

# Role of Inflammation in CAD

? Atherosclerosis  
is inflammatory disease

# Inflammation and Atherosclerosis

- Atherosclerosis pathogenesis
- Case review
- Inflammatory markers
- Clinical study

# Atherosclerosis

- Initiation
- Progression
- Complication

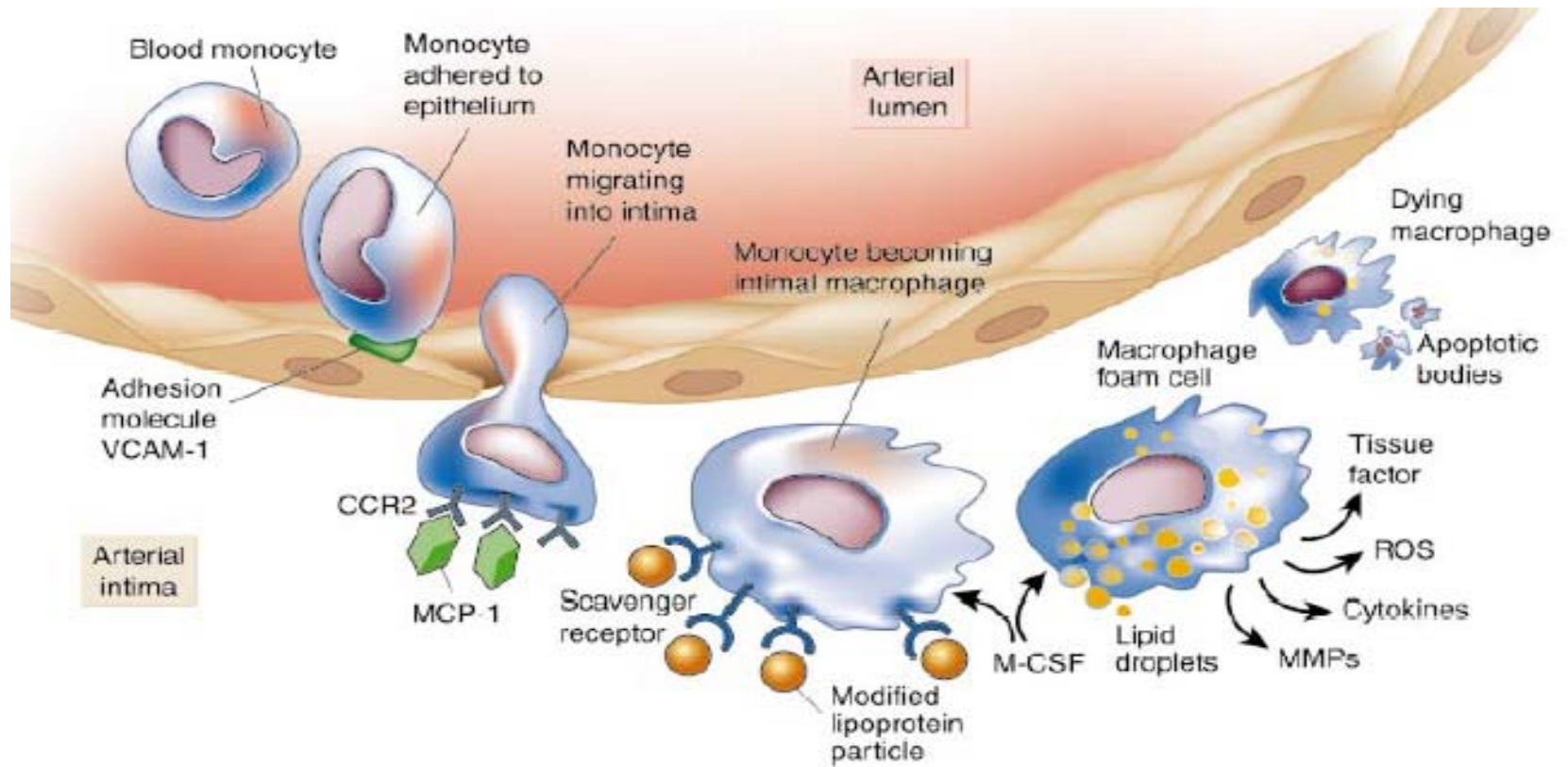
? The role of Inflammation

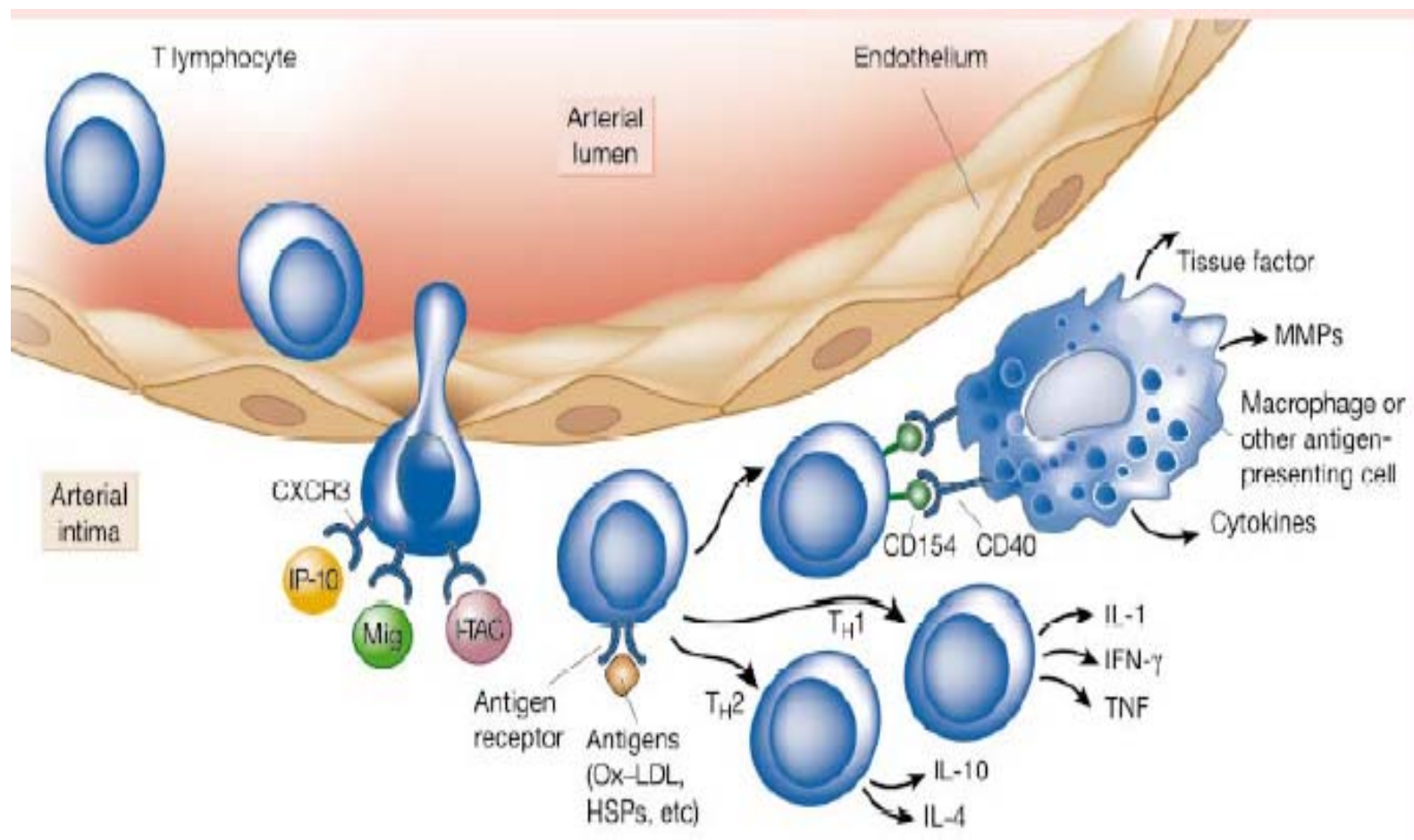
# Initiation of Atherosclerosis

- Modified lipoprotein particle (oxidized phospholipids, short chain aldehydes)
- IL - 1 beta and TNF - alpha
- VCAM - 1
- Leukocyte adhesion and recruitment

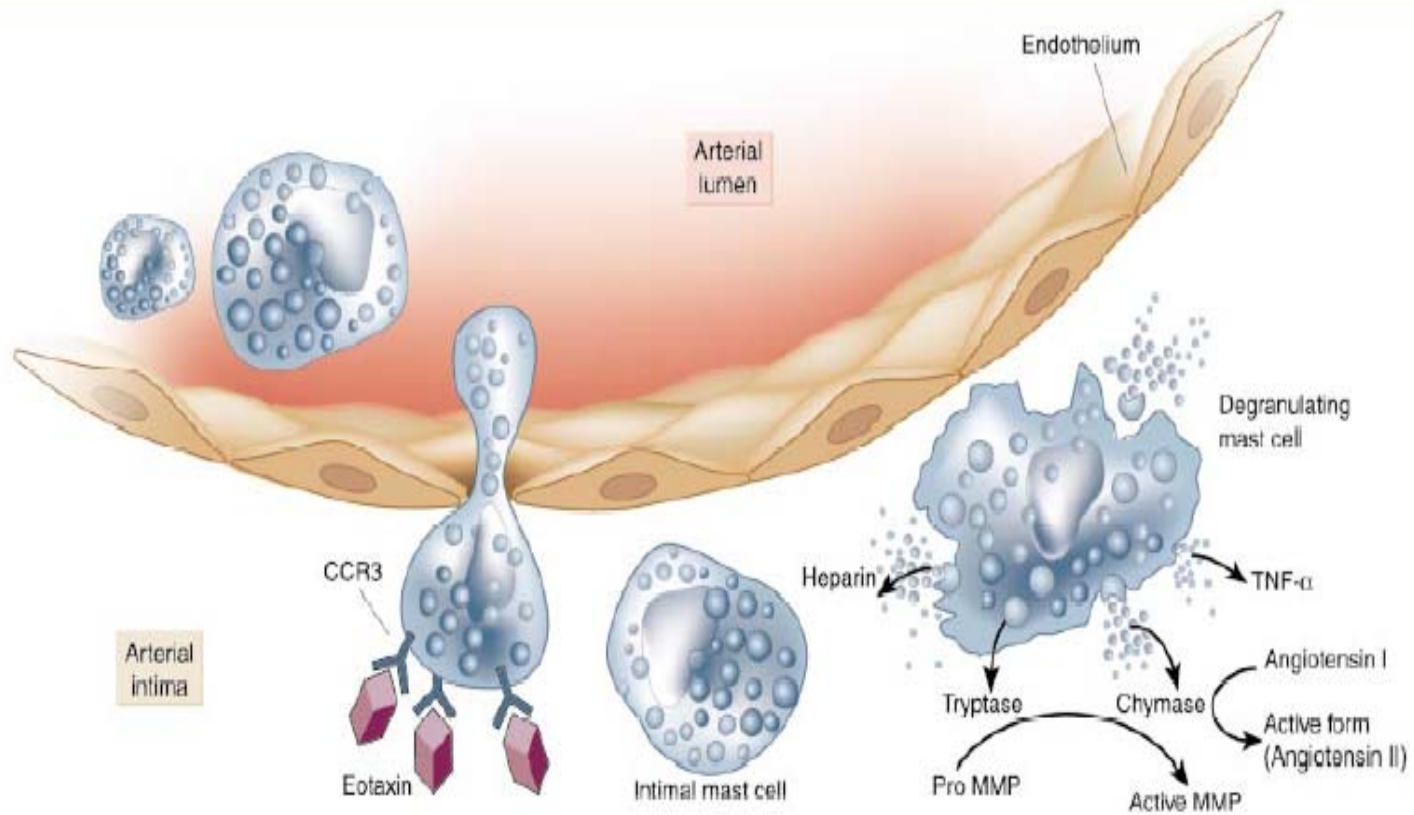
# Initiation of Atherosclerosis

- Monocyte
- T-lymphocyte
- Mast cell







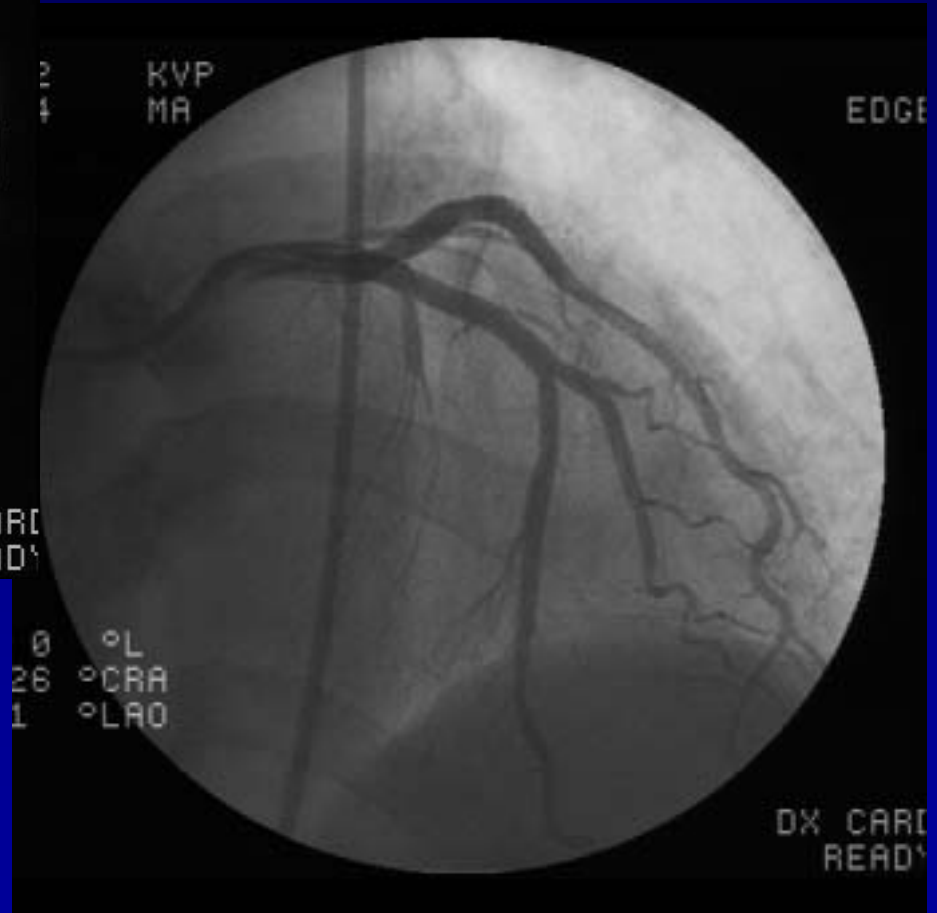
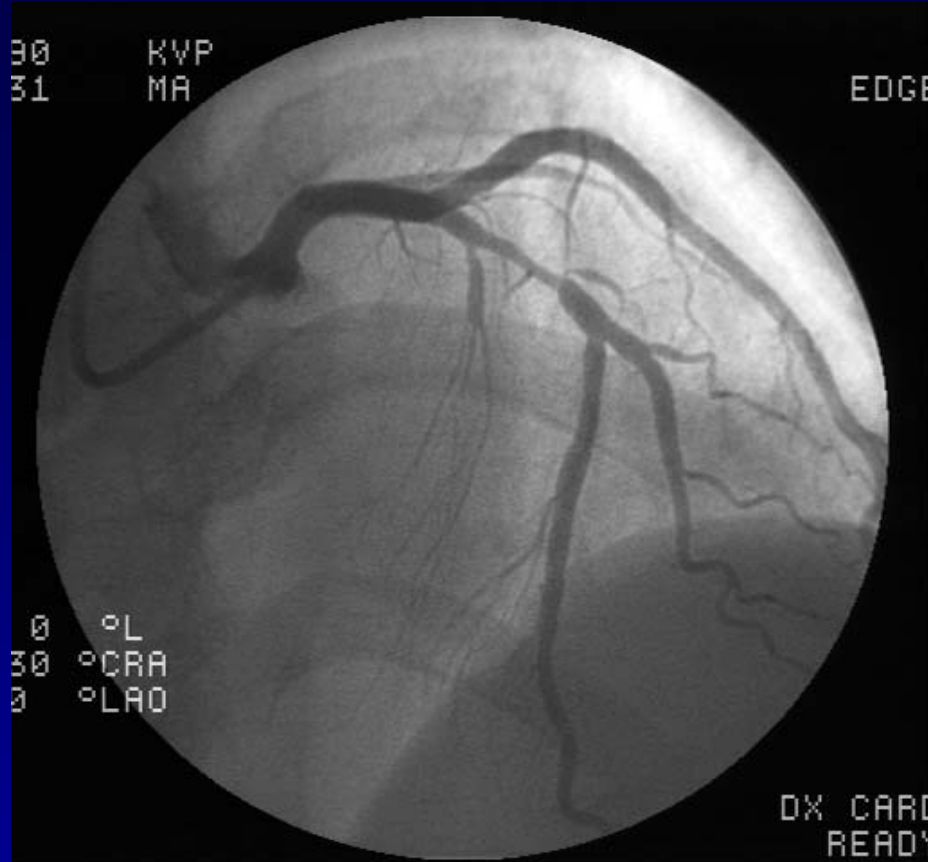


# Progression and Complication of Atherosclerosis

- Fatty streak
- Smooth muscle cell proliferation
- Abundant extracellular matrix
- Gradually progressive

# New concept

- Plaque disruption
- Discontinuous progression
- Well established in the serial CAG
- Sudden expansion of atheromatous plaque



# Physical disruption and thrombosis

- Superficial erosion :  $\frac{1}{4}$  of fatal coronary event
- Disruption of microvessels
- Fracture of fibrous cap (plaque rupture) :  $\frac{3}{4}$  of fatal

# Superficial erosion

- Inflammatory mediators and oxidized lipoprotein : MMPs expression and activation
- Endothelial cell death by Inflammatory mediators and killer T - cell

# Microvessel formation in Atheroma

- Acidic and basic fibroblast growth factor
- VEGF
- Hemorrhage in situ and thrombosis
- Blood supply to atheroma

# Fracture of fibrous cap

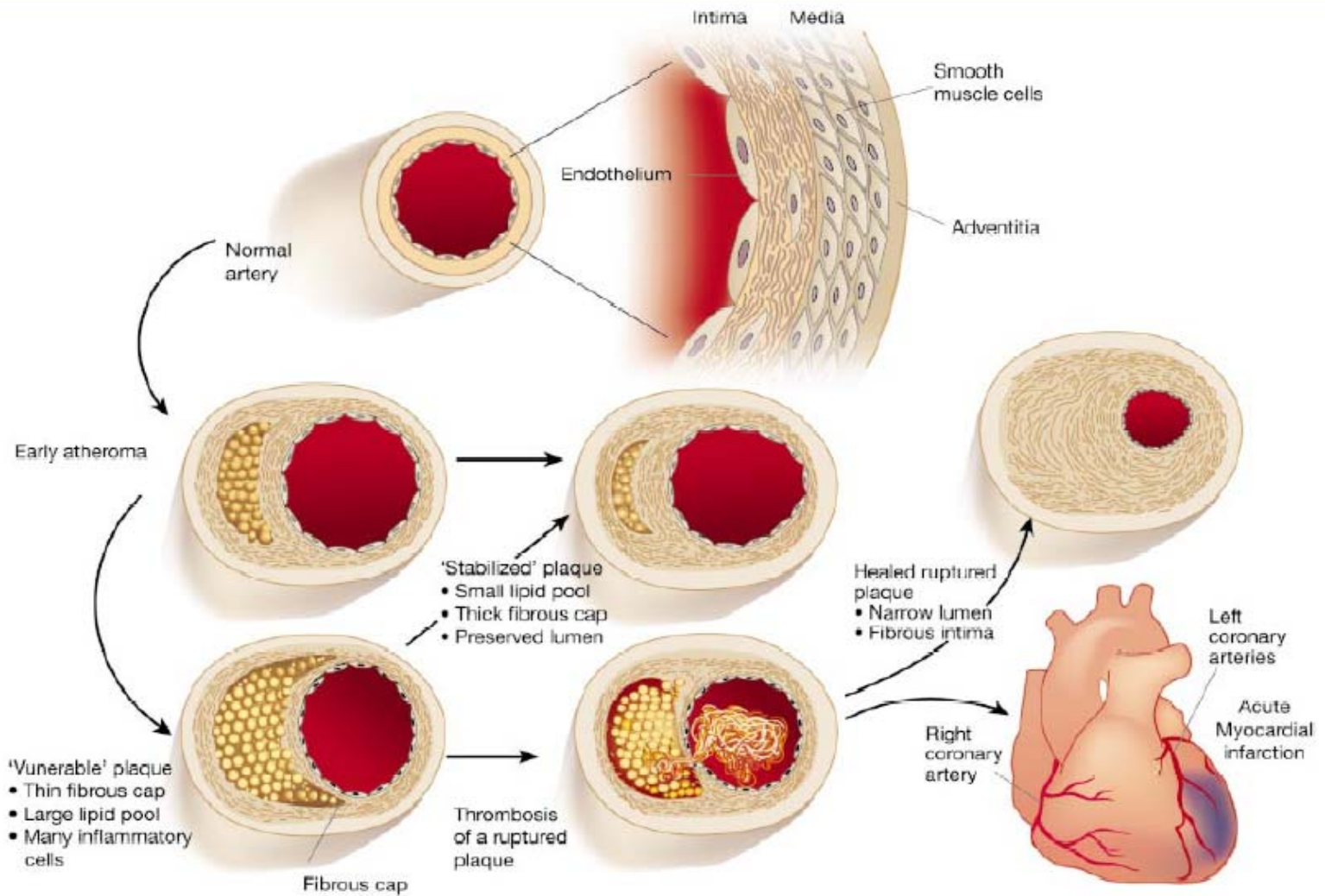
(plaque rupture) : 3/4 of fatal coronary event

- Proinflammatory cytokine; INF- $\gamma$  : inhibit collagen production of SMC
- Interstitial collagenases : MMP-1, -8, -13



# Inflammation and Atherosclerosis

- Initiation of atherosclerosis
- Monocyte, T-cell, and Mast cell recruitment and activation
- Plaque disruption and sudden expansion



# Atheroprotection

- Laminar flow vs. Turbulent flow
- Preferred atherosclerotic plaque site: Branch point
- Superoxide dismutase and NO : inhibit VCAM - 1

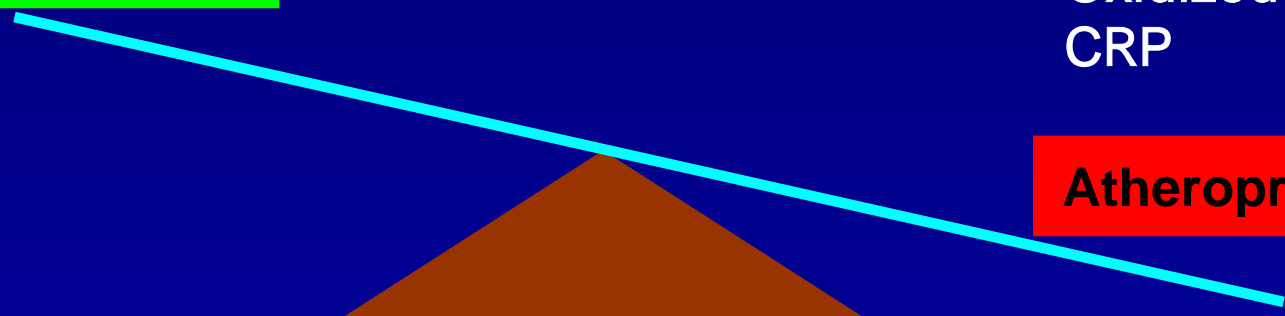
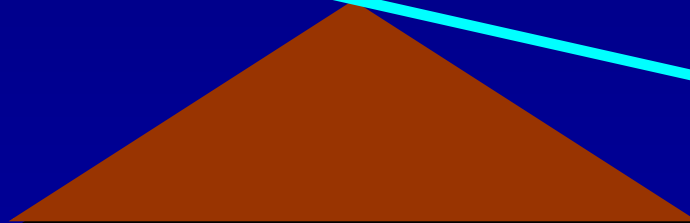
# Protection vs. Progression of Atherosclerosis

Laminar flow  
Superoxide dismutase  
NO

**Atheroprotection**

Turbulent flow  
VCAM - 1  
P - selectin  
E - selectin  
TNF - alpha  
IL - 1 beta  
Oxidized lipoprotein  
CRP

**Atheroproggression**



# Introduction of the case

- 54yr/Male

- **Medical history**

The patient presented with an effort related chest pain for 2 months. Recently, frequency of chest pain was increased and chest pain was developed at rest

- **Risk factors**

Current smoker for 35 years

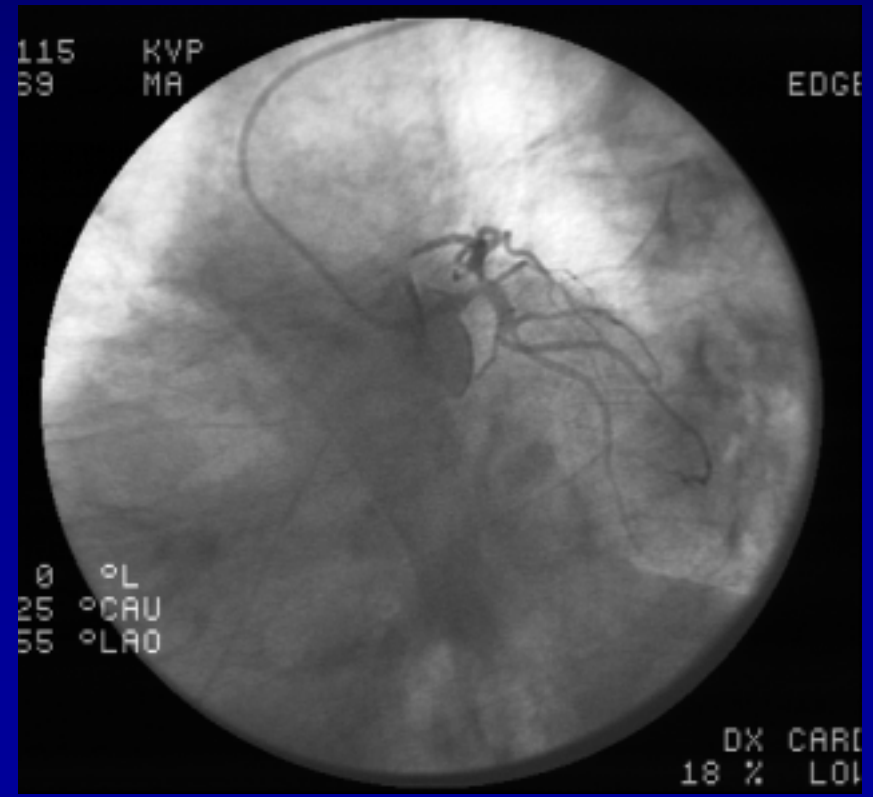
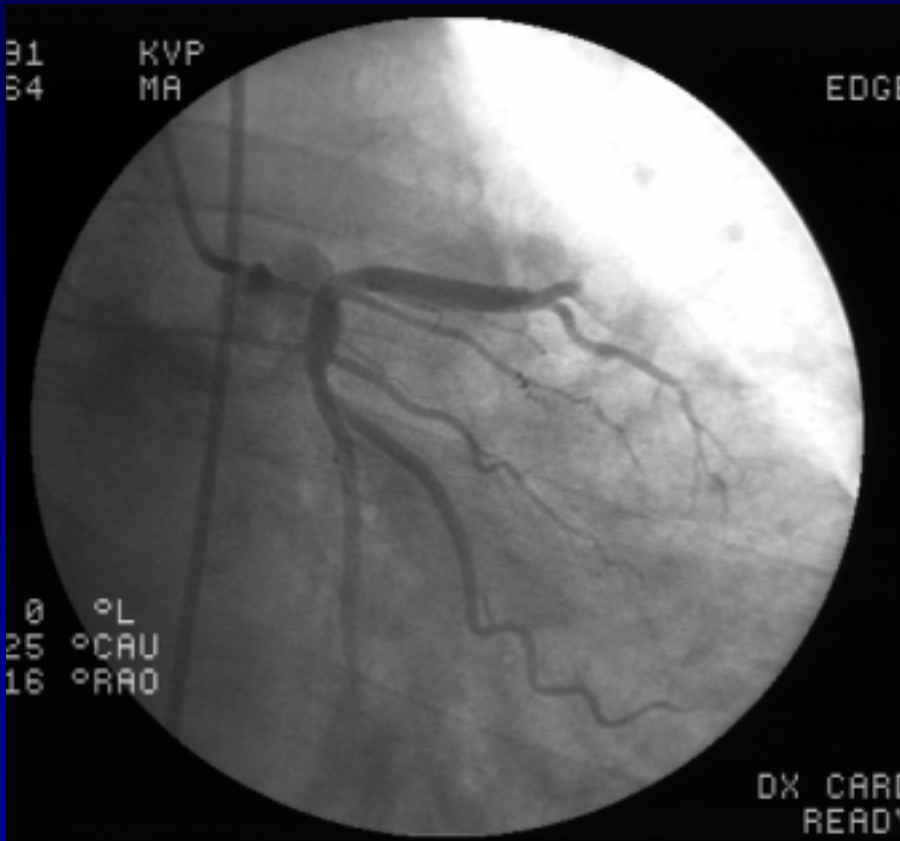
Diabetes (-)

Hypertension (-)

TC/TG/HDL/LDL :204/305/36/123

# Coronary angiography

- Lt. main bifurcation lesion
- LAD ostial stenosis



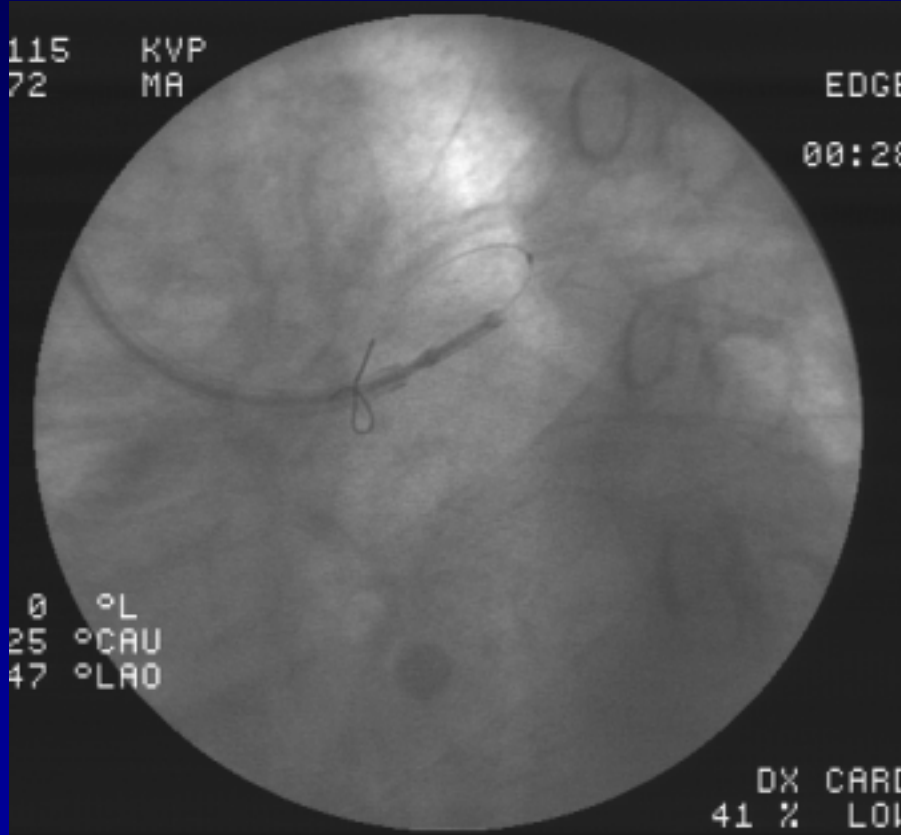


# Description of the problem

- Lt. main Bifurcation lesion
- ? CABG or PCI
- How to protect the branch in DES era:
  - ❖ Kissing stent
  - ❖ Crush stent
  - ❖ T - stent
  - ❖ DCA
  - ❖ Cross - over

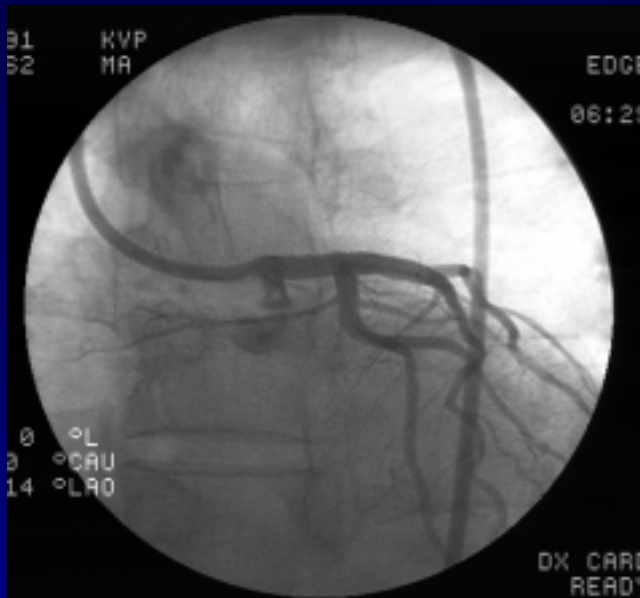


# DCA

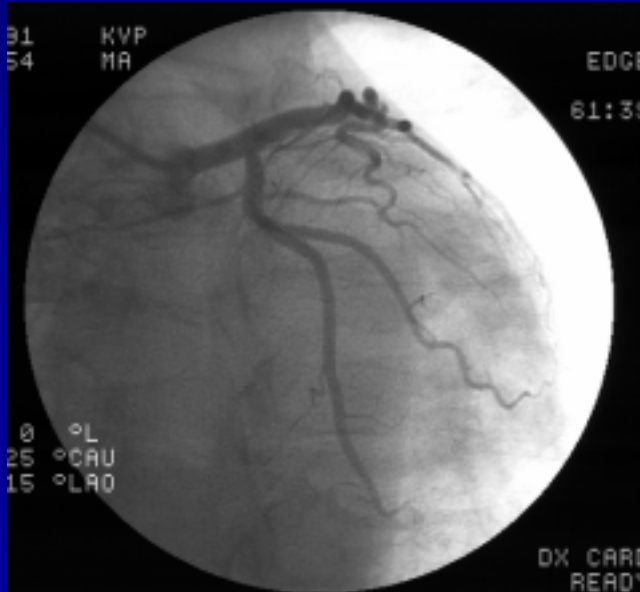


- DCA from Lt. main to LAD ostium

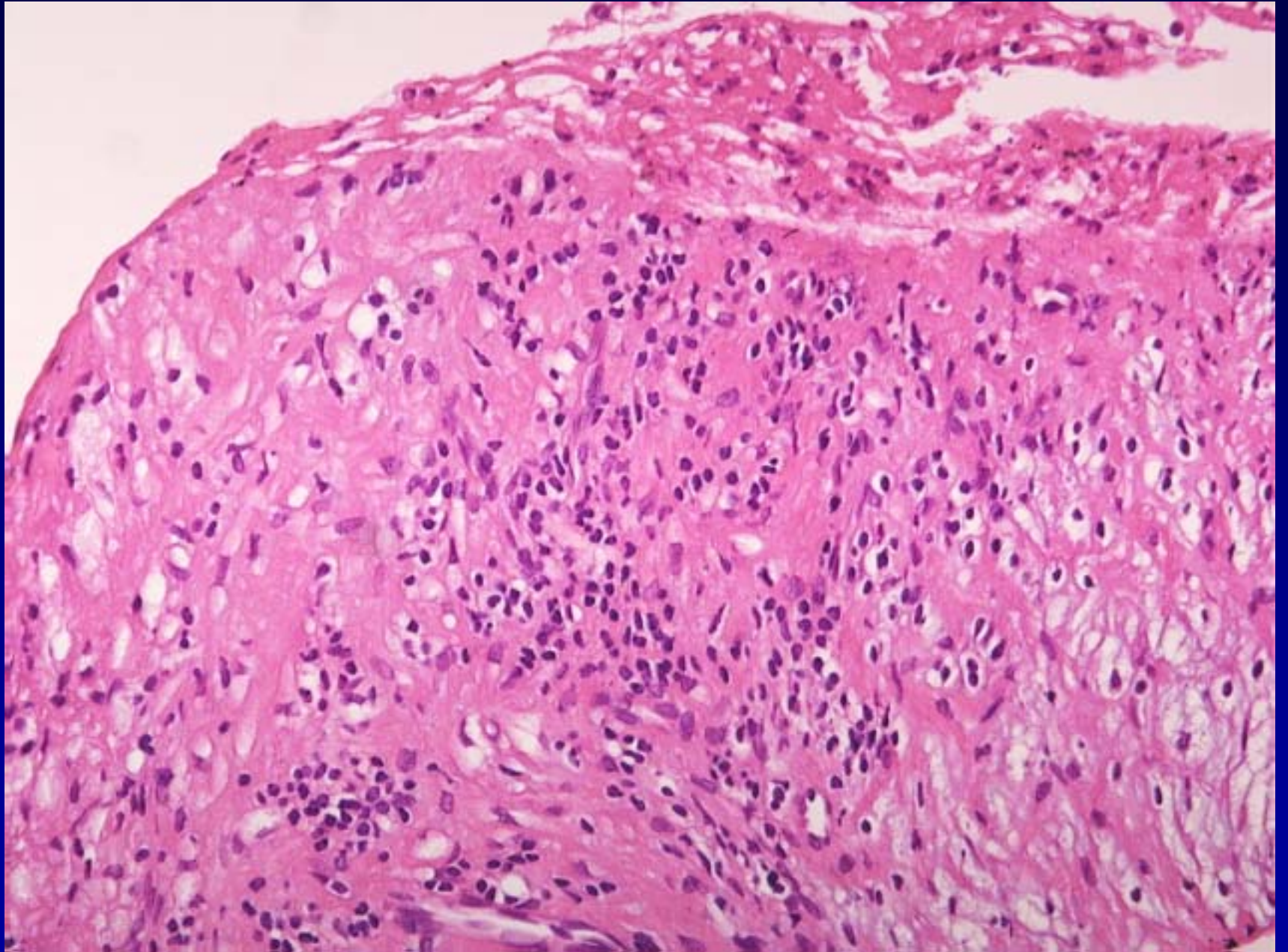
# Final results



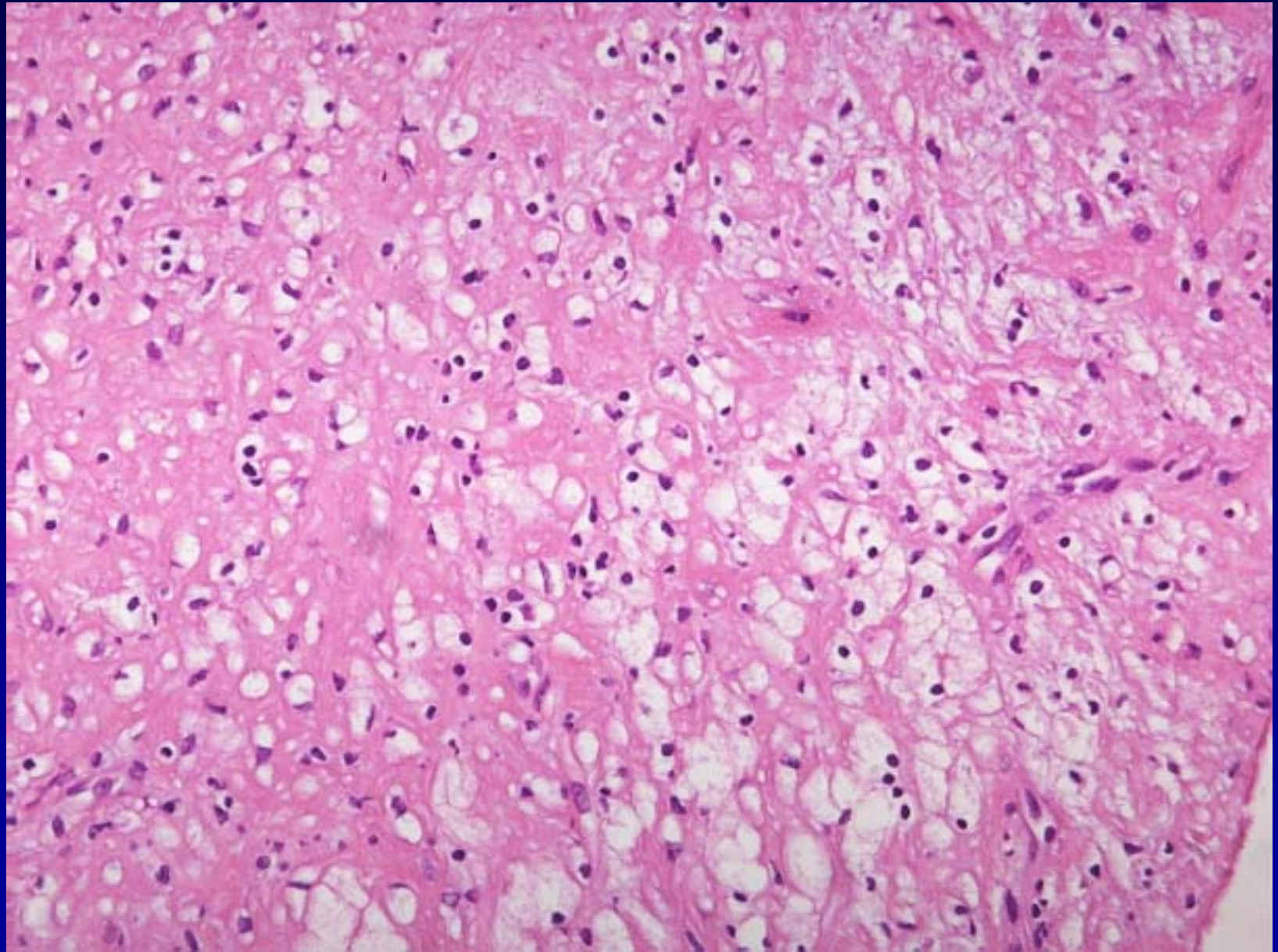
- Cross - over stenting
- LCx ostium was not compromised



- F/U CAG, 6 months later







# Summary

- A 54 year old male with unstable angina
- Lt. main bifurcation lesion and LAD ostial stenosis.
- Cross-over DES stenting after DCA

# Message

- New-onset angina, UA
- > 90% tight obstructive lesion : maybe rapid progression
- Left main bifurcation lesion : turbulent flow
- Soft and highly inflammatory lesion
- Maybe thin fibrous cap and lipid rich core

# Inflammatory markers

- TNF - alpha
- IL - 6 and IL - 1beta
- Fibrinogen
- VCAM - 1 and P, E selectin
- Serum amyloid A
- **CRP** : independent risk factor

# CRP

- Oxidized LDL : more susceptible to uptake by Macrophage
- Expression of VCAM
- Stimulate production of Tissue factor
- Impair production NO





# Prognostic Value of Troponin-I, High Sensitivity C-Reactive Protein and B-Type Natriuretic Peptide in Patients with Acute Coronary Syndrome



Division of Cardiology, Department of Internal Medicine,  
Kyungpook National University Hospital

## Methods

Baseline levels of BNP, Hs-CRP and Tn-I were determined in 139 patients with acute coronary syndromes.

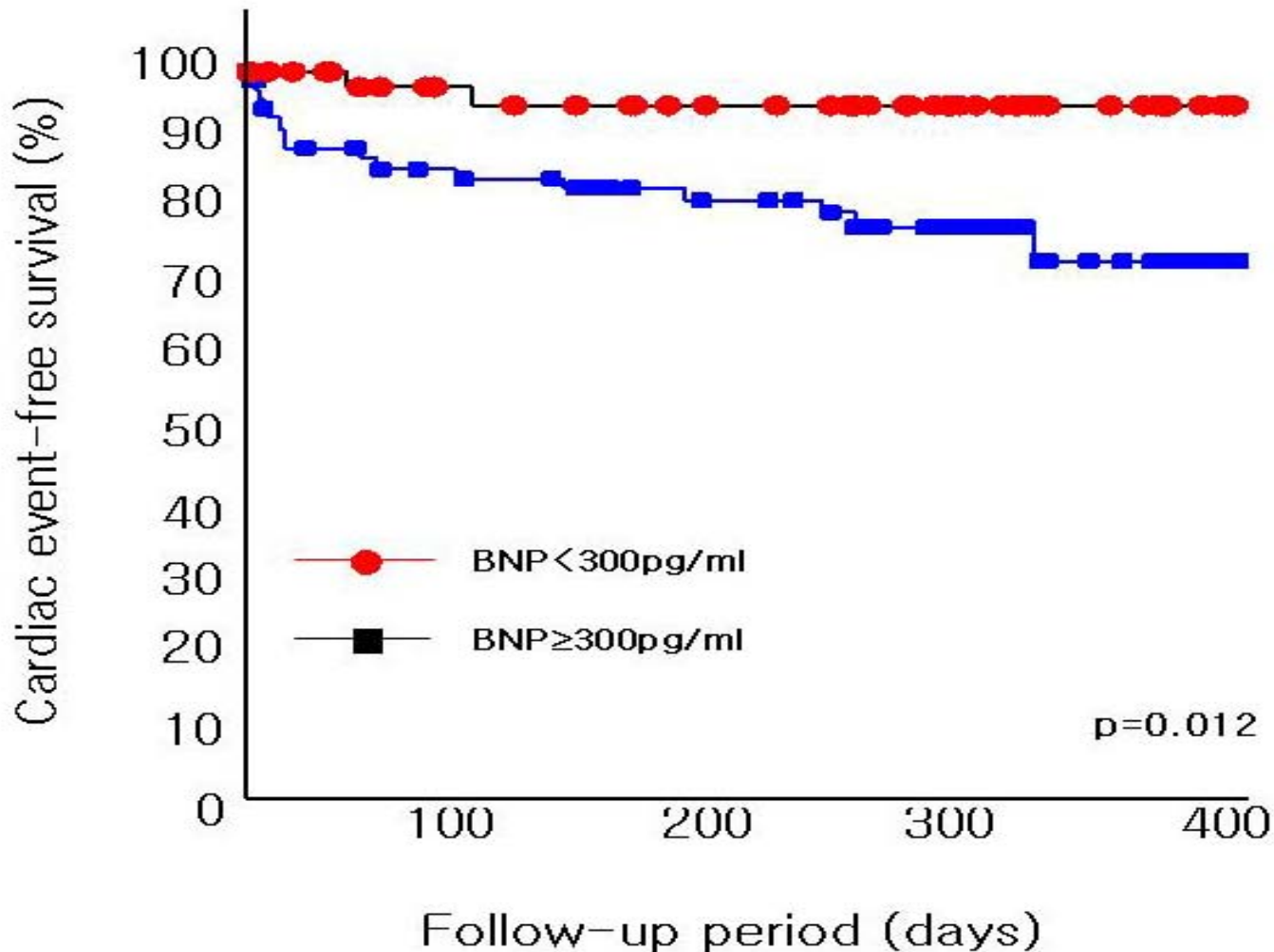
(Male : Female 88 : 51, Mean age:  $67 \pm 57$  years)

Follow-up durations:  $215 \pm 125$ days

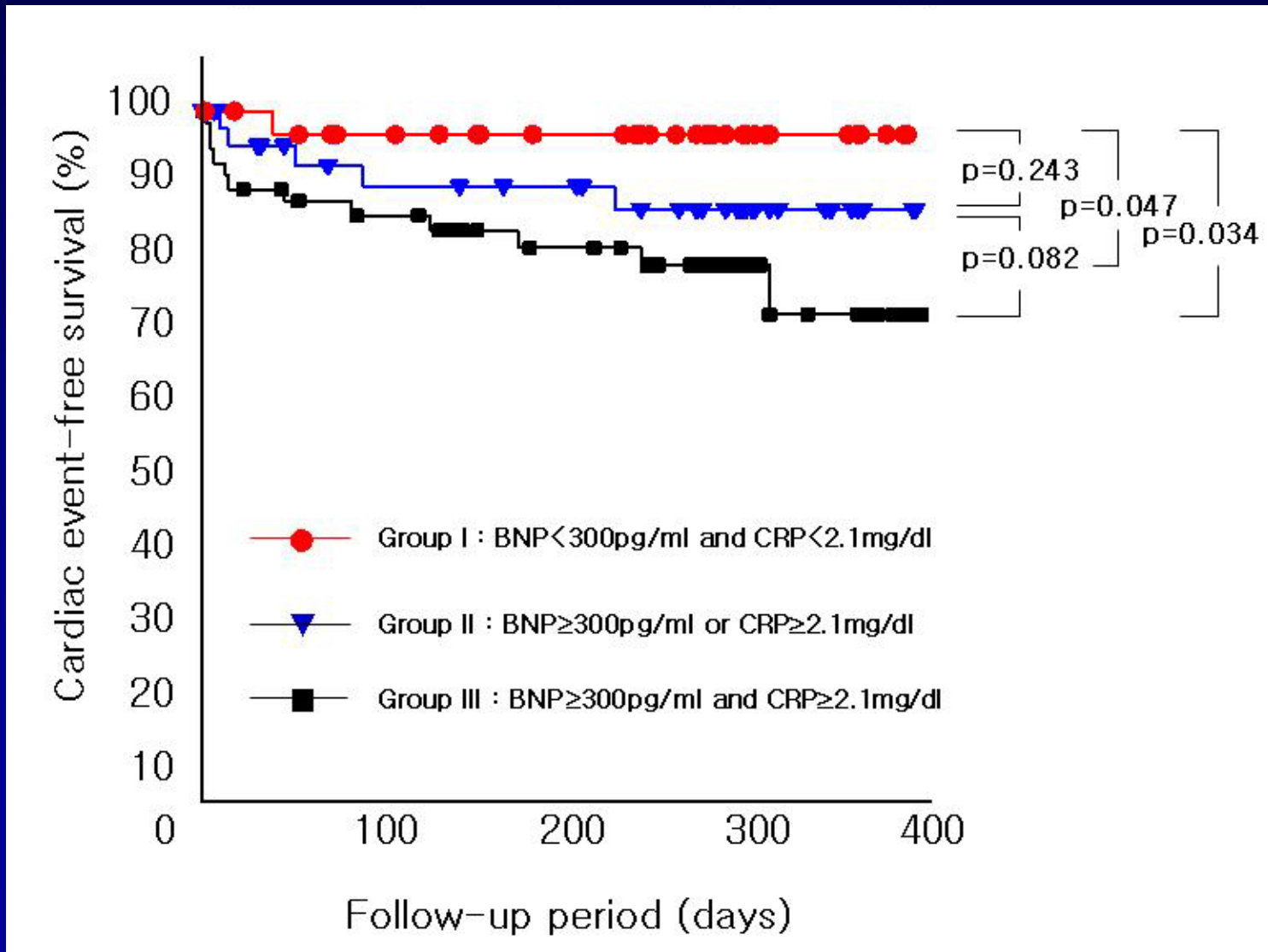
Major adverse cardiac events during follow-up

- Death
- STEMI, NSTEMI
- UA
- CHF

# Event free survival; BNP level



# Event free survival; BNP and CRP





# Relation between hs-CRP and Angiographic Findings of Coronary Lesions in Patients with ACS



Division of cardiology, Department of Internal  
Medicine,  
Kyungpook University Hospital

## Methods

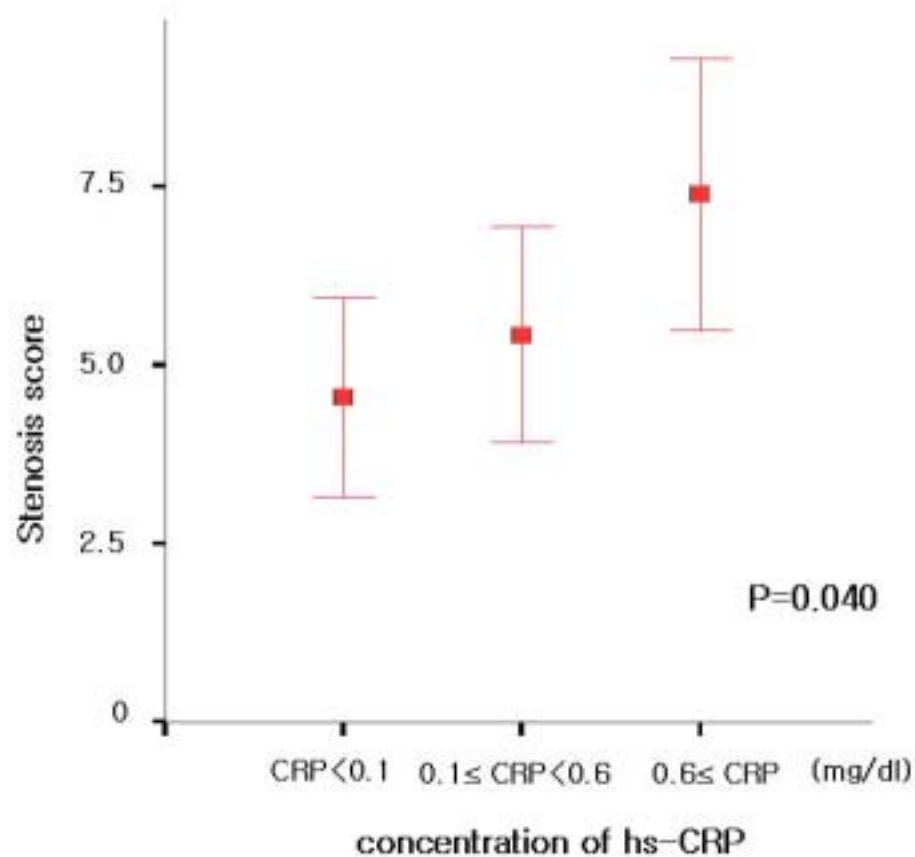
We evaluated hs-CRP level at baseline in 90 patients with ACS who underwent coronary angiography.

(Male : Female 61 : 29, Mean age:  $60 \pm 12$  years)

Patients were divided into 3 groups according to the distribution of hs-CRP levels into tertiles.

Coronary angiograms were assessed and scored according to the Sullivan's scoring system, which includes vessel score, stenosis score and extension score.

# Comparison between CRP and Stenosis score



# Anti - inflammatory effect

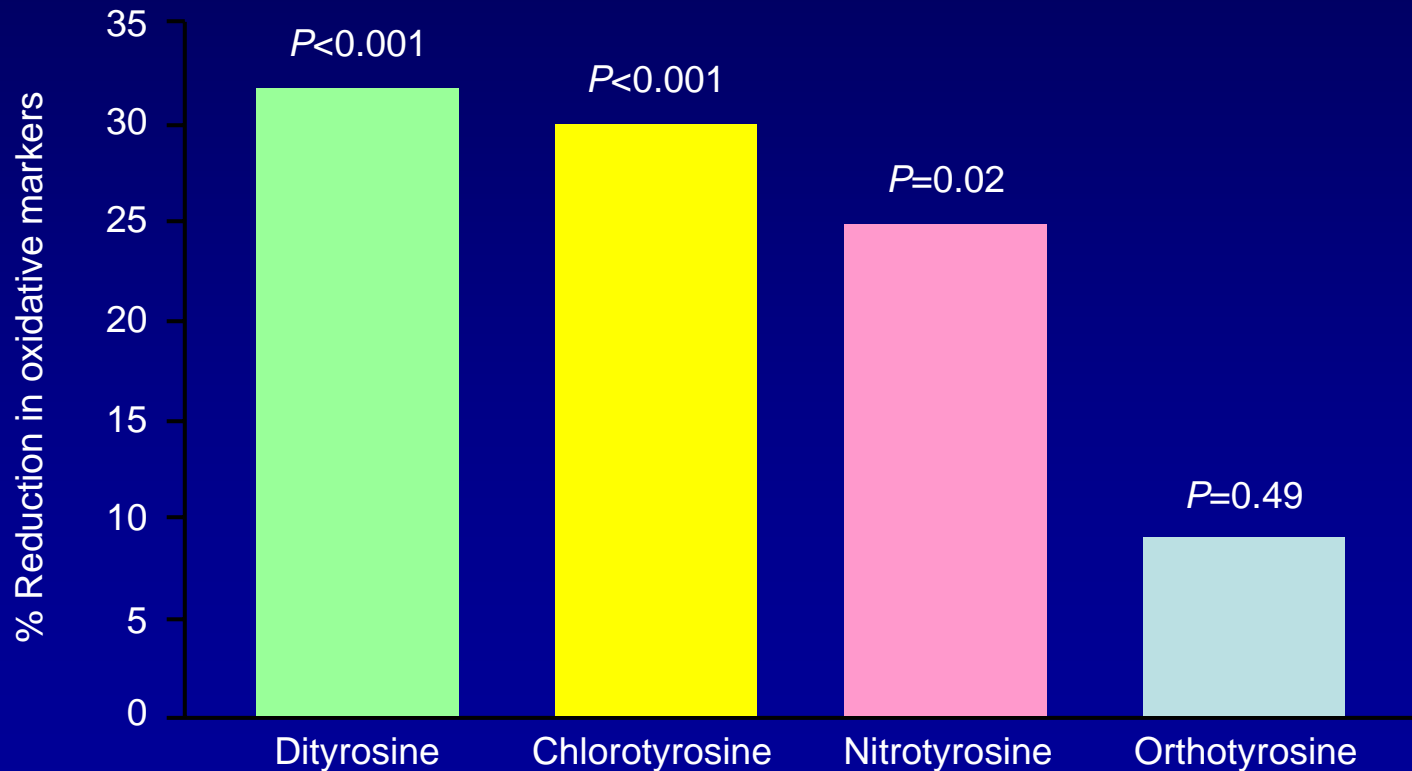
- Statin
- ACEI
- ARB
- CCB

# Statin

- Inhibit cholesterol synthesis
  - Anti-inflammatory effect
    - ❖ Reduction in leukocyte adhesion
    - ❖ Inhibition of macrophage activation, metalloproteinase, and tissue factor
    - ❖ Procoagulant gene expression
- by block the production of isoprenoid intermediates

# Antioxidant Properties

Reductions in plasma protein oxidation markers following 12 weeks of treatment with atorvastatin 10 mg





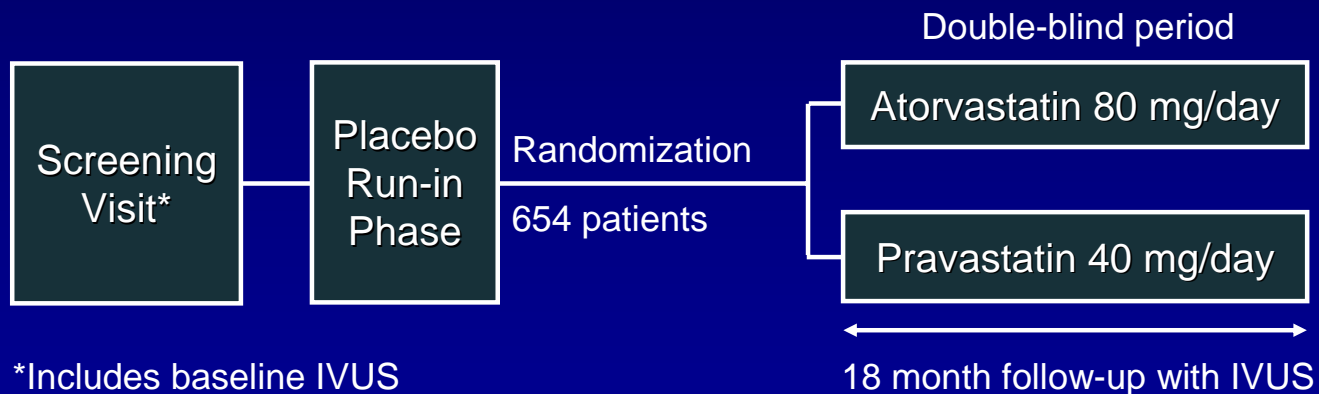
# Clinical Study

- REVERSAL
- PROVE-IT

# REVERSAL: The Reversing Atherosclerosis with Aggressive Lipid-Lowering Study

**Objective:** Compare the effects of aggressive lipid-lowering therapy (atorvastatin 80 mg/day) versus moderate lipid-lowering therapy (pravastatin 40 mg/day) on total atherosclerotic plaque volume using IVUS imaging of the coronary arteries in patients with CHD

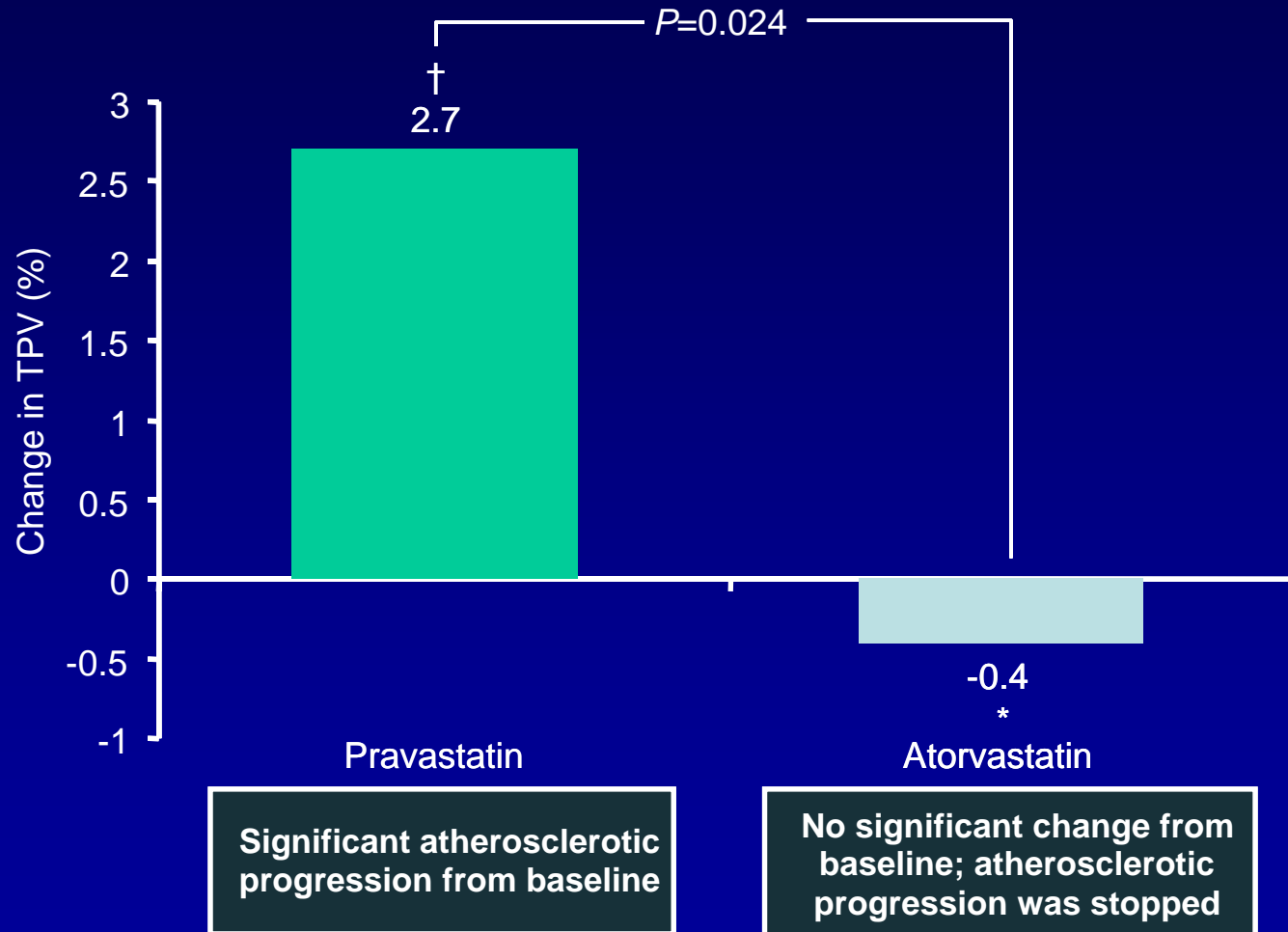
## Study Design



Design – Prospective, randomized, double-blind, multicenter trial

Setting – 34 community and tertiary care hospitals in the US

# REVERSAL: Percent Change in Total Plaque Volume at 18 Months Measured by IVUS

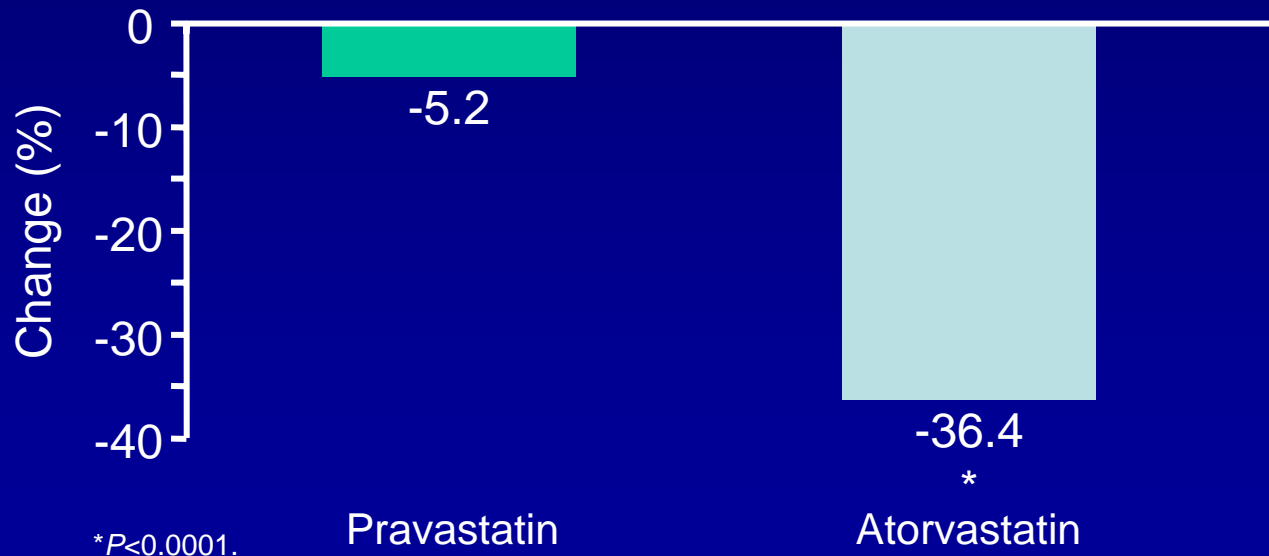


\* No change vs baseline ( $P=0.98$ ); †Progression vs baseline ( $P=0.001$ )

# REVERSAL: Effect on CRP

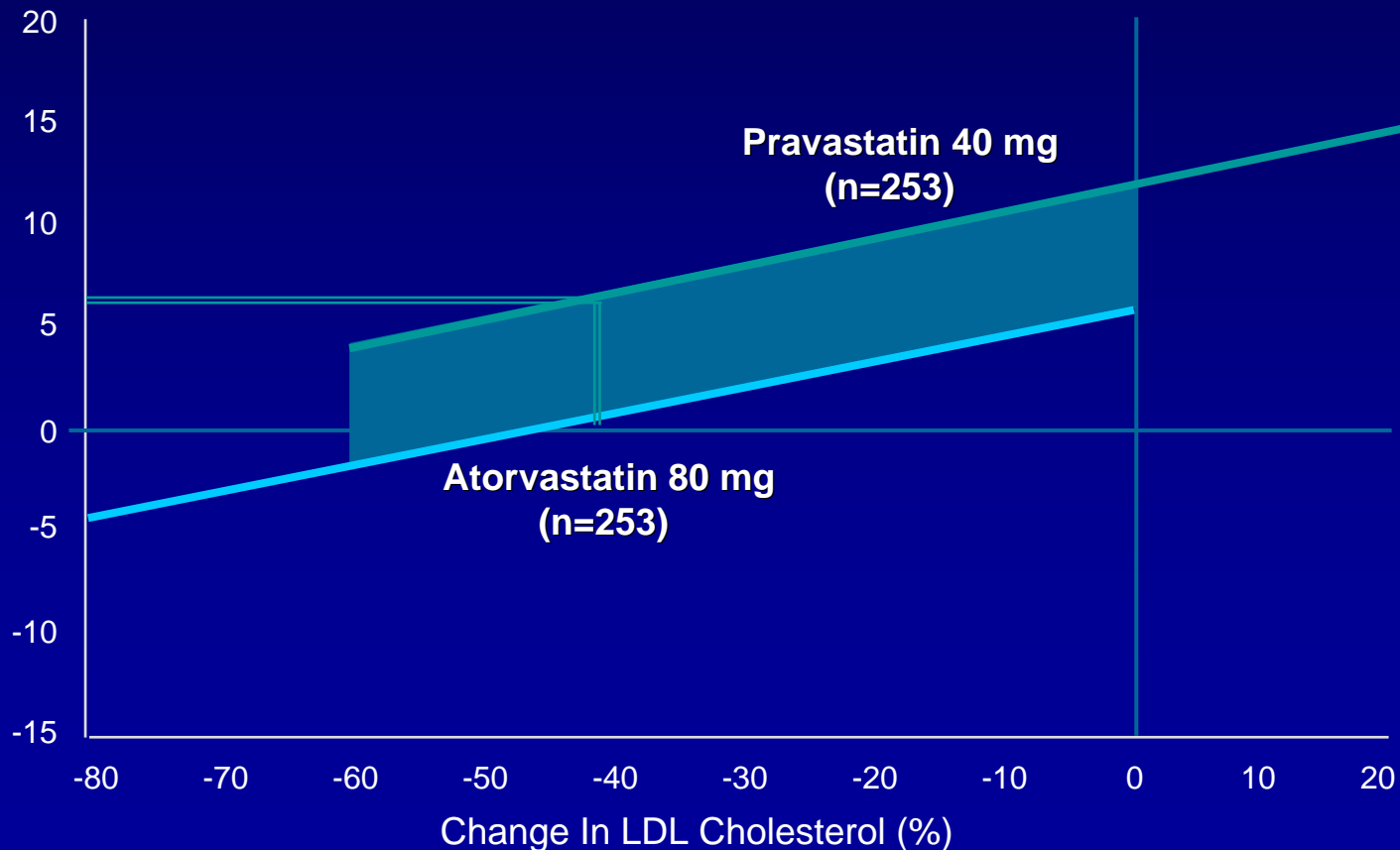
## Atorvastatin versus pravastatin

	CRP (mg/dL)	
	Pravastatin	Atorvastatin
Baseline	3.0	2.9
18 Months	2.9	1.9



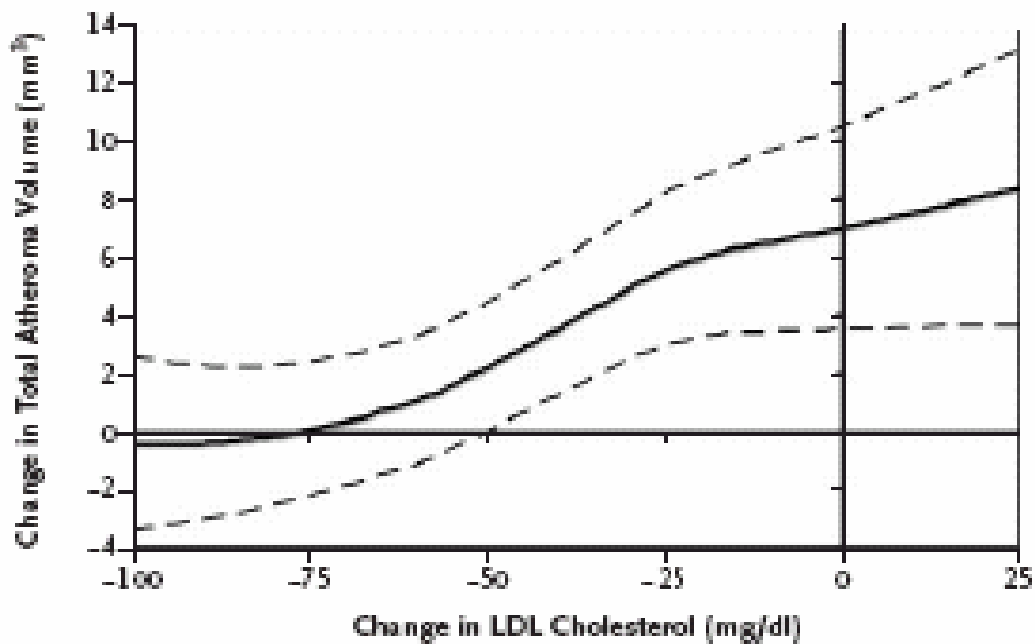
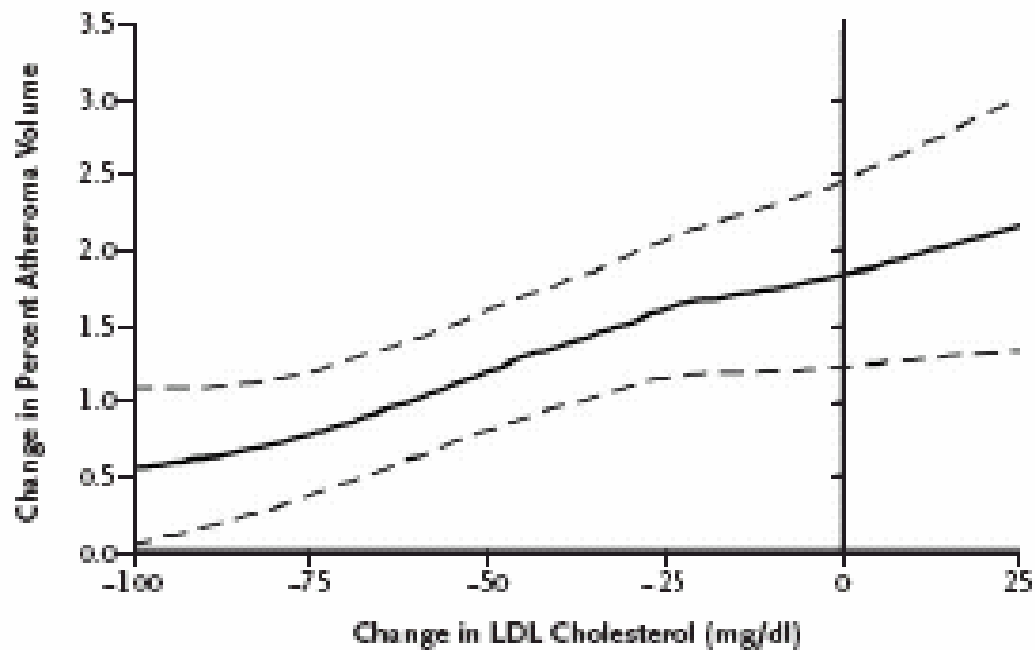
# REVERSAL: Pleiotropic Effects - May Differentiate Between Statins (Not Just LDL Reduction)

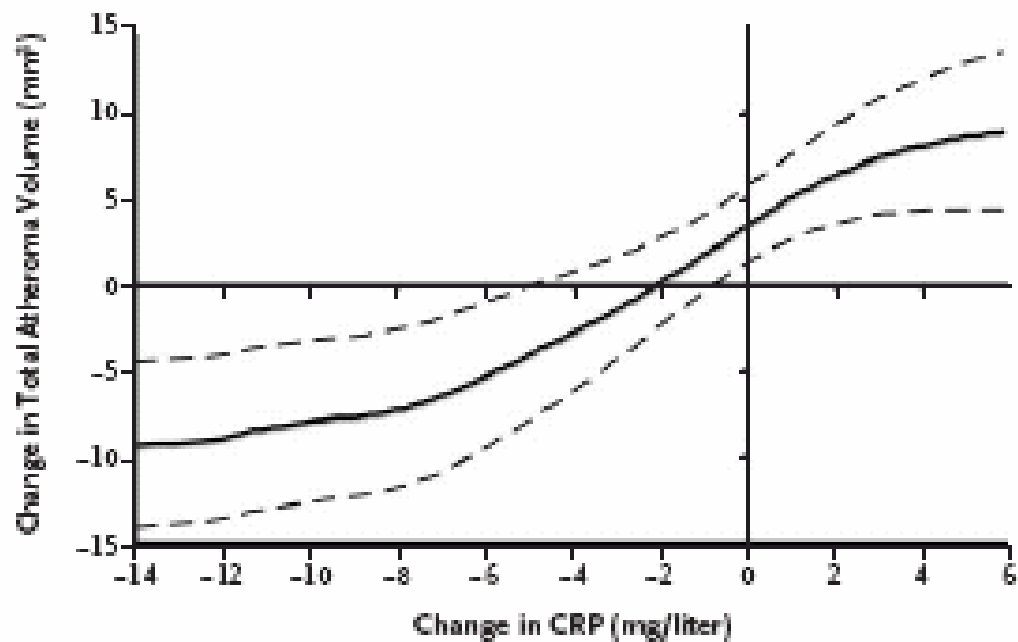
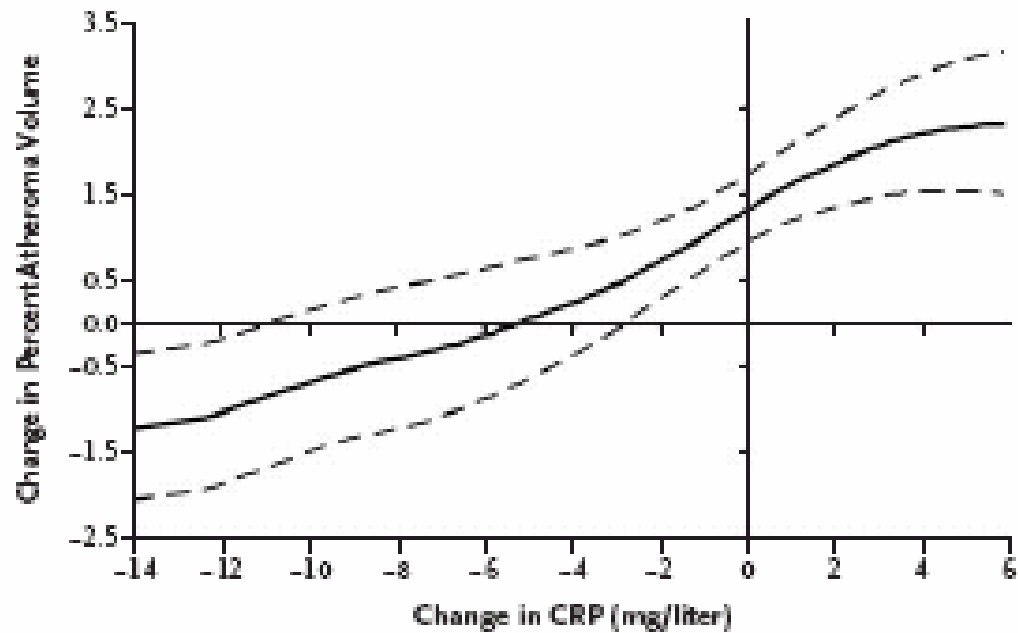
*Change in Atheroma Volume (mm<sup>3</sup>)*



# Rates of progression according to LDL and CRP

Subgroup	No. of Patients	Percent Atheroma Volume†			Total Atheroma Volume (mm <sup>3</sup> )‡		
		Median	95% CI	Mean ±SD	Median	95% CI	Mean ±SD
Reduction in LDL cholesterol and CRP both greater than median	141	0.24 (-2.8 to 3.5)†	-0.77 to 0.54	0.33±5.3	-1.98 (-23.0 to 10.8) ‡	-6.26 to 3.67	-2.41±31.6
Reduction in LDL cholesterol greater than median, reduction in CRP less than median	106	0.81 (-2.0 to 4.8)	-0.32 to 1.81	1.62±4.7	2.06 (-12.8 to 21.5)	-3.26 to 6.41	4.04±28.7
Reduction in LDL cholesterol less than median, reduction in CRP greater than median	108	1.21 (-2.0 to 4.0)	-0.31 to 2.08	0.91±4.9	-1.04 (-18.6 to 22.5)	-6.78 to 8.74	1.42±29.2
Reduction in LDL cholesterol and CRP both less than median	141	1.82 (-1.5 to 5.1)	1.0 to 2.84	2.25±5.0	8.21 (-11.8 to 27.5)	0.40 to 13.05	7.49±27.5

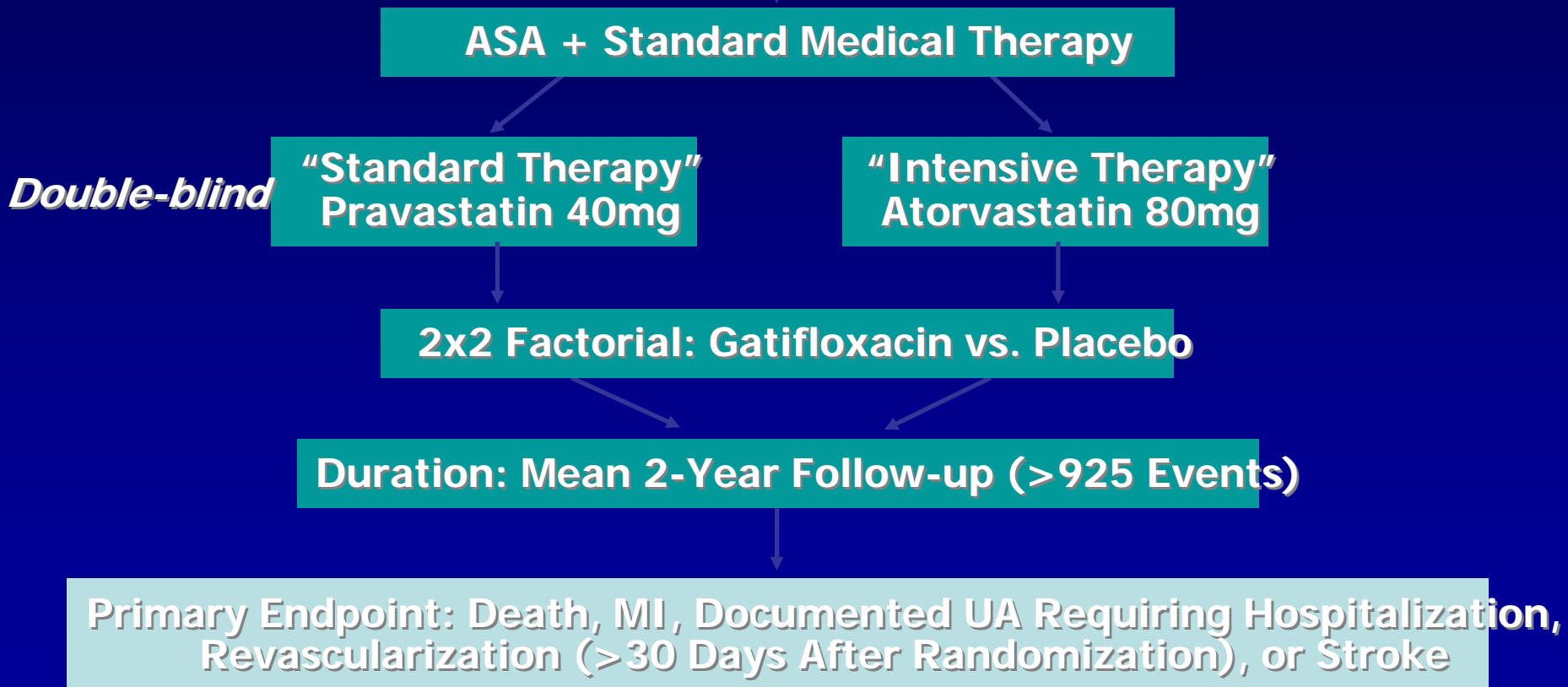






# PROVE-IT Study Design

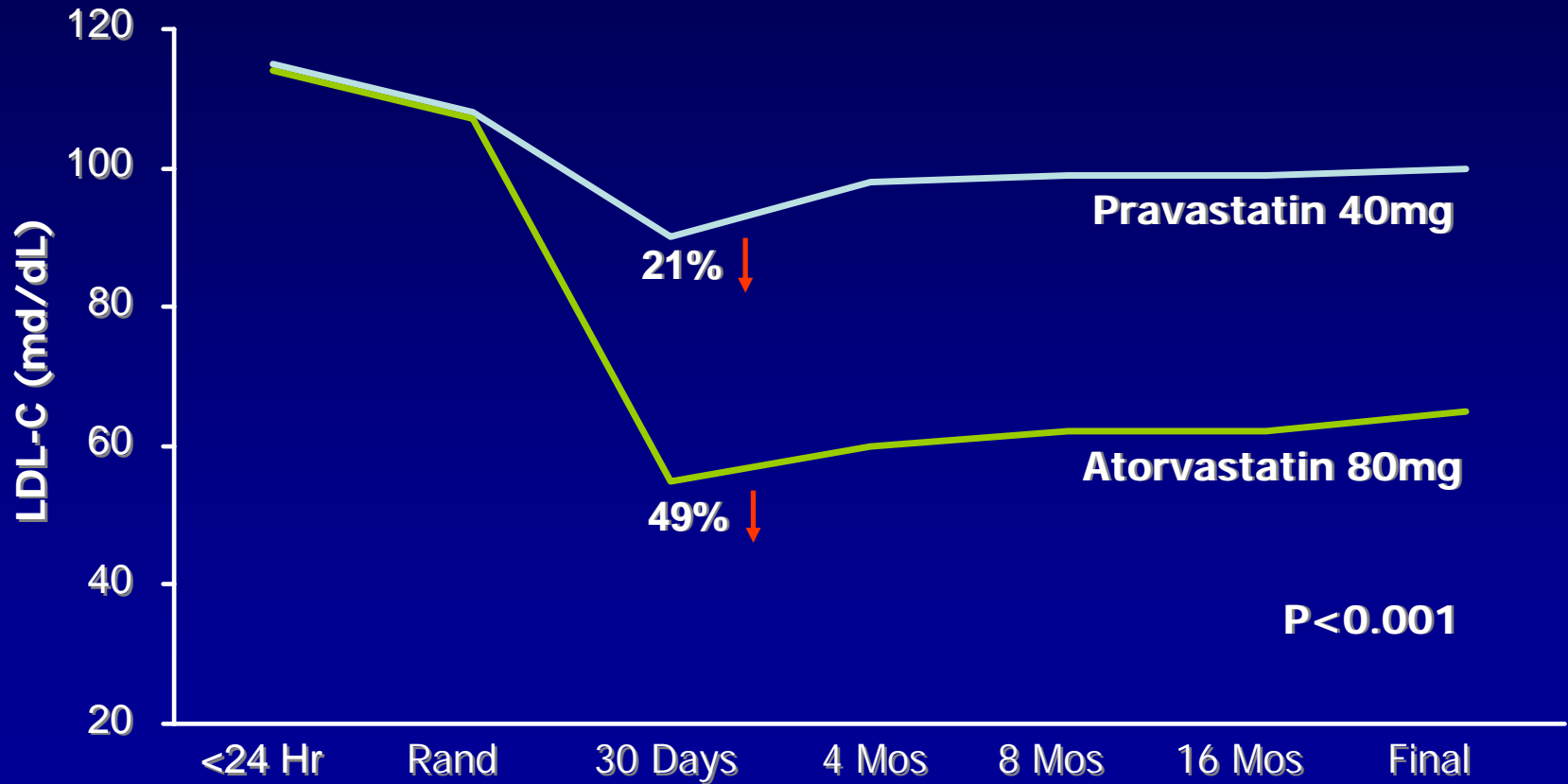
4,162 Patients With an Acute Coronary Syndrome <10 Days



# PROVE-IT Baseline Characteristics

	Atorvastatin 80mg (N=2,099)	Pravastatin 40mg (N=2,063)
Mean Age (Years)	58	58
Male/Female (%)	78/22	78/22
History of HTN (%)	51	49
Current Smoker (%)	36	37
History of Diabetes	19	18
History of CHD (%)	37	39
STEMI/NSTEMI/UA (%)	36/36/29	33/37/30
Prior Statin Use (%)	26	25

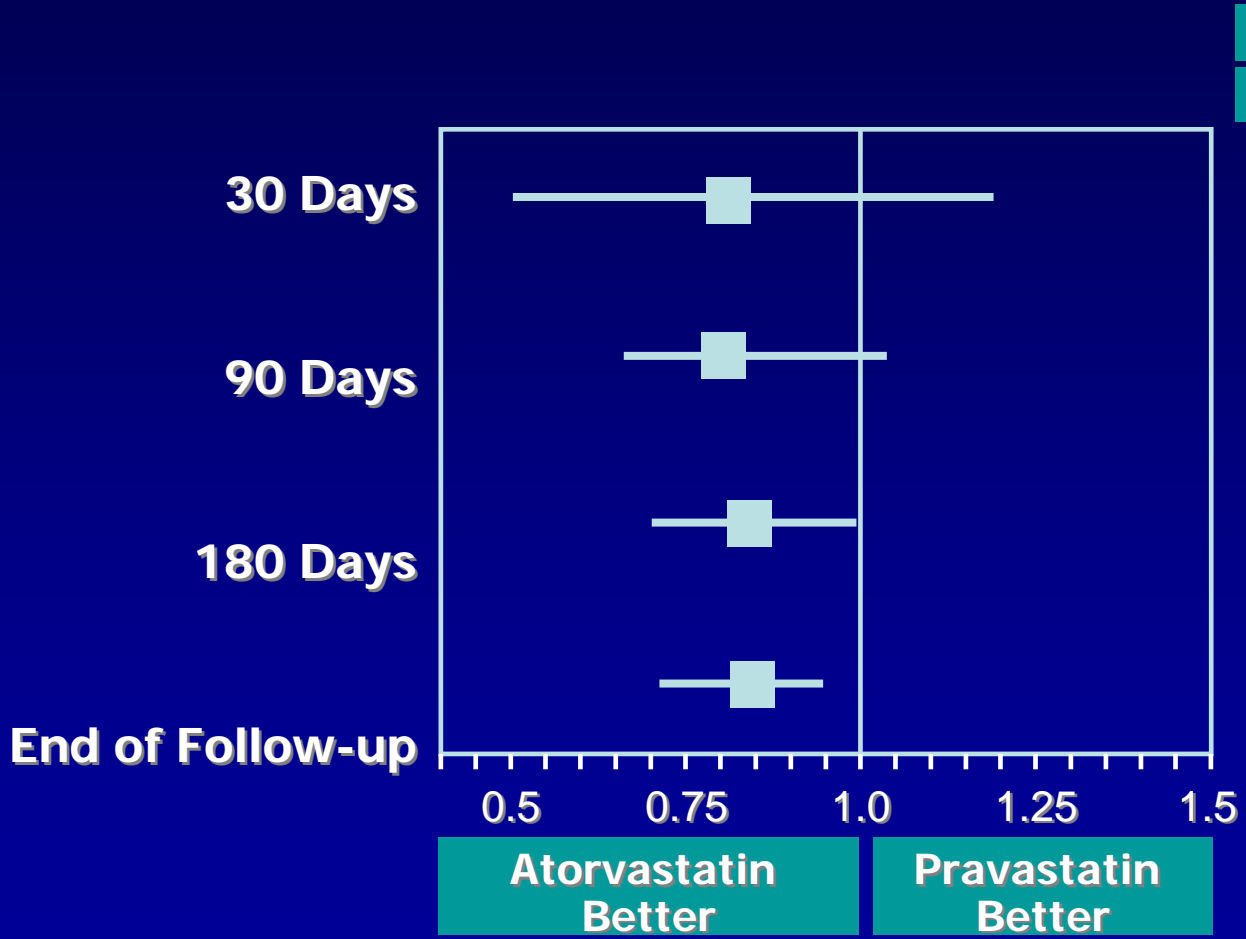
# LDL-C 중간값의 변화



# Lipid

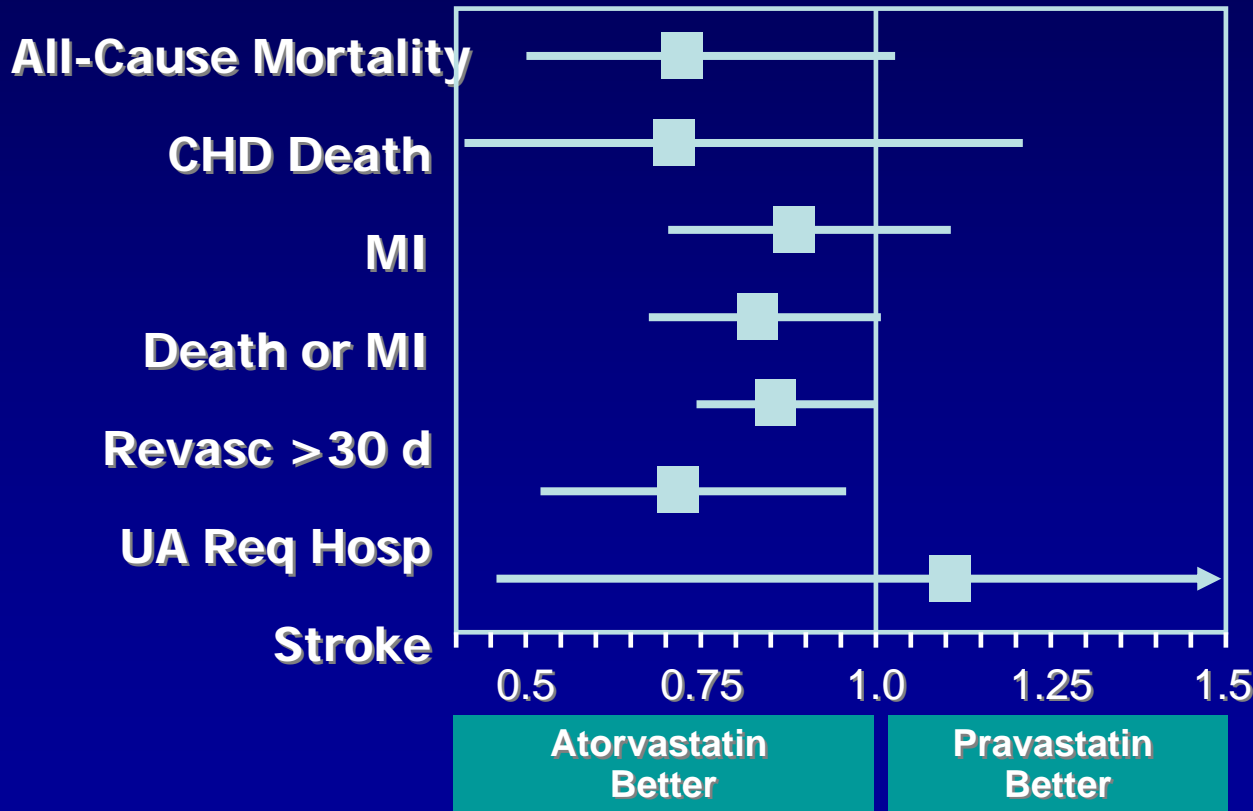
		On-Treatment Values		
Lipid	Baseline	Atorvastatin 80mg	Pravastatin 40mg	<i>P</i> value
LDL-C	106 mg/dL	62 mg/dL (-42%)	95 mg/dL (-10%)	<0.001
CRP	12.3 mg/L	1.3 mg/L (-89%)	2.1 mg/L (-83%)	<0.001
HDL	39 mg/dL	- 6.5%	- 8.1%	<0.001

# Primary Endpoint Over Time



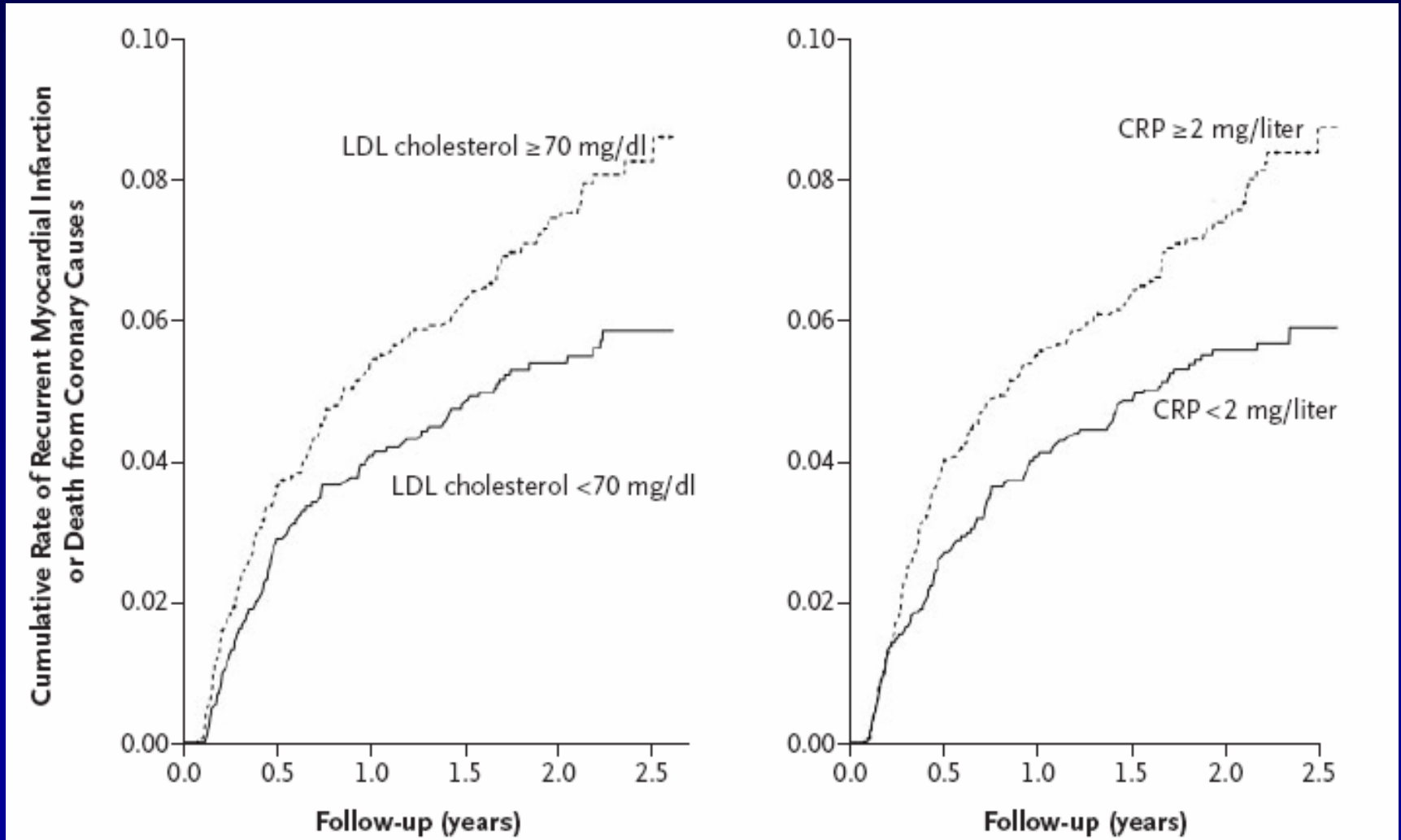
2-Year Events Rates		
RR	Atorva 80	Prava 40
17%	1.9%	2.2%
8%	6.3%	7.7%
14%	12.2%	14.1%
16%	22.4%	26.3%

# 주요 심장 사건의 감소

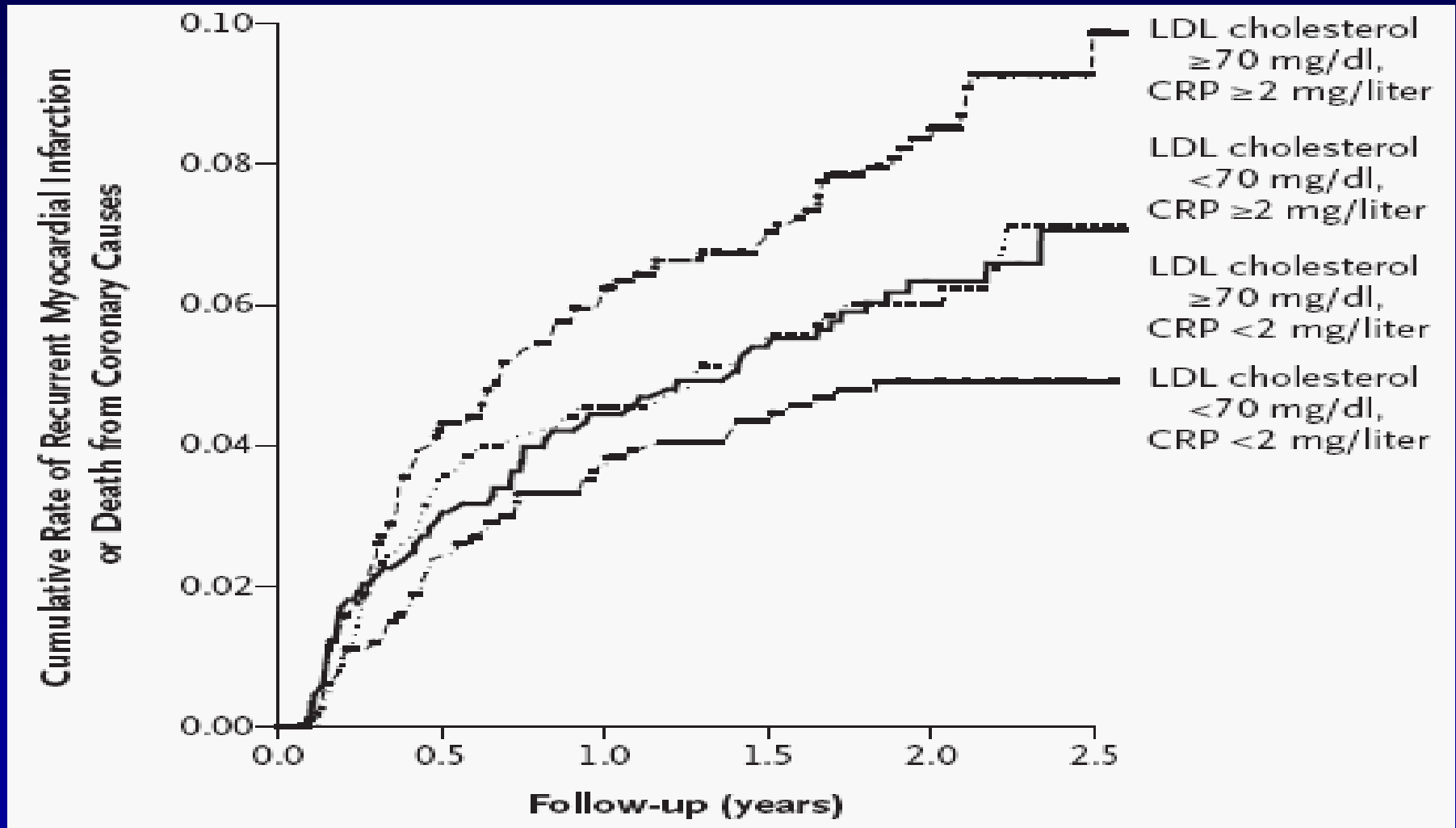


2-Year Events Rates		
RR	Atorva 80	Prava 40
28%	2.2%	3.2%
30%	1.1%	1.4%
13%	6.6%	7.4%
18%	8.3%	10.0%
14%	16.3%	18.8%
29%	3.8%	5.1%
-9%	1.0%	1.0%

# MACE according to LDL and CRP

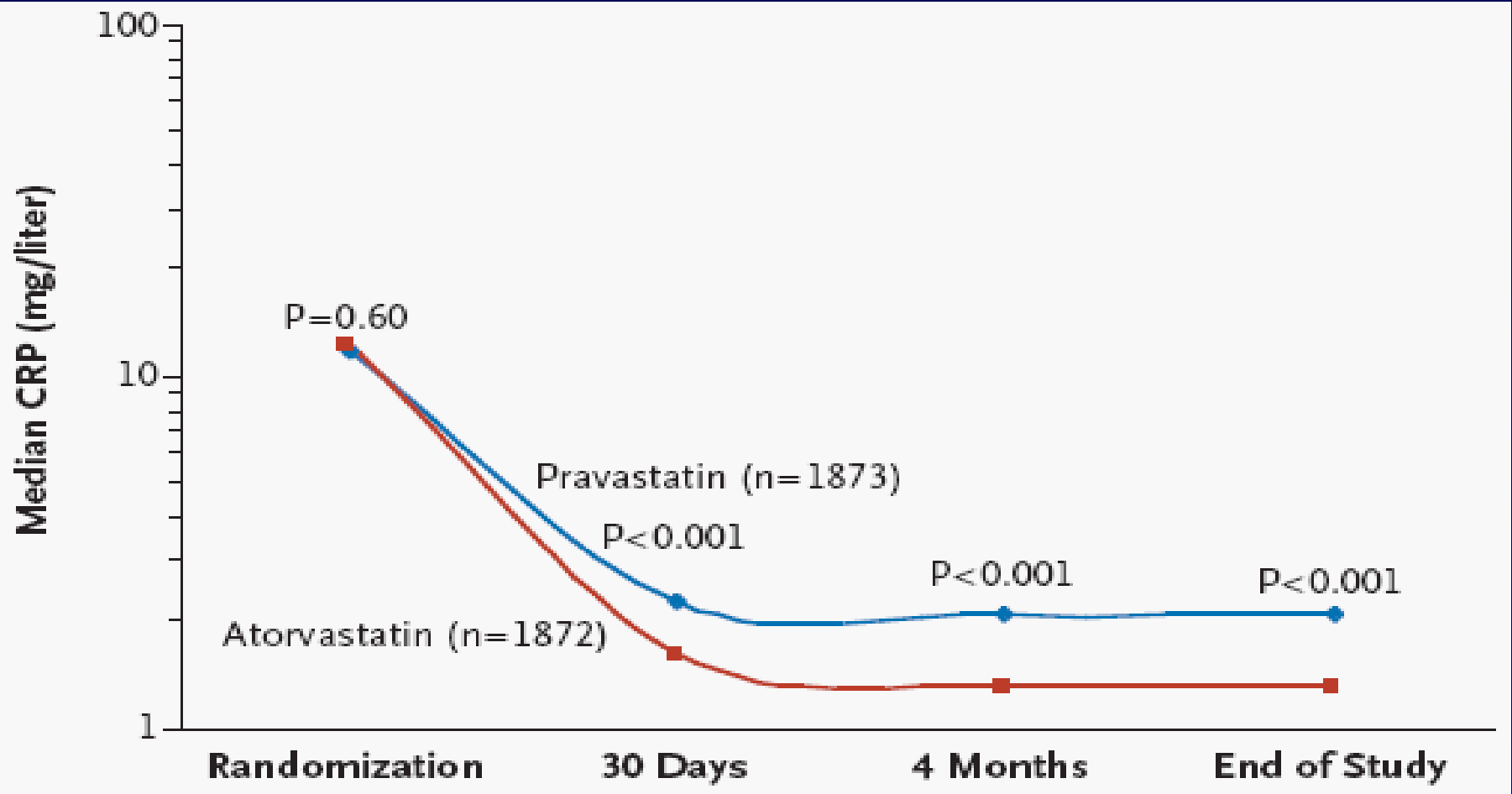


# MACE according to subgroup

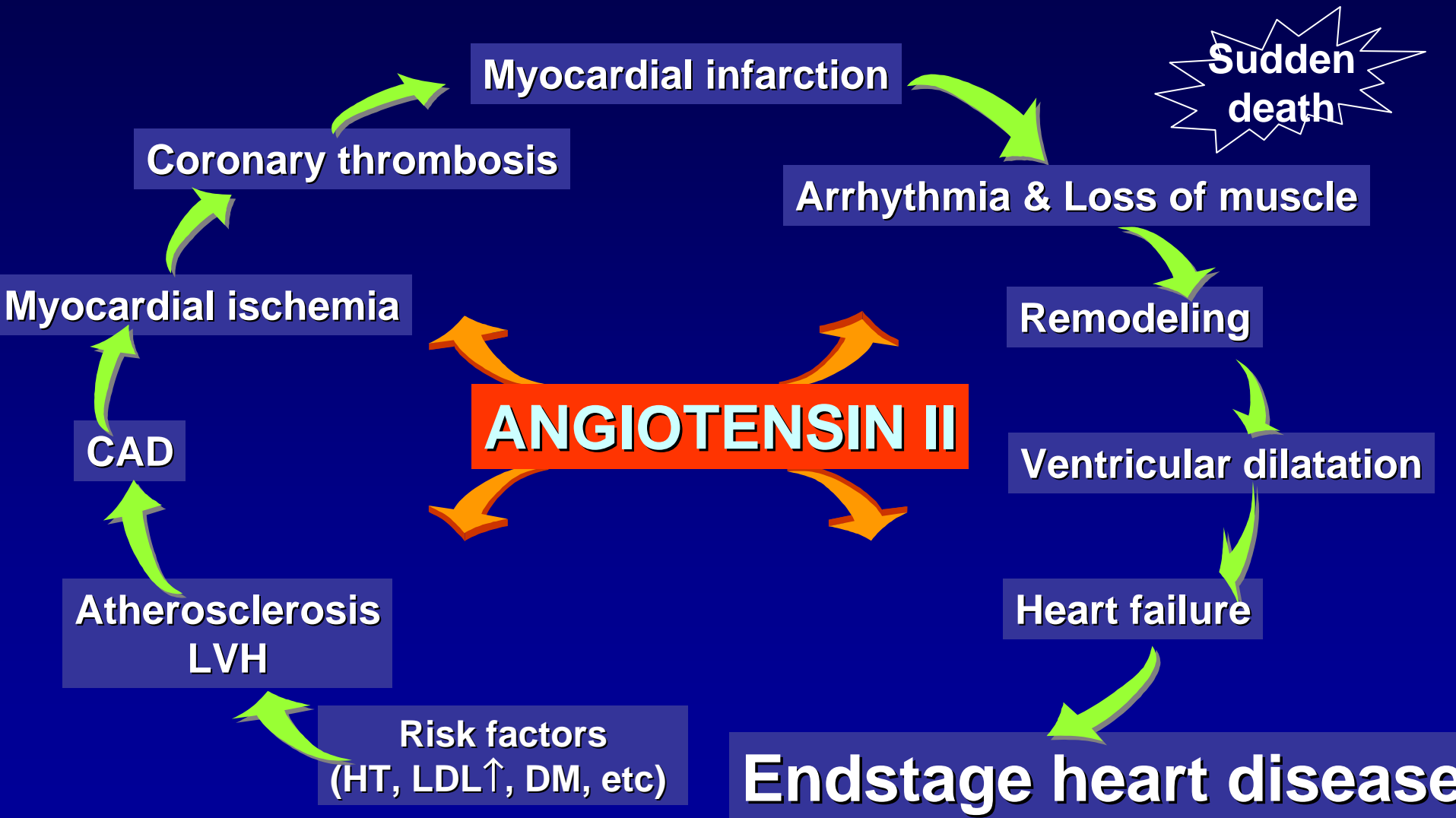




# CRP according to Statins



# Angiotensin II in Pathophysiology of CVD



# Potential mechanisms for anti-ischemic effects of ACEIs

**Antiproliferative effects**

**Modulation of  
sympathetic activity**

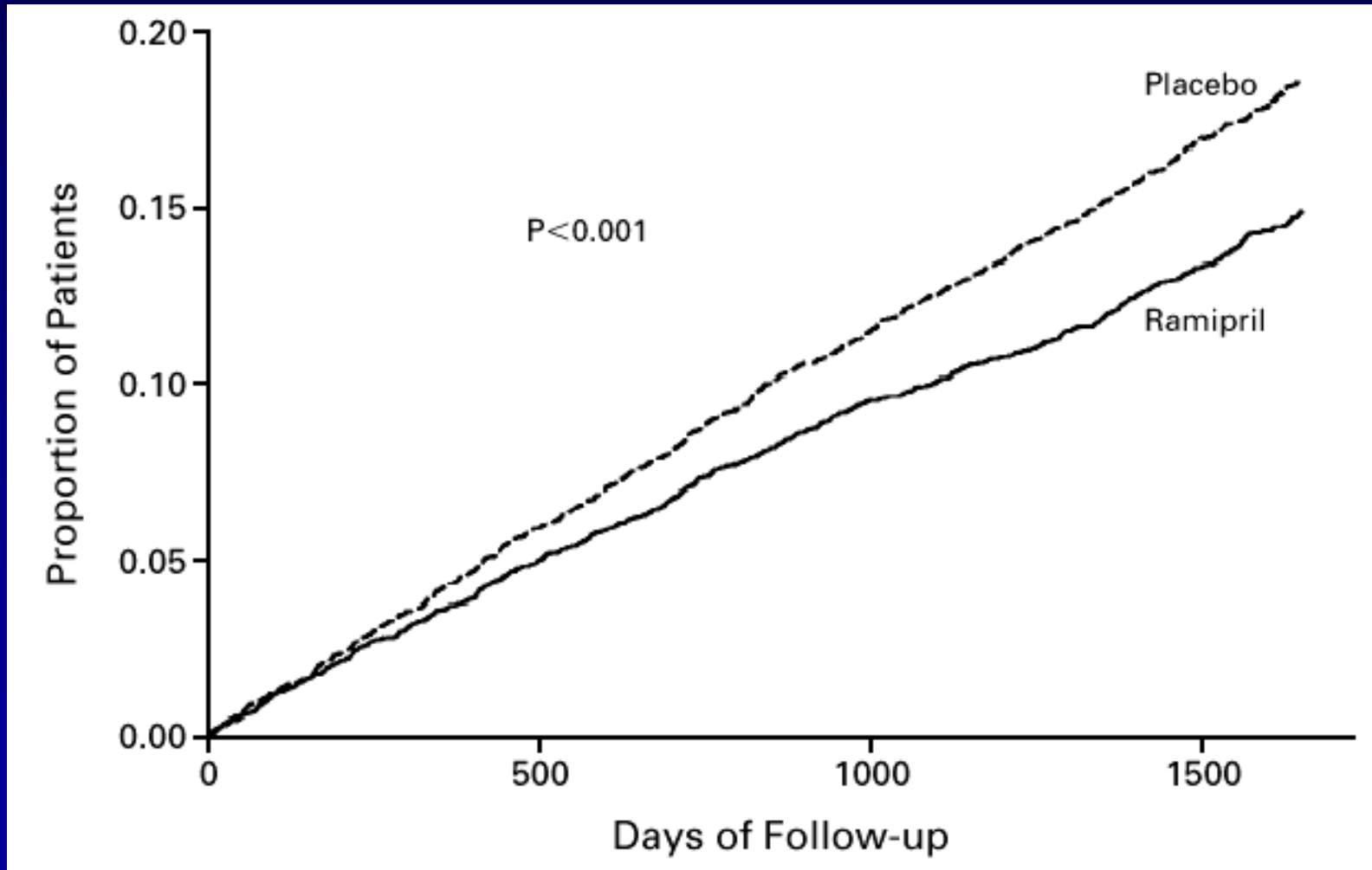
**Improvement of  
endothelial function**

**Hemodynamic Effects  
Of ACEIs**

**Antithrombotic effects**

**Antiatherogenic effect**

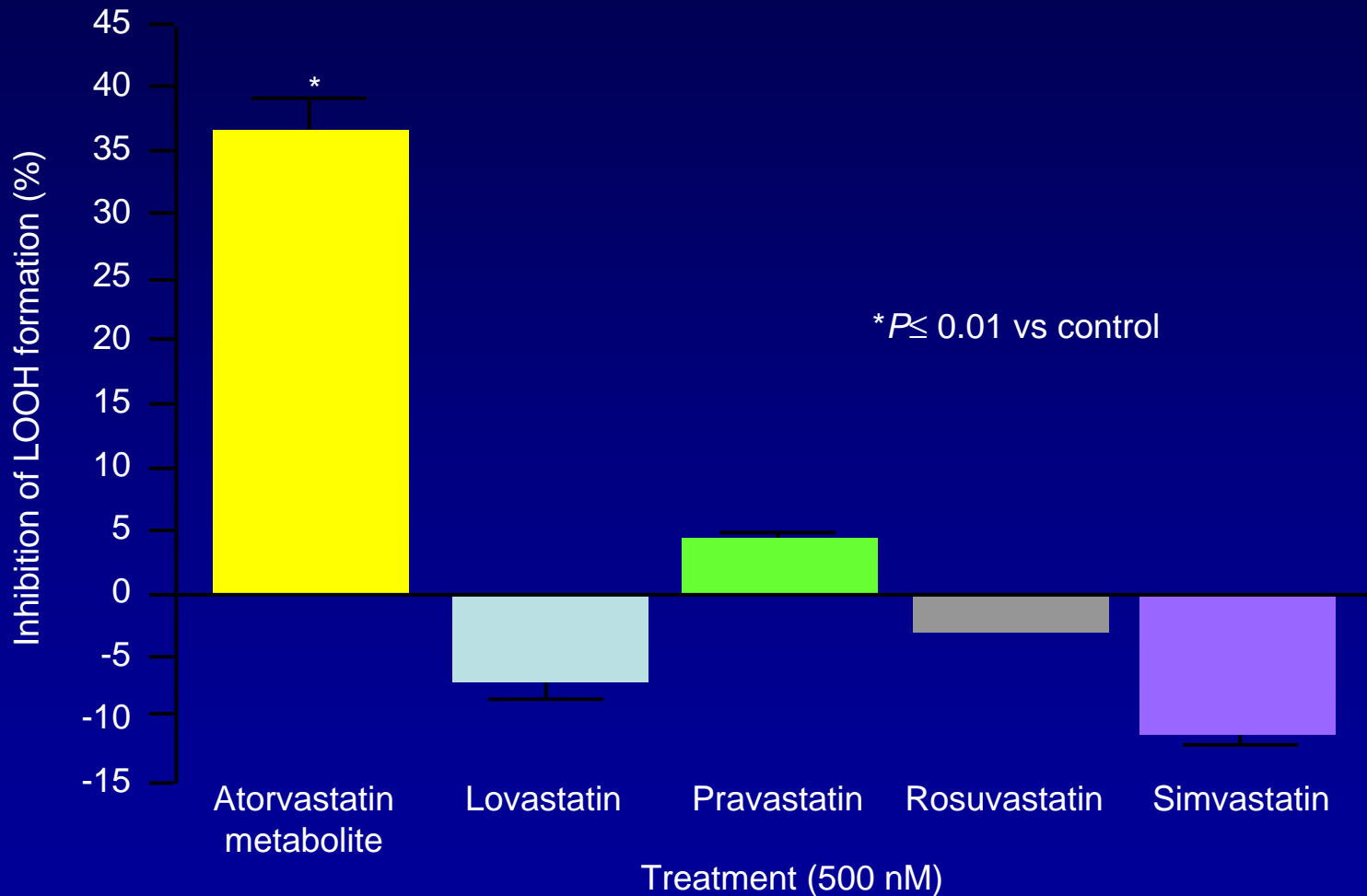
# Outcome of MI, Stroke and Death in HOPE Trial



# Conclusions

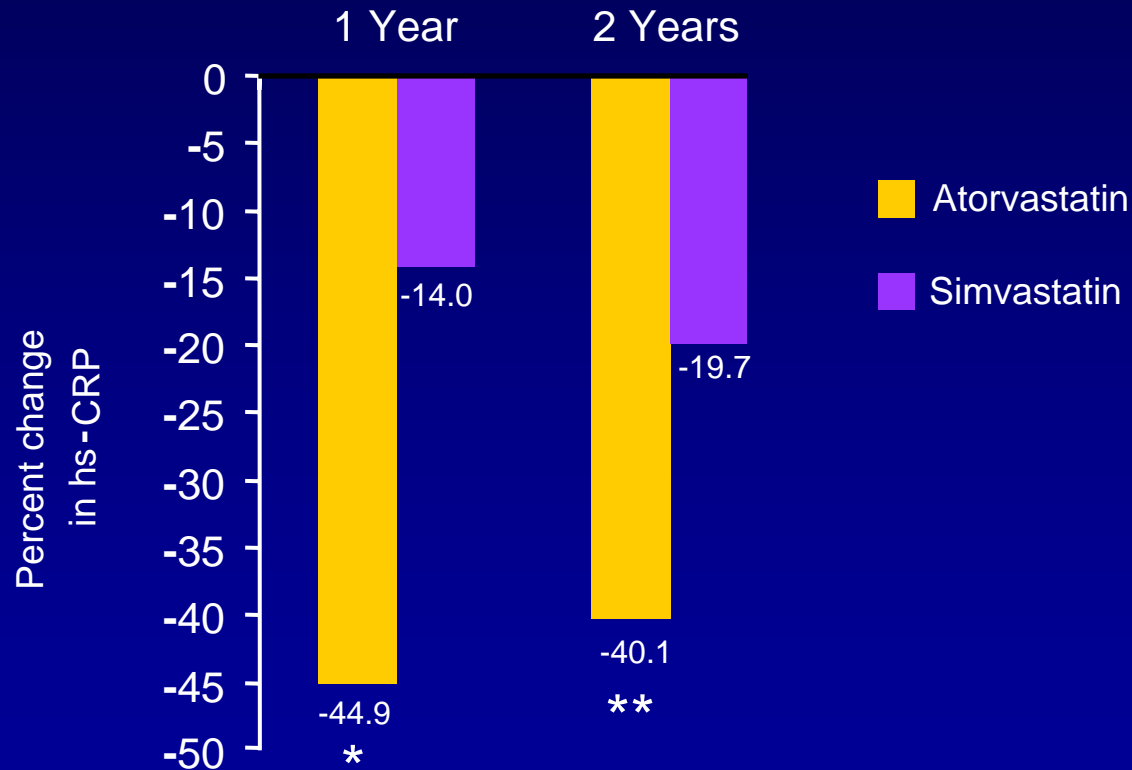
- Atherosclerosis is dynamic and inflammatory disease
- Inflammatory markers provide useful prognostic information
- Anti-inflammatory statin make a key role in prevention of Atherosclerosis beyond lipid lowering

# Comparative Effects of Statins on Oxidative Stress



# ASAP: Effect on CRP

## Atorvastatin versus simvastatin

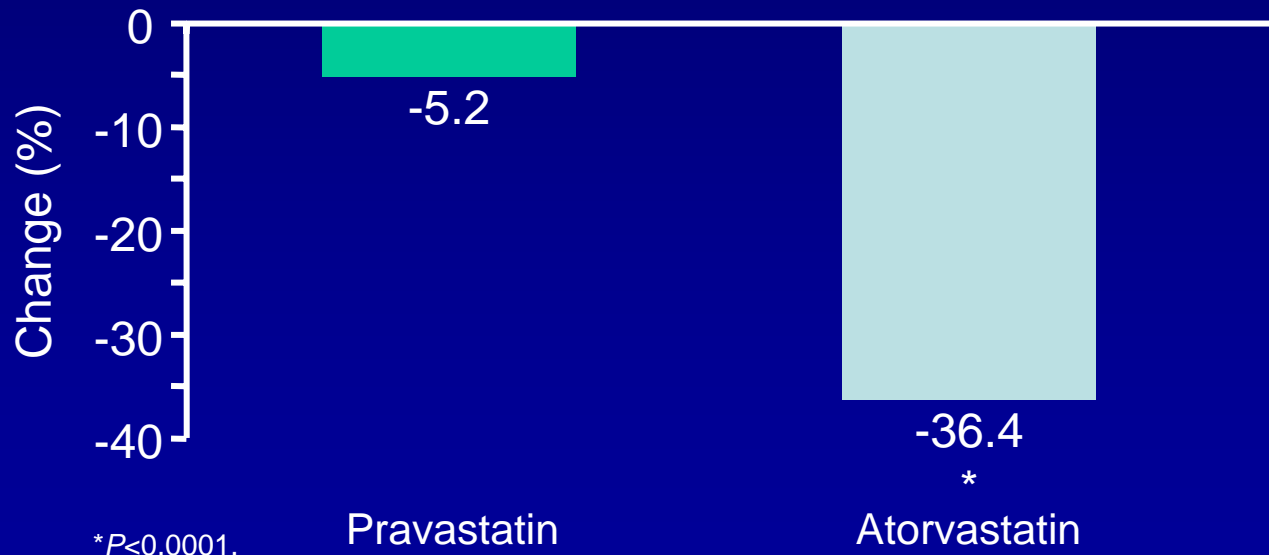


\* $P < 0.001$  for difference between groups; \*\* $P = 0.02$  for difference between groups

# REVERSAL: Effect on CRP

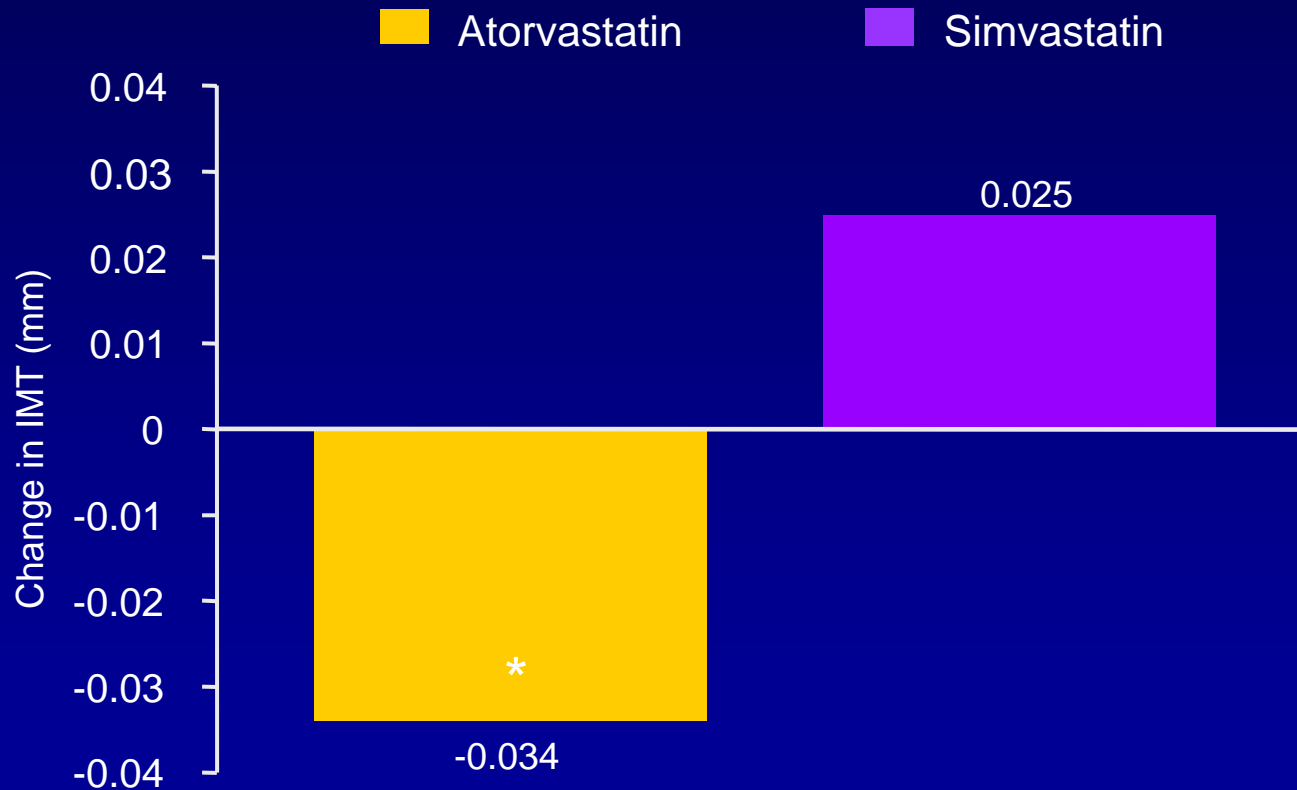
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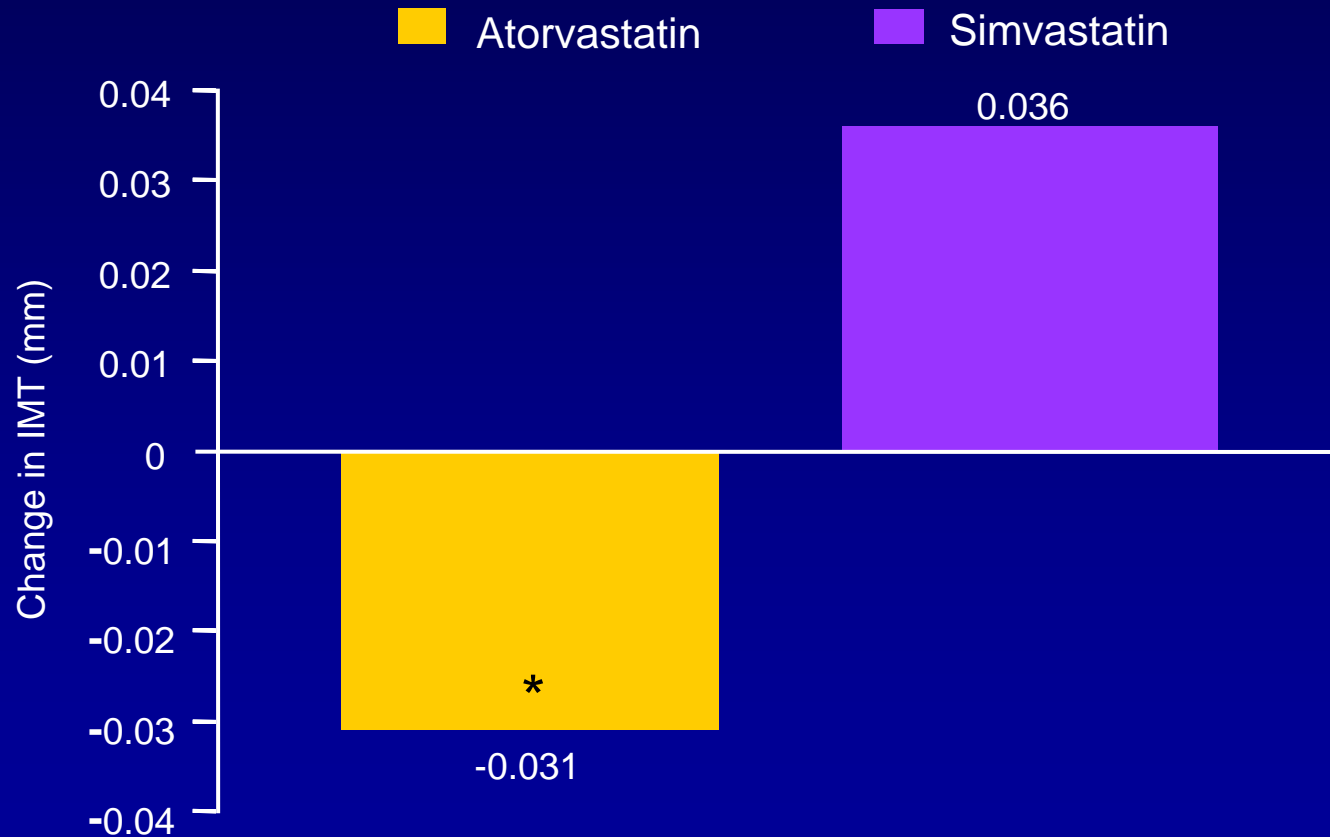


# ARBITER: Effect of Atorvastatin on Carotid Intima-media Thickness at 18 Months



\* $P=0.03$  for difference between treatment groups.

# ASAP: Effect of Atorvastatin on Carotid Intima-media Thickness at 2 Years



\* $P=0.0001$  for difference between treatment groups.

# Intended strategy

- Role of DCA in the DES era
- Cross-over stenting after DCA from Lt. main to LAD