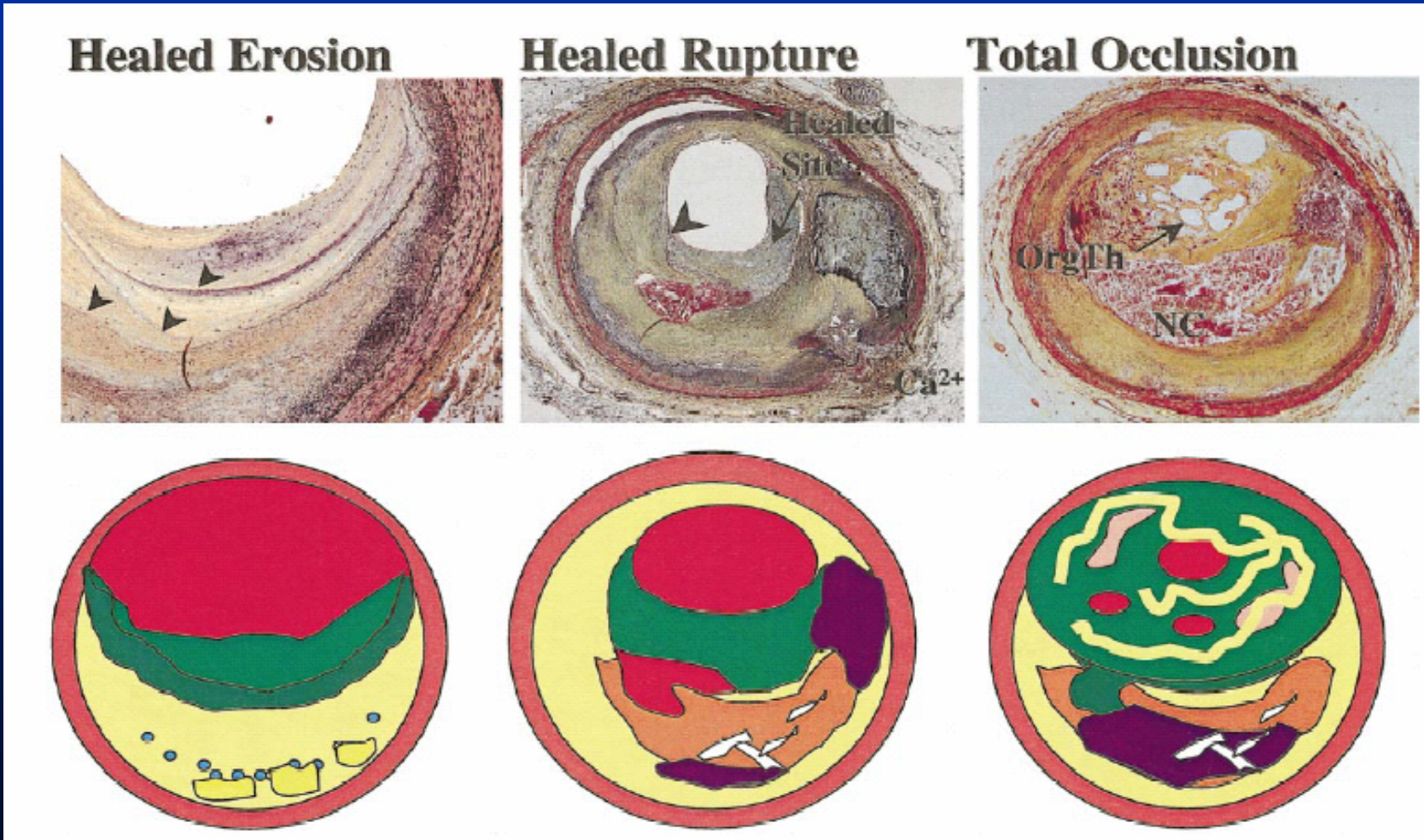
Virmani et al *Arterioscler Thromb Vasc Biol.* May 2000

Variants of fibrous cap atheromas



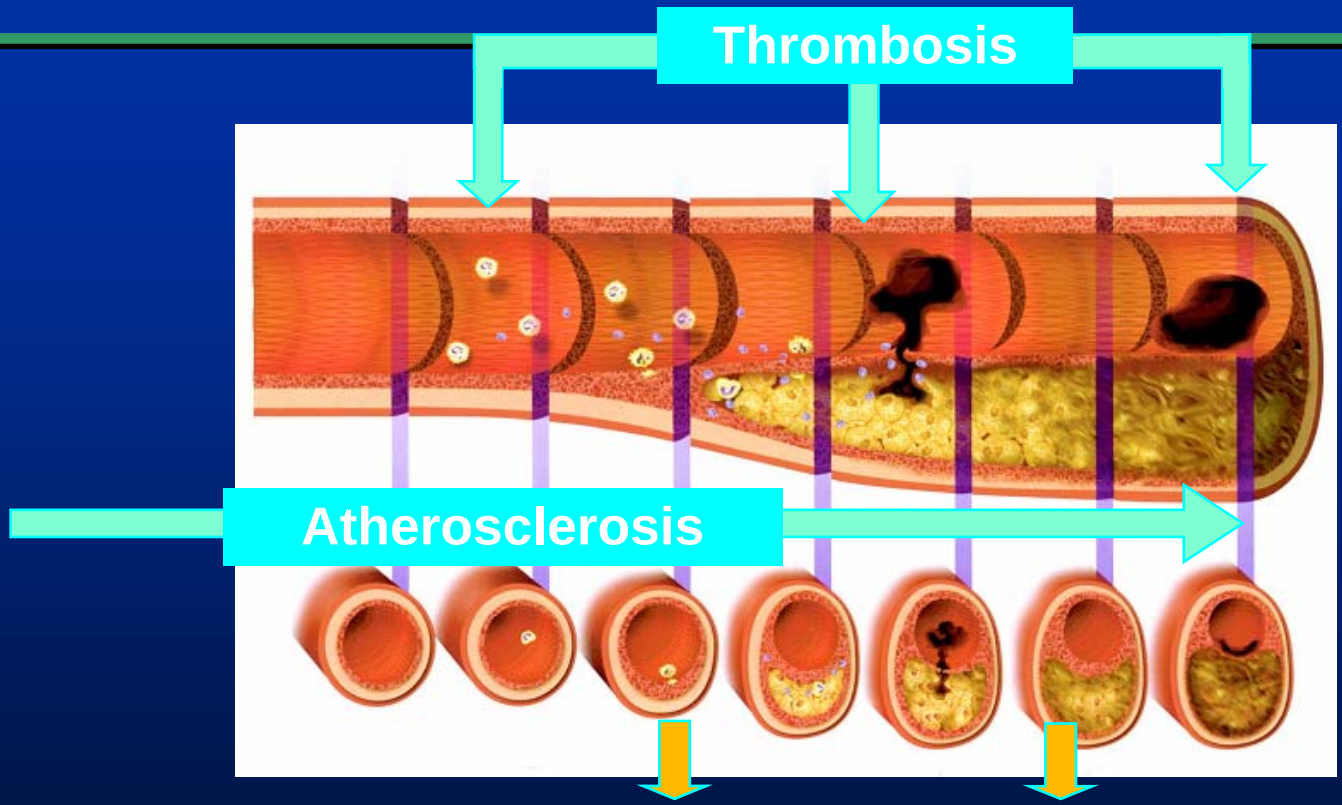
Virmani et al *Arterioscler Thromb Vasc Biol.* May 2000

Healed plaque erosion and rupture



Virmani et al *Arterioscler Thromb Vasc Biol.* May 2000

Atherothrombosis: A Generalized and Progressive Process



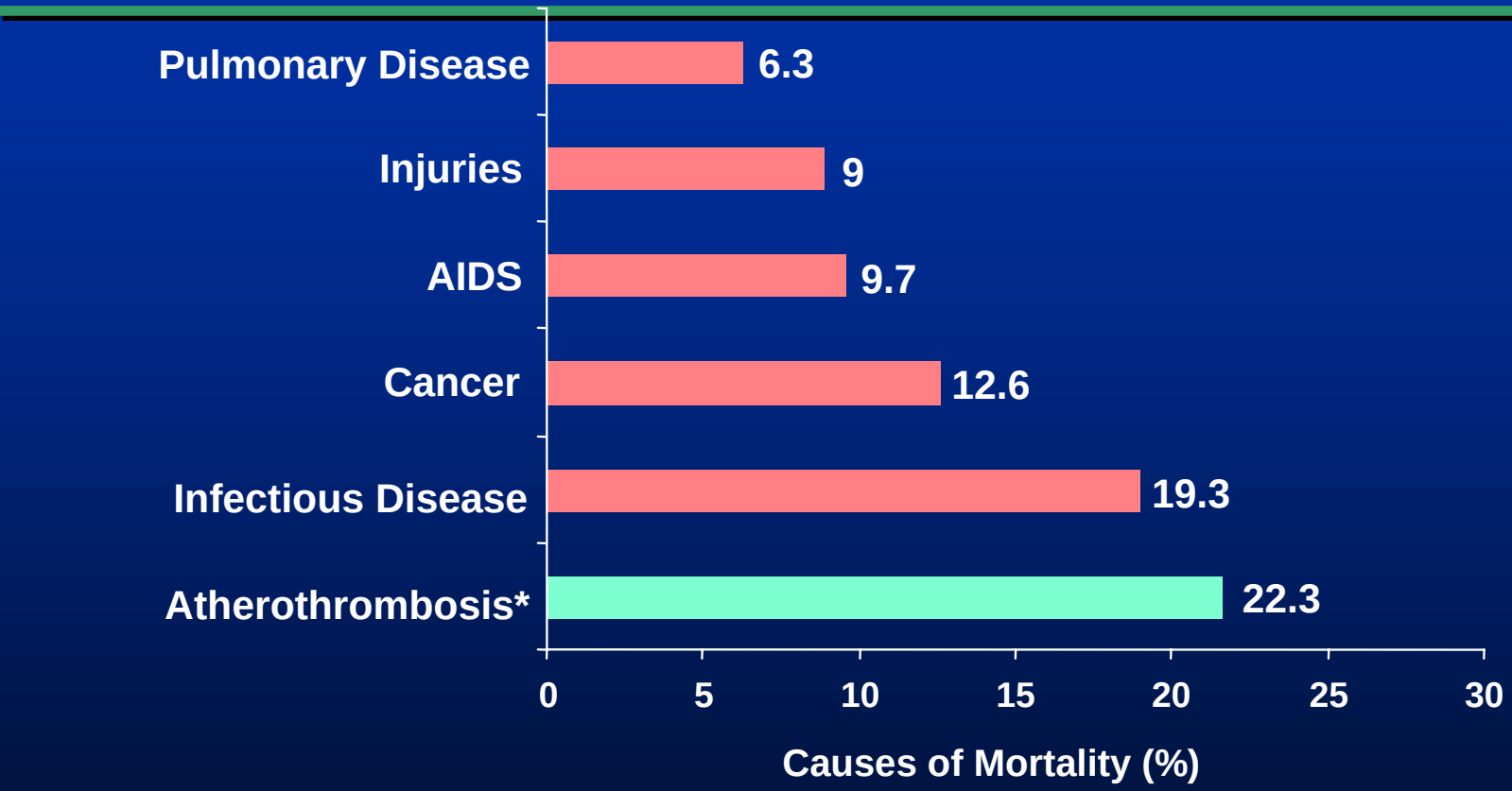
- Unstable angina
- MI

ACS

- Ischemic stroke/TIA
- Critical leg ischemia
- Intermitent claudication
- CV death

Adapted from Libby P. *Circulation.* 2001;104:365-372.

Atherothrombosis* is the Leading Cause of Death Worldwide[1]



* Atherothrombosis defined as ischemic heart disease and cerebrovascular disease.

[1] *The World Health Report 2001*. Geneva. WHO. 2001.

Evolution of Atherosclerosis model

a Gradual luminal narrowing

b Plaque rupture

c. **Inflammation**

Inflammation

Ross R.

Atherosclerosis an inflammatory disease

New Engl J Med. 1999;340:115-126

Atherosclerosis: much more dinamic

Libby p, Ridker PM, Maseri A.

Inflammation and atherosclerosis

Circulation 2002; 105:1135-1143.

Many acute coronary events are caused by rupture of an inflammatory unstable plaque

Multiple unstable plaques in ACS

Multiple unstable coronary plaques

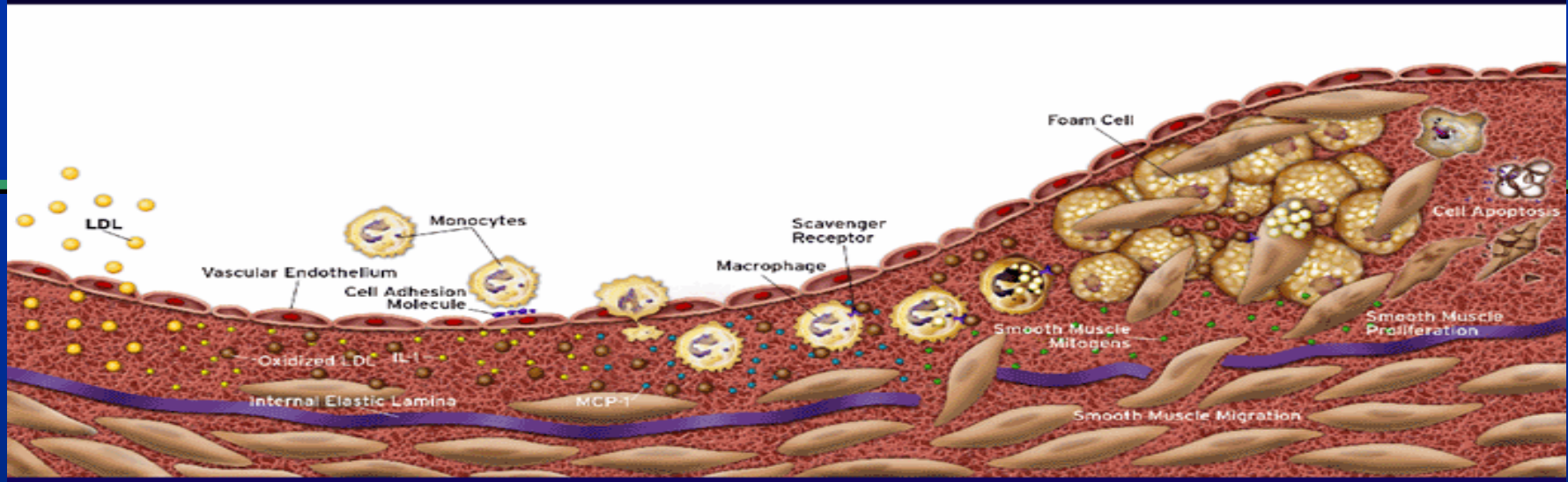
Goldstein et al, NEJM 2000

Zairis M et al, Atherosclerosis 2000

Widespread coronary inflammation

Buffon et al, NEJM 2002

Atherosclerosis is an Inflammatory Disease



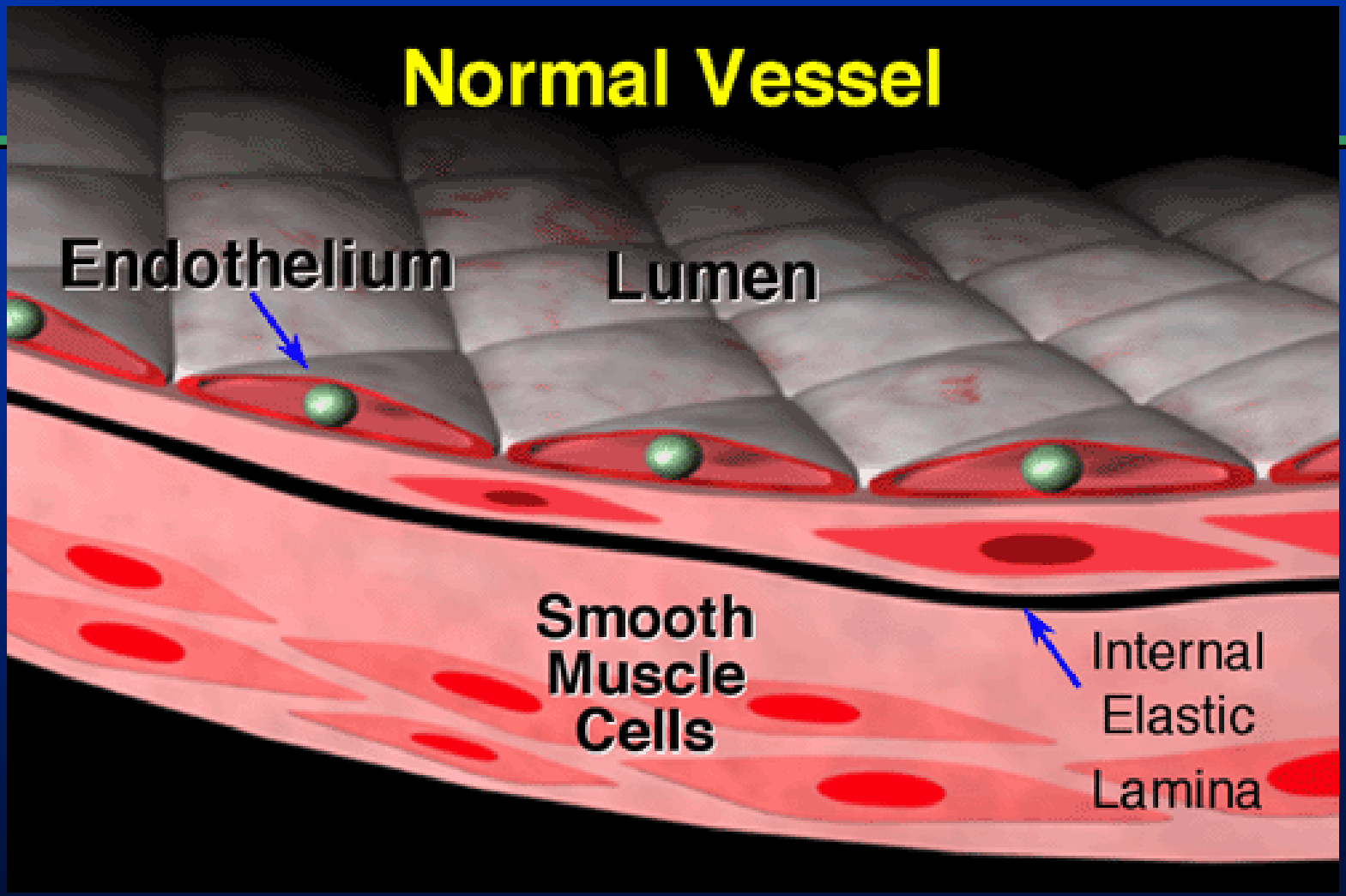
Libby, P. The Vascular Biology of Atherosclerosis.
Heart Disease (Braunwald, Zipes & Libby Eds.) 2001

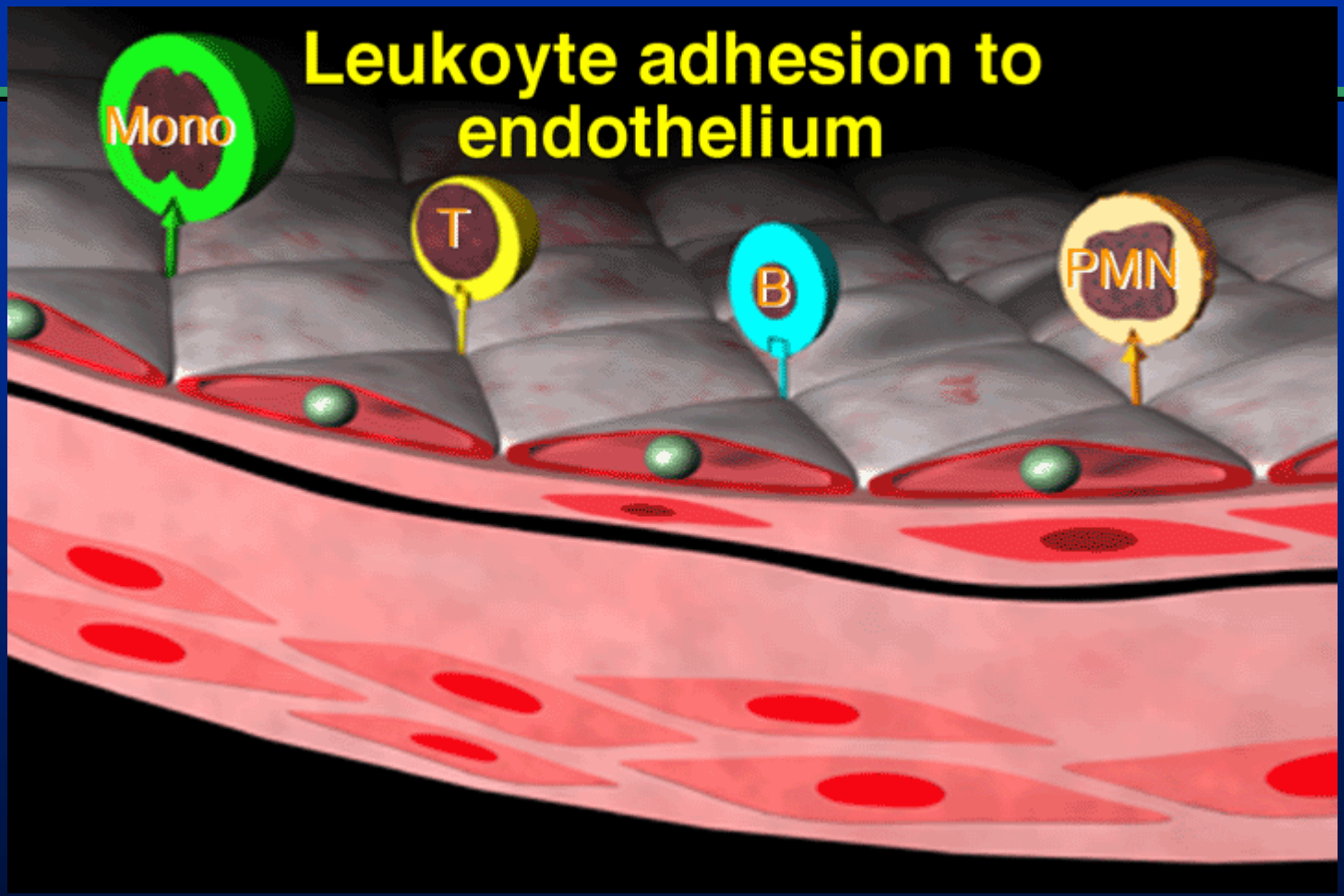
The Origins of Atherosclerosis

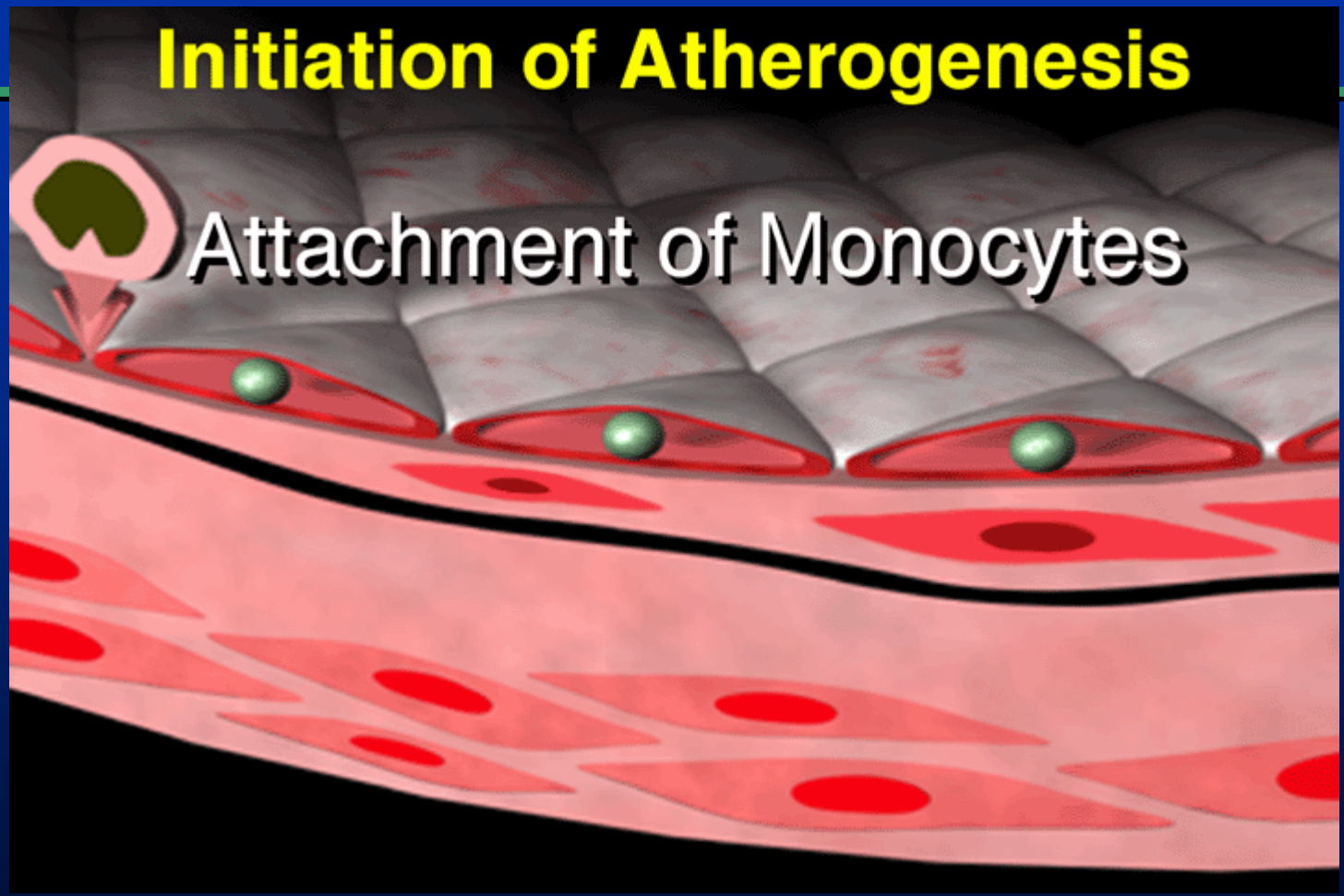
Peter Libby
Brigham & Women's Hospital
Harvard Medical School

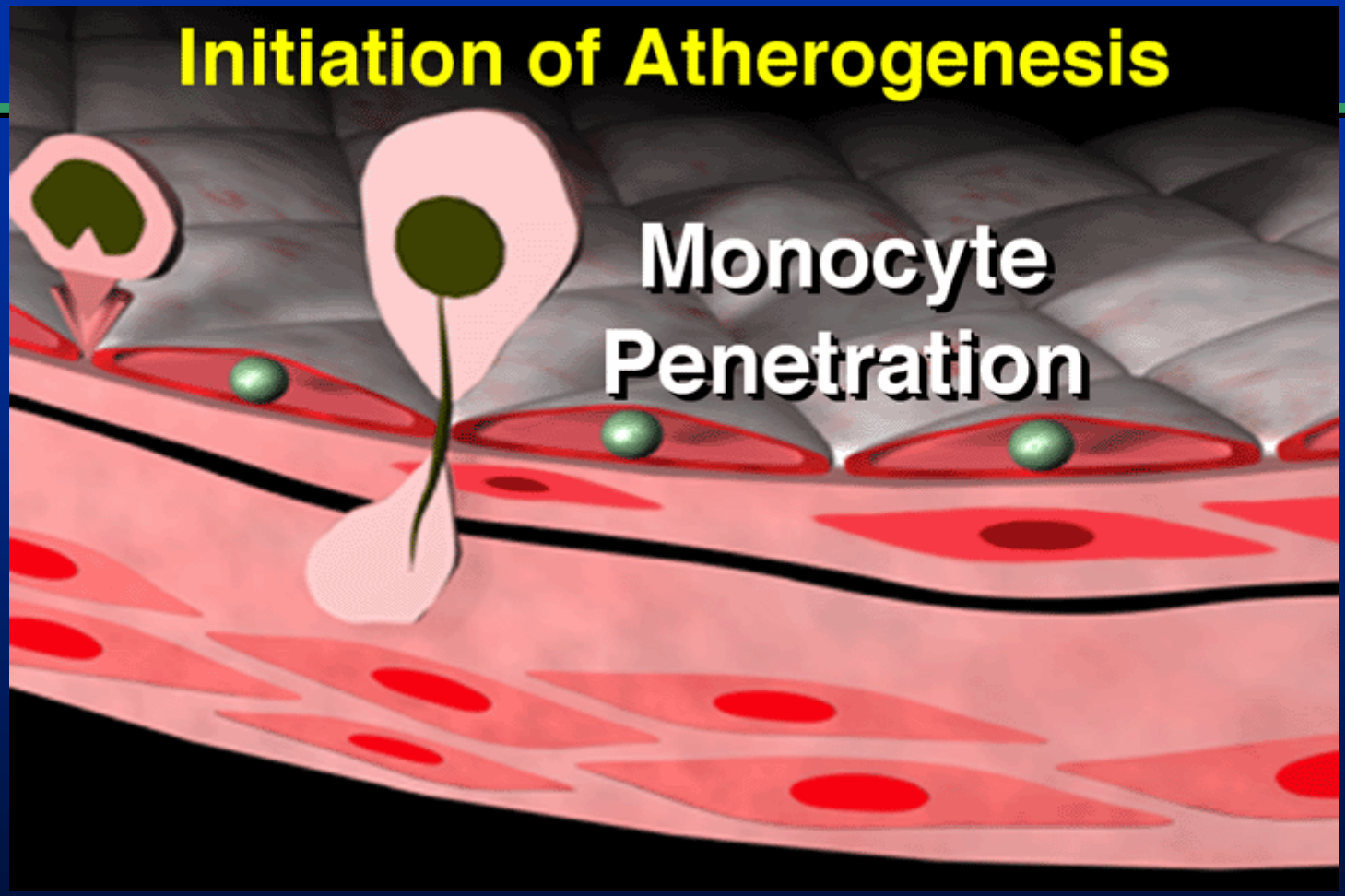
Lessons from the Lipid Legends

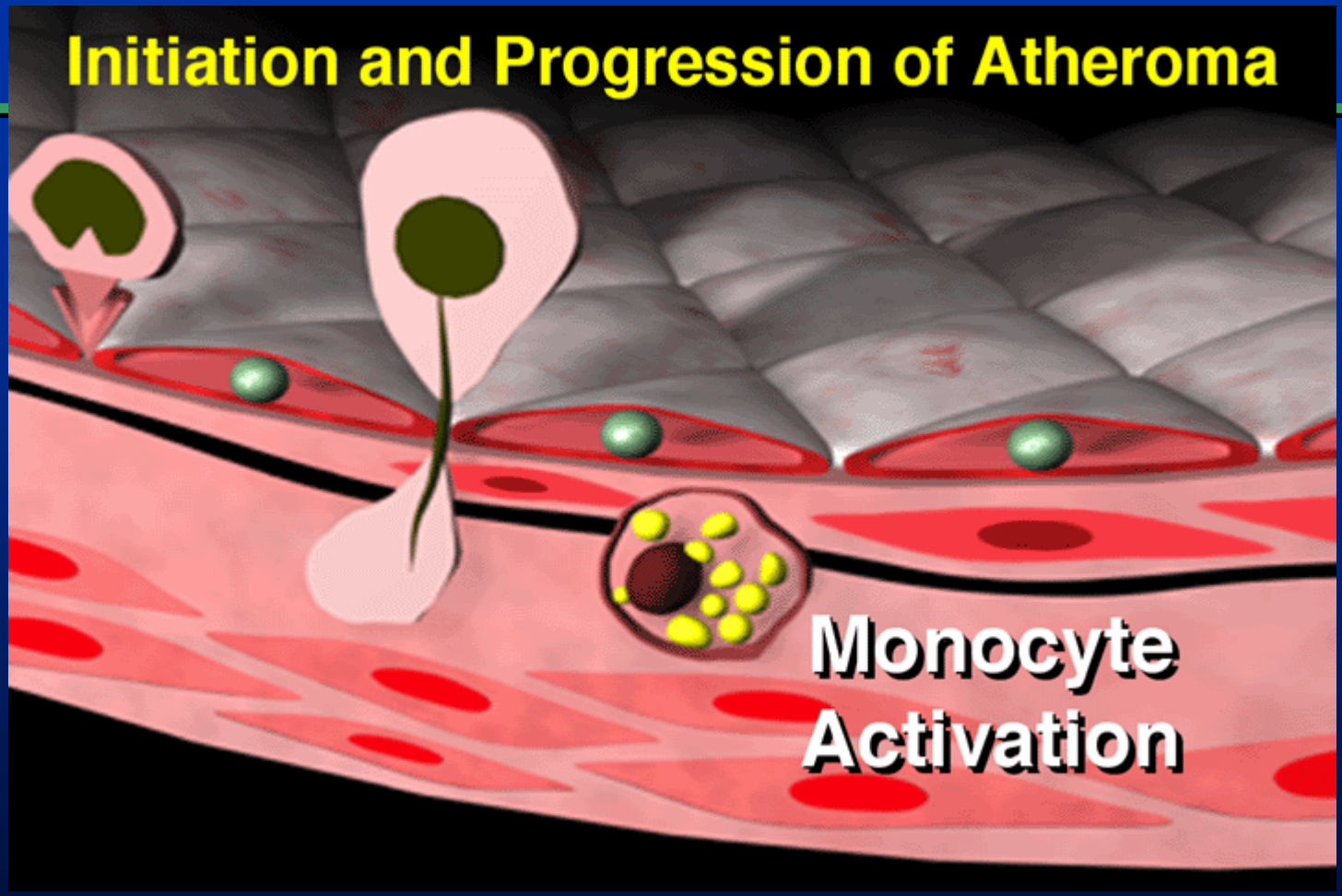
www.theheart.org 2004

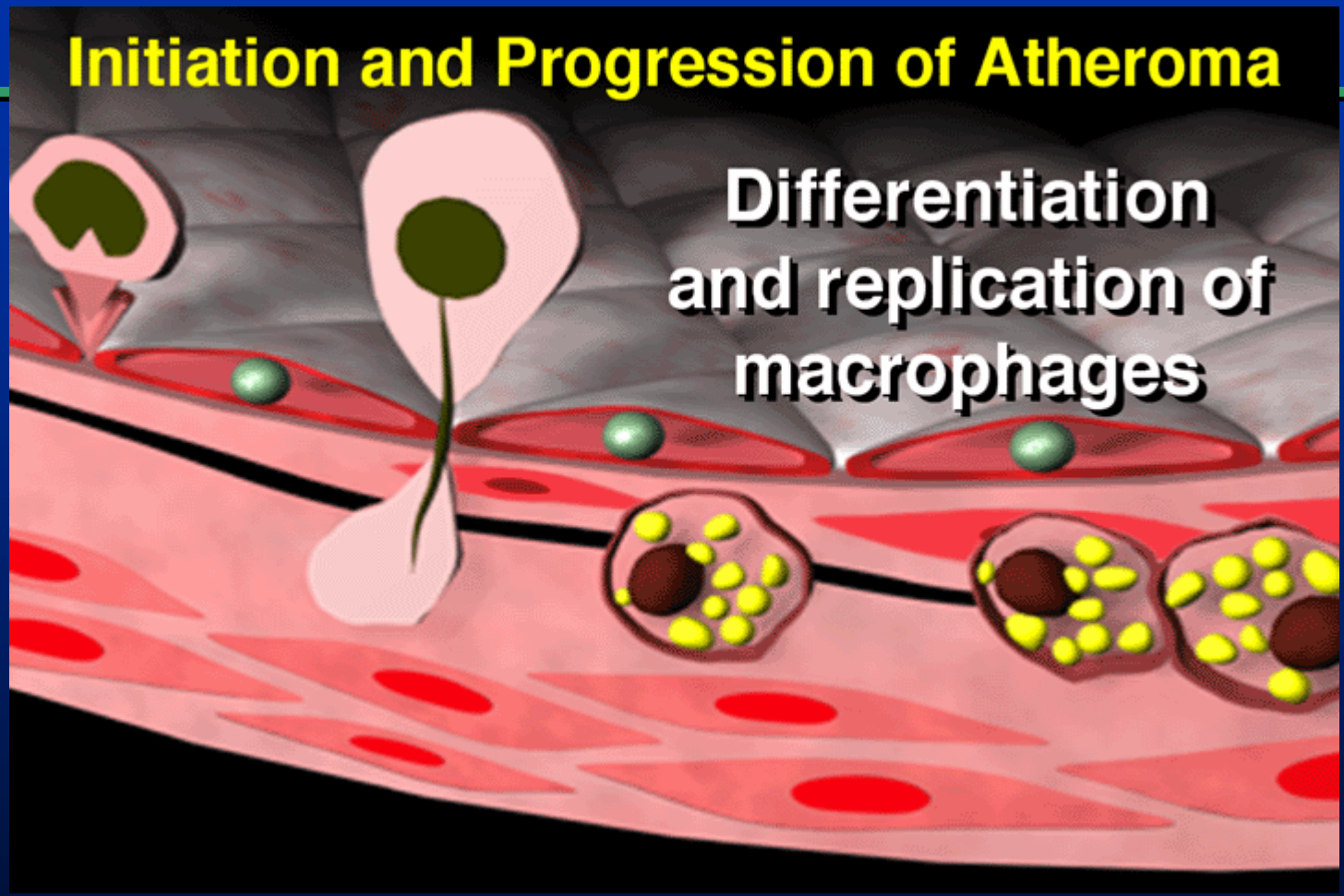

Normal Vessel
Endothelium
Lumen
Smooth
Muscle
Cells
Internal
Elastic
Lamina

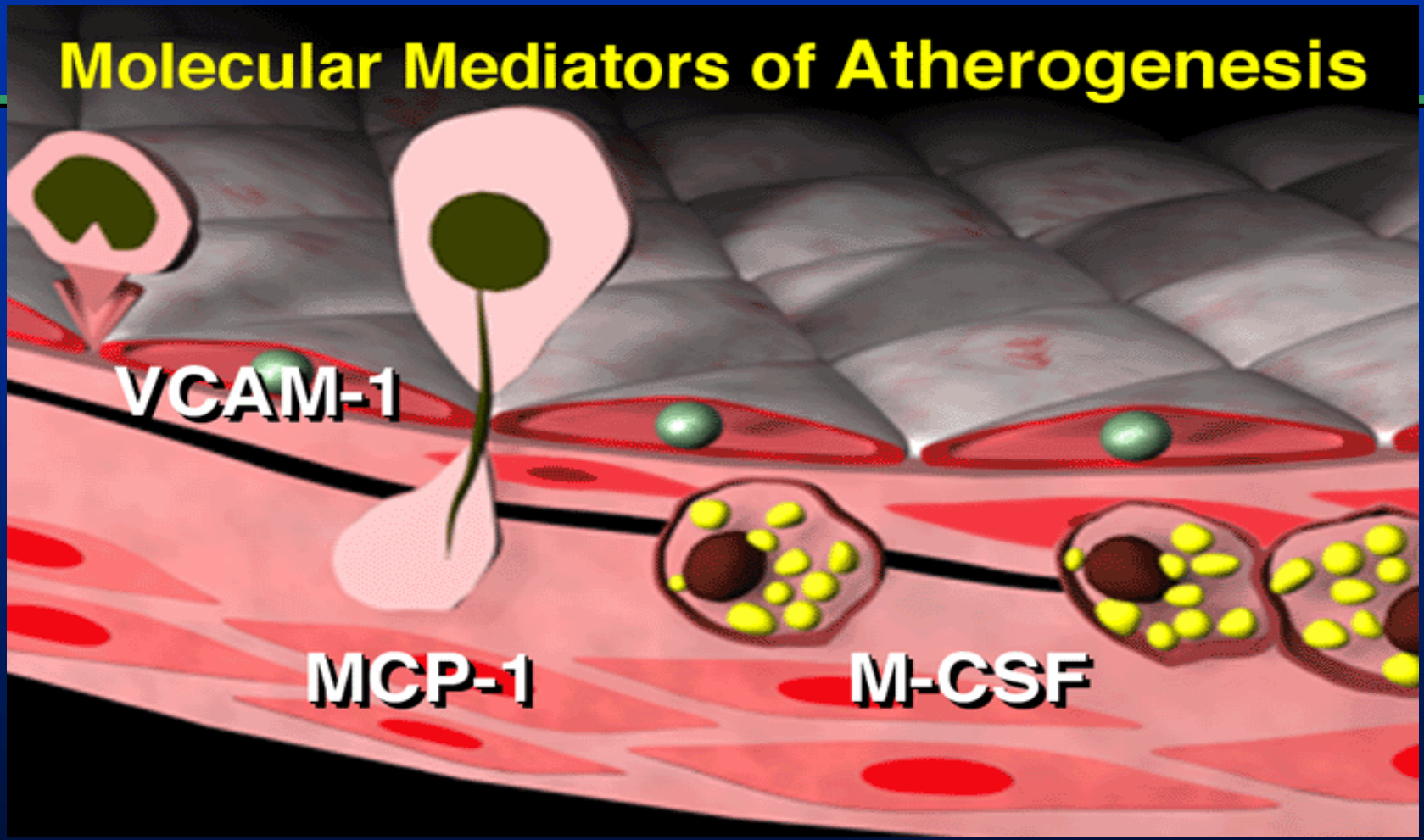

Leukoyte adhesion to endothelium
Mono
T
B
PMN


Initiation of Atherogenesis
Attachment of Monocytes


Initiation of Atherogenesis
Monocyte
Penetration


Initiation and Progression of Atheroma
Monocyte
Activation


Initiation and Progression of Atheroma
Differentiation and replication of macrophages


Molecular Mediators of Atherogenesis
VCAM-1
MCP-1
M-CSF

Statin anti-inflammatory effect

- Significant reduction in CRP after 14 days of simvastatin administration
- Independent of LDL lowering

Plenge JK, et al. Circulation 2002;105:1446-1452

Statin withdrawal-ischemic rebound

Significant increment in ischemic events within 15-30 days of discontinuing statin therapy in ACS patients

This rebound was independent of cholesterol levels

Heeschen C, Hamm CW, Laufs U et al.

Circulation 2002; 105:1446-1452.

The "New Biology" of Atherosclerosis

- ***Stabilization of lesions, by medical therapy, provides a new therapeutic target beyond revasularization***

How does lipid-lowering improve patient outcome?

Actions of Statins in Coronary Artery Disease

Chronic Atherosclerosis

- reduce plaque lipid pool
- reduce plaque inflammation
- increase plaque fibrosis
- smooth muscle cell proliferation

Acute Coronary Syndrome

- improve endothelial function
- reduce platelet thrombus deposition
- normalize hypercoagulability
- normalize fibrinolytic activity
- reduce plaque inflammation
- reduce matrix metalloproteinase activity
- reduce plaque thrombogenicity
- prevent tissue factor expression

Corti et al. Am J Med 2002;113:668-680.
Crisby et al. Circulation 2001;103:926-933.

Lipid-lowering is an *anti-inflammatory* therapy for atherosclerosis

Dissociation between Atherosclerosis and atherothrombosis

"I'm impressed as a physician that some patients have a lot of atheroma and yet they didn't have an infarction and others had very little atheroma and they have an infarction. I'm even more impressed by the fact that some patients have an infarction,have that atheroma and then for years and years have absolutely nothing with the same atheroma staying there, the same atheromatic burden."

In ACS inflammatory response is largely independent from global atherothrombotic burden.

A. Maseri at the 2nd Vulnerable Patient Symposium held by AEHA

on March 6th in conjunction with the ACC 2004 New Orleans, LA

Conclusioni (1\3)

- L’aterosclerosi coronarica è una patologia diffusa della parete, non focale, ampiamente sottostimata dall’angiografia (lume)
- Solo una minima parte delle lesioni ats dà manifestazioni cliniche (aterotrombosi)
- Gli eventi acuti sono provocati da reazioni infiammatorie, indipendenti dalla quantità di ateroma, ad antigeni non ancora identificati

Conclusioni (2\3)

- E’ probabile che i benefici clinici della terapia ipolipemizzante derivino dalla stabilizzazione di placche non serrate senza miglioramenti del lume angiografico
- La stabilizzazione riguarda diversi processi:

  Infiammazione, coagulazione, funzione endoteliale etc

Conclusioni (3\3)

In base alle evidenze, il trattamento precoce ed intensivo con statine dovrebbe essere dato a tutti i pz con PCI, a prescindere dai valori di colesterolemia basale.

I prossimi sviluppi della terapia ipolipemizzante saranno probabilmente centrati sui farmaci per HDL