Effects of Statin Treatment on Ruptured Coronary Plaques

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Underlying Pathologies of "Culprit" Coronary Lesions

- Ruptured plaques (70%)
  - Stenotic (20%)
  - Non-stenotic (50%)
- Non-ruptured plaques (30%)
  - Erosion
  - Calcified nodule
  - Others/Unknown

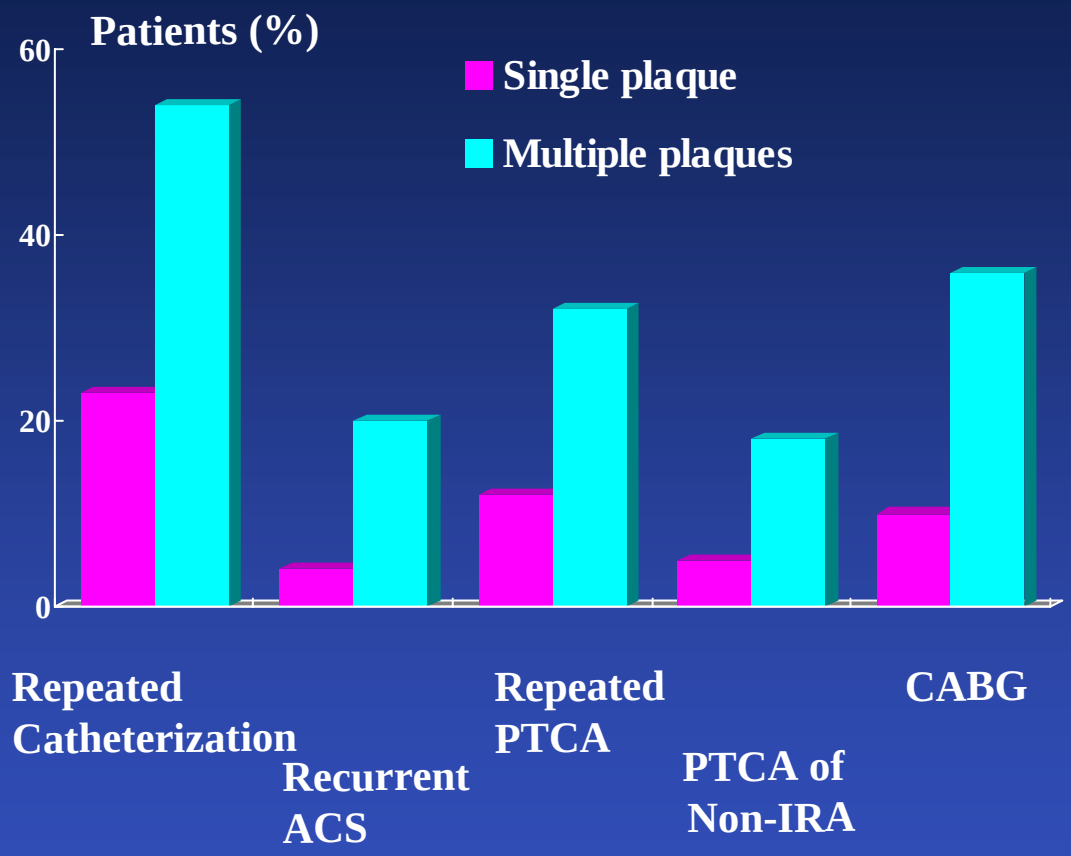
Naghavi M. Circulation 2003; 108: 1664-72

Angiographic Study

One previous study using coronary angiography:

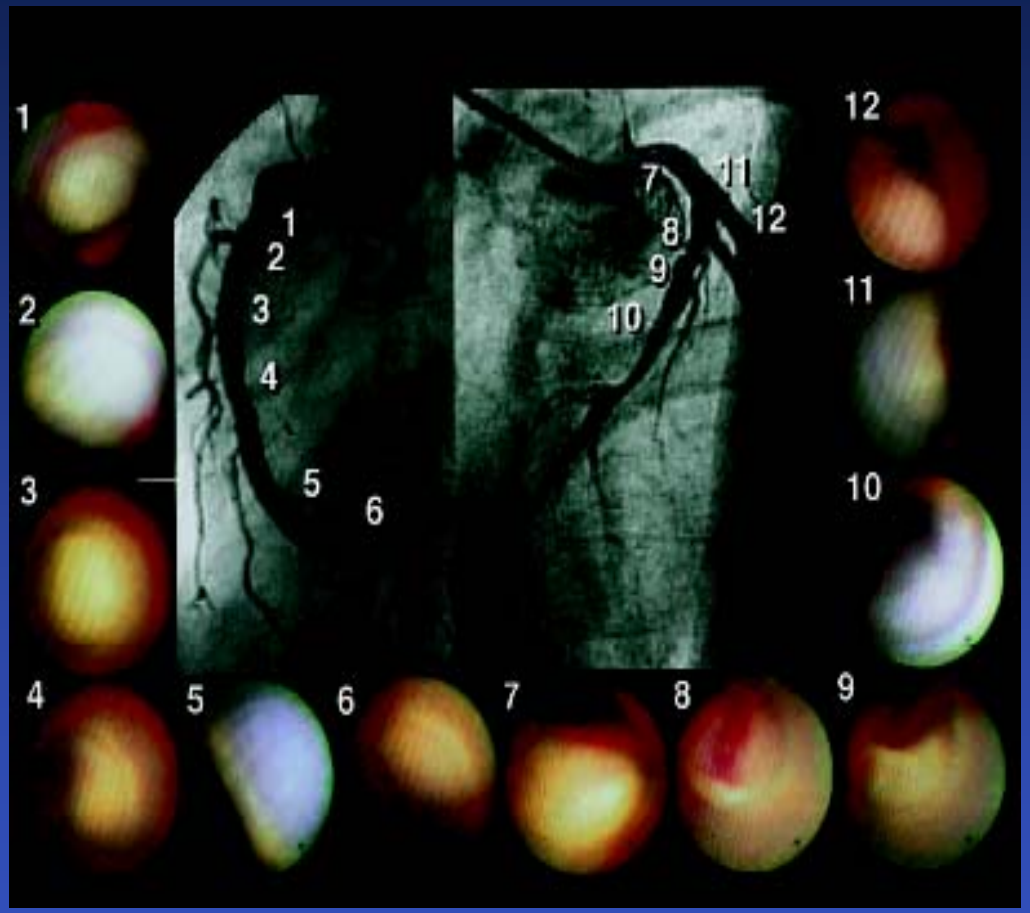
1. 40% of patients with an AMI had multiple complex plaques,

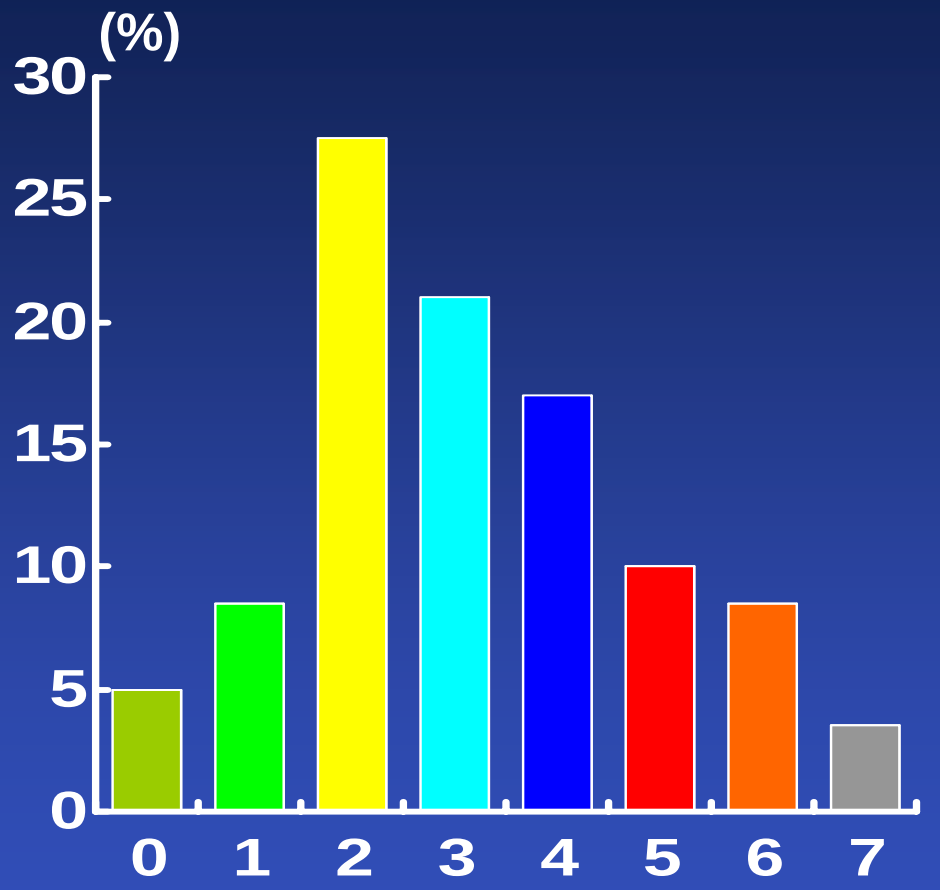
2. These patients had an increased incidence of recurrent ACS, repeat intervention (particularly of non–infarct-related lesions), and CABG in the subsequent year.



Goldstein JA, et al. *N Engl J Med.* 2000; 343:915–922.

Angioscopic study

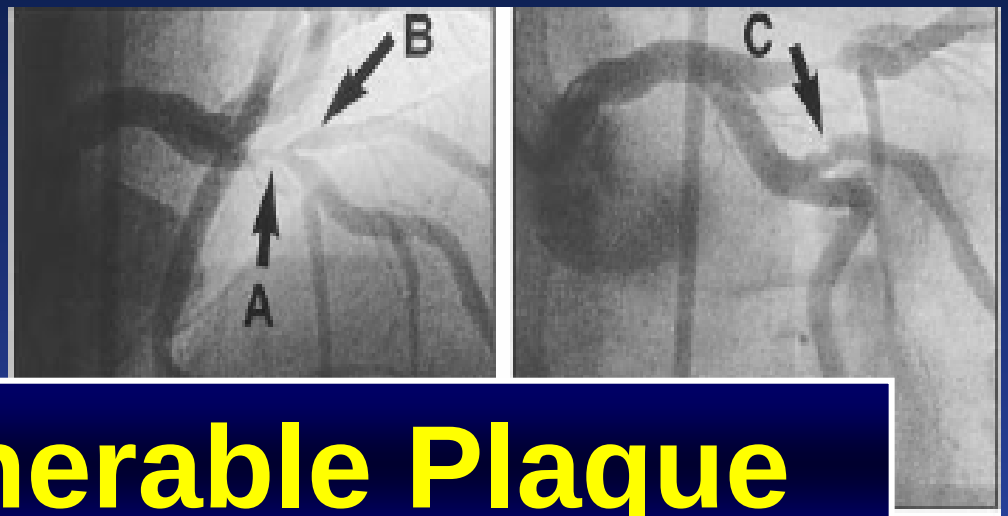




Asakura M. JACC 2001;37: 1284-88

IVUS study

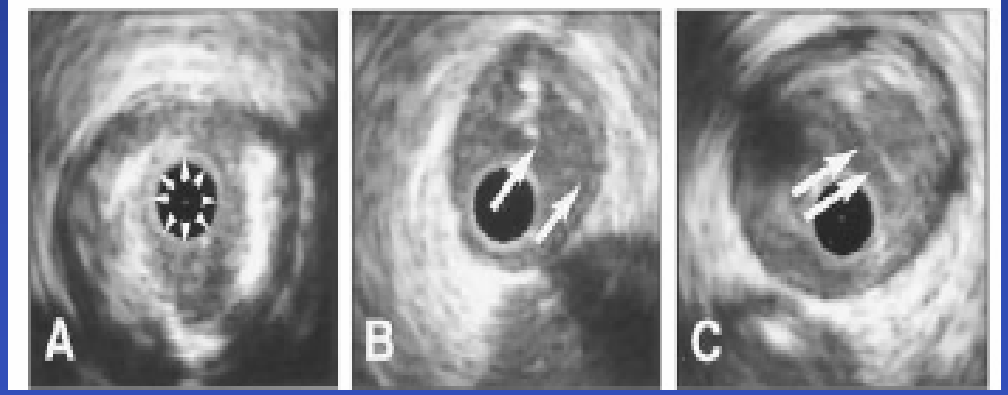
The only three-vessel IVUS study in ACS patients:



An incidence of culprit lesion plaque r

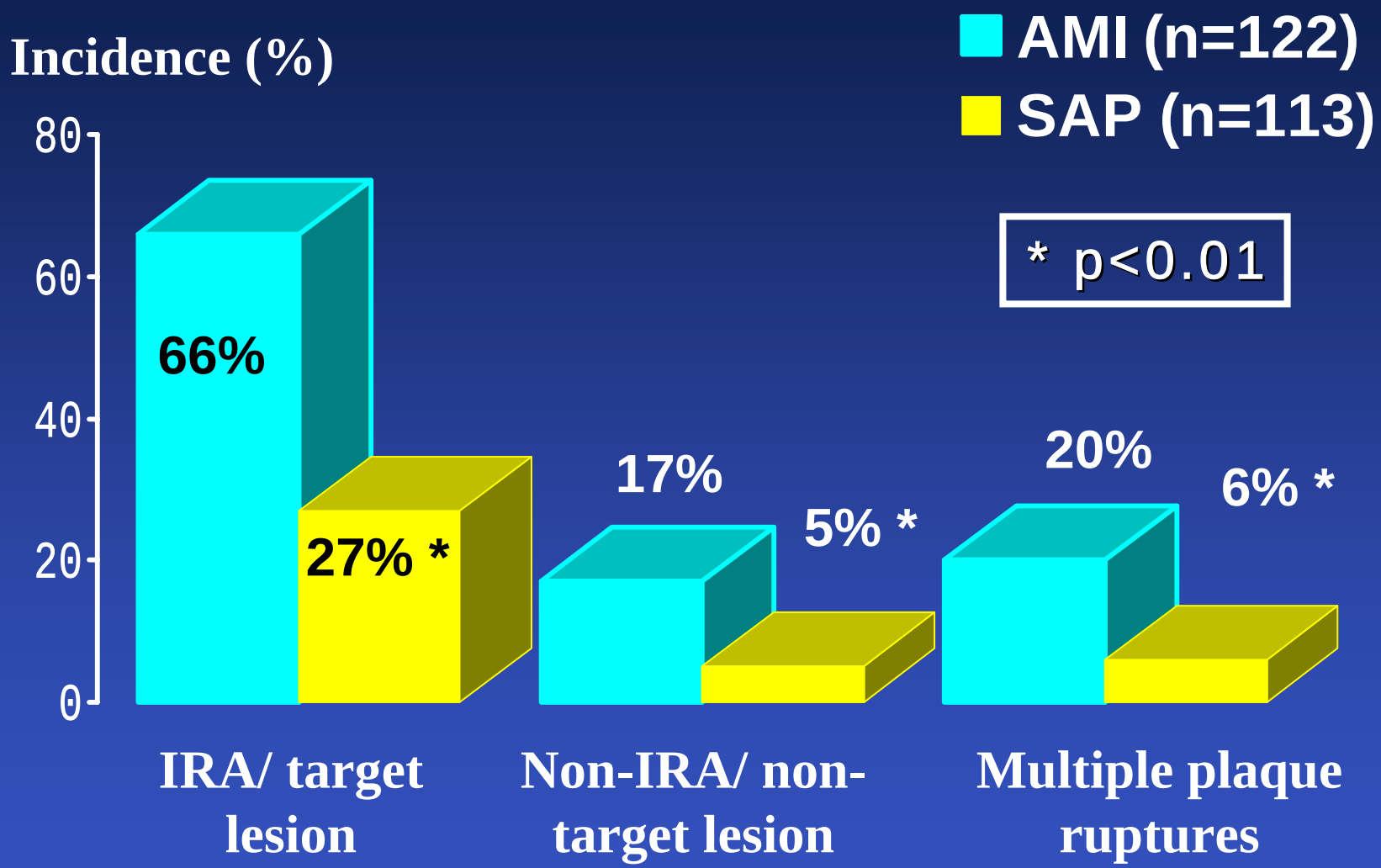
Multiple Vulnerable Plaque

At least one secondary (non-culprit) plaque rupture in 79% (19/24) of the patients



Rioufol G, et al. *Circulation*. 2002;106:804–808.

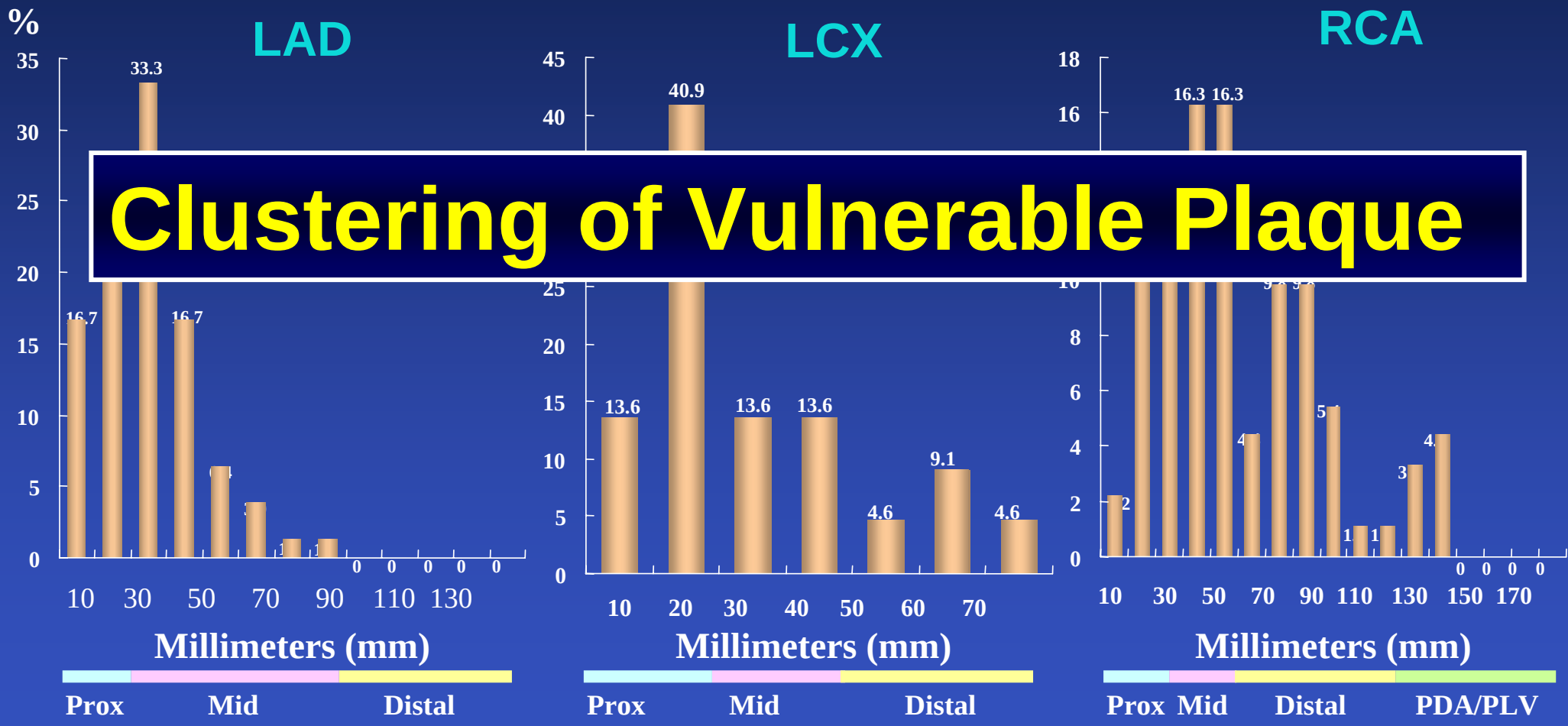
Incidence of plaque rupture



Hong MK, et al. *Circulation* 2004; 110: 928-933

Coronary Artery Spatial Distribution of AMI Occlusions

Angiographic analysis in 208 patients

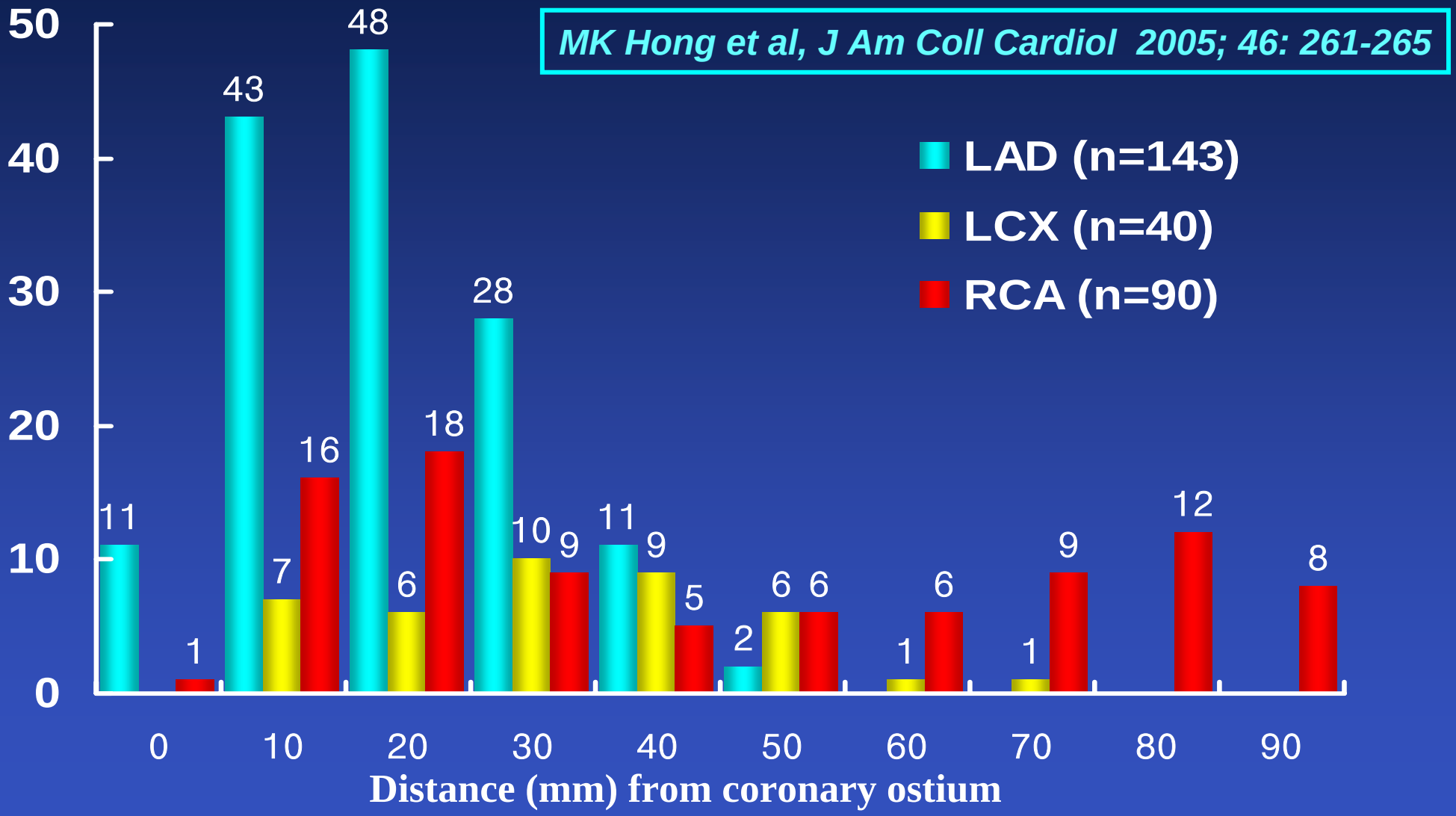


Clustering of Vulnerable Plaque

Wang JC, Circulation 2004; 110: 278-284

Location of 273 Plaque Rupture at Coronary Vessels in 158 ACS and 48 SAP

MK Hong et al, J Am Coll Cardiol 2005; 46: 261-265



Long-term Prognosis of Plaque Rupture

Recent publications about long-term prognosis about plaque rupture

- **Evolution of spontaneous atherosclerotic plaque rupture with medical therapy: long-term follow-up with intravascular ultrasound.**

  Rioufol G, et al. *Circulation* 2004; 110:2875-2880.

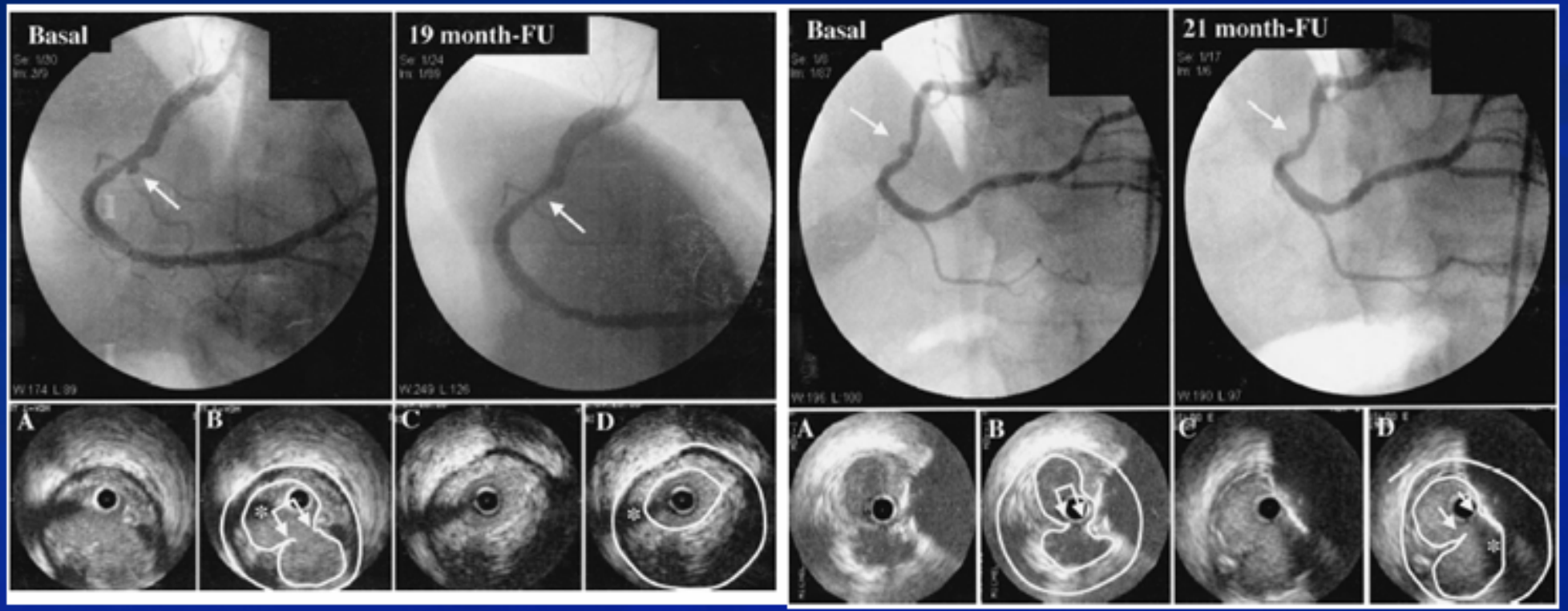
- **Angioscopic follow-up study of coronary ruptured plaques in nonculprit lesions.**

  Takano M et al, *J Am Coll Cardiol* 2005;45:652– 8

- **Cardiovascular events in patients with coronary plaque rupture and nonsignificant stenosis.**

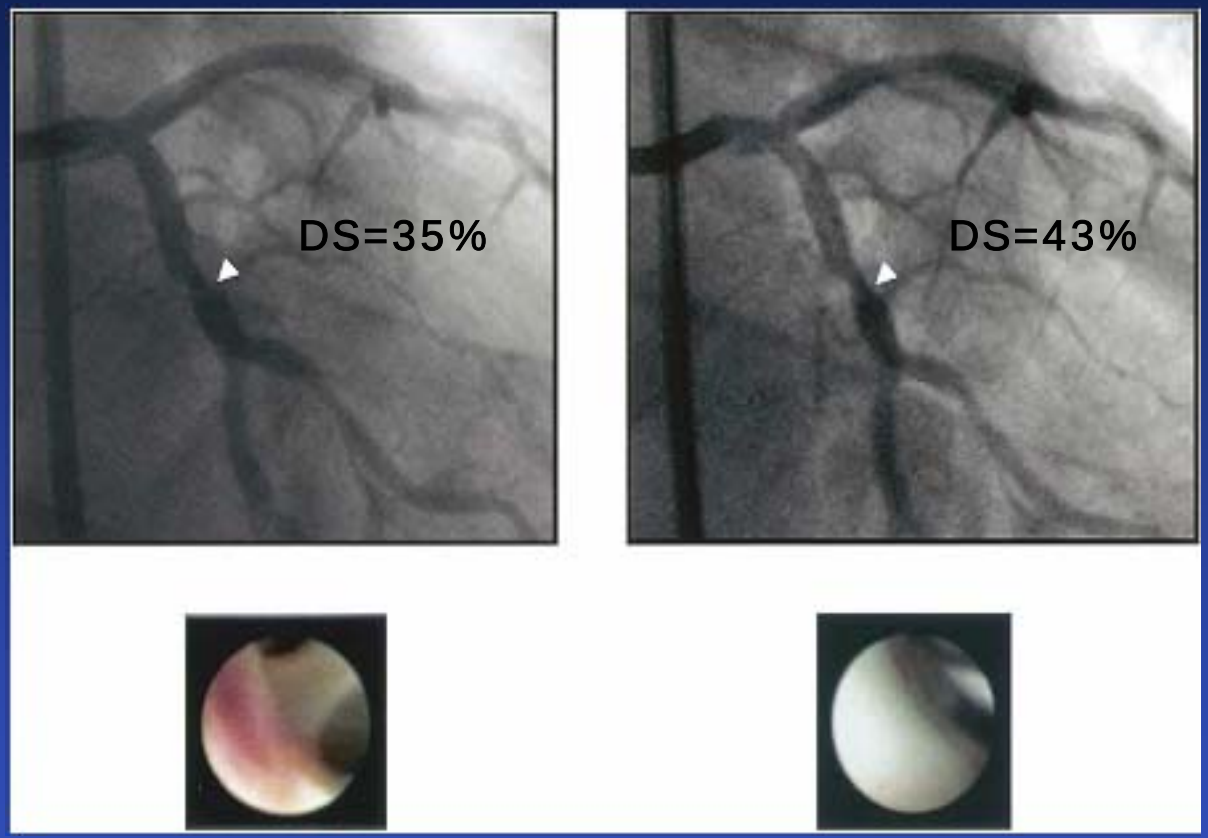
  Ohlmann P, et al, *Am J Cardiol* 2005;96: 1631-1635

Evolution of Spontaneous Atherosclerotic Plaque Rupture With Medical Therapy: Long-Term Follow-Up With IVUS (14 patients, 28 ruptured plaques)



***Conclusions*—Nearly 2 years of follow-up found that spontaneous coronary atheromatous plaque rupture without significant stenosis detected on first acute coronary syndrome healed without significant plaque modification in 50% of cases with medical therapy. (Rioufol G, et al. *Circulation*. 2004;110:2875-2880.)**

Angioscopic follow-up study of coronary ruptured plaques in nonculprit lesions.



Pinkish-white thrombus on the yellow plaque

Smooth white intima without thrombus

The mean follow-up period was 13±9 months.

The healing rate increased according to the follow-up period (23% at ≤12 months vs. 55% at >12 months, p= 0.044). The %DS at the healed plaque increased from baseline to follow-up (12.3% to 22.7%, p<0.05).

The serum CRP level in patients with healed plaques was lower than that in those without healed plaques (p= 0.007).

Takano M et al, *J Am Coll Cardiol* 2005;45:652– 8

Cardiovascular events in patients with coronary plaque rupture and nonsignificant stenosis.

Seventeen consecutive patients with plaque rupture

Mean follow-up duration: 43 ± 25 months,

Events related to those lesions were

1 death (6%) of undetermined cause (6%) after 69 months, no myocardial infarction, and

2 revascularizations (12%) at 3 and 67 months.

Overall, the cumulative rate of cardiac events was 18%.

Ohlmann P, et al, *Am J Cardiol* 2005;96: 1631-1635

Comparison of three recent studies

	Rioufol et al	Angioscopy	WHC data
No. Patients	14	30	17
No. Lesions	28	50	17
F/U duration (months)	22±13 (IVUS FU)	13±9 (angioscopic FU)	43±25 (Clinical FU)
Healing rate	14/28 lesions (50%)	15/50 lesions (30%)	---------
Events	No events	1 Rev.	1 death, 2 Rev
Statin therapy	14 (100%)	Healing (70%), Non-healing (21%)	8 (47%)

Serial intravascular ultrasound evidence of both plaque stabilization and lesion progression in patients with ruptured coronary plaques: effects of statin therapy on ruptured coronary plaque.

Myeong-Ki Hong, Cheol Whan Lee,

Duk-Woo Park, Seung-Whan Lee, Young-Hak Kim,

Jae-Joong Kim, Seong-Wook Park, Seung-Jung Park

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Atherosclerosis 2007; 191 :107-114

Background

Because culprit/target lesions with ruptured plaque morphologies typically have significant lumen compromise, there is little hesitation to treat with percutaneous revascularization.

However, secondary, *non-culprit/non-target lesions* with plaque ruptures are usually not stenotic; and the best treatment (i.e. revascularization vs. medical therapy) is controversial, in part because of a lack of natural history data.

Purpose

Using serial IVUS, to evaluate the natural evolution of secondary (non-culprit/non-target lesion) ruptured plaques and assessed the impact of statin therapy on the morphologic changes.

Study Population

- **We identified 28 patients from AMC clinical and IVUS core laboratory database with non-target/non-culprit lesions and without significant stenosis which underwent baseline and 1-year follow-up IVUS study.**

- **Statin treatment (n=14, 20mg atorvastatin in 7 patients and 40mg simvastatin in 7 patients) vs. non-statin treated group (n=14).**

Anti-platelet regimen

Aspirin, indefinitely and

Ticlopidine for 1 month in 9 patients or
Clopidogrel

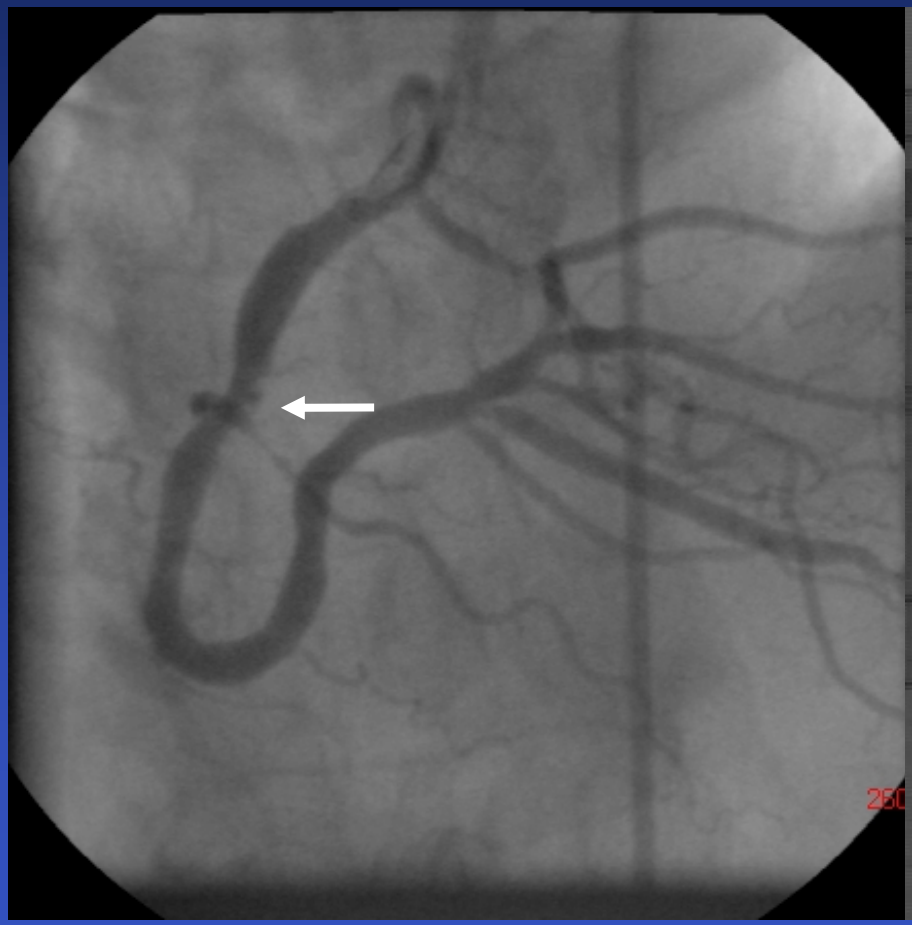
for 1 month in 17 patients after BMS implantation,
for 6 months in 2 patients after DES implantation

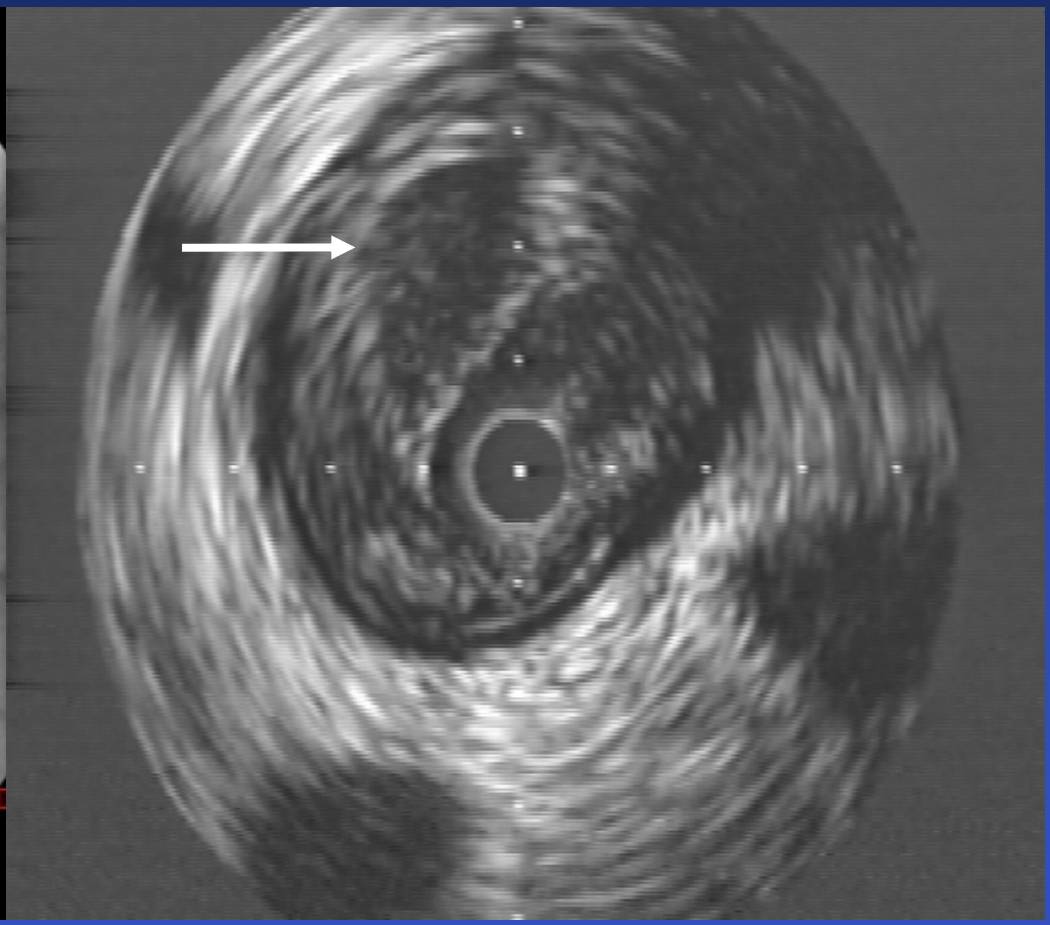
IVUS Imaging Protocol

- **Pre-intervention and 1-year follow-up IVUS**
- **Use of motorized transducer pullback (0.5 mm/sec, pullback speed multiplied by number of seconds).**
- **After intracoronary administration of 0.2mg NTG**
- **From the distal coronary artery to aorto-ostial junction**
- **CVIS system: 1,800 rpm, 3.2F IVUS catheter**

Definition of Plaque Rupture

A plaque with cavity that communicated with the lumen with an overlying residual fibrous cap fragment





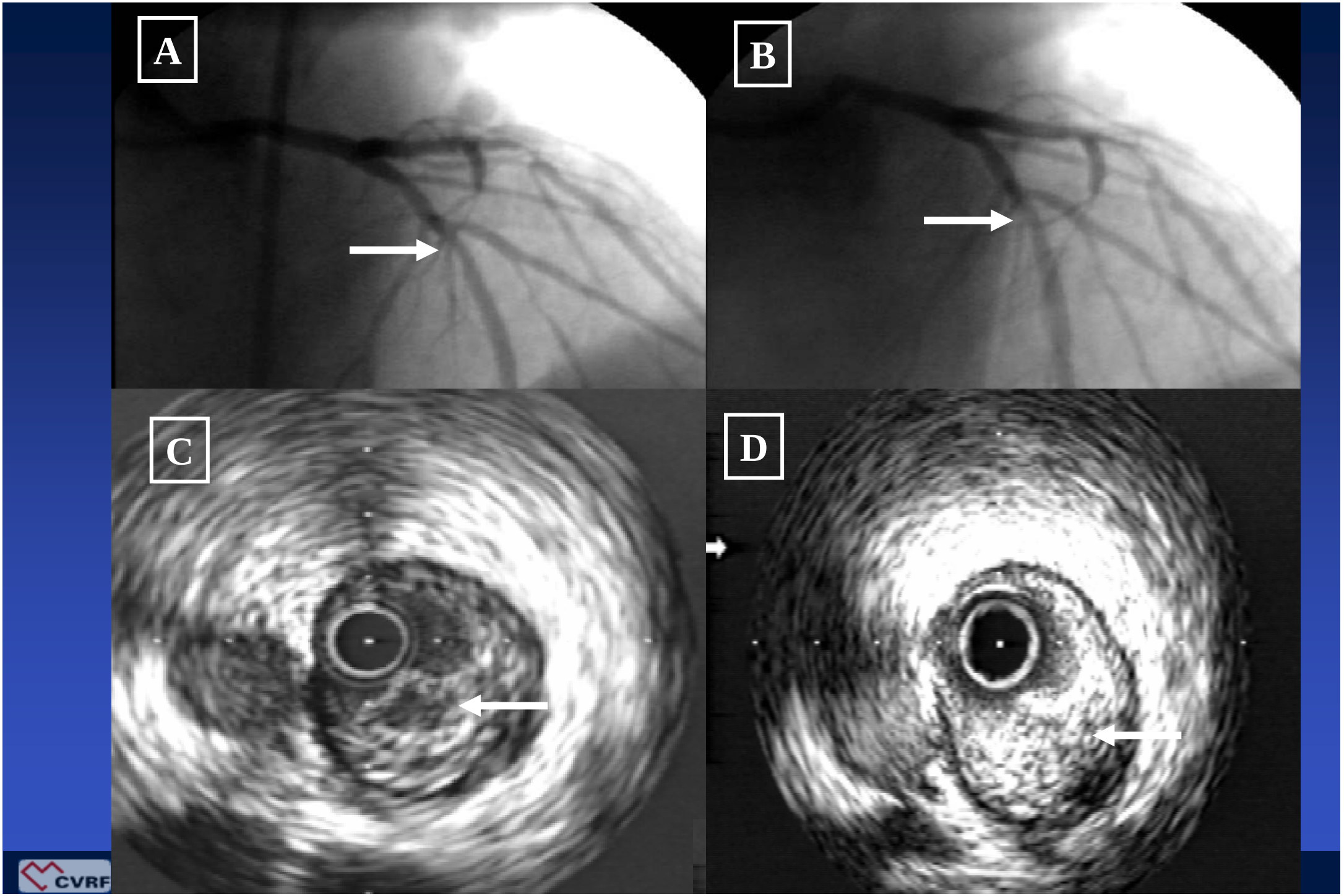
Definition of Plaque Rupture Healing

Complete plaque rupture healing:

1) the disappearance of the intraplaque cavity,
2) complete continuation of the intimal layer, and
3) no reduction of lumen CSA.

Incomplete healing:

>50% decrease in plaque cavity CSA without a reduction of lumen CSA.


A
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Overall clinical outcomes (n=28)

- **Complete healing in 4 lesions,**
- **Incomplete healing in 1 lesions,**
- **No significant changes in 20 lesions,**
- **Progression to a focal stenosis requiring PCI in 3 lesions.**

Clinical outcomes (n=28)

	Statin (n=14)	No-statin (n=14)	P
Complete healing	4	0	0.049
Incomplete healing	0	1	
No significant changes	10	10	
Progression to a focal stenosis requiring PCI	0	3	0.11

Baseline Clinical Characteristics

	Statin treatment	No-statin group	P-value
Number of patients	14	14	
Age (years)	56±10	55±8	0.3
Male gender	12 (86)	13 (93)	0.5
Hypertension	5 (36)	7 (50)	0.4
Diabetes mellitus	3 (21)	4 (29)	0.5
Cigarette smoking	9 (64)	7 (50)	0.4
Hypercholesterolemia (total cholesterol ≥ 220 mg/dl)	5 (36)	2 (14)	0.19

Baseline Clinical Characteristics

	Statin treatment	No-statin group	P-value
Number of diseased vessels			**0.9**
1	**8 (57)**	**7 (50)**	
2	**3 (21)**	**4 (29)**	
3	**3 (21)**	**3 (21)**	
Clinical diagnosis			**0.6**
Stable angina	**2 (14)**	**4 (29)**	
Unstable angina, class IIIB	**4 (29)**	**4 (29)**	
Acute MI	**8 (57)**	**6 (43)**	

Baseline Clinical Characteristics

	Statin treatment	No-statin group	P-value
Ruptured plaque location			0.9
LAD	5 (36)	5 (36)	
LCX	2 (14)	3 (21)	
RCA	7 (50)	6 (43)	
Medications			
Nitrates	12 (86)	13 (93)	0.5
Calcium channel blocker	10 (71)	10 (71)	0.7
Beta-blocker	10 (71)	8 (57)	0.4
Angiotensin II receptor antagonist	3 (21)	4 (29)	0.5
ACE inhibitor	4 (29)	4 (29)	0.7

IVUS analysis (No-statin group)

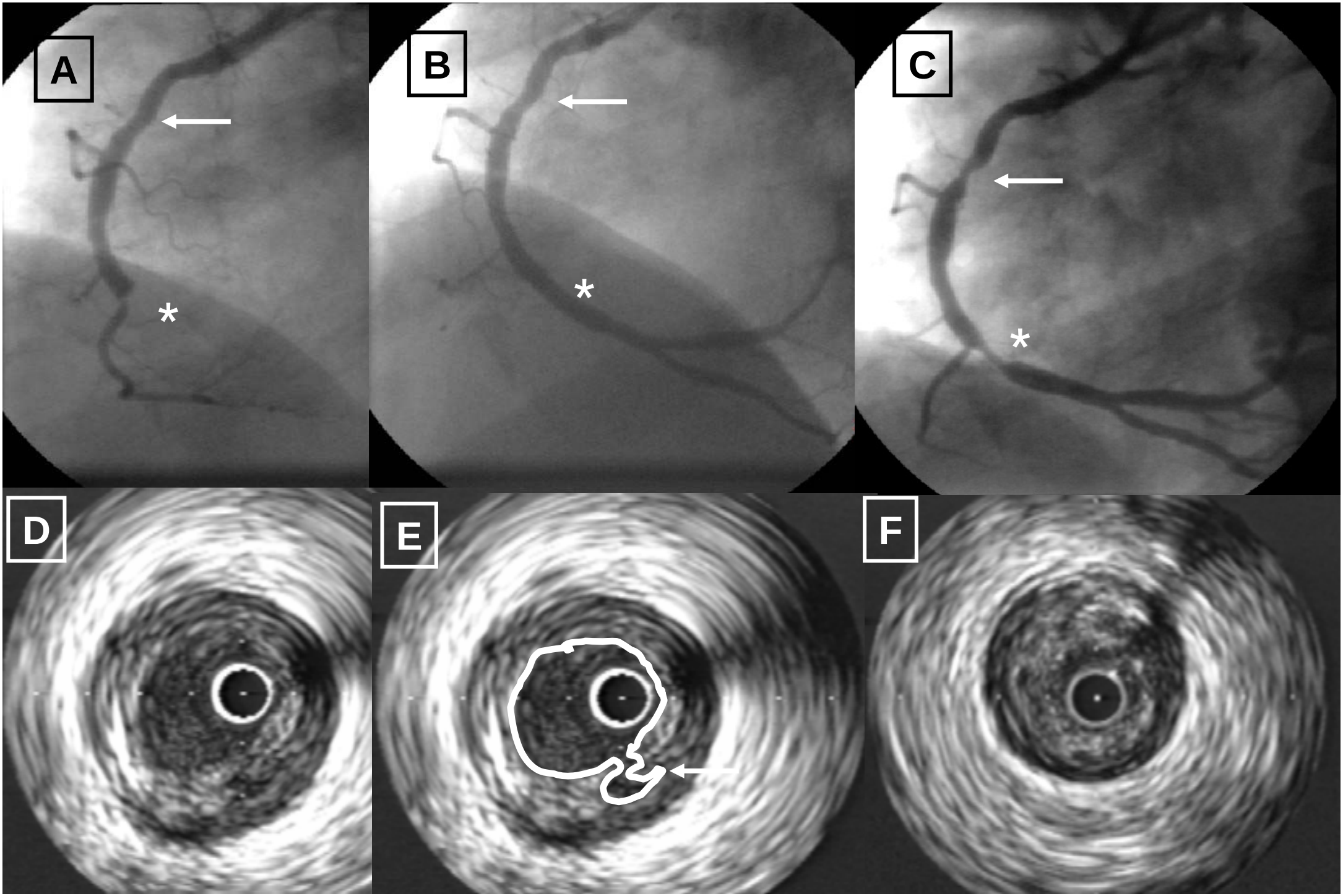
	Baseline	1-year FU	P
Proximal reference segment			
EEM CSA (mm^2)	20.7±7.6	20.6±7.7	0.6
Lumen CSA (mm^2)	11.6±5.6	11.7±5.6	0.5
Ruptured plaque segment			
EEM CSA (mm^2)	19.9±7.0	19.6±7.0	0.13
Lumen CSA (mm^2)	6.5±2.9	5.9±3.2	0.060
P&M CSA (mm^2)	10.5±4.7	11.0±4.7	0.026
Ruptured cavity CSA (mm^2)	3.0±1.6	2.7±1.9	0.073
Remodeling index	1.0±0.0	1.0±0.1	0.3
Distal reference segment			
EEM CSA (mm^2)	18.6±6.7	18.6±6.6	0.4
Lumen CSA (mm^2)	10.6±5.4	10.5±5.5	0.5

IVUS analysis (Statin treatment group)

	Baseline	1-year FU	P
Proximal reference segment			
EEM CSA (mm^2)	21.1±6.6	21.1±6.6	0.7
Lumen CSA (mm^2)	12.0±4.1	12.0±4.1	0.2
Ruptured plaque segment			
EEM CSA (mm^2)	20.0±6.8	19.8±6.8	0.2
Lumen CSA (mm^2)	7.2±3.9	7.6±4.3	0.057
P&M CSA (mm^2)	10.5±4.1	10.4±3.8	0.9
Ruptured cavity CSA (mm^2)	2.3±0.8	1.8±1.4	0.011
Remodeling index	1.0±0.1	1.0±0.1	0.4
Distal reference segment			
EEM CSA (mm^2)	19.1±7.0	19.1±7.0	0.2
Lumen CSA (mm^2)	10.5±4.5	10.6±4.5	0.3

Changes in ruptured plaque segment analysis between statin-treated and control lesions.

	Statin treatment	No-statin group	P
ΔEEM CSA (mm^2)	-0.1±0.1	-0.3±0.7	0.4
ΔLumen CSA (mm^2)	0.4±0.8	-0.6±1.0	0.007
ΔP&M CSA (mm^2)	0.0±0.7	0.6±0.9	0.051
ΔRuptured cavity CSA (mm^2)	-0.5±0.7	-0.3±0.6	0.4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Changes in ruptured plaque segment analysis between TLR and non-TLR lesions.

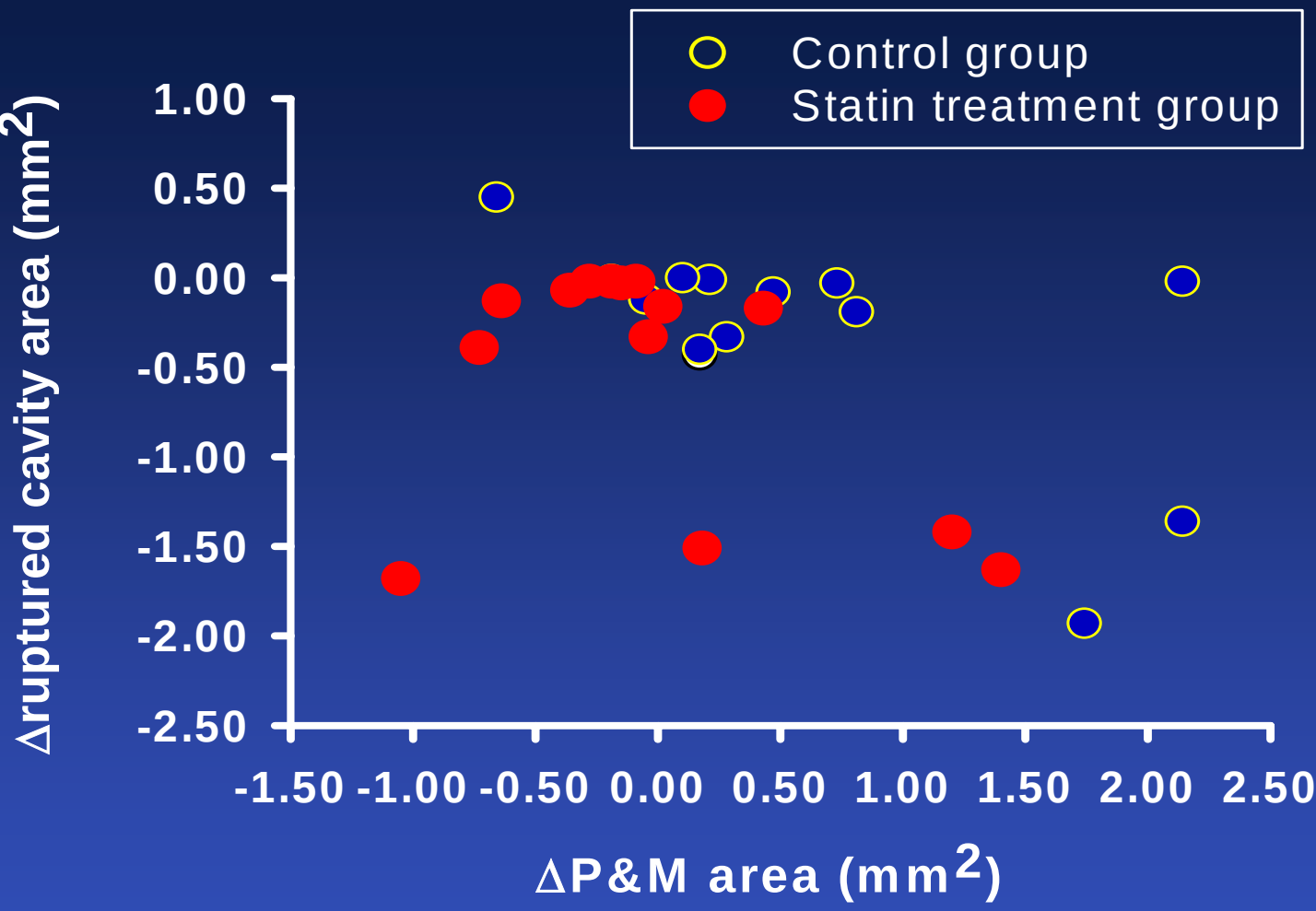
	TLR (n=3)	Non-TLR (n=25)	P
ΔEEM CSA (mm^2)	-0.6±1.4	-0.2±0.3	0.6
ΔLumen CSA (mm^2)	-1.7±1.4	0.1±0.8	0.001
ΔP&M CSA (mm^2)	1.6±1.0	0.1±0.7	0.002
ΔRuptured cavity CSA (mm^2)	-0.5±0.7	-0.4±0.7	0.8

Predictors of healing.

- **Using △ruptured cavity CSA as a continuous measure of plaque rupture healing**

- **The only independent predictor of △ruptured cavity CSA was △P&M CSA:**
overall (r=0.412, p=0.029, 95% CI= -0.614 to -0.035);

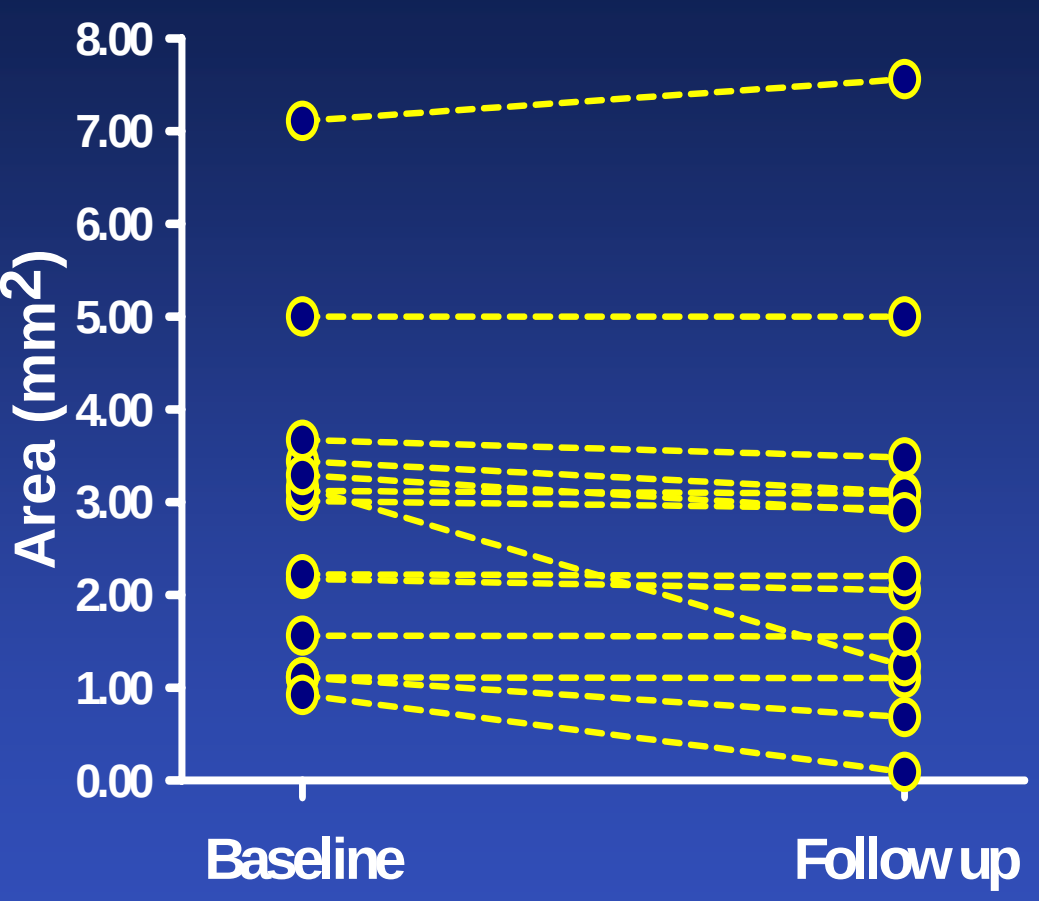
in statin-treated patients (r=0.387, p=0.172, 95% CI= -0.973 to 0.194); and in non-statin treated patients (r=0.646, p=0.017, 95% CI= -0.821 to -0.100).

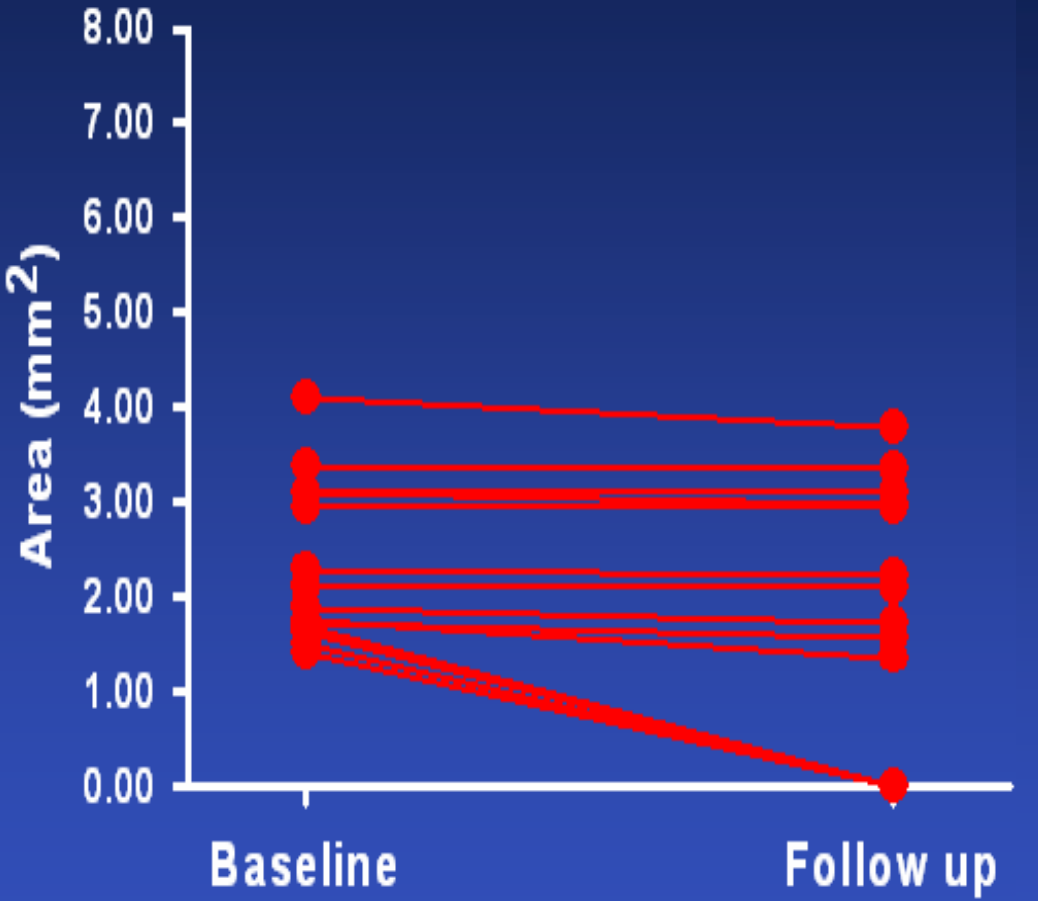


in statin-treated patients; r=0.387, p=0.172

in non-statin treated patients; r=0.646, p=0.017.

Changes of ruptured plaque area





Control group
Statin treatment group

Conclusion

- **The current 12-month follow-up IVUS study showed beneficial effects of statin treatment on reduction of revascularization rates and stabilization of non-culprit/non-target lesion plaque ruptures without significant stenosis.**

- **Conversely, healing of non-statin-treated non-culprit/non-target lesion plaque ruptures can be responsible for lesion progression requiring revascularization.**

Next step – – →
To identify vulnerable plaque before it rupture and to start statin therapy

Comparison of Virtual Histology to Intravascular Ultrasound of Culprit Coronary Lesions in Acute Coronary Syndrome and Target Coronary Lesions in Stable Angina Pectoris

Myeong-Ki Hong, Cheol Whan Lee, Young-Hak Kim, Duk-Woo Park, Seung-Hwan Lee, Jae-Joong Kim, Seong-Wook Park, and Seung-Jung Park

Asan Medical Center, Seoul, Korea

Am J Cardiol 2007 (in press)

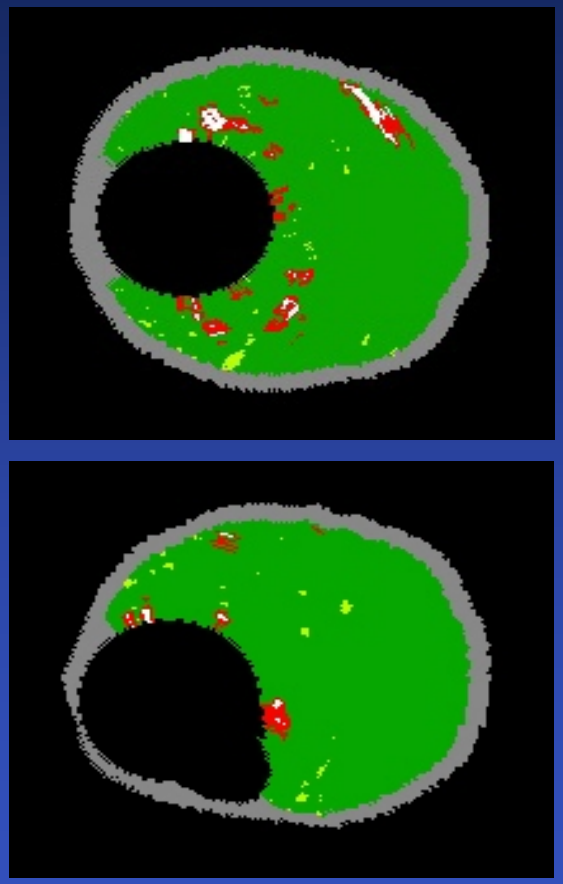
VH Study in AMC

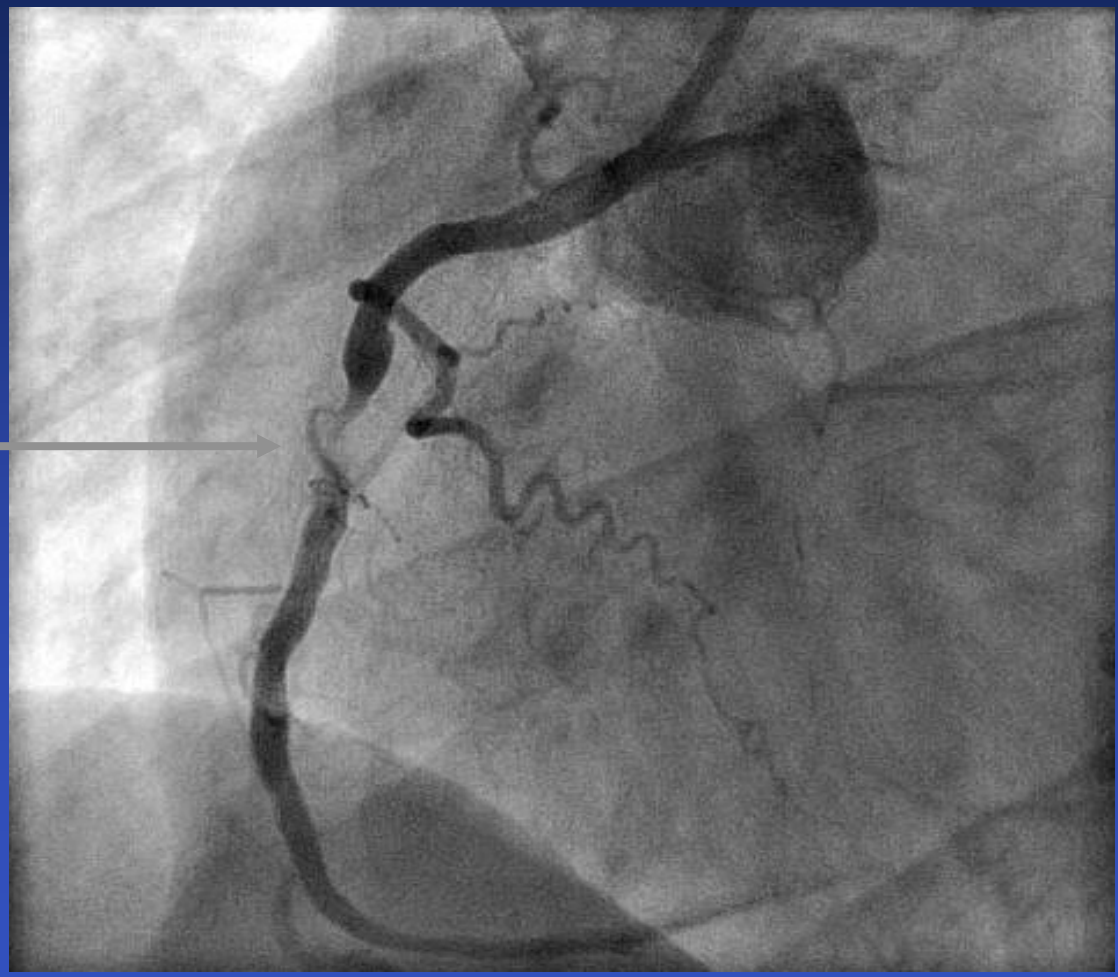
Plaque Composition of Target/ Culprit Lesions in Stable vs. ACS

- **Three hundred eighteen patients who underwent VH-IVUS in the target/culprit lesions from May 2005 to July 2006.**

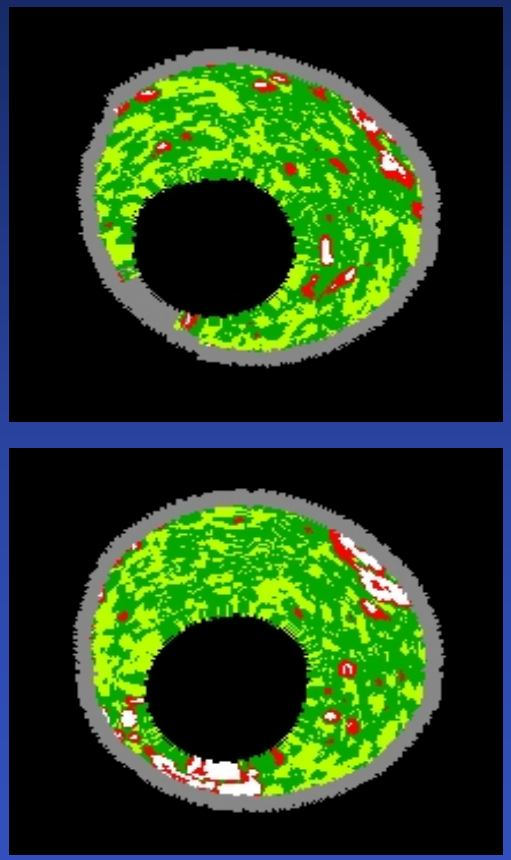
- **Three hundred eighteen patients composed of 195 SAP patients and 123 ACS patients.**

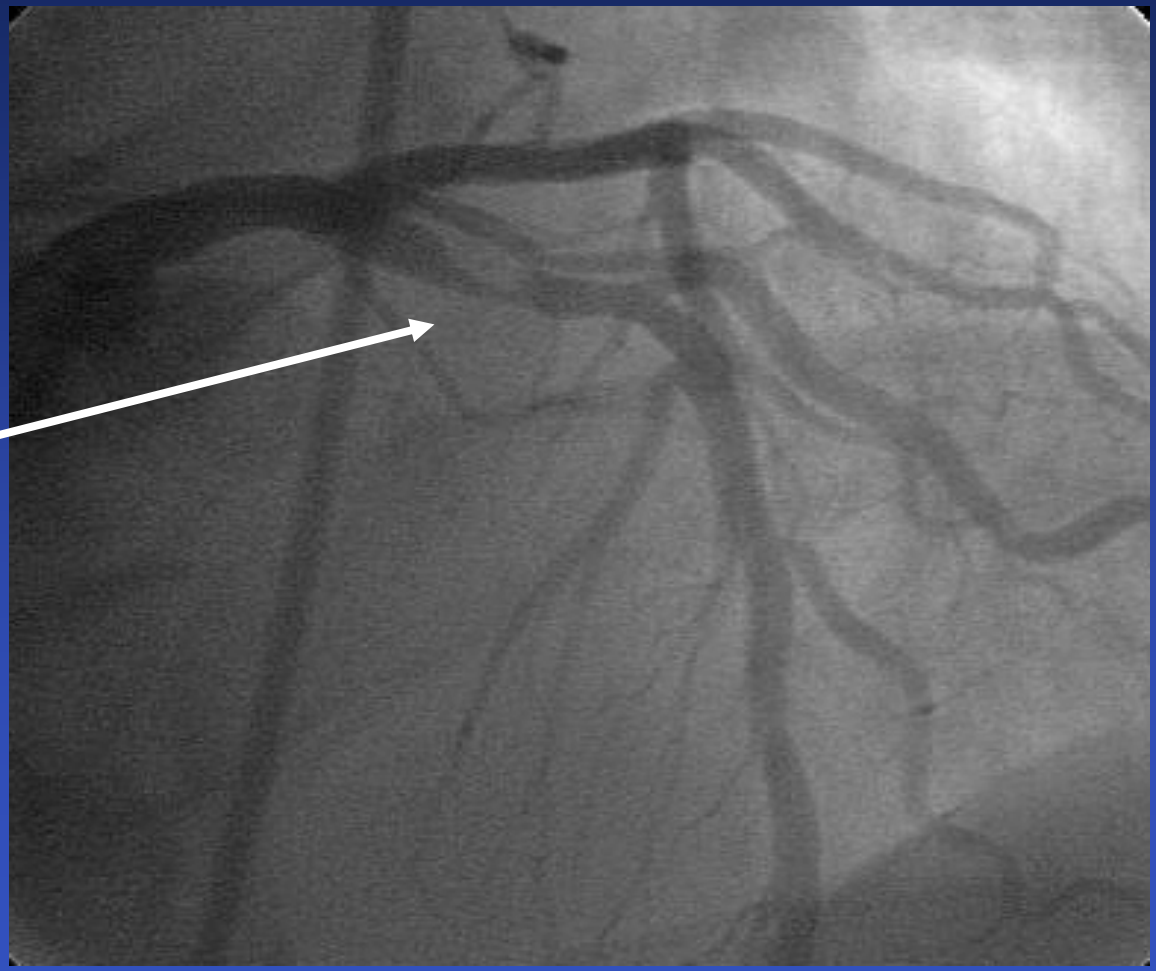
Fibrotic Plaque



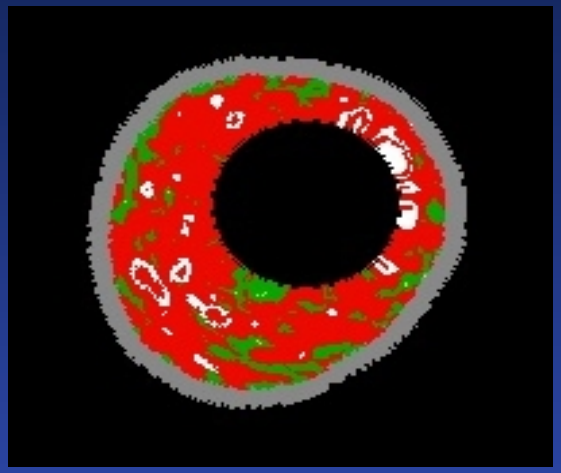


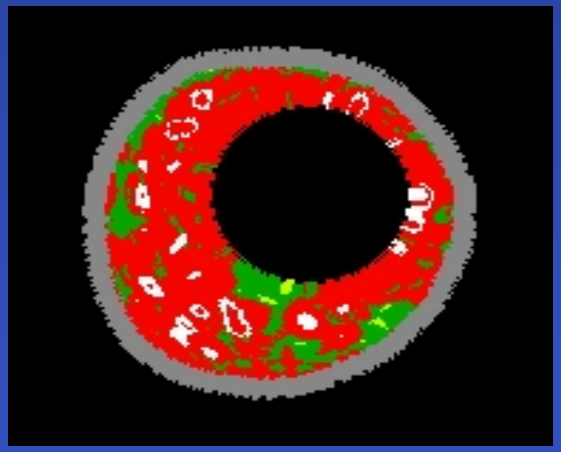
Fibrofatty Plaque

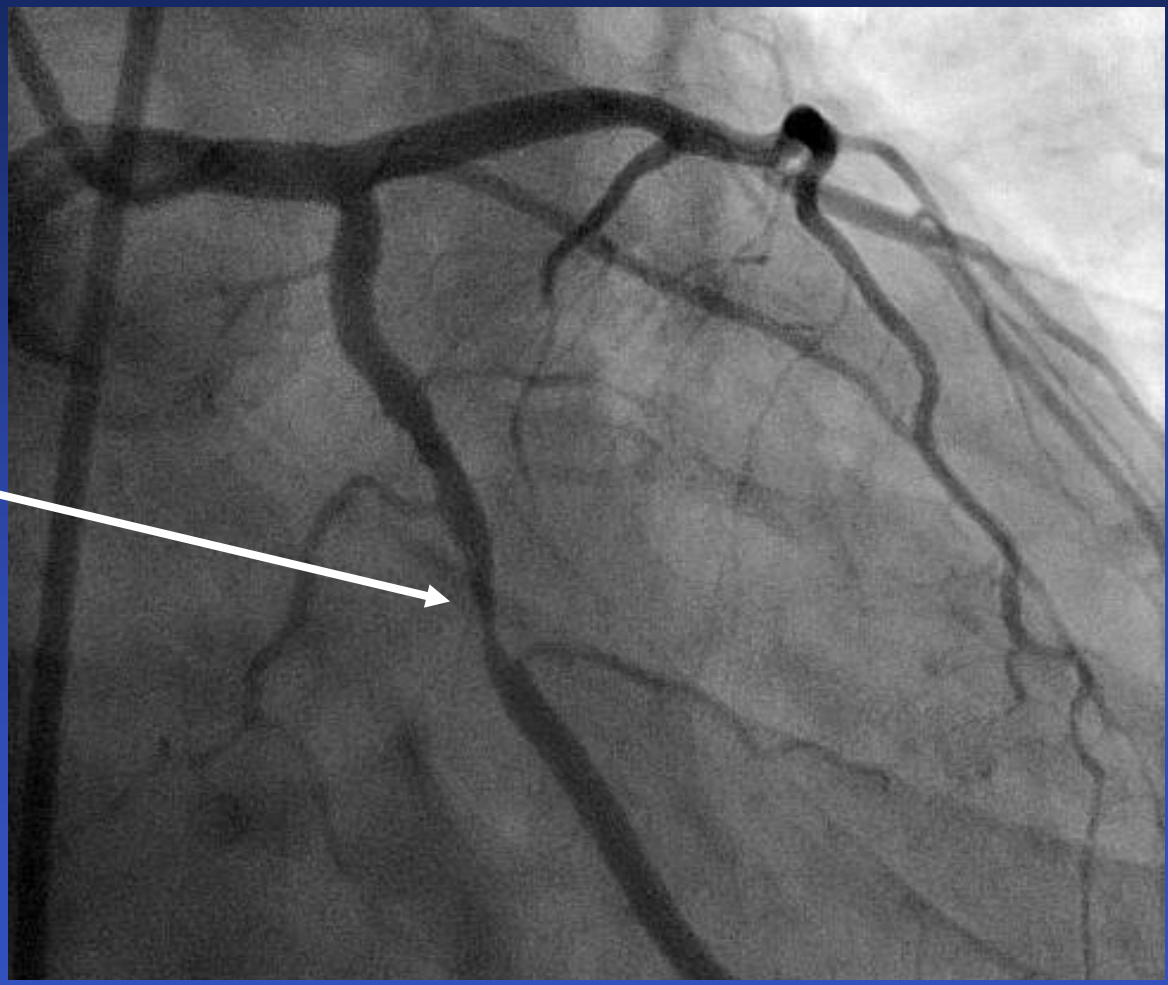




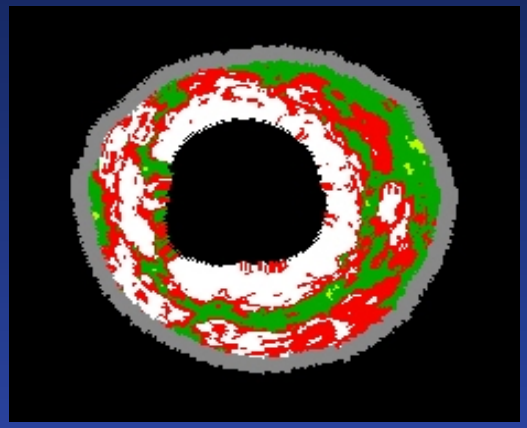
Necrotic Core

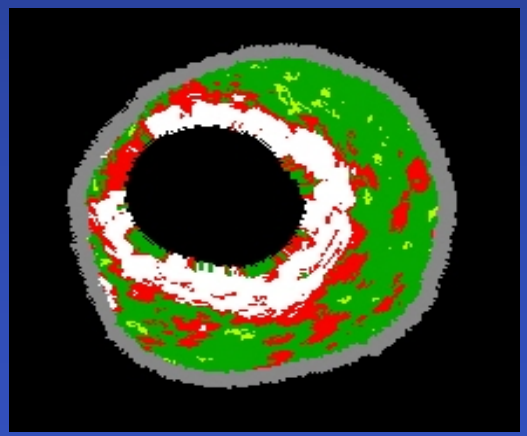


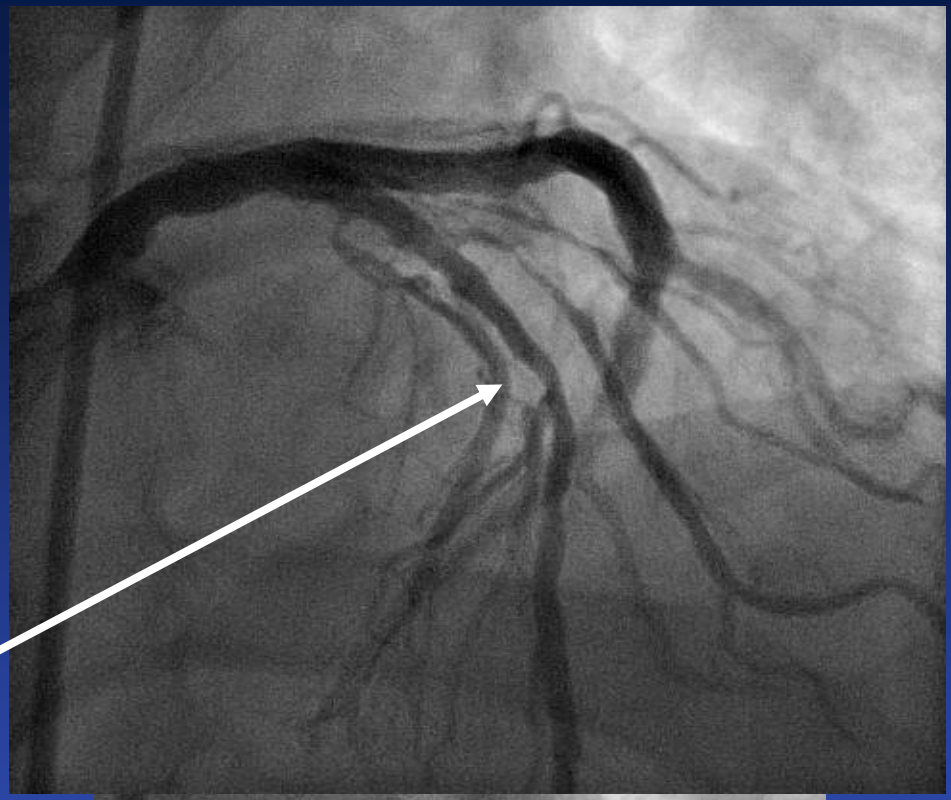


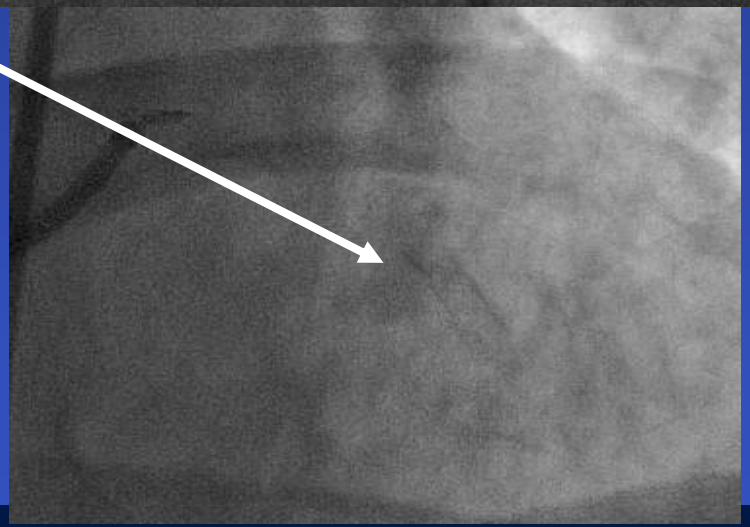


Dense Calcium





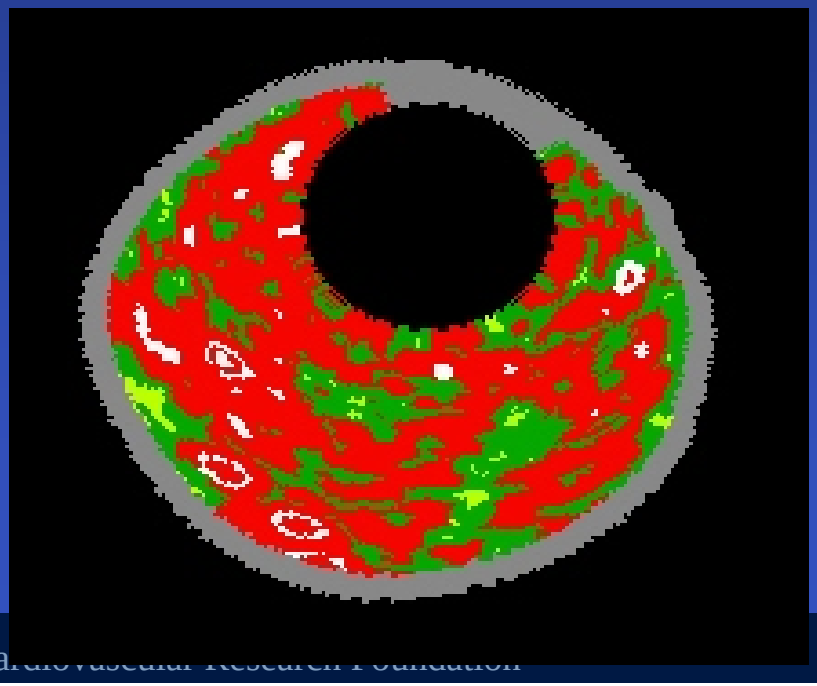


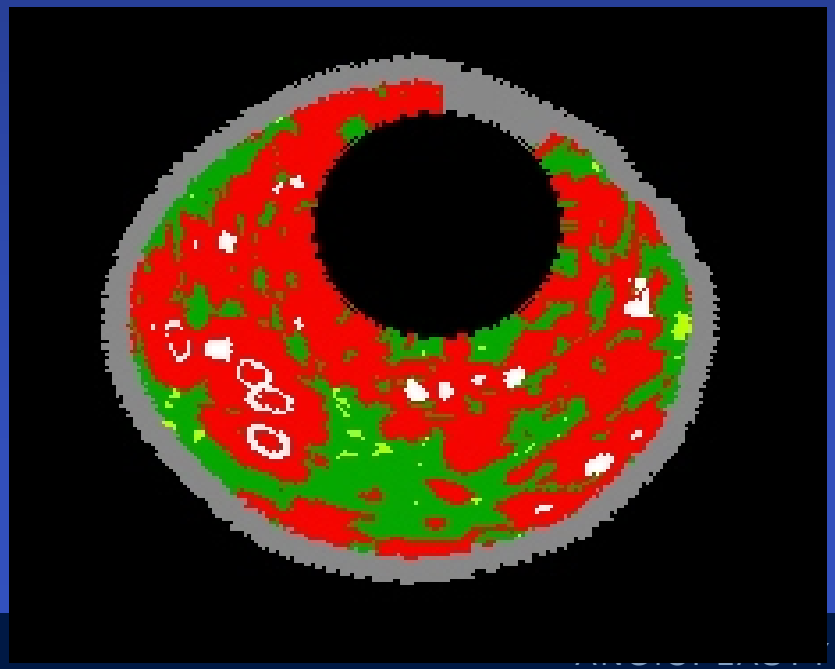


Thin-Cap FibroAtheroma (TCFA) by VH-IVUS

- In at least three consecutive frames:
- 1) necrotic core ≥ 10% without evident overlying fibrous tissue and
- 2) percent atheroma area ≥ 40%.

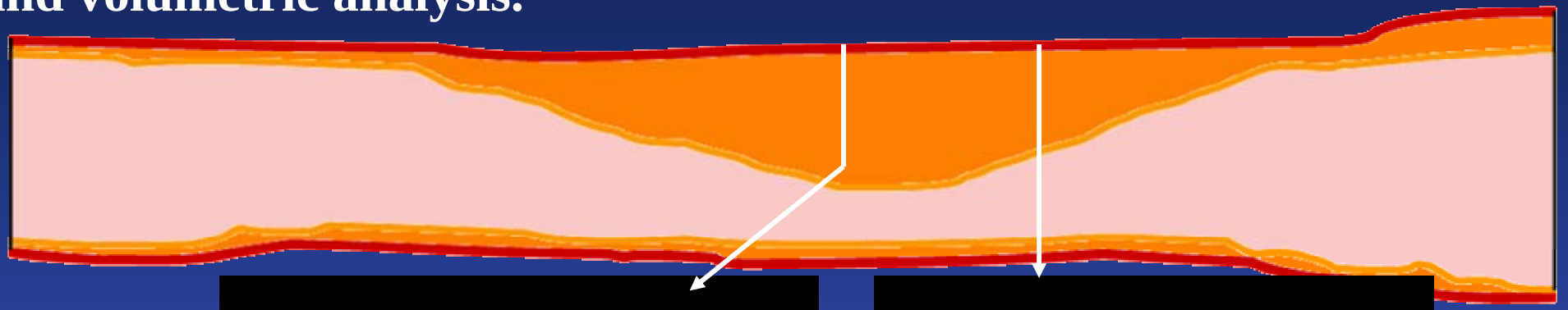
(Rodriguez-Granillo GA et al. *J Am Coll Cardiol* 2005;46:2038–42)

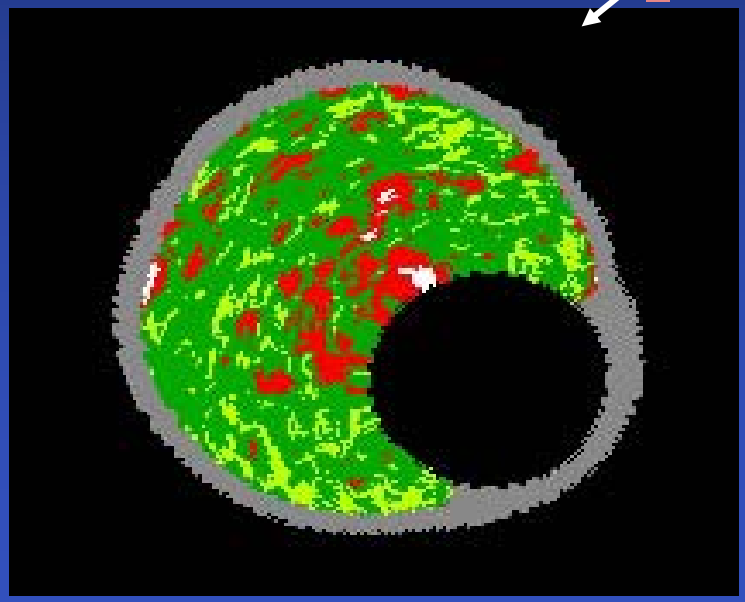




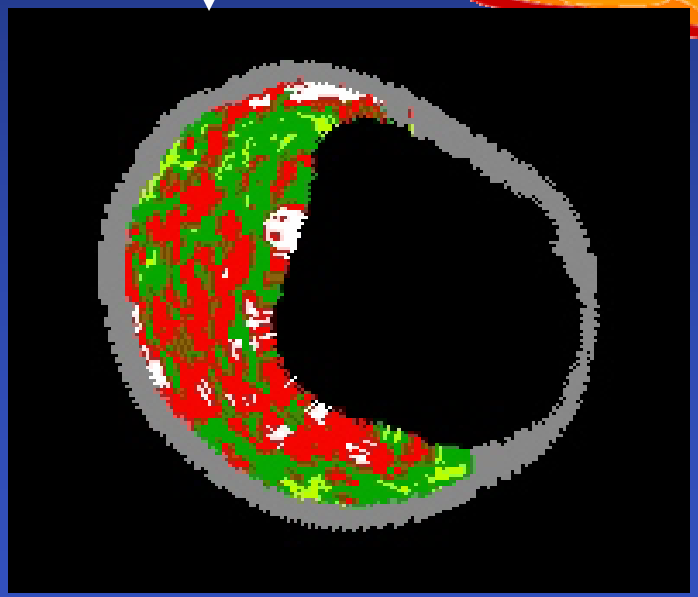
IVUS Measurements

Planar VH-IVUS measurements were performed at 2 lesion segments (minimum lumen cross-sectional area and the largest of necrotic core) and volumetric analysis.





Minimal lumen CSA



Largest necrotic core burden

VH-IVUS in minimum lumen area

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^2)			
Fibrotic	**5.3±2.7**	**4.6±3.0**	**0.030**
Fibrofatty	**0.5±0.6**	**0.5±0.6**	**0.6**
Dense calcium	**0.8±0.7**	**0.6±0.6**	**0.001**
Necrotic core	**3.1±1.9**	**2.1±1.3**	**0.001**
Percentage (%)			
Fibrotic	**53±15**	**56±15**	**0.073**
Fibrofatty	**5±5**	**7±6**	**0.020**
Calcific	**9±7**	**8±8**	**0.4**
Necrotic	**33±14**	**29±14**	**0.015**

VH-IVUS in largest necrotic core

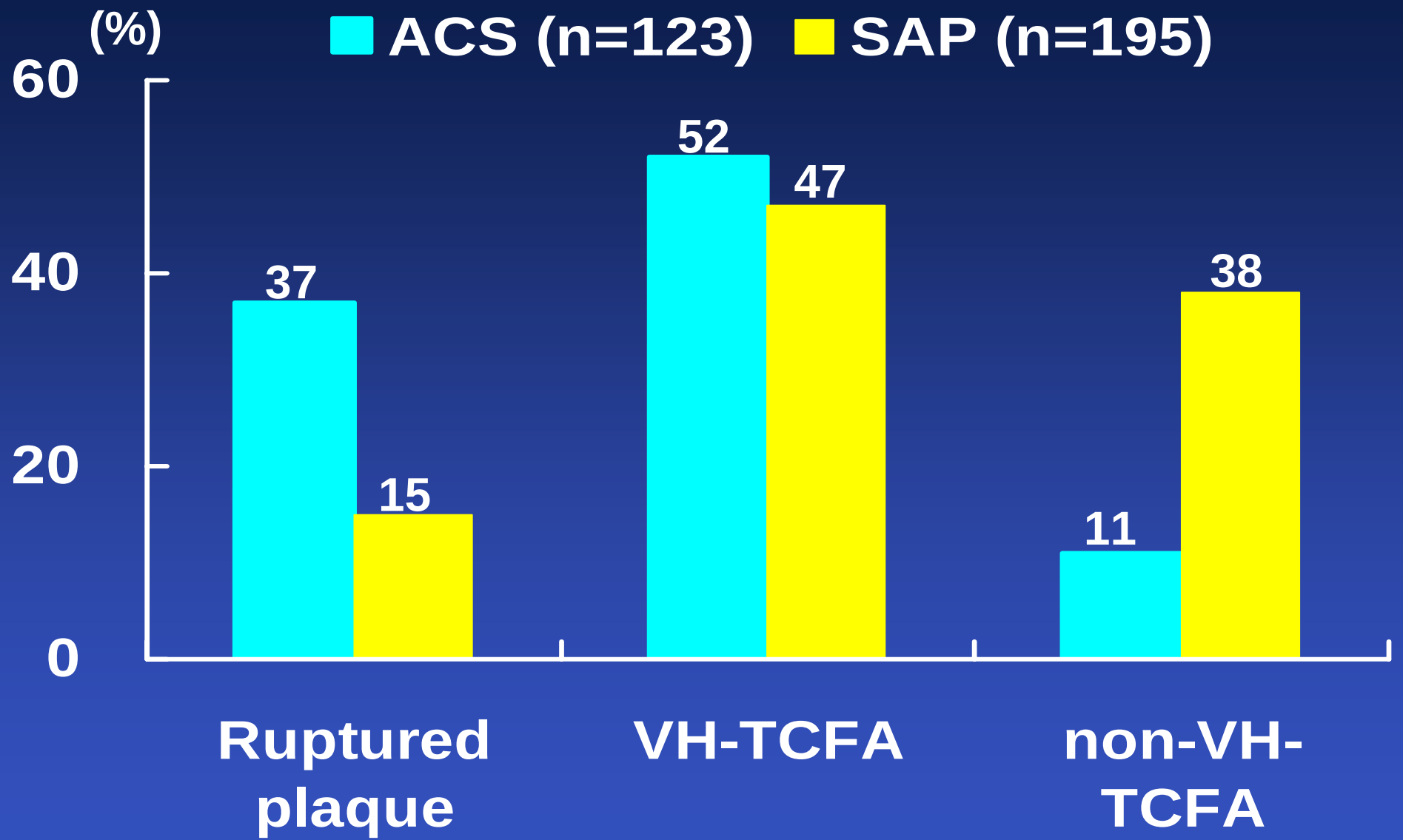
AMC-VH

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^2)			
Fibrotic	**5.0±4.3**	**4.0±2.8**	**0.015**
Fibrofatty	**0.4±0.4**	**0.4±0.5**	**0.6**
Dense calcium	**0.9±0.7**	**0.7±0.7**	**0.003**
Necrotic core	**3.4±2.0**	**2.3±1.6**	**0.001**
Percentage (%)			
Fibrotic	**50±15**	**53±15**	**0.105**
Fibrofatty	**4±4**	**5±5**	**4**
Calcific	**10±7**	**9±8**	**0.5**
Necrotic	**36±13**	**33±14**	**0.034**

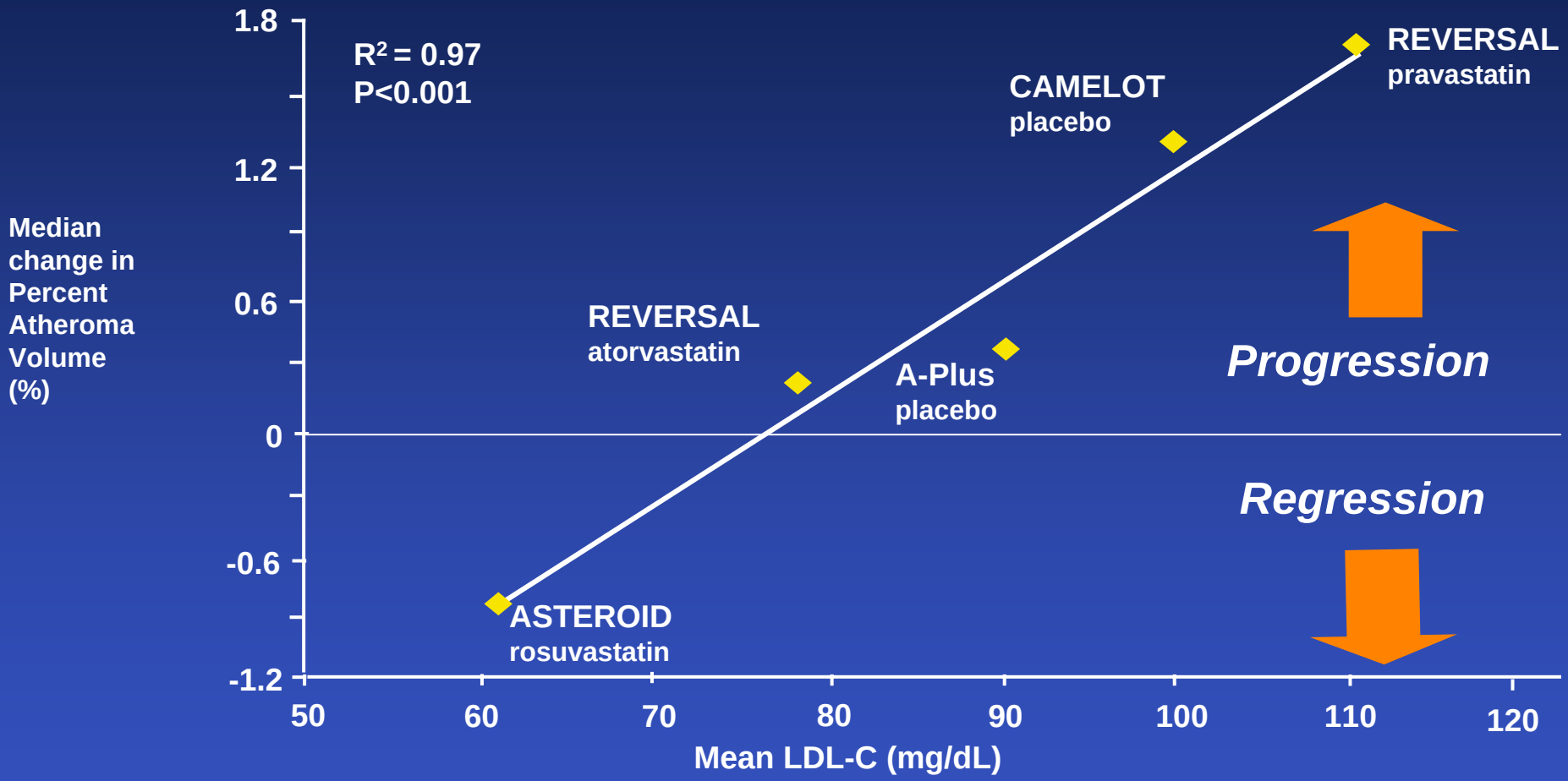
VH-IVUS in volumetric analysis

AMC-VH

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^3)			
Fibrotic	41.9±22.4	32.3±20.8	0.001
Fibrofatty	4.7±4.5	4.5±4.7	0.7
Dense calcium	6.4±5.1	4.4±4.6	0.001
Necrotic core	20.3±12.6	14.3±9.5	0.001
Percentage (%)			
Fibrotic	56±13	57±13	0.3
Fibrofatty	6±5	8±5	0.045
Calcific	9±7	9±8	0.5
Necrotic	29±12	27±11	0.081


(%)
ACS (n=123)
SAP (n=195)
60
40
20
0
37
15
52
47
11
38
Ruptured plaque
VH-TCFA
non-VH-TCFA

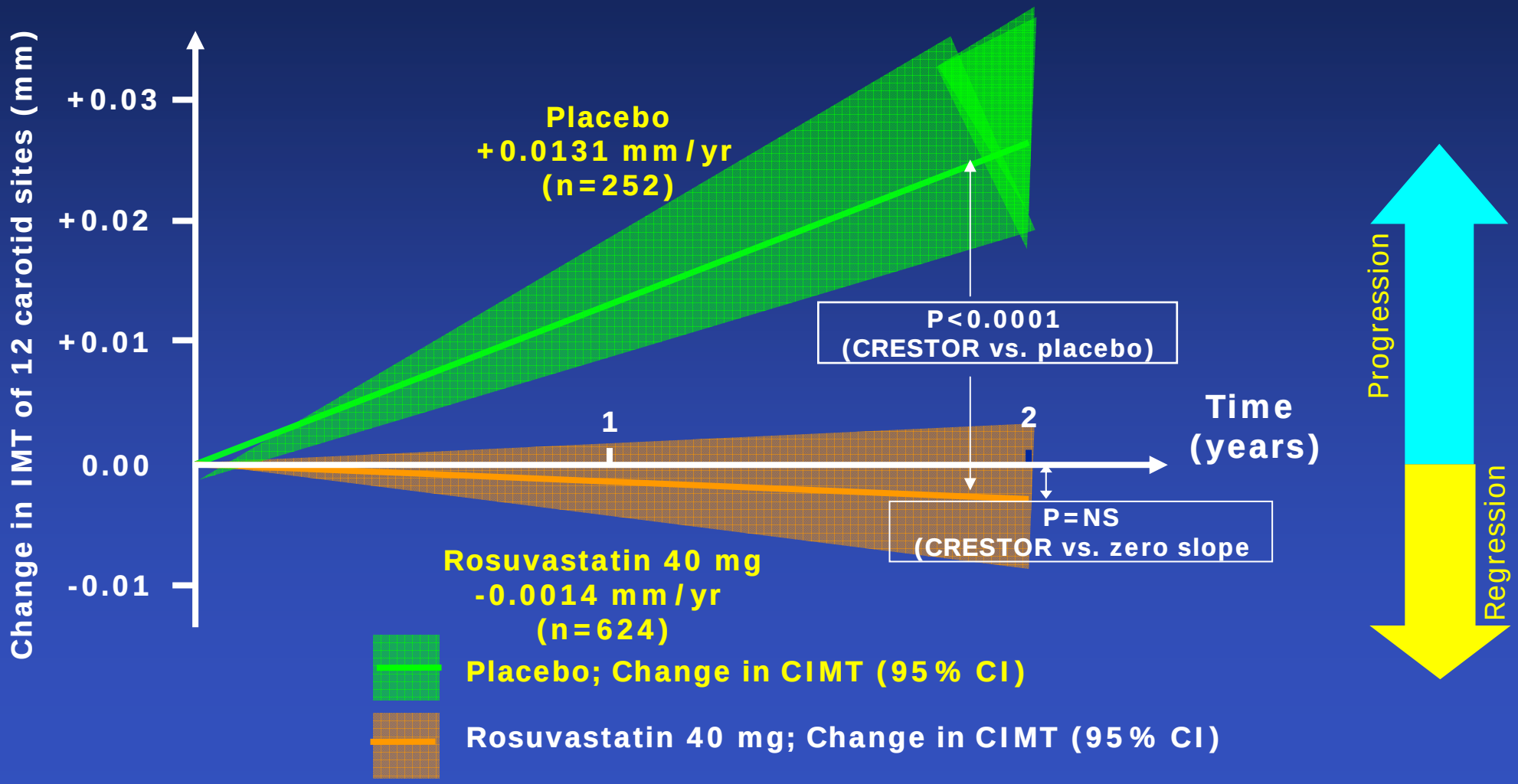
Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials



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

METEOR study end-points:

Rate of change of maximum IMT at 12 carotid sites
Rosuvastatin vs placebo



Crouse JR, et al. *JAMA* 2007;297:(doi:10.1001/jama.297.12.joc70024)