

**37<sup>es</sup> JHTA**  
JOURNÉES DE L'HYPERTENSION ARTÉRIELLE  
DU DIAGNOSTIC AUX COMPLICATIONS

**14-15**  
décembre 2017  
**Paris**

[www.jhta2017.fr](http://www.jhta2017.fr)

Cité Universitaire (CIUP)

**11<sup>th</sup> INTERNATIONAL MEETING OF THE FRENCH SOCIETY OF HYPERTENSION**

Société Française d'Hypertension Artérielle  
[www.sfhta.org](http://www.sfhta.org)

Société Belge d'Hypertension

Société Française d'Hypertension Artérielle

Société Suisse d'Hypertension

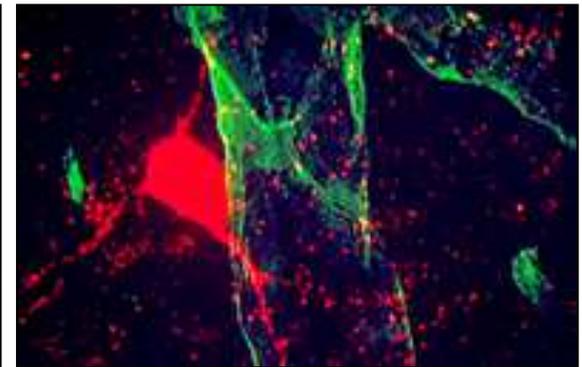
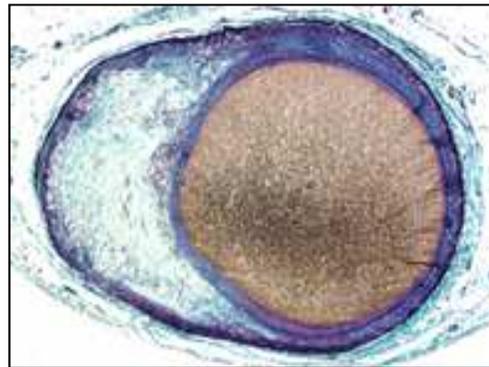
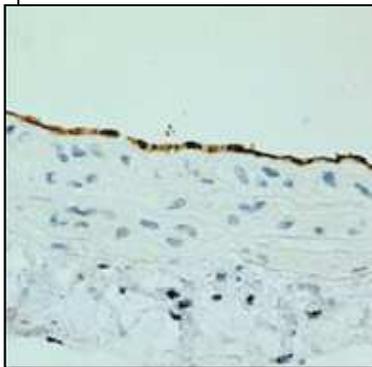
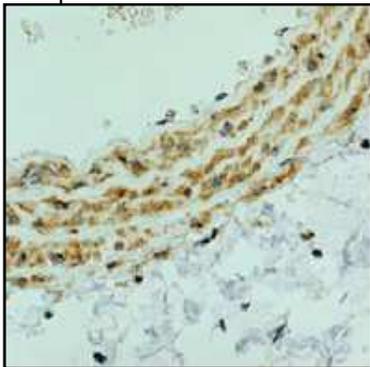
**Alain TEDGUI**  
**PARCC-INSERM U970**  
**Hôpital Européen Georges Pompidou, Paris**

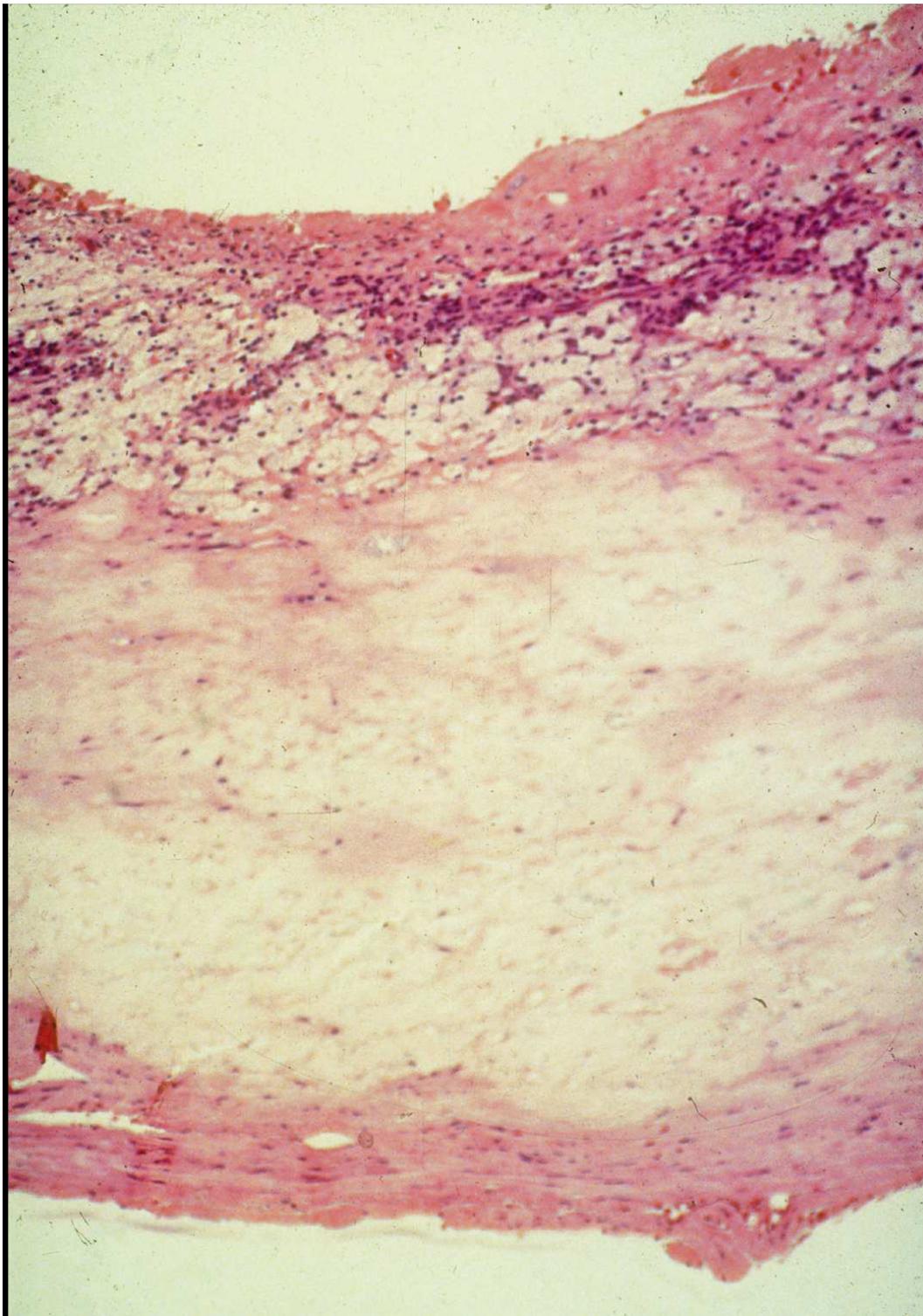
*L'auteur déclare n'avoir aucun conflit d'intérêt concernant les données de sa communication*



Alain Tedgui

Vaisseaux, Lipides & HTA





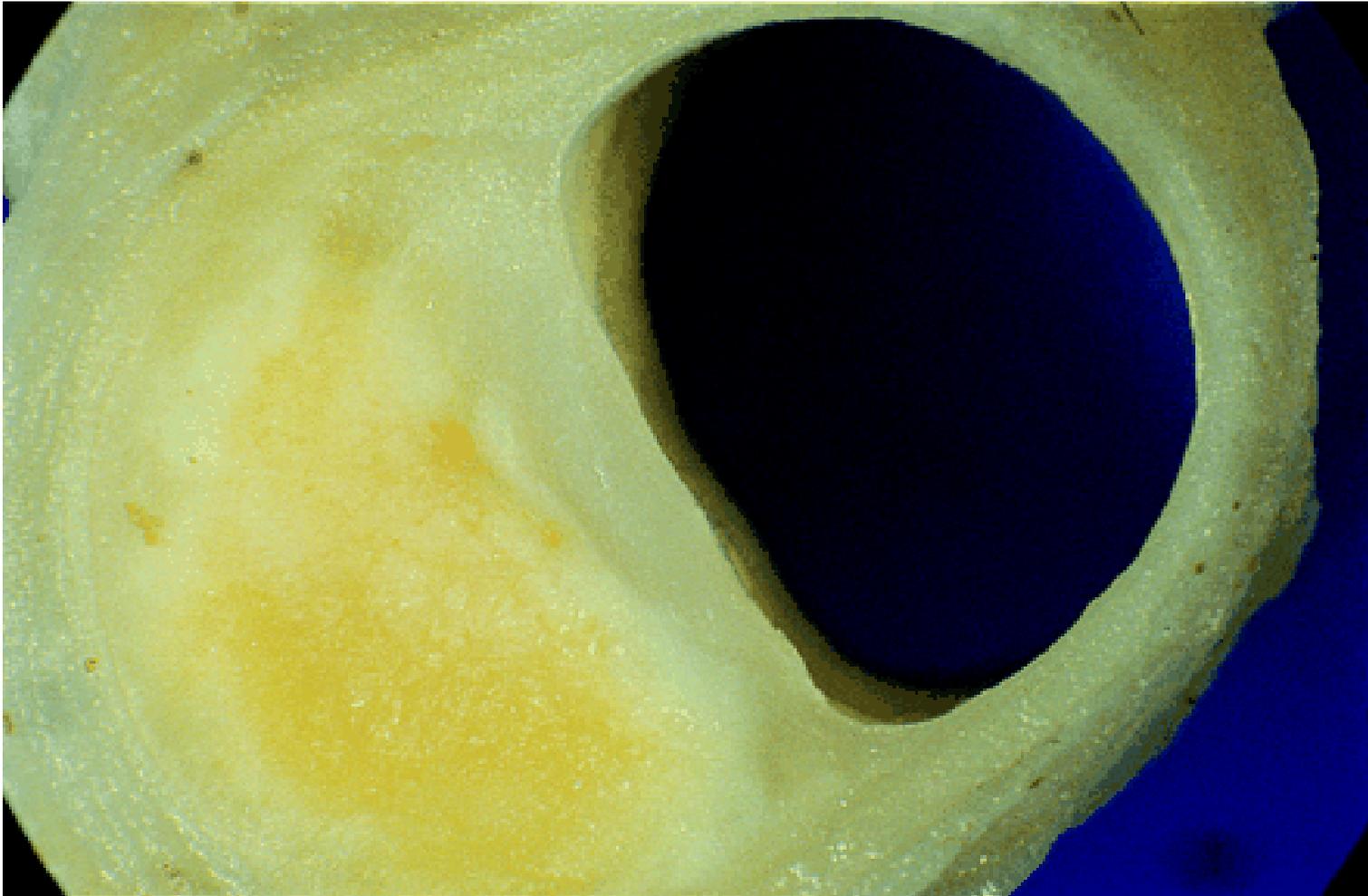
Fibrous cap

Macrophages/T-cells

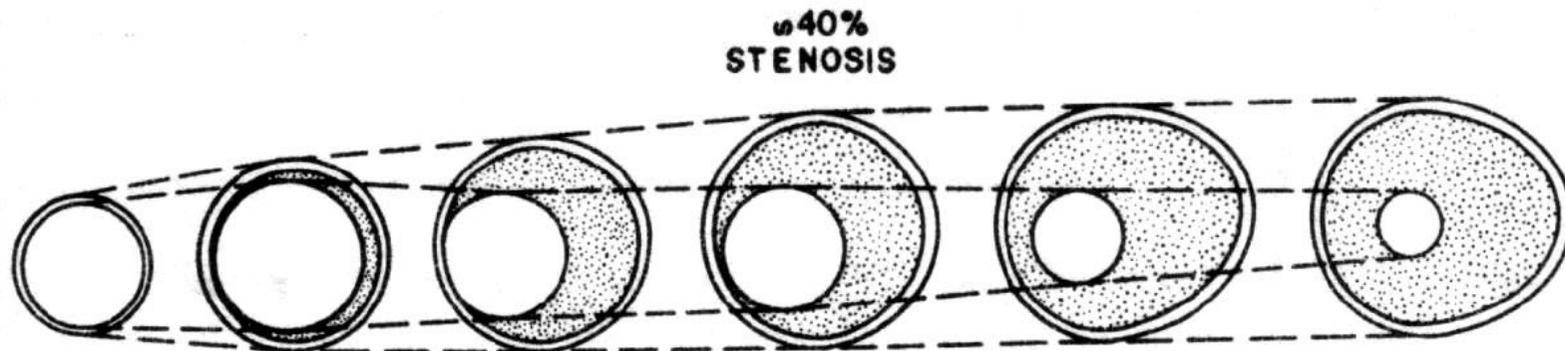
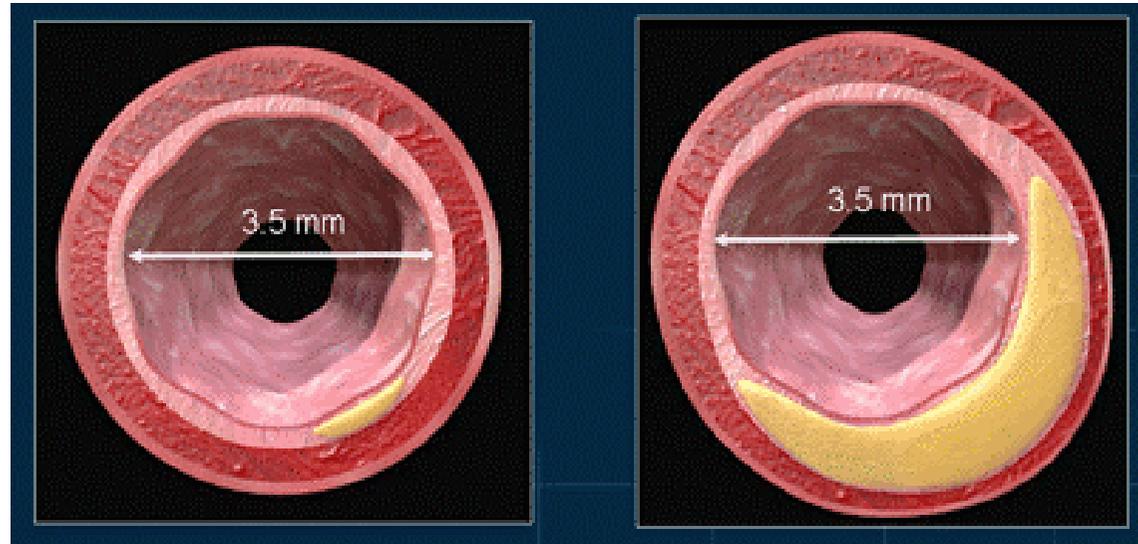
Lipid Core

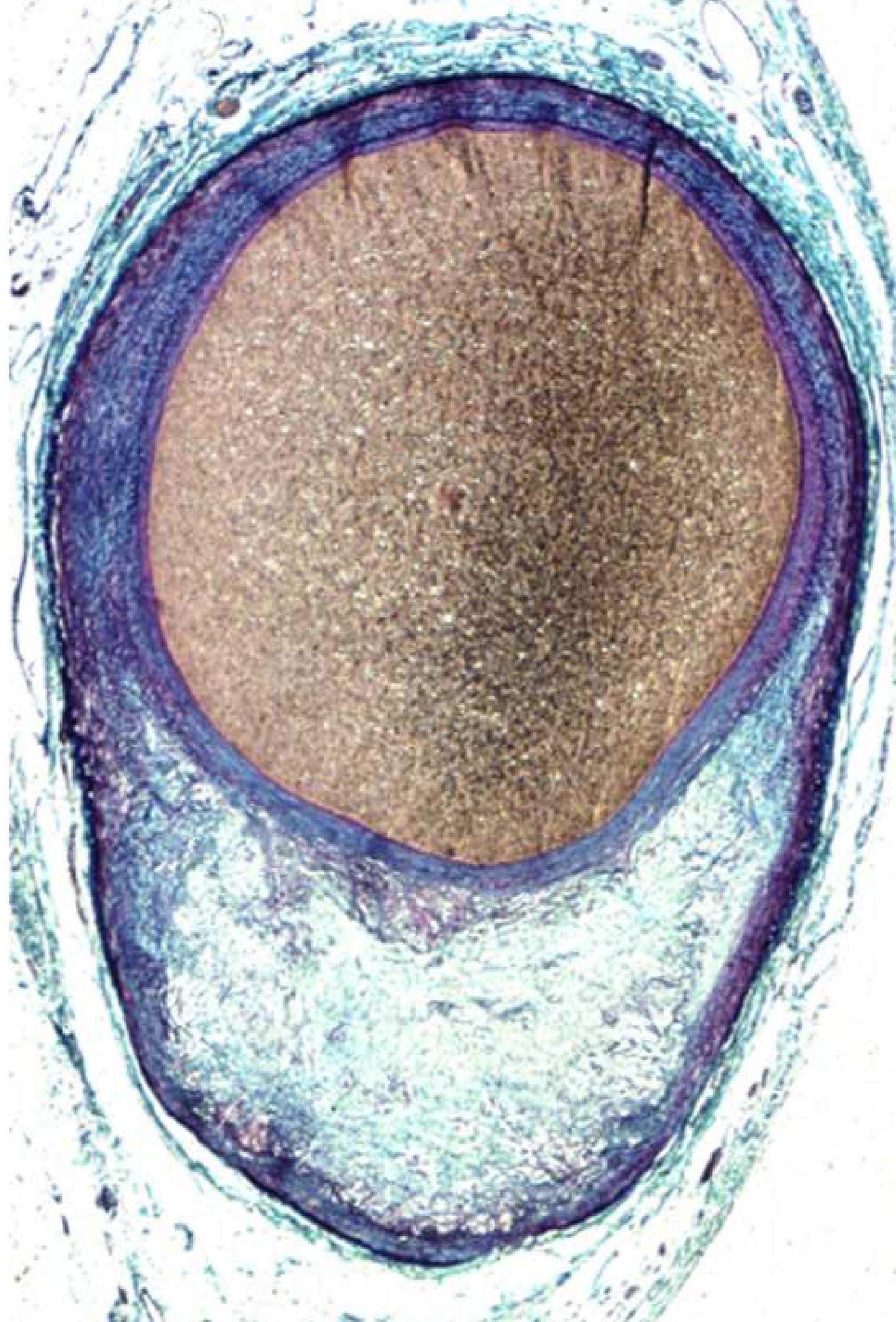
Media

# Stable Plaque



# Compensatory Enlargement

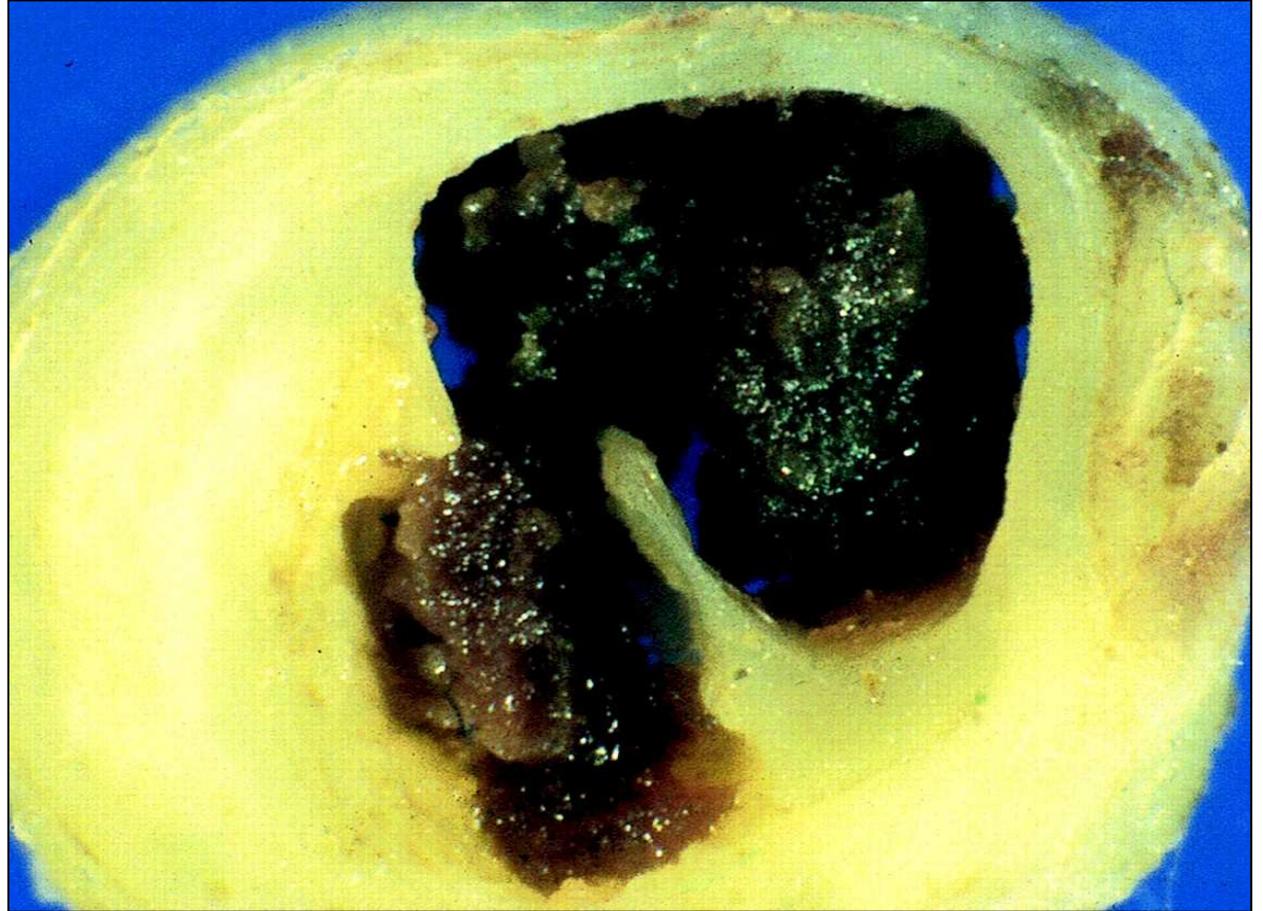




# Acute Heart Attack

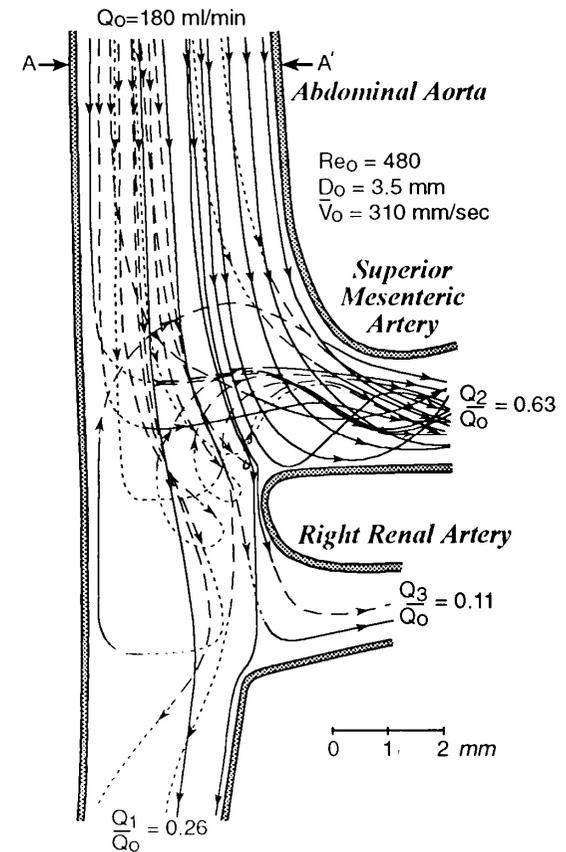
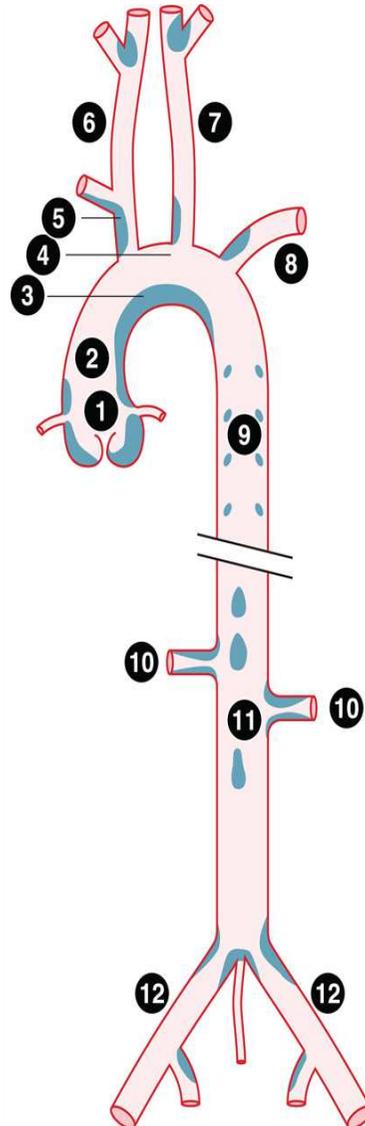
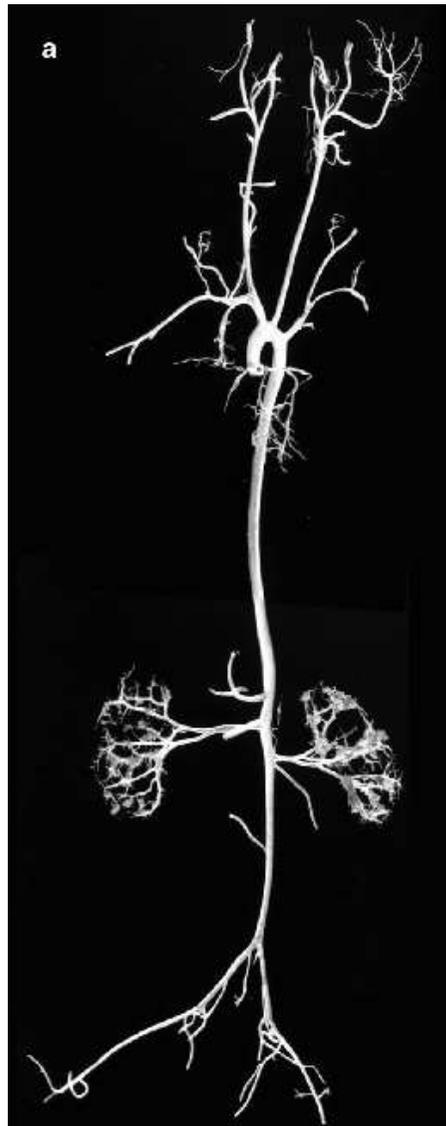


Plaque rupture → Thrombosis



- I. **Atherosclerosis & Vessels**
- II. Atherosclerosis & Lipids
- III. Atherosclerosis & Inflammation
- IV. Atherosclerosis & Hypertension
- V. Hypertension & Inflammation

# Favoured Sites for Atherosclerotic Plaque Development

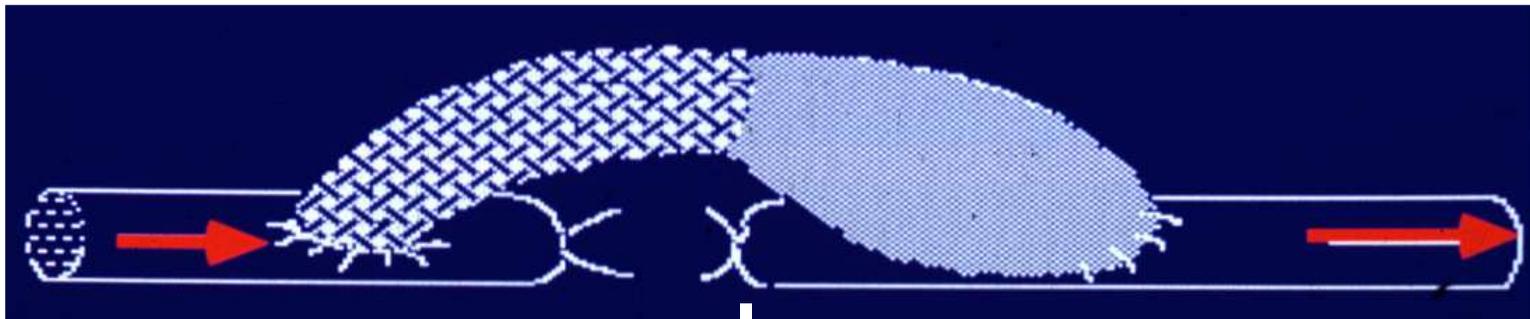


*Barakat et al., 1997*

# Vein Graft Atherosclerosis

**Proximal  
Common carotid art.**

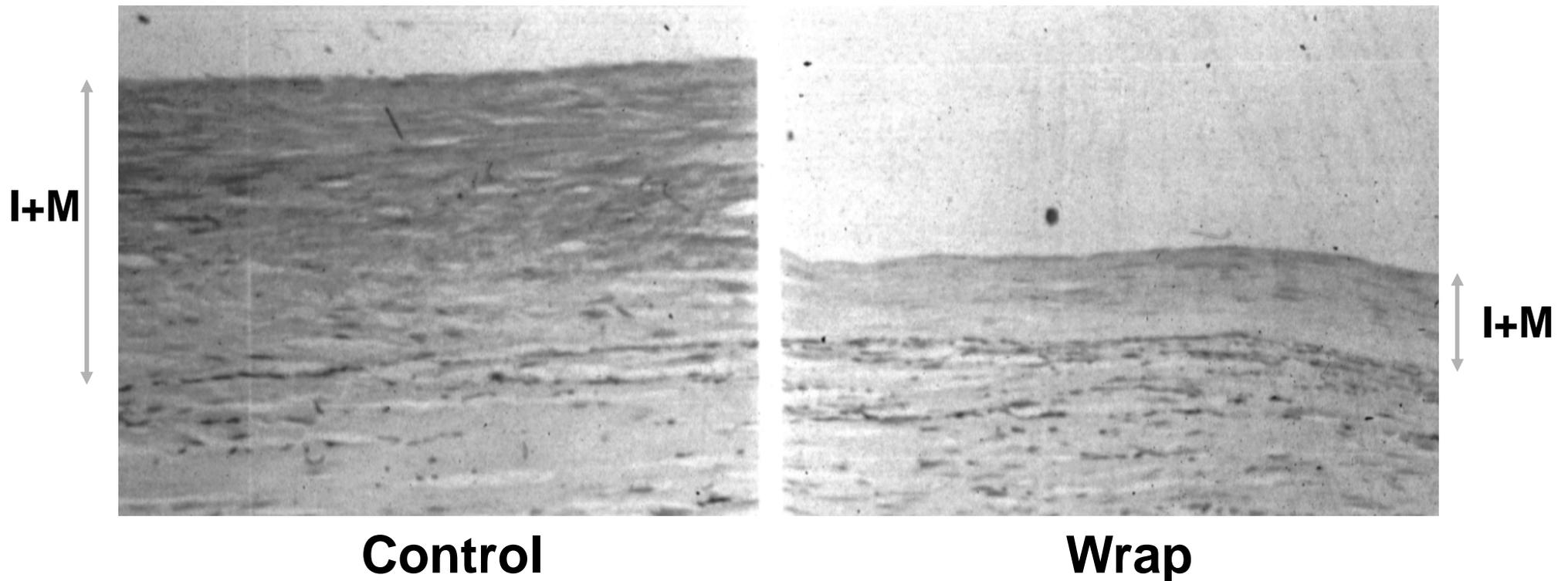
**Distal  
Common carotid art.**



**Wrapped vein graft  
PTFE i.d. 4 mm**

**Control vein graft  
diameter: 7.5 mm**

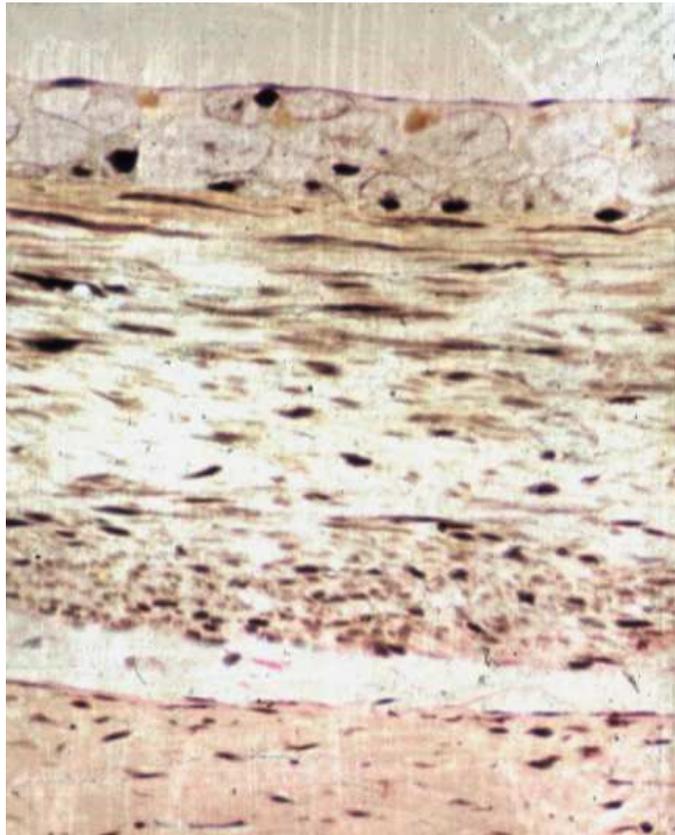
# Effect of Pressure-Induced Stretch on Vein Graft Thickening



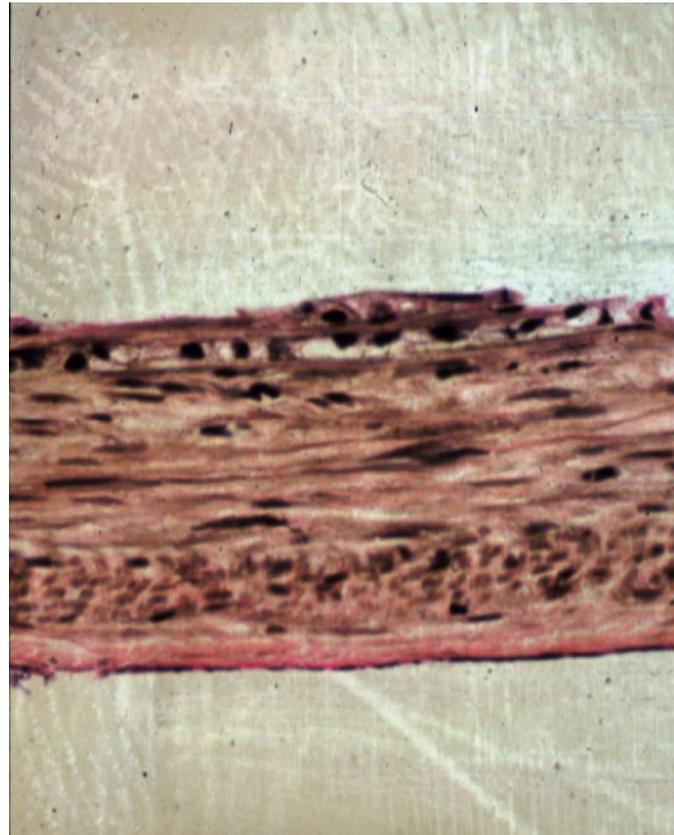
Batellier et al. *Arterioscler Thromb*, 1993, 13:379-384.

# Protection from Atherosclerosis in Vein Graft by Reduction of Wall Distension

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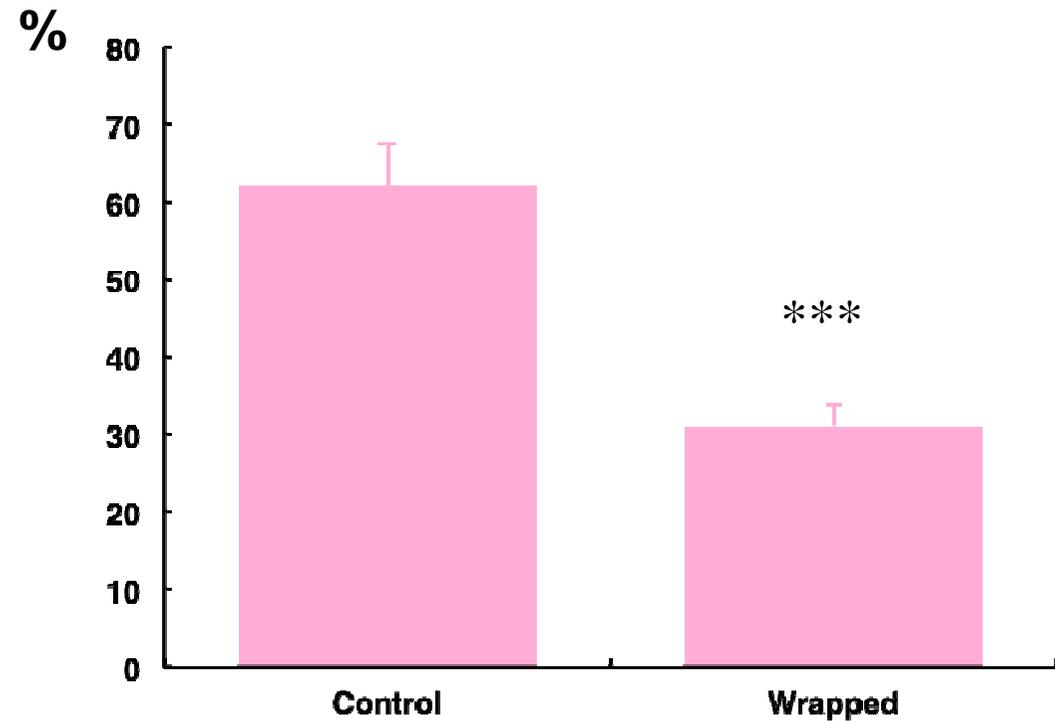
**Control**



**Wrapped**

# Protection from Atherosclerosis in Vein Graft by Reduction of Wall Distension

## Atherosclerotic lesions



- I. Atherosclerosis & Vessels
- II. Atherosclerosis & Lipids**
- III. Atherosclerosis & Inflammation
- IV. Atherosclerosis & Hypertension
- V. Hypertension & Inflammation

Quark & ARTE G.E.I.E.

présentent / zeigen

Cholestérol

Le grand bluff

18 Octobre 2016

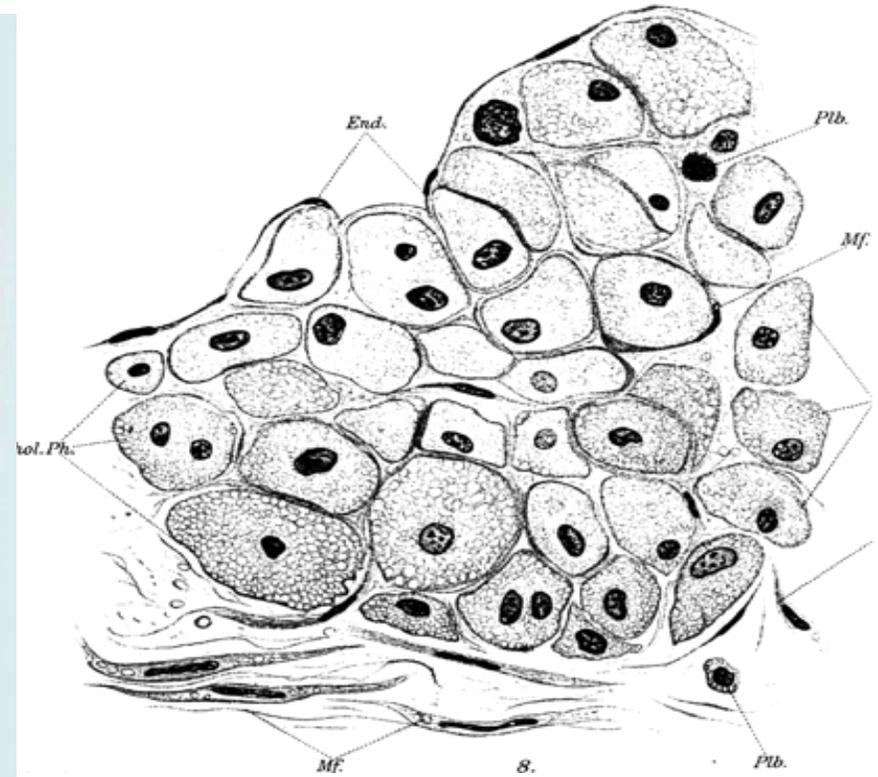
« La théorie qui fait du cholestérol le principal responsable des maladies cardio-vasculaires est contestée depuis les années 60 mais s'est imposée avec l'appui considérable de l'industrie agro-alimentaire et des laboratoires pharmaceutiques fabriquant des statines, ces médicaments anti-cholestérol prescrits par millions autour du globe...Le dogme d'un cholestérol coupable est aujourd'hui si enraciné que ses détracteurs ont toutes les peines du monde à convaincre de son innocence, même preuves à l'appui. »

Télérama

# An animal model – Anitchkow 1913



Nikolai Anitschkow (1885-1964)

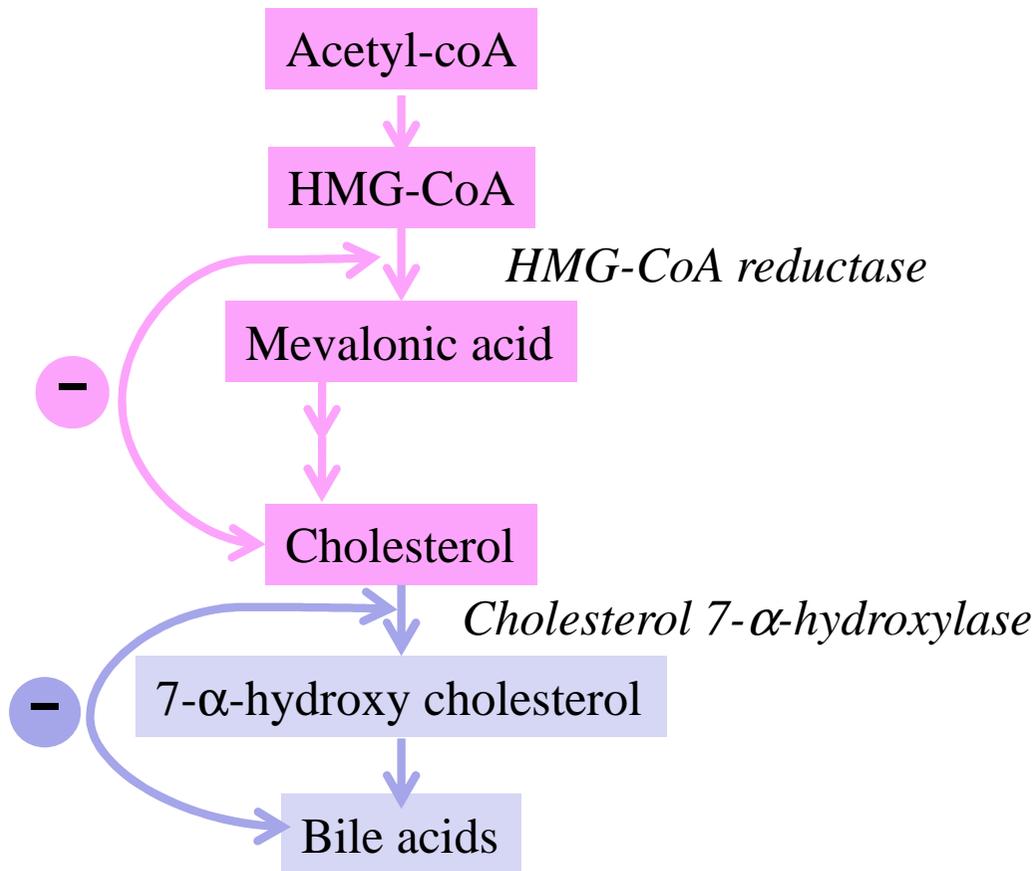


Nobel Prize-winning microbiologist I. Metschnikow proposed that an excess of protein in the diet was potentially toxic so Ignatowski fed rabbits a protein-rich diet containing meat, eggs, and milk.

Anitchkow and Chalotow narrowed things down to cholesterol purified from egg yolks!

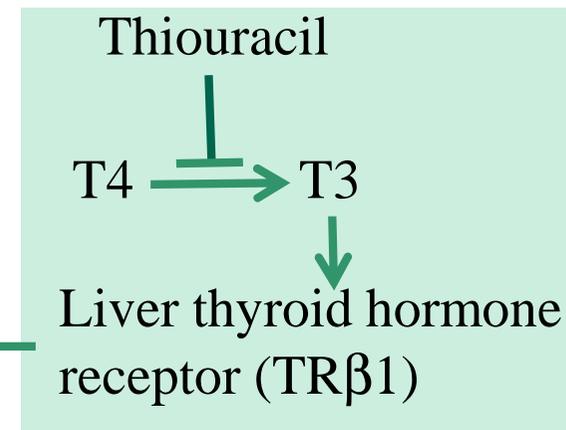
# Atherosclerosis in dogs following ingestion of cholesterol and thiouracil

## Cholesterol and bile acid synthesis



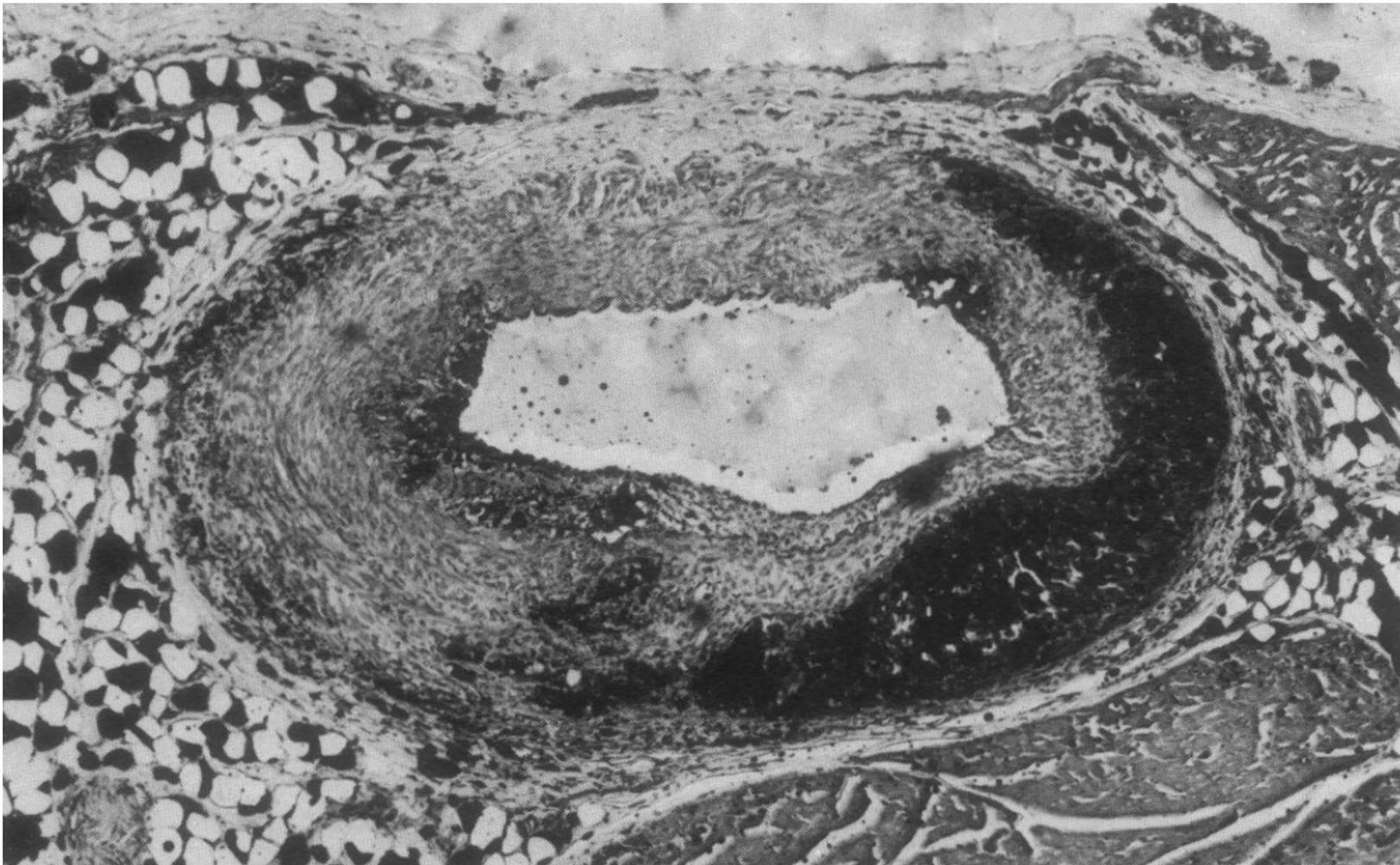
Dogs receiving a high cholesterol diet plus thiouracil have an impaired capacity to convert excess dietary cholesterol into bile acids.

## Thiouracil depresses thyroid function



# Atherosclerosis in hypothyroid dogs fed saturated fat and cholesterol

## Coronary artery



# All animal species tested develop atherosclerosis by raising blood cholesterol levels

Baboon

Cat

Chimpanzee

Dog

Goat

Guinea pig

Hamster

Monkey

Mouse

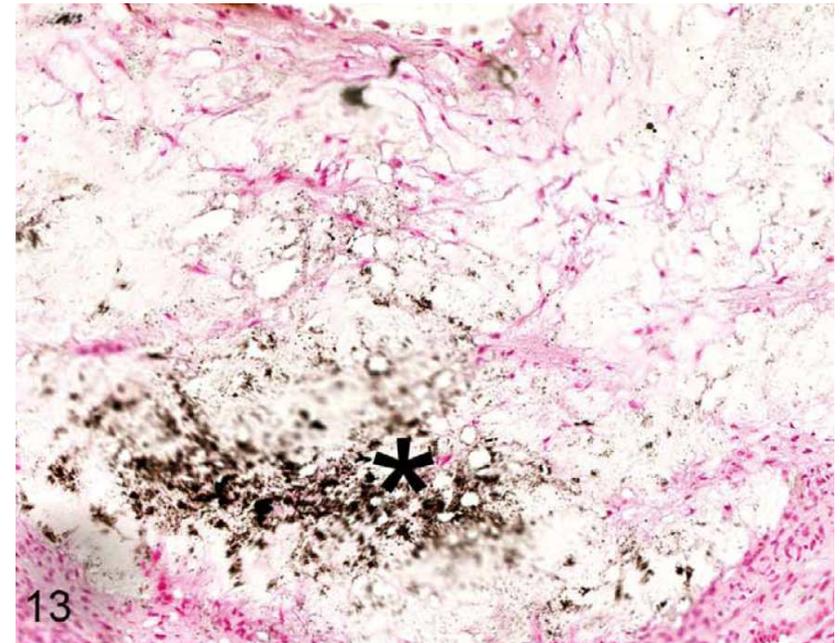
Parrot

Pig

Pigeon

Rabbit

Rat



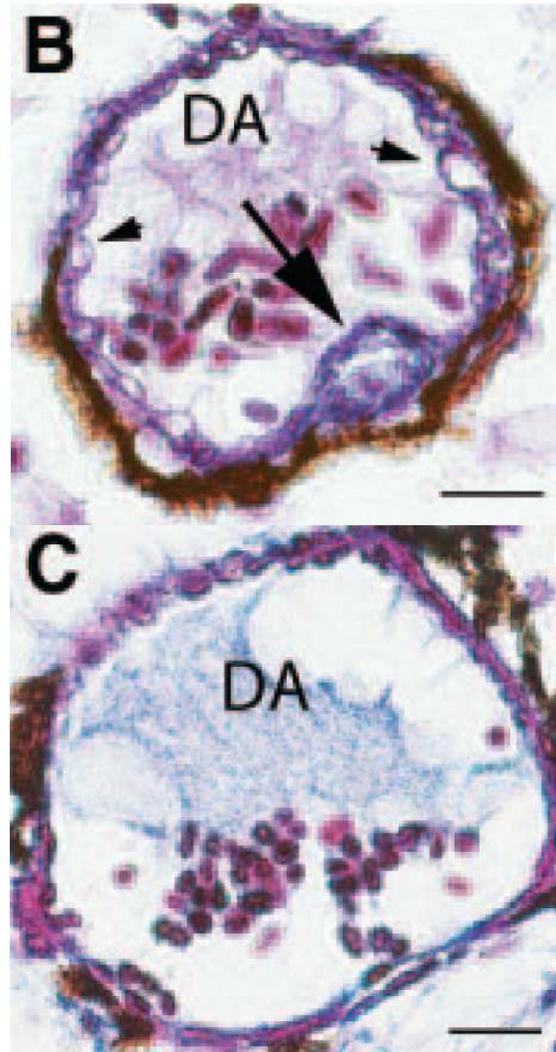
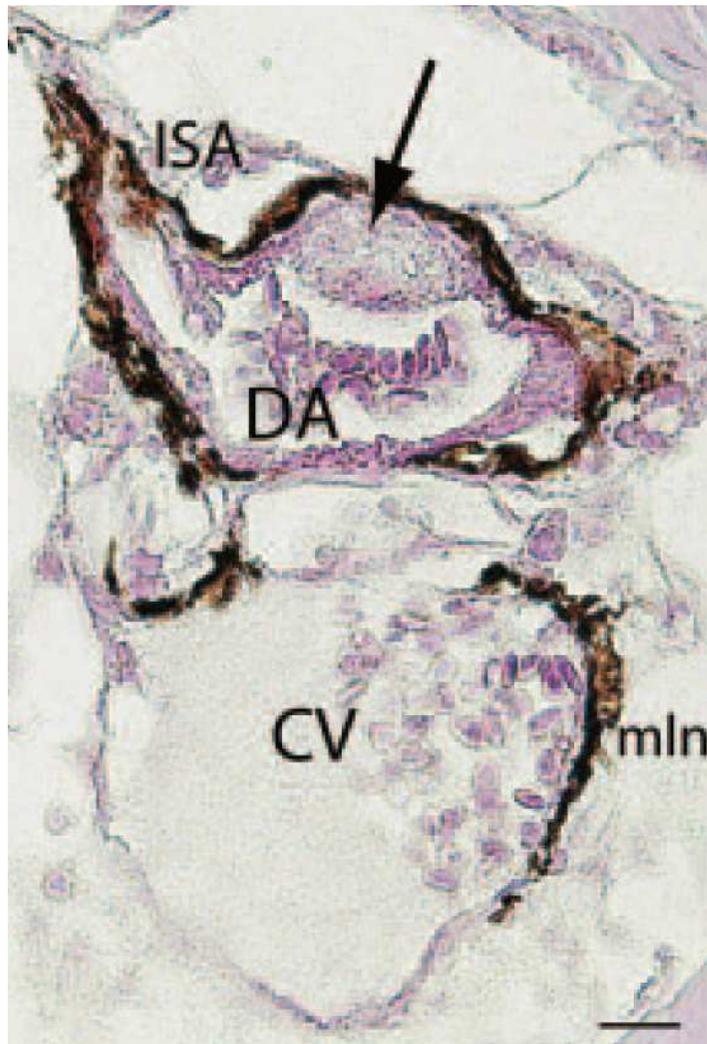
## **Brachiocephalic artery; Quaker parrot**

8-month atherogenic diet (1% cholesterol).

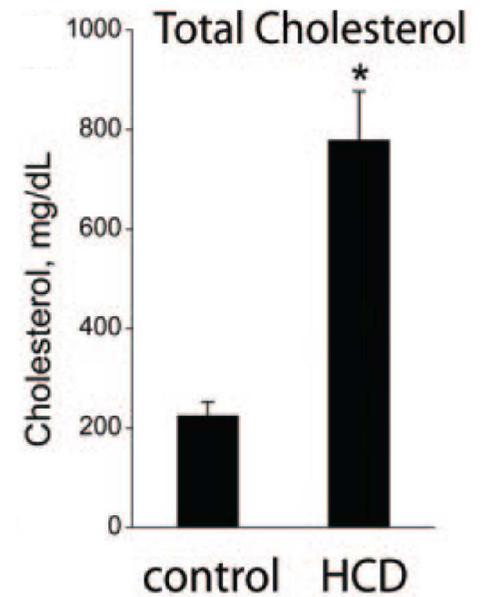
Type V lesion with calcification of the lipid core (\*)

Von Kossa staining.

# Macrophage lipid uptake and foam cell formation in hypercholesterolemic Zebrafish

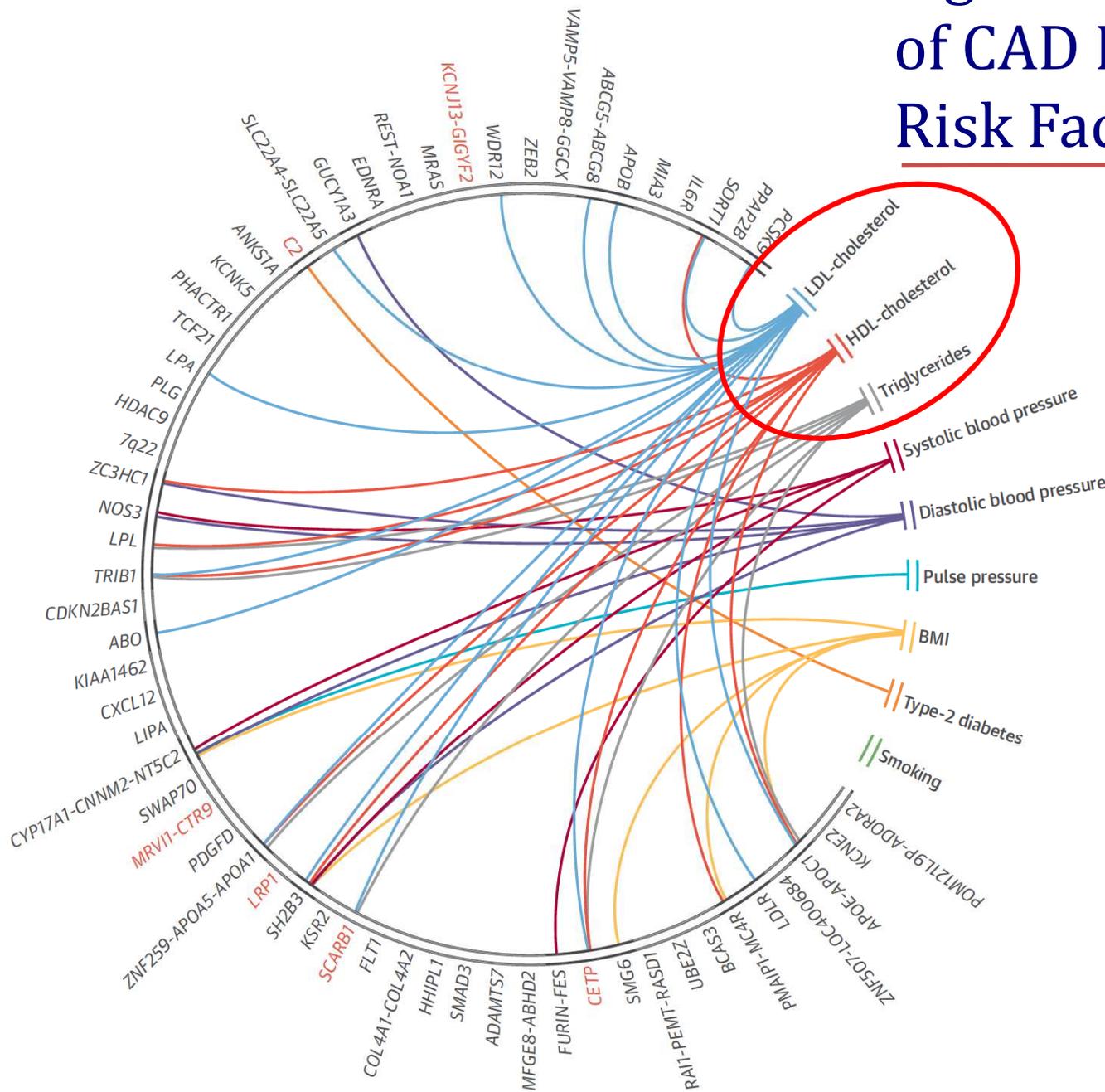


high-cholesterol (4%) diet



Control diet

# Significant Associations of CAD Loci With Cardiovascular Risk Factors



42,335 CAD cases

78,240 control

29,383 common SNPs

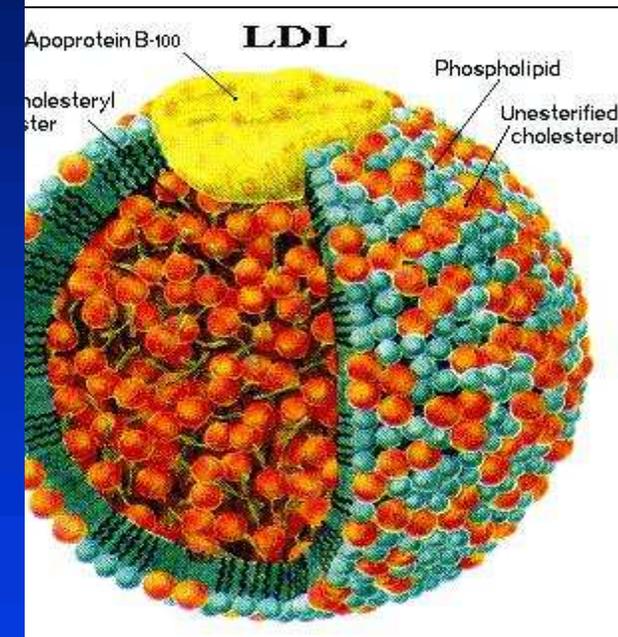
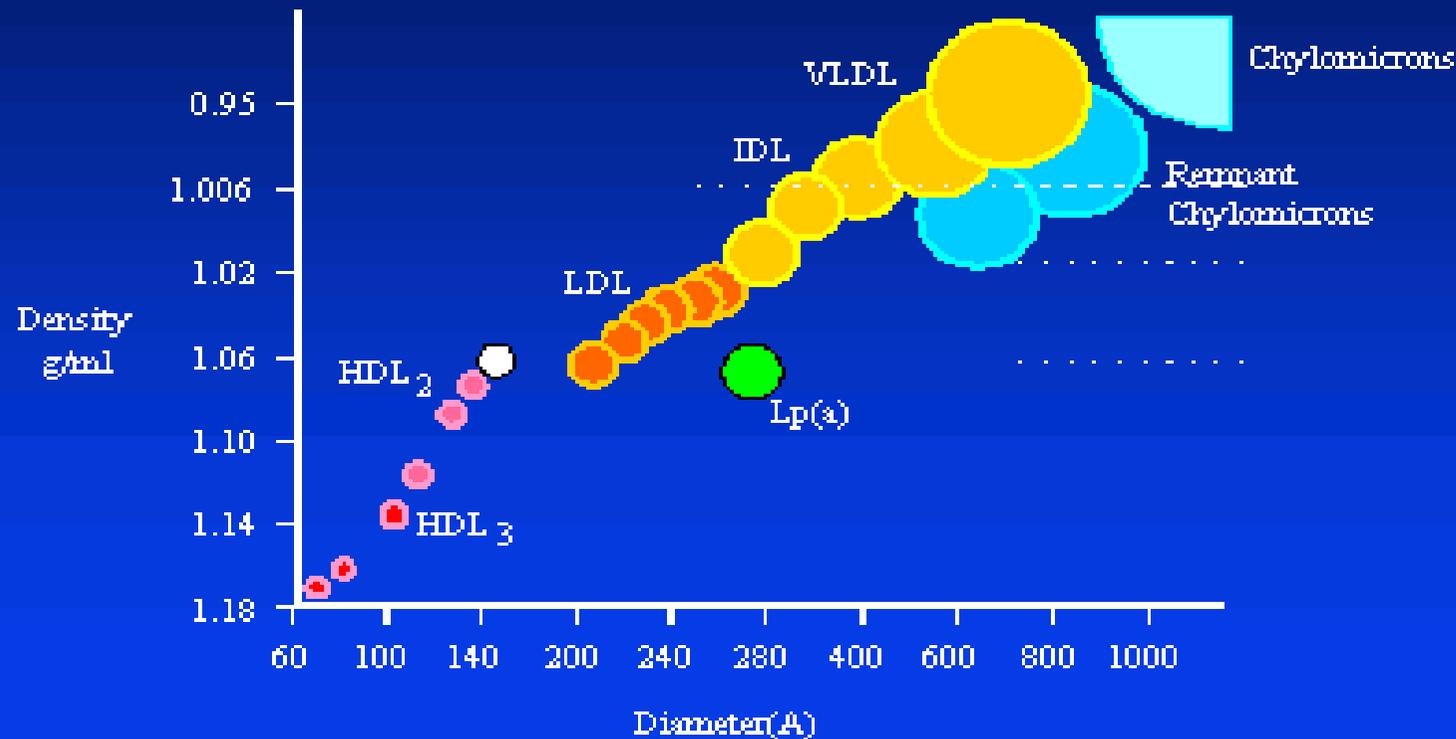
Out of 62 CAD loci,  
**30 associated with Lipids**

Webb, T.R. et al.

*J Am Coll Cardiol.* 2017;69(7):823–36.

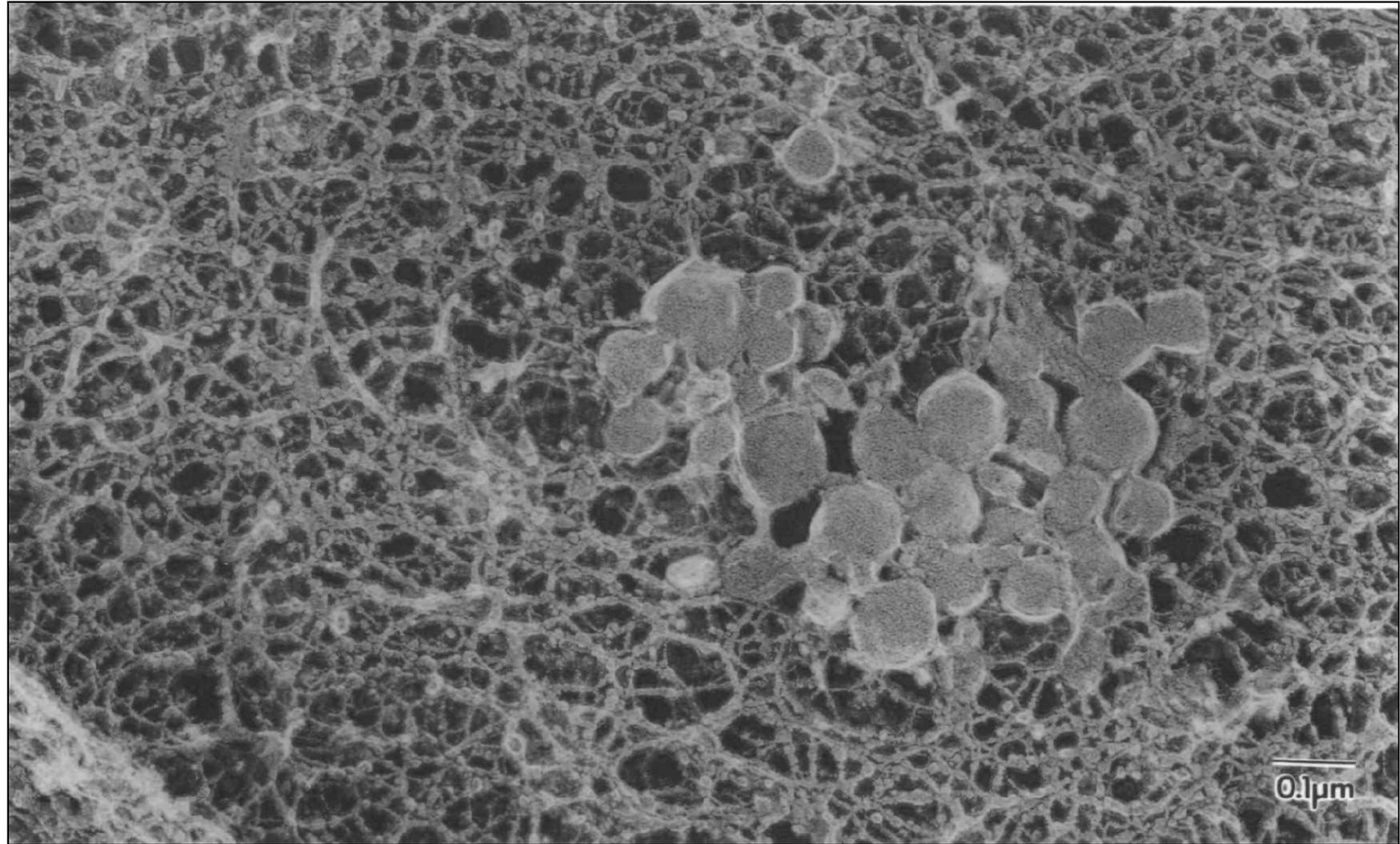
# Fractionation of lipoproteins using the ultracentrifuge

## Plasma Lipoprotein Species and Subspecies



Lipoprotein structure (1951 on) CB Anfinsen and ED Korn

# LDL Retention in the Intimal Extracellular Matrix



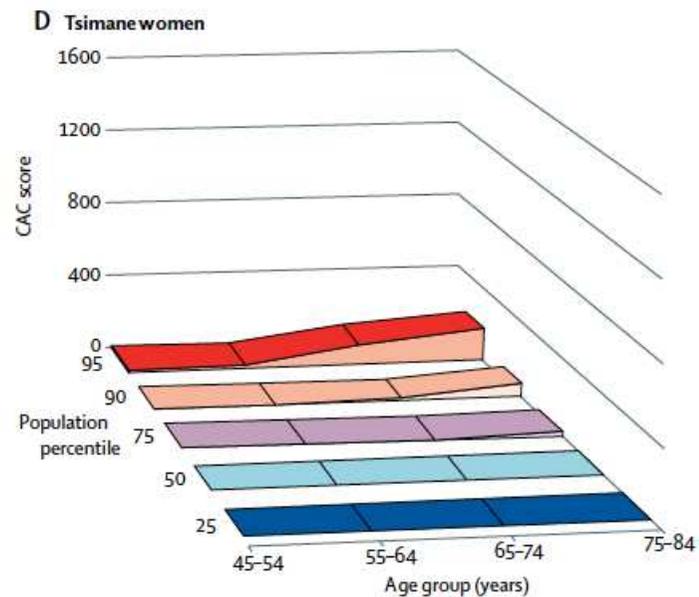
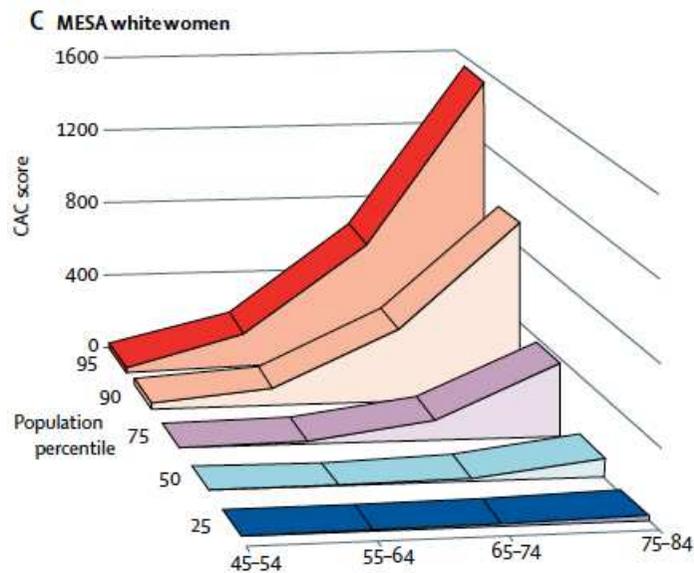
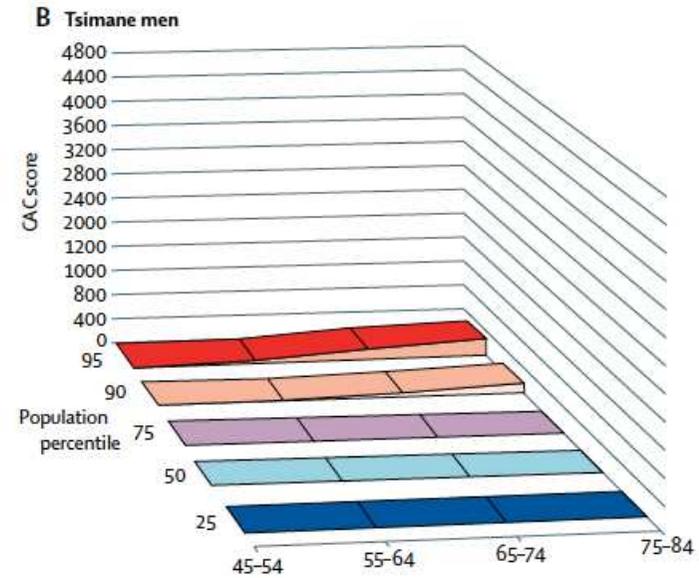
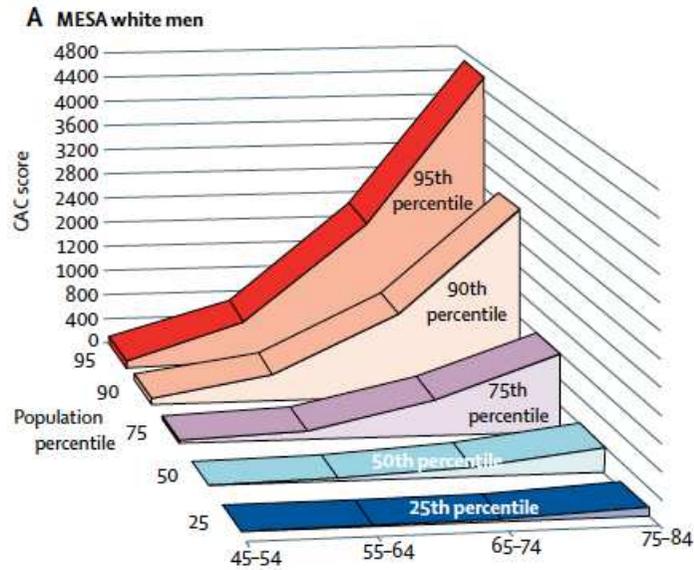
Nivelstein et al. *Arterioscler Thromb.* 1991, 11:1795-1805.

# Coronary atherosclerosis in indigenous South American Tsimane



	40-44 years (n=31)	45-54 years (n=298)	55-64 years (n=204)	65-74 years (n=124)	75+ years (n=48)	Total (n=705)	p value
<b>Anthropometry</b>							
Proportion of men (%)	50 (0.5)	50 (0.5)	50 (0.5)	50 (0.5)	40 (0.5)	50 (0.5)	0.6301
Mean weight (kg)	58.8 (9.0)	60.3 (9.0)	58.5 (10.9)	56.2 (9.5)	52.1 (9.5)	58.4 (9.9)	<0.0001
Height (cm)	157.4 (7.5)	157.2 (7.0)	154.9 (8.0)	154.5 (8.3)	151.2 (8.3)	155.7 (7.8)	<0.0001
Body-mass index (kg/m <sup>2</sup> )	23.7 (3.0)	24.4 (3.1)	24.4 (4.1)	23.5 (3.3)	22.6 (2.8)	24.1 (3.5)	0.0220
Body fat (%)	21.8% (8.3)	21.9% (8.2)	22.8% (8.3)	21.7% (8.4)	21.7% (6.5)	22.1% (8.2)	0.6726
<b>Lipids</b>							
Total cholesterol (mmol/L)	4.0 (0.7)	<b>1.5 g/L</b> 3.9 (0.7)	4.0 (0.9)	3.9 (0.8)	3.6 (0.7)	3.9 (0.8)	0.0203
LDL cholesterol (mmol/L)	2.5 (0.6)	<b>0.9 g/L</b> 2.4 (0.7)	2.4 (0.8)	2.3 (0.7)	2.1 (0.7)	2.4 (0.7)	0.3200
HDL cholesterol (mmol/L)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.4630
Triglycerides (mmol/L)	1.0 (0.5)	1.1 (0.5)	1.2 (0.6)	1.2 (0.5)	1.1 (0.4)	1.2 (0.5)	0.2780
ApoA (mg/dL)	90.0 (60.5)	109.6 (77.8)	141.1 (86.2)	142.7 (87.8)	140.7 (99.5)	126.0 (84.9)	<0.0001
ApoB (mg/dL)	86.4 (24.0)	86.9 (33.8)	109.4 (47.0)	104.1 (44.0)	97.1 (44.7)	97.2 (41.5)	<0.0001
Oxidised LDL (U/L)	82.9 (22.6)	78.0 (21.8)	74.8 (22.9)	77.4 (23.4)	70.4 (21.2)	76.6 (22.4)	0.0374
<b>Inflammatory markers</b>							
hs-CRP (mg/L)	3.2 (2.6)	3.5 (3.0)	3.8 (3.6)	4.0 (3.0)	4.0 (3.9)	3.7 (3.2)	0.6320

# Coronary atherosclerosis in indigenous South American Tsimane



## Statin era : 1976 -

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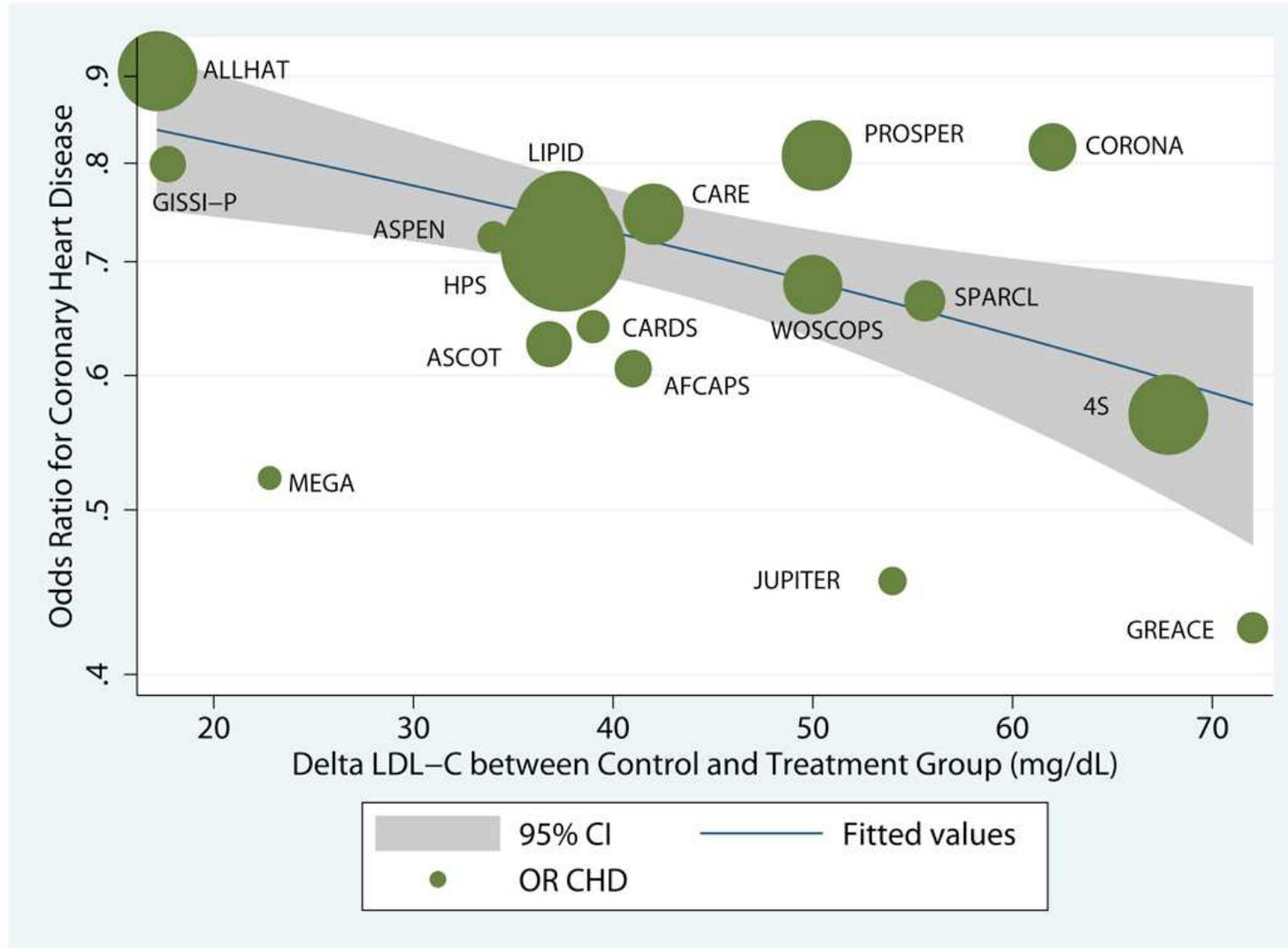


Akira Endo (1933- )  
Lasker Prize 2008

6000 tests of fungal broths  
(*Penicillium citrinum*) in a high  
throughput screen identified  
'compactin' as a inhibitor of  
cholesterol synthesis.  
Other statins quickly followed.

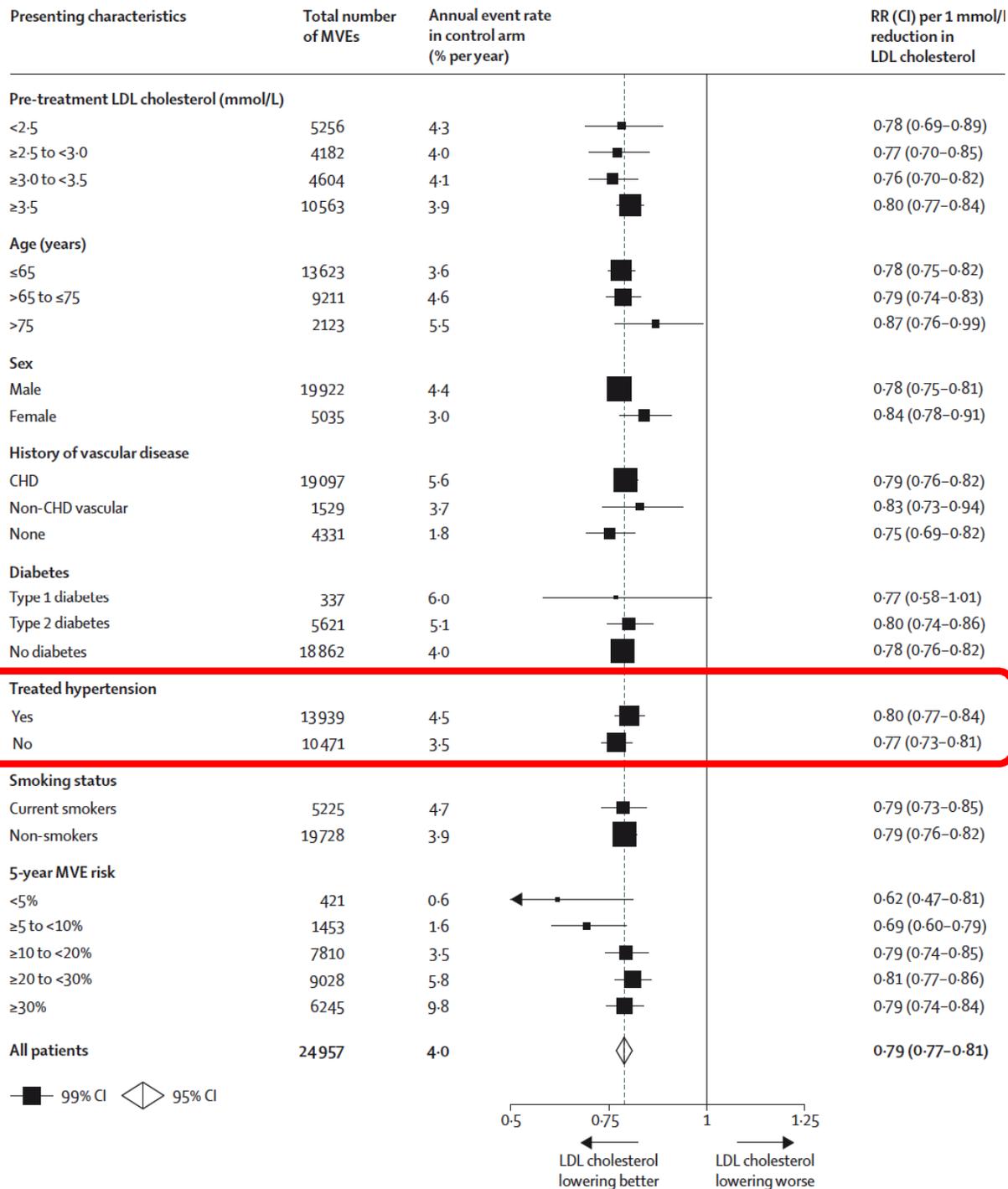
# Meta-Regression Analysis of Large-Scale Trials of Statin Therapy

17 large randomized controlled trials ; 124,302 participants ; 8,332 major CHD events



23% relative reduction in CHD risk for every 0.4 g/L absolute inter-group decrease in LDL-C

Kizer et al. *Am J Cardiol.* 2010;105(9):1289-96.



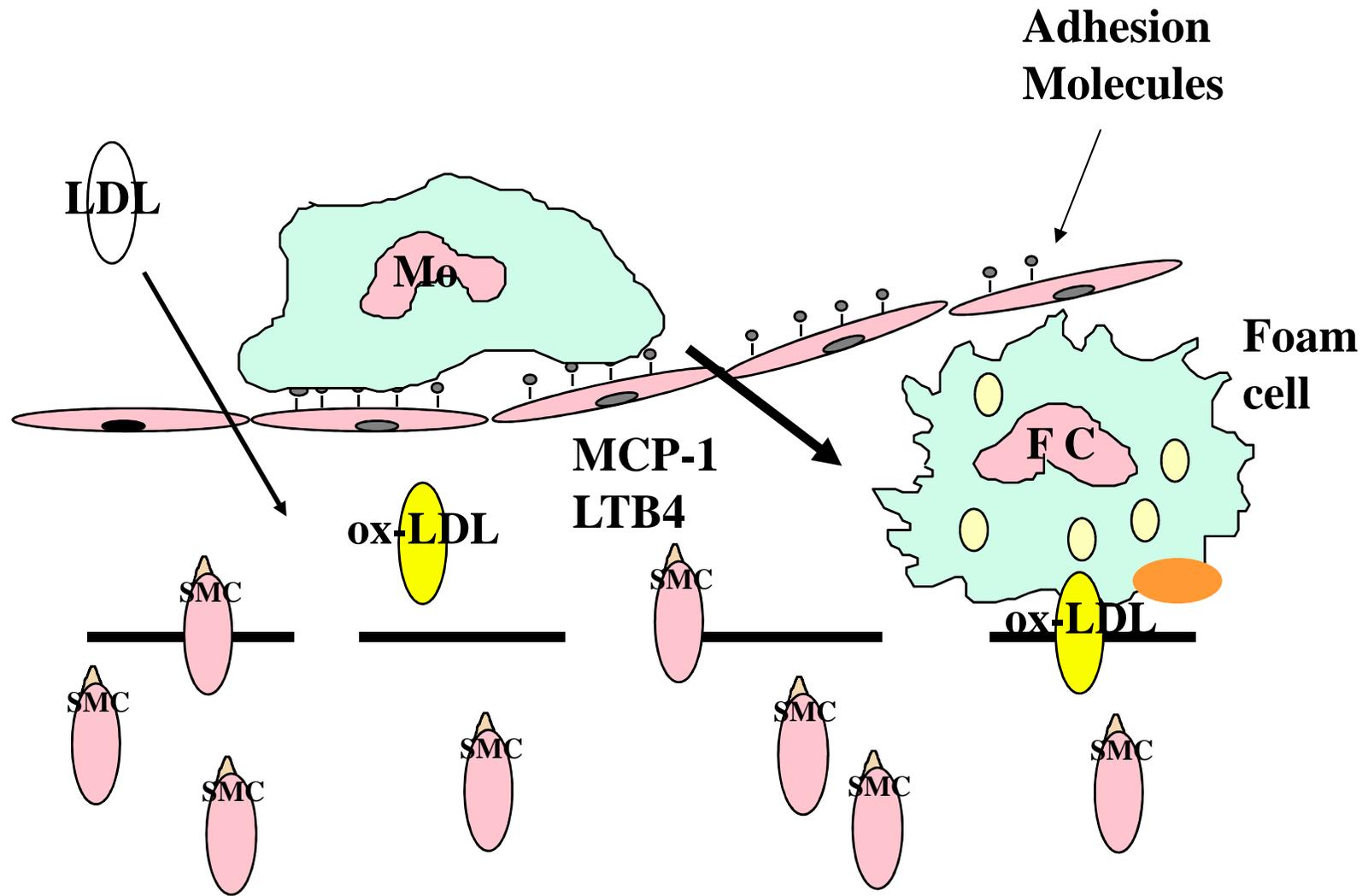
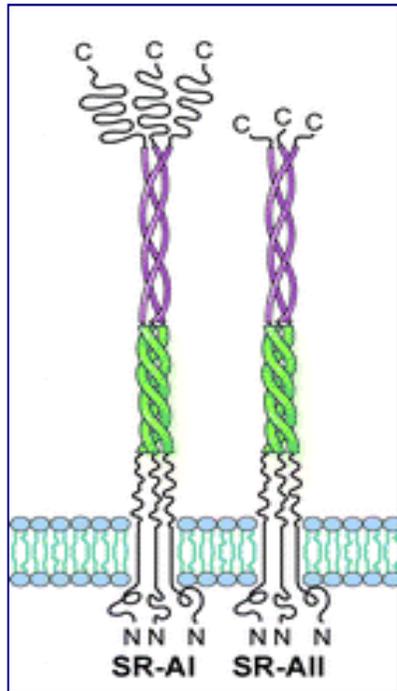
Reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics

- I. Atherosclerosis & Vessels
- II. Atherosclerosis & Lipids
- III. Atherosclerosis & Inflammation**
- IV. Atherosclerosis & Hypertension
- V. Hypertension & Inflammation

# Oxidized LDL - Uptake by Scavenger Receptors & Inflammation



Dan Steinberg (1922-2015)



# Bioactive Lipid Mediators

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Oxidized LDL

4-hydroxy-2-nonenal (4HNE)

Oxysterols

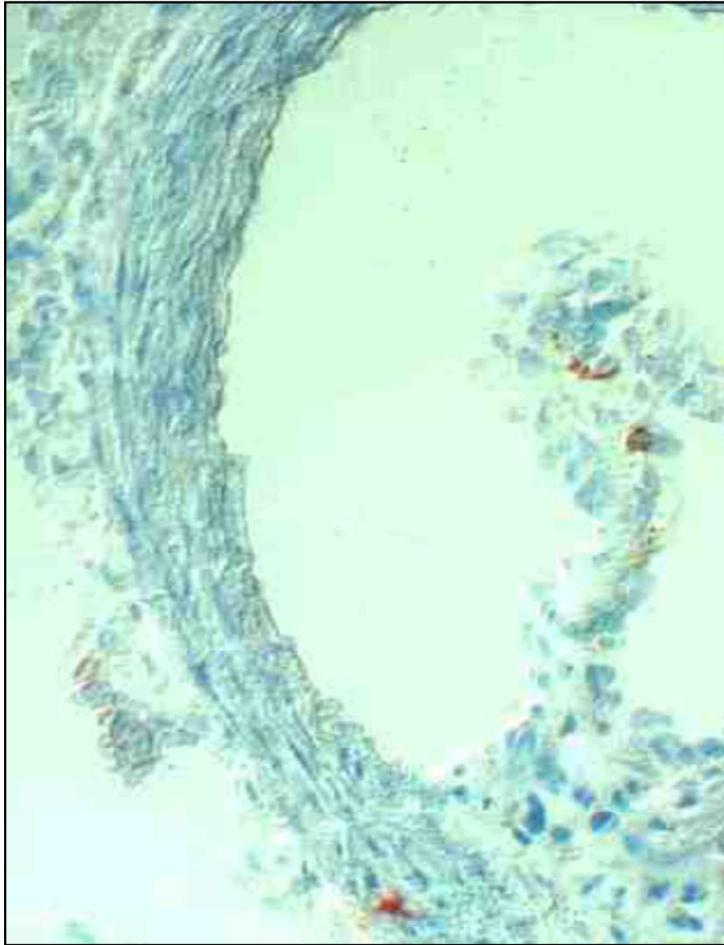
Oxidized phospholipids (oxPL)

lysophosphatidylcholine (lysoPC)

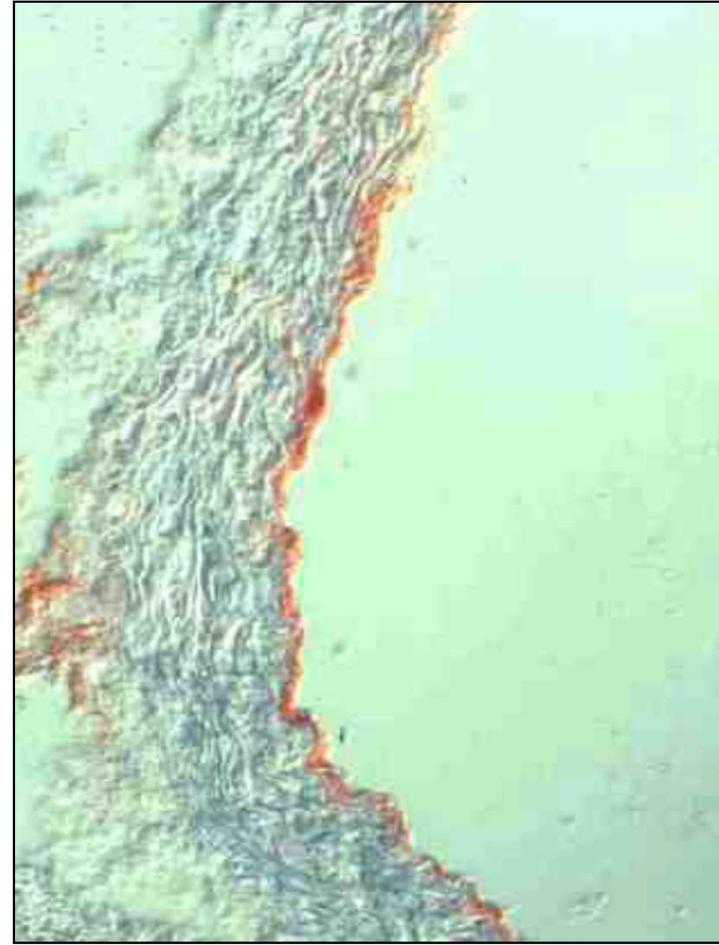
oxPAPC

Platelet activating factor (PAF)

# Early Endothelial Activation of NF- $\kappa$ B in Atherosclerosis

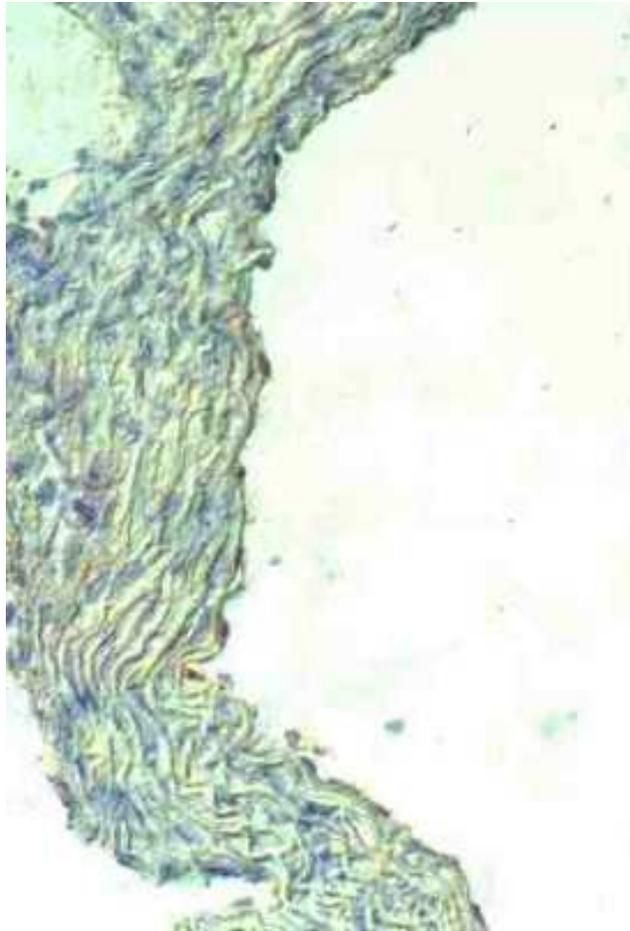


Chow diet

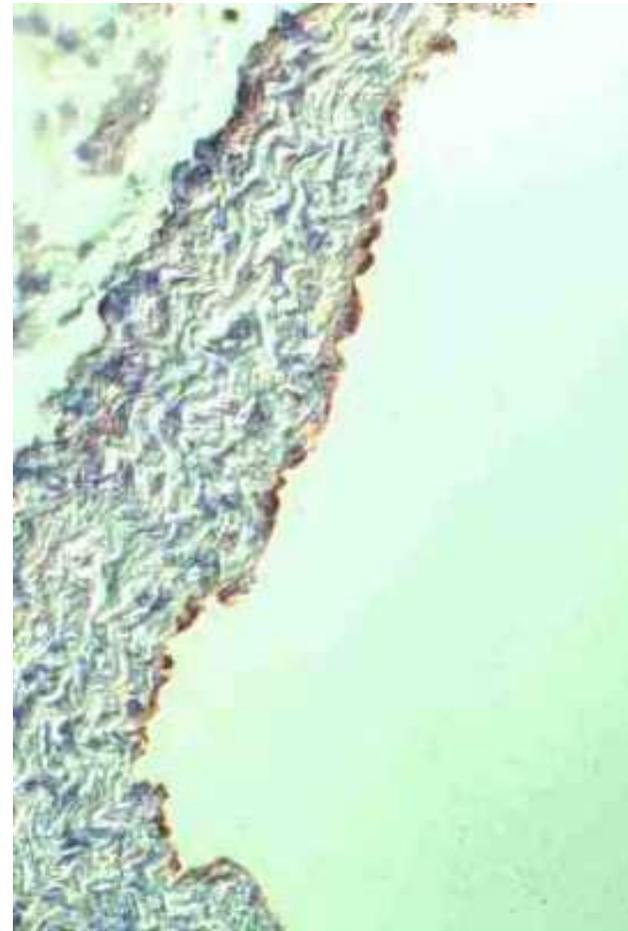


10-day atherogenic diet

# Early Endothelial Expression of VCAM-1



Chow diet



10-day atherogenic diet

# Vascular Inflammation

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HSPs

Immune complexes

Infectious agents/PAMPs

Oxygen radicals

Angiotensin II

AGEs

Defective clearance of apoptotic cells

Inflammasome (inflammatory caspases)

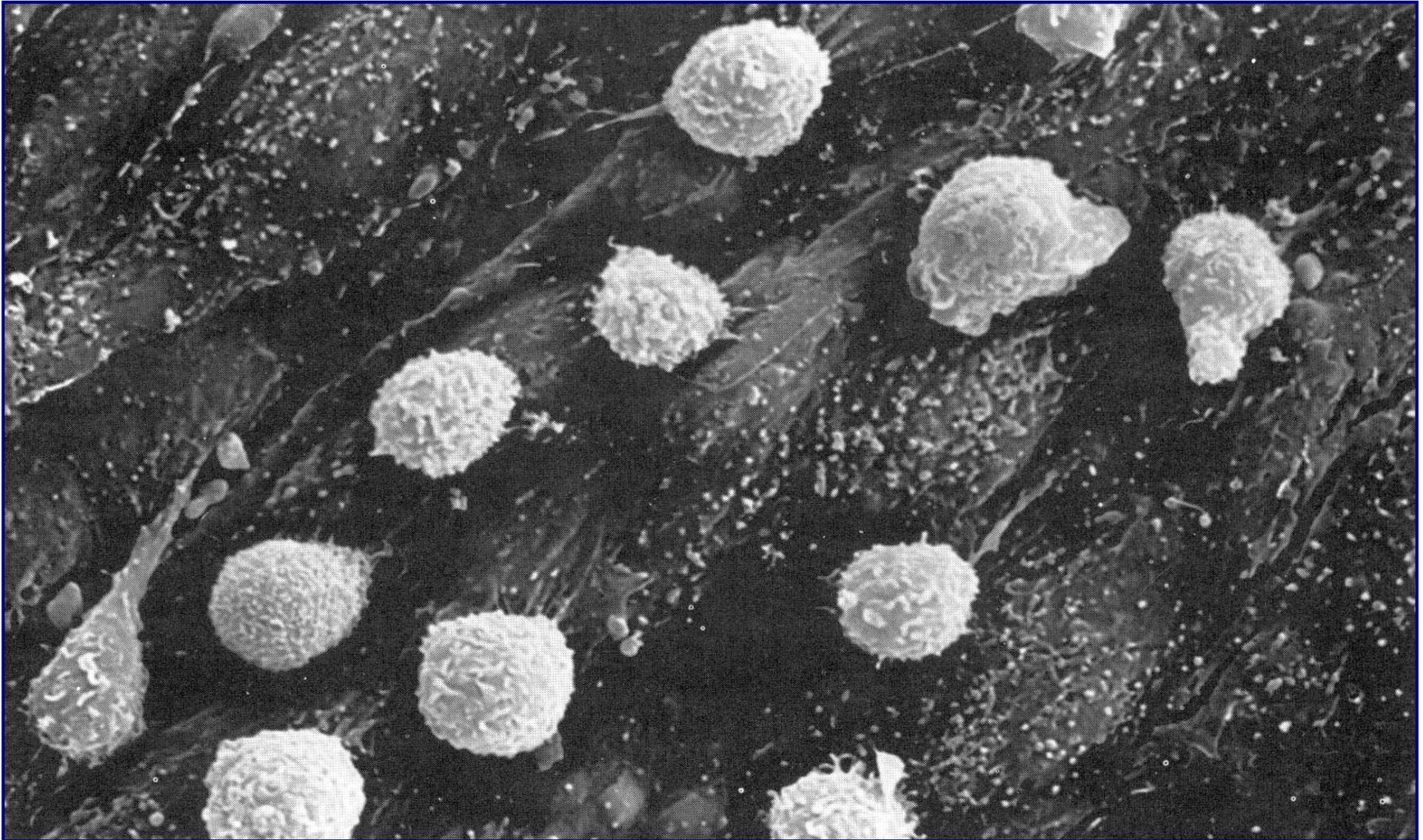
Mechanical factors

**Hypertension**

Disturbed flow

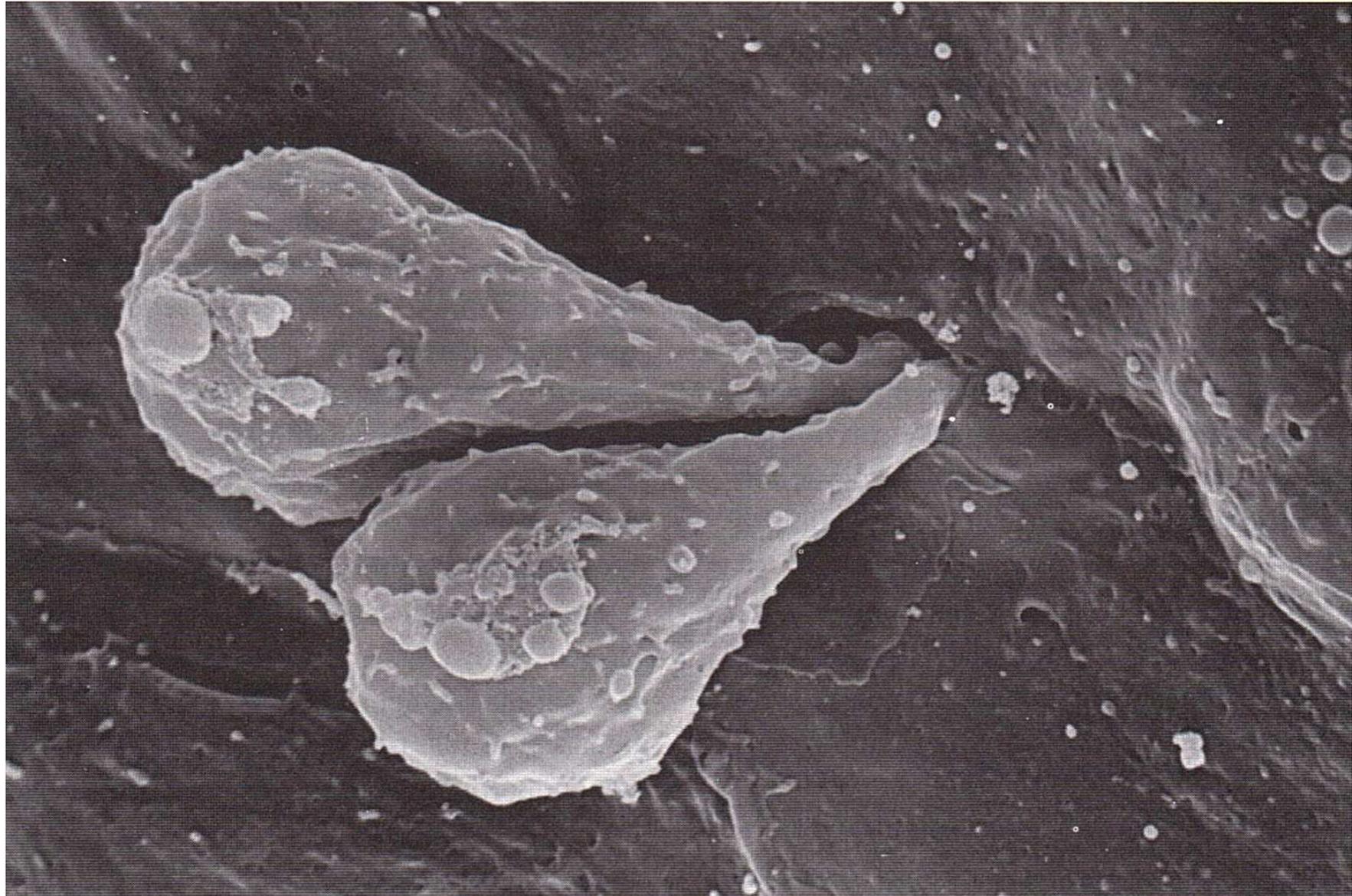
Platelet products/Coagulation factors

# Atherosclerosis is an Inflammatory Disease



# Monocyte transmigration through endothelial cells

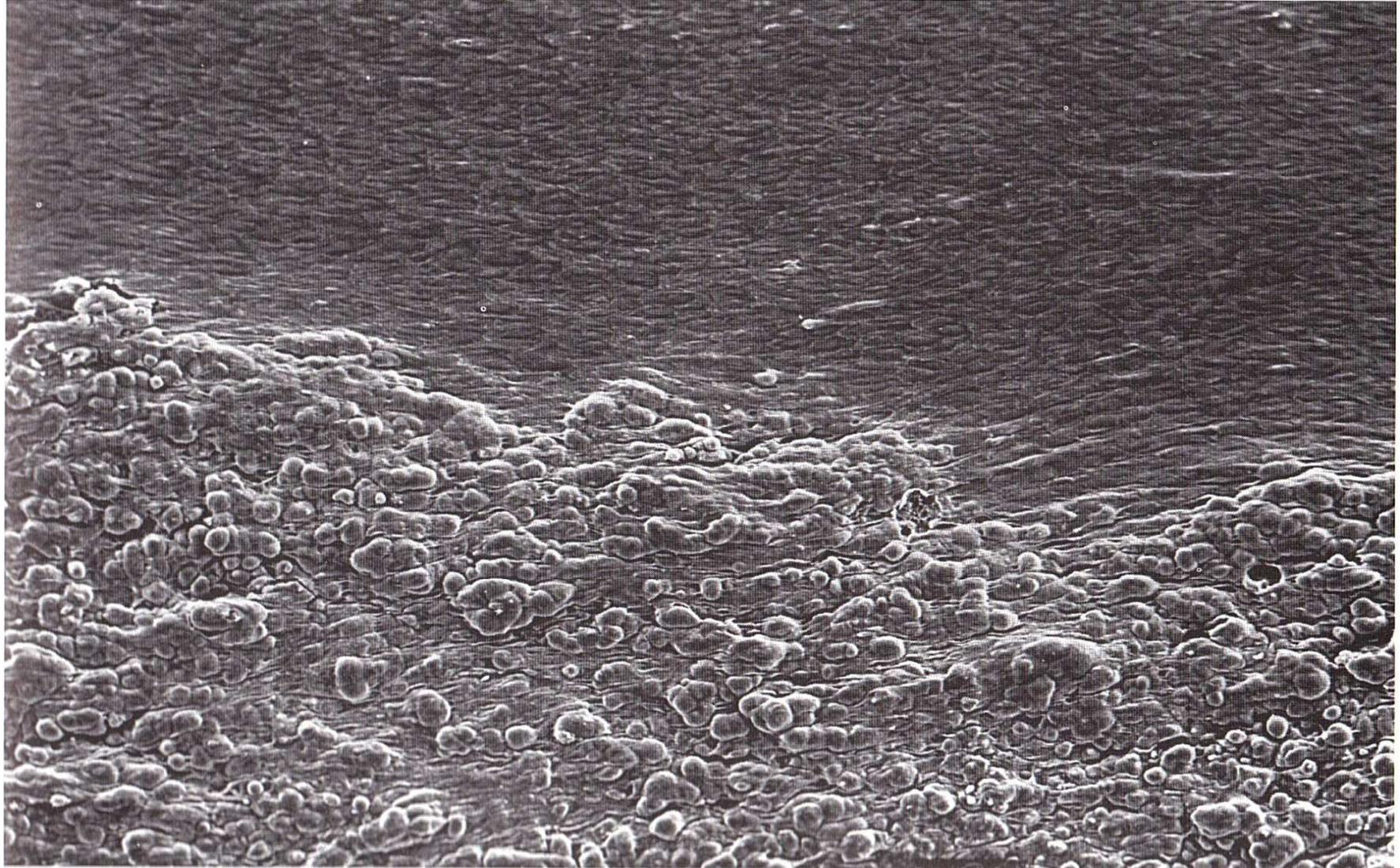
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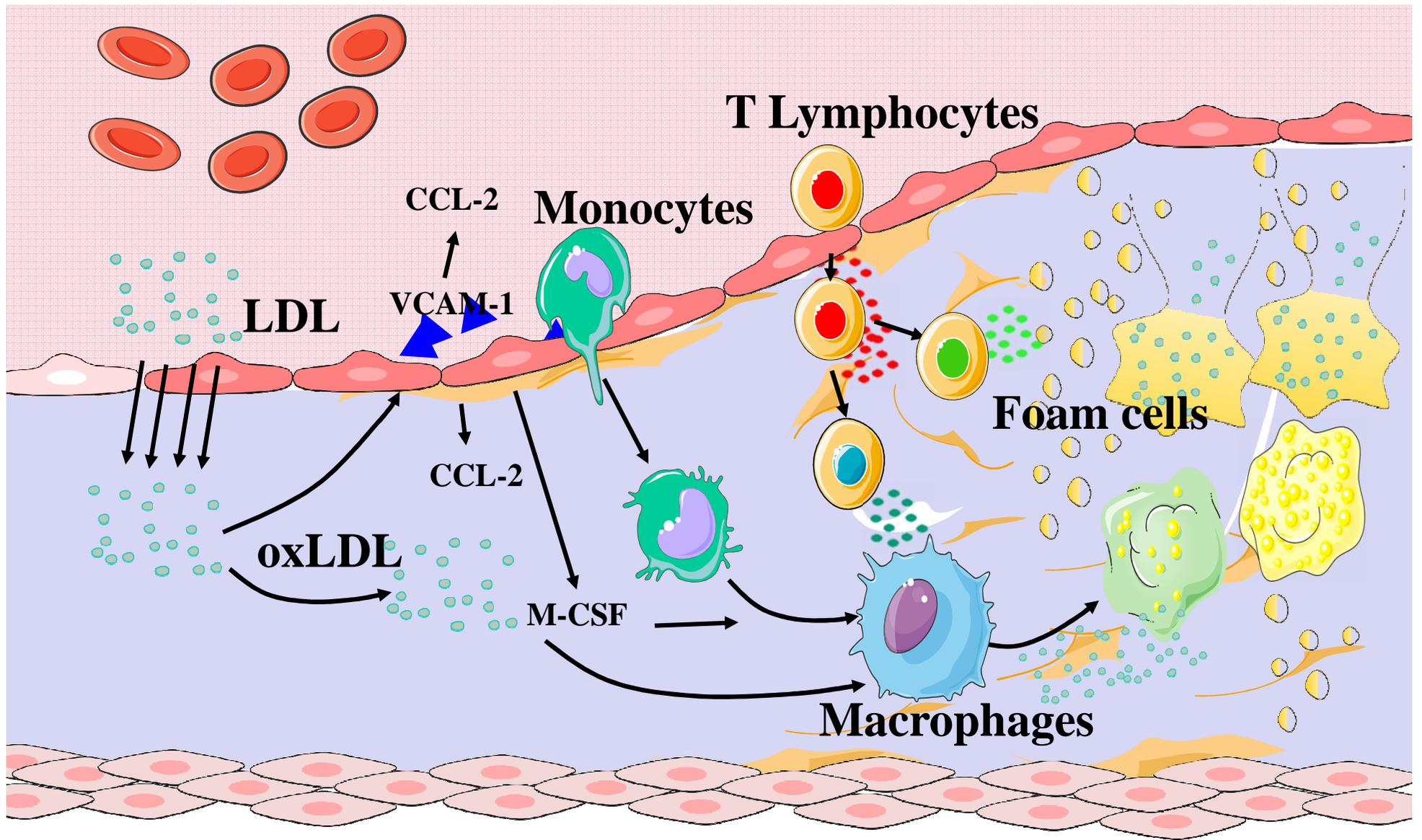
Masuda & Ross. *Arteriosclerosis*. 1990;10:164-177

# Endothelium overlying fatty lesions

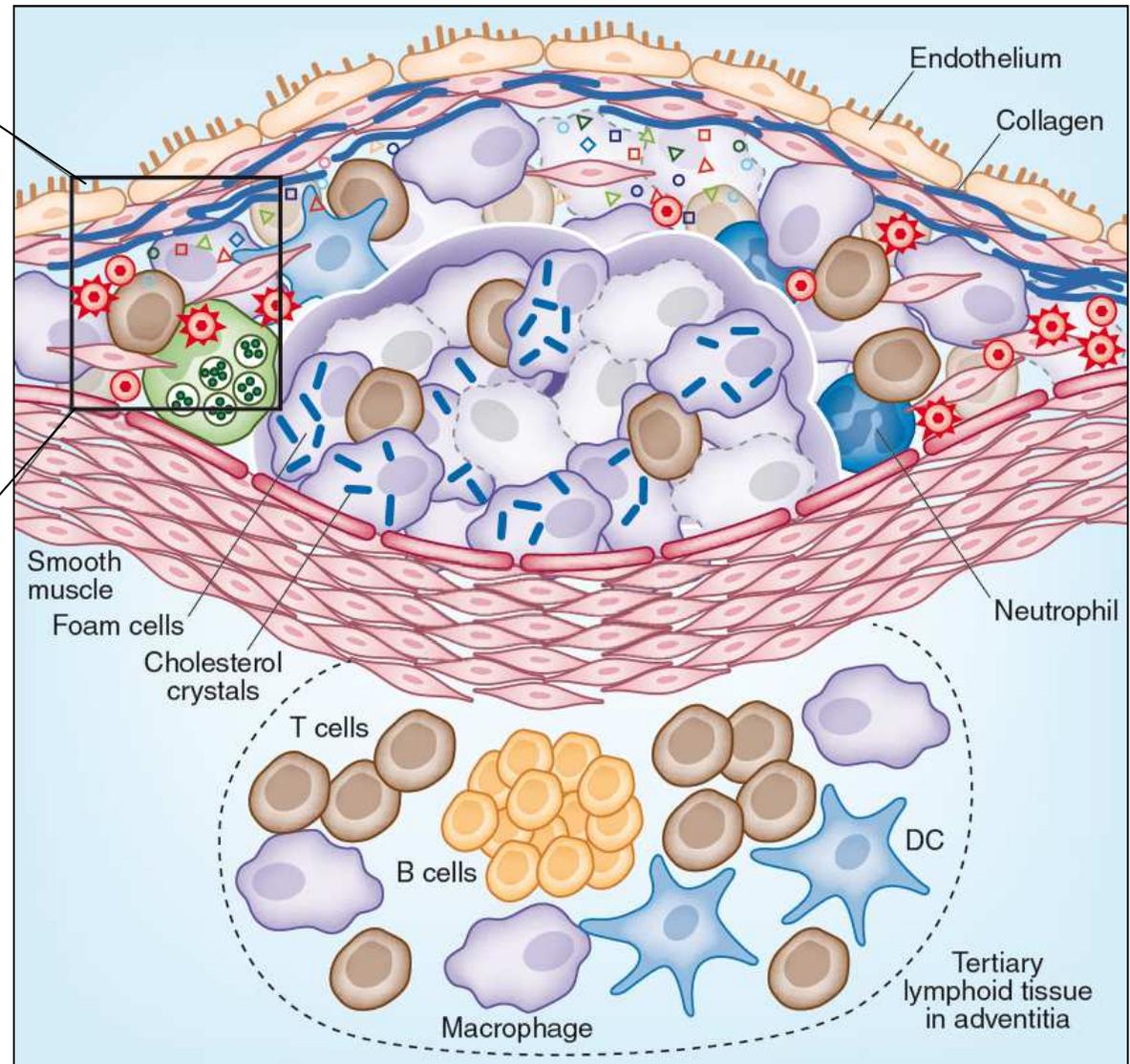
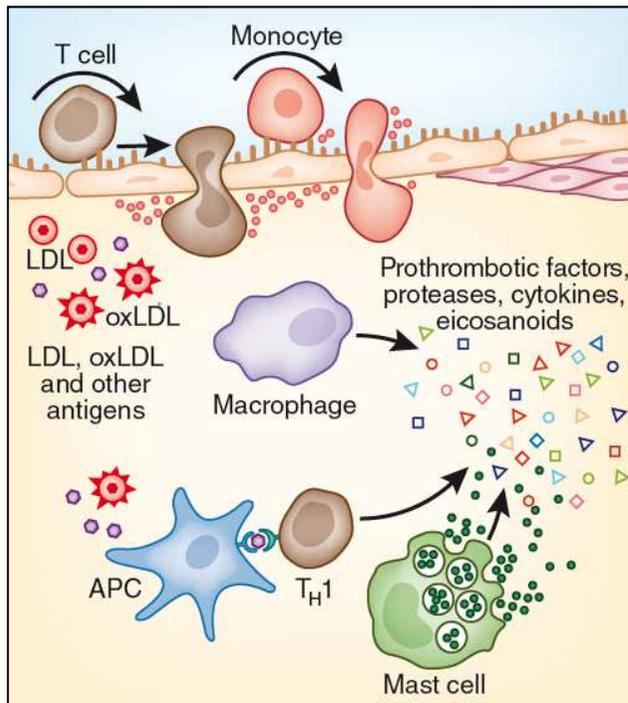
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from R. Ross

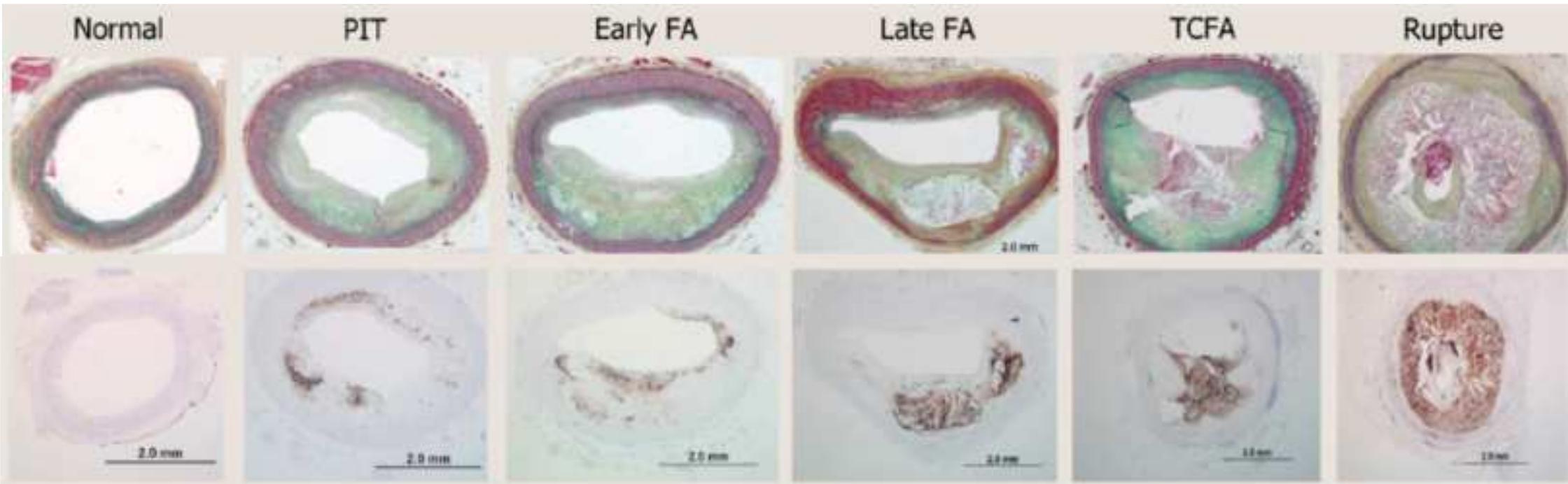


# The atherosclerotic plaque: a Site of Immune Inflammation



Hansson & Hermansson.  
*Nat Immunol* 2011;12:204-12.

# Increasing inflammation with evolving severity of atherosclerotic lesions



immunohistochemical staining with CD68 antibody

- I. Atherosclerosis & Vessels
- II. Atherosclerosis & Lipids
- III. Atherosclerosis & Inflammation
- IV. Atherosclerosis & Hypertension**
- V. Hypertension & Inflammation

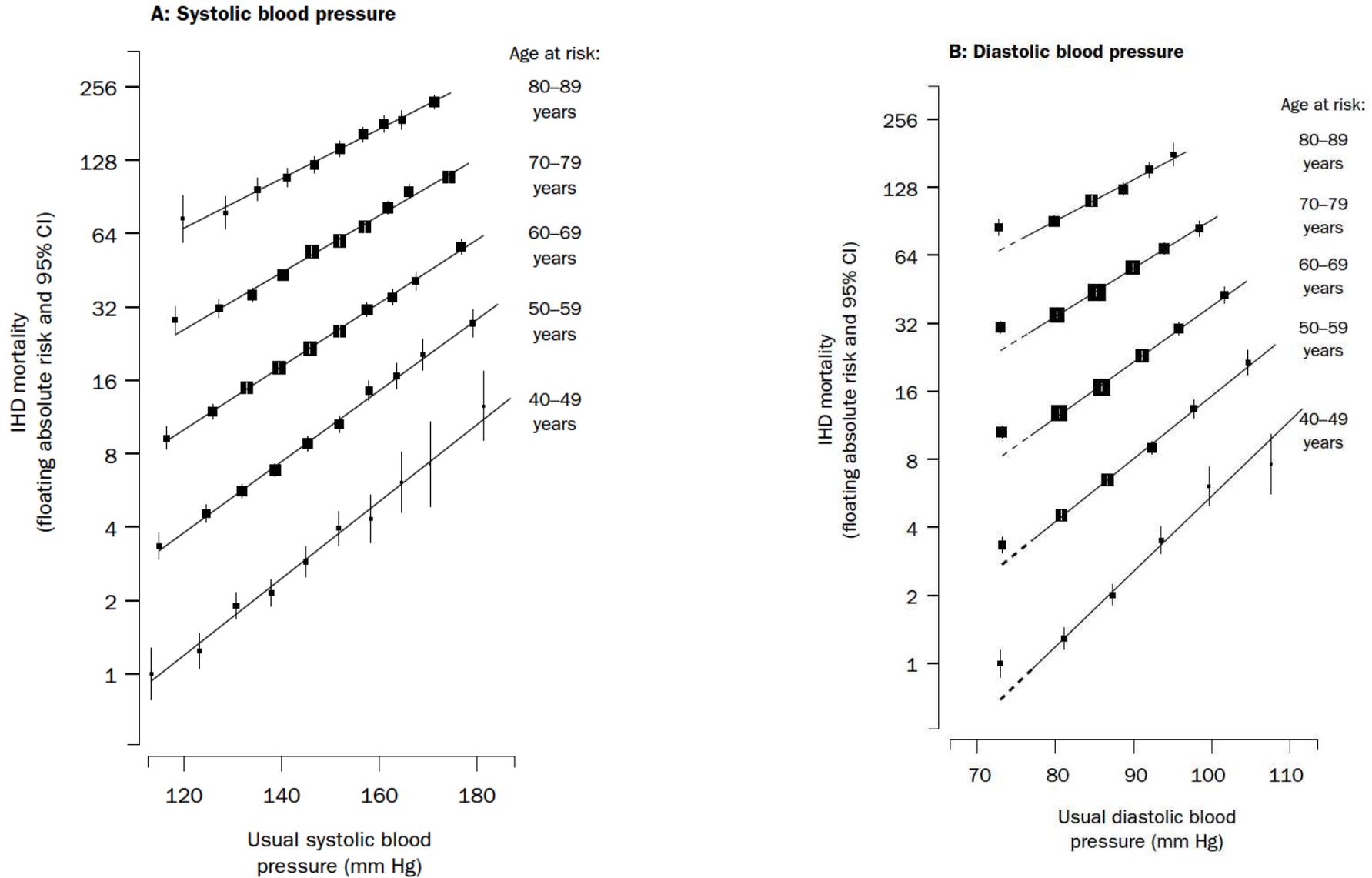
# INTERHEART study

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Case (15,152 patients) /control (14,820) study of risk factors for acute myocardial infarction in 52 countries

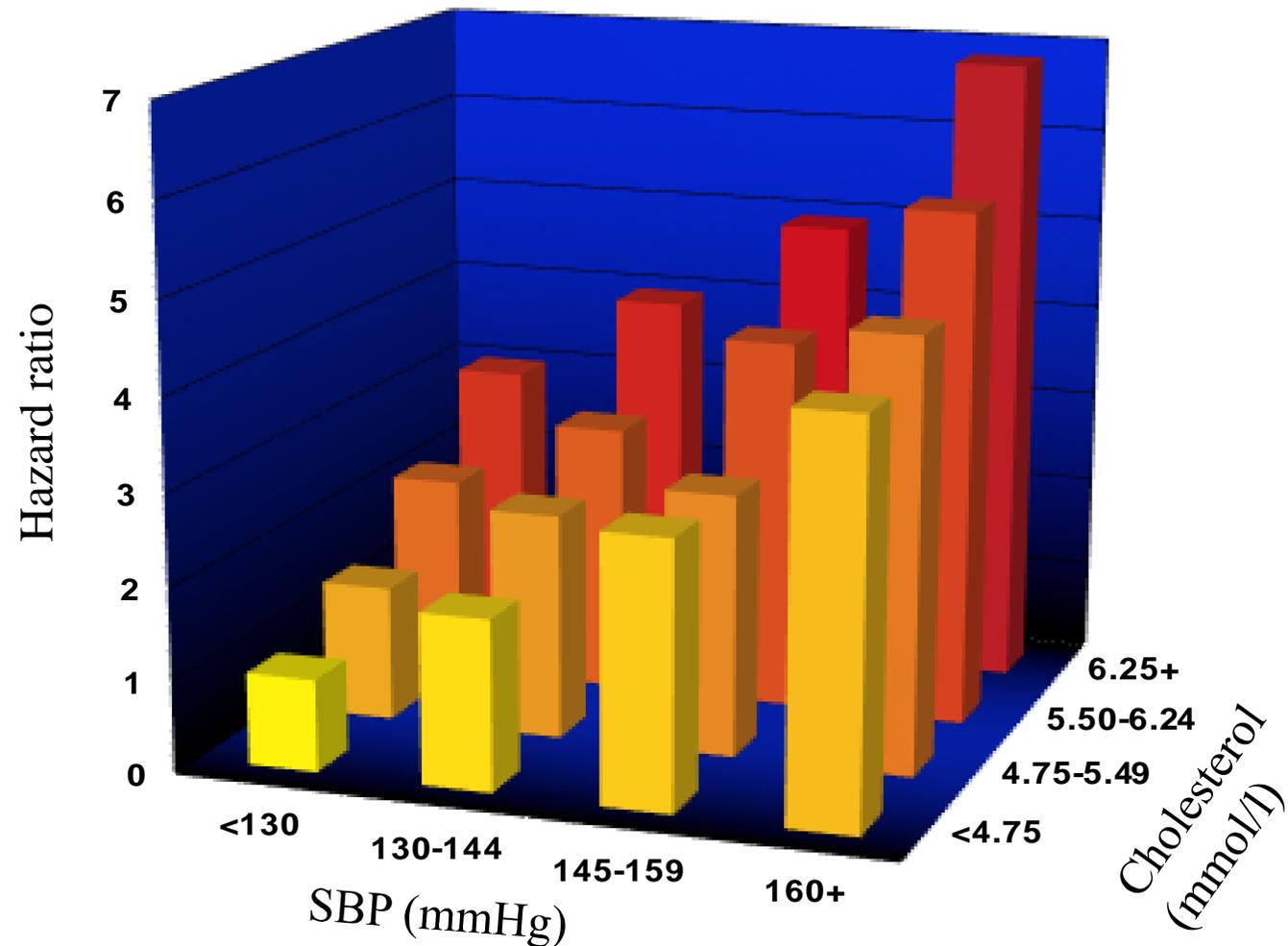
1. Nine simple risk factors are strongly associated with acute myocardial infarction worldwide.  
ApoB/apoA1 ratio, diabetes, abdominal obesity, smoking, **hypertension**, psychosocial index, fruits/veg., exercise, alcohol.
2. Consistent in men and women, across all ethnic groups and all regions.
3. All 9 risk factors account for >90% of the population attributable risk globally and in most regions.

# Ischemic Heart Disease and BP

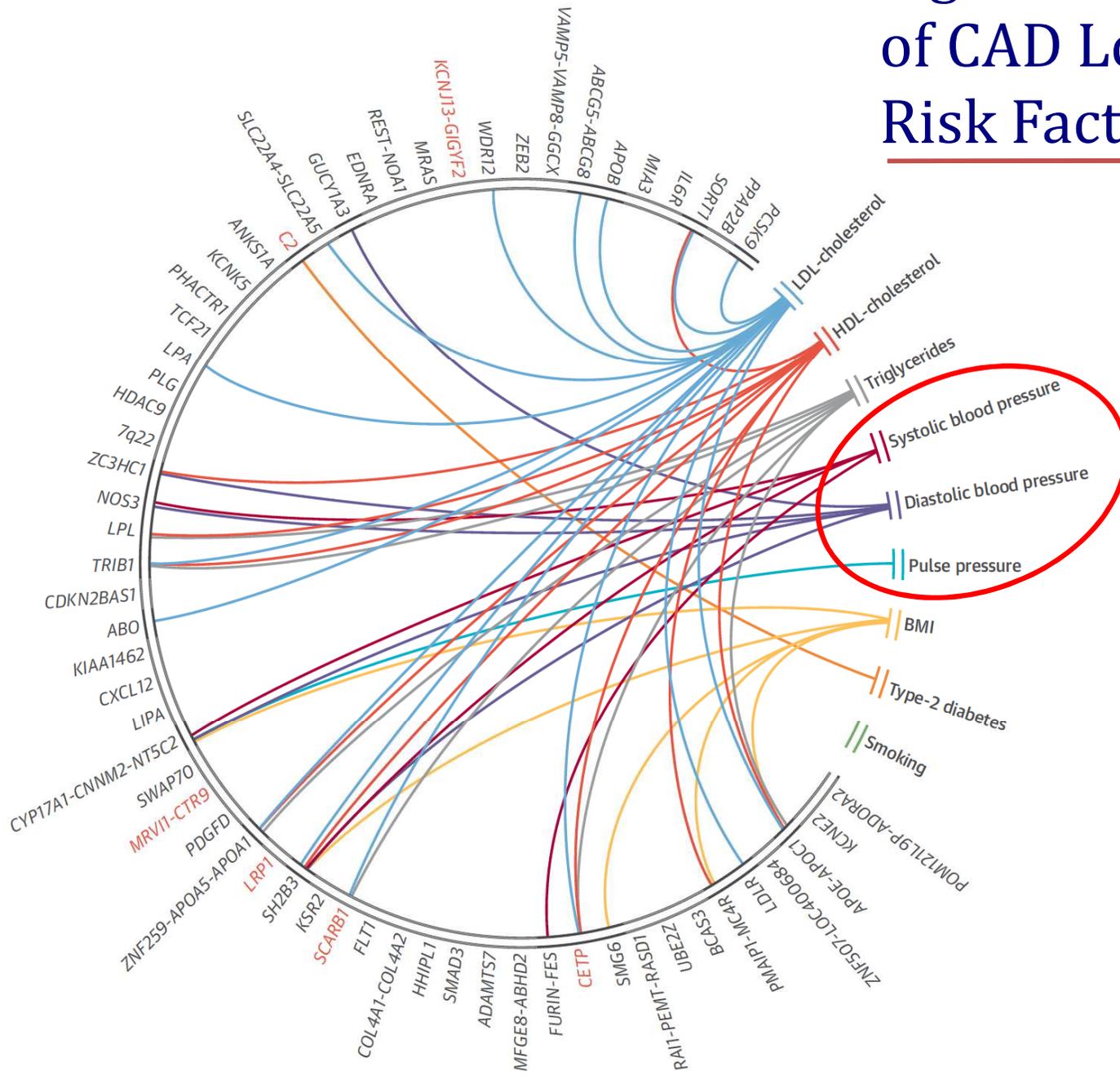


# Hypertension as a risk factor for heart disease

Combined effects of SBP and total cholesterol on the risk of CHD



# Significant Associations of CAD Loci With Cardiovascular Risk Factors



42,335 CAD cases

78,240 control

29,383 common SNPs

Out of 62 CAD loci,

**10 associated with BP**

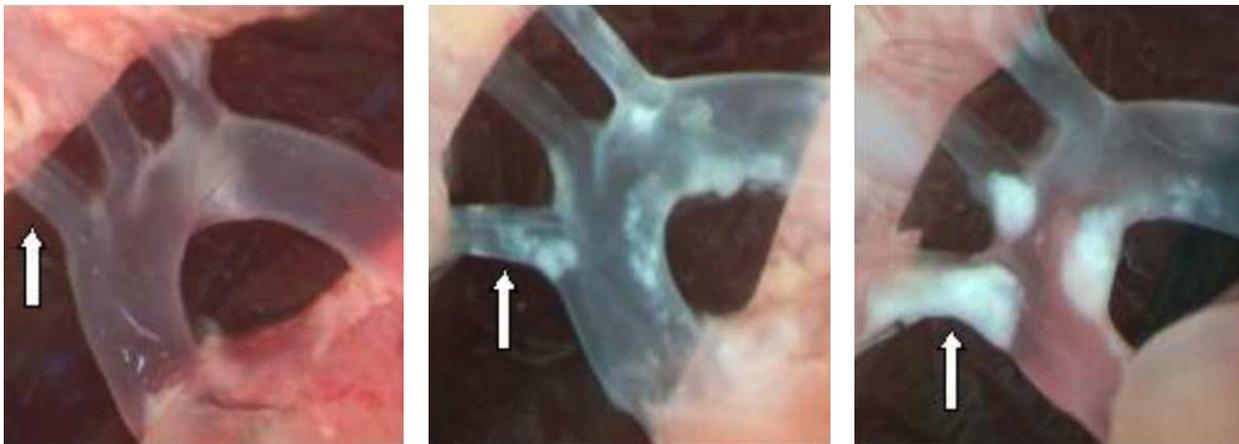
Webb, T.R. et al.

*J Am Coll Cardiol.* 2017;69(7):823–36.

# Hypertension exacerbates atherosclerotic plaque formation

Hypercholesterolemic ApoE<sup>-/-</sup> mice 4 weeks after surgery

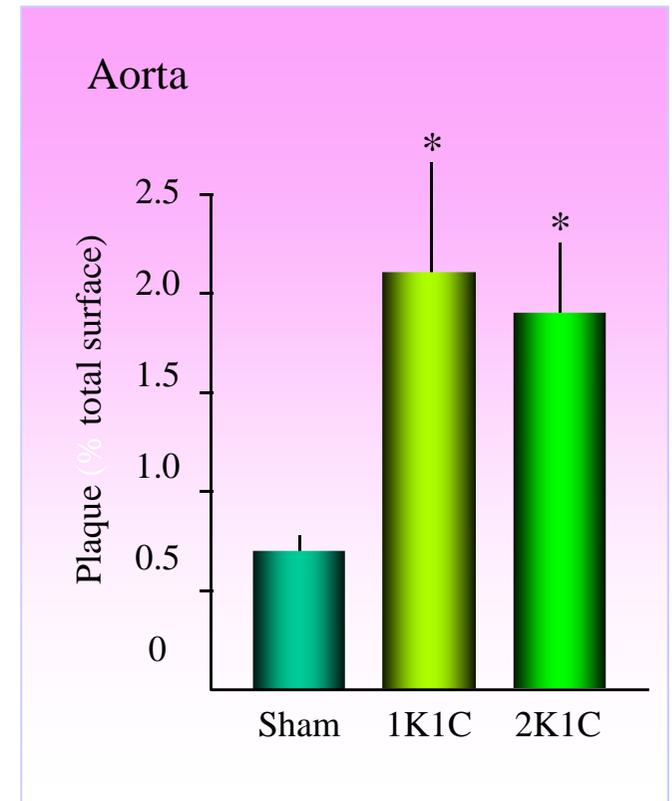
## Brachiocephalic artery



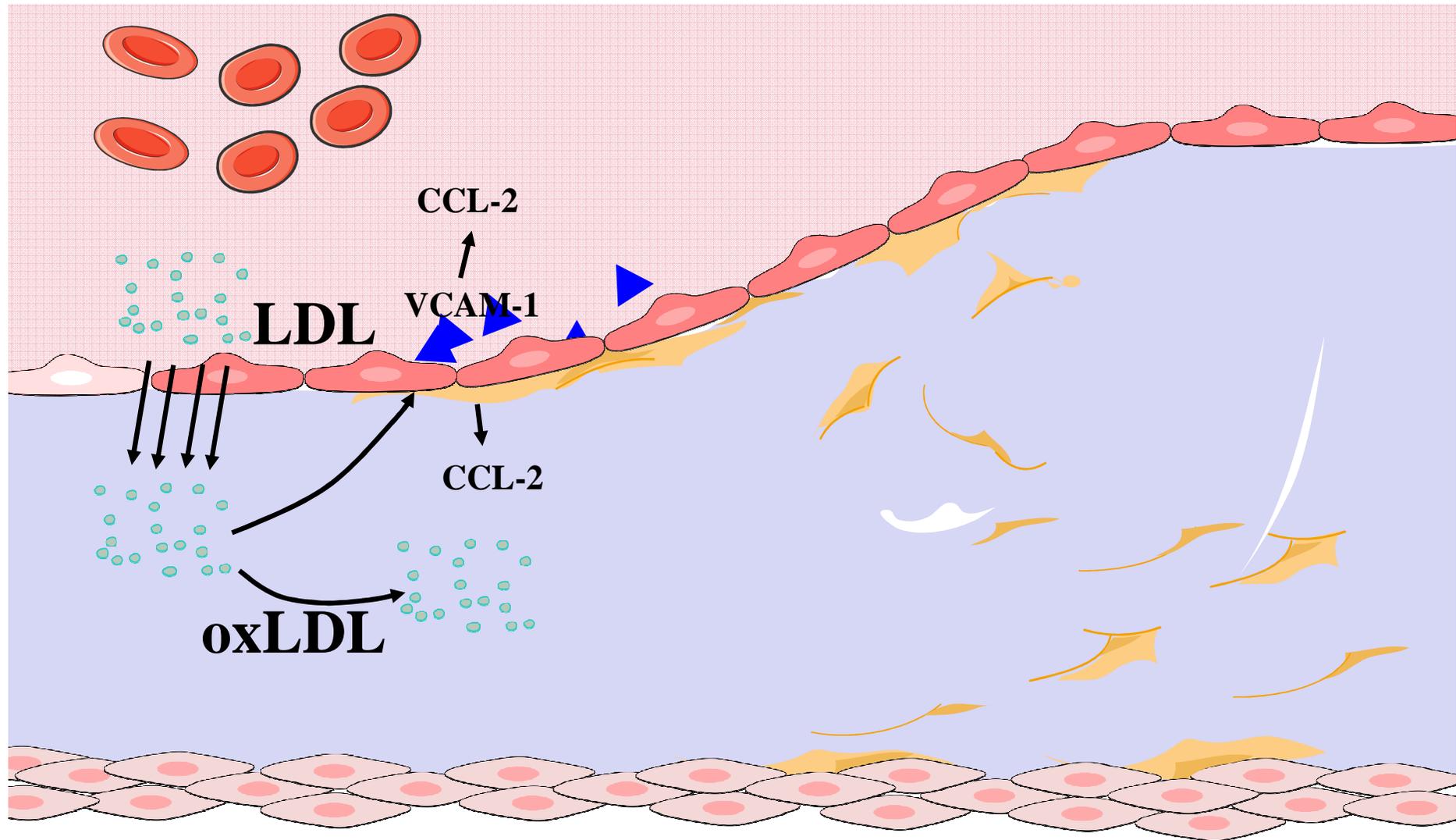
Sham

1K1C

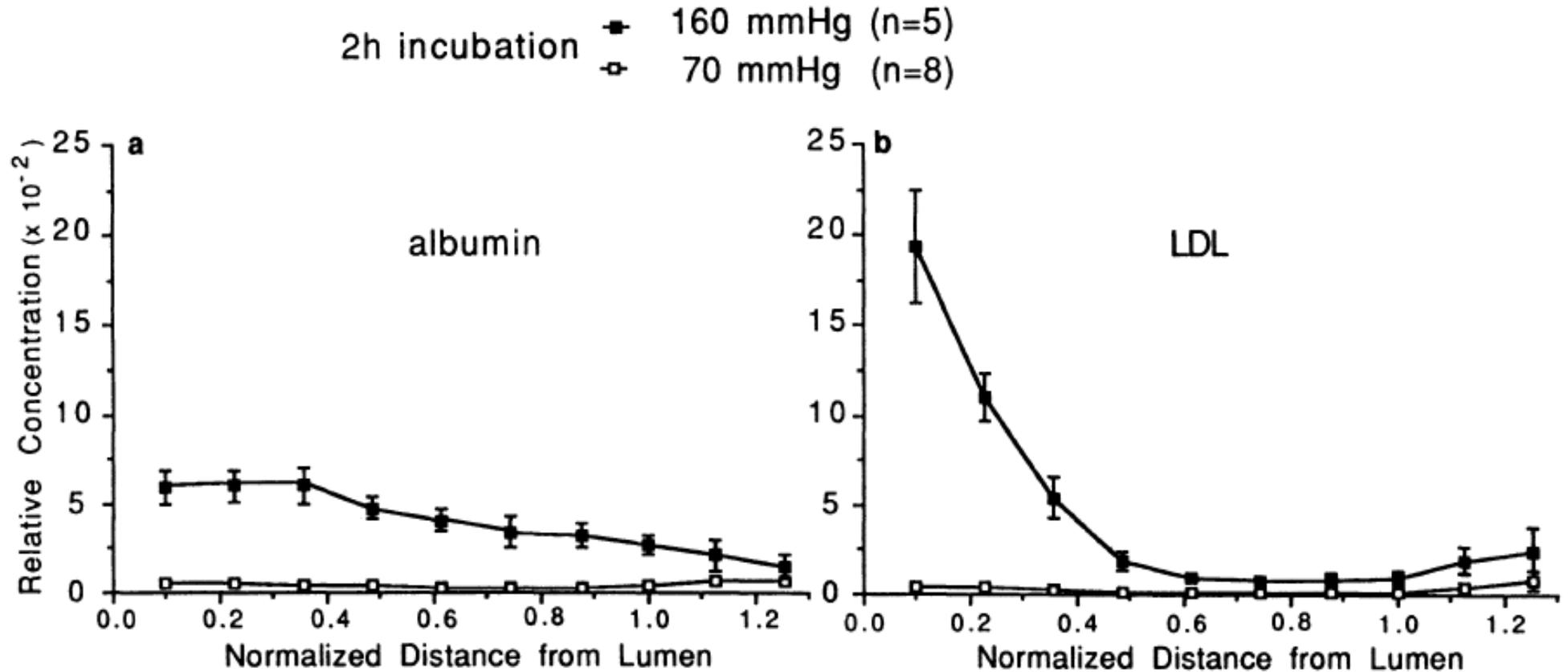
2K1C



# LDL accumulation in the intima

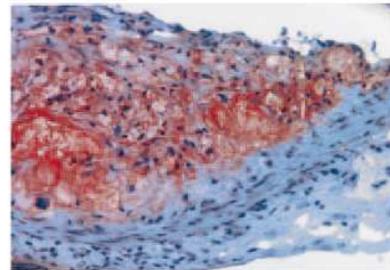


# LDL Retention in the Inner Wall of Large Arteries

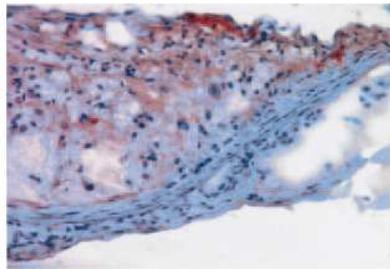


Angiotensin II, the link between  
hypertension and atherosclerosis?

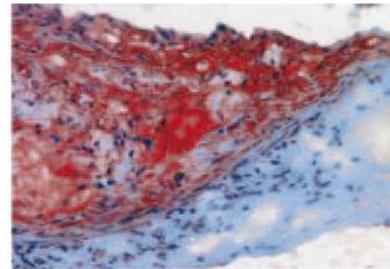
# Hypercholesterolemia activates the renin-angiotensin system



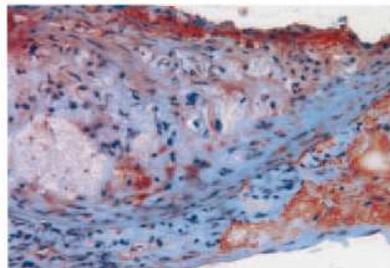
A. Macrophage



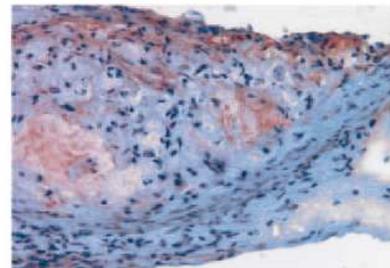
B. Angiotensinogen



D. ACE



C. Renin

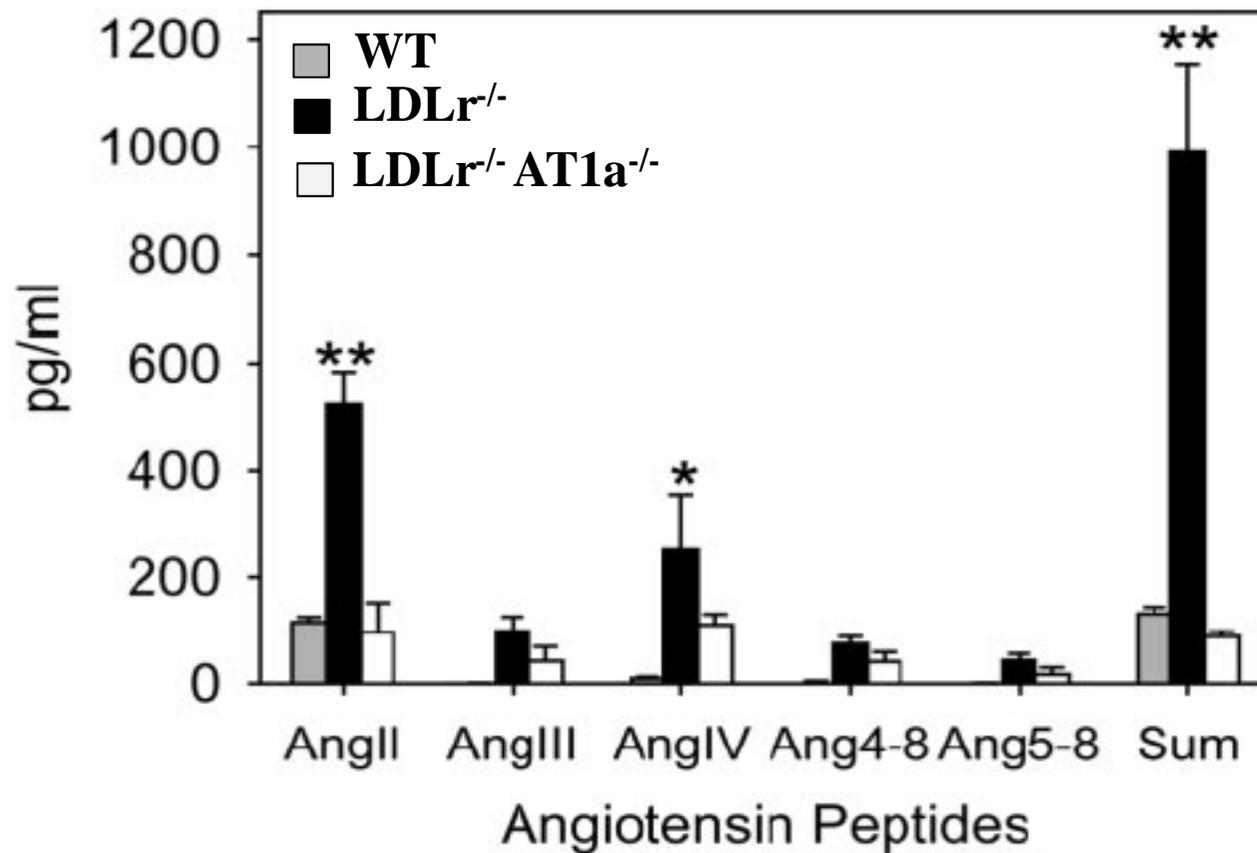


E. Angiotensin peptides  
**Ang II, II, IV**

All components for angiotensin peptide synthesis are present in atherosclerotic lesions, associated predominantly with macrophages

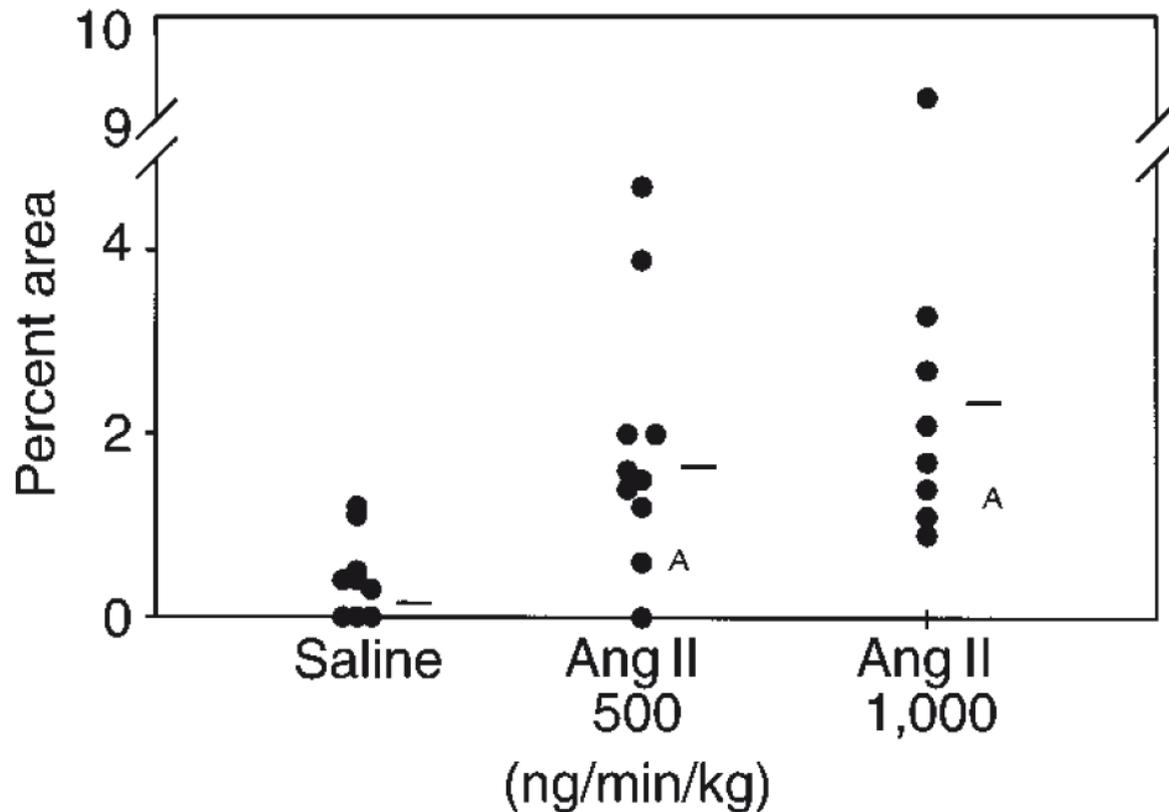
# Hypercholesterolemia activates the renin-angiotensin system

## Circulating angiotensin peptides

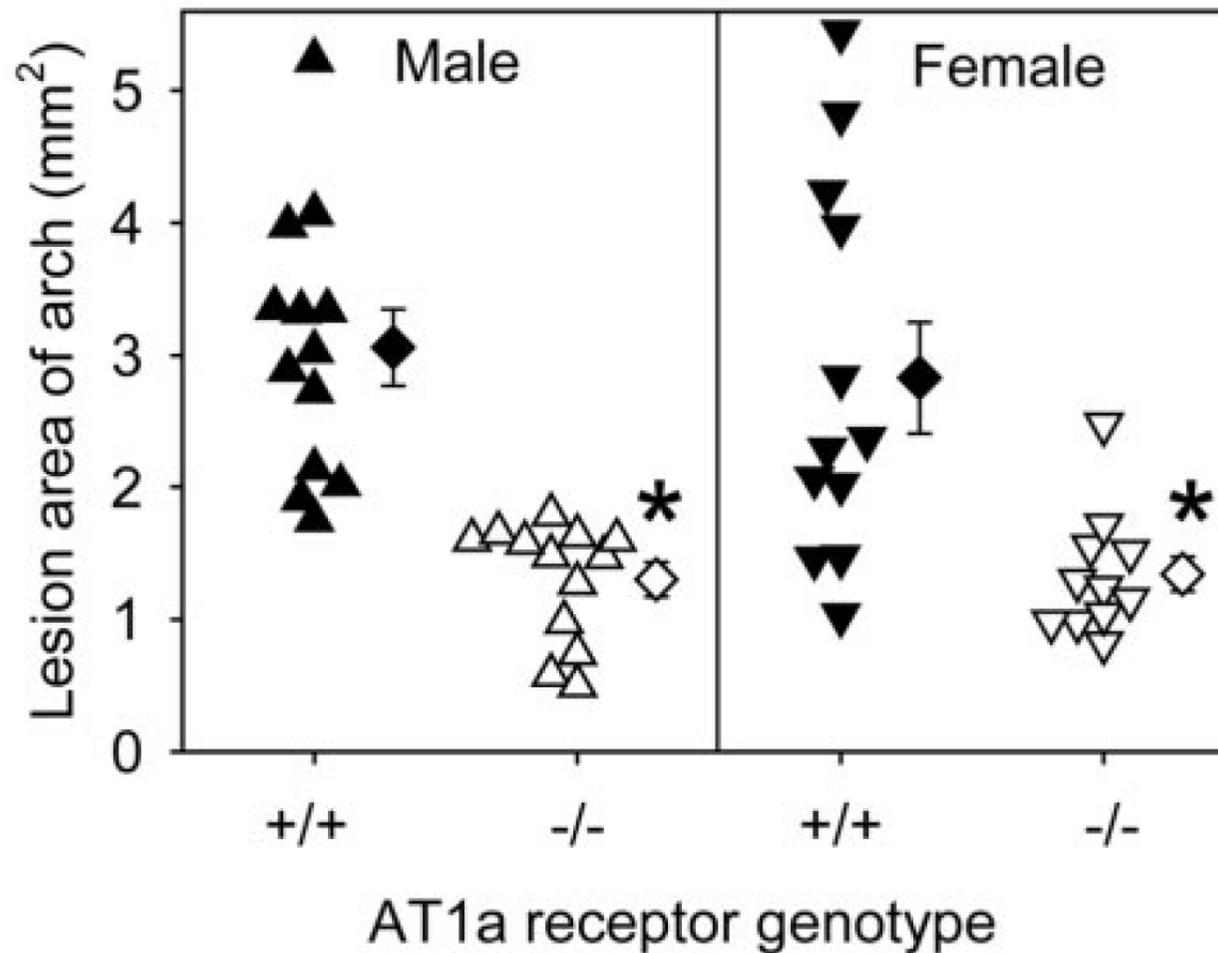


# Angiotensin II promotes atherosclerosis and aneurysms in apoE<sup>-/-</sup> mice

## Atherosclerotic lesions in the thoracic aorta

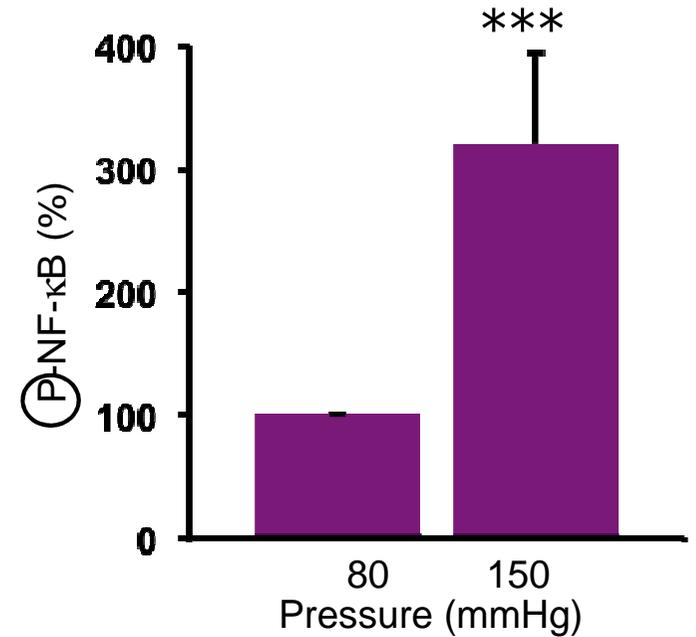
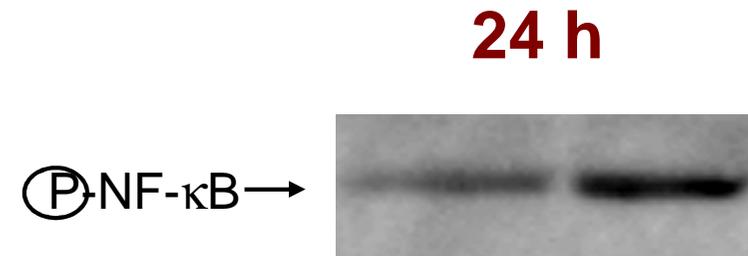
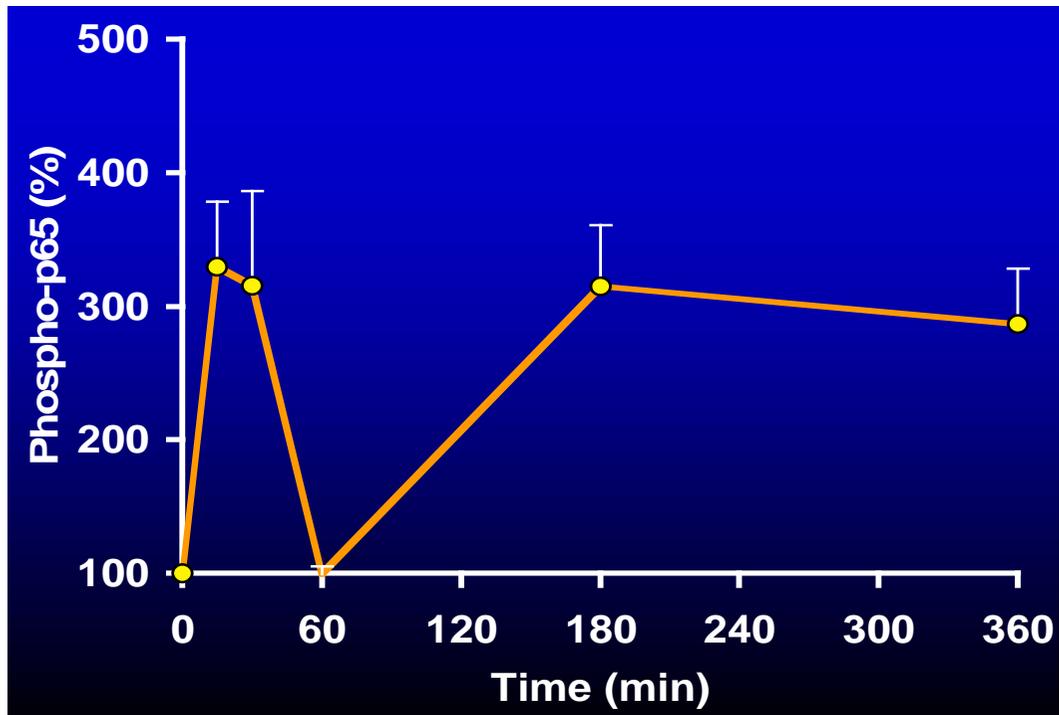
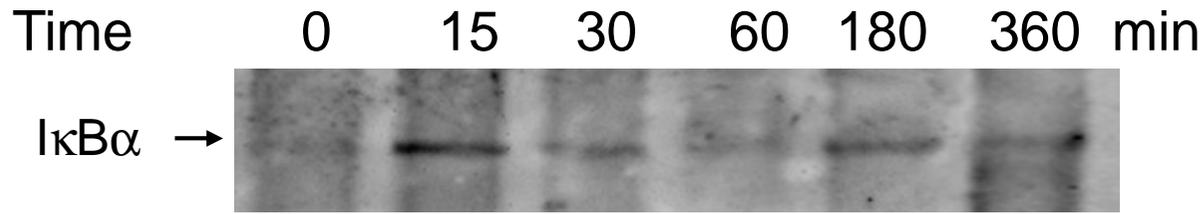


# Atherosclerosis is attenuated in AT1a receptor-deficient LDLr<sup>-/-</sup> mice

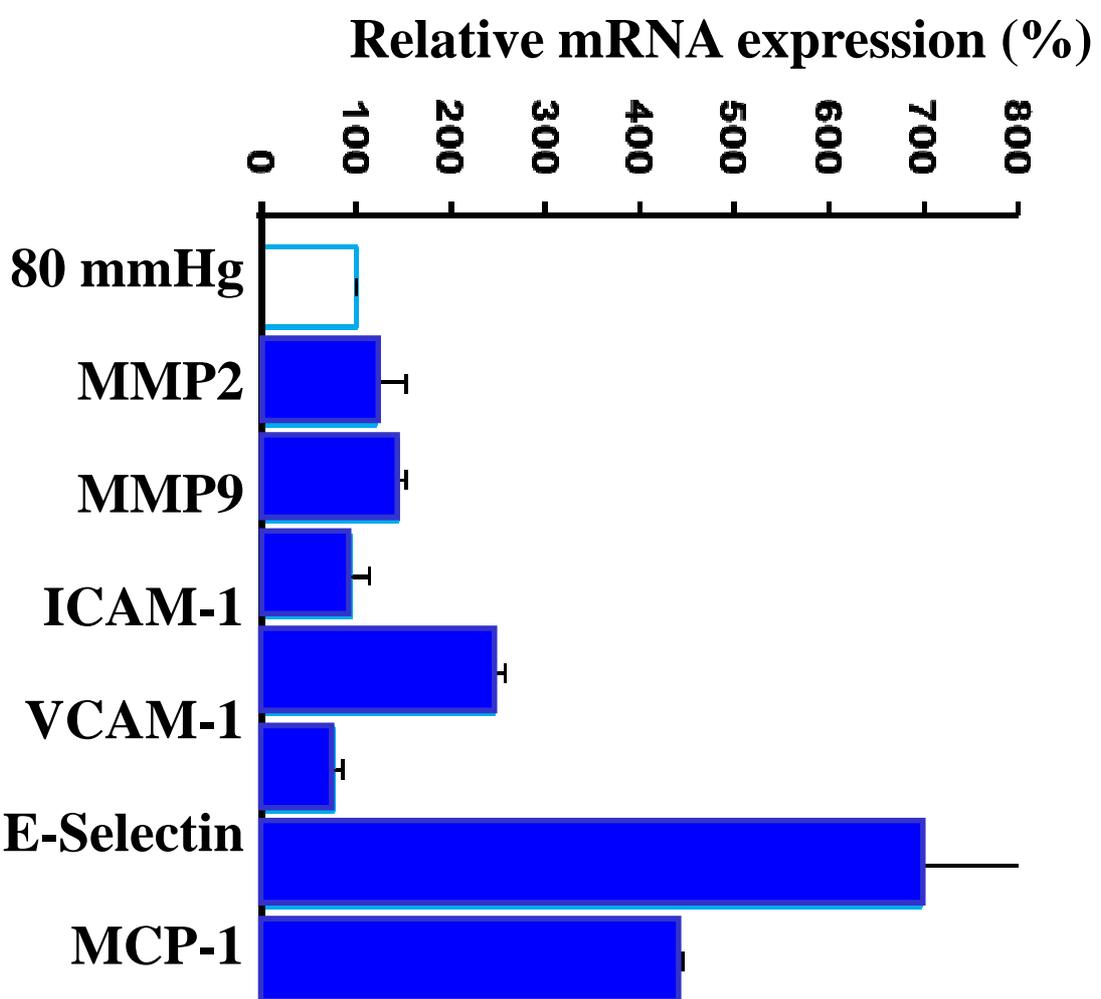


- I. Atherosclerosis & Vessels
- II. Atherosclerosis & Lipids
- III. Atherosclerosis & Inflammation
- IV. Atherosclerosis & Hypertension
- V. Hypertension & Inflammation**

# Activation of NF- $\kappa$ B by high intraluminal pressure

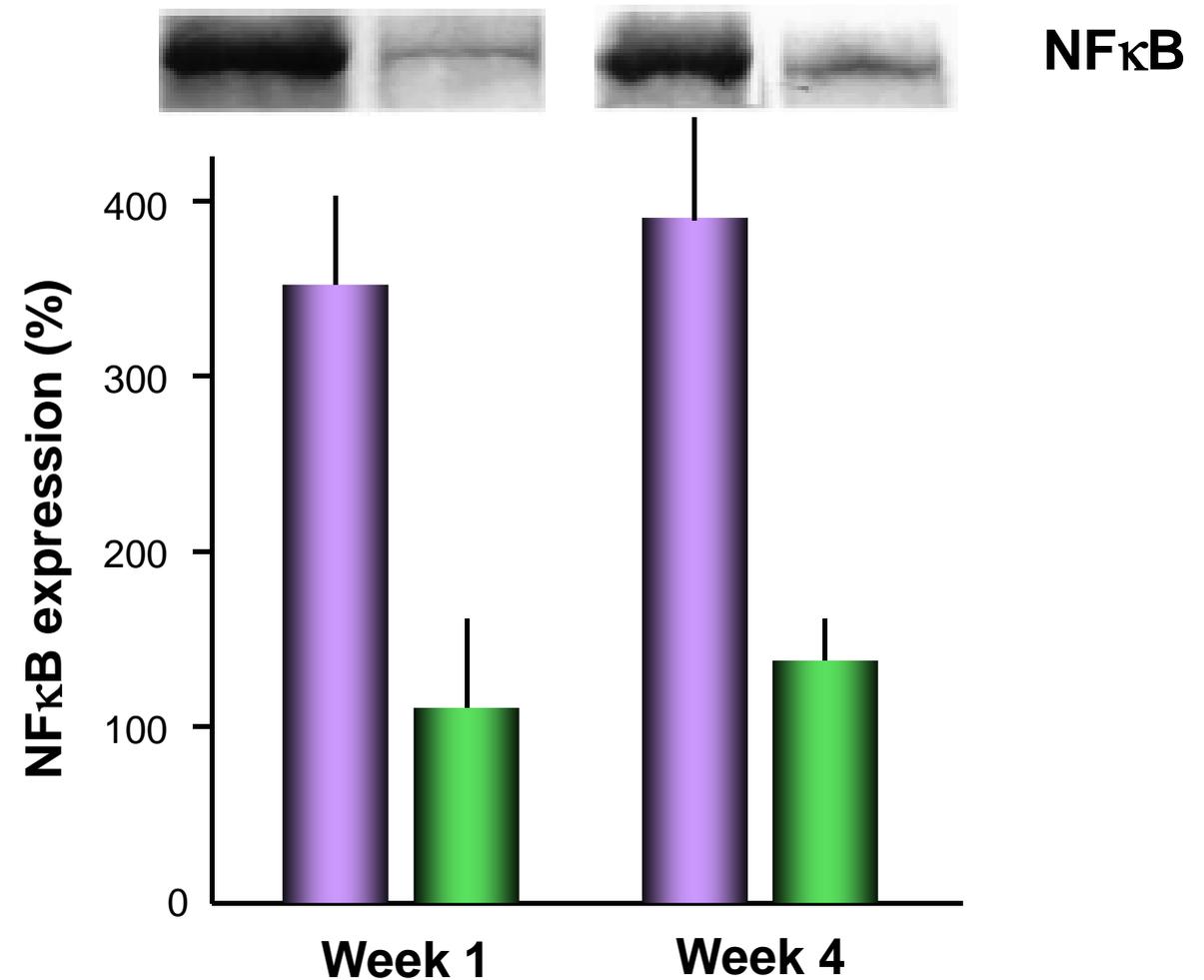


# High intraluminal pressure activates vascular inflammatory genes



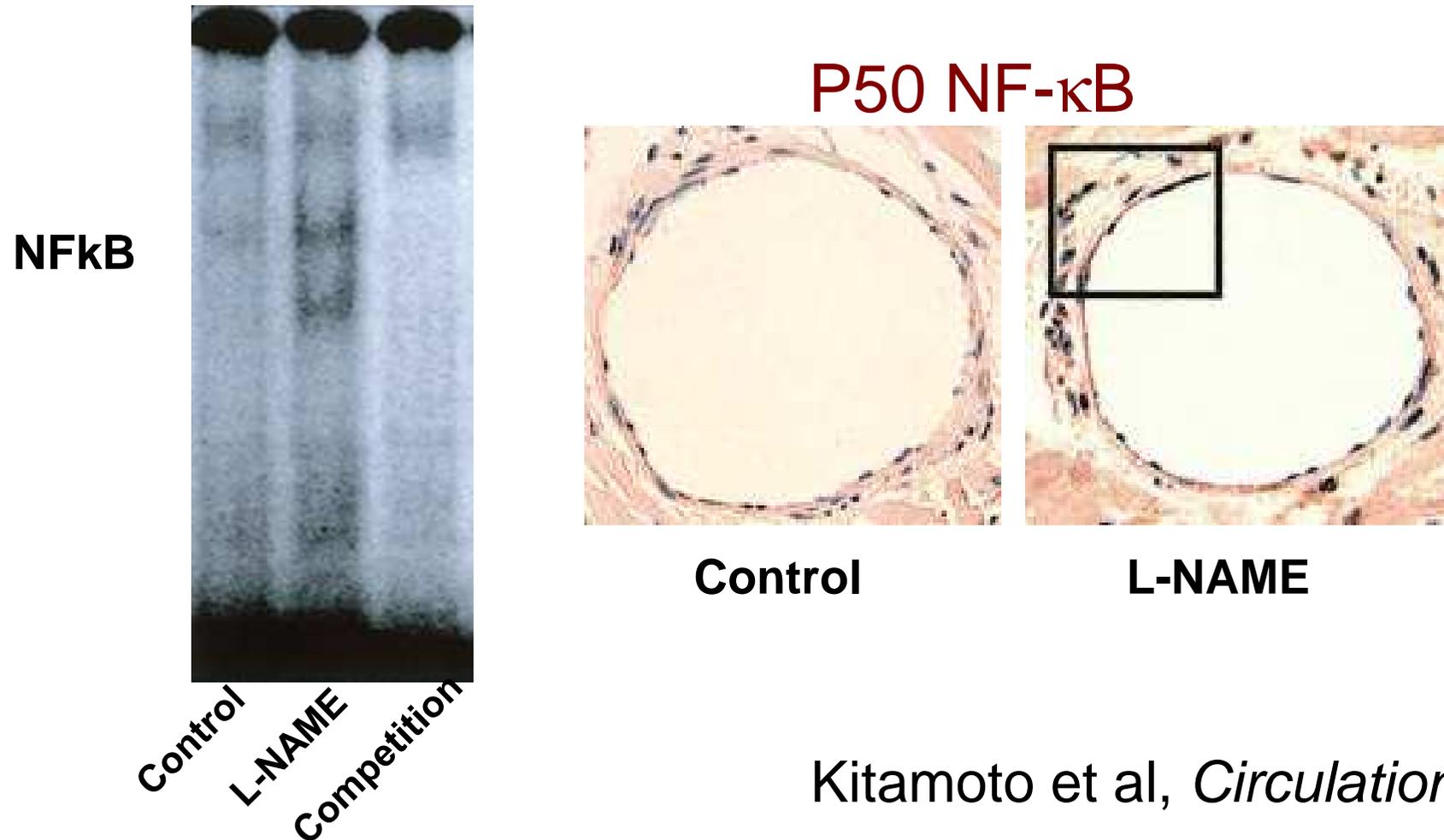
# NF $\kappa$ B expression in hypertension

## Rat model of aortic stenosis



# Activation of NF- $\kappa$ B by high intraluminal pressure

## L-NAME-induced hypertension in rats



Kitamoto et al, *Circulation* 2000

# Adhesion molecules are induced by hypertension

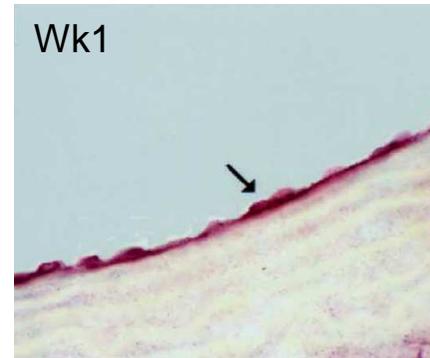


Pressure (mmHg)      All (pg/ml)

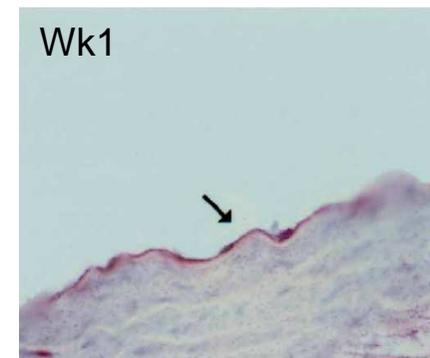
$160 \pm 5$        $124 \pm 28$

**ICAM**

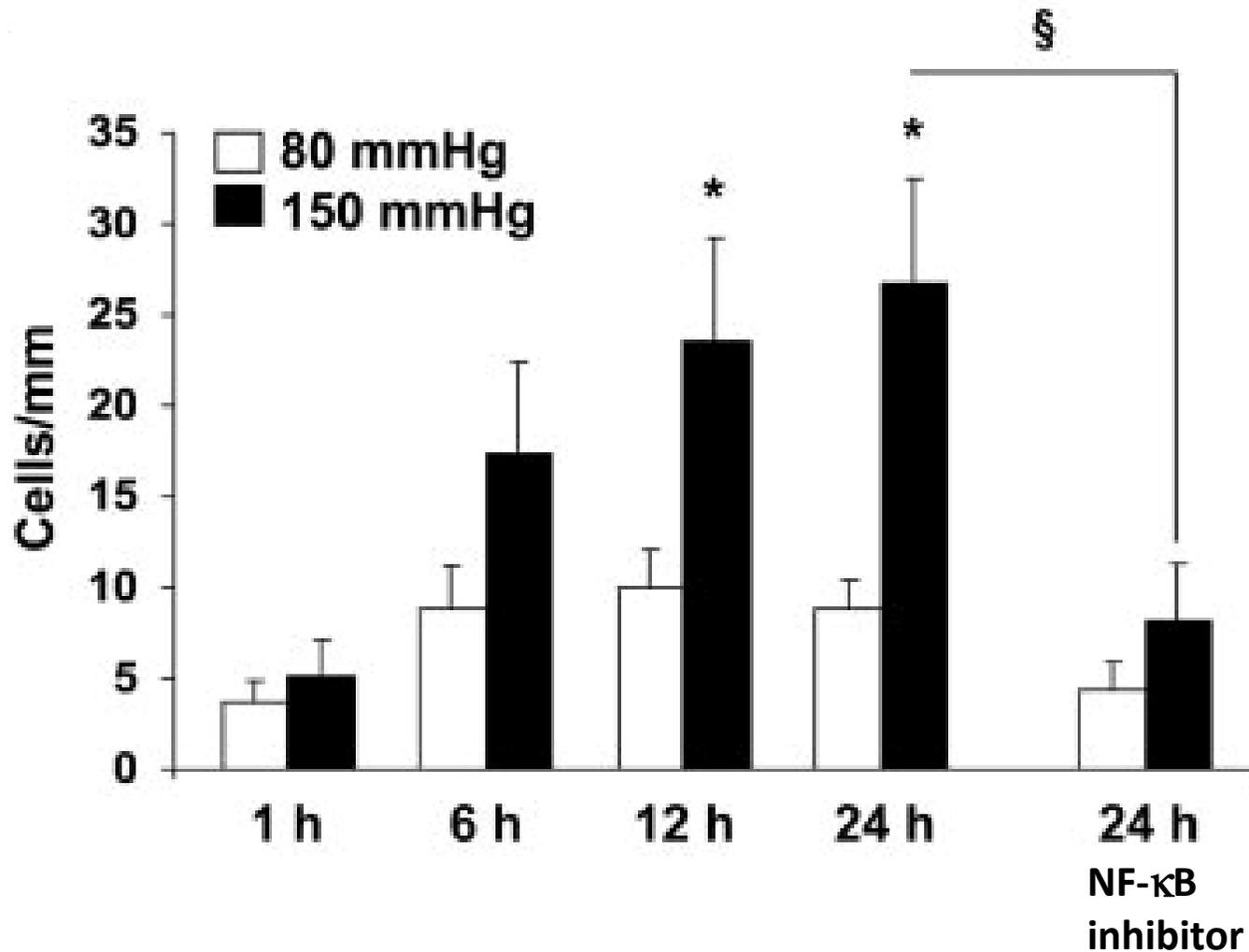
**P-Sel**



$111 \pm 10$        $124 \pm 28$



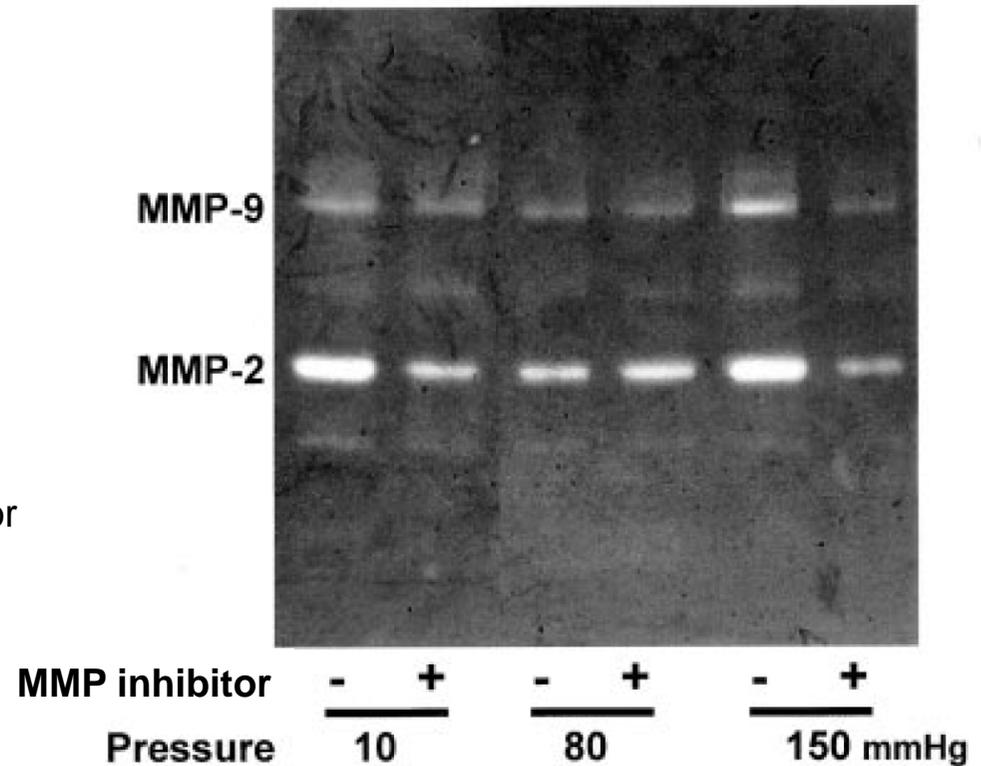
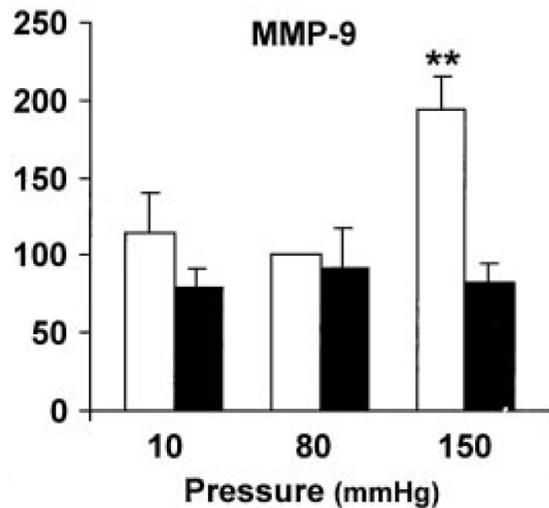
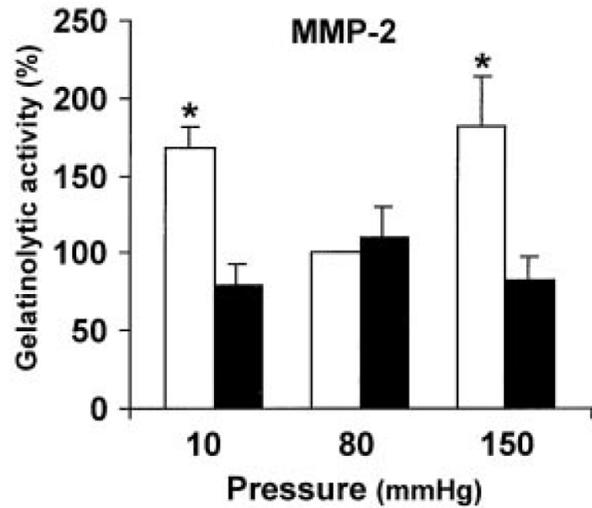
# High intraluminal pressure increases endothelial monocyte adhesion via NF- $\kappa$ B



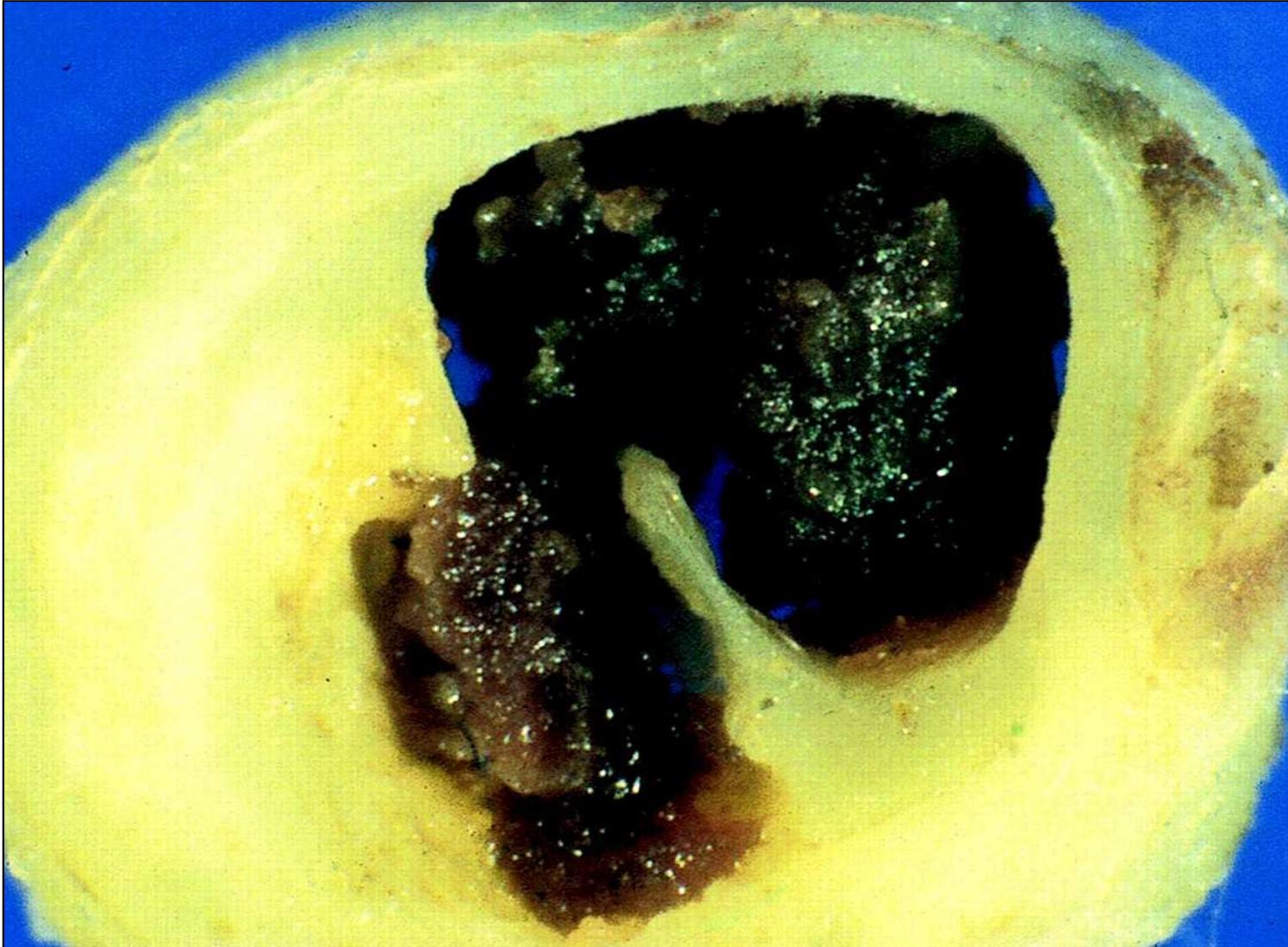
# Hypertension & Plaque Rupture

# Hypertension Induces MMP-2 and MMP-9

Mouse carotid arteries maintained in organ culture for 3 days



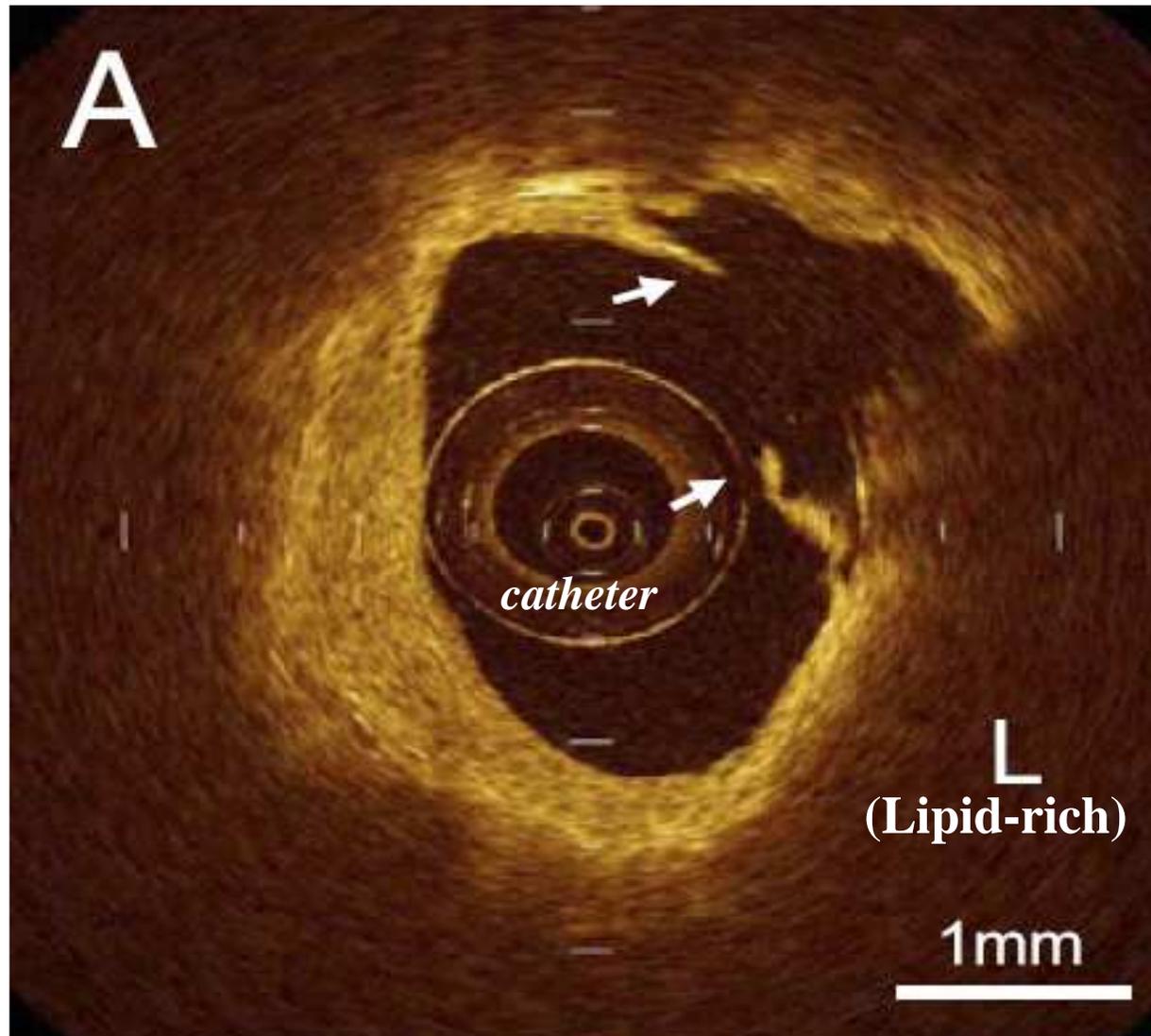
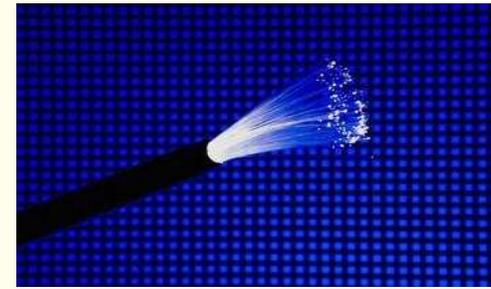
# Plaque Rupture Causes Myocardial Infarction



Davies, MJ  
*Heart* 2000;  
83:361-6

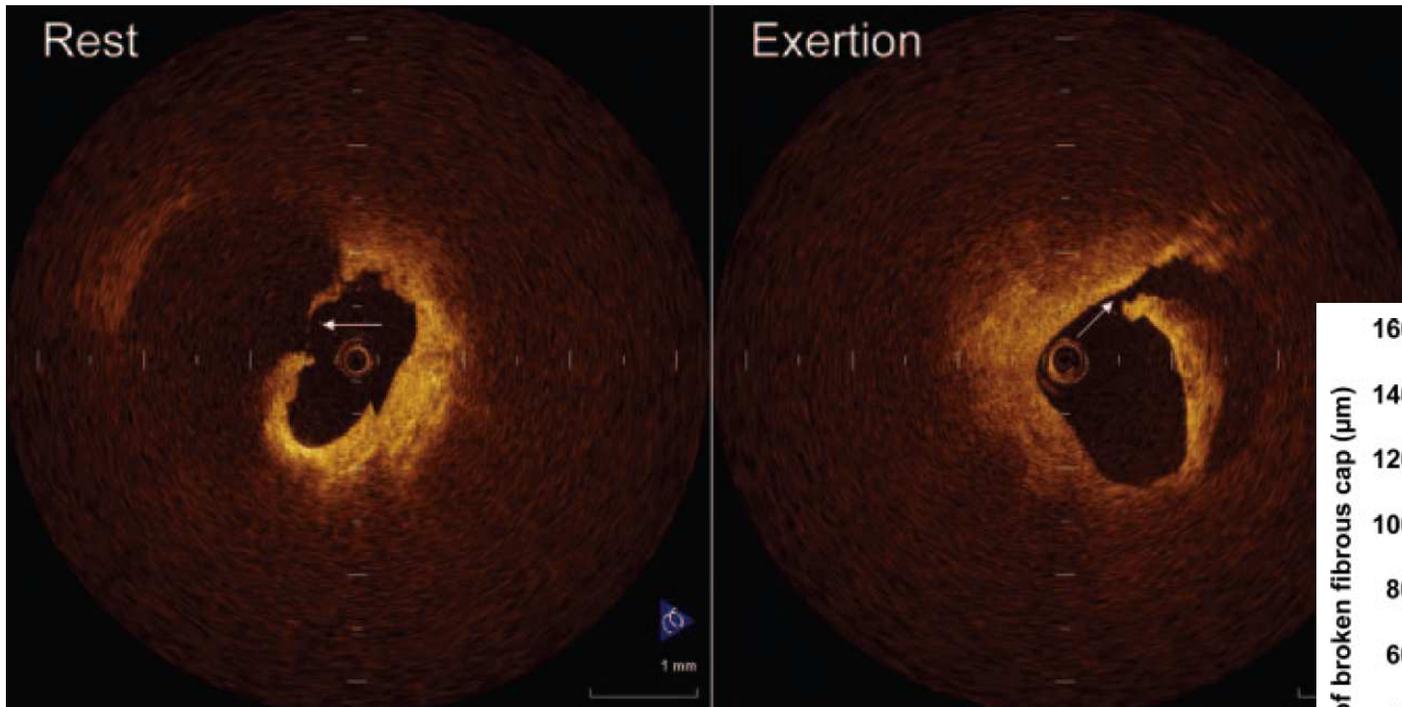
# Assessment of Culprit Lesion Morphology in Acute Myocardial Infarction

Ability of **Optical Coherence Tomography** Compared  
With Intravascular Ultrasound and Coronary Angioscopy

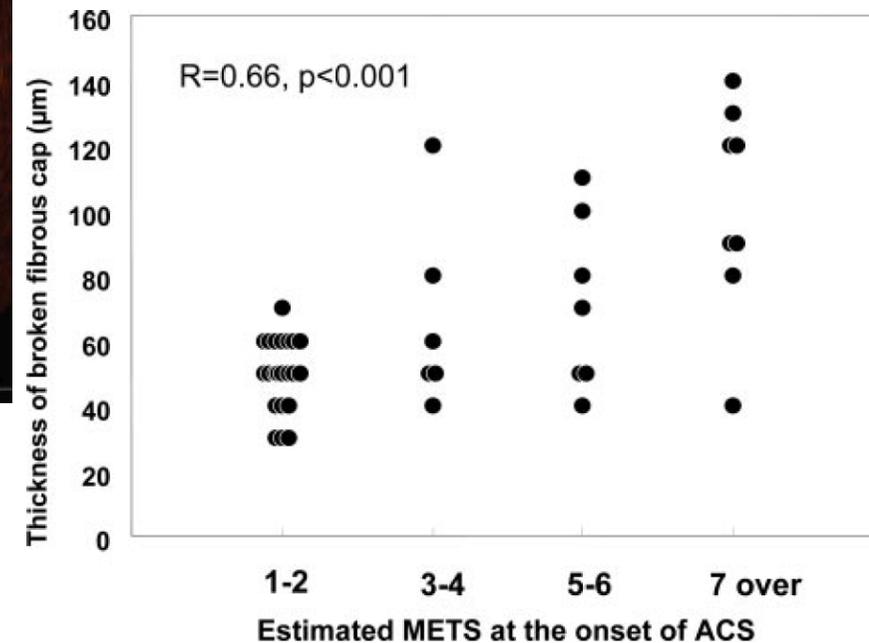


Kubo et al. *JACC* 2007 50:933-9

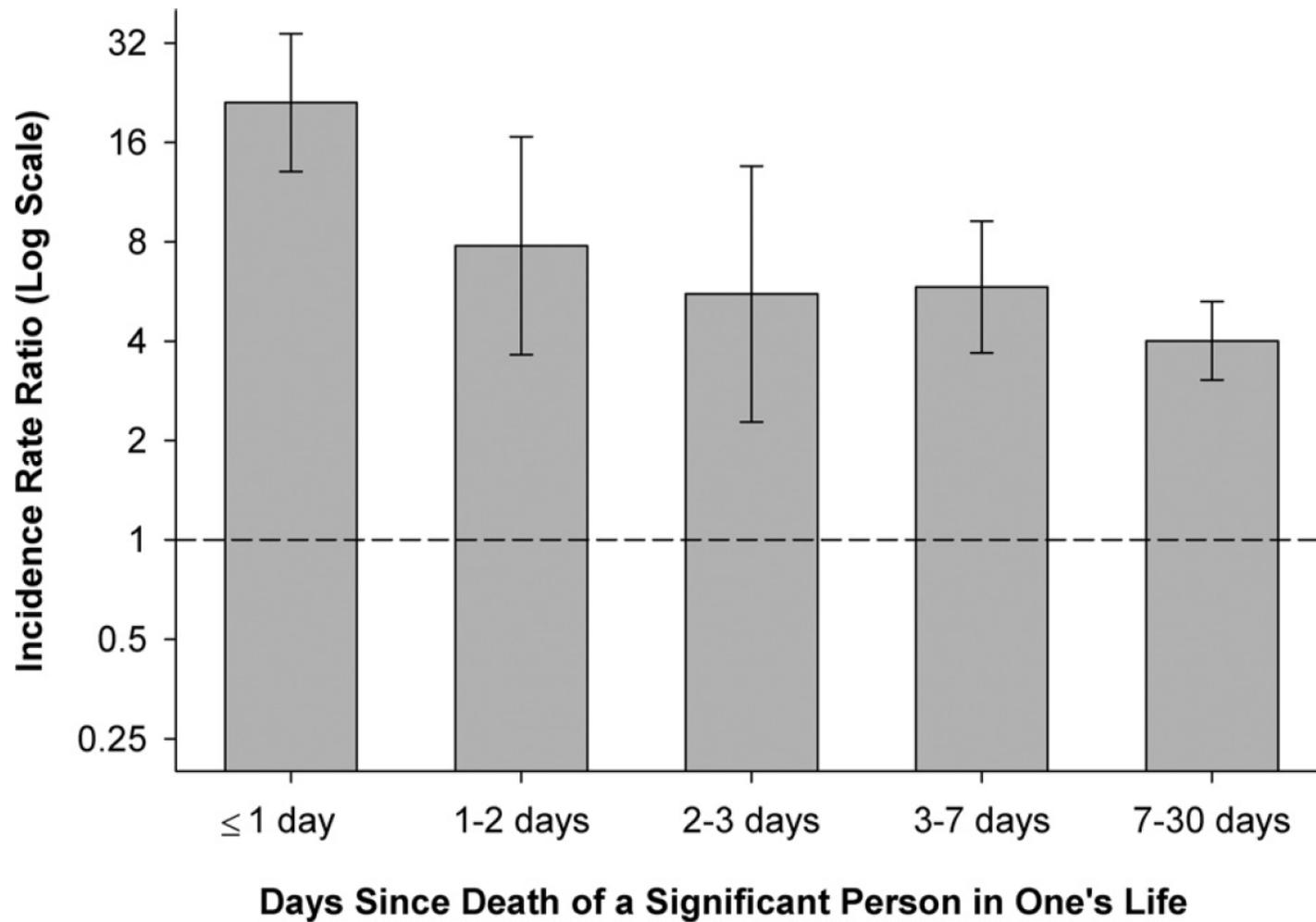
# Morphology of Exertion-Triggered Plaques in Patients with Acute Coronary Syndrome



Thickness of the broken fibrous cap in the exertion group was significantly higher than in the rest-onset group (rest onset: 50  $\mu\text{m}$ ; exertion: 90  $\mu\text{m}$ ,  $P < 0.01$ ).



# Risk of Acute Myocardial Infarction After the Death of a Significant Person in One's Life



Mostofsky et al. *Circulation* 2012;125:491-496.

# Cardiovascular Events during 2006 World Cup Soccer

