Serial IVUS Findings in Patients with Untreated Ruptured Coronary Plaques: Evidence of Both Plaque Stabilization and Lesion Progression

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Atherosclerosis (in press)

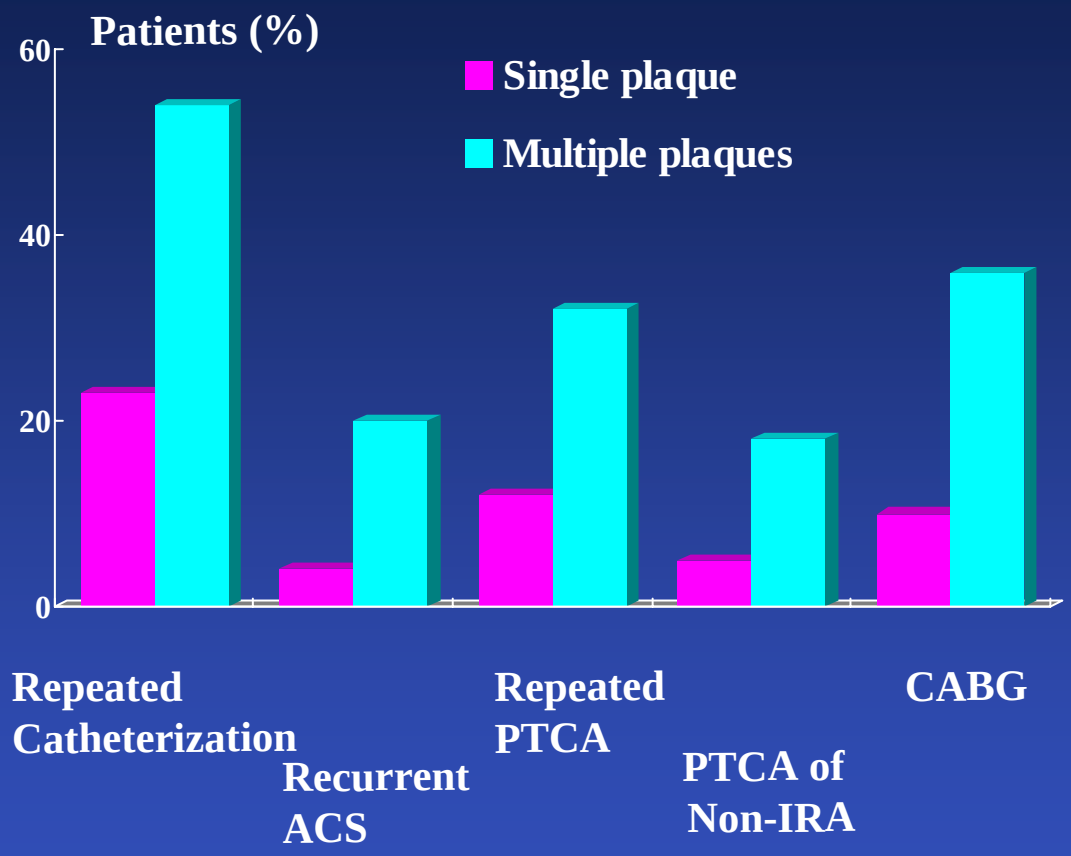
Multiple Vulnerable Plaque

Angiographic Study

One previous study using coronary angiography:

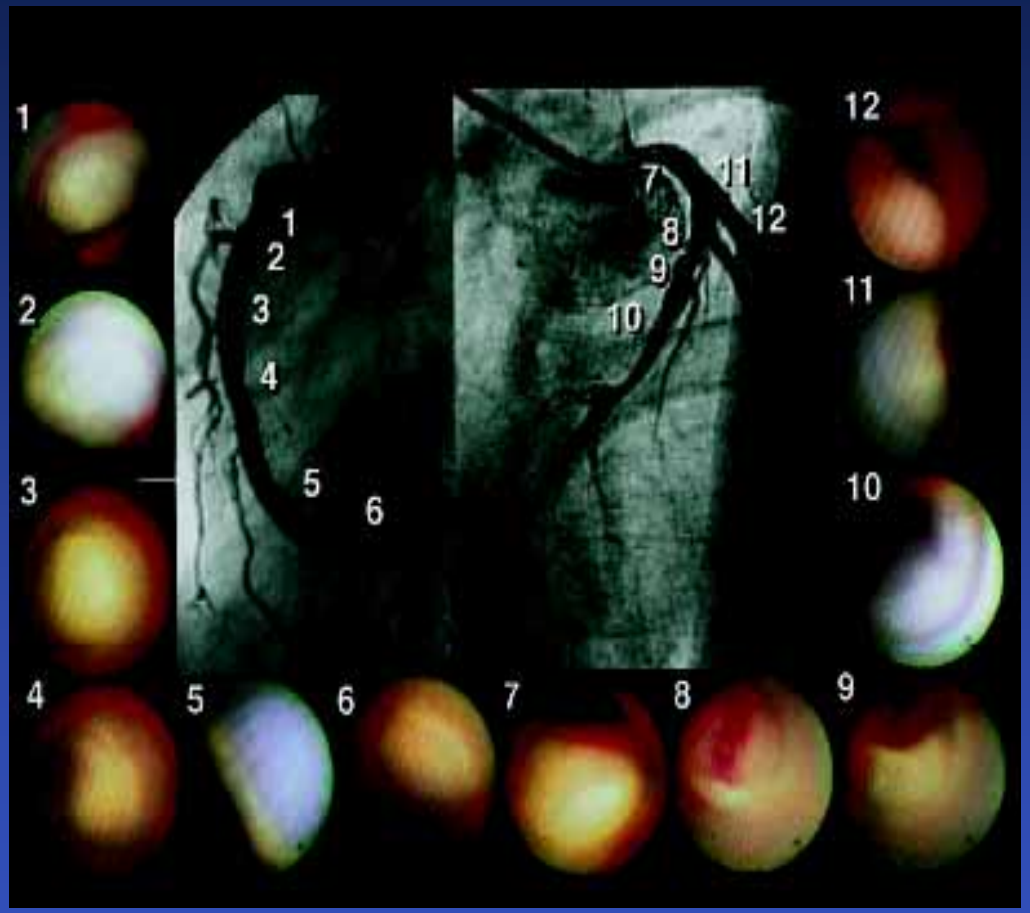
1. 40% of patients with an AMI had multiple complex plaques,

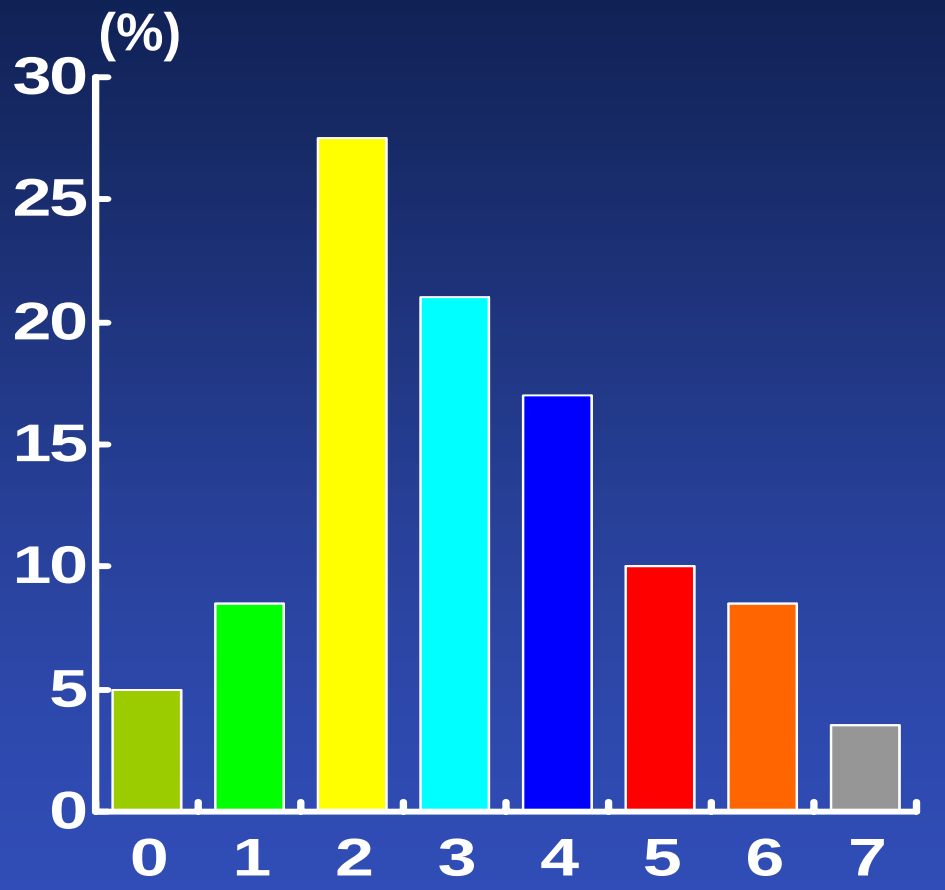
2. These patients had an increased incidence of recurrent ACS, repeat intervention (particularly of non–infarct-related lesions), and CABG in the subsequent year.



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

Angioscopic study





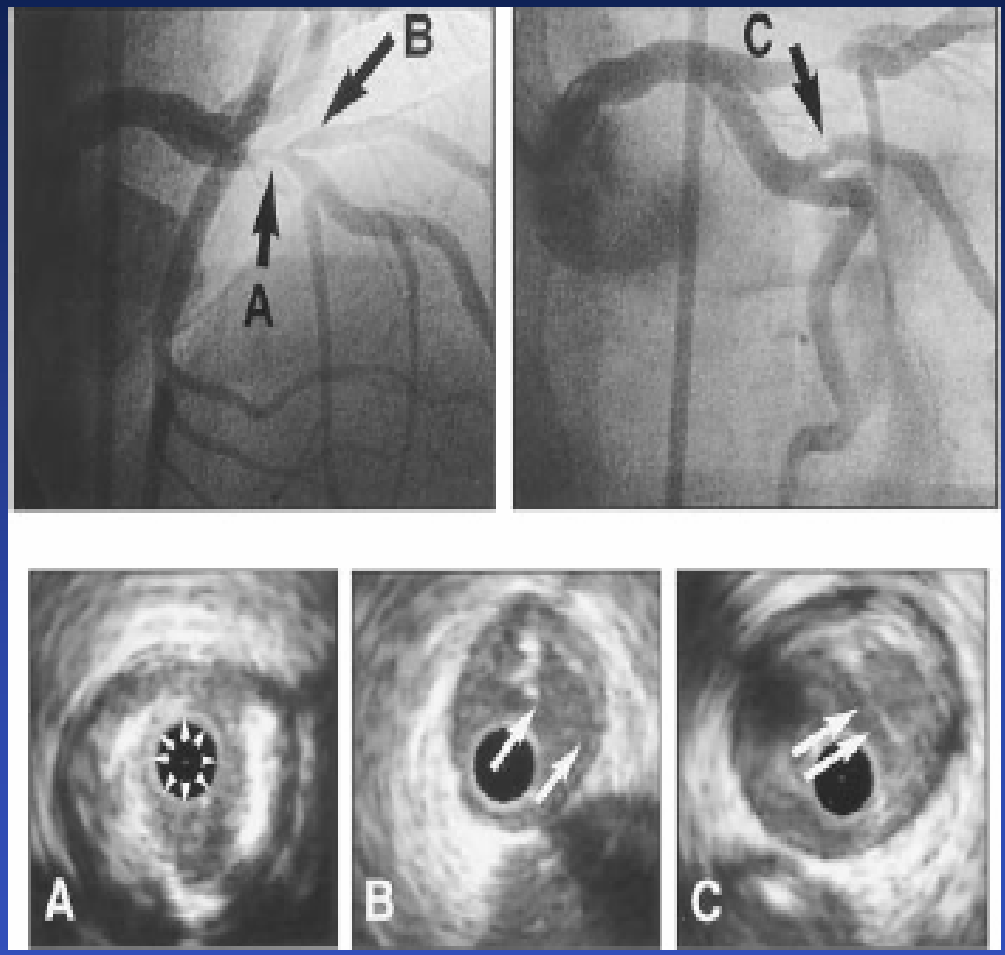
Asakura M. JACC 2001;37: 1284-88

IVUS study

The only three-vessel IVUS study in ACS patients:

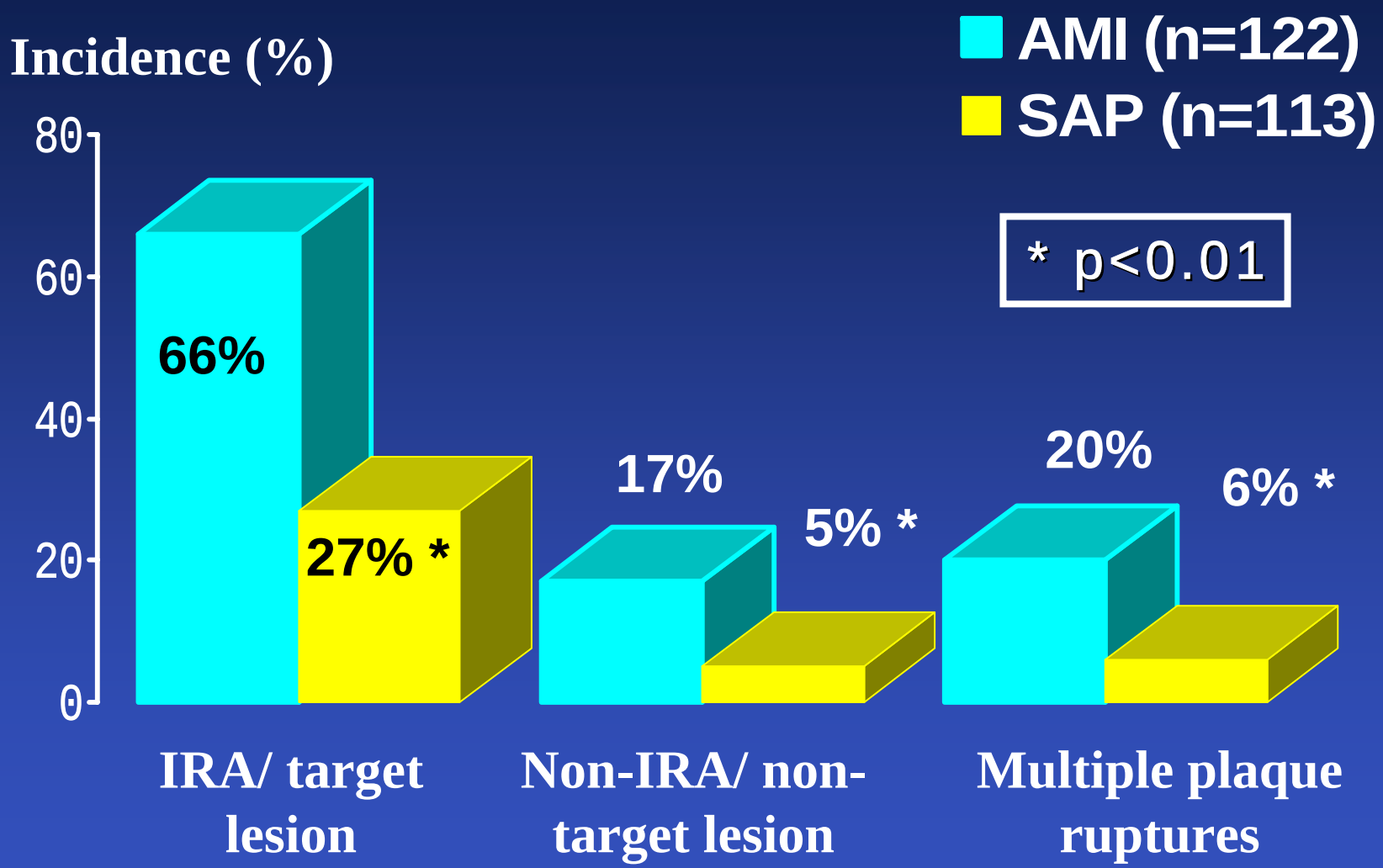
An incidence of culprit lesion plaque rupture: 37.5% (9/24);

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

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.

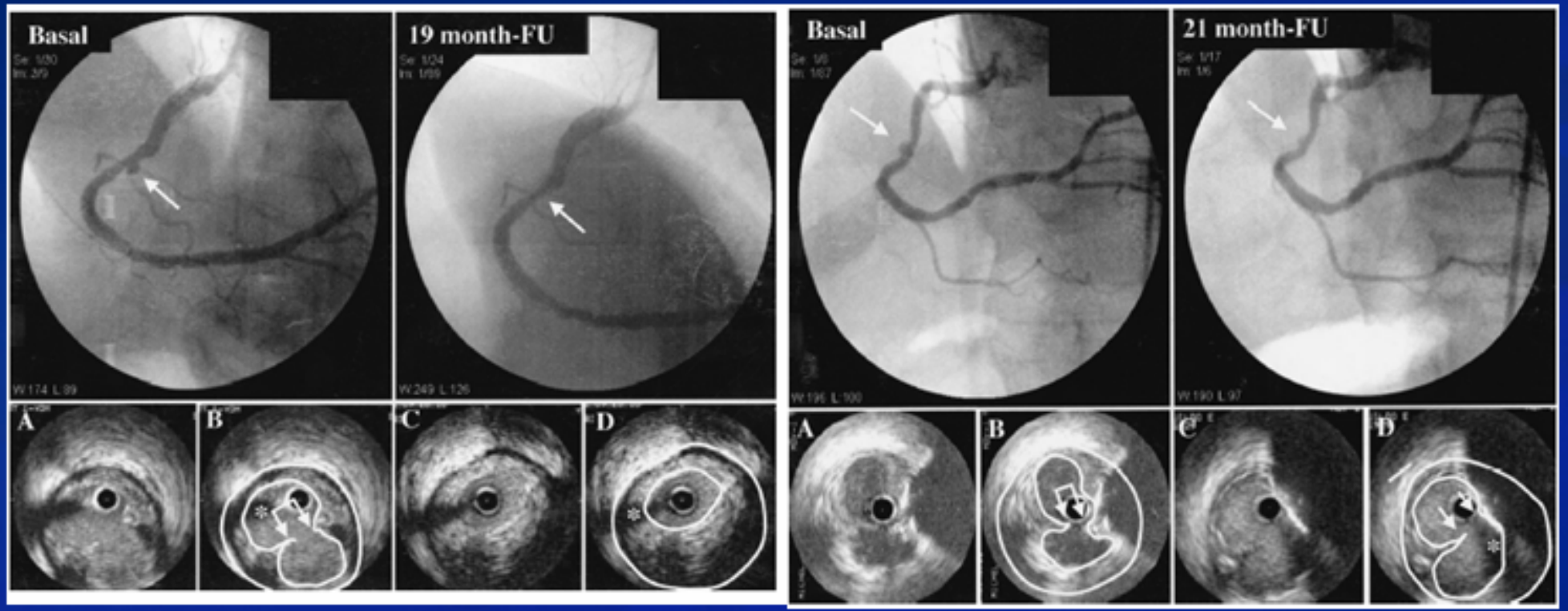
- **Angioscopic follow-up study of coronary ruptured plaques in nonculprit lesions.**

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

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

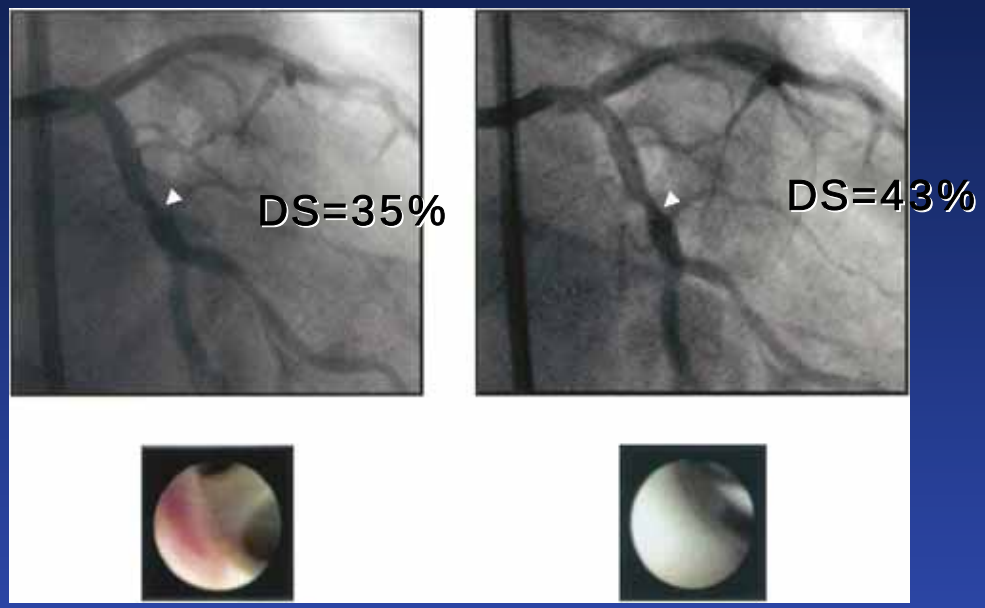
  Ohlmann P, et al, *Am J Cardiol* 2005;96: 1631-1635

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

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

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).

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%)

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

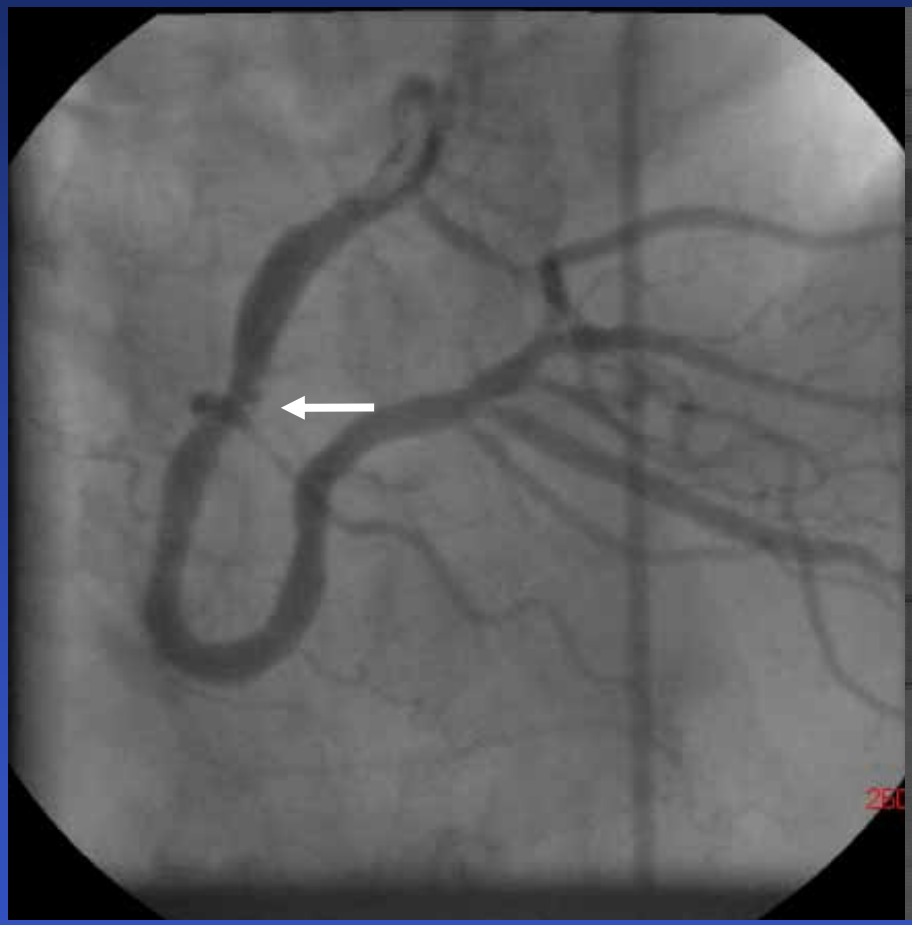
for 1 month in 17 patients after BMS implantation,
for 6 months in 2 patients after DES implantation

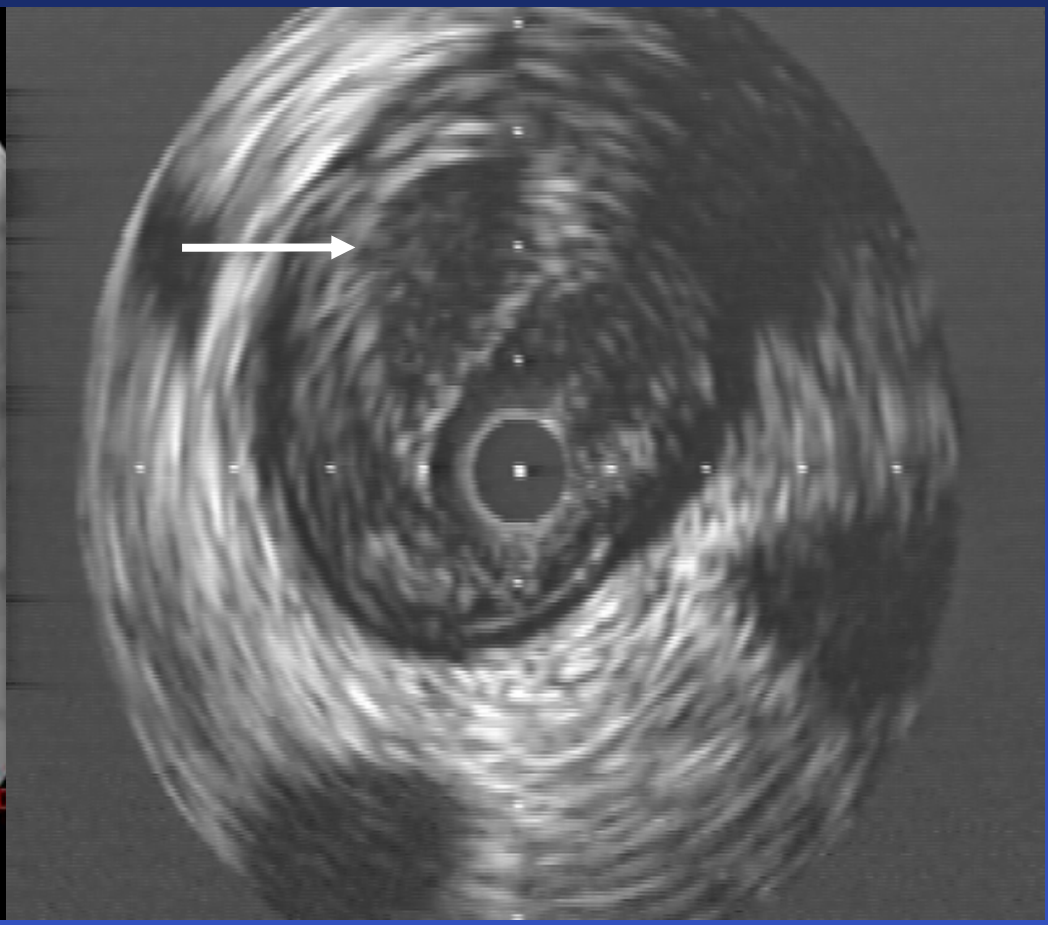
IVUS Imaging Protocol

- **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





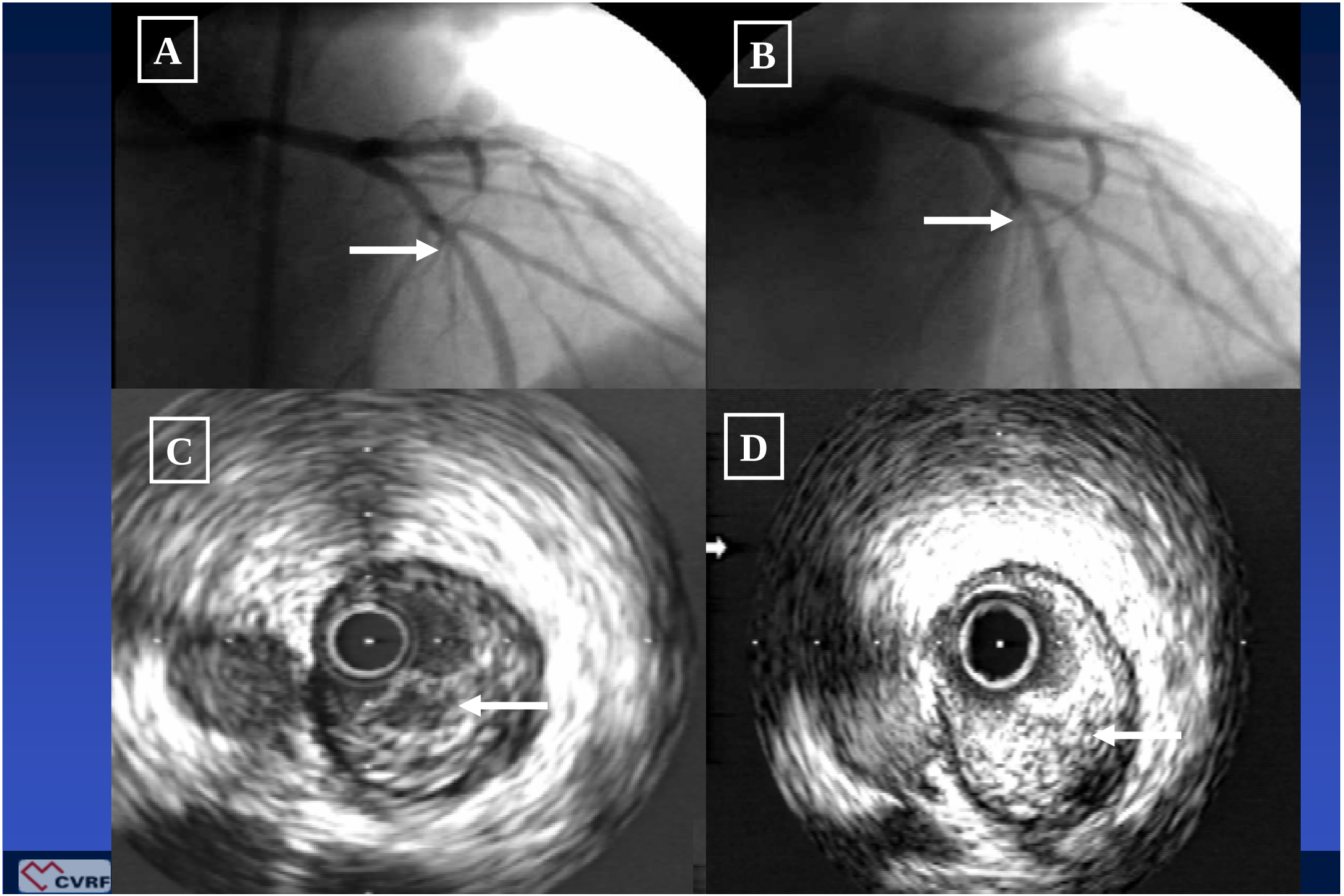
Definition of Plaque Rupture Healing

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.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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)

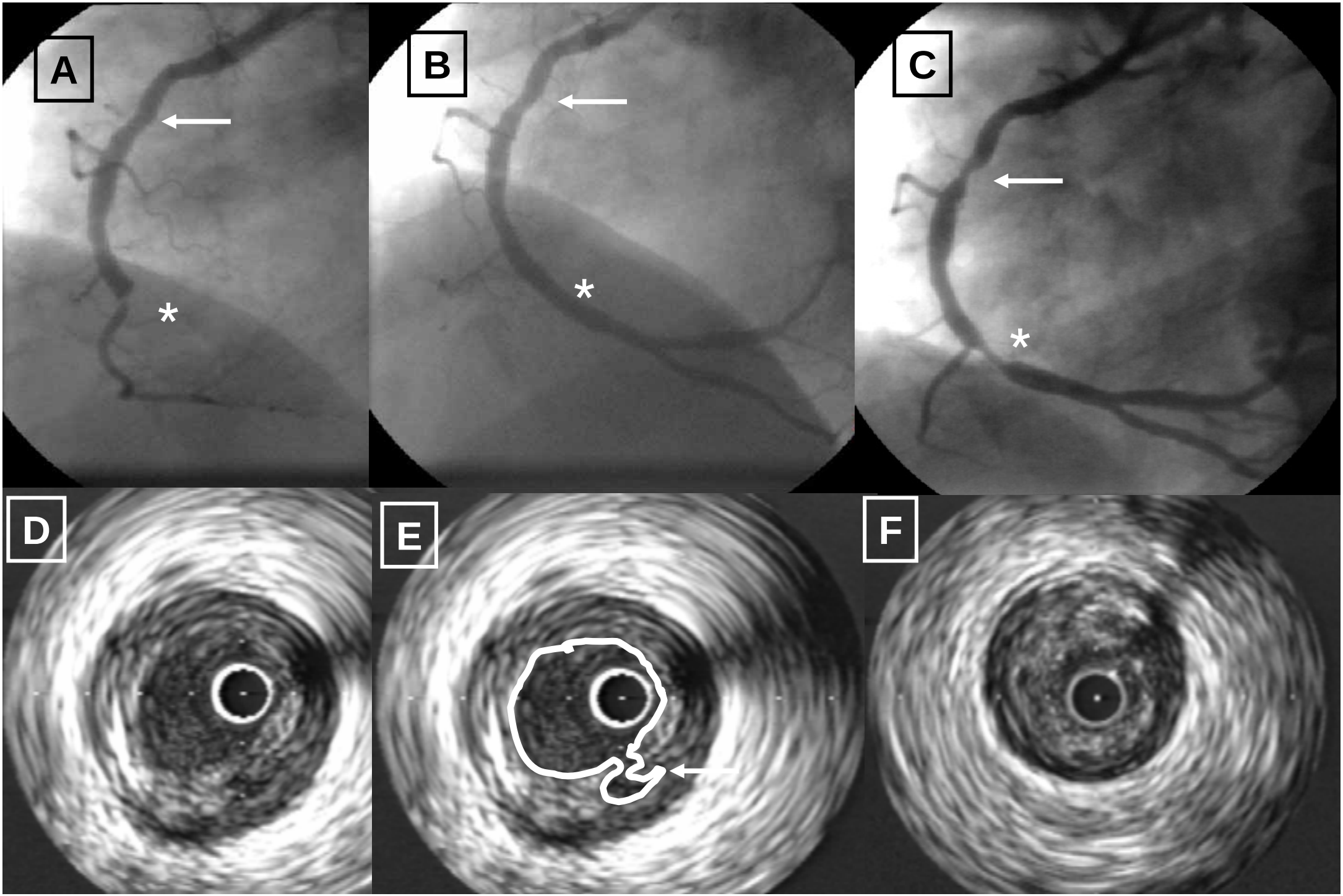
	Baseline	1-year FU	P
Proximal reference segment			
EEM CSA (mm^2)	20.7±7.6	20.6±7.7	0.6
Lumen CSA (mm^2)	11.6±5.6	11.7±5.6	0.5
Ruptured plaque segment			
EEM CSA (mm^2)	19.9±7.0	19.6±7.0	0.13
Lumen CSA (mm^2)	6.5±2.9	5.9±3.2	0.060
P&M CSA (mm^2)	10.5±4.7	11.0±4.7	0.026
Ruptured cavity CSA (mm^2)	3.0±1.6	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.

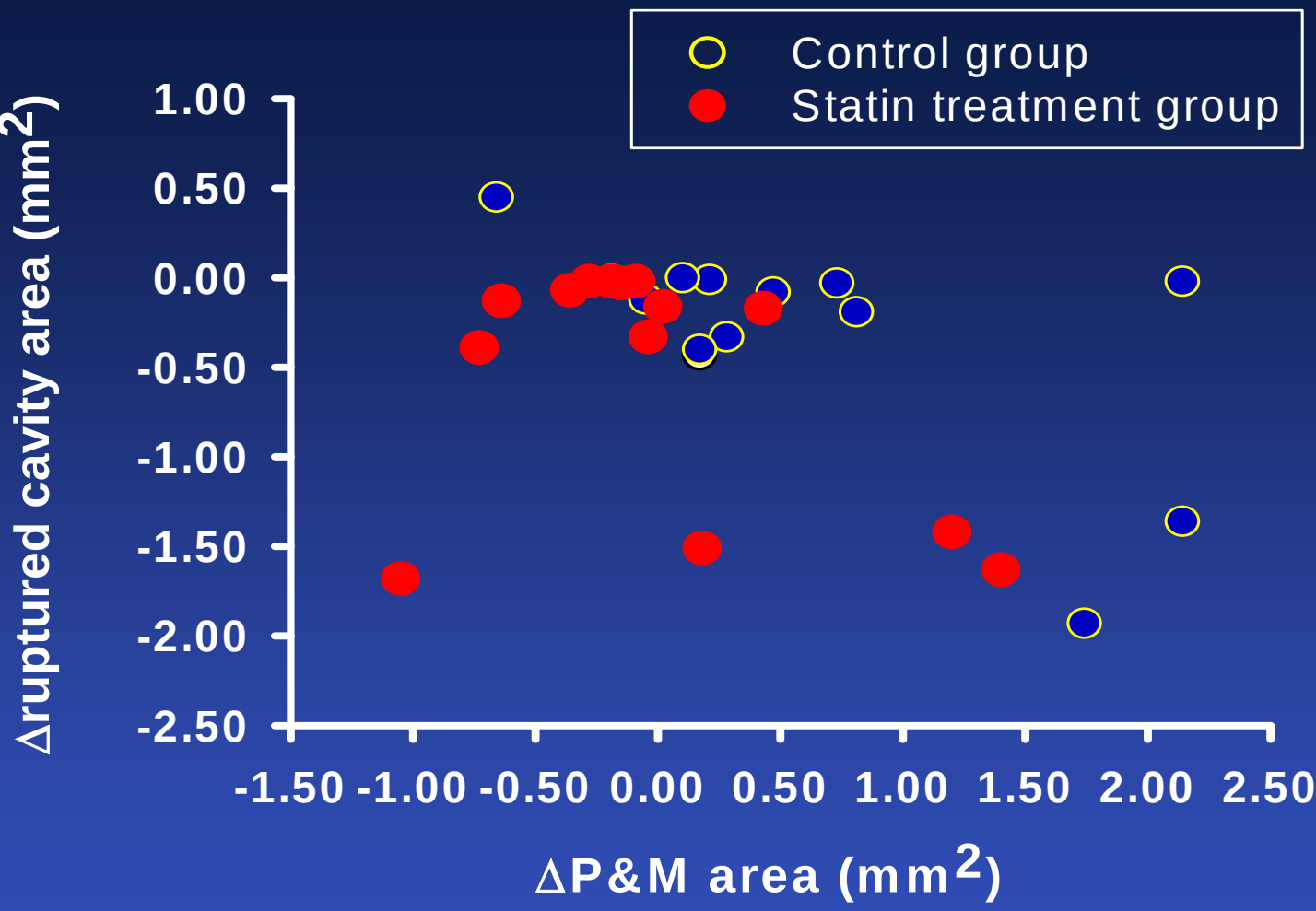
	TLR (n=3)	Non-TLR (n=25)	P
ΔEEM CSA (mm^2)	-0.6±1.4	-0.2±0.3	0.6
ΔLumen CSA (mm^2)	-1.7±1.4	0.1±0.8	0.001
ΔP&M CSA (mm^2)	1.6±1.0	0.1±0.7	0.002
ΔRuptured cavity CSA (mm^2)	-0.5±0.7	-0.4±0.7	0.8

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);

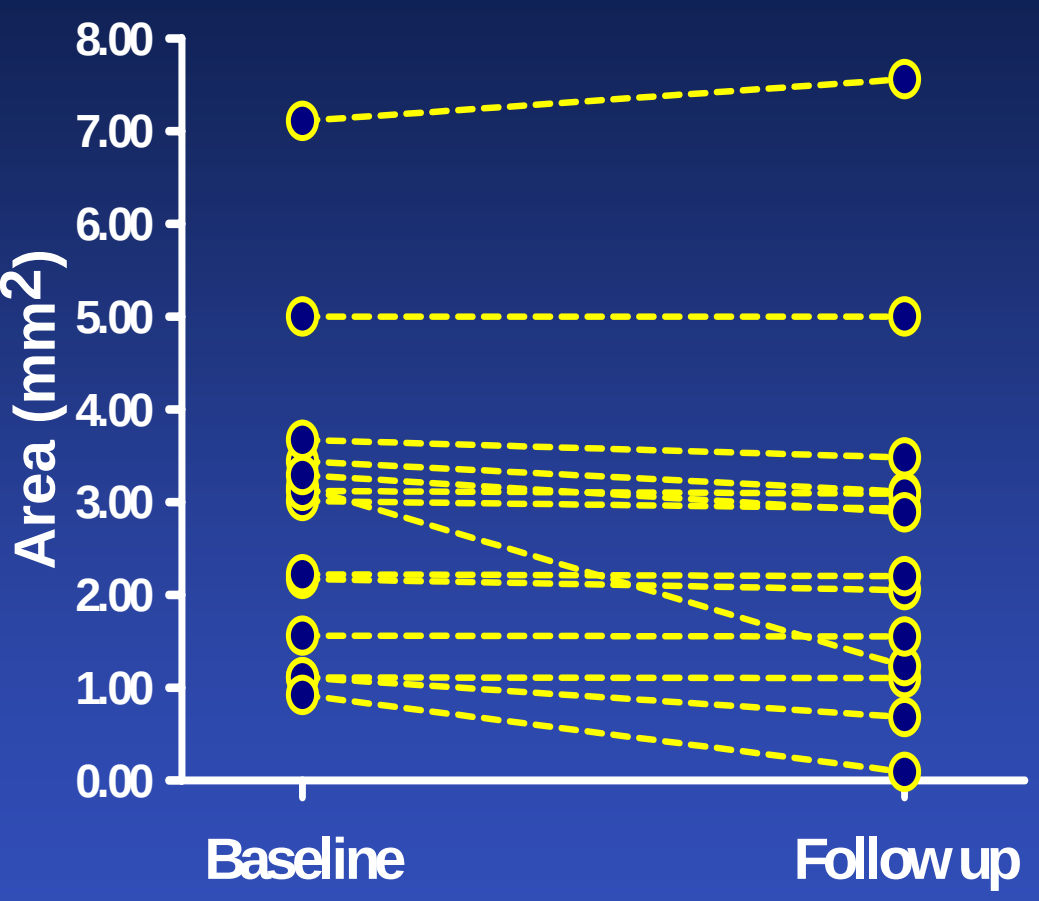
in statin-treated patients (r=0.387, p=0.172, 95% CI= -0.973 to 0.194); and in non-statin treated patients (r=0.646, p=0.017, 95% CI= -0.821 to -0.100).

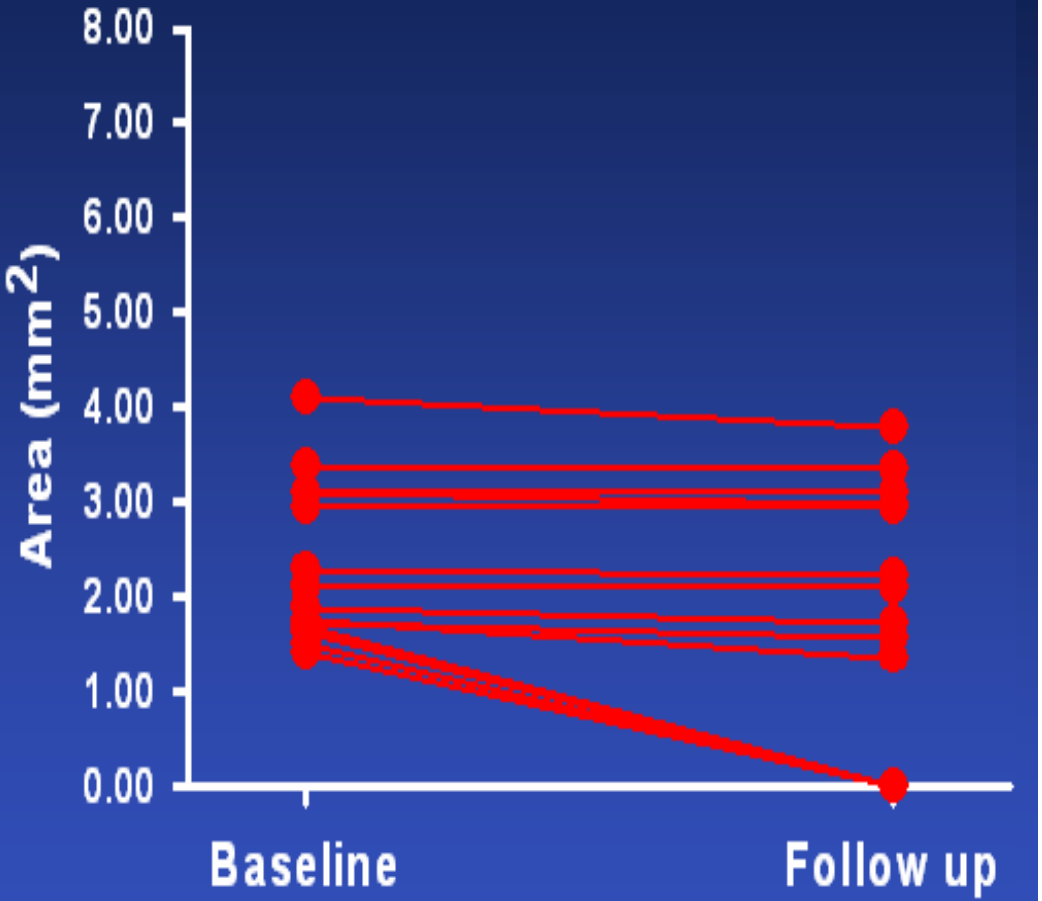


in statin-treated patients; r=0.387, p=0.172

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.**