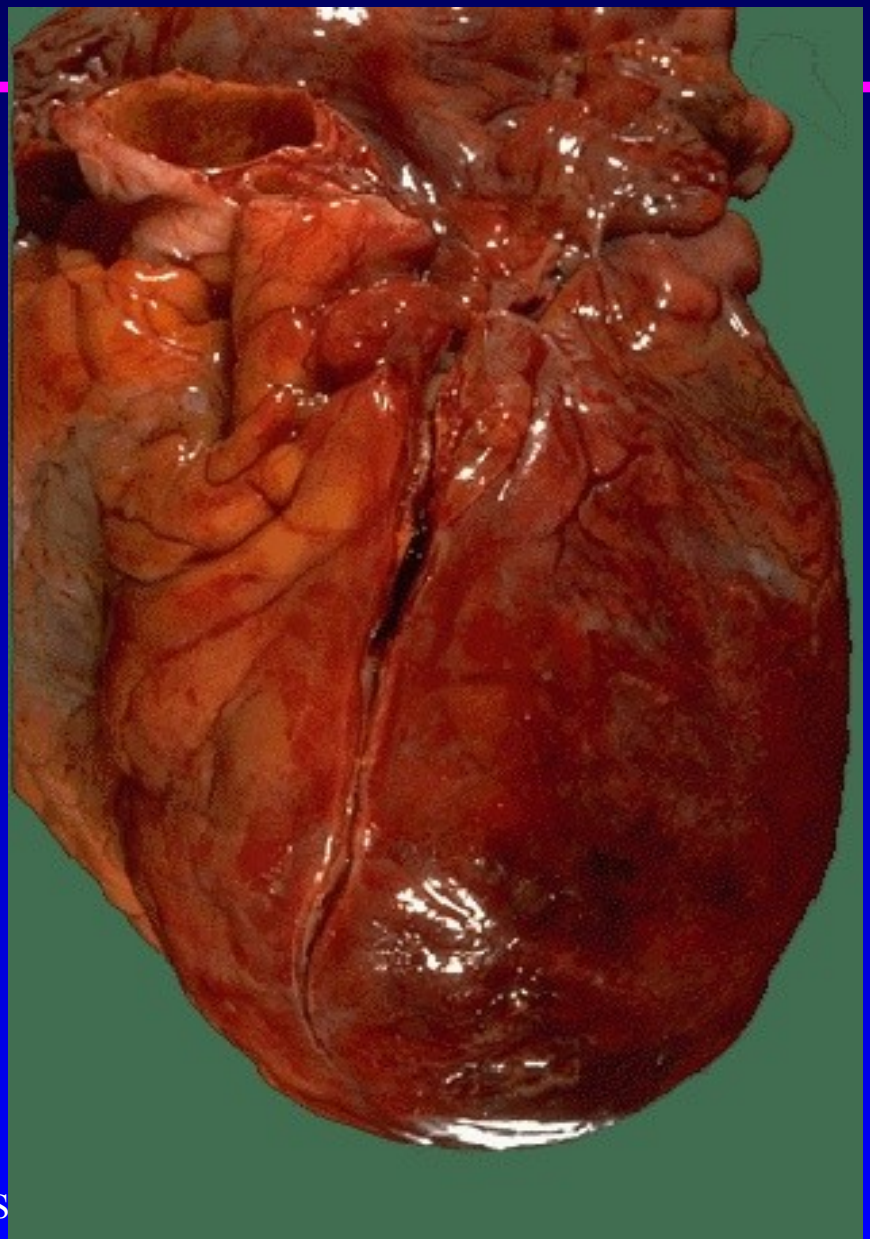
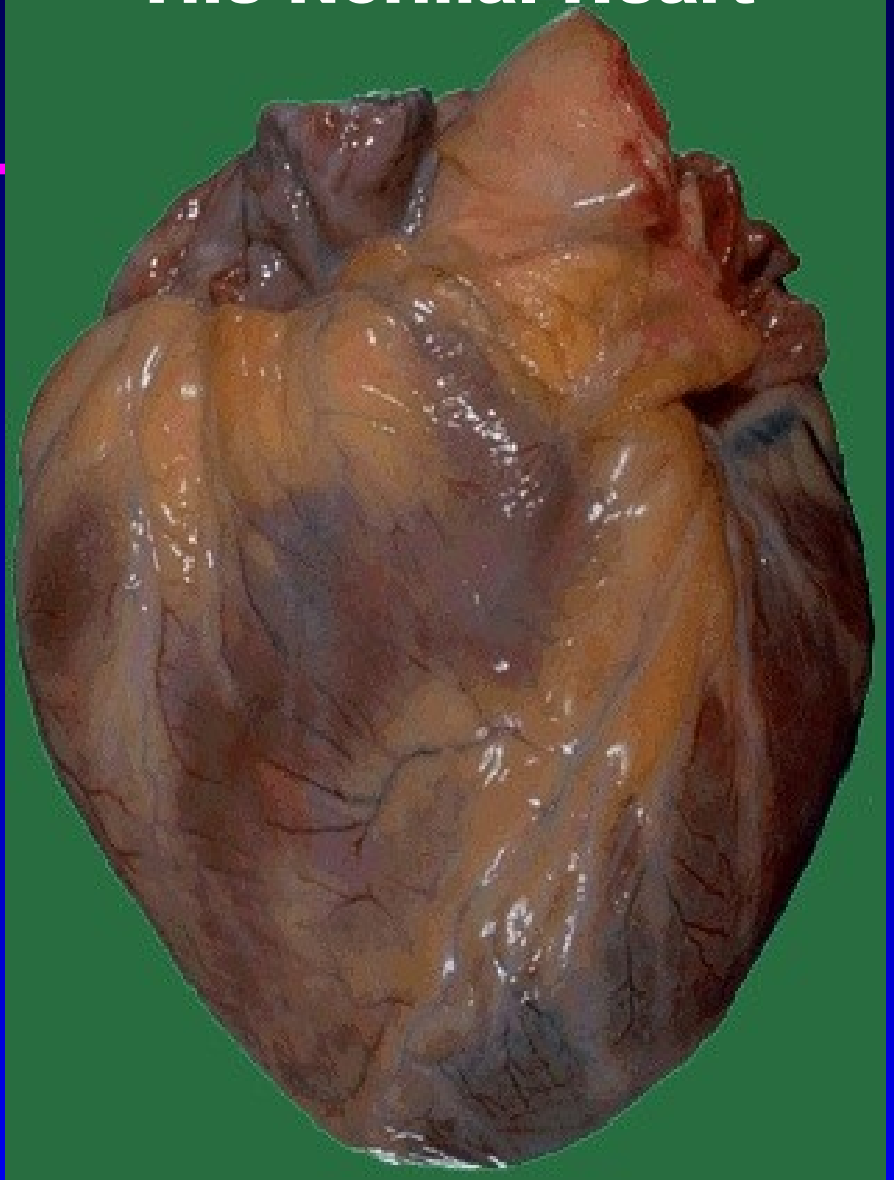
Pathophysiology of Atherosclerosis

פרופ' שמואל בנאי
המרכז הרפואי תל אביב

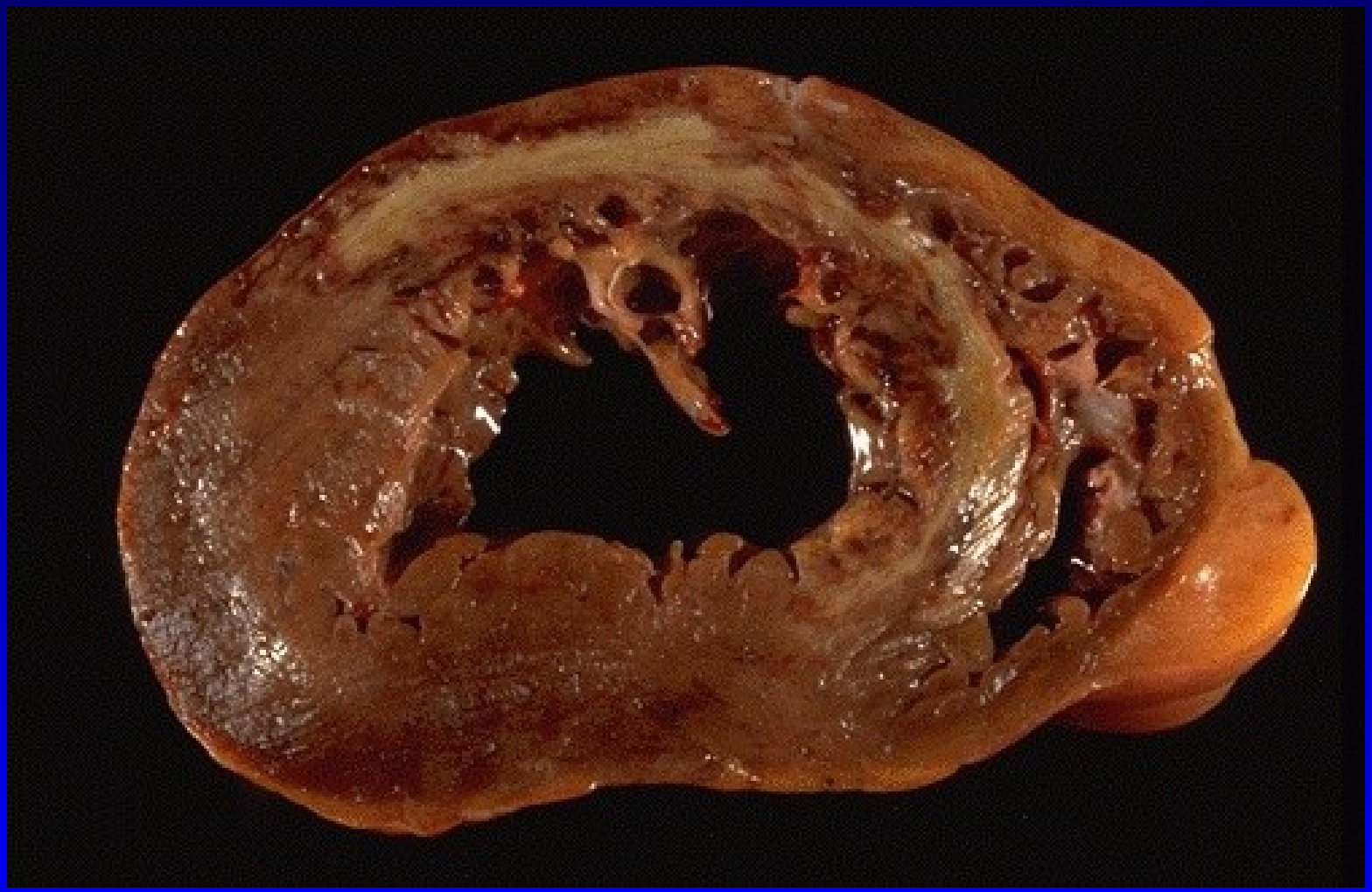
Acute anterior wall MI



The Normal Heart

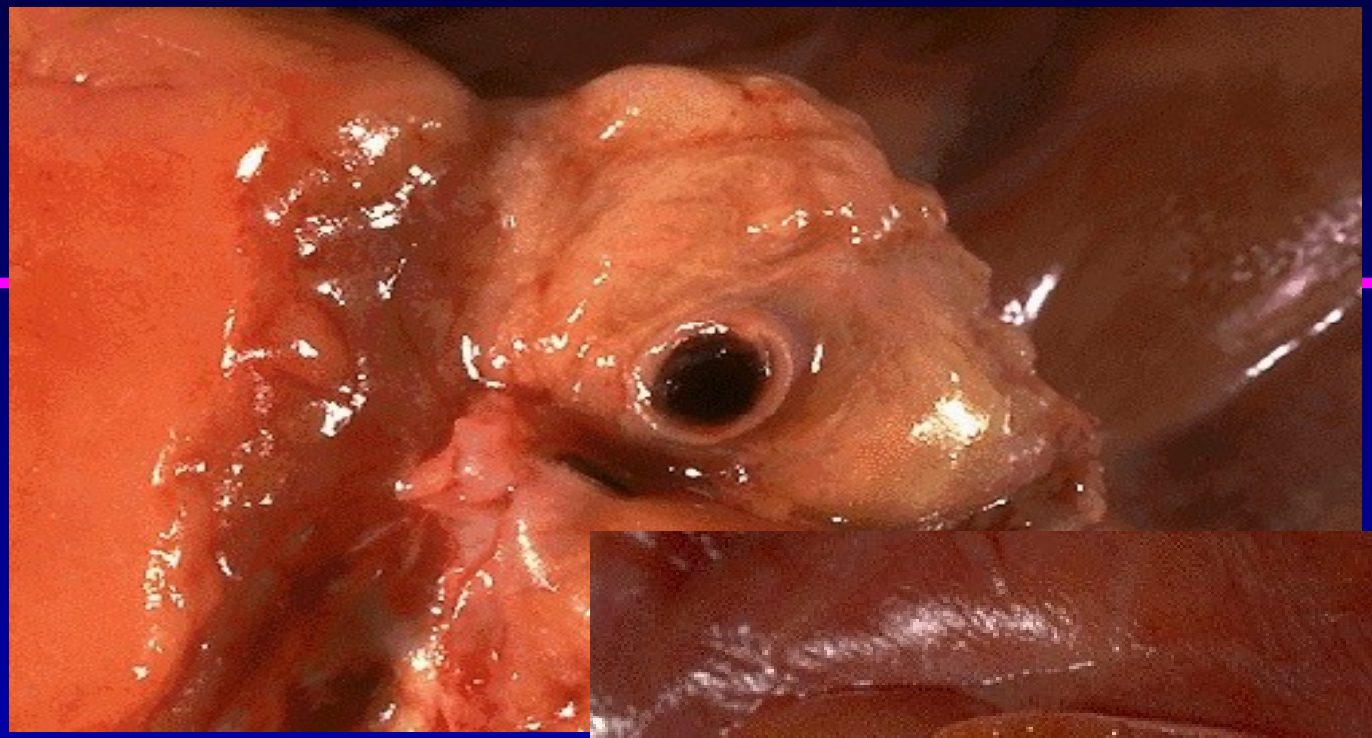


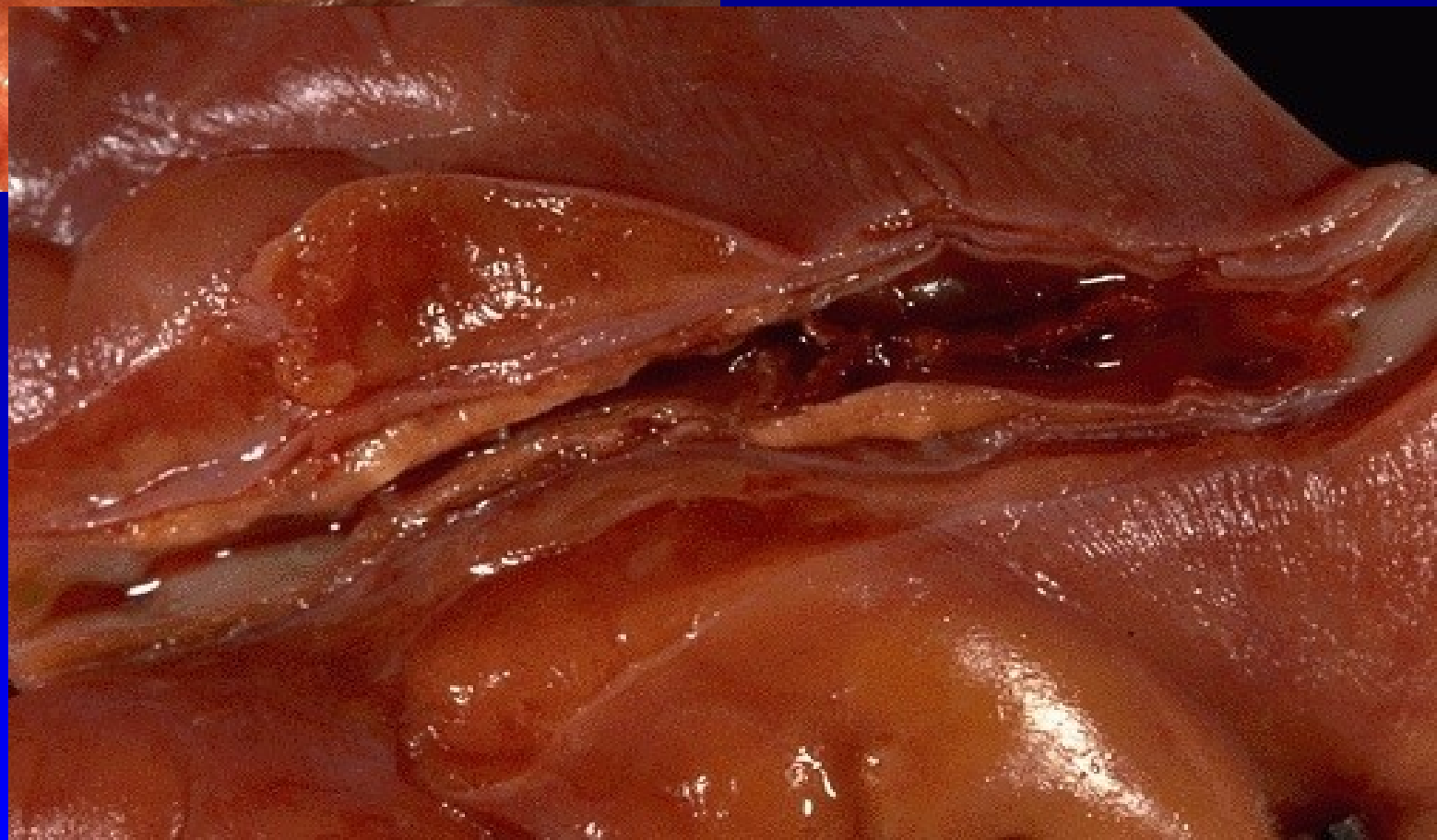
Recent large Antero-Septal Myocardial Infarction



Banai S.

Acute Myocardial Infarction





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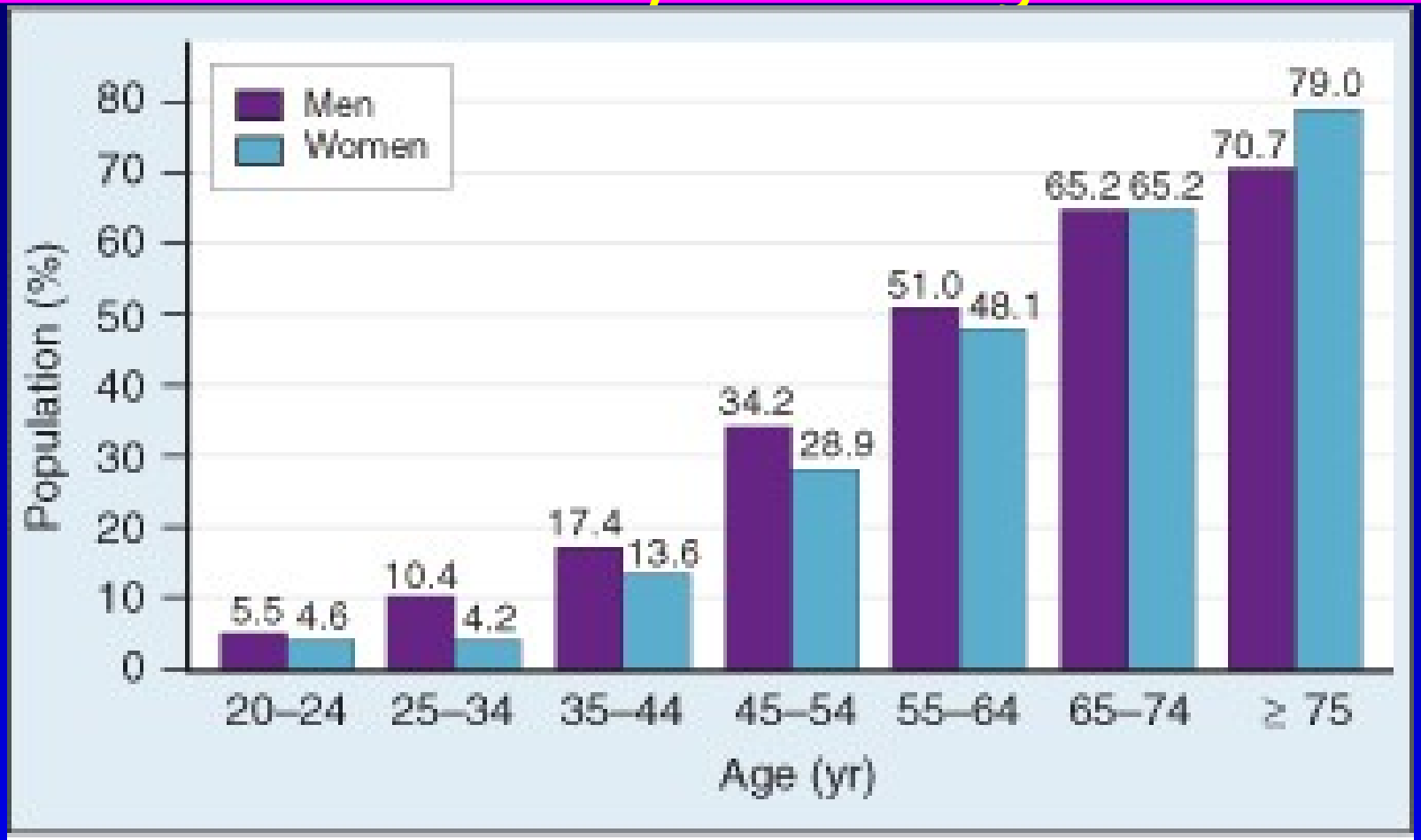
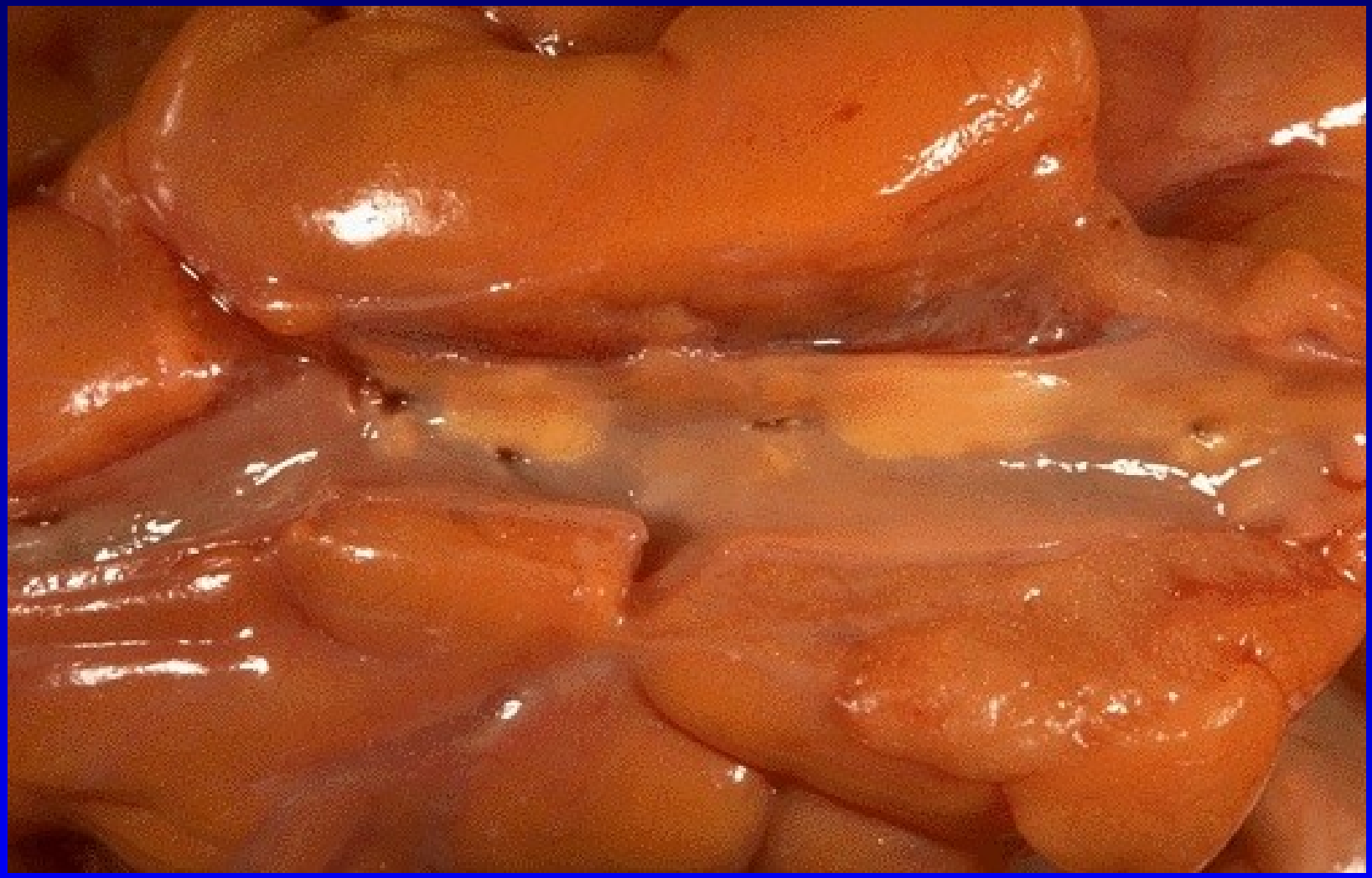
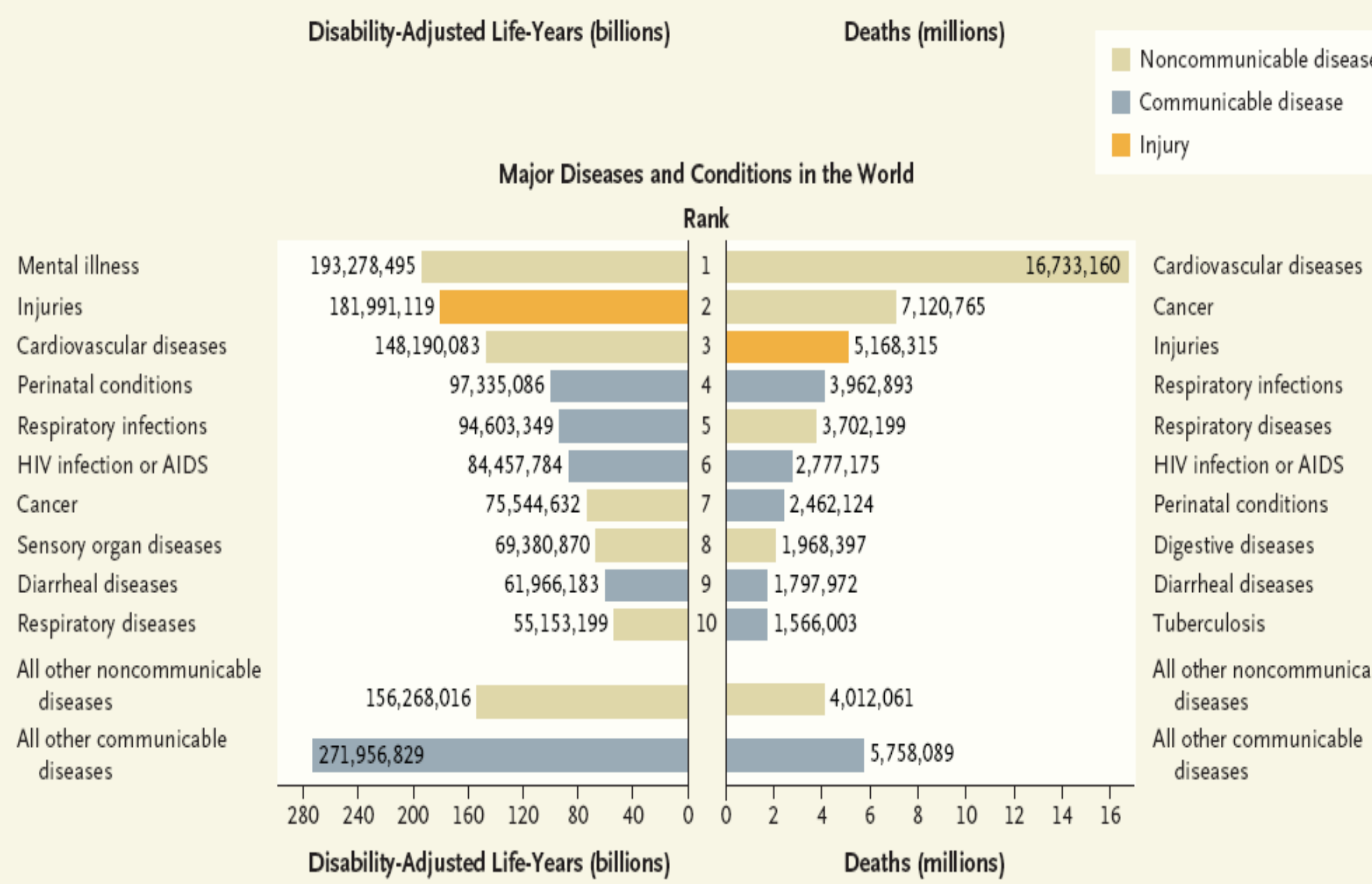
Estimated prevalence of cardiovascular disease in Americans 20 years of age and older



From American Heart Association: 2003 Heart and Stroke Statistical Update. Dallas, American Heart Association, 2003

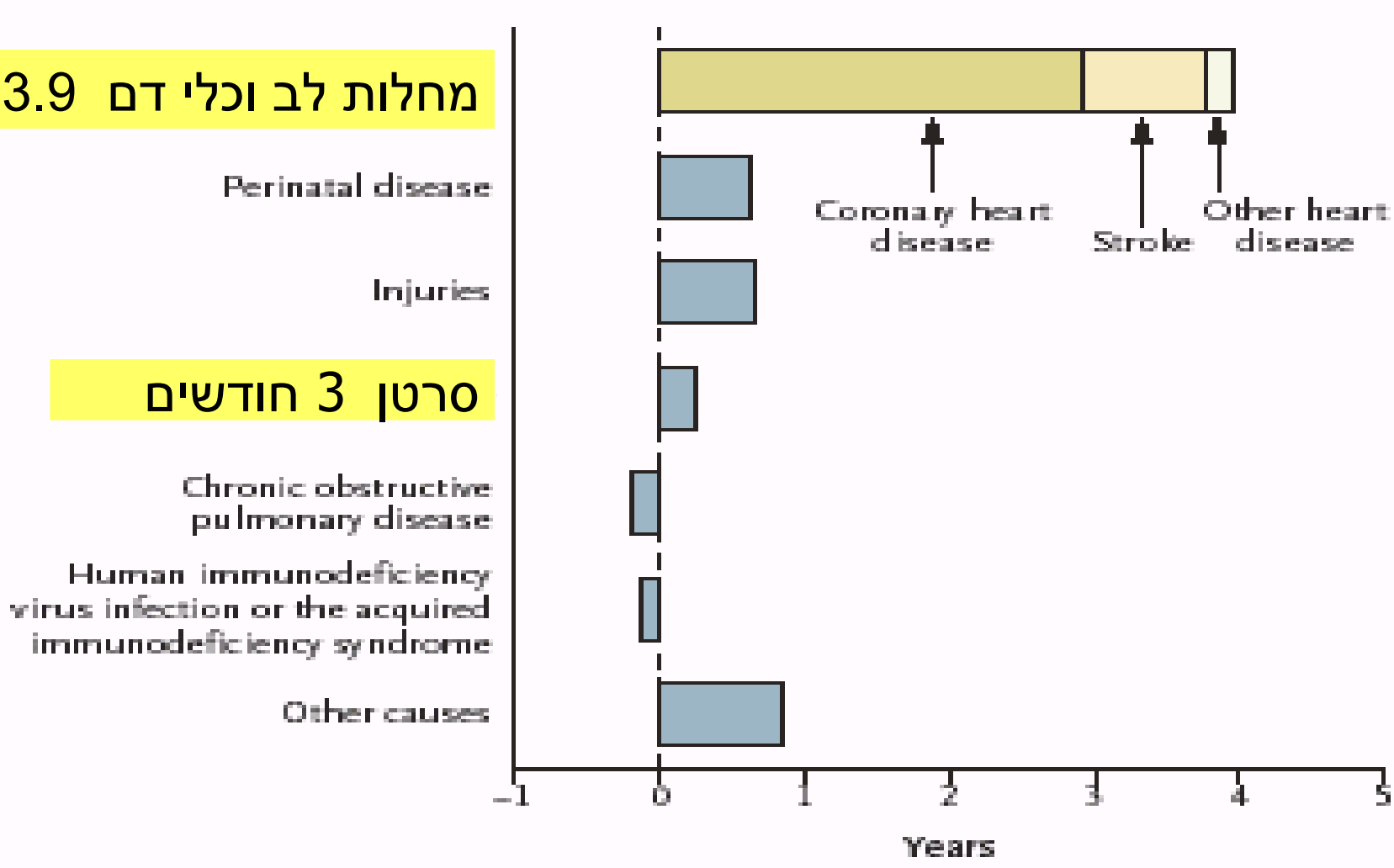
טרשת בעורק כלילי של בחור בן 17





NEJM 18.01.2007

מחלות לב וכלי דם 3.9 שנים



סרטן 3 חודשים

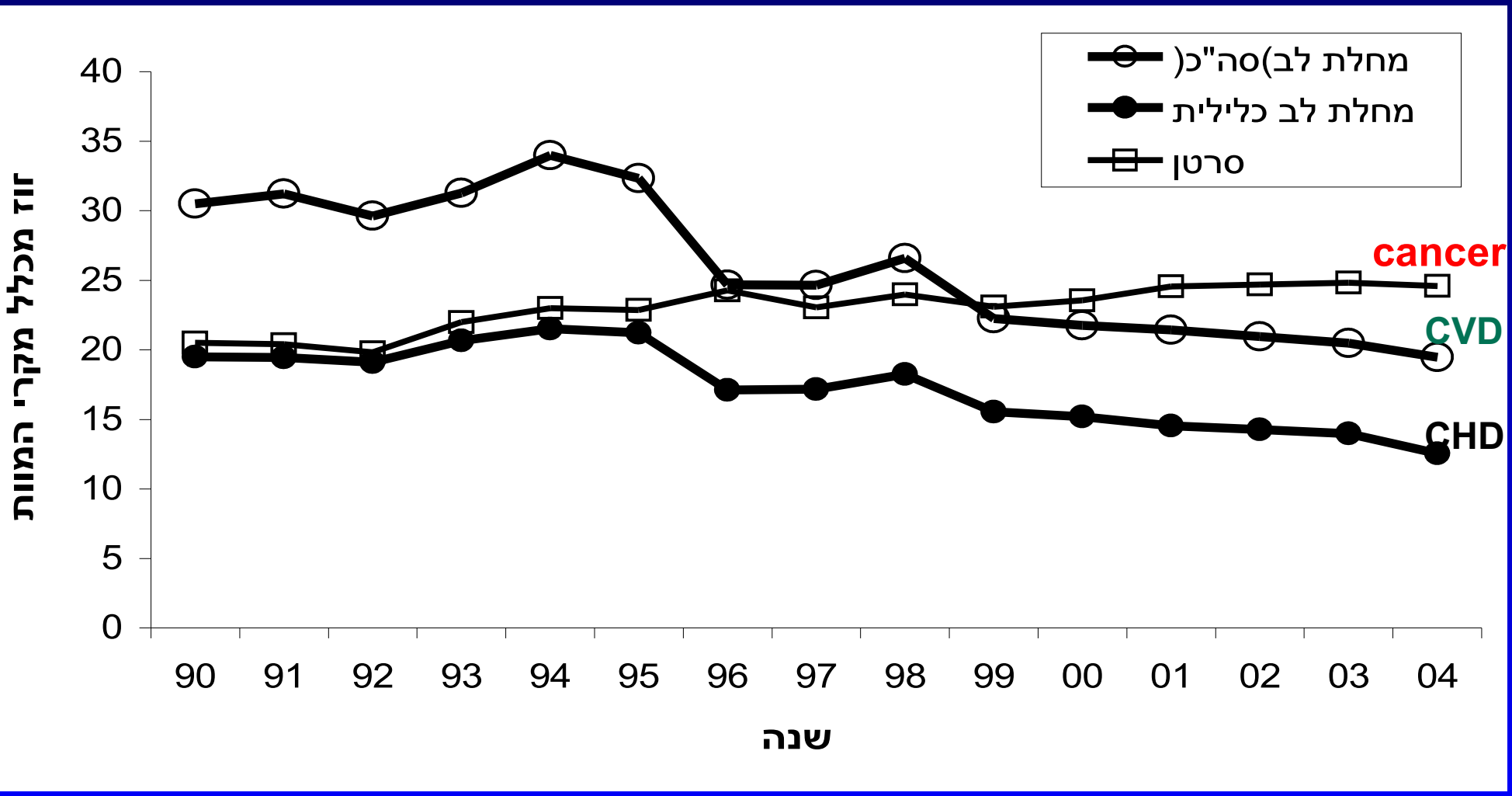
עליה בתוחלת חיים בארה"ב בין השנים 1970-2000 6 שנים

Between 1970 and 2000, life expectancy in the United States increased by 6.0 years overall, with 3.9 years of the increase due to reductions in mortality from cardiovascular causes. The data are from the Centers for Disease Control and Prevention.

CDC

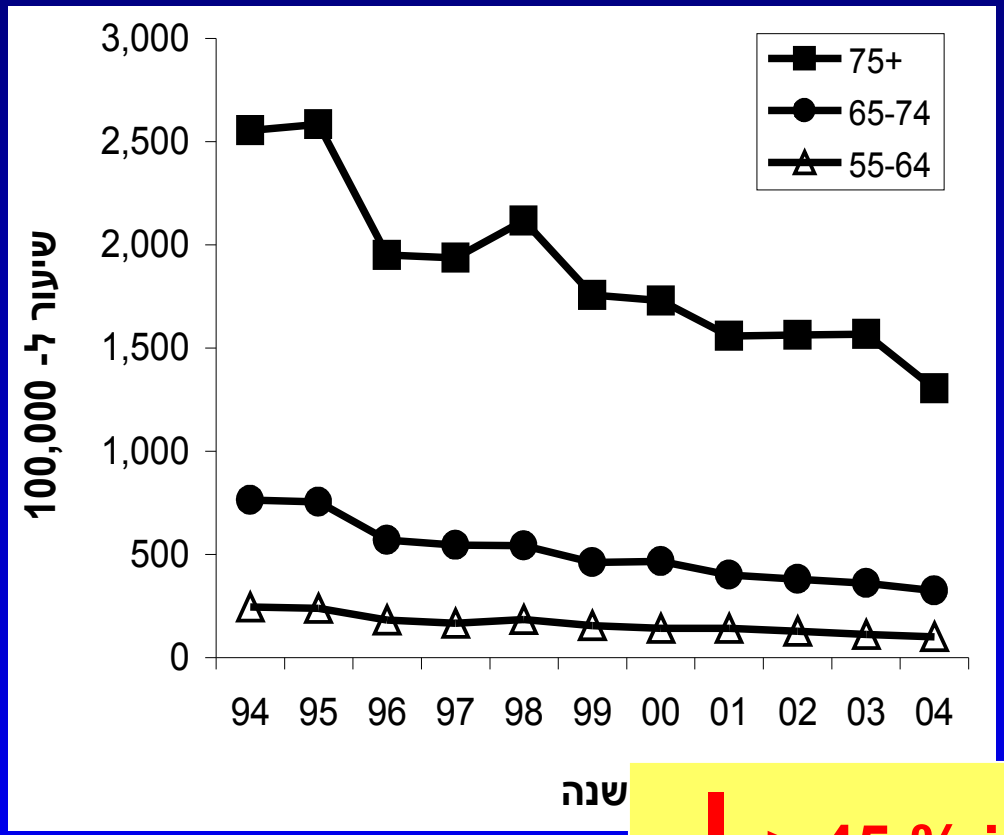
התפלגות סיבות המוות העיקריות בישראל

2004 - 1990

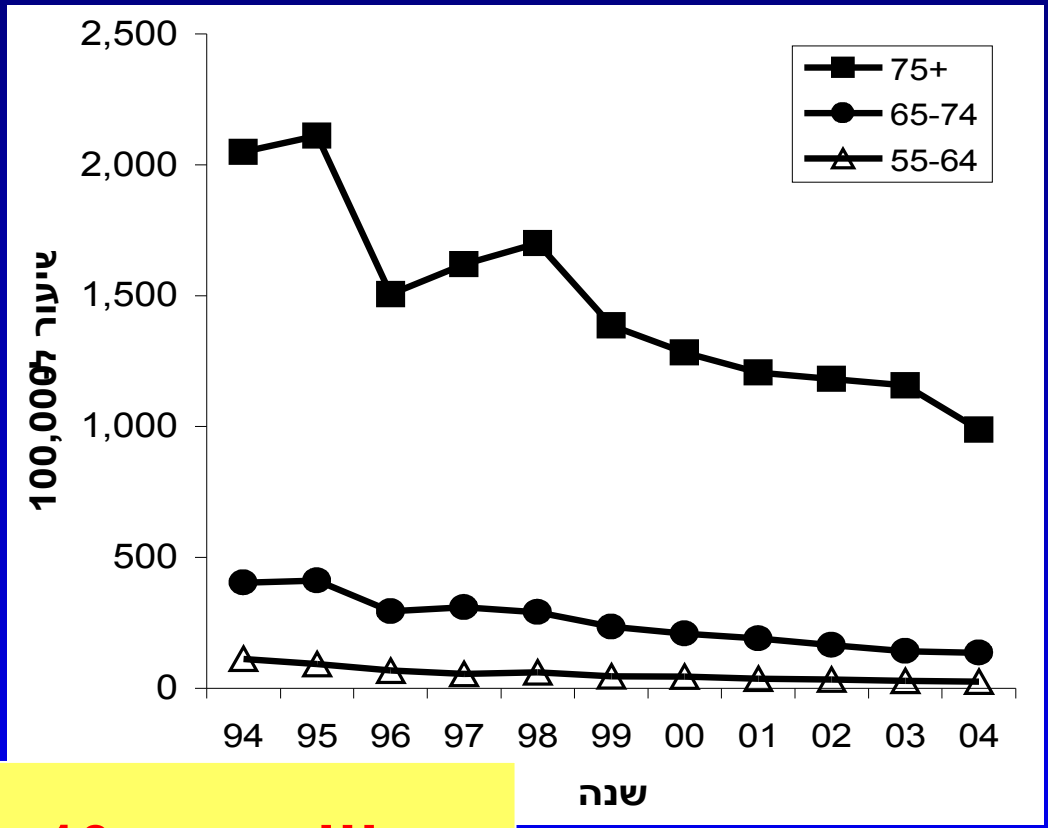


מוות ממחלת לב כלילית בקבוצות גיל ומין
ישראל 1994 – 2004

גברים



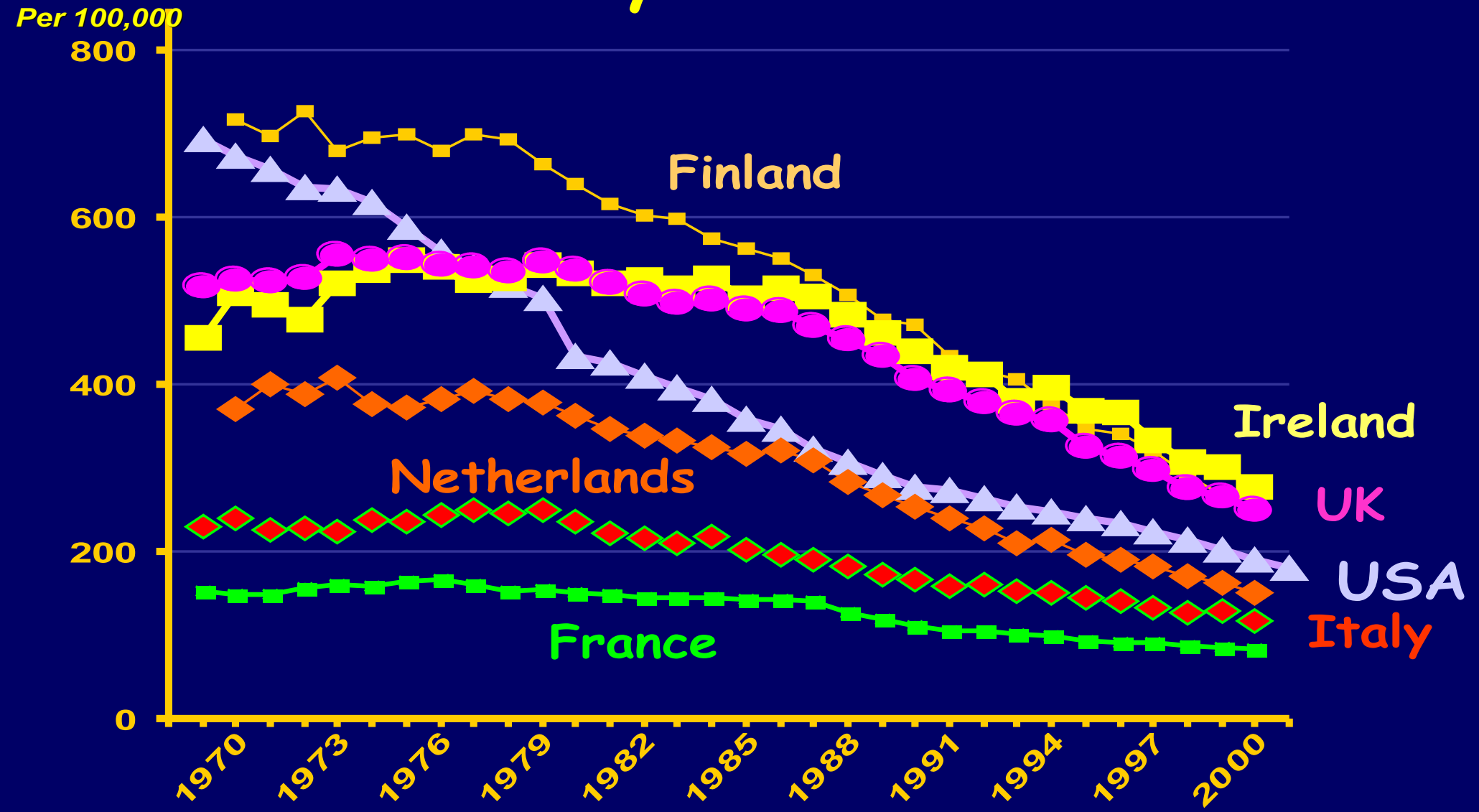
נשים



↓ > 45 % in 10 years !!!

Banai S.

International mortality trends in men, coronary heart disease

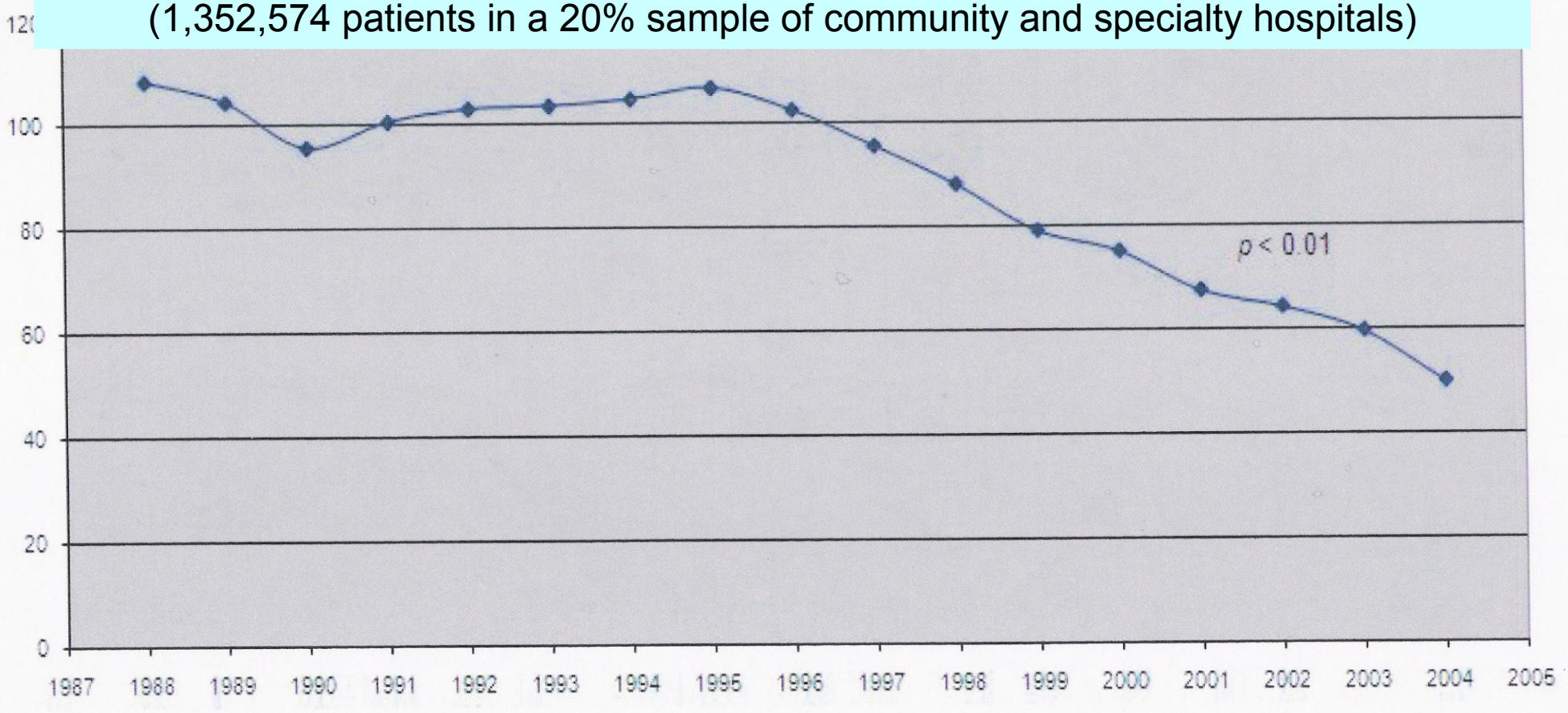


BHF Heartstats (WHO statistics - Men aged 35 - 74 - Standardised)

Age adjusted STEMI rate per 100,000 in the US

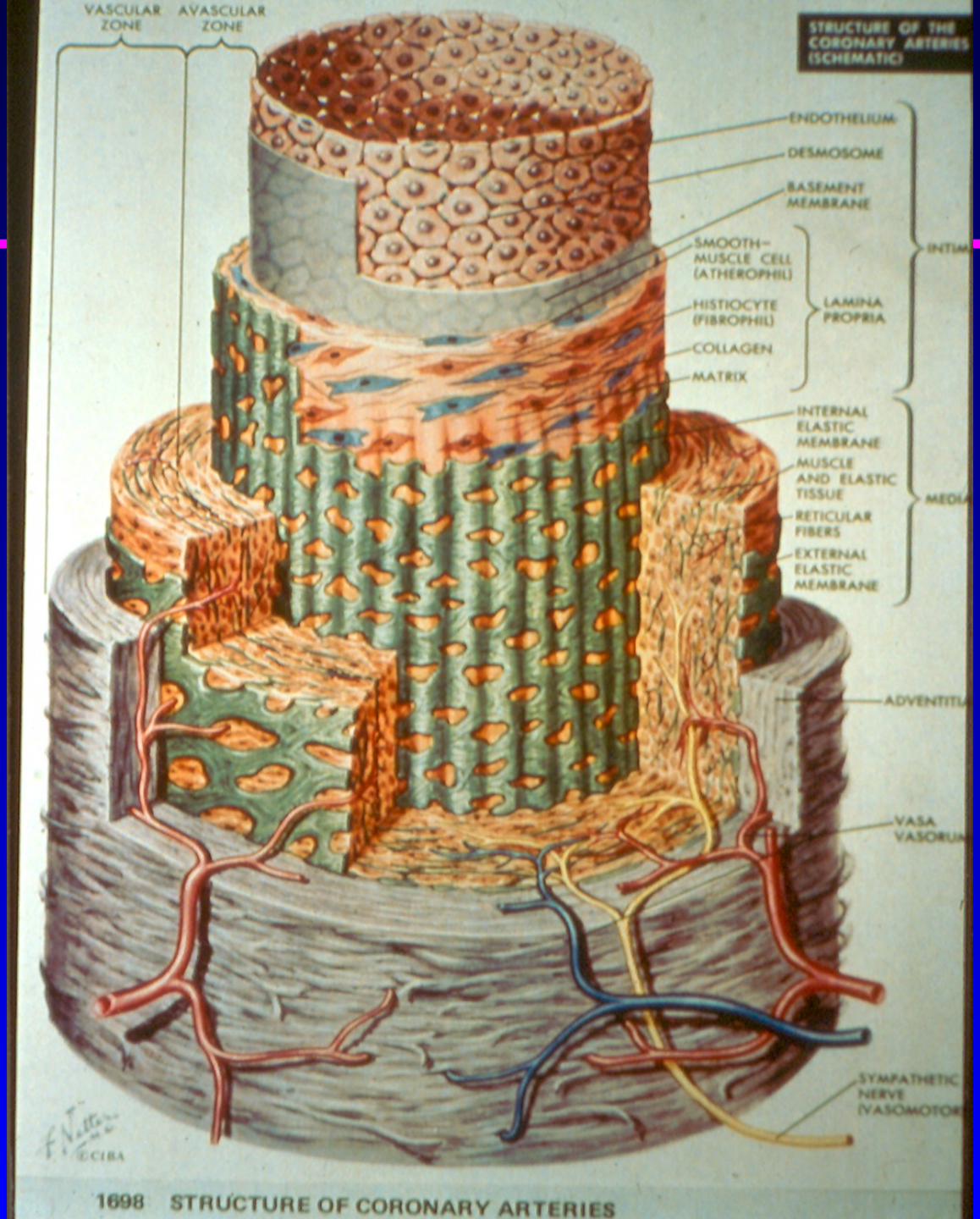
NIS* database

(1,352,574 patients in a 20% sample of community and specialty hospitals)



* Nationwide Inpatient Sample

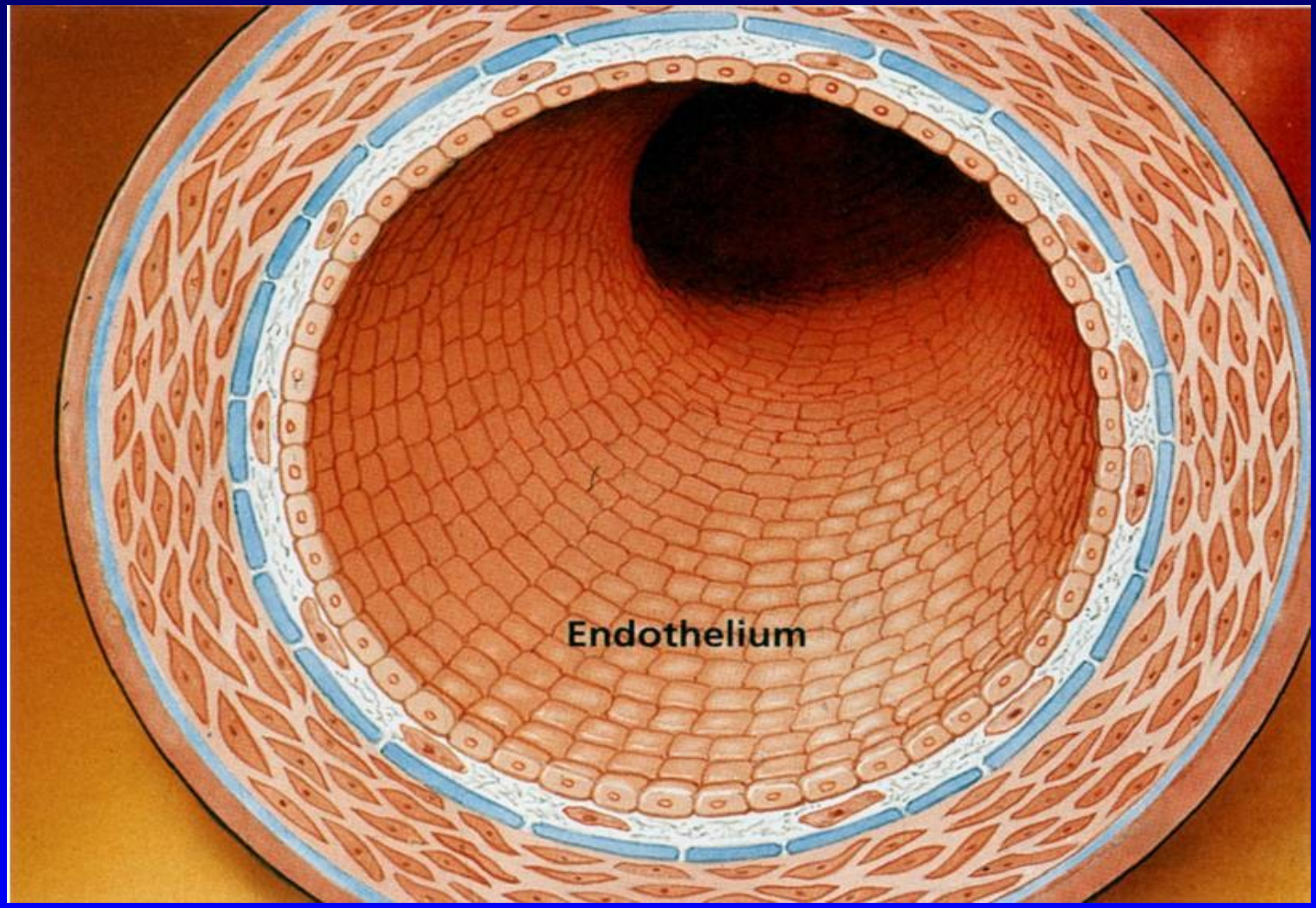
Mohaved, MR. World Congress of Cardiology. Buenos Aires, 21.5.08



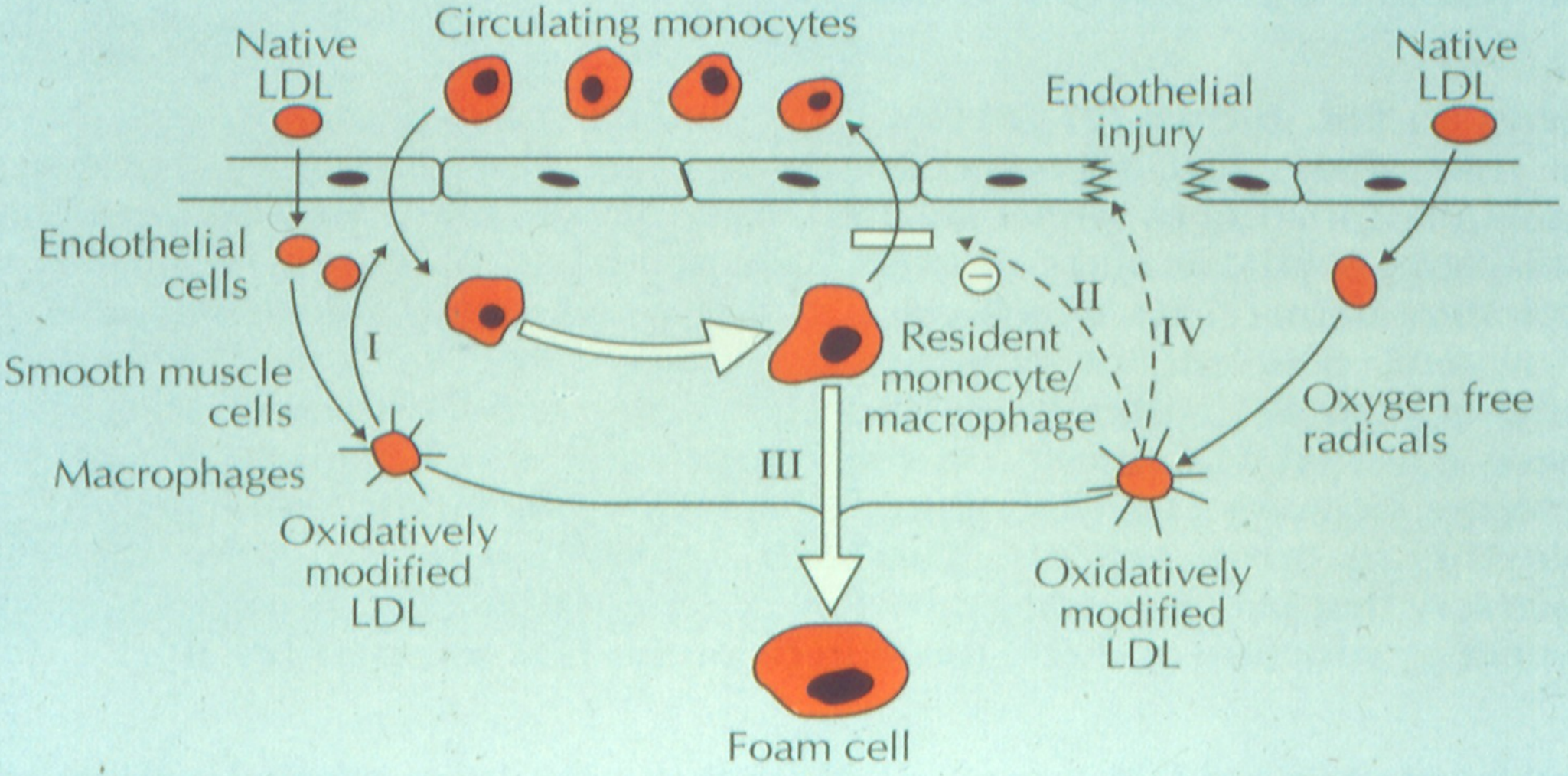
1698 STRUCTURE OF CORONARY ARTERIES

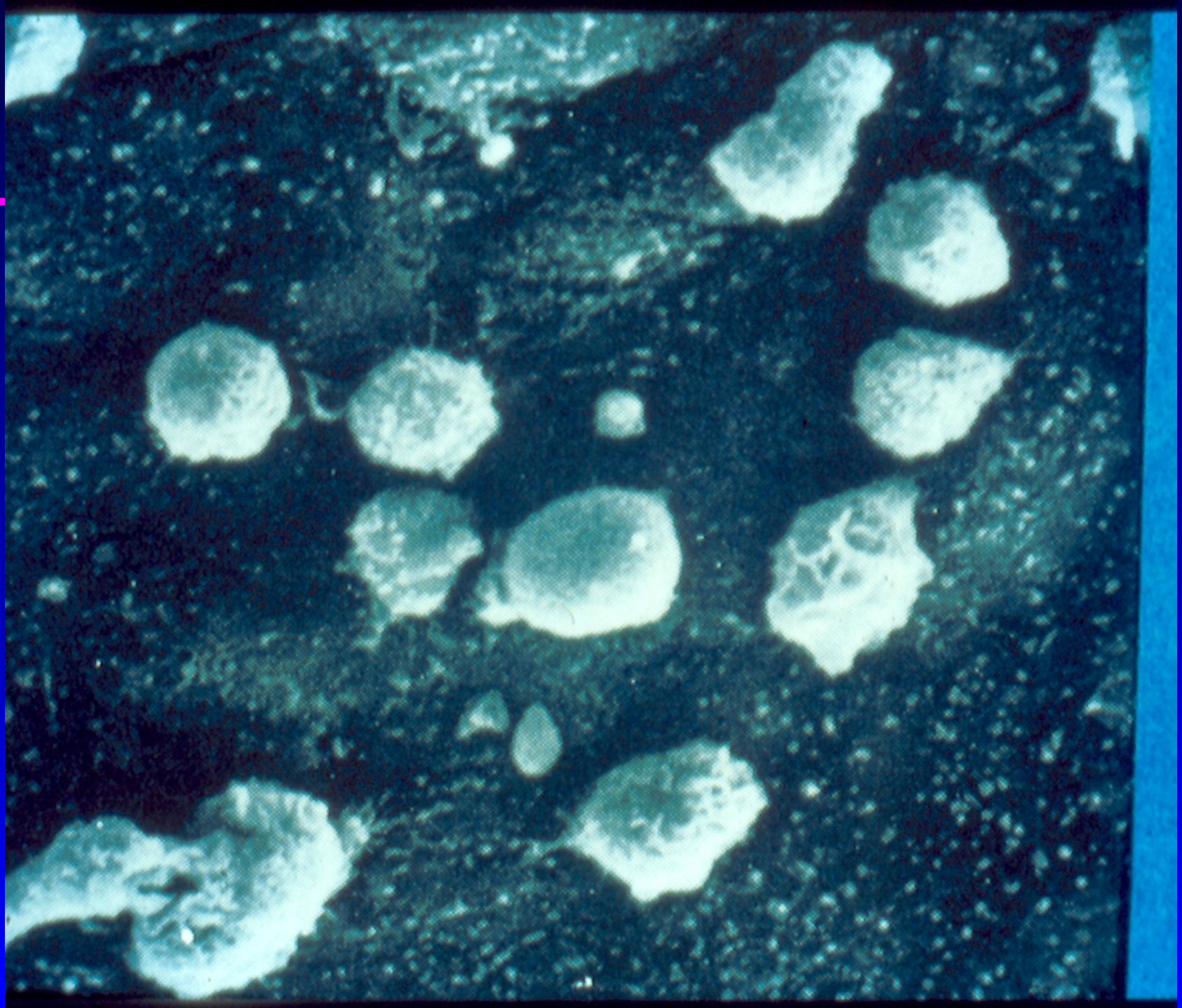
Banai S.

Normal coronary Artery



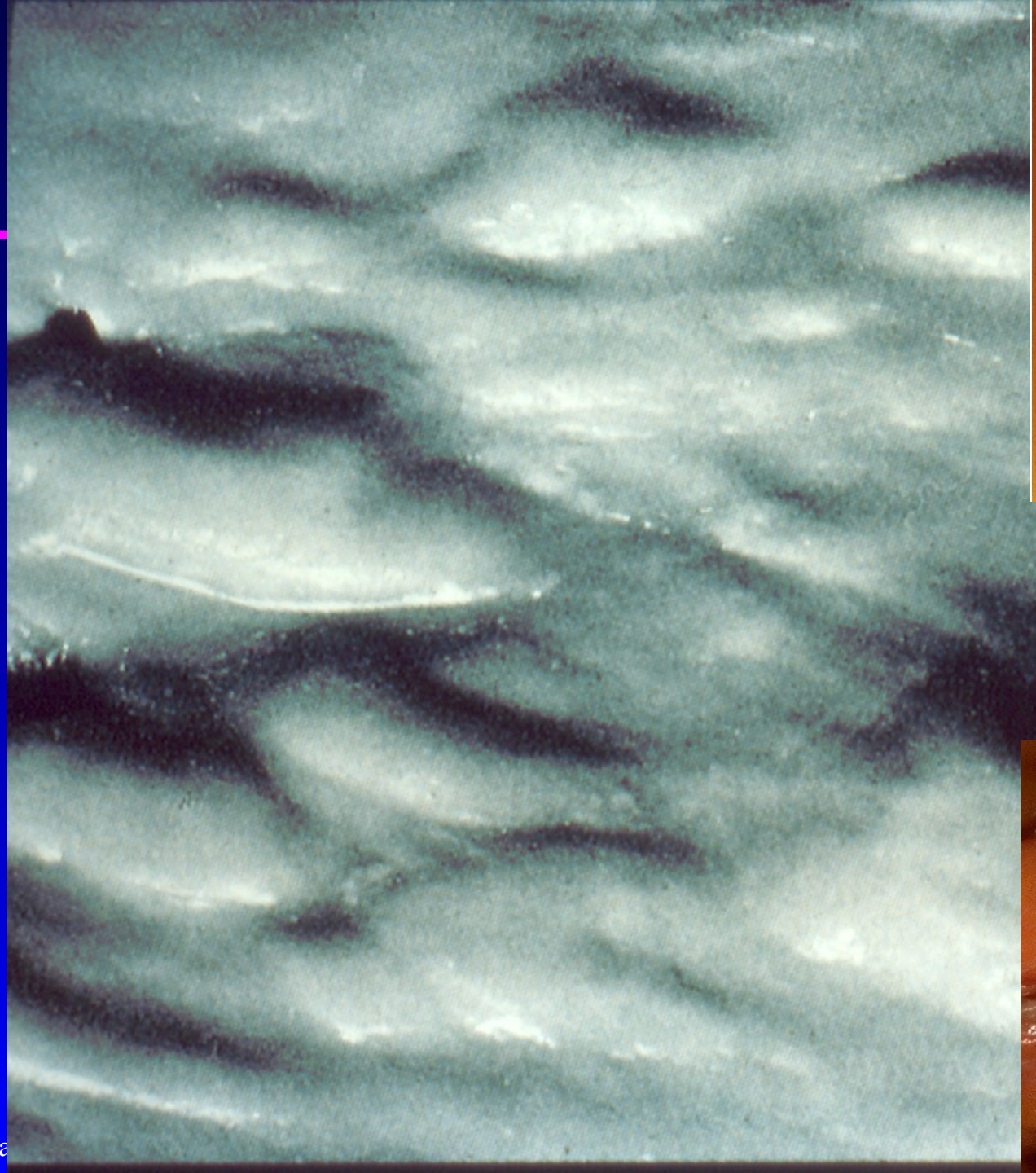
LDL disruption of endothelial integrity

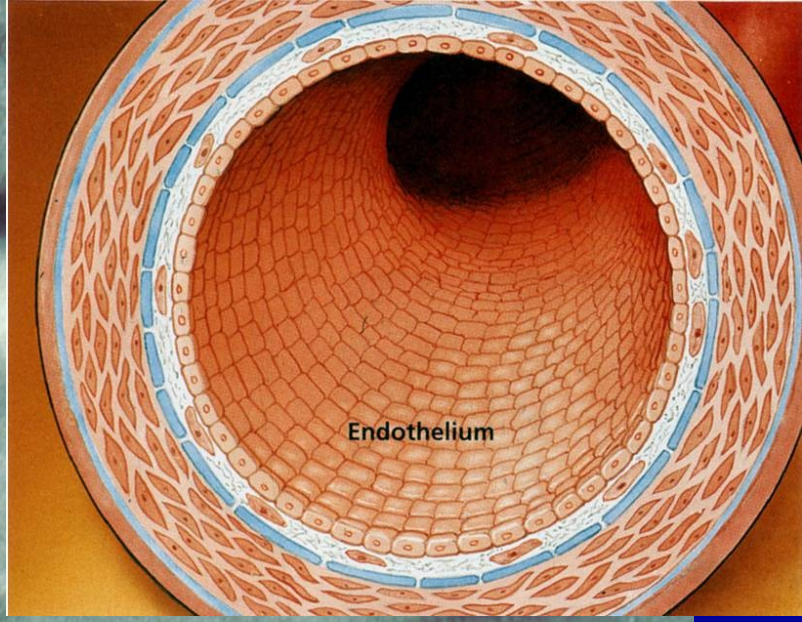


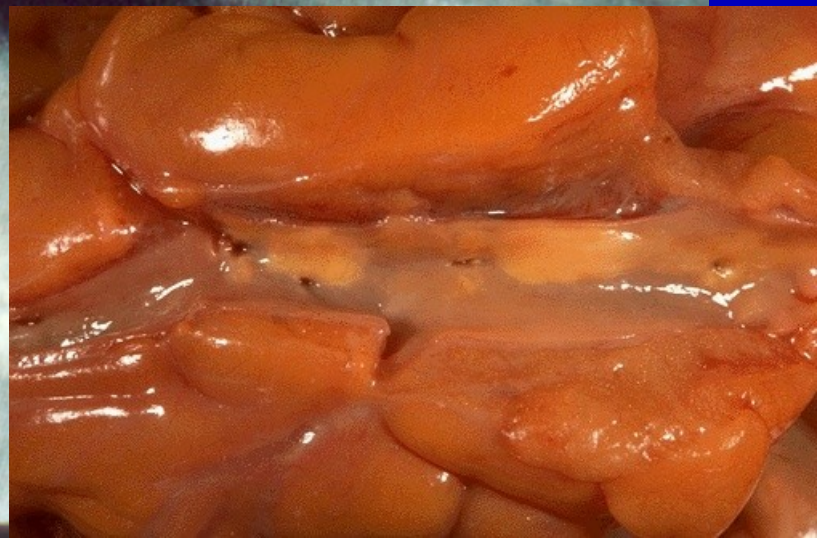


Banai S.

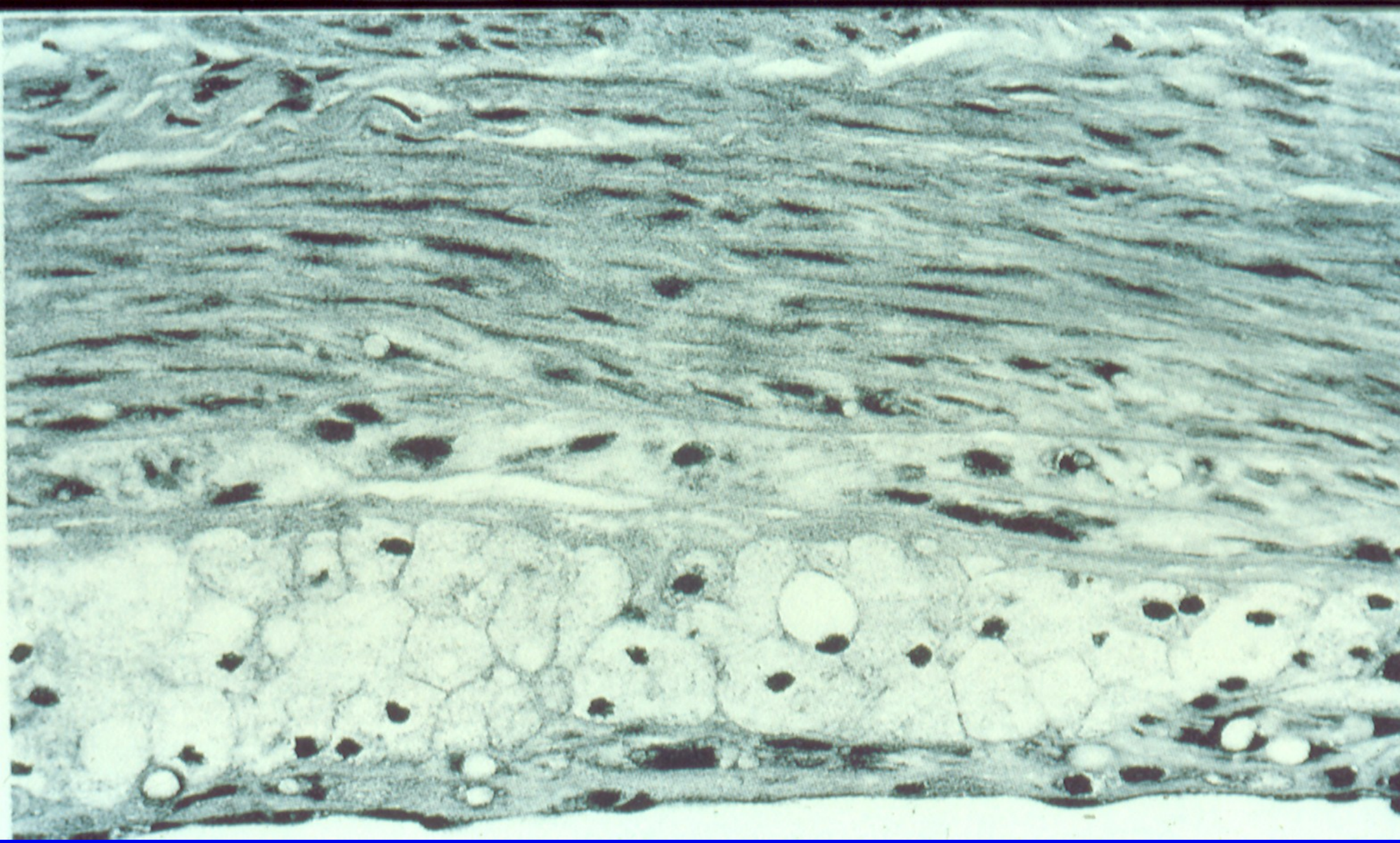
Banai S.





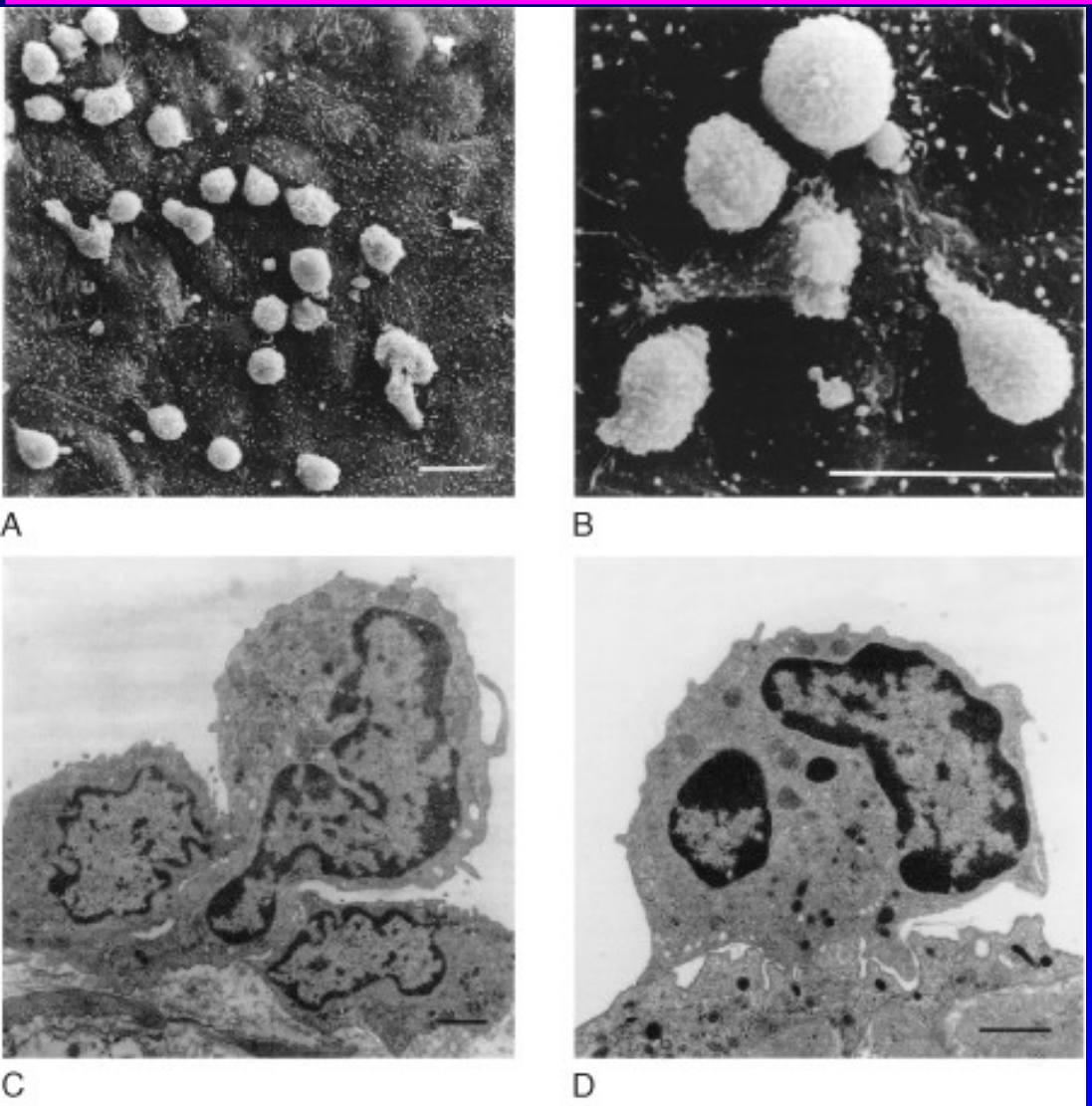


Bana



Banai S.

Leukocyte interactions with the artery wall in hypercholesterolemic nonhuman primates

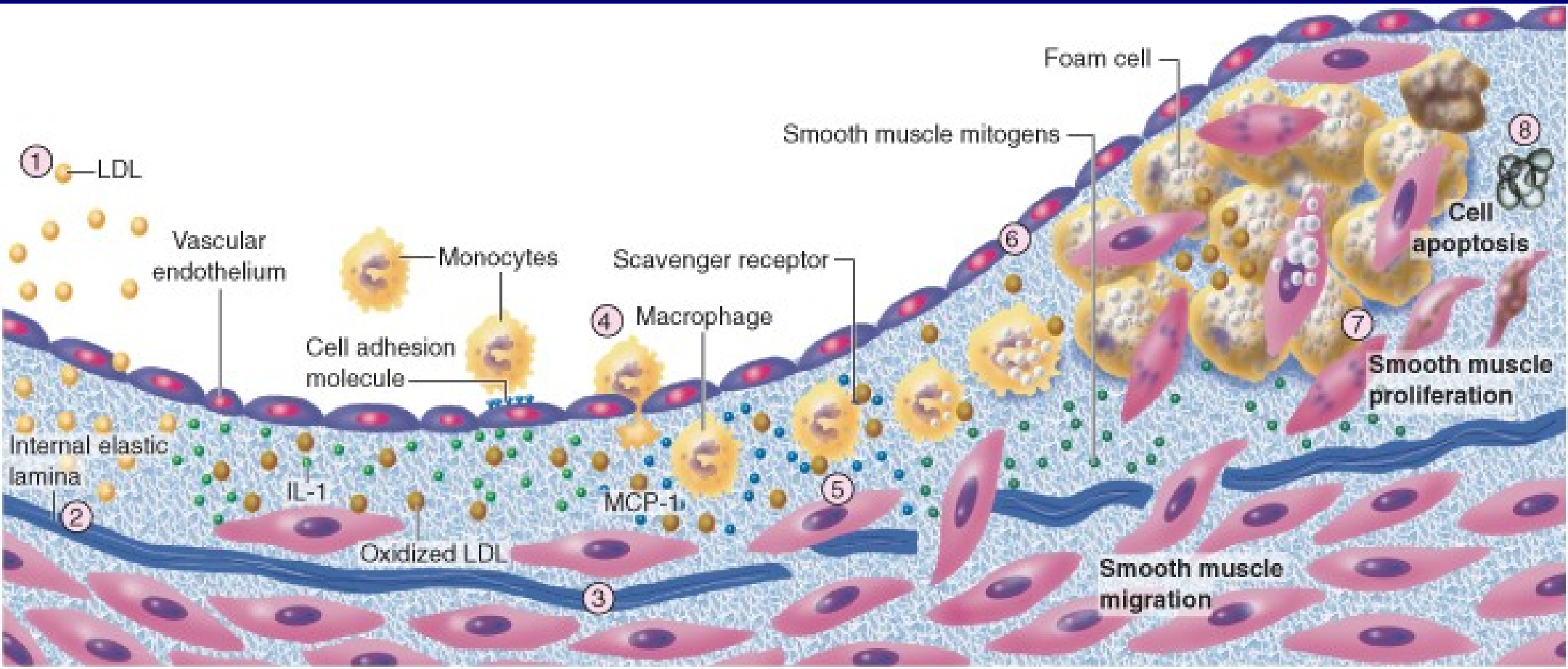


Adhesion of mononuclear phagocytes to the intact endothelium 12 days after initiating a hypercholesterolemic diet

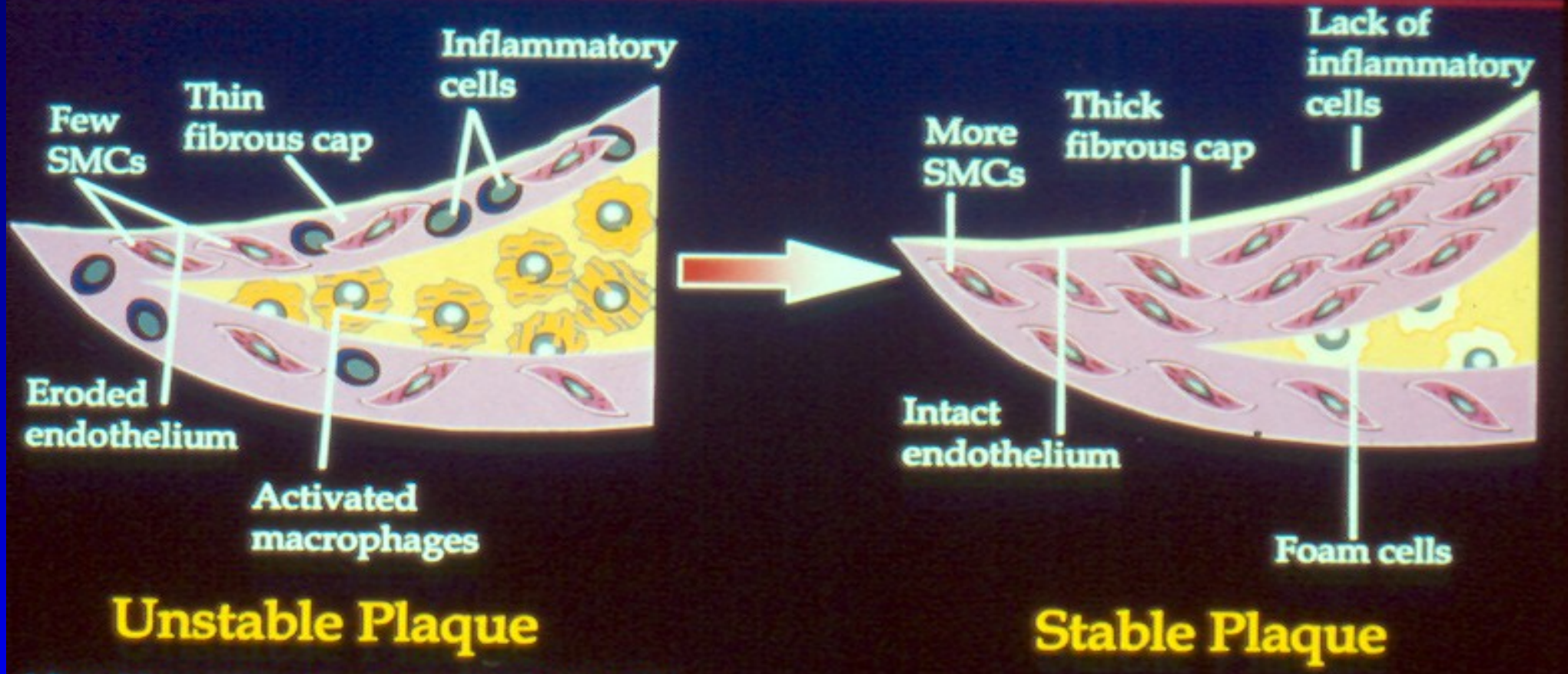
Interdigitations and intimate association of the monocyte with the endothelium when a monocyte appears to diapedese between two endothelial cells to enter the intima

From Faggiotto A, Ross R, Harker L: Studies of hypercholesterolemia in the nonhuman primate. Arteriosclerosis 4:323, 1984

Schematic of the evolution of the atherosclerotic plaque



Atherosclerosis Involves More Than Just Lipids



Unstable Plaque

Stable Plaque

Adapted from Libby: *Circulation* 1995;91:2844–2850

Vascular inflammation and the vulnerable plaque

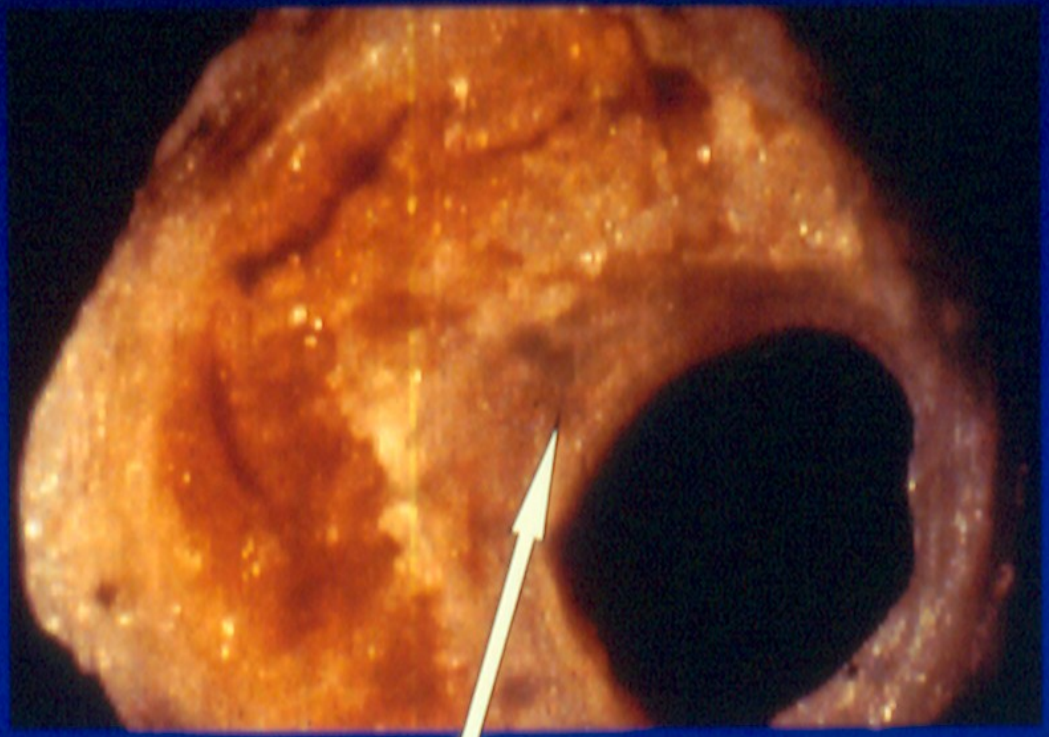
Plaque Stability

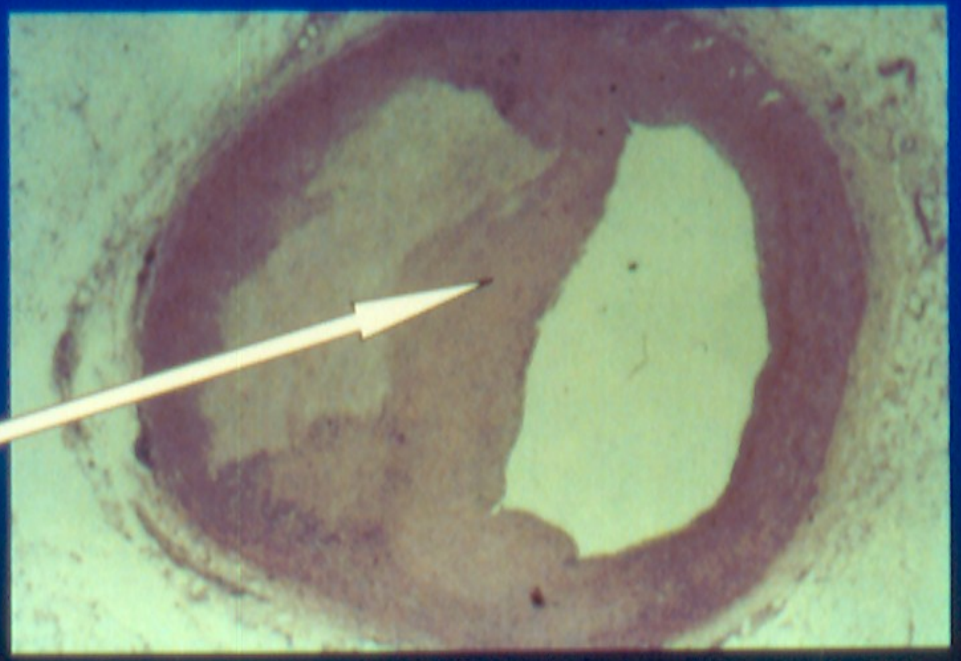
- Amount of SMCs
- Collagen synthesis by SMCs

Plaque Vulnerability

- Amount of macrophages
- Collagen degradation by MMPs
- Activated T lymphocyte accumulation
- Interferon-γ produced by T lymphocytes inhibits SMC collagen synthesis

The stable atherosclerotic plaque





Thick, VSMC-rich fibrous cap

Plaque Growth From Fatty to Fibrous

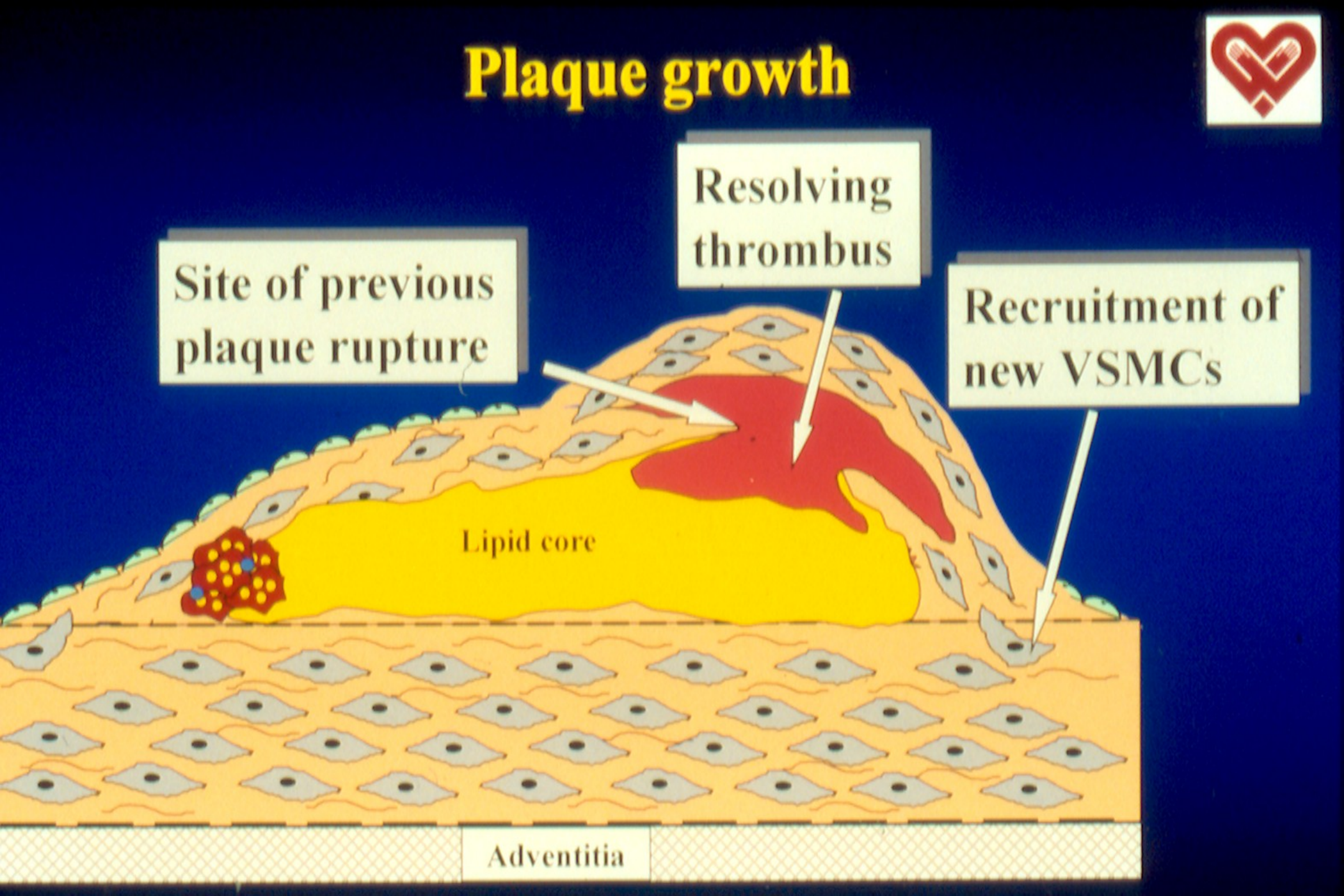
Evolves by Cycles Of:

- Disruption
- Non occlusive mural thrombus formation
- Healing

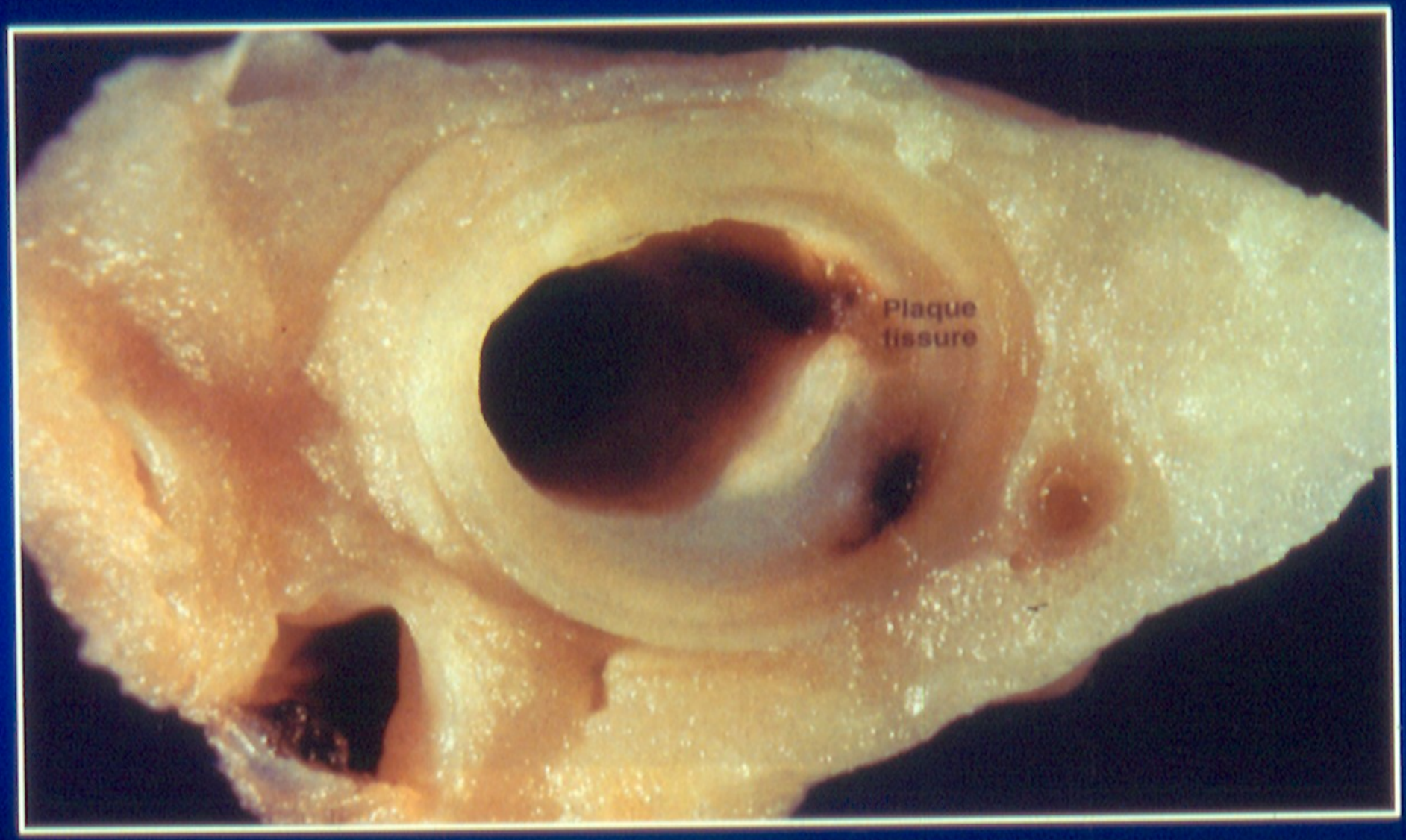
OR

- Hemorrhage into the plaque
- Healing and organization

Plaque growth



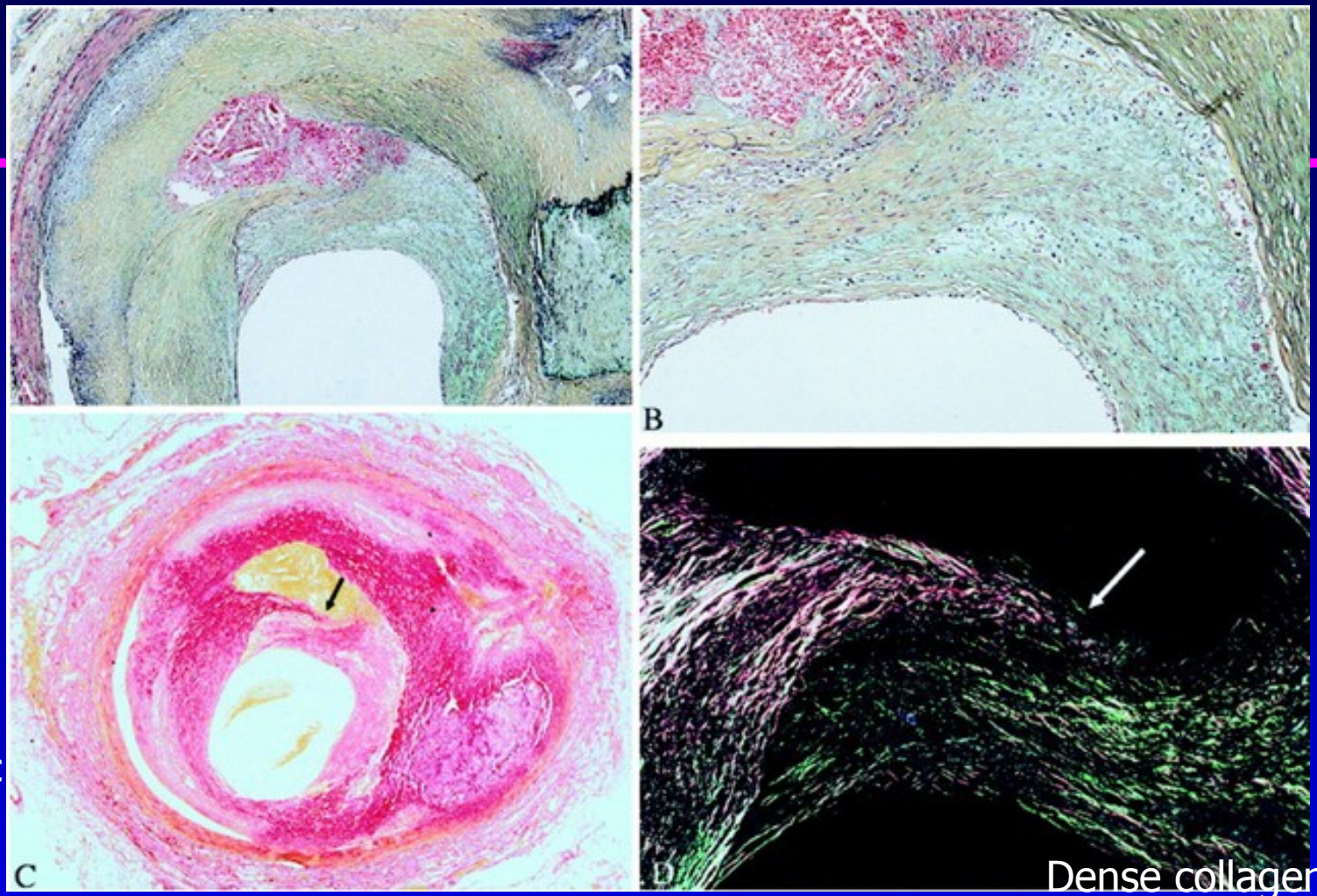
The healed atherosclerotic plaque



Healed plaque rupture

Lipid-rich core with hemorrhage

Dark-red collagen surrounding lipid hemorrhagic cores



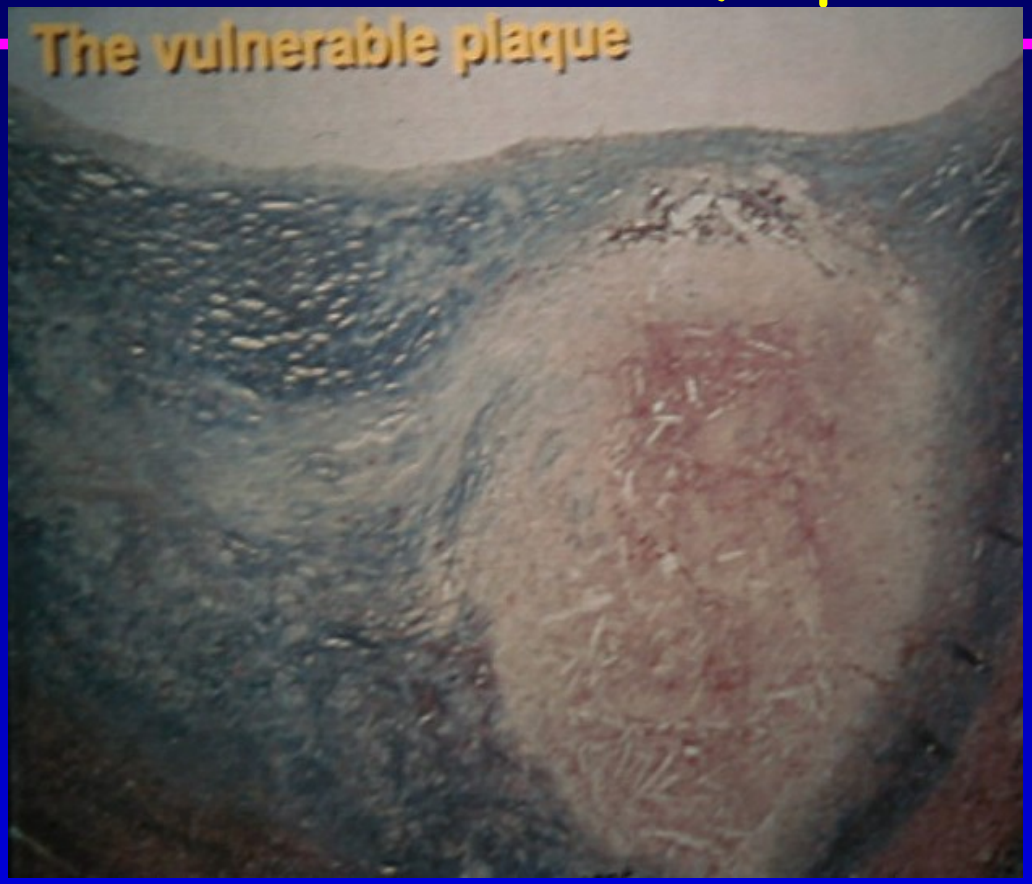
SMC formation within collagenous proteoglycan-rich neointima showing clear demarcation, with more fibrous regions of old plaque to right

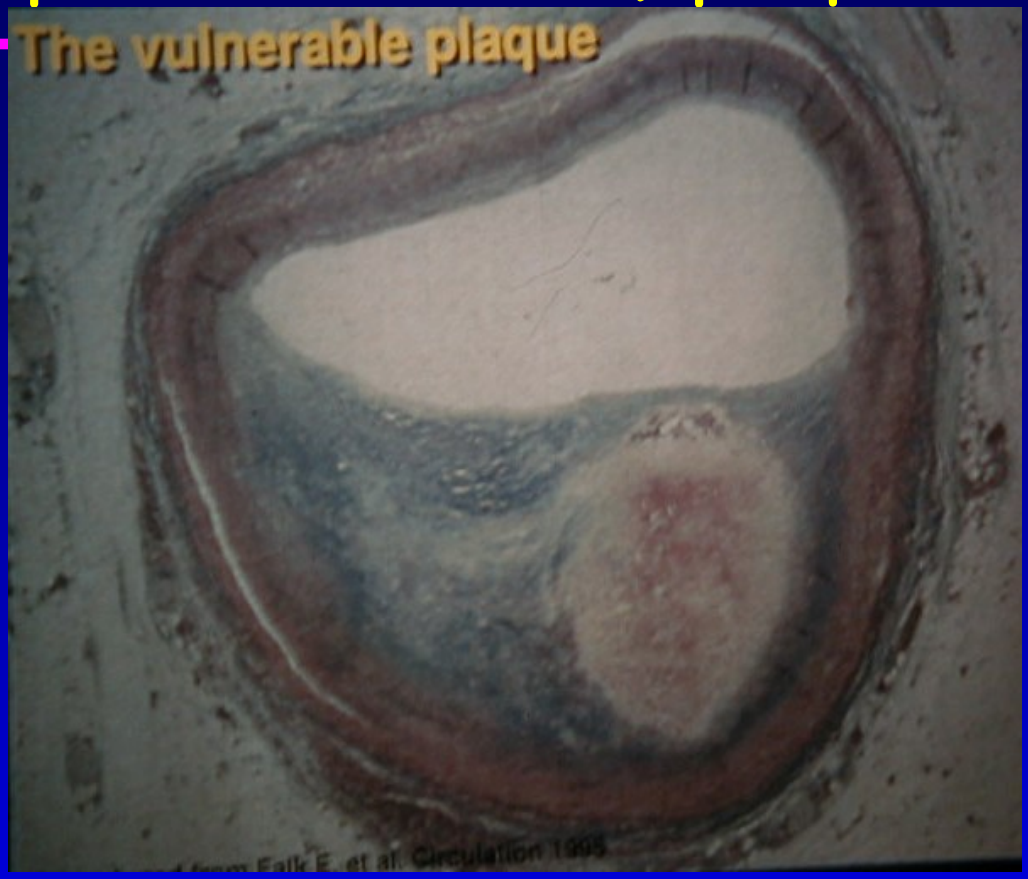
Dense collagen (type 1) that forms fibrous cap is lighter reddish-yellow is disrupted (arrow), with newer greenish type III collagen on right and above rupture site

Banai S.

Burke AP, Virmani R: *Circulation* 2001;103:934

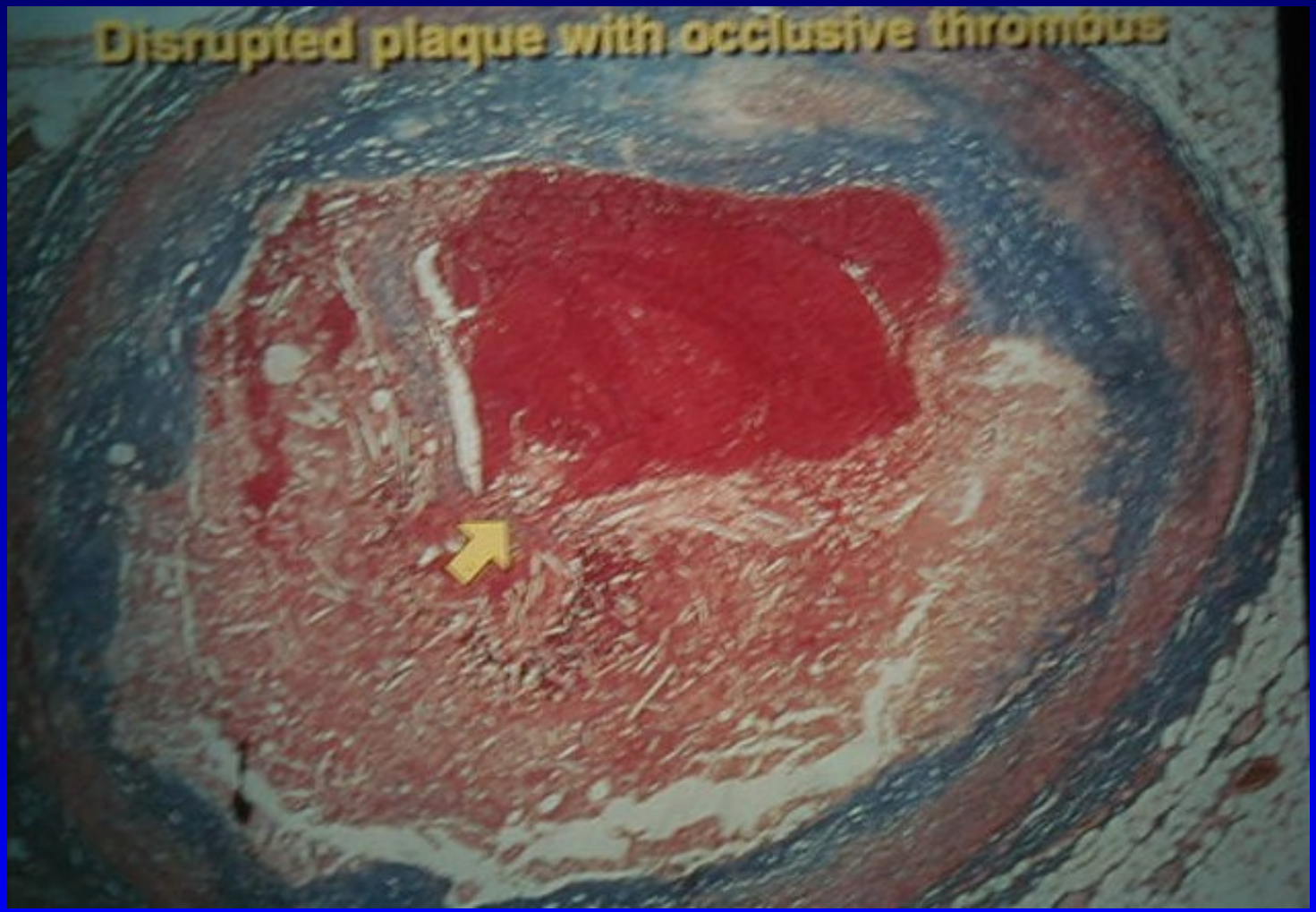
The vulnerable (rupture-prone, unstable) plaque

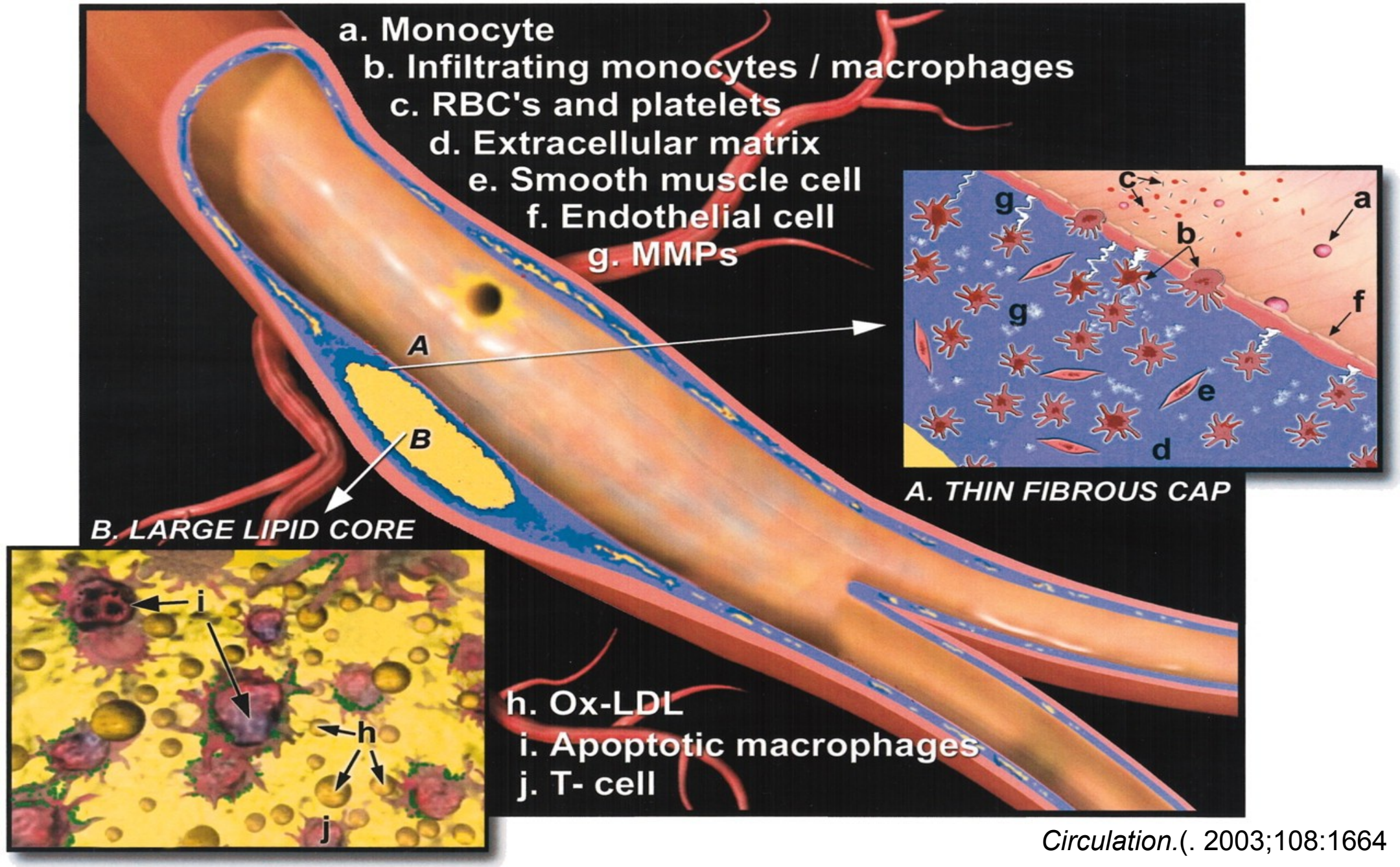




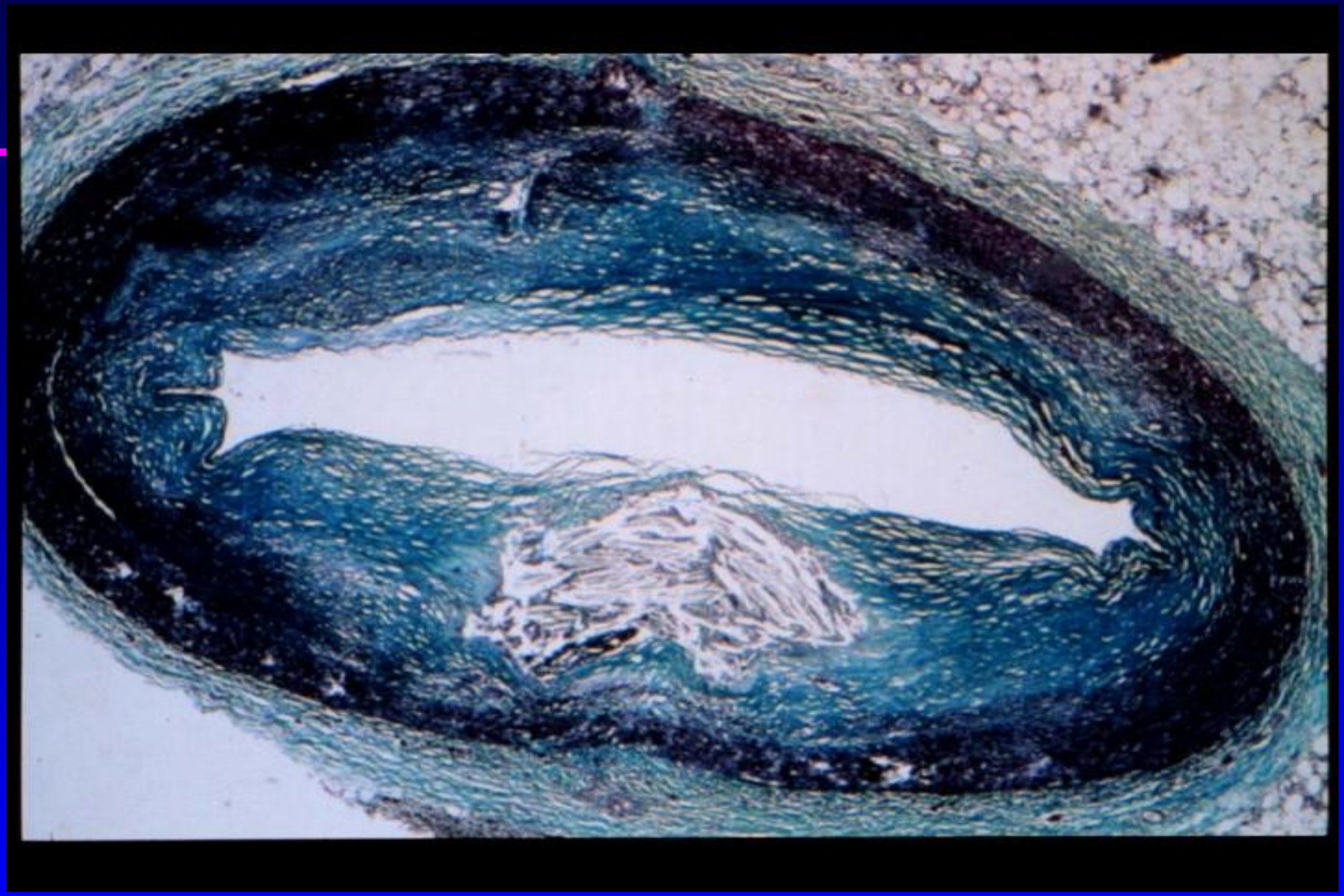
- Size of atheromatous core
- Thickness of fibrous cap
- Inflammation in fibrous cap

Plaque Rupture



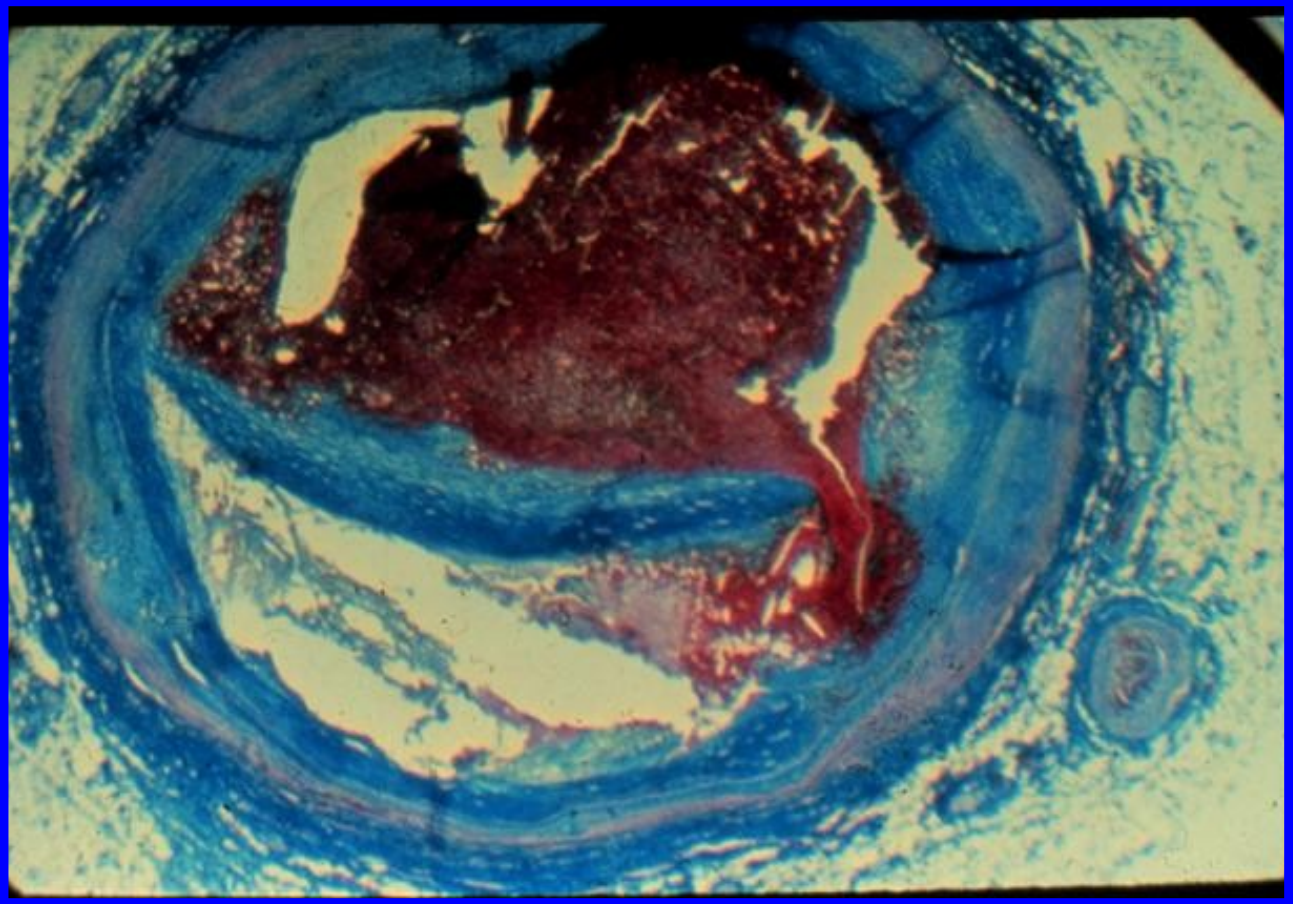


Circulation.(. 2003;108:1664

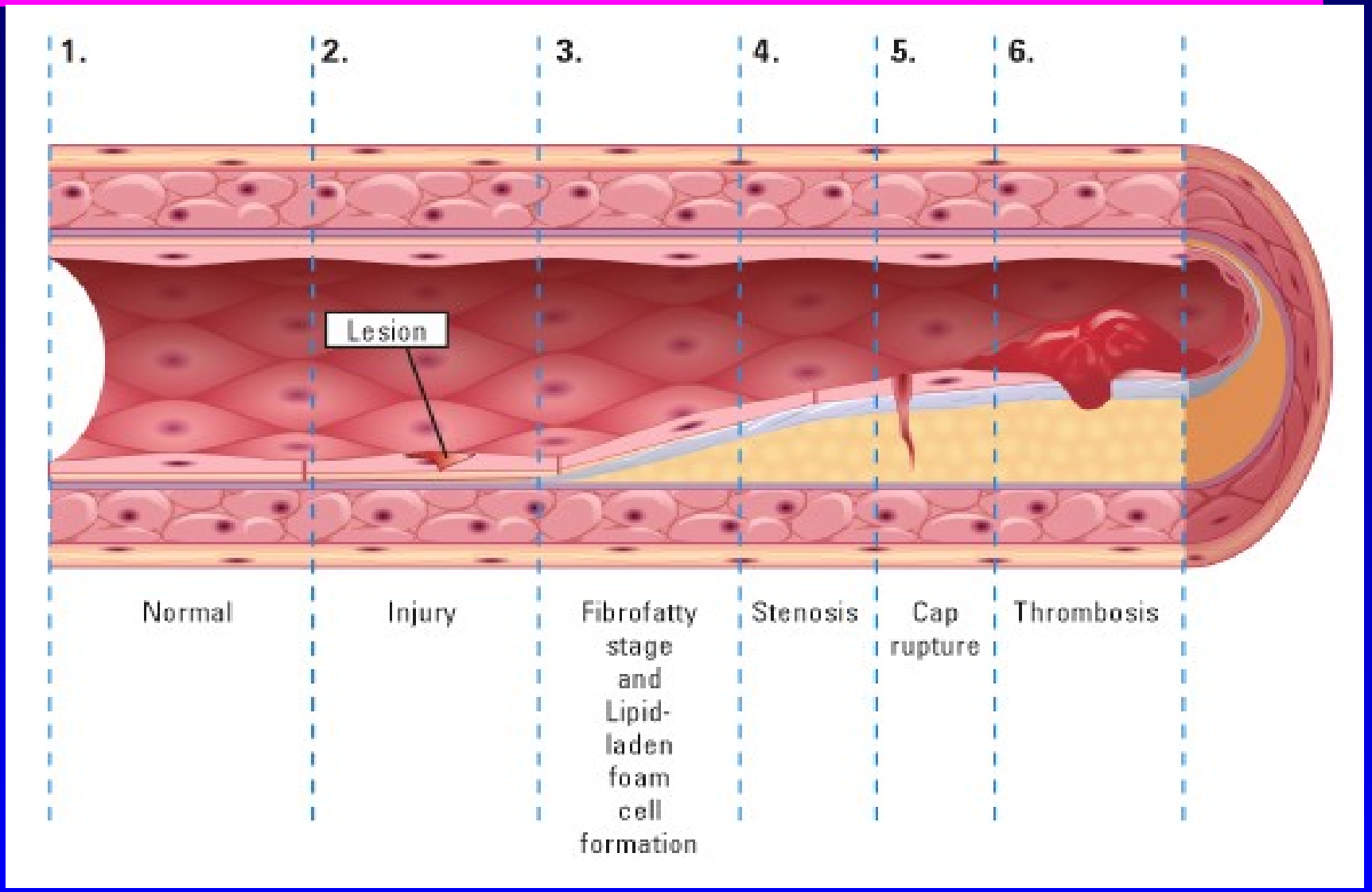


Banai S.

Plaque Rupture



התפתחות טרשת בעורק כלילי



Heart Attack Should be Treated Early

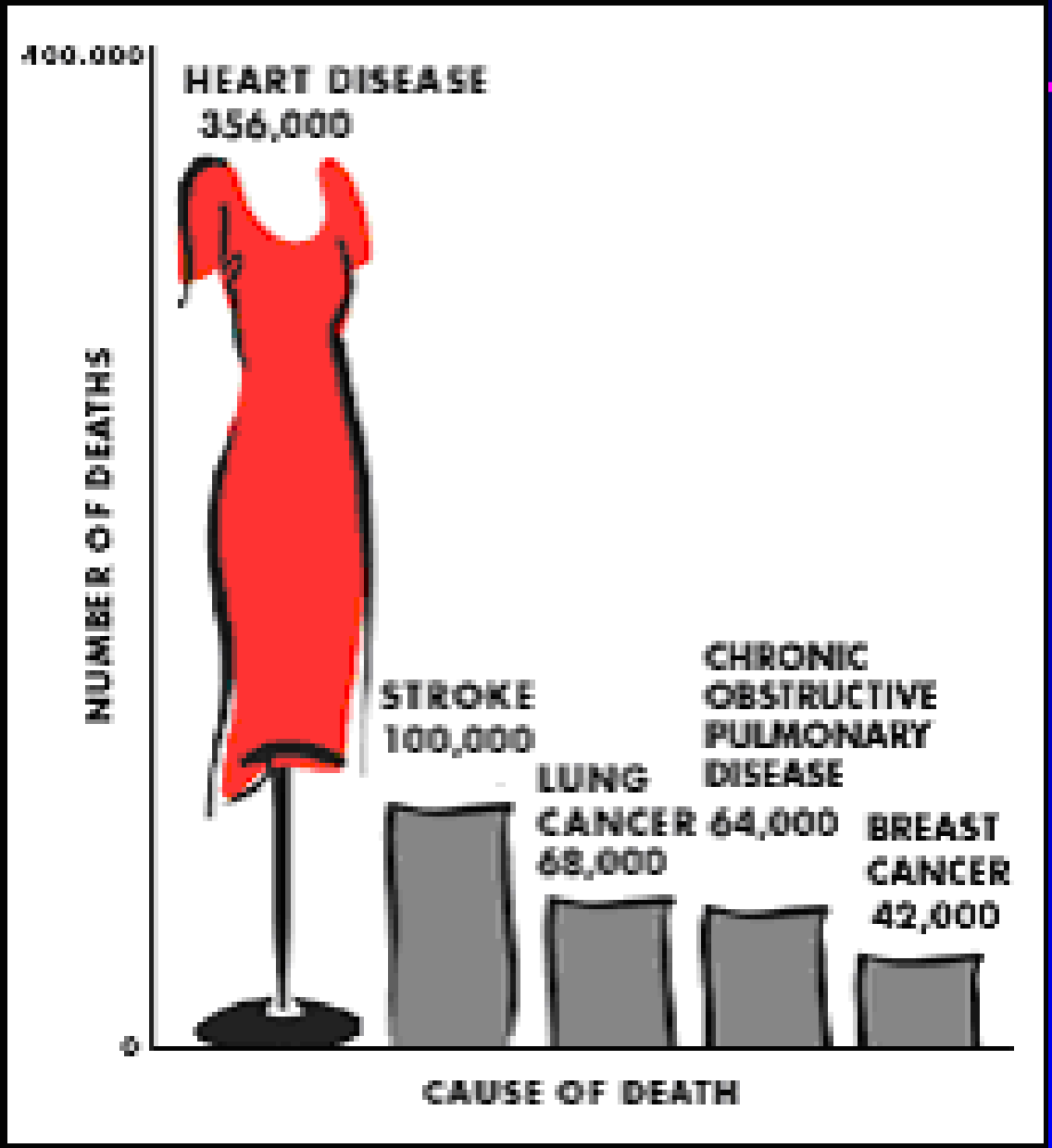
Say, 50 years before it happens

TIME

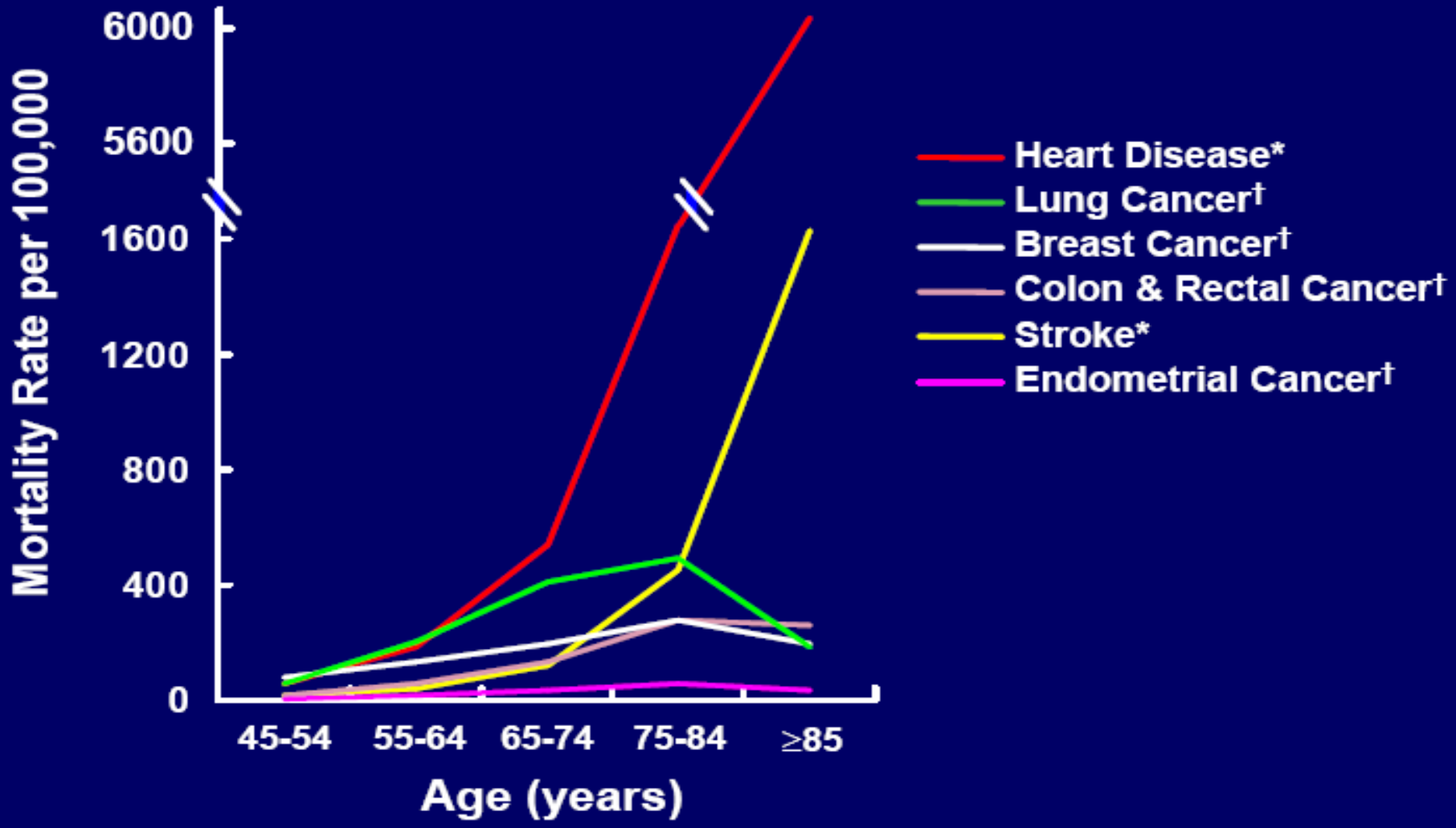
WOMEN & HEART DISEASE

Is your biggest worry breast cancer? Think again. ONE OUT OF THREE women will die of heart disease. What you can do to protect yourself

LEADING CAUSES OF DEATH FOR AMERICAN WOMEN (2002)



Mortality Rates in Women



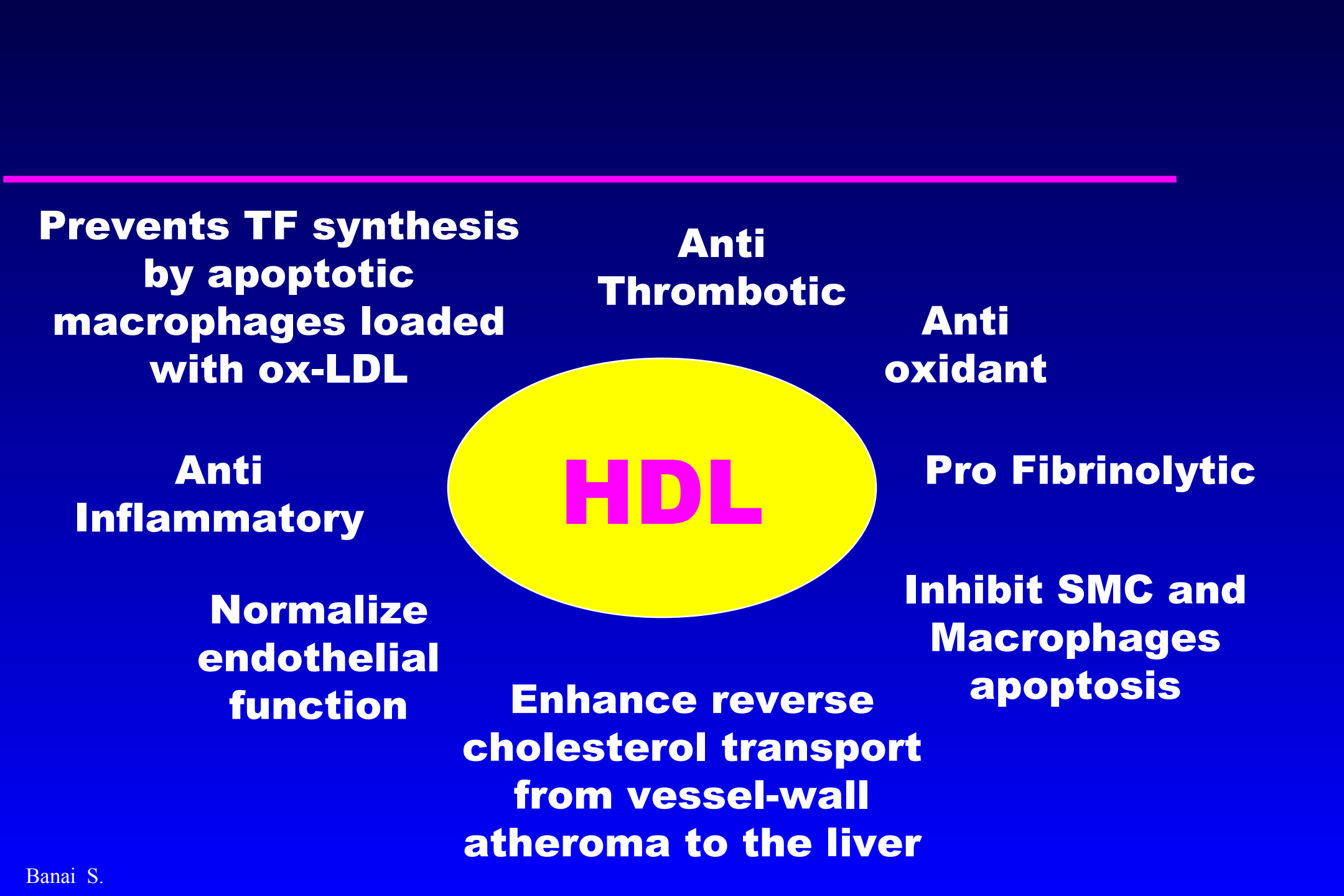
*Mean of years 1995-1998; †1994-1998.

Eberhardt VMS, et al. *Health, United States, 2001*. National Center for Health Statistics, 2001:189,192.
Ries LAG, et al. *SEER Cancer Statistics Review, 1973-1998*. National Cancer Institute, 2001.

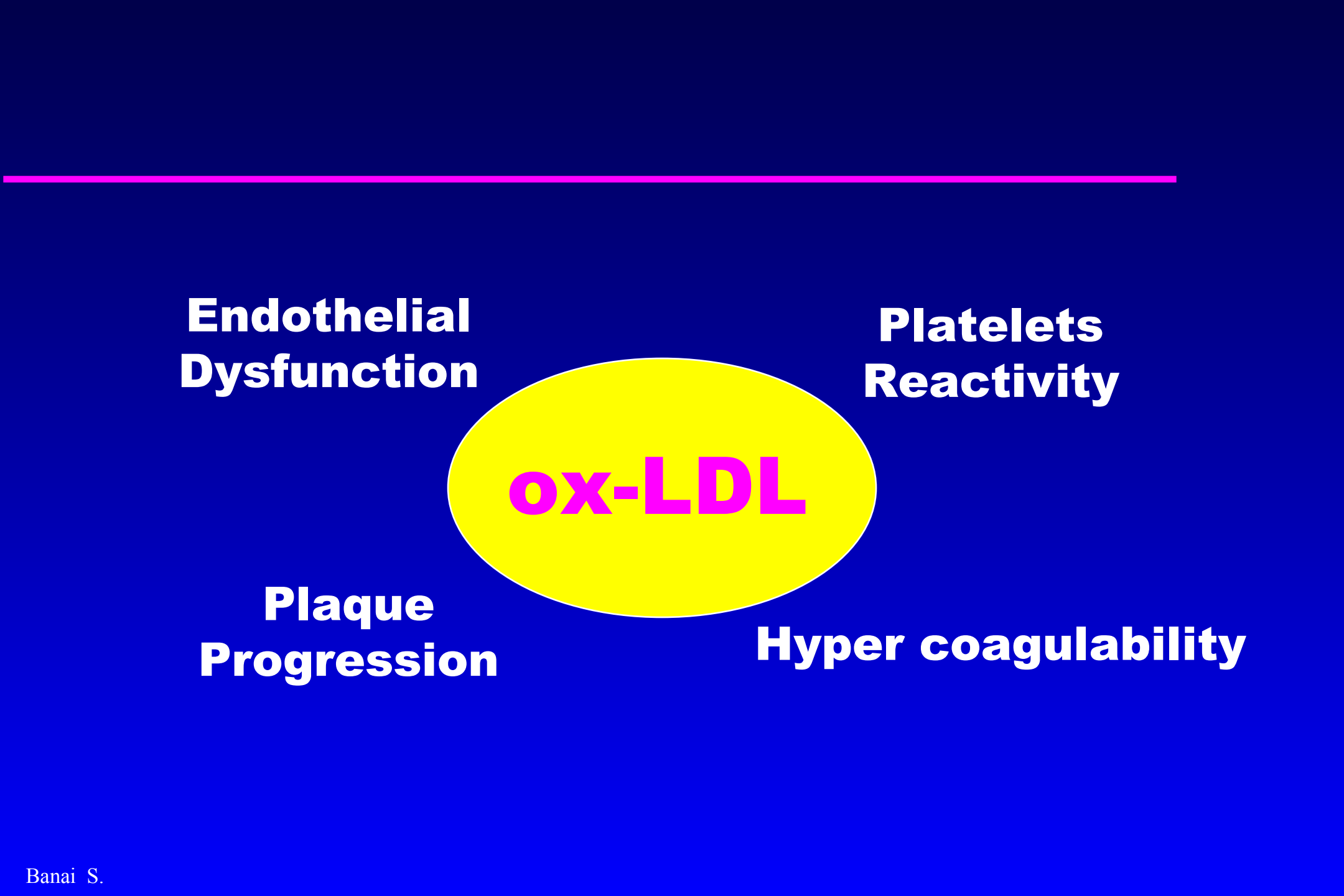
Major risk factors for CVD

- High LDL cholesterol levels
- Low HDL cholesterol levels
- High triglyceride levels
- Obesity
- Insulin resistance
- Hypertension
- Smoking
- Diabetes mellitus
- Family history

Metabolic syndrome


Prevents TF synthesis by apoptotic macrophages loaded with ox-LDL
Anti Thrombotic
Anti oxidant
HDL
Anti Inflammatory
Pro Fibrinolytic
Normalize endothelial function
Inhibit SMC and Macrophages apoptosis
Enhance reverse cholesterol transport from vessel-wall atheroma to the liver

Banai S.


Endothelial Dysfunction
Platelets Reactivity
ox-LDL
Plaque Progression
Hyper coagulability

Acute Coronary Syndromes (ACS)

The clinical manifestation of coronary atherothrombosis

- A spectrum of conditions in which an atherosclerotic coronary plaque is ruptured and subsequently an intraluminal thrombus is formed
- Majority of patients with ACS have no prior symptom

Atherothrombosis

The thrombotic complications of atherosclerosis

Atherosclerosis

A multifactorial systemic inflammatory disease

Inflammation

The link between atherosclerosis and thrombosis

Atherothrombosis

The thrombotic complications of atherosclerosis

Inflammation

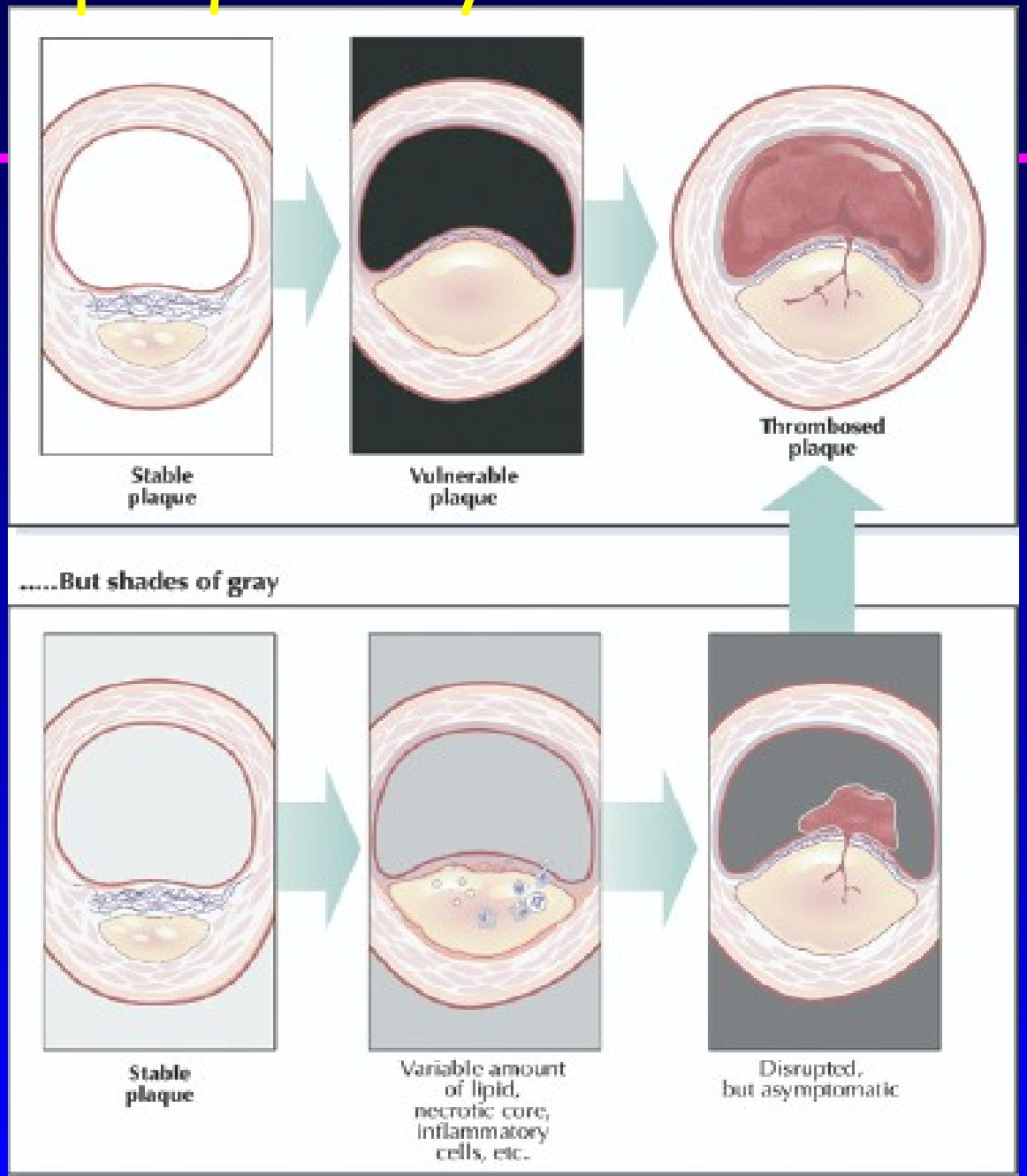
The link between atherosclerosis and thrombosis

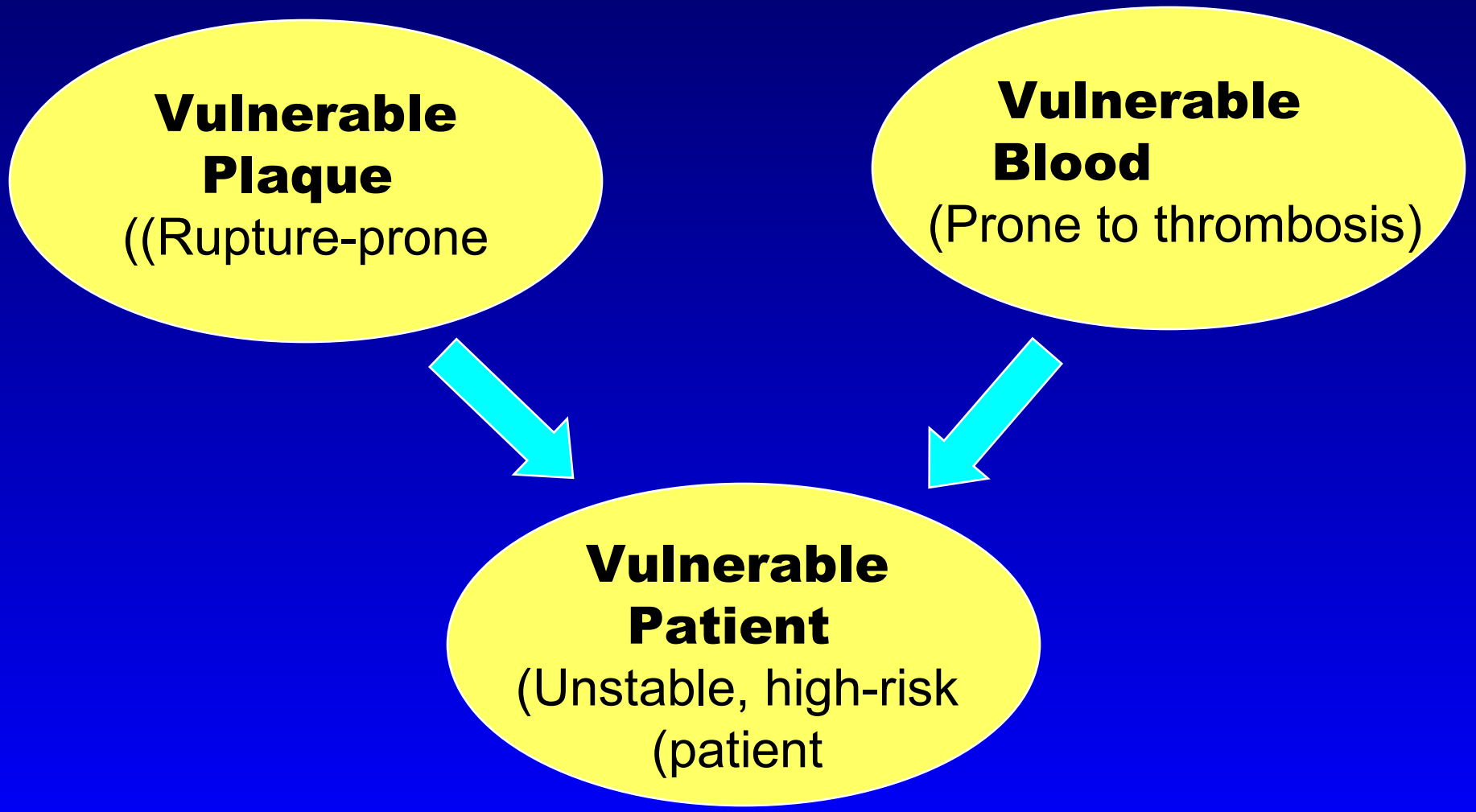
- Responsible for plaque progression
- Responsible for plaque rupture
- The cause for acute coronary syndromes

ACS - Rupture of the Fibrous Cap

- Ongoing Inflammation at the site of Plaque Disruption

Vulnerable plaque may not be black or white



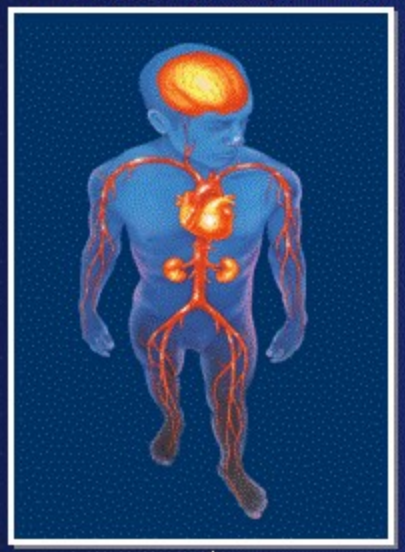

Vulnerable Plaque
((Rupture-prone
Vulnerable Blood
(Prone to thrombosis)
Vulnerable Patient
(Unstable, high-risk
(patient

Vulnerable Plaque and Patient Risk

Vulnerable Blood

- Hypercoagulability
- Increased platelet activation and aggregation
- Increased coagulation factors
- Decreased fibrinolysis
- Increased thrombogenic factors

Vulnerable Patient



Vulnerable Plaque

- Active inflammation
- Cap thickness
- Lipid core size
- Endothelial denudation
- Injured plaque

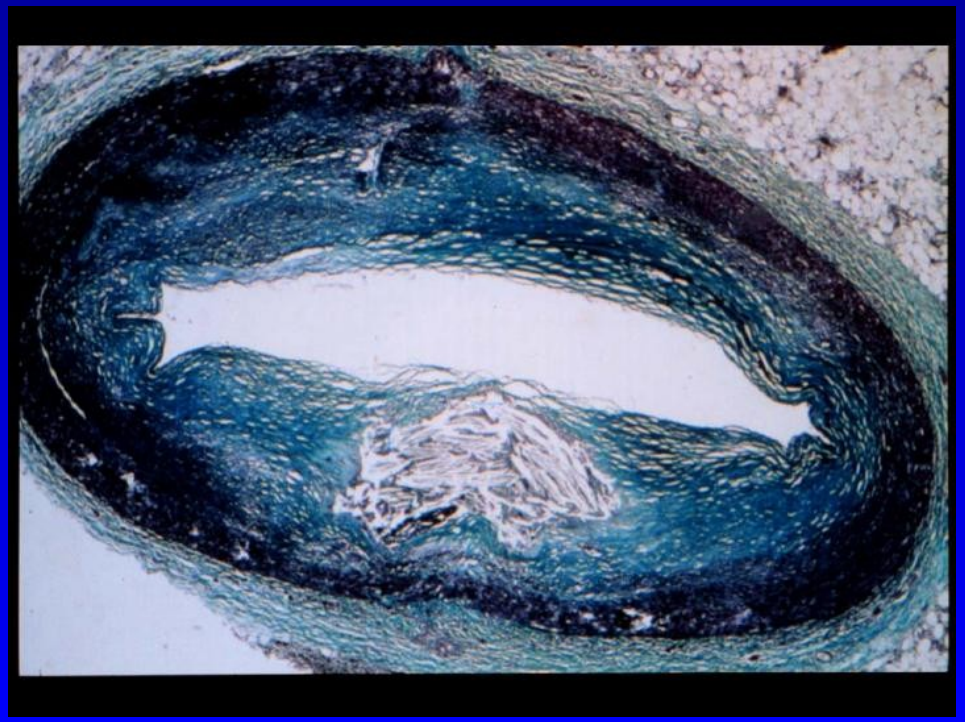
Vulnerable Myocardium

- Myocardial ischemia
- Electrophysiological disorders
- Myocarditis

Adapted from Naghavi M et al. *Circulation*. 2003;108:1664-1672.
Naghavi M et al. *Circulation*. 2003;108:177[illegible]1778.

The Challenge:
Stabilizing the vulnerable plaque

- The treatment of CAD must be aimed at stabilising the vulnerable plaques, which are at risk of becoming a site for acute thrombosis



Vascular inflammation and activation:

The target for lipid lowering

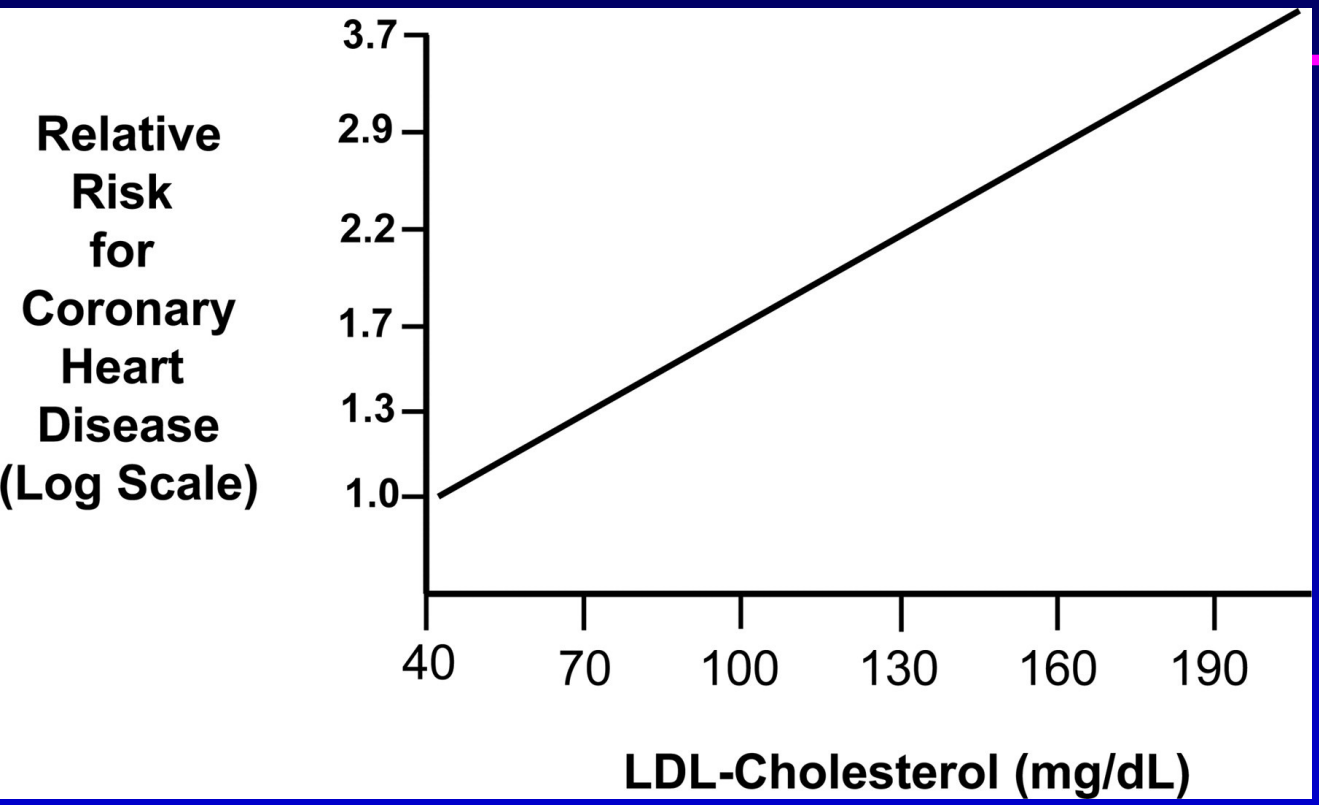
LDL lowering

- Reduce the incidence of coronary events and stroke by changing the quality of the plaque
- Produces only modest improvements in the luminal caliber of fixed atherosclerotic lesions

Lipid lowering and qualitative changes in the plaque

- Reduces macrophage accumulation
- Reduces proteolytic activity and expression (MMPs)
- Reduces TF expression and activity
- Improves SMCs activation
- Reduces ECs activation

Log-linear relationship between LDL-C levels and relative risk for CHD



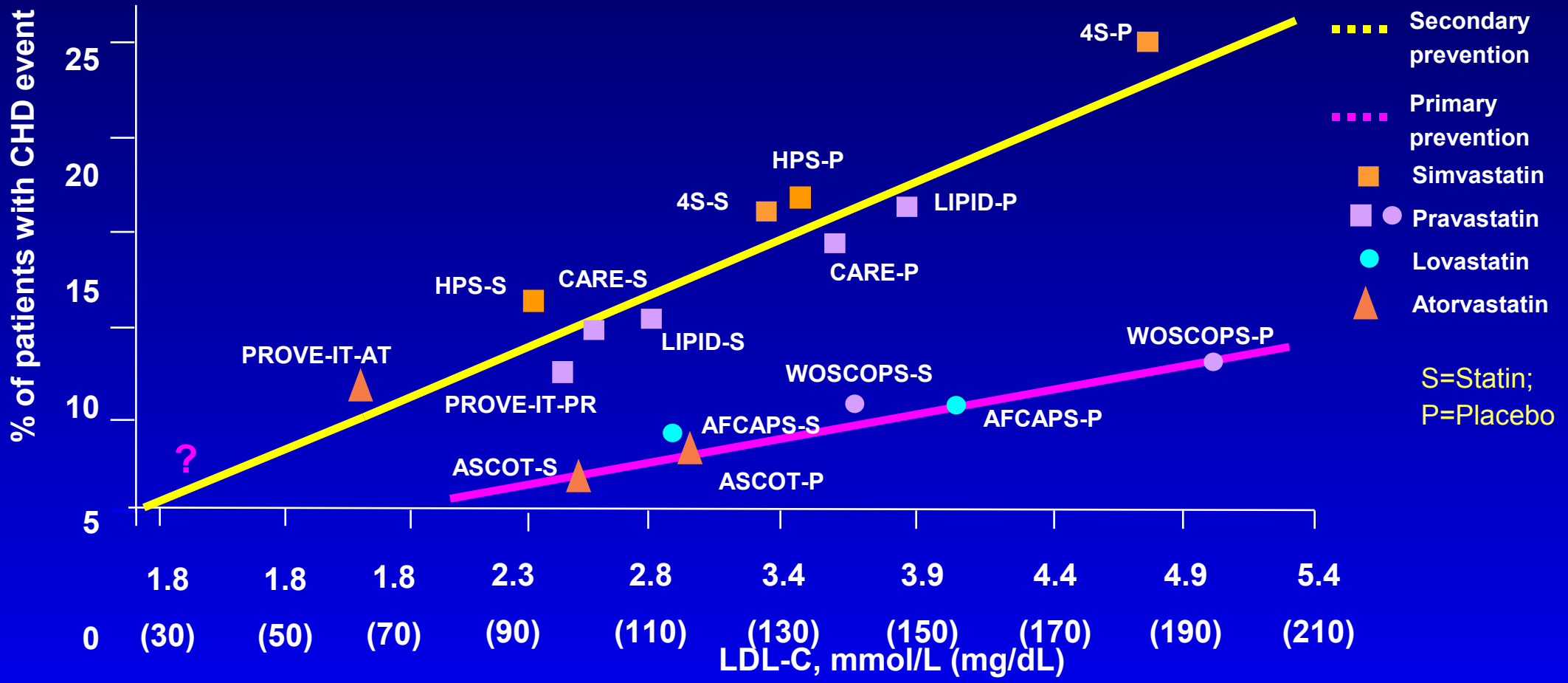
This relationship is consistent with a large body of epidemiological data and with data available from clinical trials of LDL-lowering therapy

For every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by 30%. The relative risk is set at 1.0 for LDL-C=40 mg/dL

Banai S.

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines *Circulation.* 2004;110:227-239

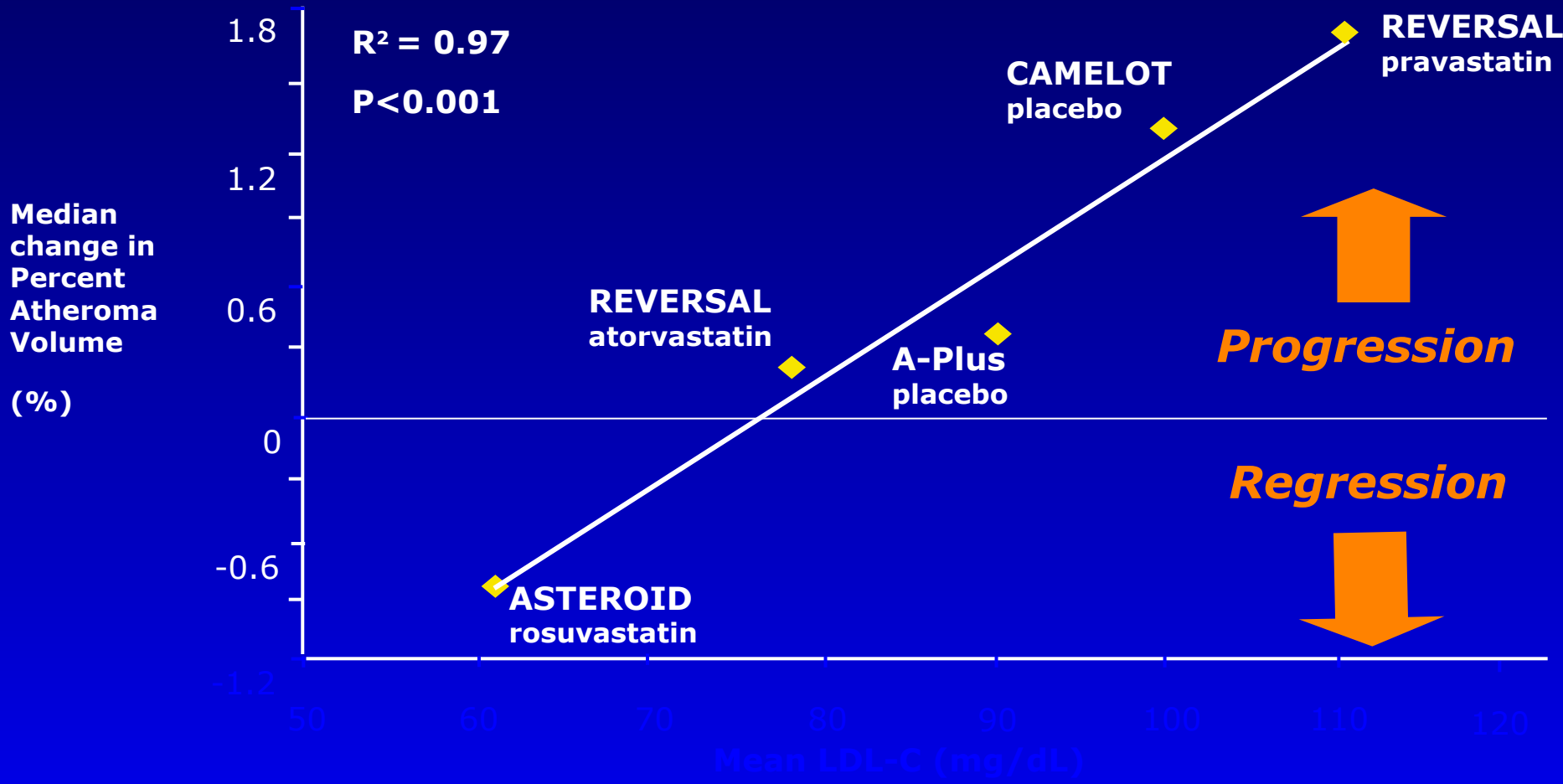
LDL-C Levels vs Events in Statin Trials: How Low to Go?



Adapted from –

- Barai S. The Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better. O'Keefe, JR et al. J Am Coll Card. 2004; 2;43(11):2142-6

Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials



Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

Atherosclerosis
Vascular Inflammation
and the
(Renin-Angiotensin System (RAS

Banai S.

The Renin-Angiotensin System as a Risk Factor and Therapeutic Target for Cardiovascular Diseases

The RAS activity may represent an ideal target for pharmaceutical treatment in a number of cardiovascular diseases, including:

- Hypertension
- Congestive heart failure
- Renal disease
- Stroke
- Myocardial infarction
- Atherosclerosis

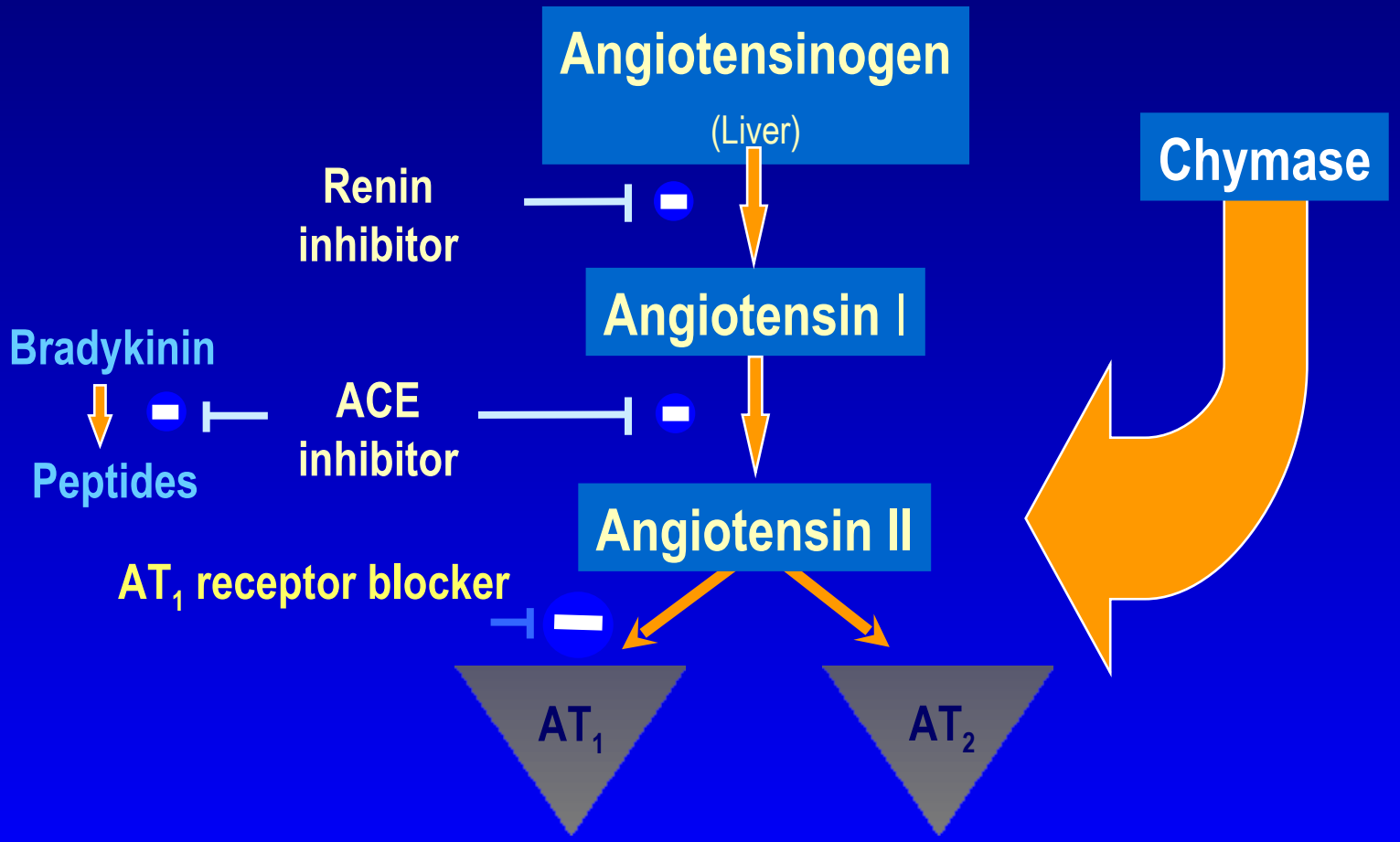
The Renin-Angiotensin System as a Risk Factor and Therapeutic Target for Cardiovascular Diseases

The RAS activity may represent an ideal target for pharmaceutical treatment in a number of cardiovascular diseases, including:

- Atherosclerosis/Atherothrombosis
- Hypertension
- Congestive heart failure
- Renal disease
- Stroke
- Myocardial infarction

Several pathways of Ang II generation

Local Ang II synthesis is independent of ACE



de Gasparo et al. Pharmacol Rev 2000; 52:415

Different roles of AT_1 and AT_2 receptors

Vasoconstriction
Vascular cell proliferation
Aldosterone secretion
Cardiac myocyte hyperthrophy
Increased sympathetic tone

Vasodilation
Antiproliferation
Apoptosis
Anti oxidant action

de Gasparo et al. *Pharmacol Rev* 2000; 52:415

The biologic functions of AngII under physiologic conditions

- Homeostasis of the cardiovascular system
- Blood Pressure
- Perfusion pressure of a number of organs
- Salt and water balance
- Cellular growth and replication

Volpe M: *J Am Soc Nephrol* 13:S173-S178, 2002
Laragh JH: In: Handbook of Physiology, edited by Orloff J, Berliner RW, American Physiological Society, 1973, pp 831–907

The RAS and Atherosclerosis

- Angiotensin II is a most important bioactive factor involved in the development and progression of atherosclerosis

- The pro-inflammatory effects of Ang II are mediated by the AT_1-R, whereas AT_2-R seems to confer vascular-protection

Atherosclerosis, Vascular Inflammation and the Renin-Angiotensin System

The RAS, through the actions of Ang II:

Production of reactive oxygen species (ROS) in the vessel wall

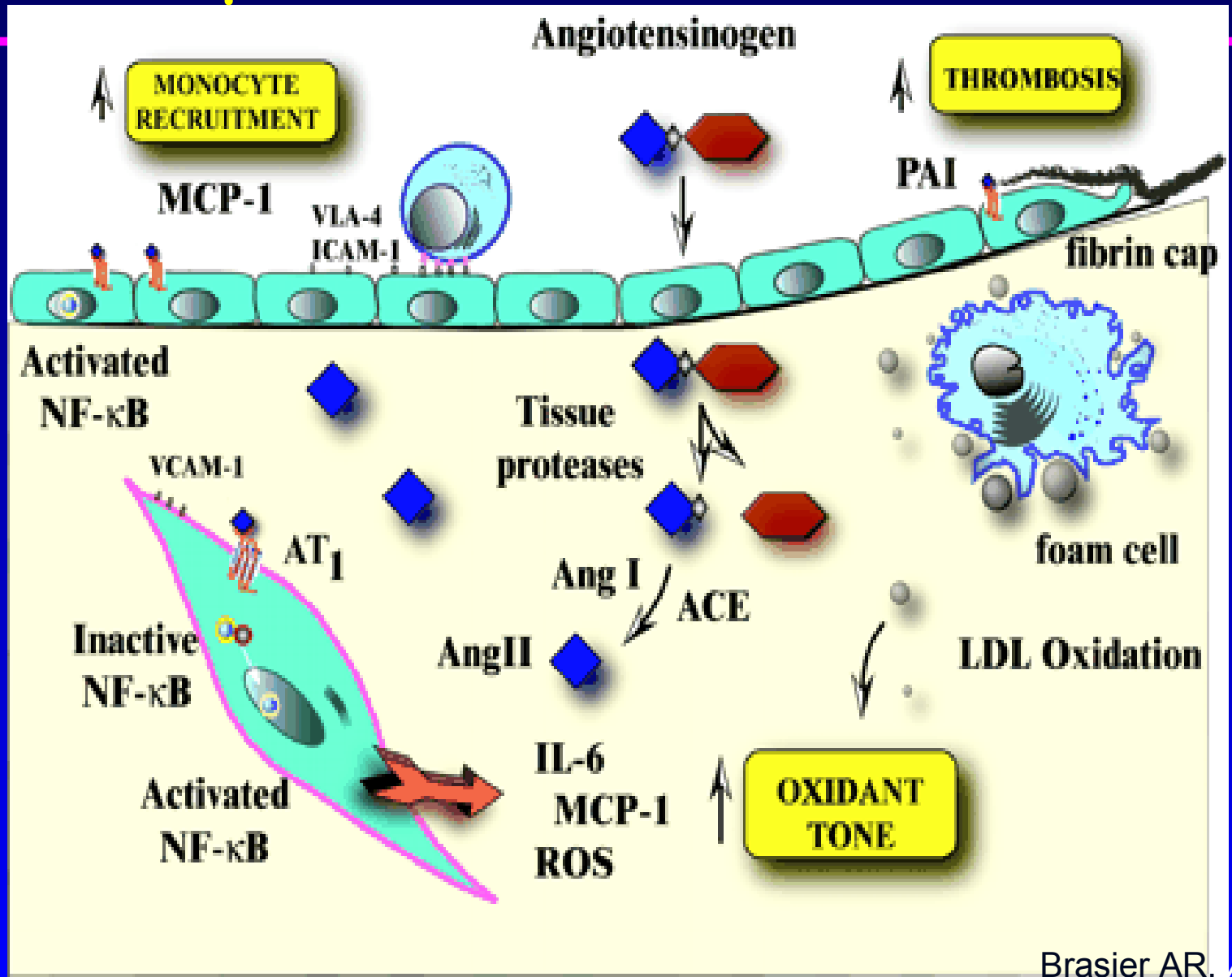
- Enhances vascular oxidant tone to produce EC dysfunction
- Enhances vascular LDL oxidation

- Upregulate vascular cell adhesion molecule-1 (VCAM-1) on ECs
- Increase the expression of the proinflammatory cytokines interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1)
- Promotes macrophages migration into the intima

Griendling KK, et al. *Hypertension.* 1997;29:366

Kranzhofer R, et al. *ATVB* 1999;19:1623

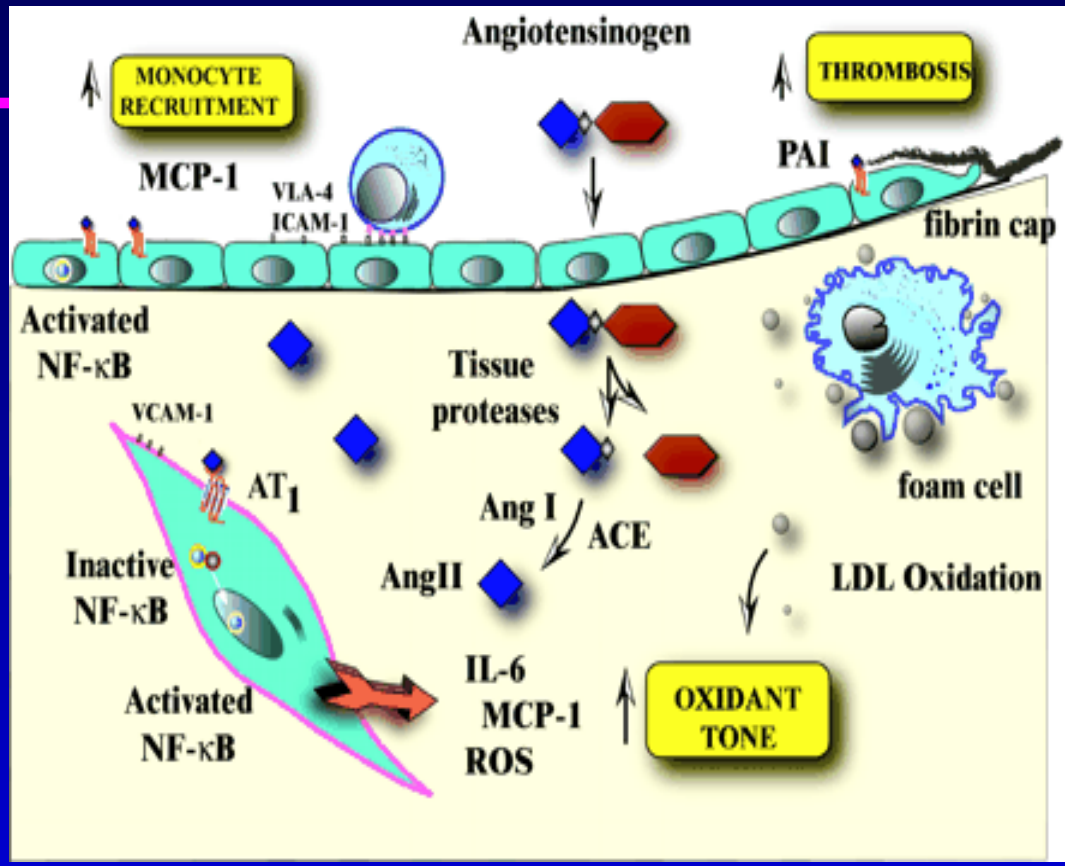
Proatherogenic mechanisms for Ang II produced in the vessel wall



Brasier AR. *ATVB* 2002;22:1257

The Pro-Atherogenic role of the RAS

- Ang II is proatherogenic, especially in the presence of hyperlipidemia
- locally produced Ang II synergizes with oxidized lipid to perpetuate atherosclerotic vascular inflammation



- **Therefore, RAS antagonists prevent atherosclerosis by reducing vascular inflammation**

Brasier AR, et al. :*ATVB.* 2002;22:1257

Oxidative Stress

- During normal cellular metabolism, several enzyme systems reduce molecular oxygen, resulting in formation of a variety of reactive oxygen species, including superoxide ($O_2^{\cdot -}$), hydroxyl radical ($HO^{\cdot}$), hypochlorous acid (HOCl), lipid radicals, and hydrogen peroxide (H_2O_2)

- ROS play a critical role in the normal functioning of cells. For example, the normal growth of vascular SMC.

Oxidative Stress

- Excessive production of ROS, outstripping antioxidant defense systems = oxidant stress
- Oxidant stress has been implicated in many pathophysiological conditions in the CVS, including:
  - cigarette smoking
  - hypercholesterolemia
  - diabetes
  - hypertension
  - and heart failure

Harrison DG. *Clin Cardiol.* 1997; 20 (suppl II): 11–17

Untoward events that occur as a consequence of oxidant stress

- Oxidative modifications of DNA
- Lipid oxidation
- Modification of proteins
- Activation of redox sensitive genes, such as:
  vascular cell adhesion molecule-1 (VCAM-1)
  intercellular adhesion molecule-1 (ICAM-1)
  monocyte chemoattractant protein-1 (MCP-1)
- Activation of matrix metalloproteinases (MMPs)

Nickenig G, Harrison DG*: Circulation.* 2002;105:393

Oxidative stress is involved in the pathogenesis of atherosclerosis

- Under oxidative stress, macrophages generate reactive oxygen species leading to LDL oxidation

AT1 receptor and Oxidative Stress

- AT_1 receptor activation by angiotensin II leads to production of ROS in the vessel wall and inactivation of nitric oxide
- Loss of nitric oxide via this mechanism leads to endothelial dysfunction, one of the earliest steps in the atherosclerotic process
- Inhibition of AT_1R activation by ARBs or ACE-I improves endothelial dysfunction

Mancini JGB: *Circulation.*1996;94: 258–265

Prasad A: *Circulation.* 2000;101:2349–2354

Angiotensin II Inhibits Endothelial Cell Motility Through an AT_1-Dependent Oxidant-Sensitive Decrement of Nitric Oxide Availability

- The migratory capability of vascular EC plays a pivotal role in the maintenance of vessel wall integrity, and is stimulated by nitric oxide
- Angiotensin II inhibits EC motility by reducing NO availability
- Such reduction is due to AT_1 receptor -dependent increment in intracellular ROS generation

Desideri G: *ATVB* 2003;23:1218-1223

AT_1 Receptor and all Stages of Atherogenesis

Loss of nitric oxide and formation of peroxynitrite promote atherosclerosis at virtually all stages of the disease

AT_1 Receptor and all Stages of Atherogenesis

The earliest stages:

Increased attraction and adhesion of monocytes to the endothelium

- Inflammatory molecules: MCP-1, VCAM-1 are critically important in this process
- Angiotensin II induces their production and secretion via generation of ROS and suppression of nitric oxide

AT_1 Receptor and all Stages of Atherogenesis

Fatty streak formation:

- Increased oxidation of LDL
- Uptake of oxLDL by macrophages, and foam cell formation

These processes are promoted by AT_1 receptor activation by angiotensin II

The expression of the receptor for oxidized LDL (LOX receptor), is dramatically increased by AT_1 receptor activation

Morawietz H: *Circulation.* 1999;100:899–902

AT_1 Receptor and all Stages of Atherogenesis

Plaque formation:

Is propagated by migration and proliferation of vascular SMCs

Oxidant stress induced by angiotensin II plays a major role in stimulating growth and migration of vascular SMCs

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

Harrison DG: *Clin Cardiol.* 1997;20(suppl II):11–17

AT_1 Receptor and all Stages of Atherogenesis

Plaque rupture:

- Inflammatory events
- Apoptosis
- Accelerated matrix degradation

AT_1 receptor activation via angiotensin II initiates:

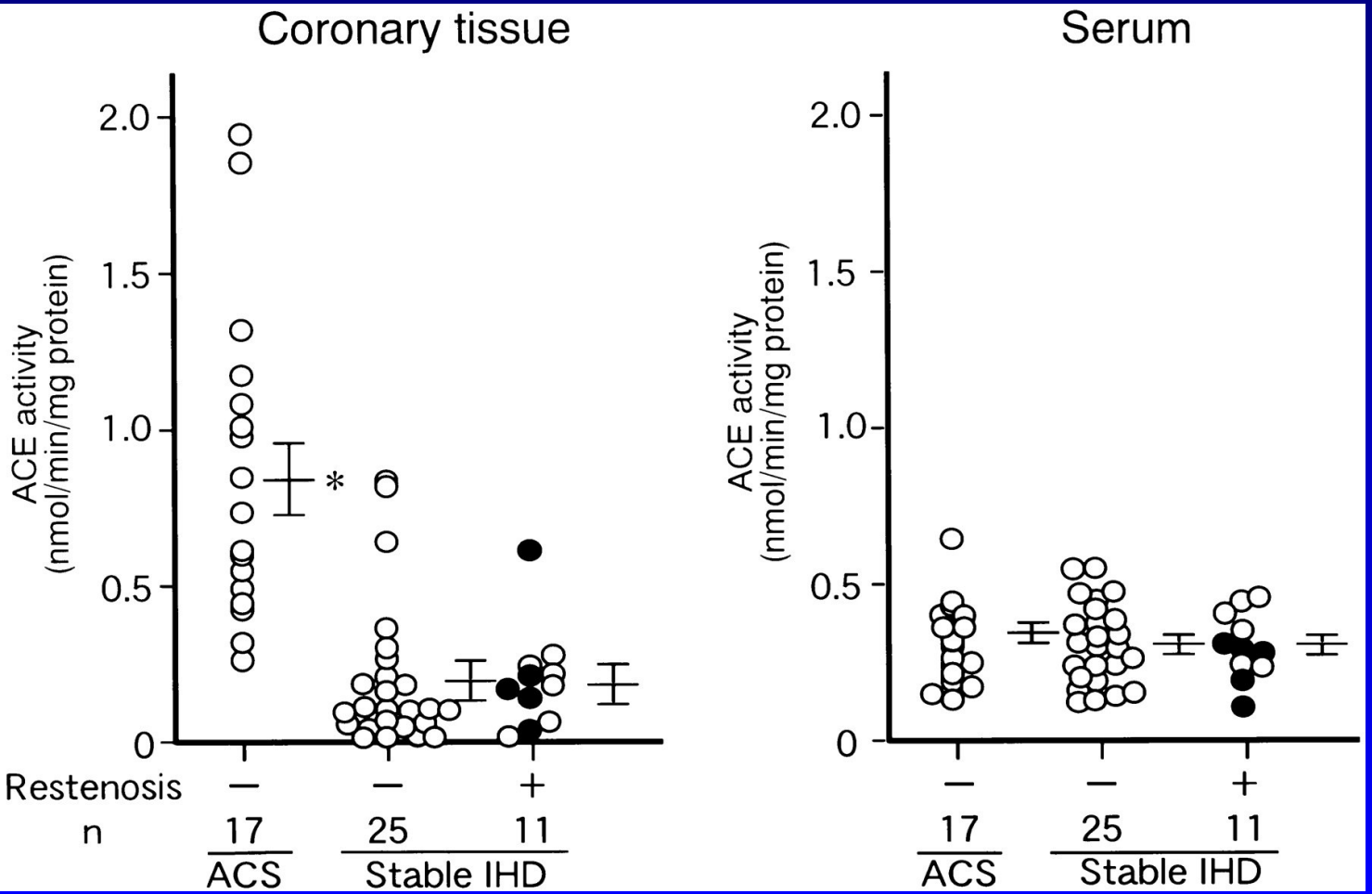
- Inflammatory processes such as IL-6 production
- Vascular SMCs apoptosis, a prelude to plaque rupture
- Increases MMP activity, resulting in plaque degradation and ultimately rupture

Funck RC: *Adv Exp Med Biol.* 1997;432:35–44

Schieffer B: *Circulation.* 2000;101:1372–1378

Increased ACE activity in culprit lesions in ACS

Enhanced ACE activity is related to the causative mechanism of active coronary lesions



ACE activity in coronary tissue obtained from directional coronary atherectomy and in serum of patients with ACS and with stable IHD

Hoshida *S, Circulation* 2001;103:630

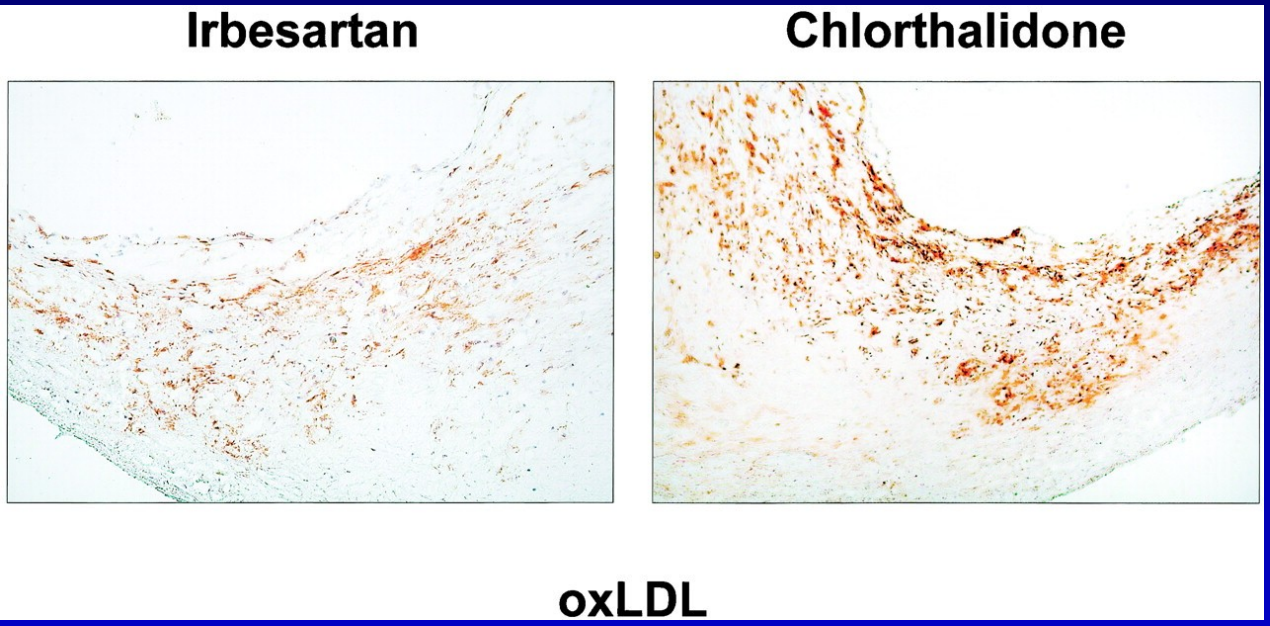
Blockade of the Angiotensin II Type 1 Receptor Stabilizes Atherosclerotic Plaques in Humans by Inhibiting Prostaglandin E_2-Dependent Matrix Metalloproteinase Activity

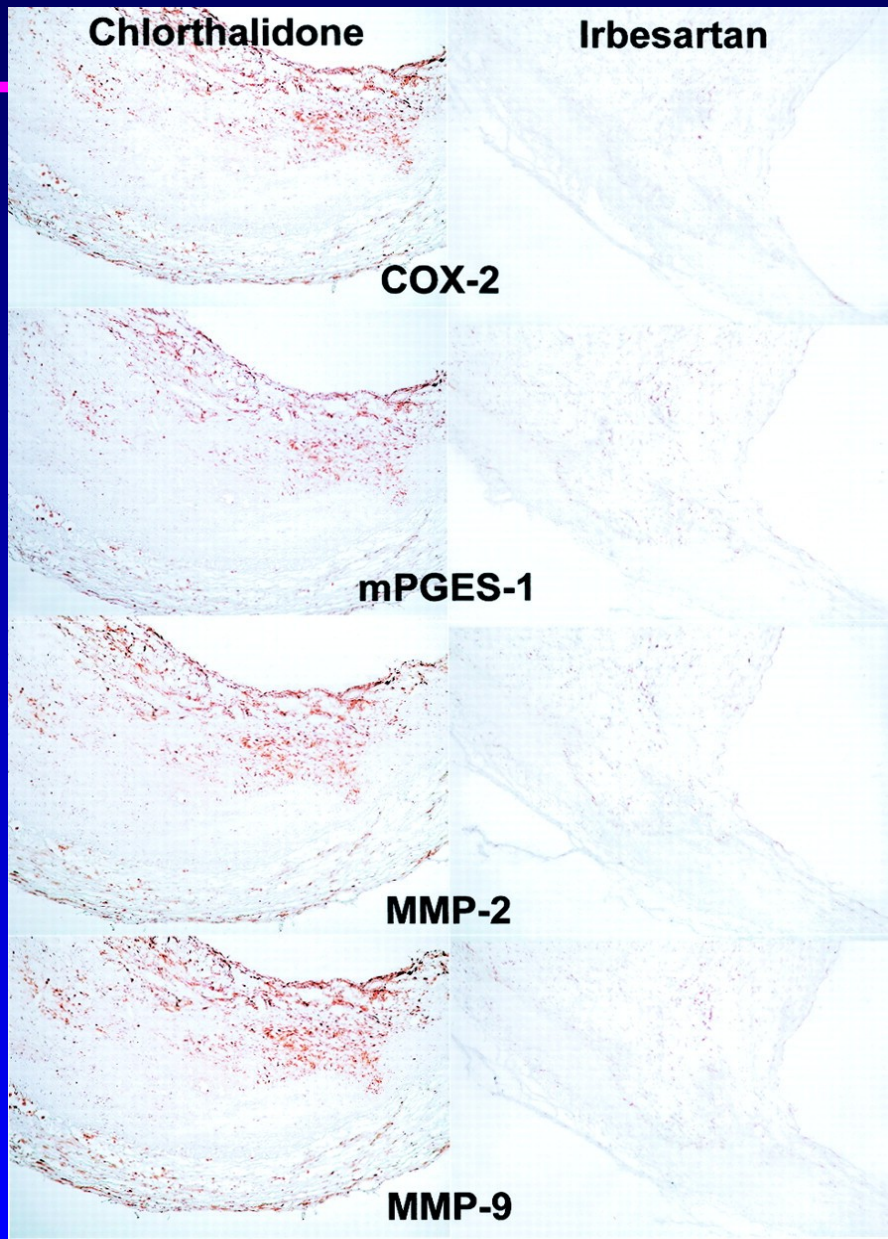
- Pre-treatment with AT_1R blockade in patients with symptomatic carotid artery stenosis for 4 months before endarterectomy, decreases inflammation and inhibits COX-2/mPGES-1 expression in plaque macrophages
- This effect contributes to plaque stabilization by inhibition of MMP-induced plaque rupture

Banai S.

Cipollone F*: Circulation.* 2004;109:1482-1488

Blockade of the AT_1R provides a novel form of therapy for plaque stabilization





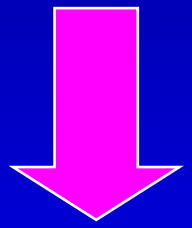
Cipollone F*: Circulation.* 2004;109:1482-1488

Banai S.

Conclusions:

RAS blockade:

- attenuates the degree of atherosclerosis
- reduces macrophage accumulation
- increases collagen deposition within the plaque



- reduces the frequency of plaque disruption

Michael T. Johnstone, *Circulation.* 2004;110:2060-2065

The additional benefit of RAS inhibitors beyond the BP lowering effect

- RAS inhibitors improved structural abnormalities and normalized endothelial function of small arteries from patients with essential hypertension
- None of these effects was found in a parallel group of hypertensive patients treated with ß-blockers, despite similar BP lowering

Schiffrin EL: Circulation. 2000;101:1653

Vascular protective effect of RAS inhibitors

- This vascular-protective effects of RAS inhibitors will translate into improved outcome in hypertensive and CHF patients beyond the effect of blood pressure lowering itself,

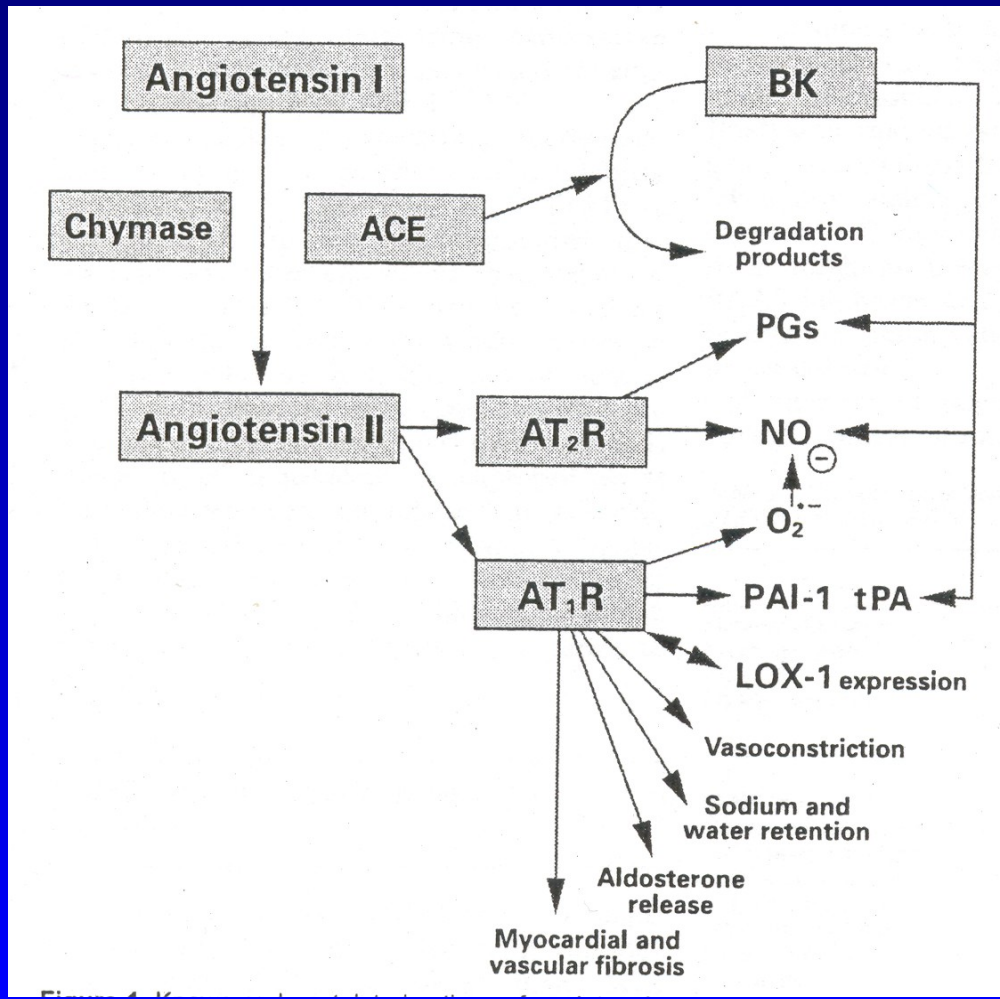
  with reduced morbidity or mortality.

Vascular protective effect of ACE-I and ARB

Ox-LDL is taken into EC via the LOX-1 receptor

Ang II produces EC dysfunction by upregulation of the LOX-1 receptor

Inhibition of Ang II and blockade of the AT_1R will improve endothelial function



Conclusions:

- The RAS plays a key role in the development and acceleration of all stages of atherosclerosis, from endothelial dysfunction, lipid accumulation and fatty streak formation, through plaque progression, inflammation to plaque destabilization and rupture
- Inhibitors of the RAS inhibit LDL oxidation, improve endothelial function, decrease inflammation, and stabilize the atherosclerotic plaque

Conclusions:

- Therefore, inhibitors of the RAS should be used routinely for primary and secondary prevention of atherosclerosis and atherothrombosis

Tissue Factor

Tissue factor (TF)

A low molecular weight (45-kDa) membrane-bound glycoprotein,

Binding of TF to factor VIIa is the first step in the extrinsic coagulation cascade

Tissue Factor

A major regulator of coagulation and a critical determinant of thrombin generation in normal hemostasis and in atherothrombotic disease

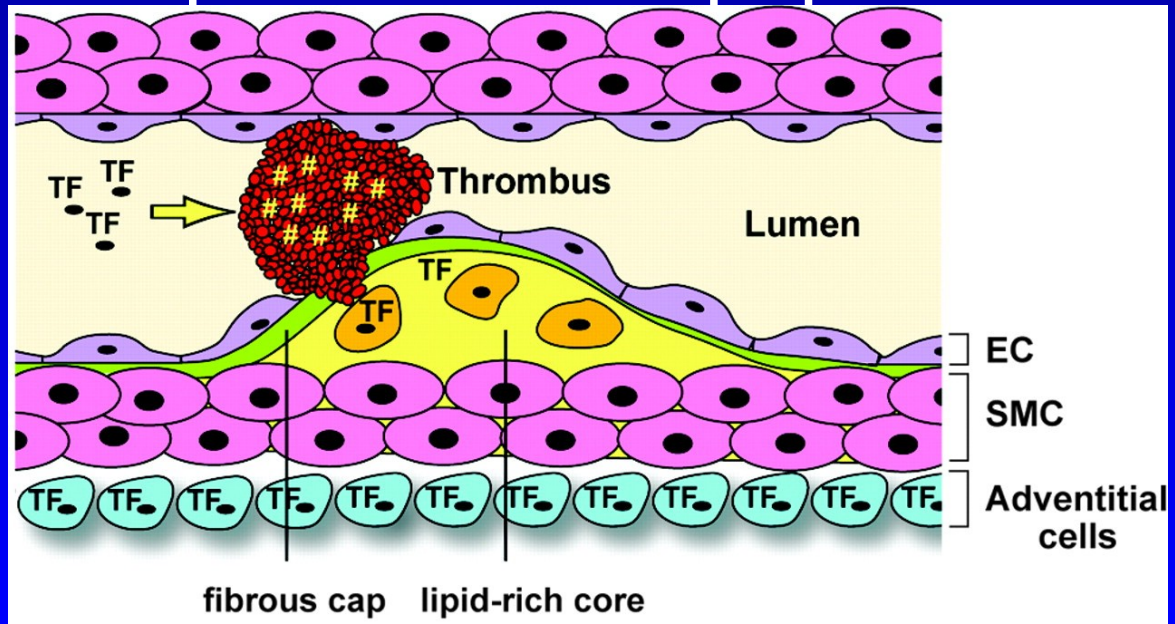
The clinical consequences of high intravascular expression of TF are catastrophic

Intraluminal TF activity triggers thrombogenic cascade that underlies the often-lethal thrombotic complications of:

- Atherosclerosis
- Consumptive coagulopathy and hemorrhagic diathesis of systemic infections
- Prothrombotic state of cancer patients

Tissue Factor in human atherosclerotic vessels

- Expressed by monocyte-derived macrophages
- Abundant within the acellular lipid core of the plaques, and in the "shoulder region" close to the lumen
- The source for TF in the lipid core are apoptotic macrophages



Nigel Mackman: *ATVB* 2004;24:1015

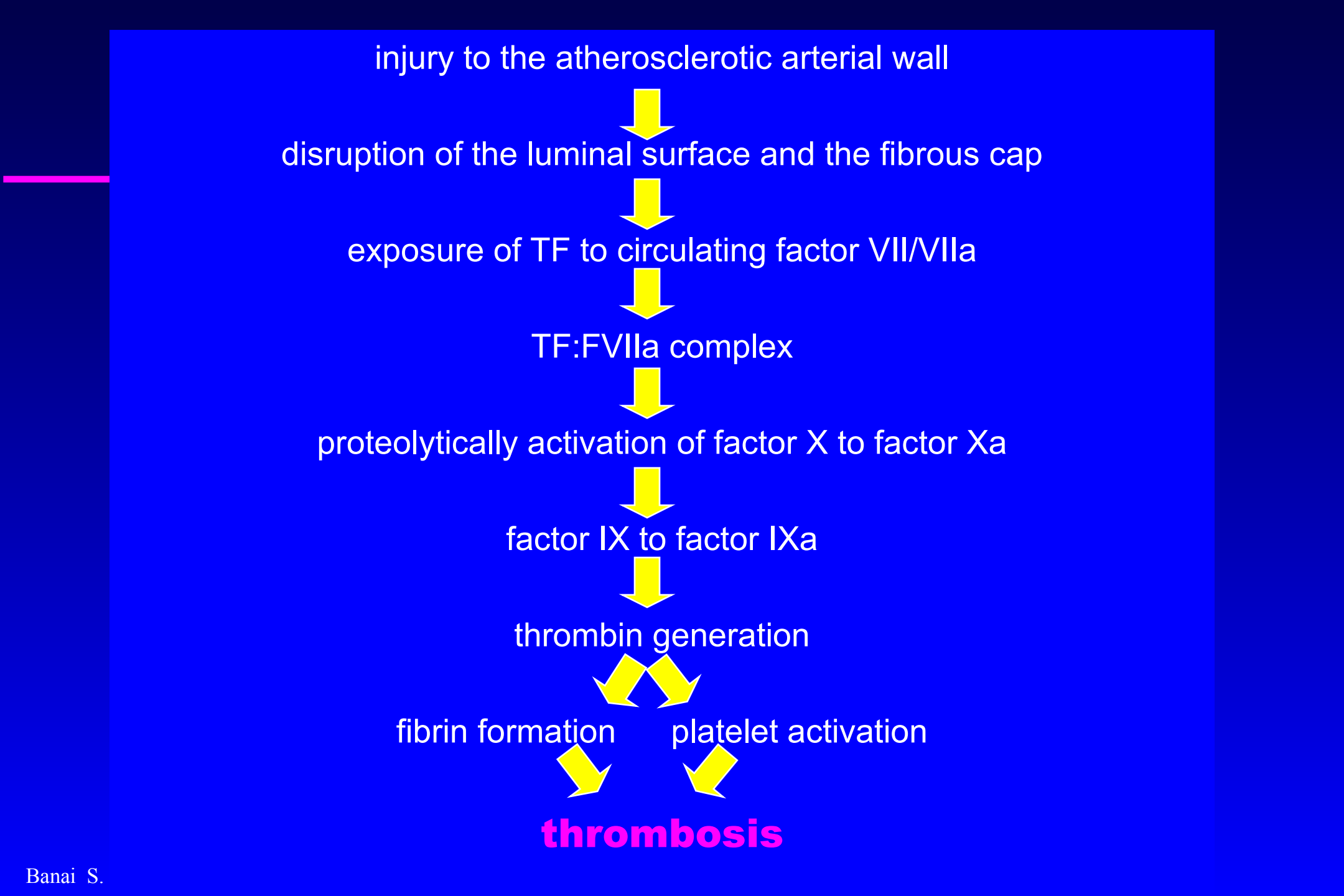
Tissue Factor in the human atherosclerotic plaque

- The high TF content within the lipid-core is the reason for the high thrombogenicity of this component in human coronary arteries

- Thus, the ability to inhibit TF-dependent procoagulant activity after plaque disruption would likely alleviate many of the acute clinical manifestations of cardiovascular disease

Banai S.

Pozza LM, Austin RC: Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25:1529


injury to the atherosclerotic arterial wall
disruption of the luminal surface and the fibrous cap
exposure of TF to circulating factor VII/VIIa
TF:FVIIa complex
proteolytically activation of factor X to factor Xa
factor IX to factor IXa
thrombin generation
fibrin formation
platelet activation
thrombosis

Tissue factor pathway inhibitor (TFPI) the endogenous inhibitor of TF

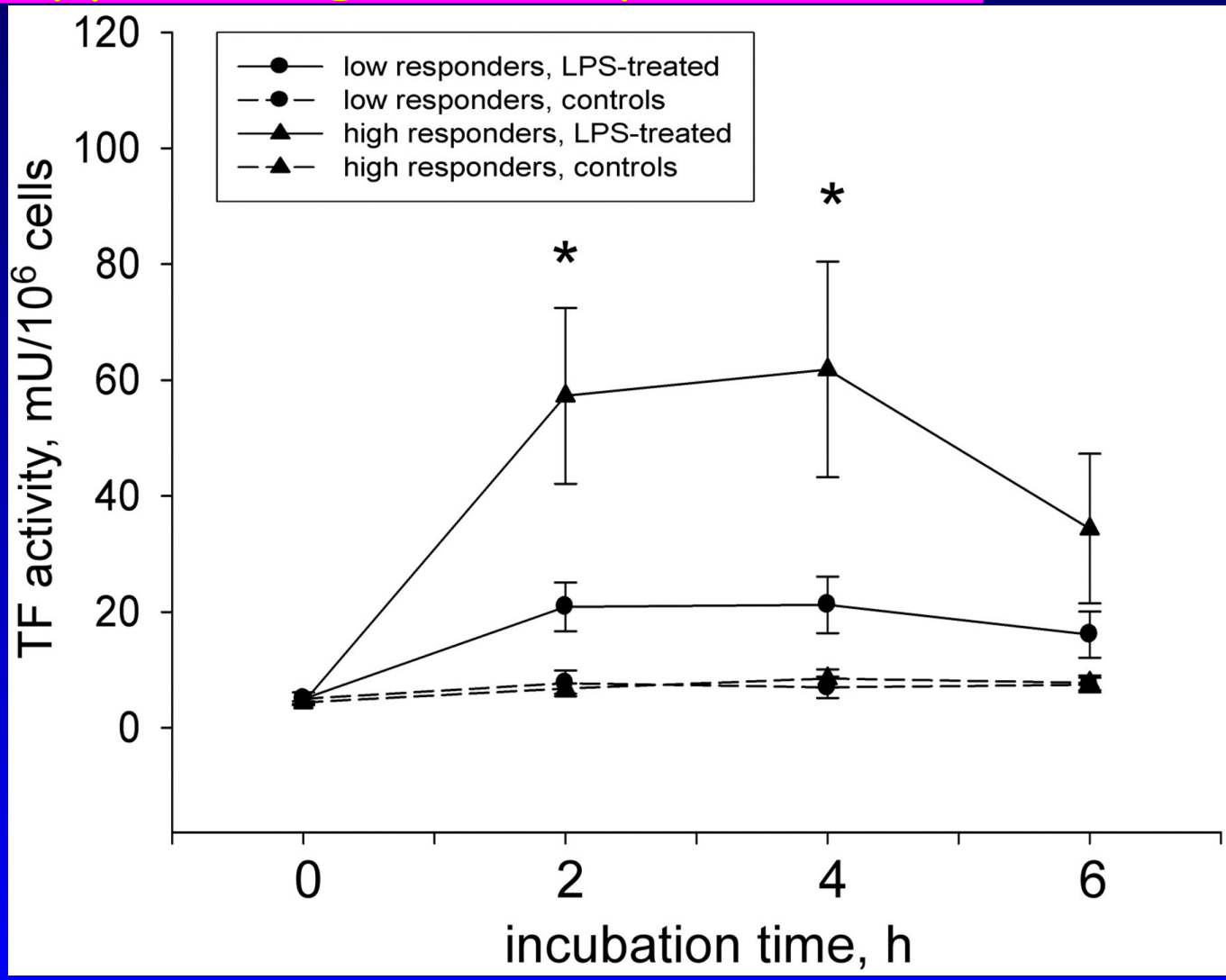
- The activity of TF:FVIIa complex is regulated by the endogenous inhibitor: TF pathway inhibitor
- The major pool of TFPI is in the endothelium
- TFPI forms an inactive complex consisting of TFPI, TF, factor VIIa, and factor Xa, which inhibits the TF-dependent coagulation cascade

Systemic expression of TF

Increased systemic expression of TF by activated circulating monocytes contribute to the enhanced thrombogenic state in patients with an acute coronary syndrome

Surface Distribution of Monocyte Tissue Factor and hypercoagulability

Individuals with higher availability of surface TF antigen on MNCs, are more susceptible to hypercoagulation



Banai S.

Egorina, E. M. et al. *Arterioscler Thromb Vasc Biol* 2005;25:1493-1498

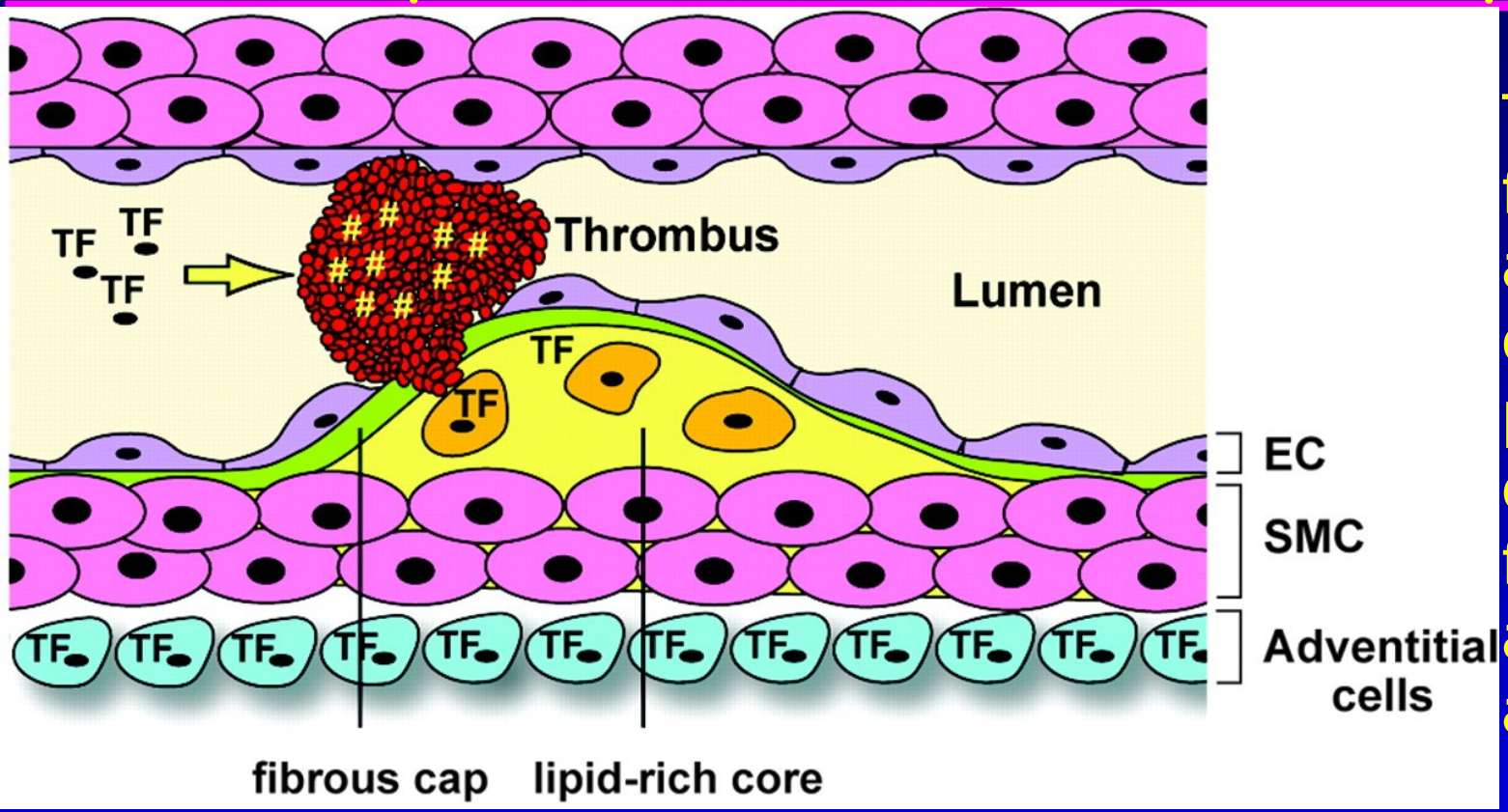
Tissue Factor and ACS

- Plasma TF levels are increased in patients with unstable angina compared to those with stable AP
- Plaques from patients with ACS have significantly greater concentrations of TF antigen and activity than those from patients with stable angina
- Systemic TF levels are an important predictor of outcome in patients with ACS

Tissue Factor and Human Atherosclerosis

TF, by its local and systemic effects, plays a major role in the pathogenesis of advanced human atherosclerosis and its thrombogenicity

Role of TF in thrombus formation after rupture of an atherosclerotic plaque



TF expressed by foam cells (orange) and in the necrotic core (yellow) of the plaque would be exposed to clotting factors in the blood and initiate clotting after plaque rupture

Blood-borne TF may contribute to thrombus propagation

TF is expressed by adventitial cells (blue). EC, and SMC

Banai S.

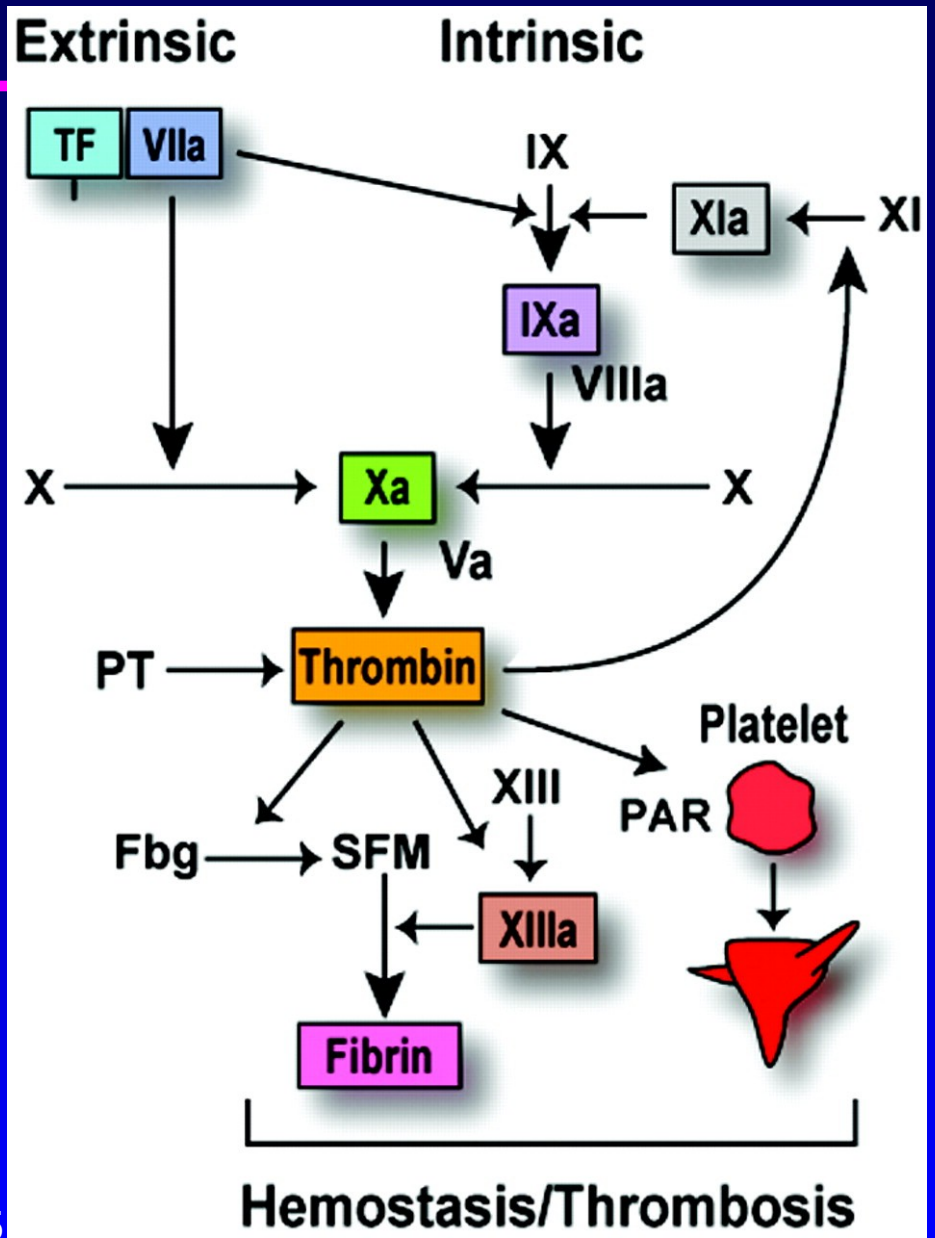
Nigel Mackman:*ATVB* 2004;24:1015

The coagulation protease cascade

Formation of the TF:FVIIa complex initiates clotting by activating FX and FIX. Alternatively, FXI can activate FIXa.

The prothrombinase complex (FVa:FXa) activates prothrombin (PT).

Thrombin activates various proteases and cofactors. Thrombin cleavage of fibrinogen to soluble monomers (SFM), which are cross-linked by FXIIIa, and activation of protease-activated receptors (PARs) on platelets leads to the formation of a clot.



Banai S.

Nigel Mackman: *ATVB* 2004;24:1015

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