It is important to find and treat the vulnerable plaques

Myeong-Ki Hong, MD, PhD.

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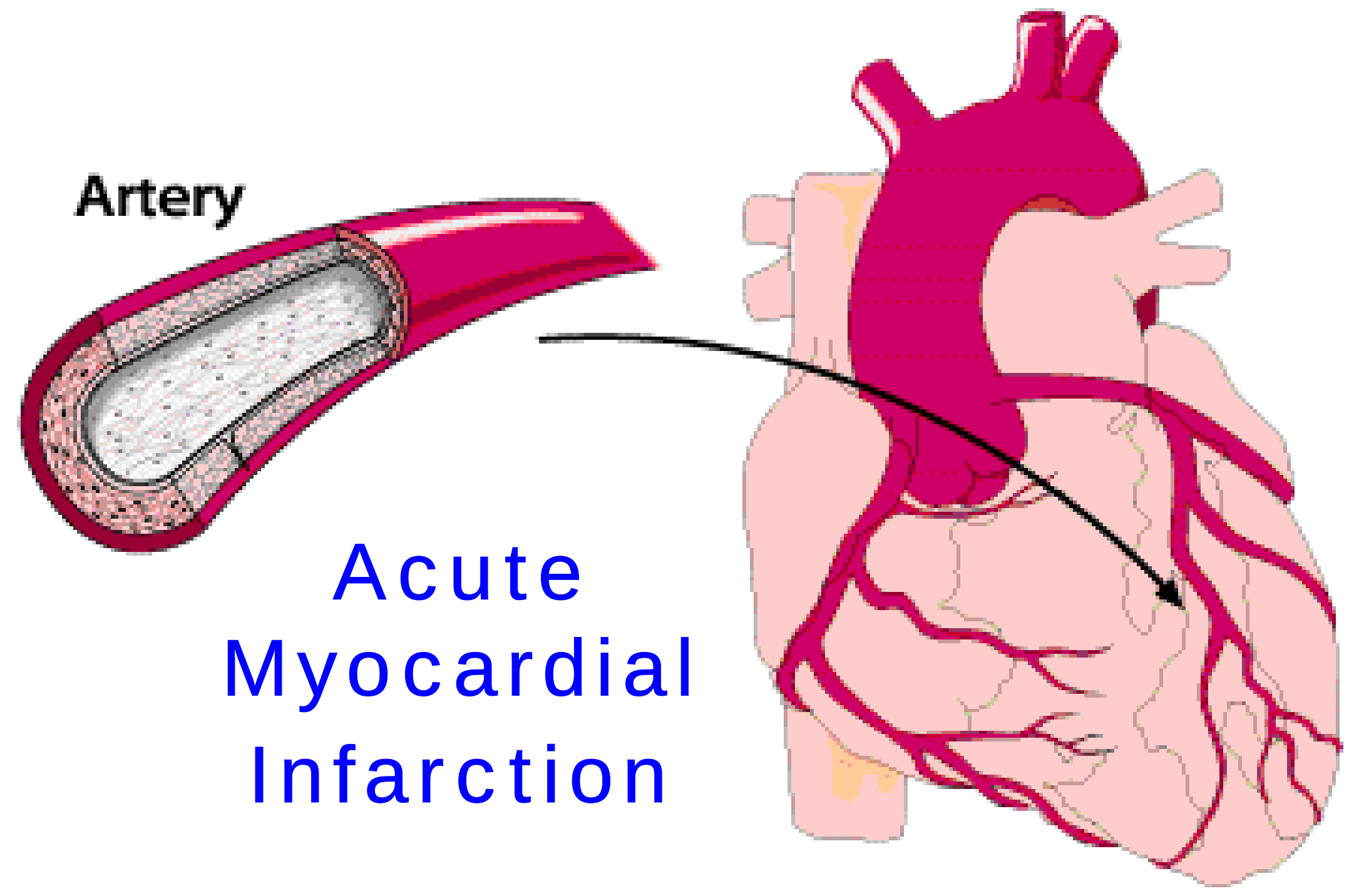
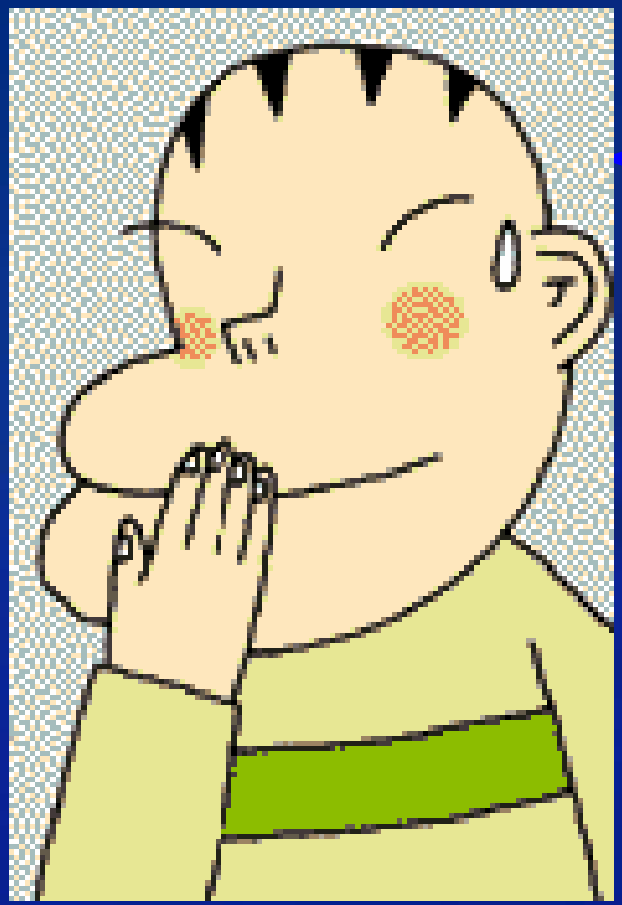

Artery
Acute
Myocardial
Infarction

Plaque Rupture

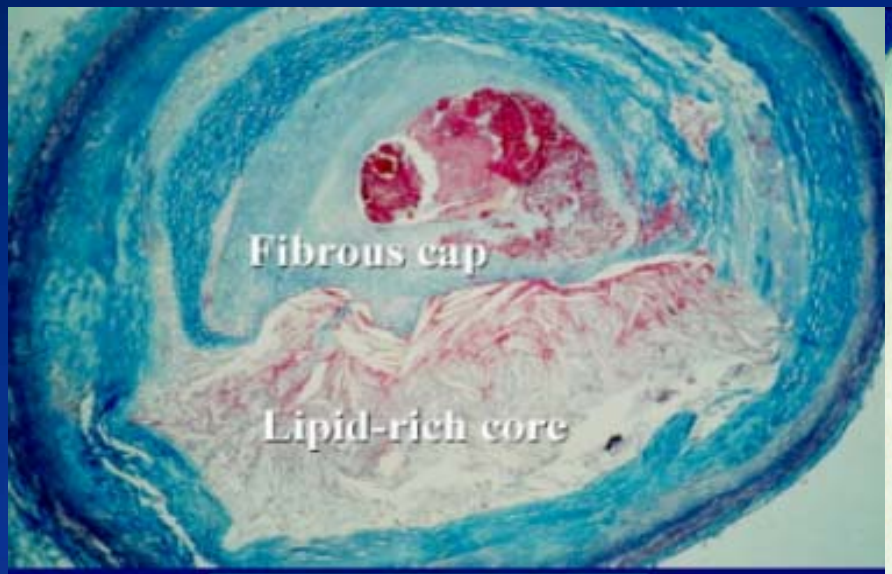
Question: Is it important to find and treat the vulnerable plaques ?

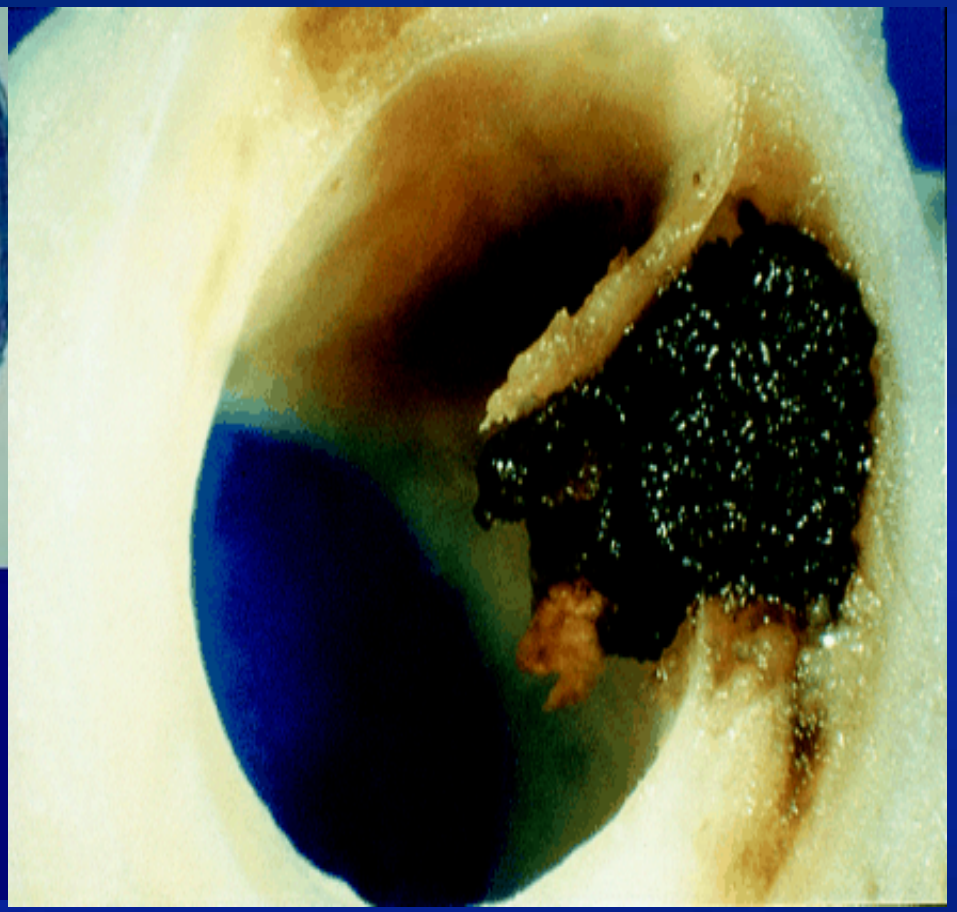
광수 생각



이렇게 위험한 것을 찾아서 치료하지 않으면 심장내과 의사의 존재의 가치는 무엇이지 ???

What is vulnerable plaque ?



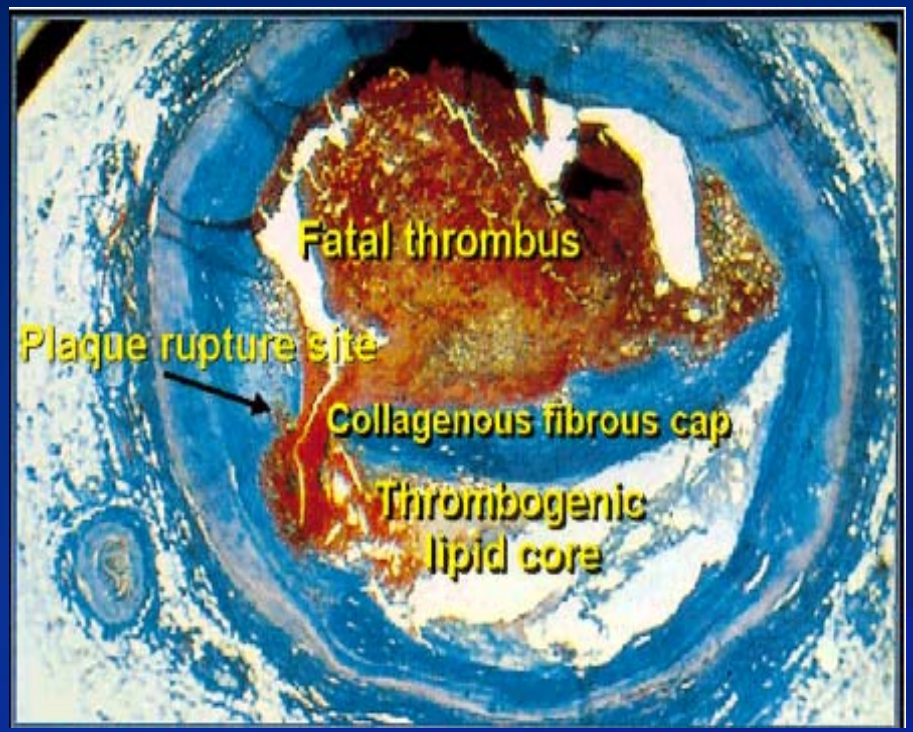


Underlying Pathologies of "Culprit" Coronary Lesions in ACS patients

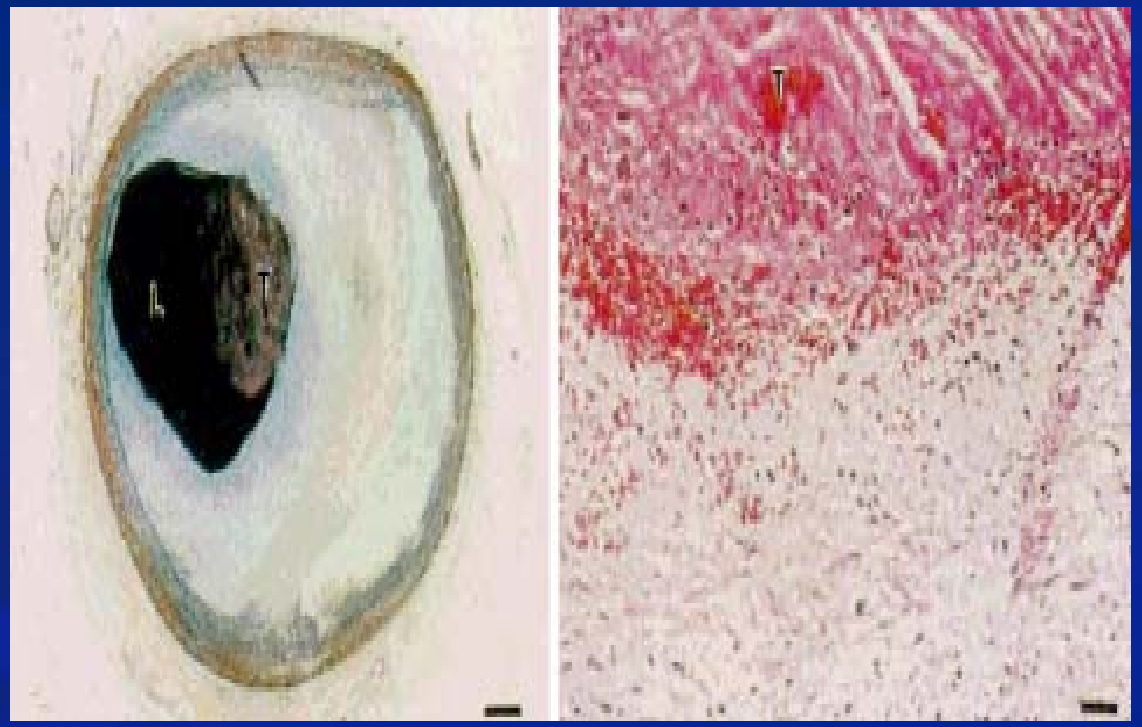
- **Ruptured plaques (70%)**
  - **Stenotic (20%)**
  - **Non-stenotic (50%)**
- **Non-ruptured plaques (30%)**
  - **Erosion**
  - **Calcified nodule**
  - **Others/Unknown**

Naghavi M. Circulation 2003; 108: 1664-72

Vulnerable plaque



Rupture of fibrous cap



Superficial erosion

Welt & Simon: CCI 2001; 53: 56-63

Criteria for defining vulnerable plaque, based on the study of culprit plaque

Major criteria

- Active inflammation
  (monocyte/macrophage and sometimes T-cell infiltration)
- Thin cap with large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured plaque
- Stenosis > 90%

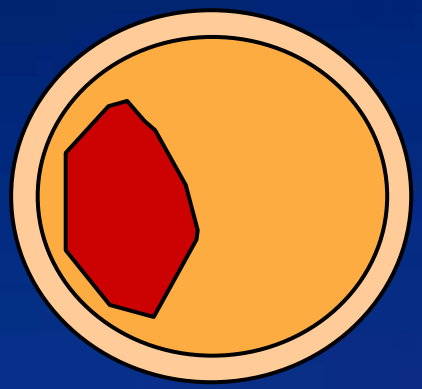
Minor criteria

- Superficial calcified nodule
- Glistening yellow
- Intraplaque hemorrhage
- Endothelial dysfunction
- Outward (positive) remodeling

Naghavi M. Circulation 2003; 108: 1664-72

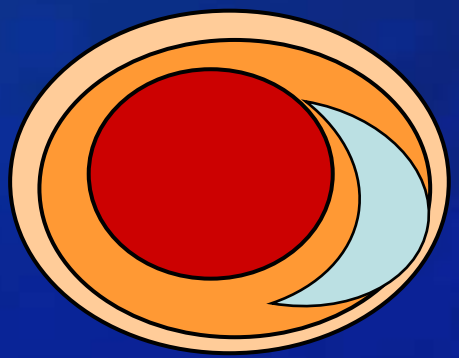
Stable vs. Vulnerable Plaque

Stable (obstructive)



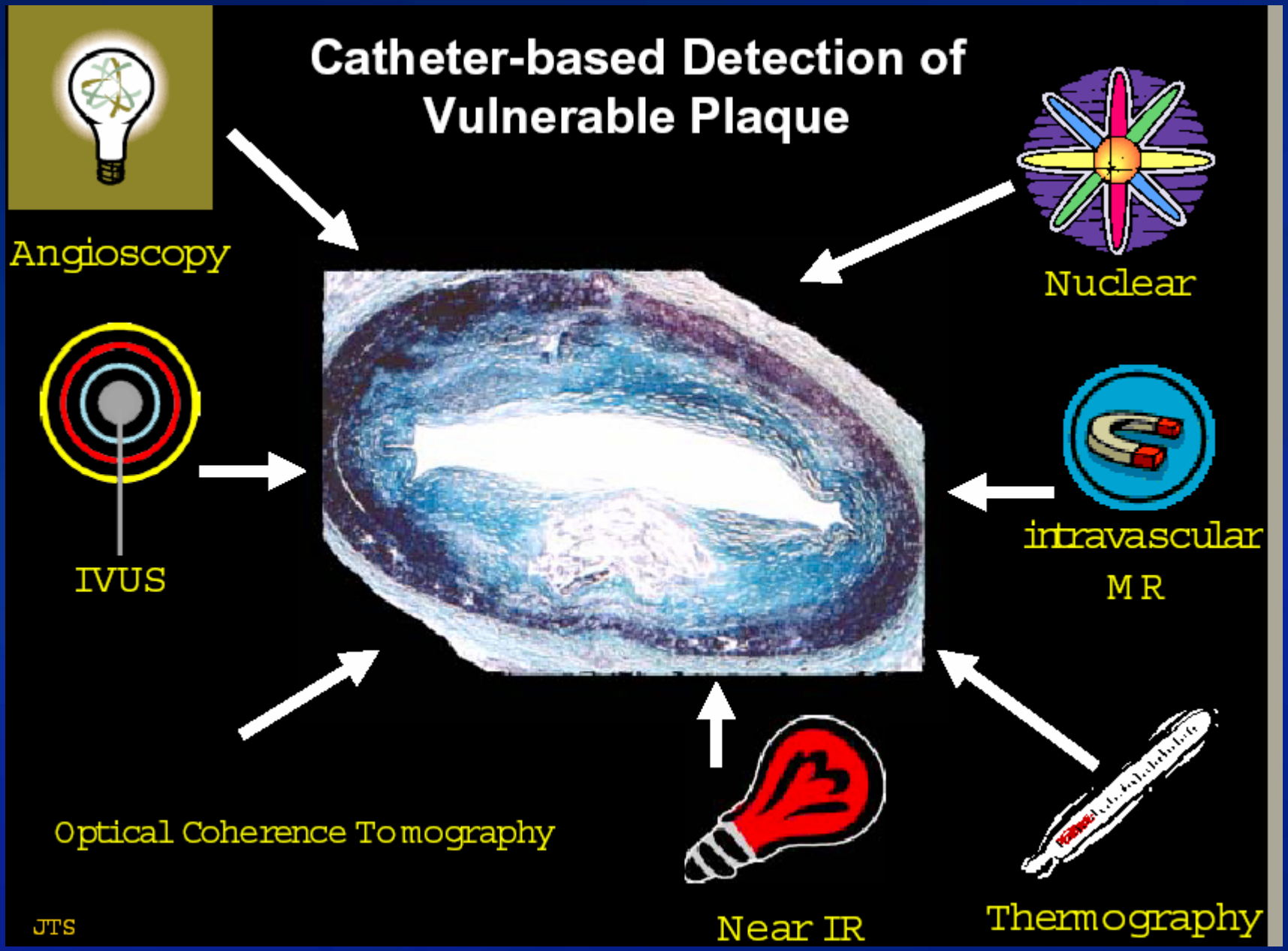
- Progressively flow-limiting
- Often causes chest pain
- Detected by X-ray angiography
- Main target of interventional therapies (angioplasty, stents)

Vulnerable (non-obstructive)

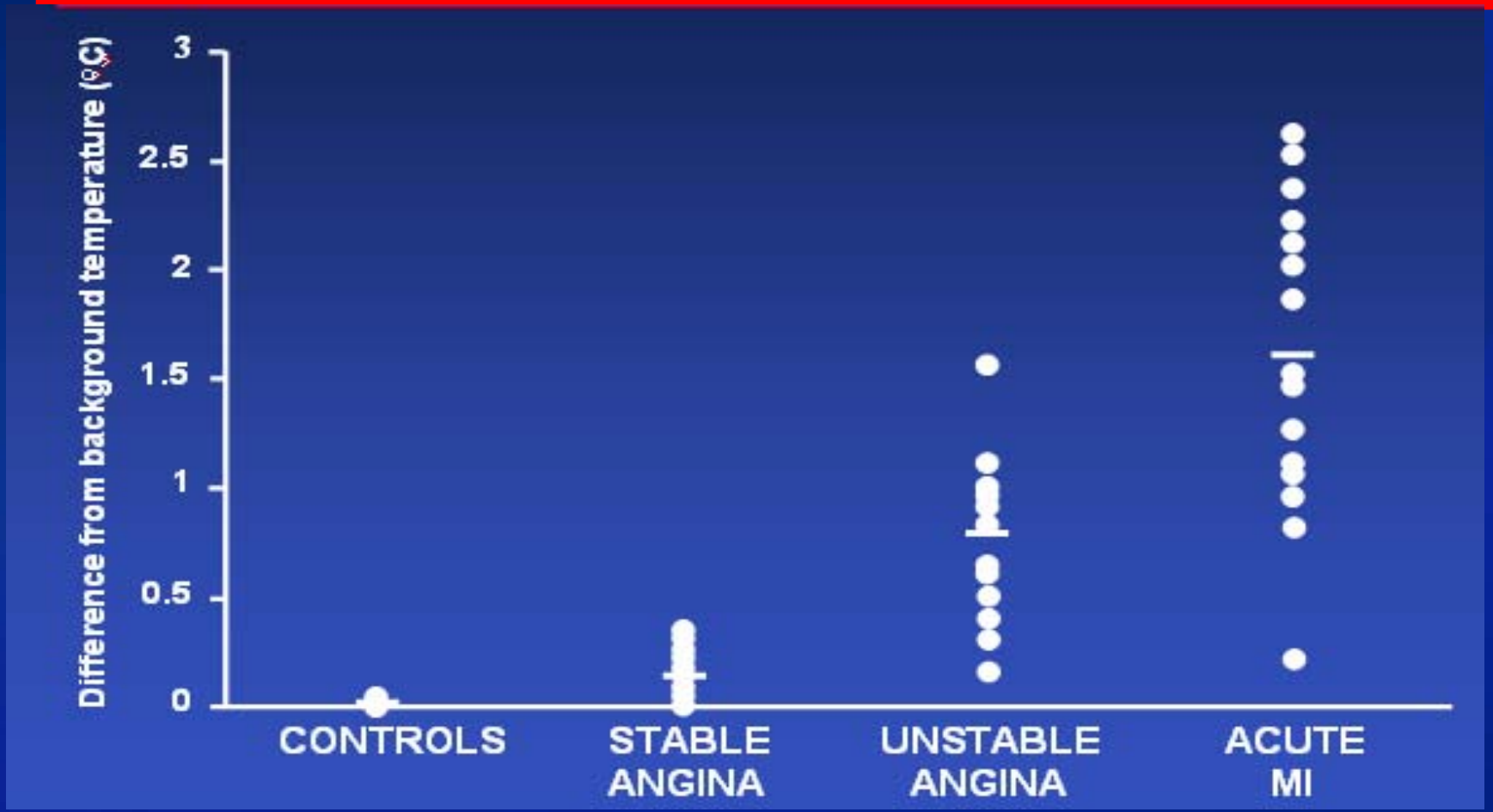


- Minimal effect on blood flow
- First symptom is often sudden death
- No established detection method
- Preventative drug therapies; directed therapies still unproven

Stanford

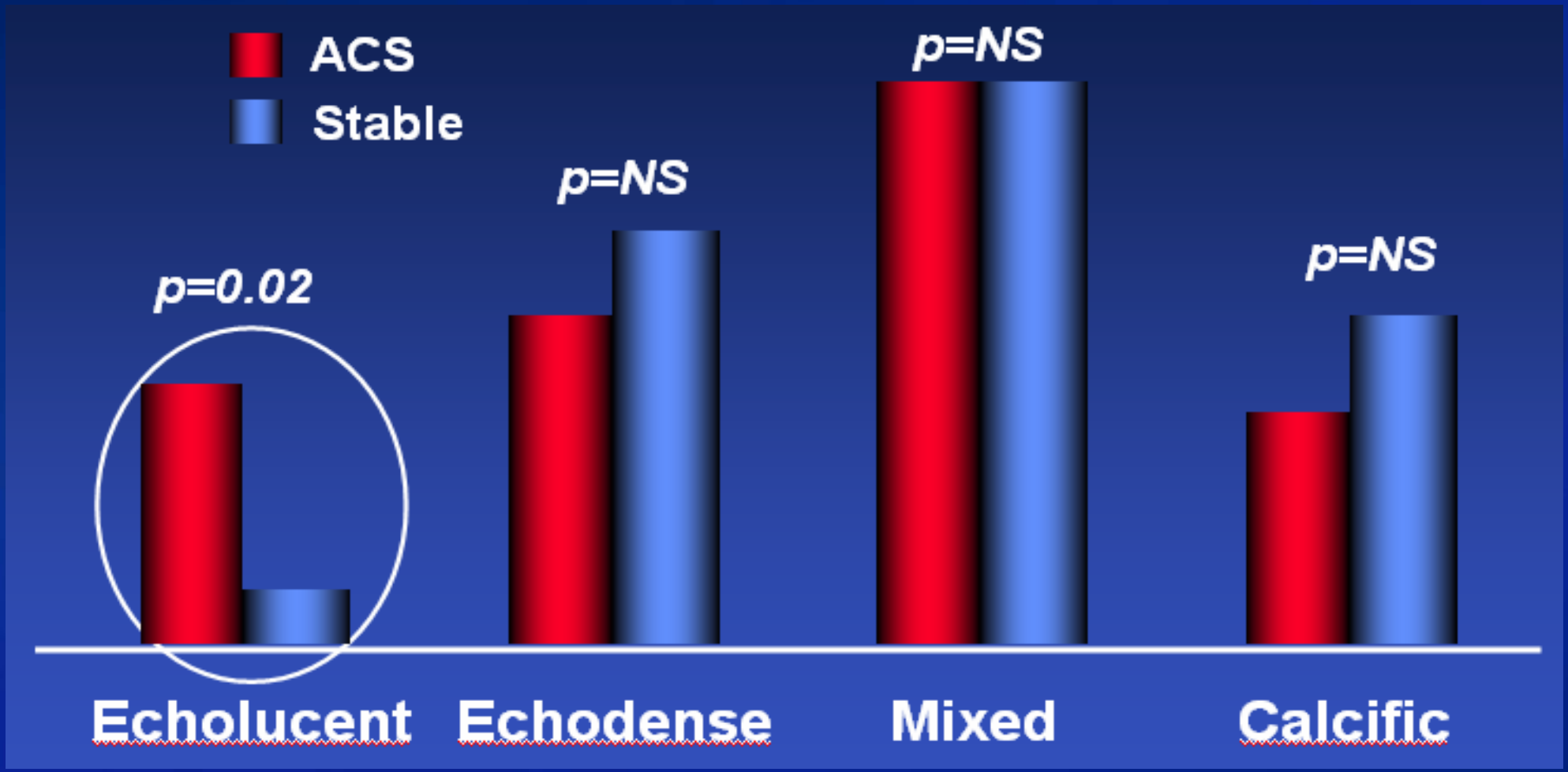

Catheter-based Detection of Vulnerable Plaque
Angioscopy
Nuclear
IVUS
intravascular MR
Optical Coherence Tomography
Near IR
Thermography
JTS

Thermal Heterogeneity is Detected In Vivo in Human Coronary Atherosclerotic Lesions



Stefanadis et al, Circulation 1999

Plaque Composition In ACS



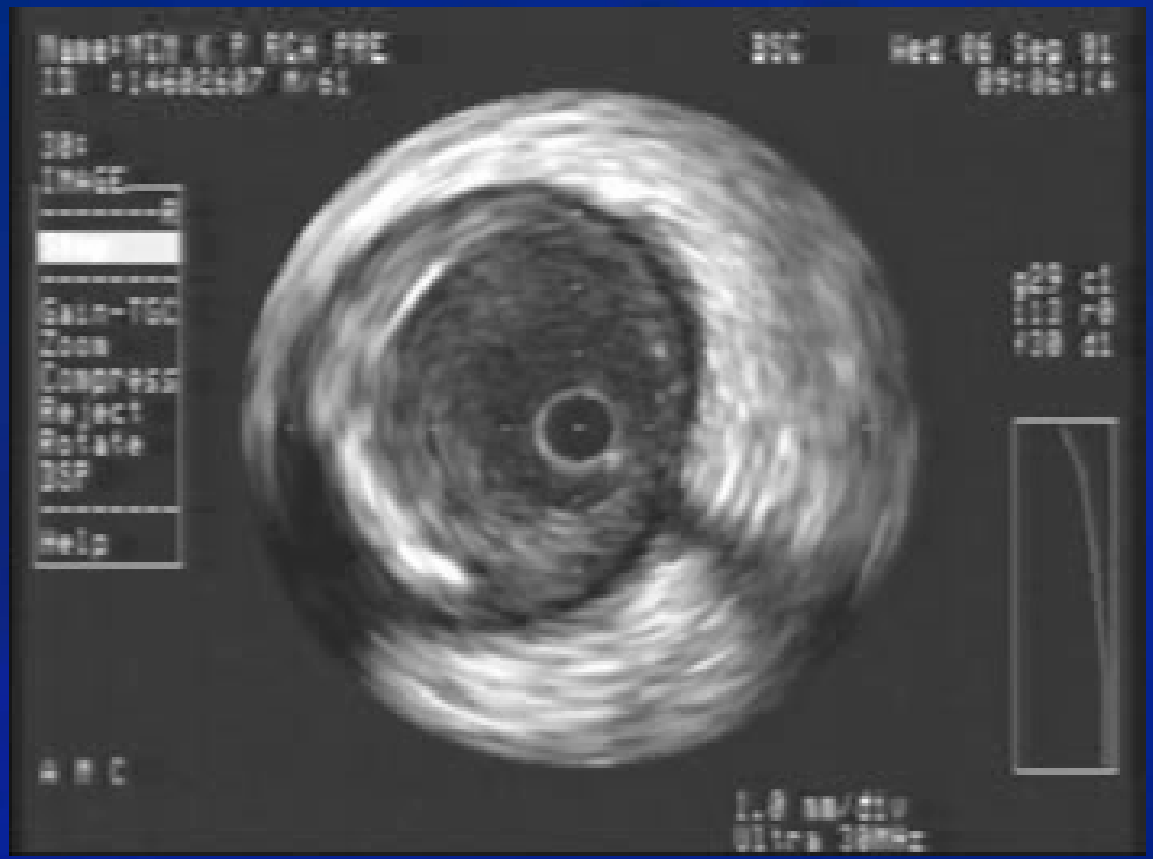
Schoenhagen et al. Circulation 2000;101:598-603

Types of Vulnerable Plaque

1. **Plaque rupture**
2. **Lipid pool-like images**
3. **Thrombus alone without above 2 types**

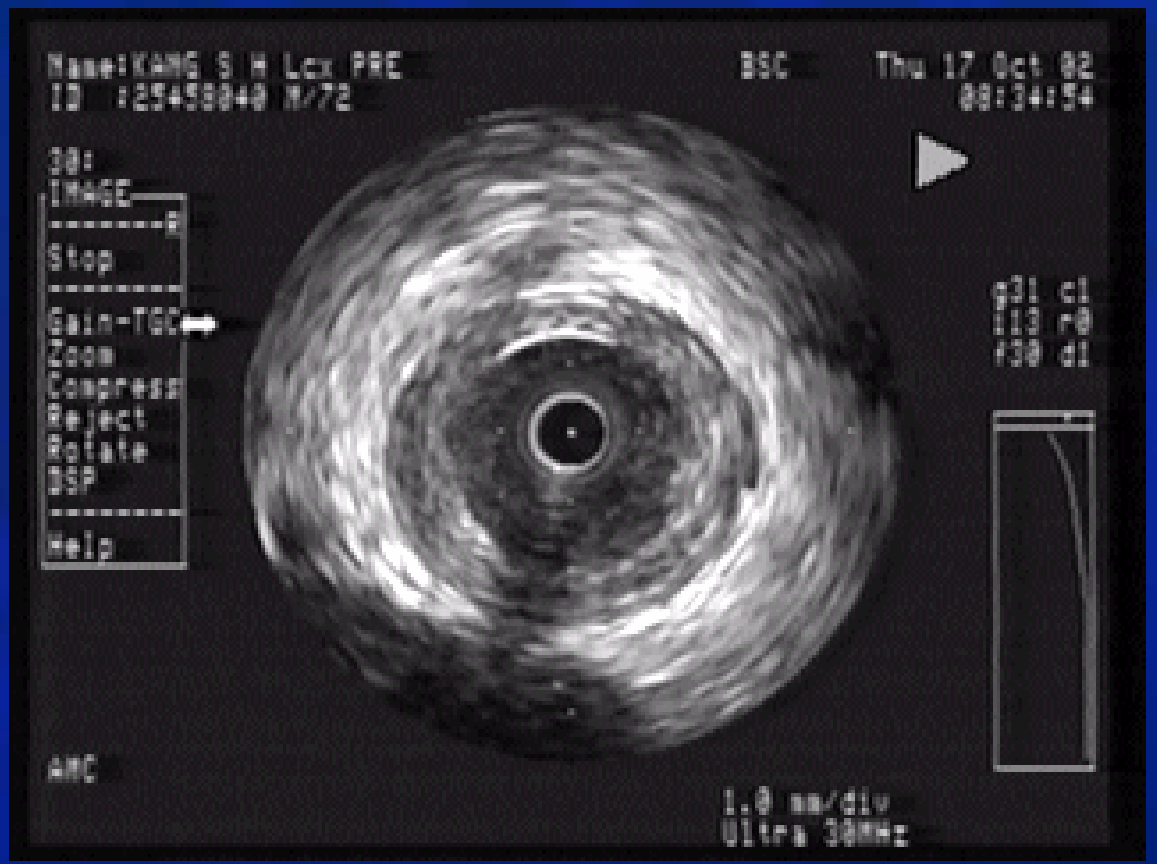
Definition of Plaque Rupture

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



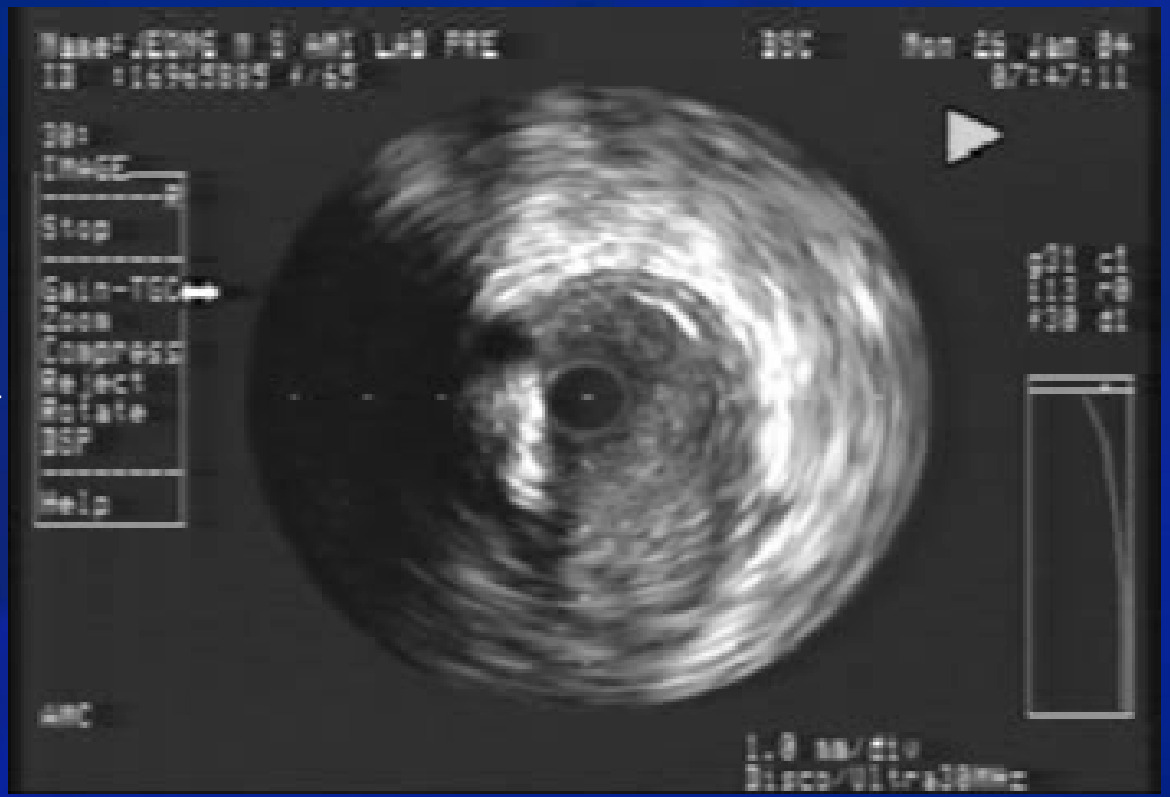
Definition of Lipid Pool-like Images

A pooling of low-echogenic material or echolucent material covered with a high-echogenic layer



Definition of Thrombus

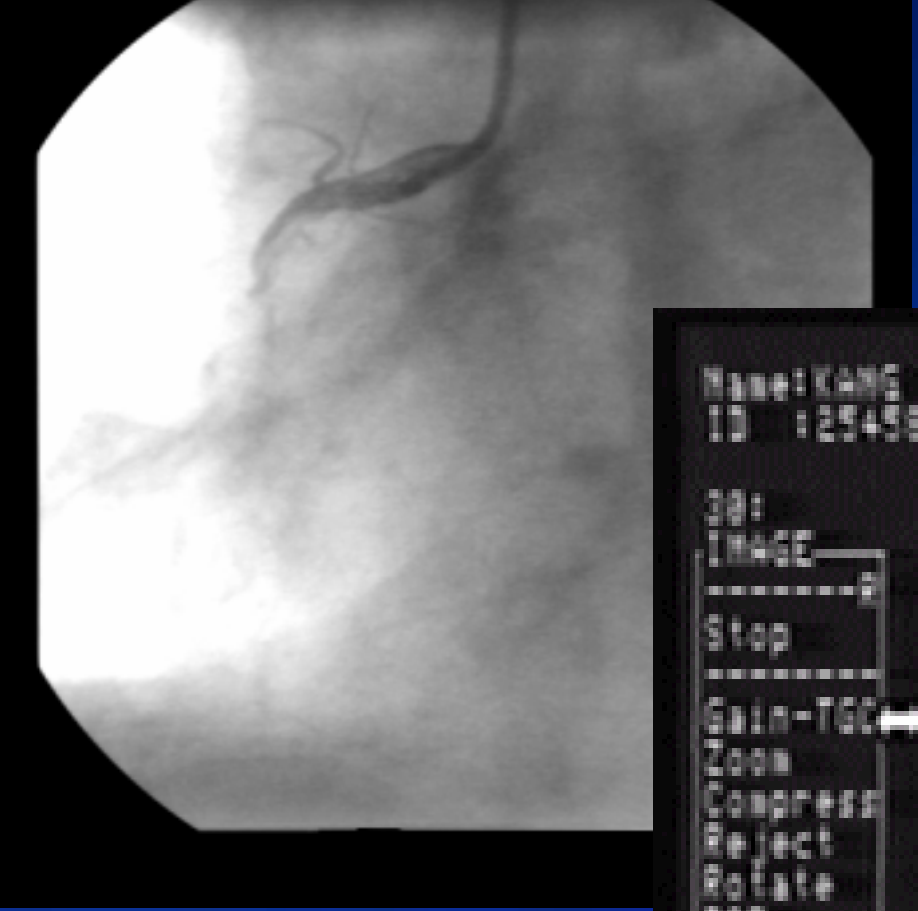
An intraluminal mass having a layered or lobulated appearance, evidence of blood flow within the mass, and speckling or scintillation

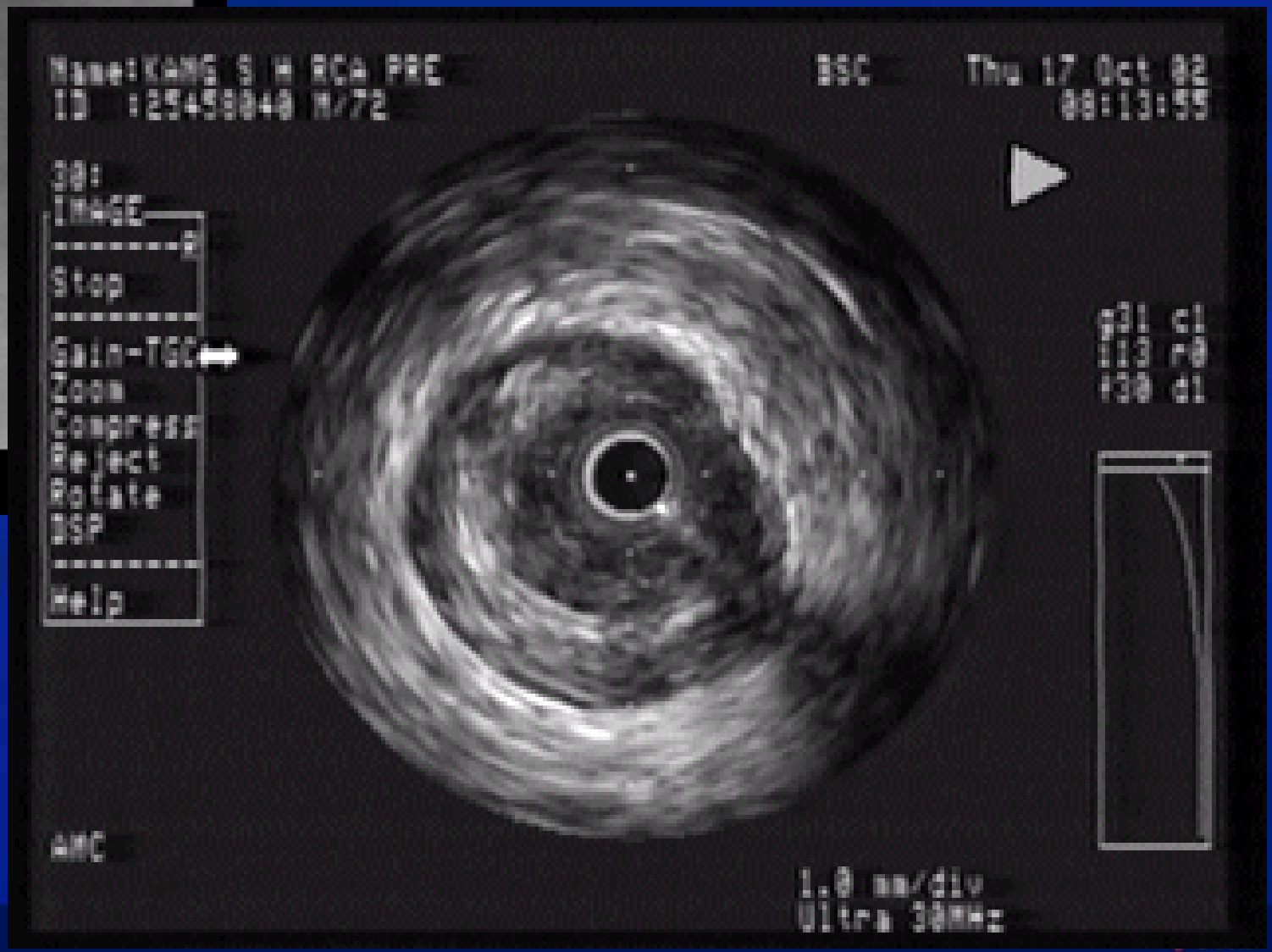


Question 1: Is it important to find the vulnerable plaques ?

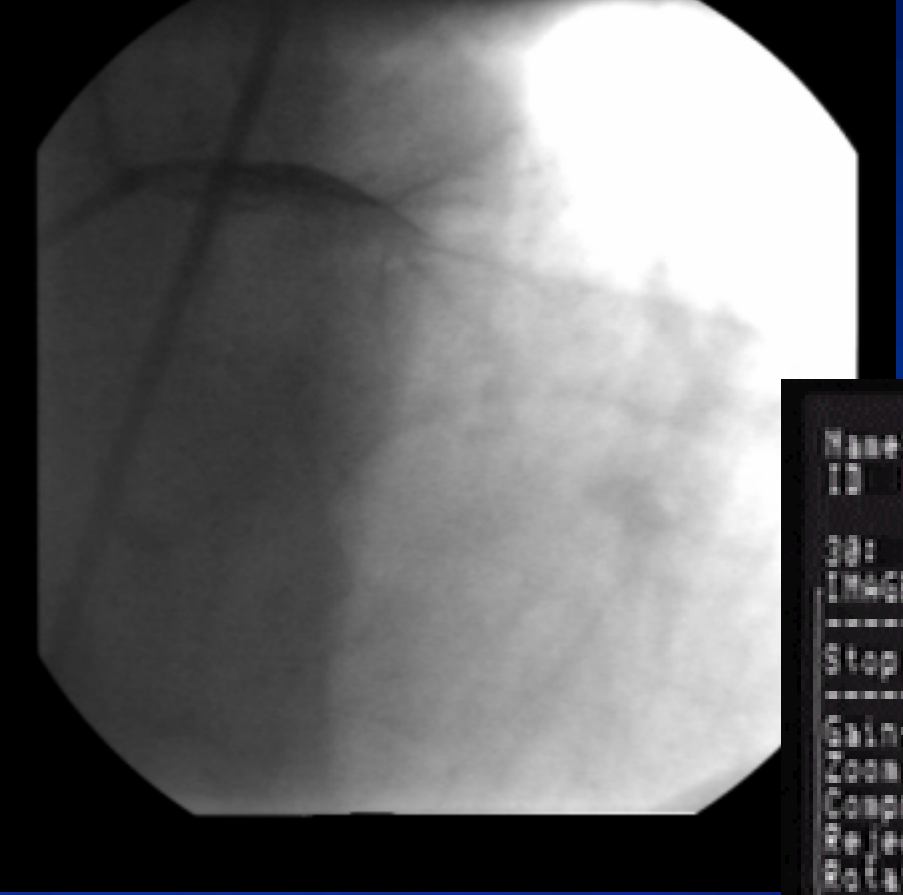
Multiple Vulnerable Plaque

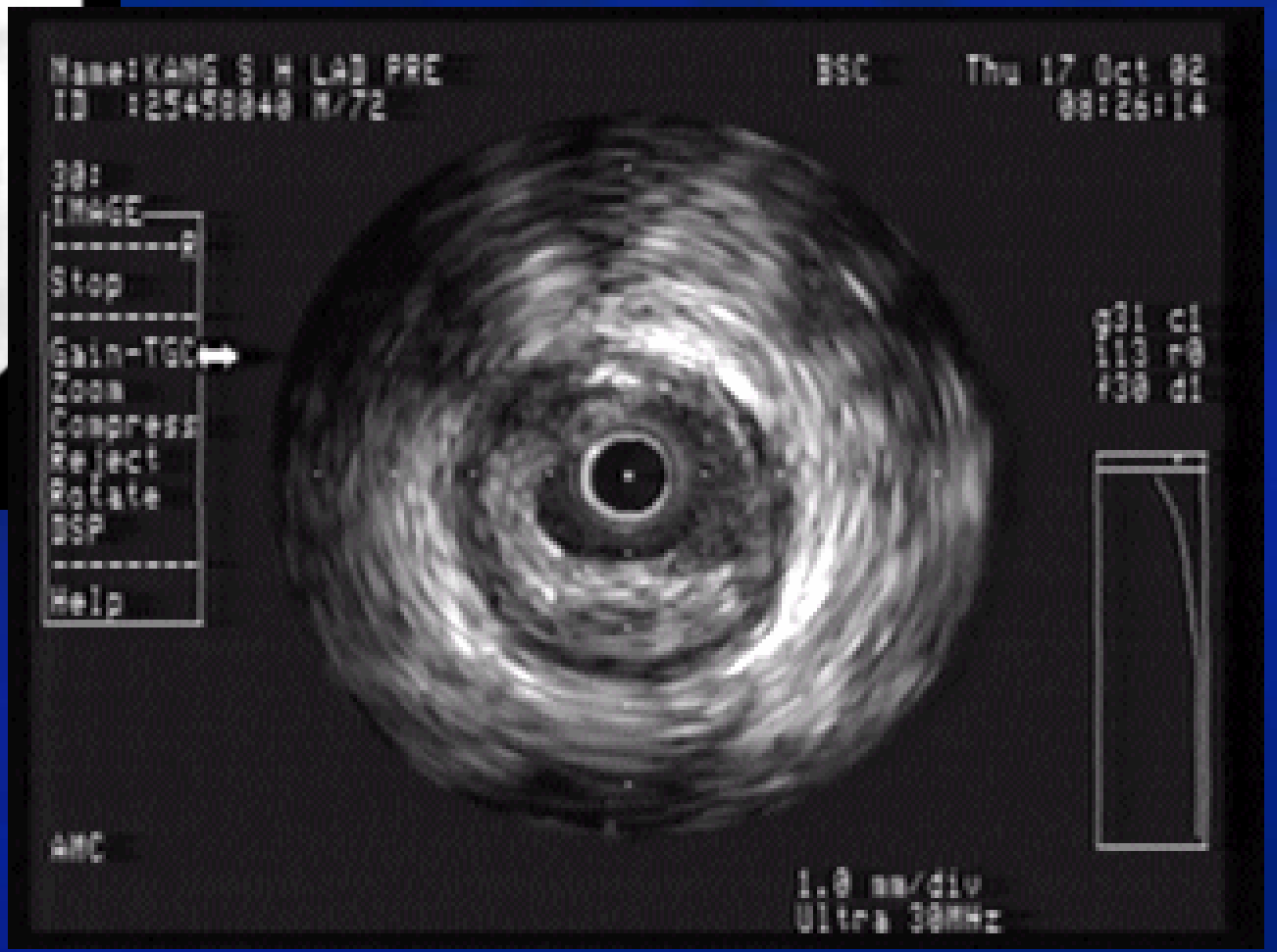
Vulnerable plaque in RCA



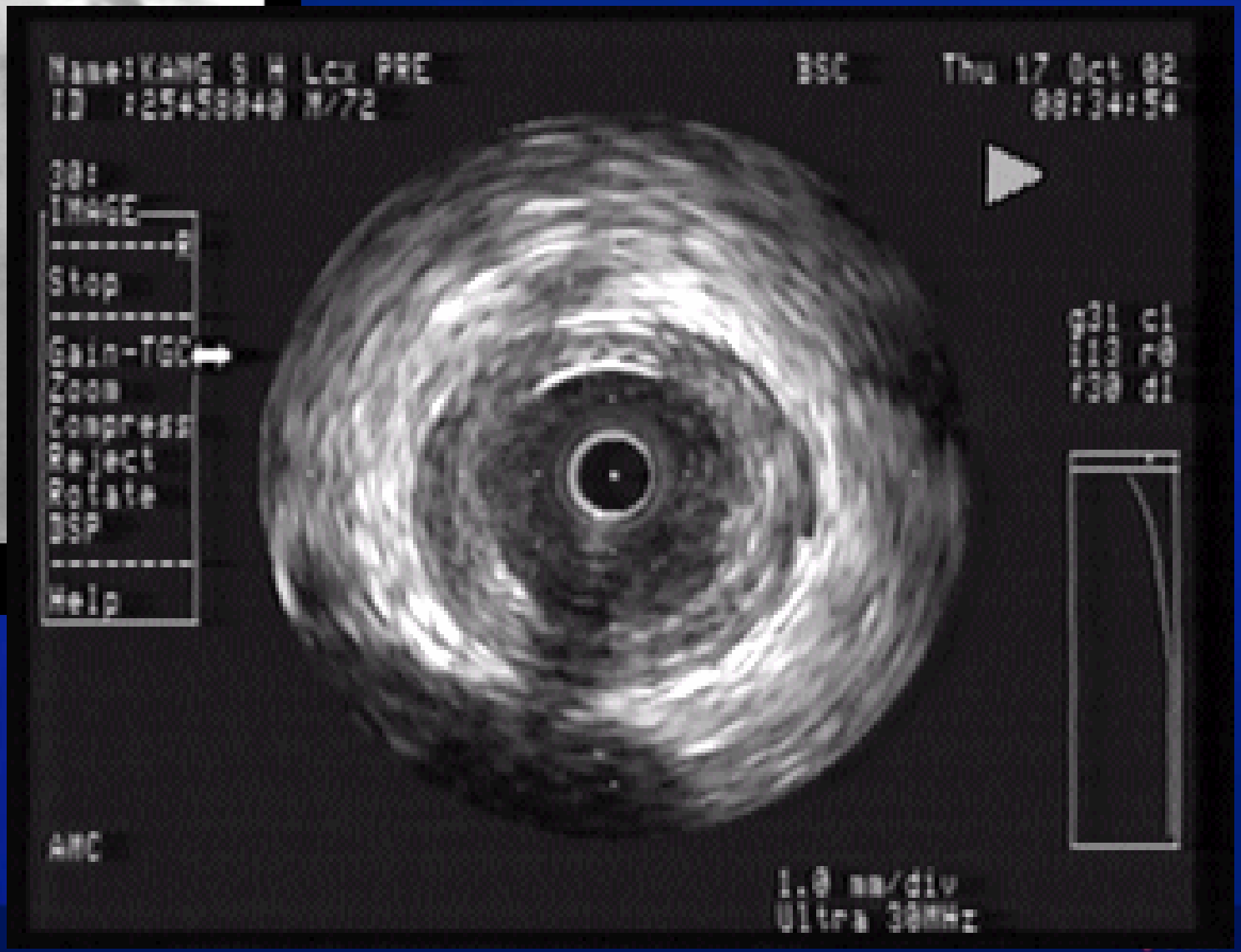


Vulnerable plaque in LAD





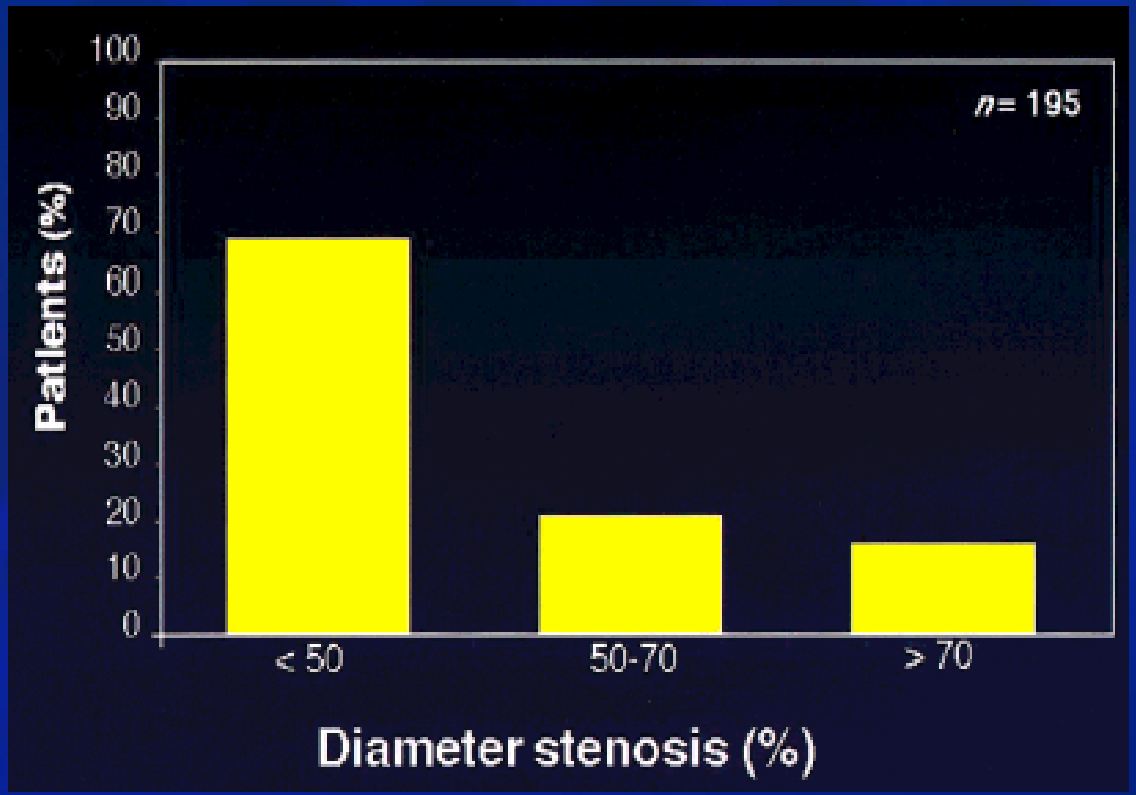
Vulnerable plaque in LCX



Severity of coronary artery stenosis before AMI

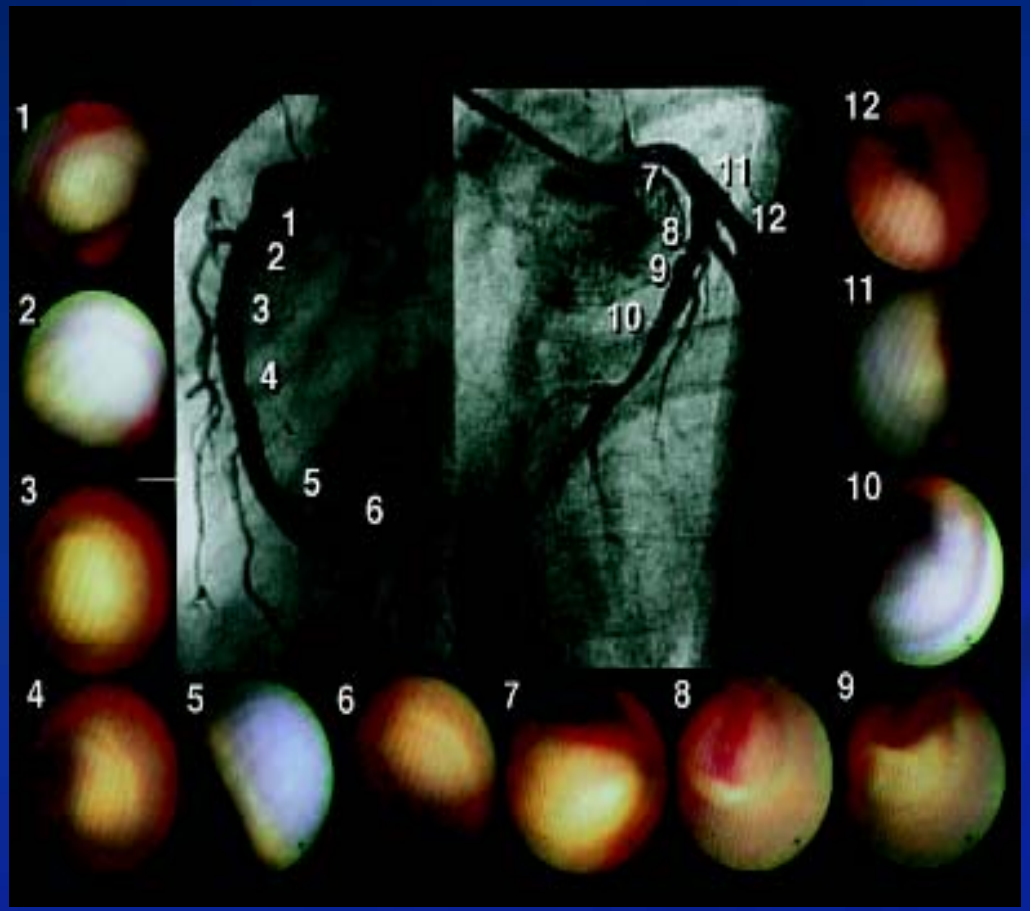
Critical luminal stenosis due to atheroma growth does not cause most ACS.

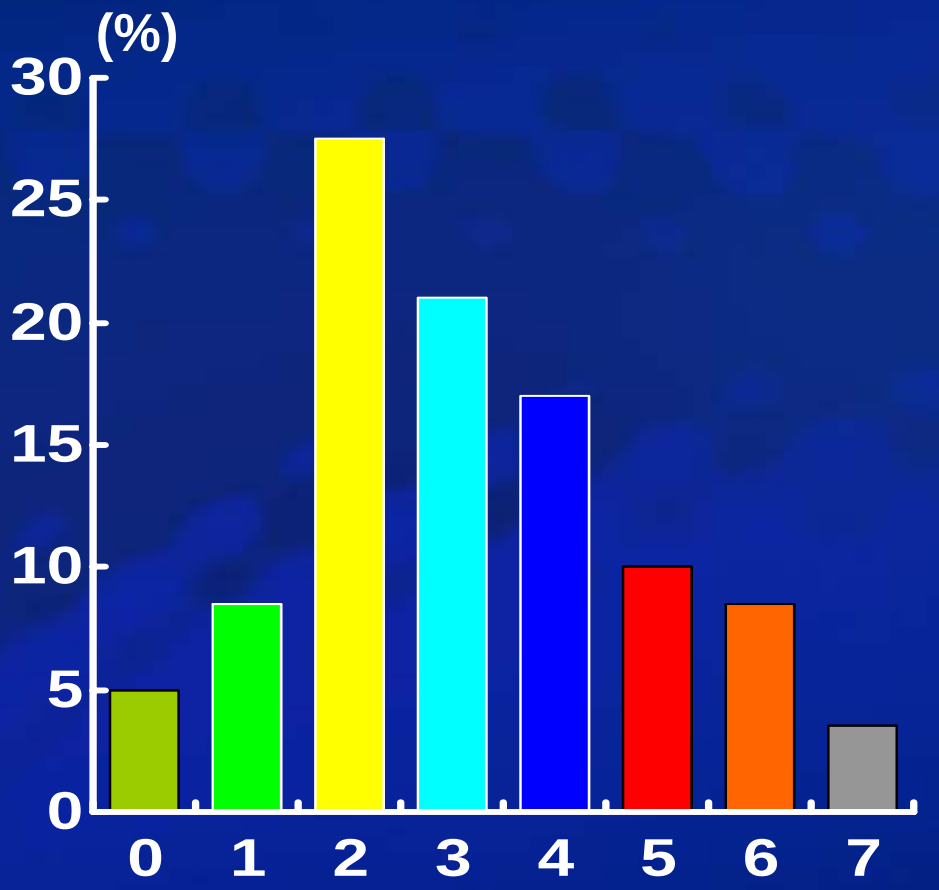
Rather, thrombosis of a non-critical stenosis caused by lesion disruption causes the majority of ACS.



Welt & Simon: CCI 2001; 53: 56-63

Angioscopic study





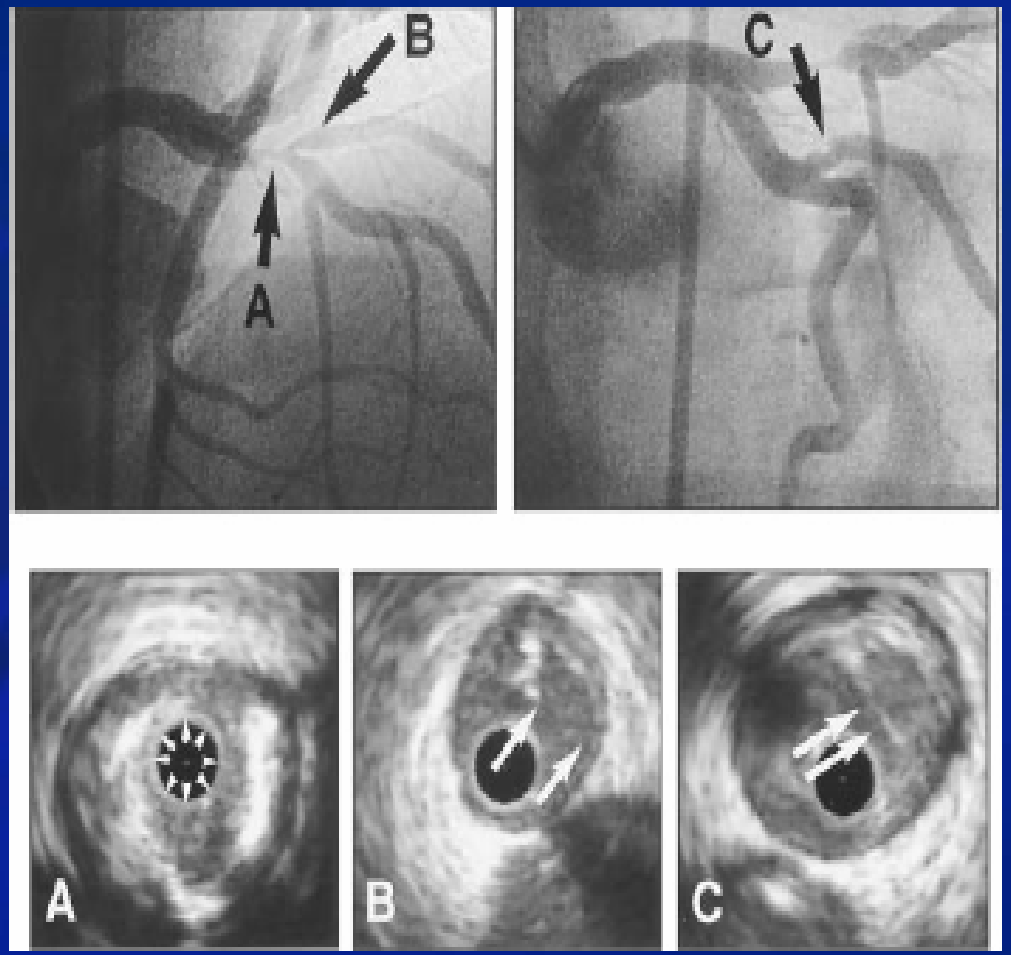
Asakura M. JACC 2001;37: 1284-88

IVUS study

The only three-vessel IVUS study in ACS patients:

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

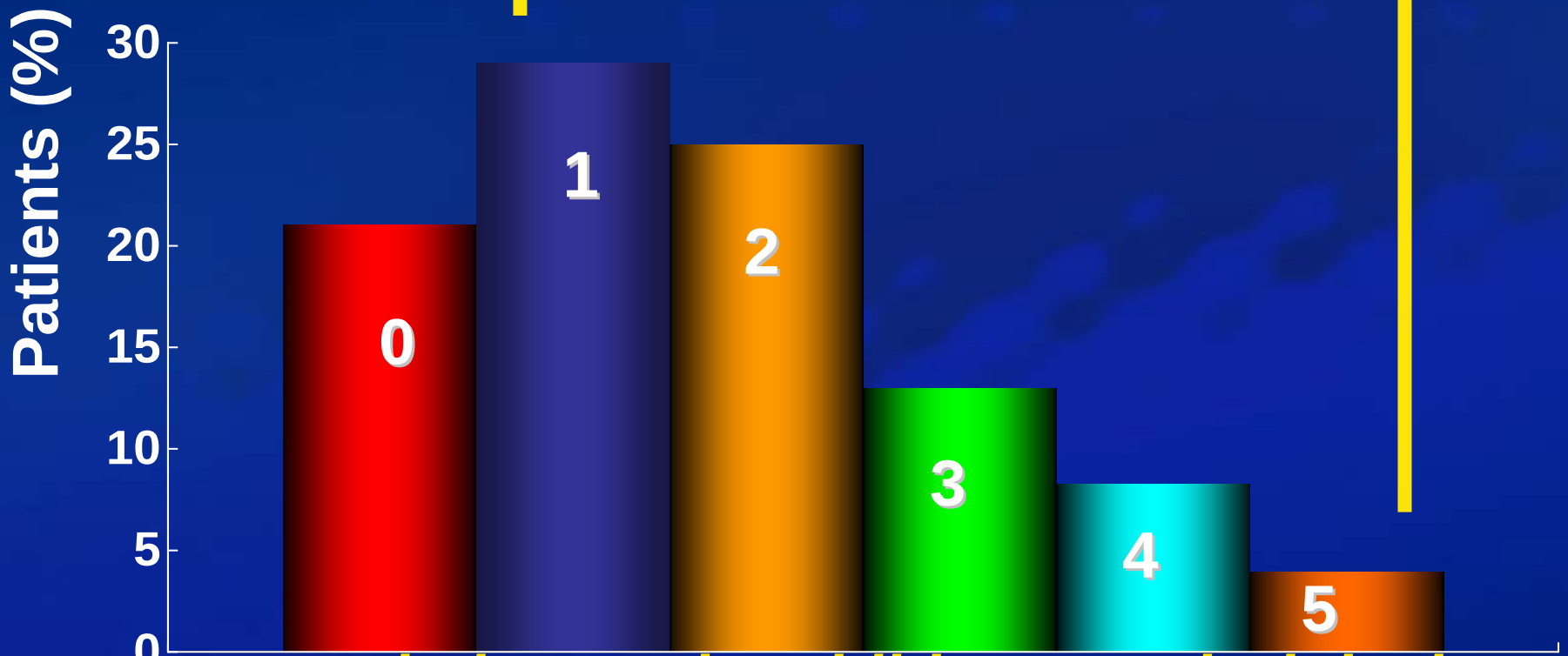
At least one secondary (non-culprit) plaque rupture in 79% (19/24) of the patients



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

IVUS study

80% of ACS patients have > 1 ruptured plaque



 # ruptured plaques in addition to culprit lesion

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

Prospective comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel IVUS study in 235 patients.

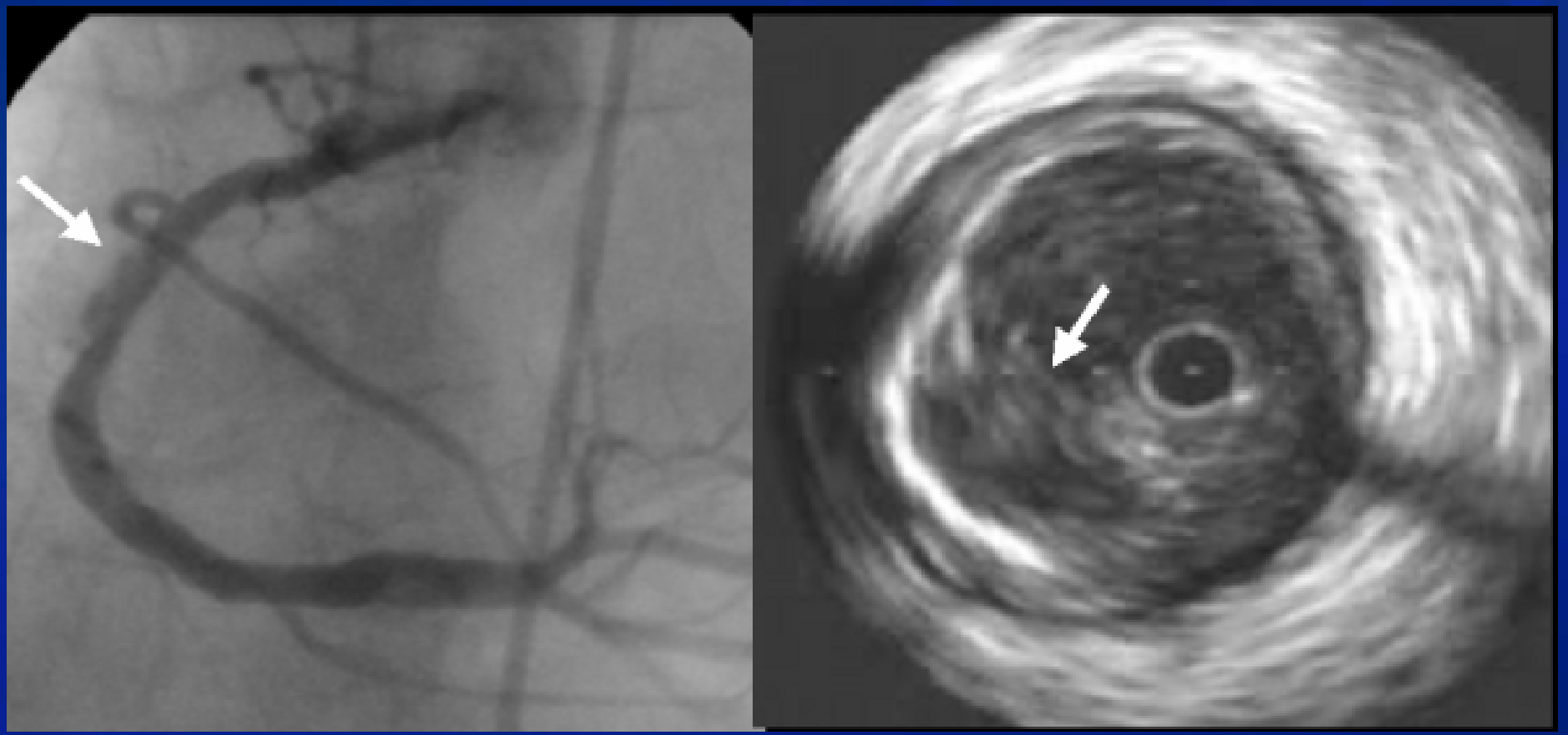
Myeong-Ki Hong, Cheol Whan Lee, Young-Hak Kim, Seung-Whan Lee, Ki-Hoon Han, Jae-Joong Kim, Seong-Wook Park, and Seung-Jung Park

Asan Medical Center, Seoul, Korea

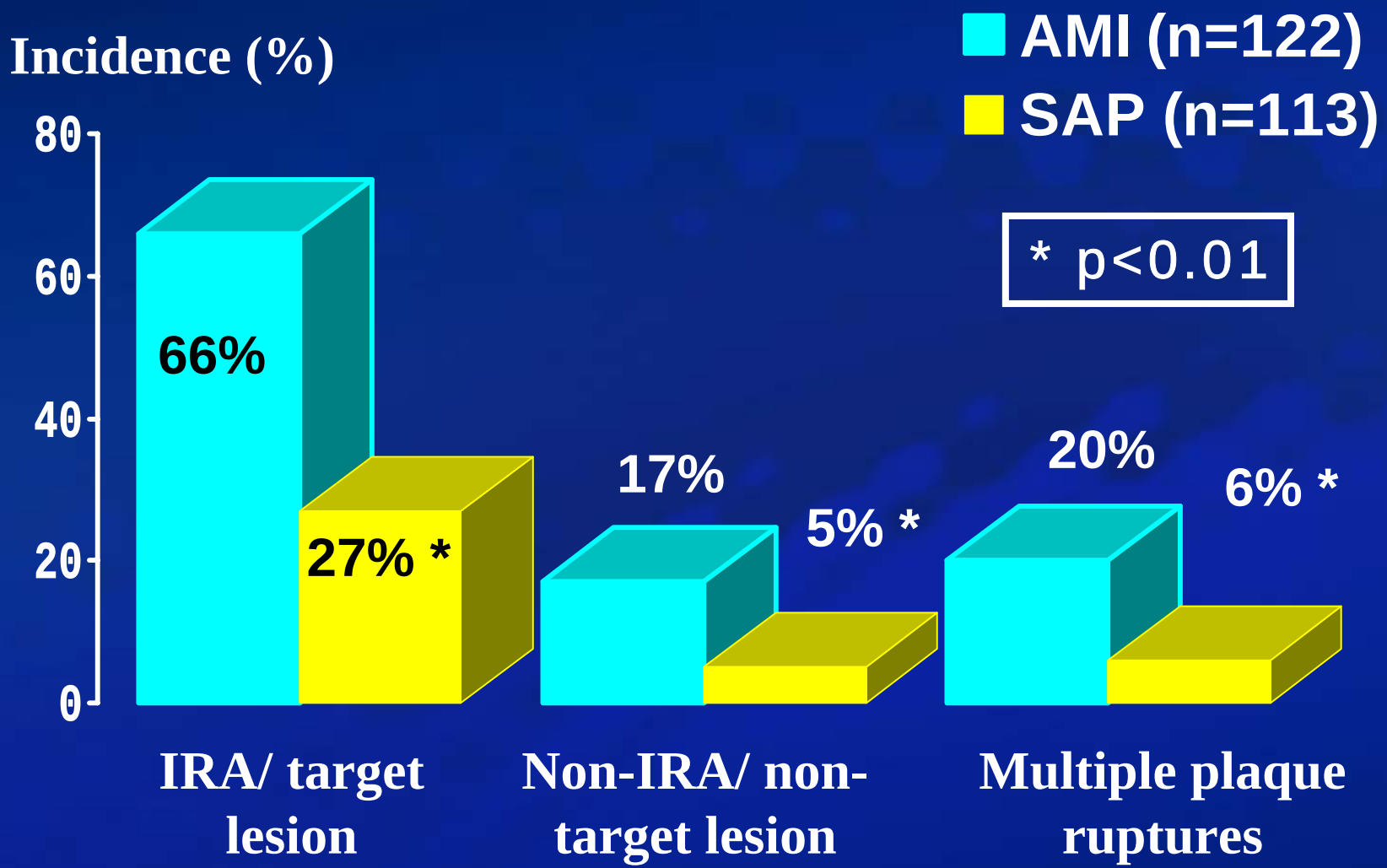
***Circulation* 2004; 110: 928-933**

Definition of Plaque Rupture

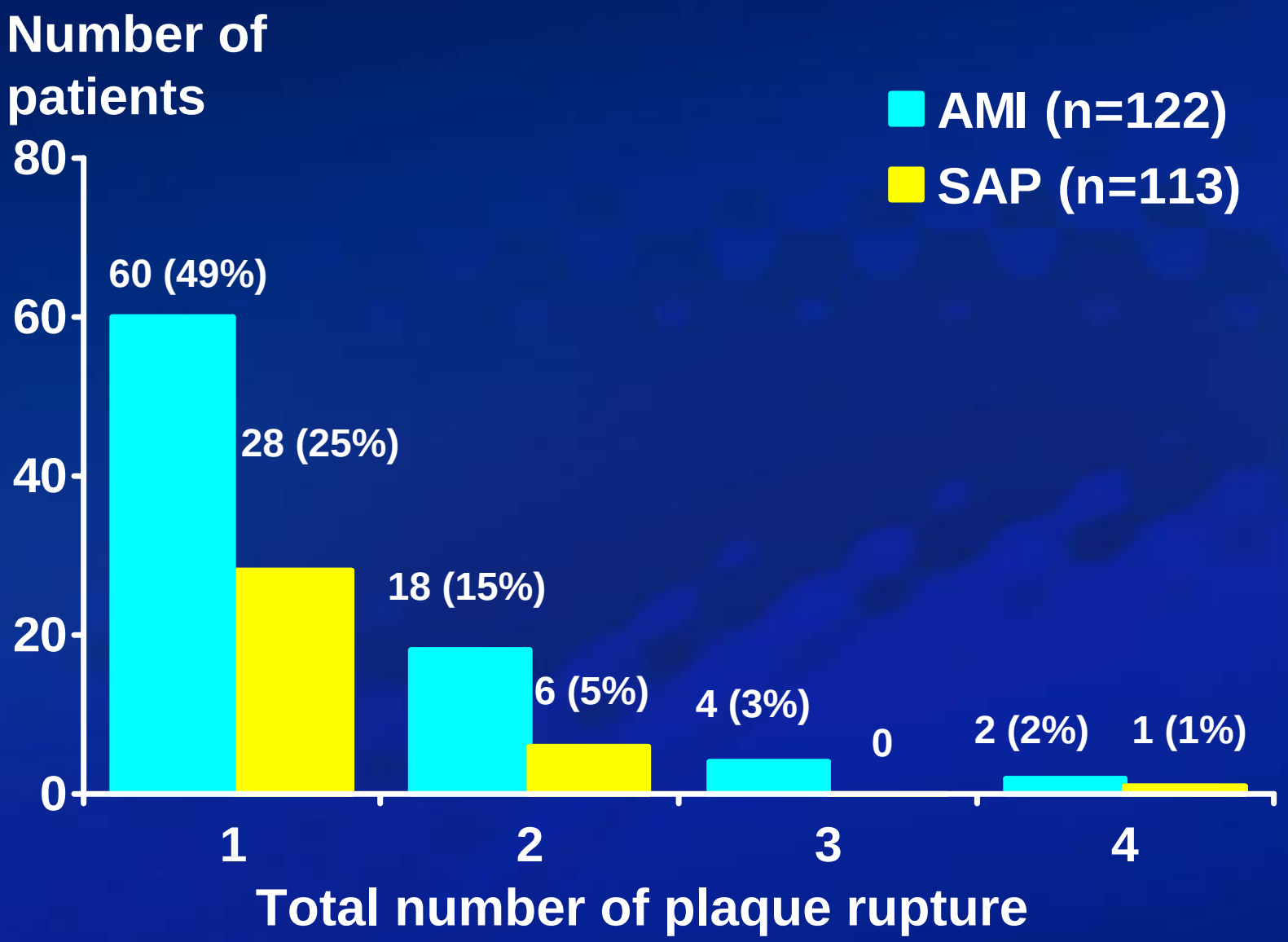
A plaque with cavity that communicated with the lumen with an overlying residual fibrous cap fragment



Incidence of plaque rupture



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



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

Question 1: Limitations

- **Practical definition of vulnerable plaques before plaque rupture**
- **Non-invasive diagnostic tool (MSCT, MR, et al)**
- **Other simple biochemical markers suggesting vulnerable plaque (CRP, other inflammatory markers)**

Question 2: Is it important to treat the vulnerable plaques ?

- **Treatment or not: Lack of data about natural history**
- **If it is treated, what types of treatment modalities?**

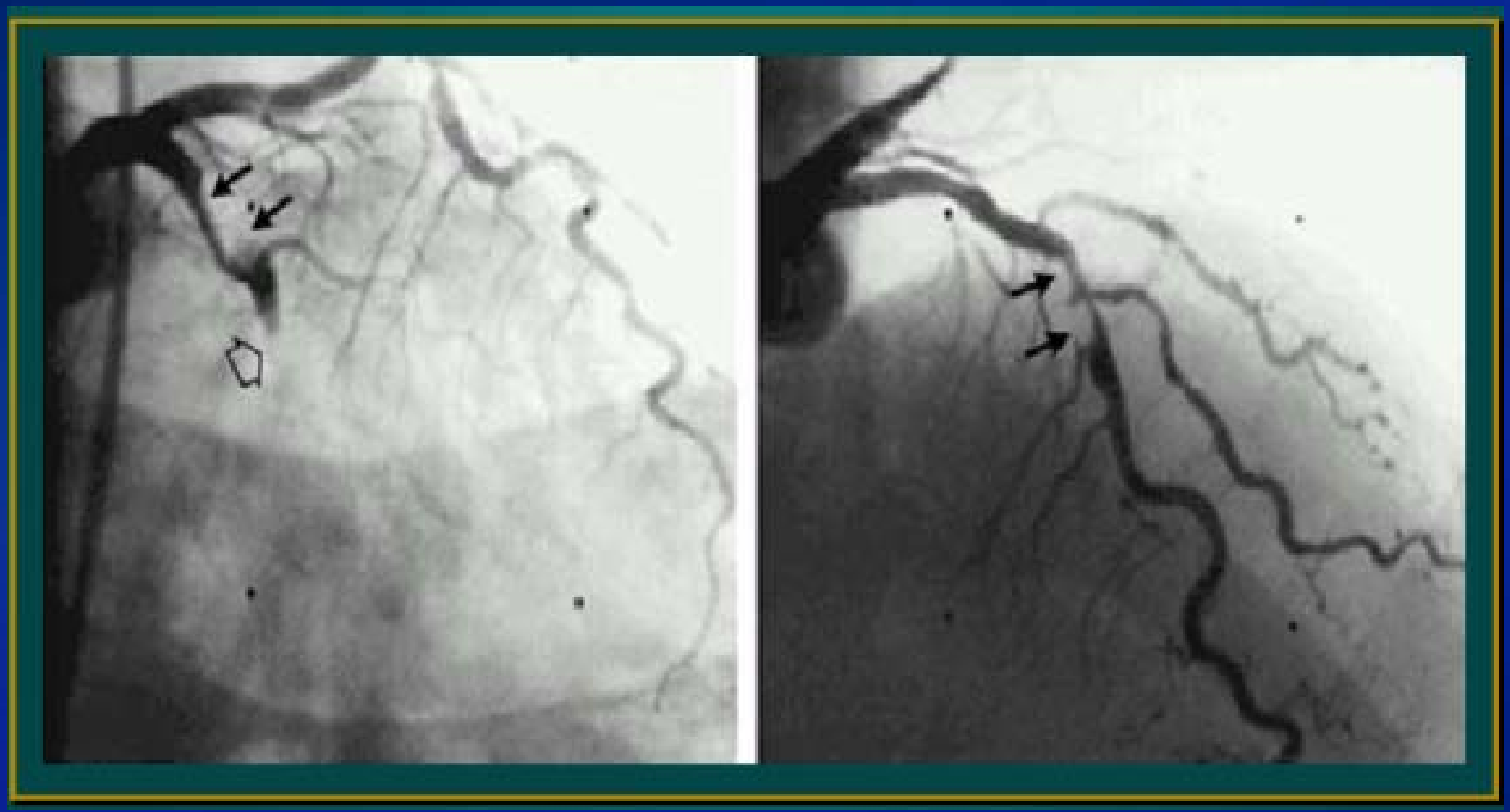
  Medical (Which drugs?),

  PCI,

  CABG

Long-term Follow-up

Angiographic study: multiple complex plaque



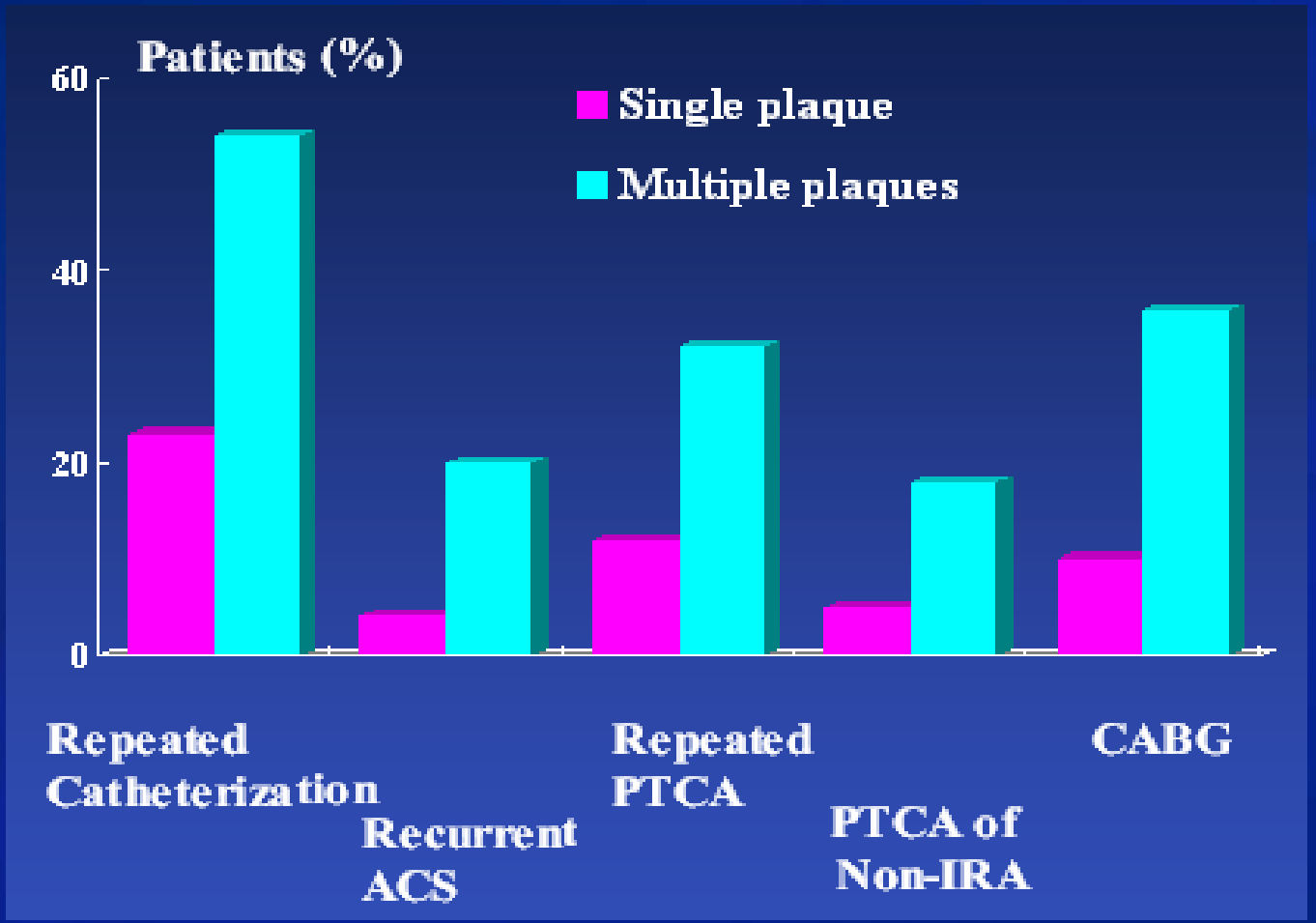
Goldstein JA, et al. *N Engl J Med.* 2000; 343:915–922.

Angiographic study

One previous study using coronary angiography:

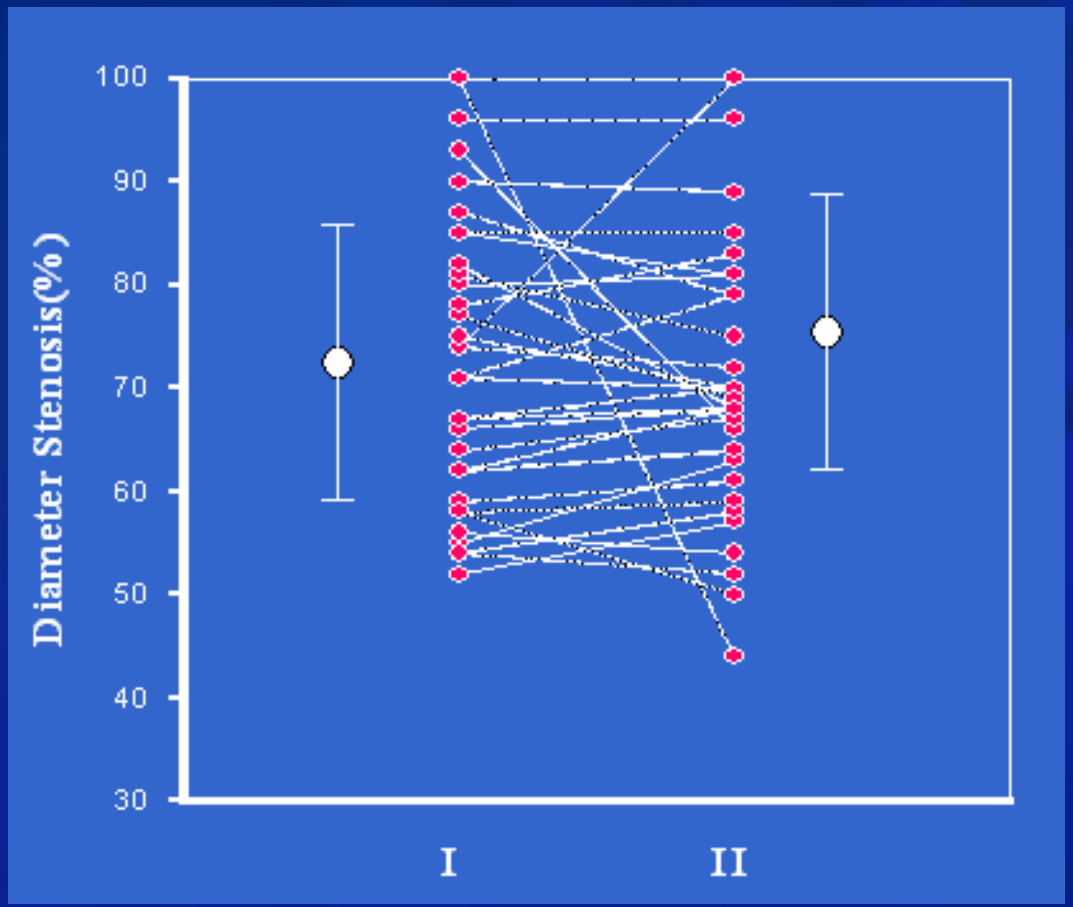
1. 40% of patients with an AMI had multiple complex plaques,

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



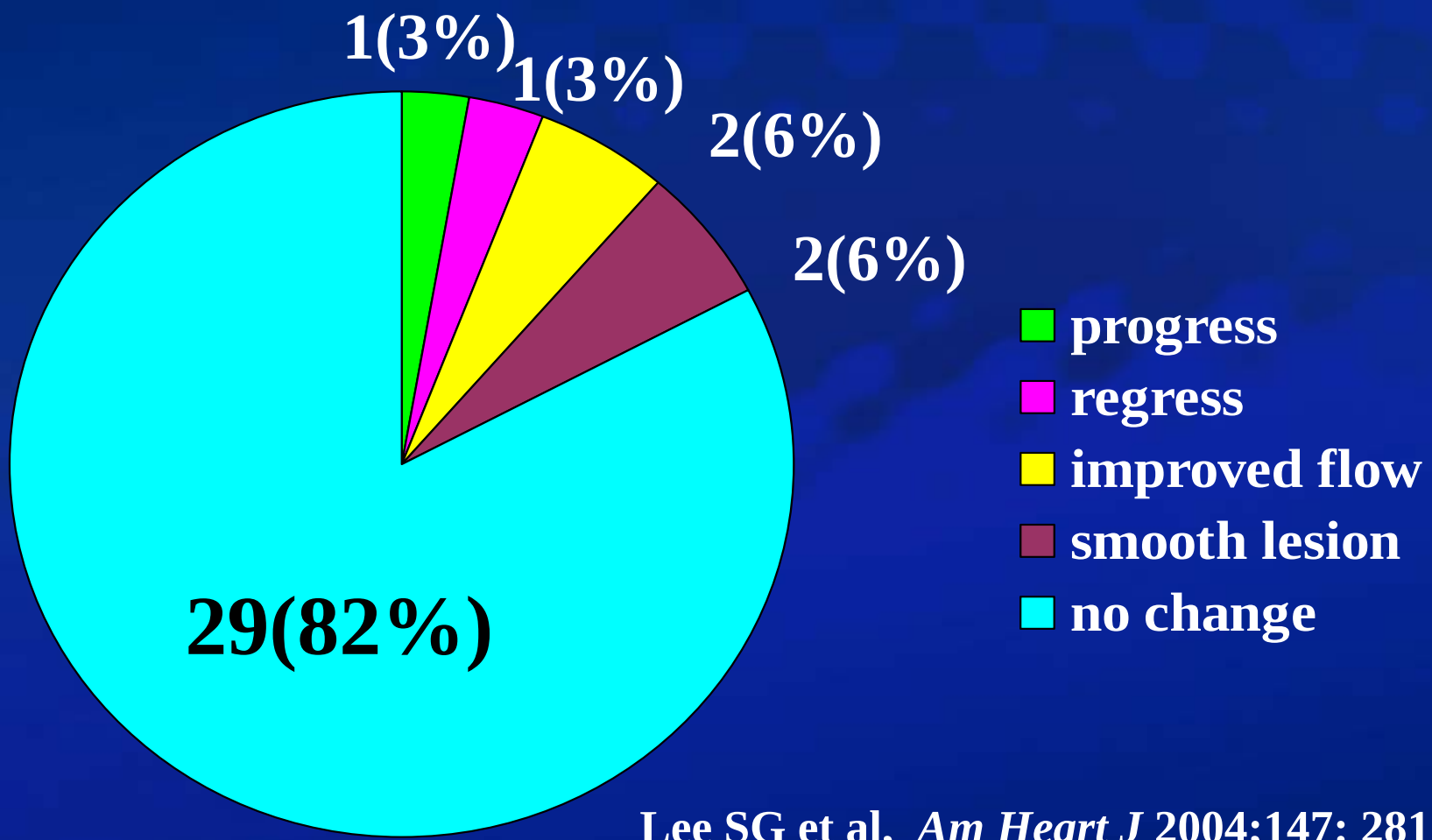
Goldstein JA, et al. *N Engl J Med.* 2000; 343:915–922.

Changes of DS in non-culprit complex plaque as detected at first (I) and follow-up (II) coronary angiography



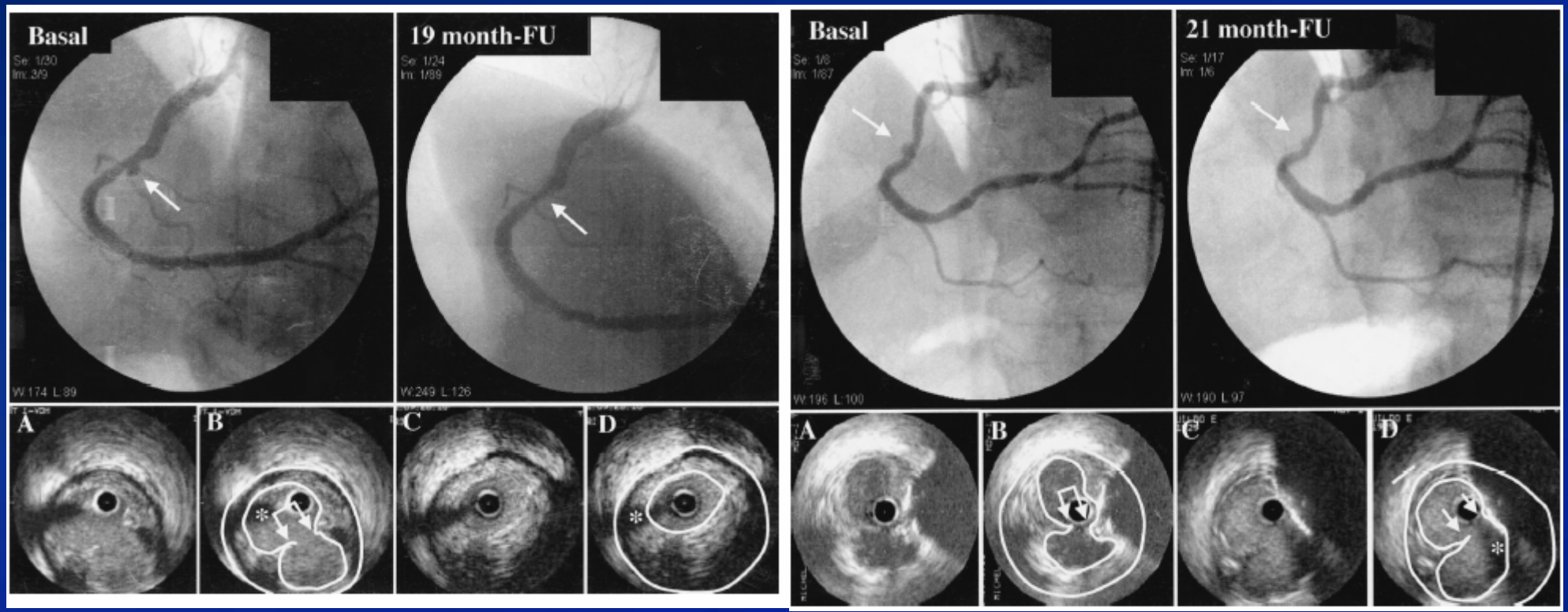
Lee SG et al, *Am Heart J* 2004;147: 281-286

Change in morphology of complex plaques



Lee SG et al, *Am Heart J* 2004;147: 281-286

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 Non-culprit Lesions

1) The study population was 30 patients with 50 ruptured plaque lesions. The mean angioscopic follow-up period was 13± 9 months.

2) The healing rate according to the angioscopic follow-up period (23% at ≤12 months vs. 55% at >12 months, p 0.044).

3) The percent DS at the healed plaque increased from baseline to follow-up (12.3% vs. 22.7%, respectively; p 0.0004).

4) The serum CRP level at follow-up was the independent predictor of healing of ruptured plaques

Takano M, Am J Coll Cardiol 2005; 45:652-8

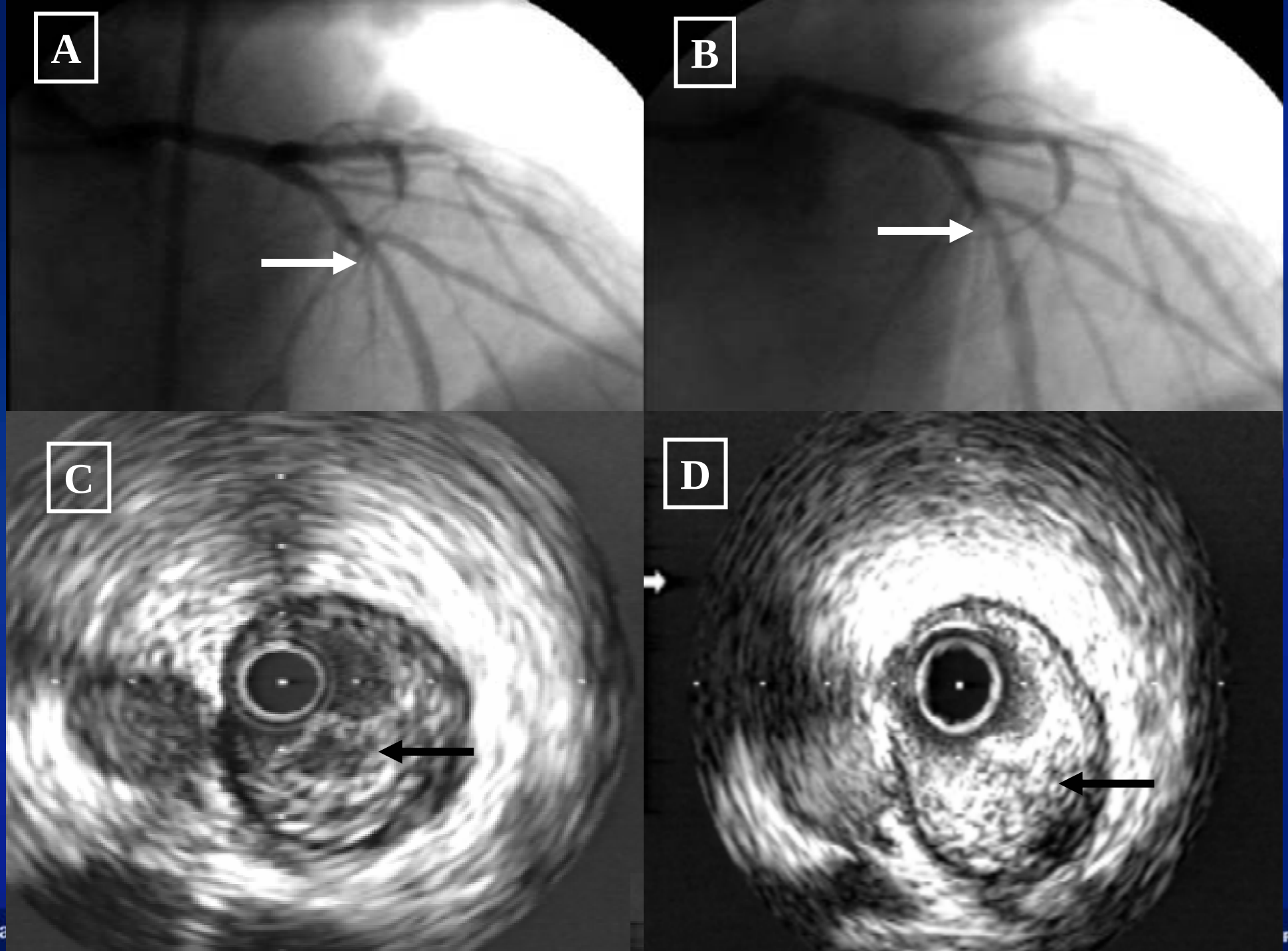
Serial IVUS Findings in Patients with Untreated Ruptured Coronary Plaques: Evidence of Both Plaque Stabilization and Lesion Progression

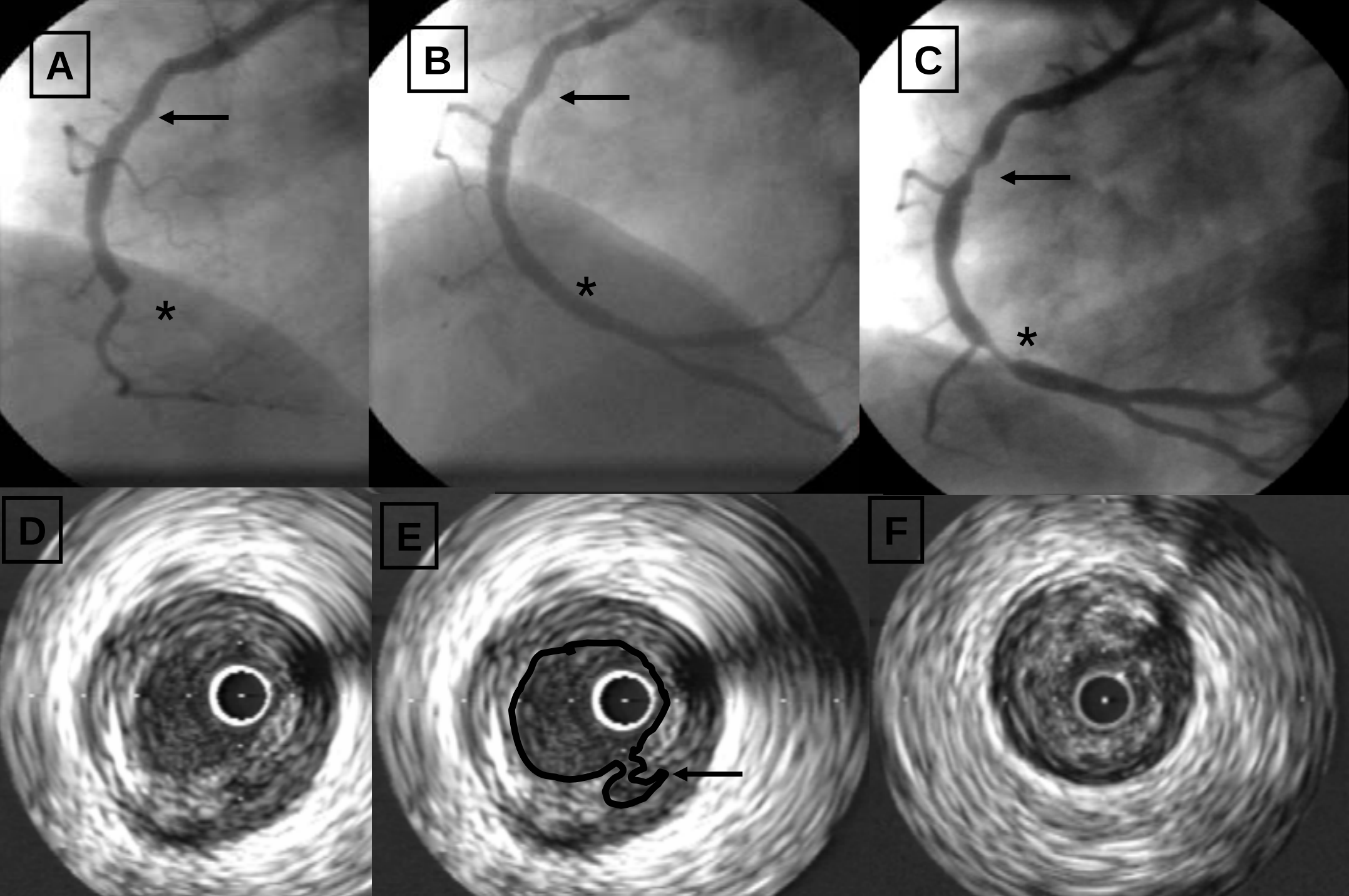
Myeong-Ki Hong, Cheol Whan Lee, Young-Hak Kim, Bong-Ki Lee, Jae-Joong Kim, Seong-Wook Park, and Seung-Jung Park

Asan Medical Center, Seoul, Korea

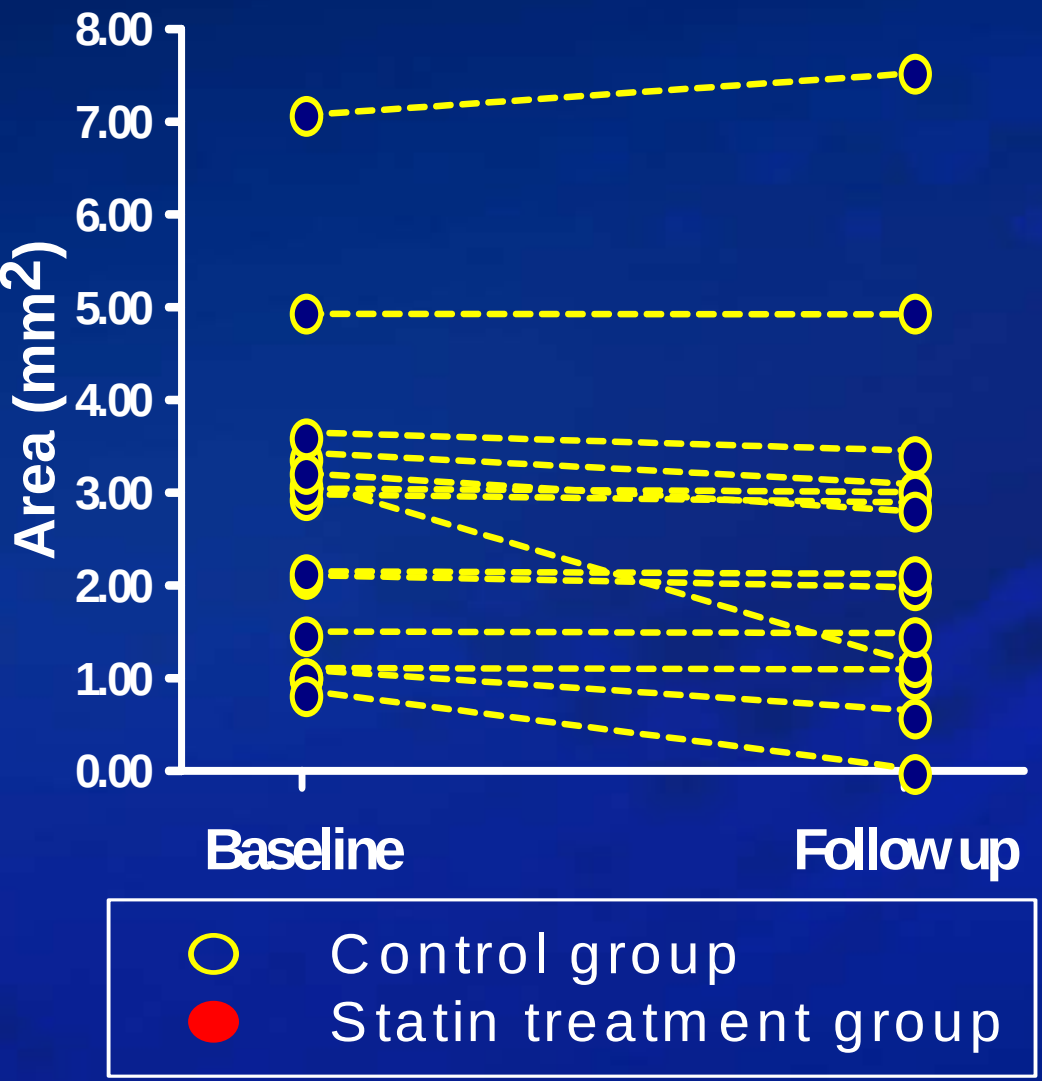
Clinical outcomes (n=28)

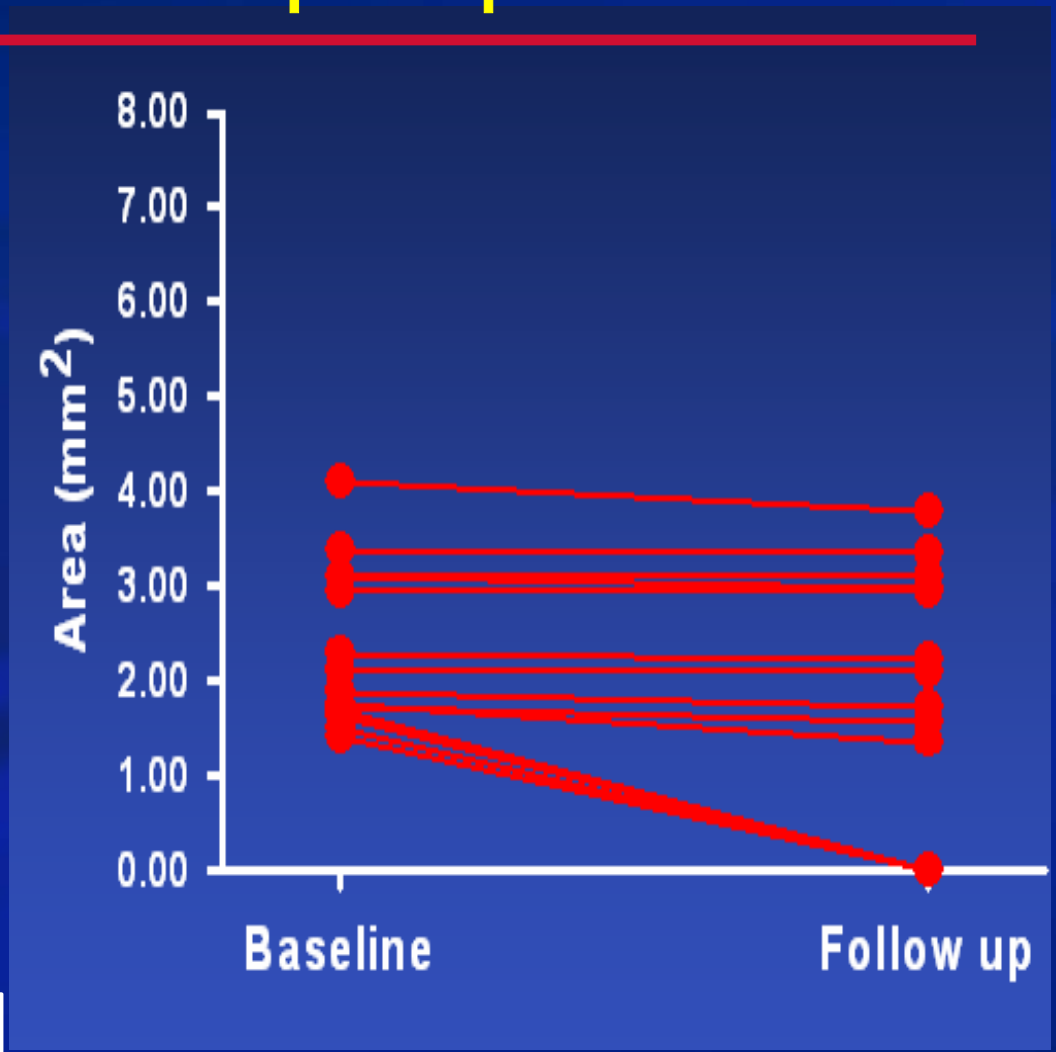
	Statin (n=14)	Control (n=14)	P
Complete healing	4	0	0.049
Incomplete healing	0	1	
No significant changes	10	10	
Progression to a focal stenosis requiring PCI	0	3	0.11


A
B
C
D


A
B
C
D
E
F

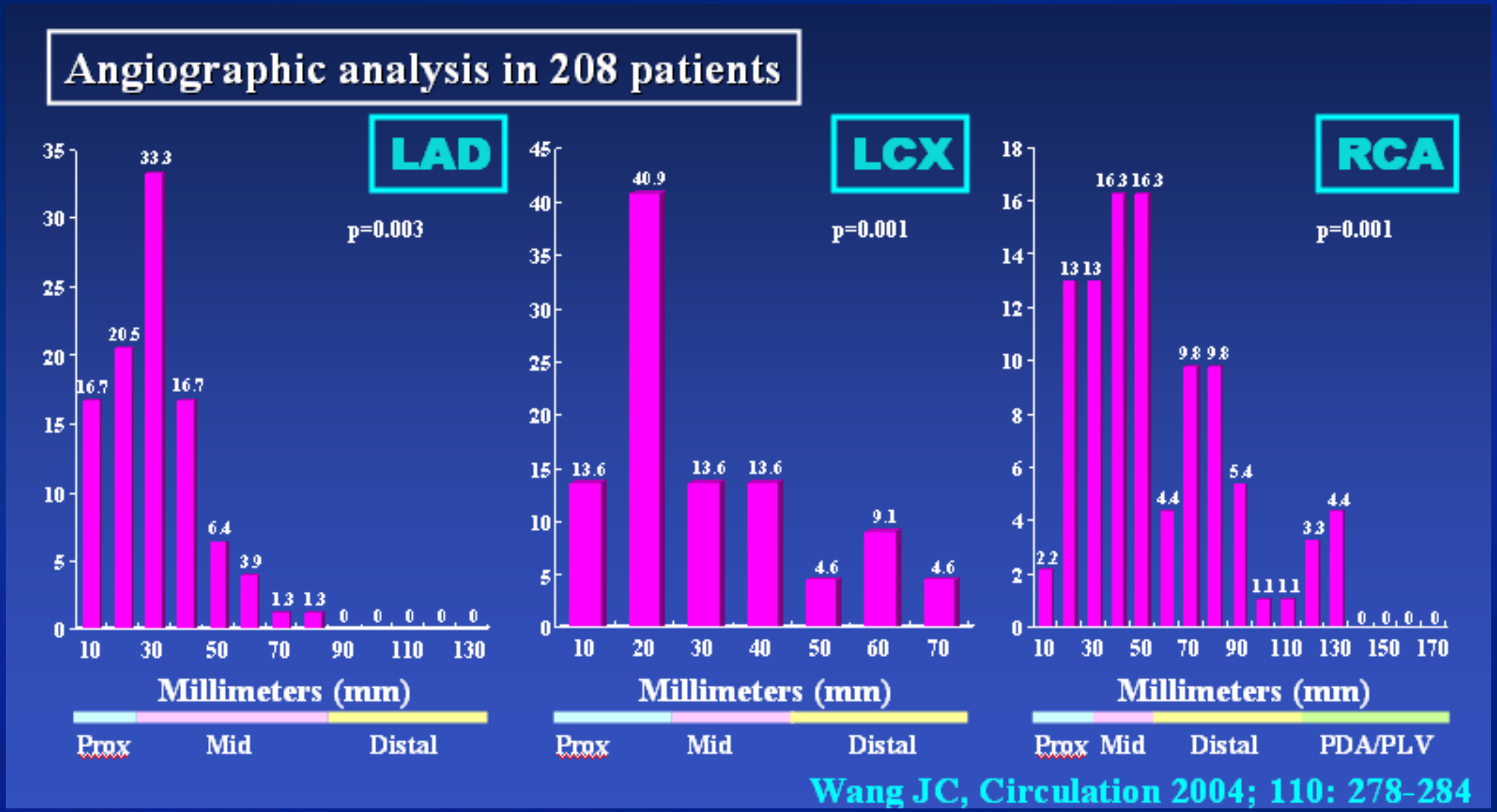
Changes of ruptured plaque area





Predilection site of Vulnerable Plaque-Clustering of Vulnerable Plaque

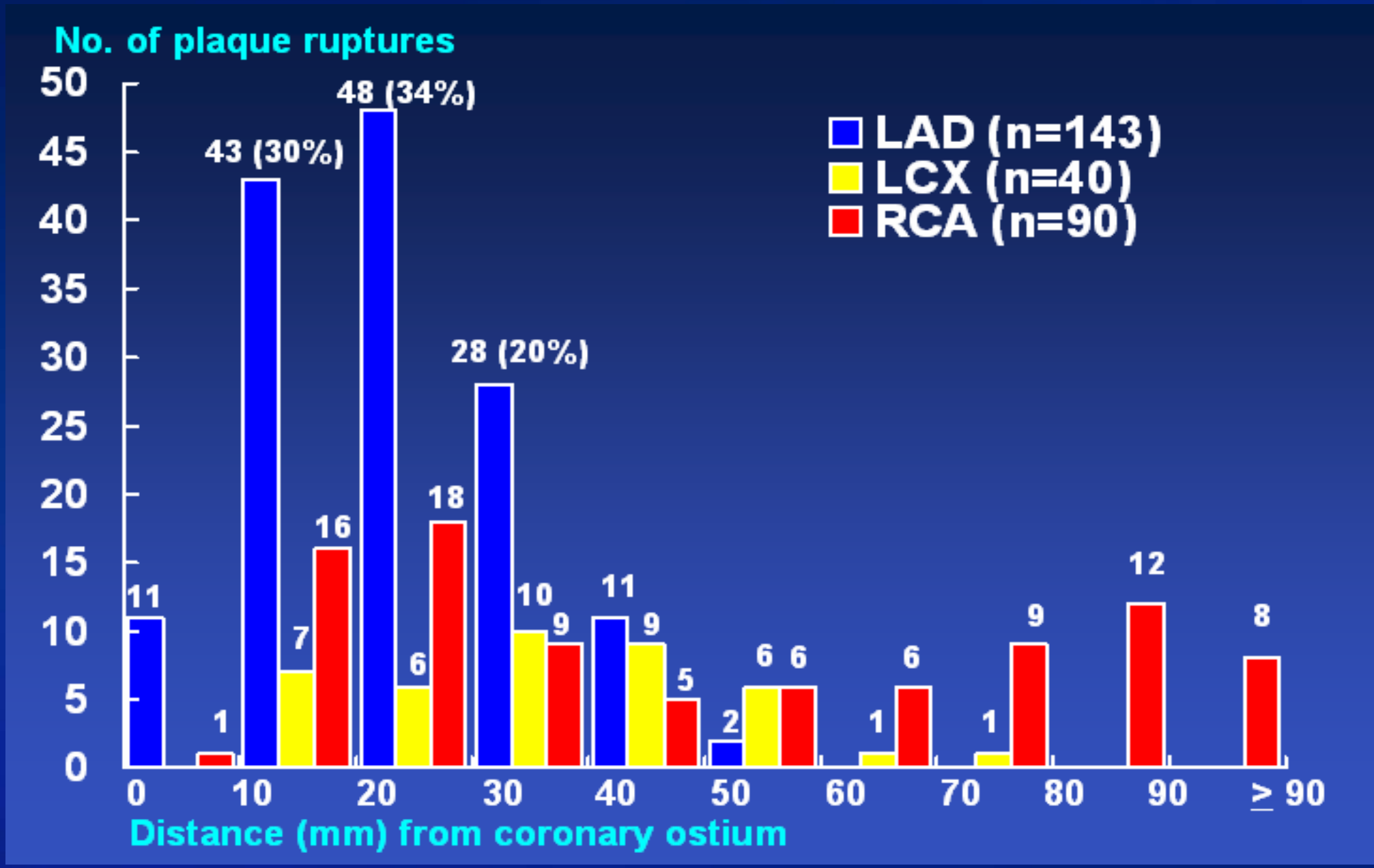
Coronary Artery Spatial Distribution of AMI Occlusions

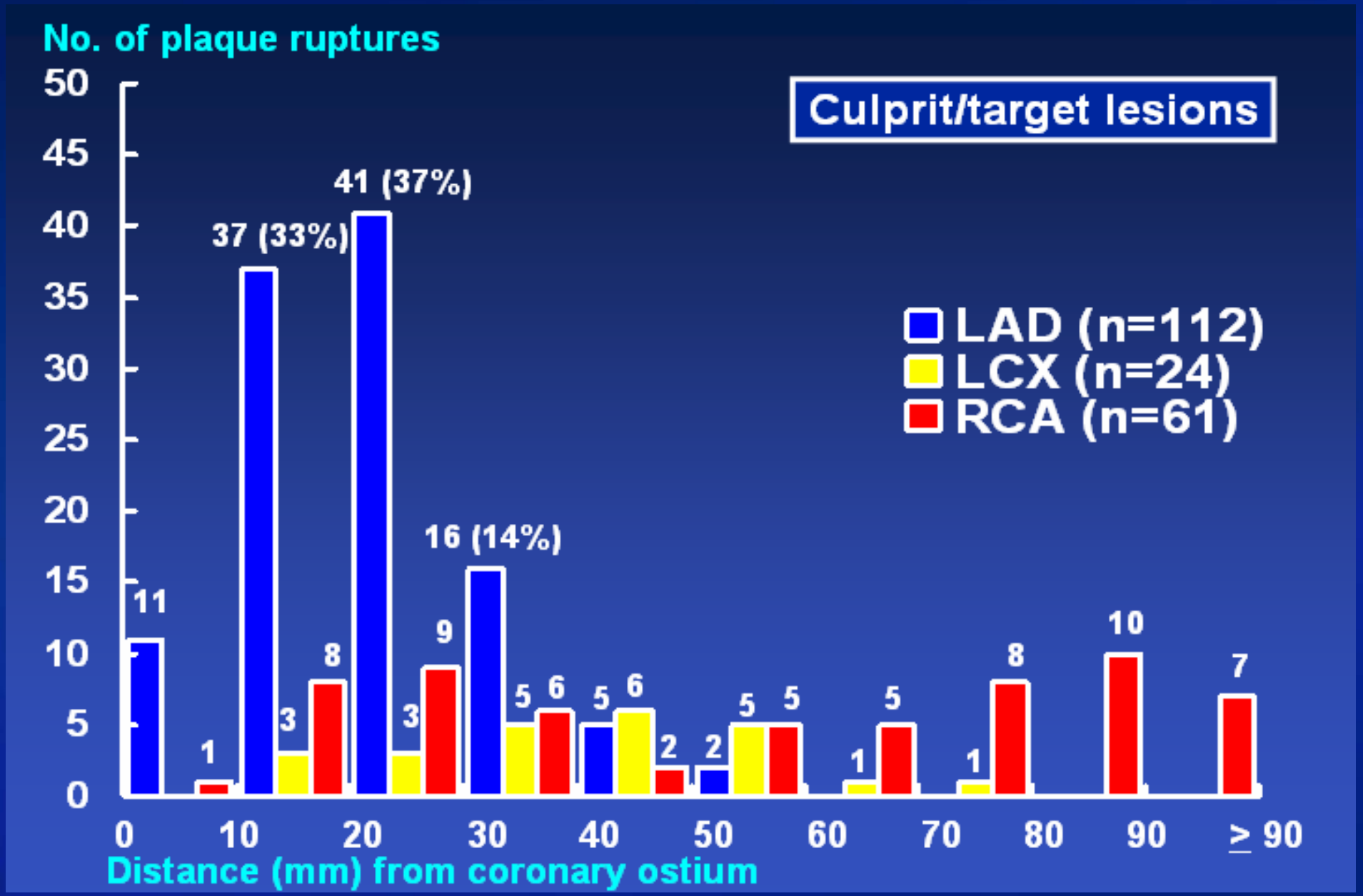


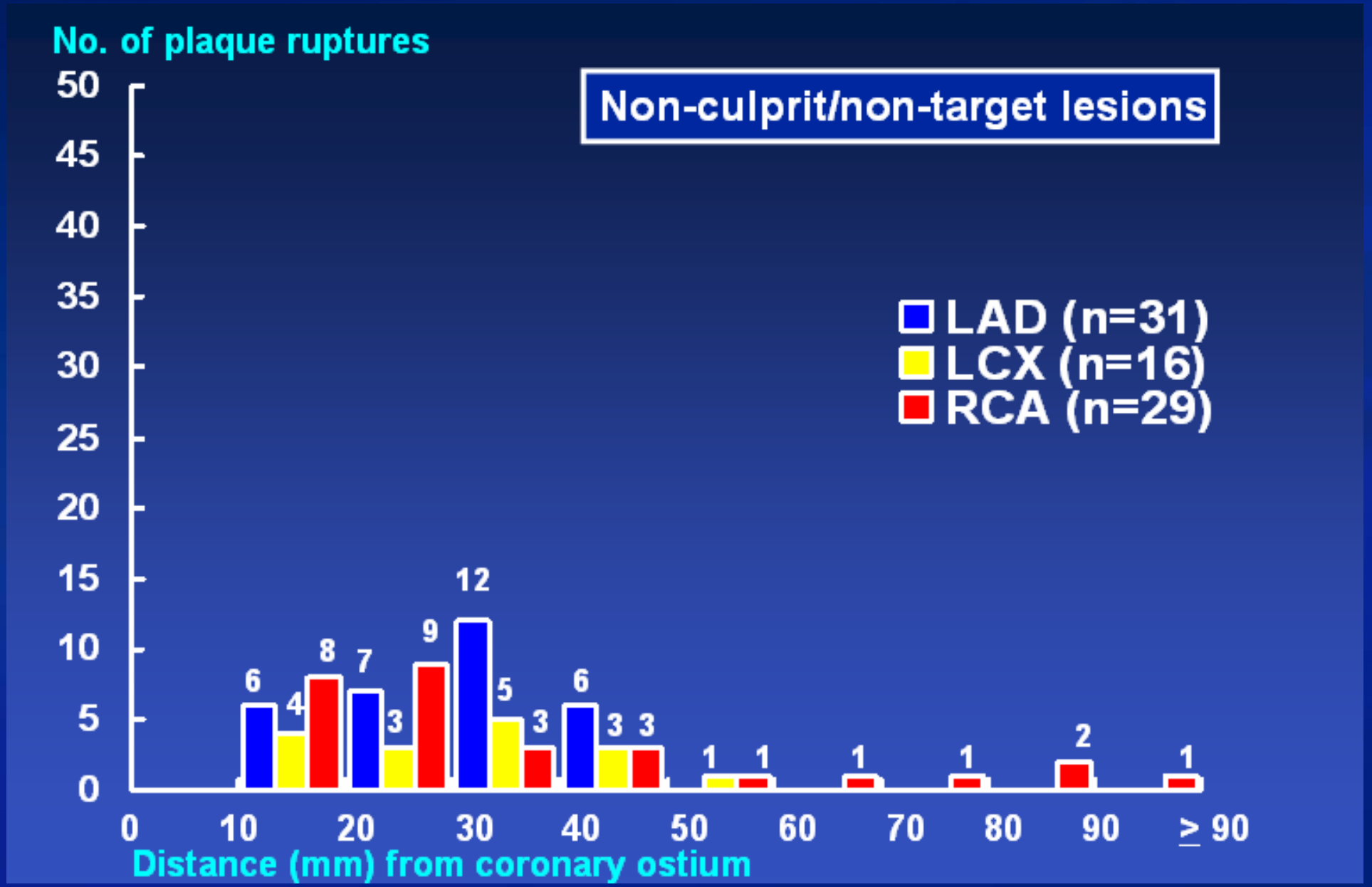
The Site of Plaque Rupture in Native Coronary Arteries: a Three-Vessel IVUS Analysis.

Myeong-Ki Hong, Cheol Whan Lee, Young-Hak Kim, Ki-Hoon Han, Jae-Joong Kim, Seong-Wook Park, and Seung-Jung Park

***J Am Coll Cardiol* 2005; (in press)**

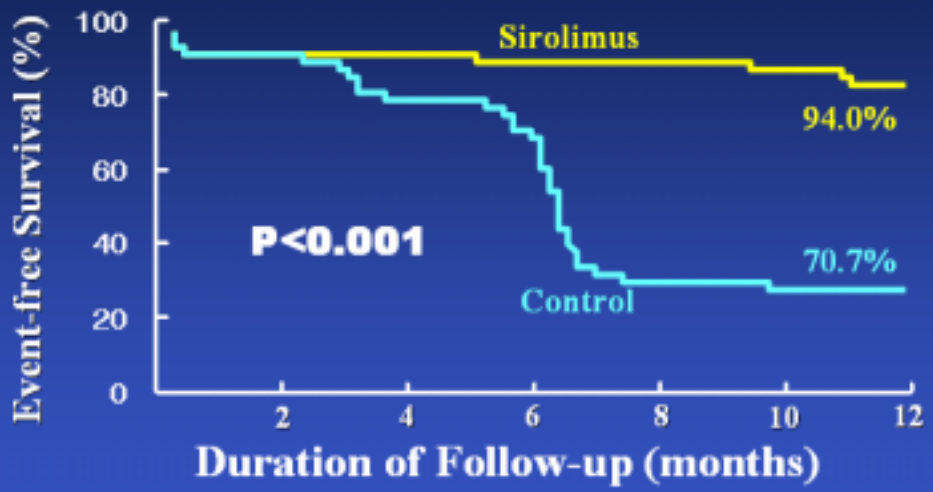

No. of plaque ruptures
50
45
40
35
30
25
20
15
10
5
0
LAD (n=143)
LCX (n=40)
RCA (n=90)
43 (30%)
48 (34%)
28 (20%)
11
1
7
16
6
18
10
9
11
9
5
2
6
6
1
6
1
9
12
8
0
10
20
30
40
50
60
70
80
90
≥ 90
Distance (mm) from coronary ostium


No. of plaque ruptures
50
45
40
35
30
25
20
15
10
5
0
Culprit/target lesions
LAD (n=112)
LCX (n=24)
RCA (n=61)
41 (37%)
37 (33%)
16 (14%)
11
1
3
8
3
9
5
6
5
6
2
2
5
5
1
5
1
8
10
7
0
10
20
30
40
50
60
70
80
90
≥ 90
Distance (mm) from coronary ostium


No. of plaque ruptures
Non-culprit/non-target lesions
LAD (n=31)
LCX (n=16)
RCA (n=29)
50
45
40
35
30
25
20
15
10
5
0
6
4
8
7
3
9
12
5
3
6
3
3
1
1
1
1
2
1
0
10
20
30
40
50
60
70
80
90
≥ 90
Distance (mm) from coronary ostium

Event-free Survival in RAVEL:

Death, MI, CABG, Re-PCI

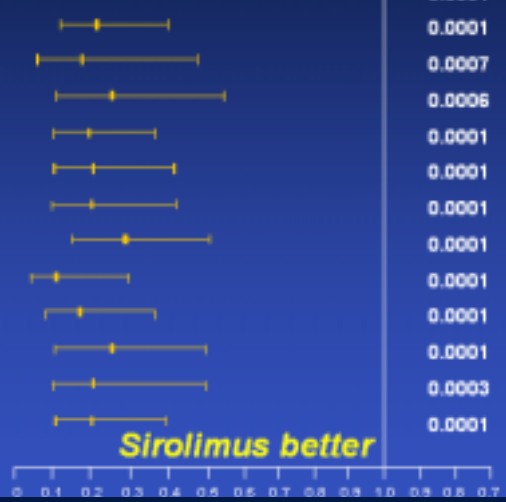


Morice MC et al, NEJM 2002;346:17

TLR Events

SIRIUS

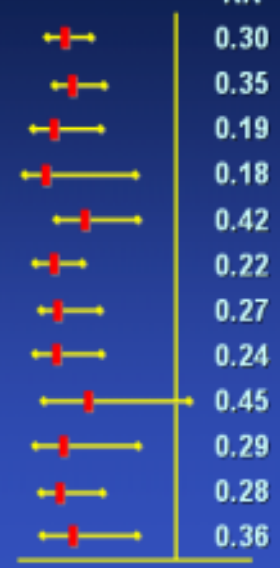
	Sirolimus	Control	P-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



Restenosis Rate

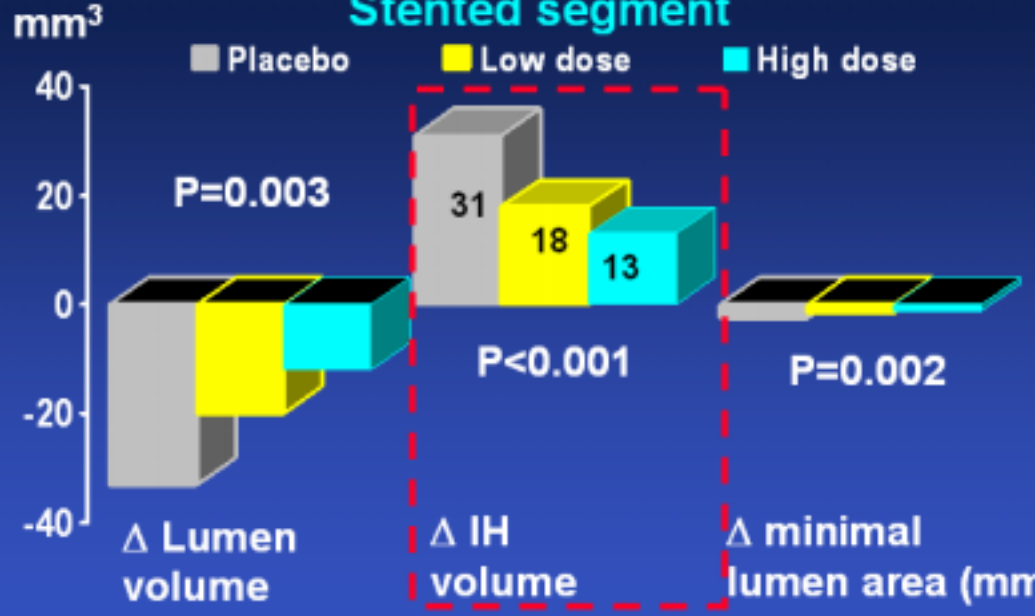
TAXUS IV

	RR	TAXUS	Control	P
All	0.30	7.9	26.6	<0.0001
Non-diabetic	0.35	8.5	24.4	<0.0001
Diabetic, oral meds	0.19	5.8	29.7	0.003
Diabetic, insulin	0.18	7.7	42.9	0.007
LAD	0.42	11.3	26.9	0.004
Non-LAD	0.22	5.7	26.4	<0.0001
RVD ≤2.5 mm	0.27	10.2	38.5	<0.0001
RVD 2.5-3.0 mm	0.24	6.7	27.8	0.0001
RVD ≥3.0 mm	0.45	6.8	15.2	0.10
Lsn length <10 mm	0.29	5.6	18.9	0.01
Lsn length 10-20 mm	0.28	7.2	25.8	<0.0001
Lsn length >20 mm	0.36	14.9	41.5	0.004



IVUS analysis (Δ: comparison)

Stented segment



Hong MK, et al. Circulation 2003; 107: 517-520

Meta-Analysis Comparing Drug-Eluting Stents With Bare Metal Stents in 10 Randomized trials of 5,066 Patients with 6-12 Months Follow-up.

TABLE 2 Clinical Outcomes

Trials	Sample size		Follow-up (mo)	Outcomes With Drug-eluting Stents			Outcomes With Bare-metal Stents		
	DES	Control		Death (cardiac)	AMI (Q wave)	Thrombosis (1st mo)	Death (cardiac)	AMI (Q wave)	Thrombosis (1st mo)
TAXUS-I	31	30	12	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TAXUS-II	266	270	12	0 (0)	8 (3)	3 (1)	2 (1)	14 (3)	0 (0)
TAXUS-IV	662	652	12	ND (9)	23 (5)	4 (2)	ND (8)	31 (2)	5 (4)
ASPECT	117	59	6	1 (ND)	3 (0)	4 (4)	0 (0)	1 (0)	0 (0)
ELUTES	152	38	12	1 (1)	2 (0)	1 (1)	0 (0)	0 (0)	1 (1)
DELIVER	522	519	9	5 (ND)	6 (2)	2 (ND)	5 (ND)	5 (1)	0 (0)
RAVEL	120	118	12	2 (0)	4 (2)	0 (0)	2 (1)	5 (1)	0 (0)
SIRIUS	533	525	9	5 (ND)	15 (4)	2 (1)	3 (ND)	17 (2)	4 (1)
E-SIRIUS	175	177	9	2 (1)	8 (2)	2 (2)	1 (0)	4 (0)	0 (0)
C-SIRIUS	50	50	9	0 (0)	1 (0)	1 (1)	0 (0)	2 (0)	1 (0)

AMI = acute myocardial infarction; DES = drug-eluting stent; ND = no data available.

Katritsis DG, Am J Cardiology 2005; 45: 652-8

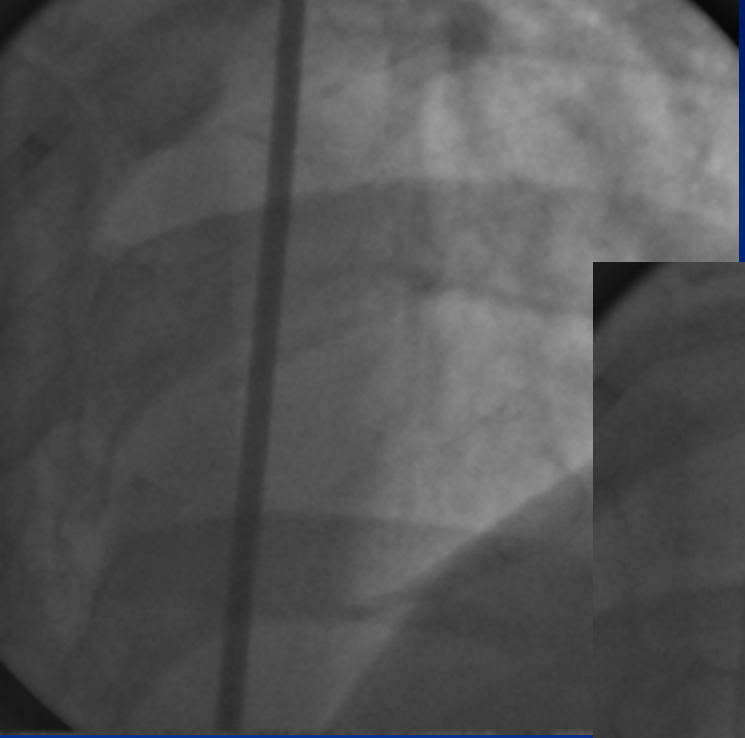
Effectiveness of Sirolimus-Eluting Stent Implantation for Coronary Narrowings <50% in Diameter

Angela Hoye, MB, ChB, Pedro A. Lemos, MD, Chourmouzios A. Arampatzis, MD, Francesco Saia, MD, Kengo Tanabe, MD, Muzaffer Degertekin, MD, Joost Daemen, Pieter C. Smits, MD, PhD, Eugene McFadden, MB, ChB, Sjoerd H. Hofma, MD, Georgios Sianos, MD, PhD, Pim de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Ron T. van Domburg, PhD, and Patrick W. Serruys, MD, PhD

- A consecutive series of 20 patients were treated with sirolimus-eluting stent implantation for 23 angiographically mild de novo lesions (defined as a diameter stenosis <50% by quantitative coronary angiography).

- At a mean follow-up of 399 ± 120 days, the survival-free of major adverse events was 95%, with no patient requiring target lesion revascularization.

Am J Cardiol 2004;94: 112-114



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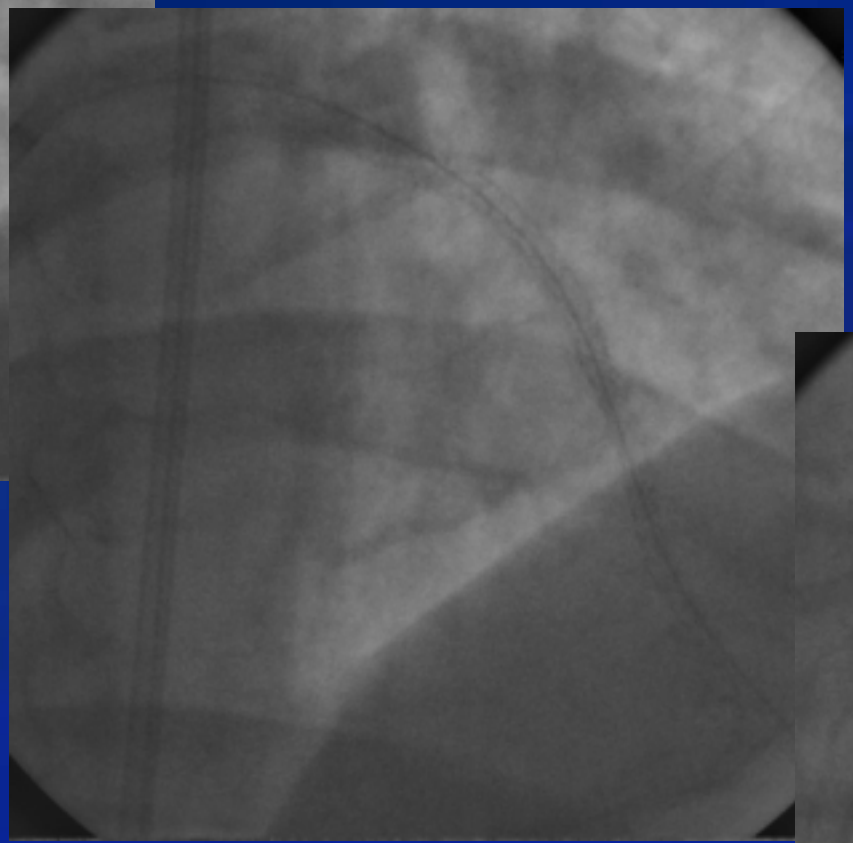
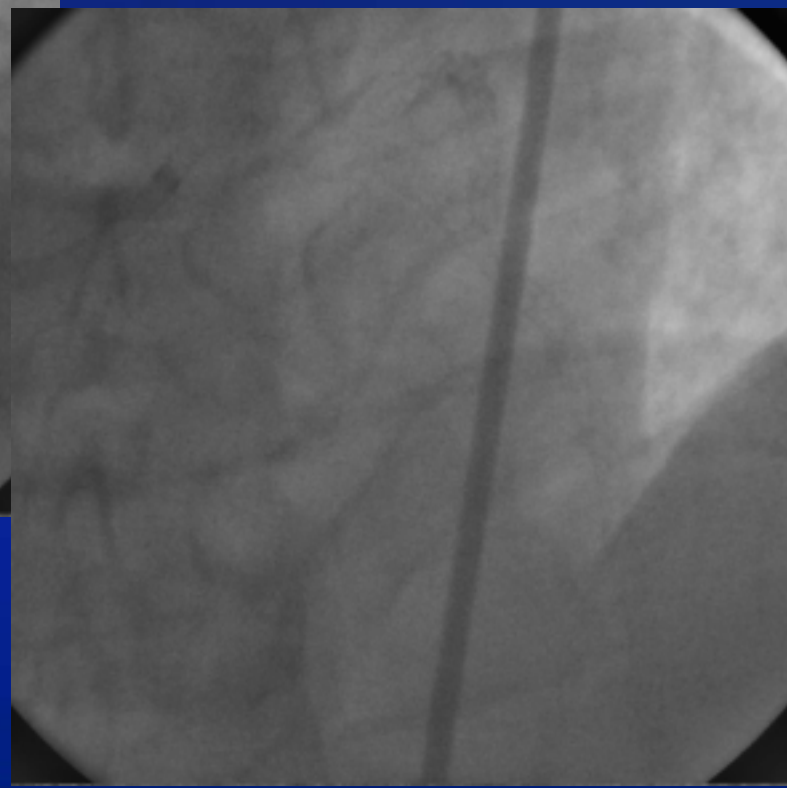
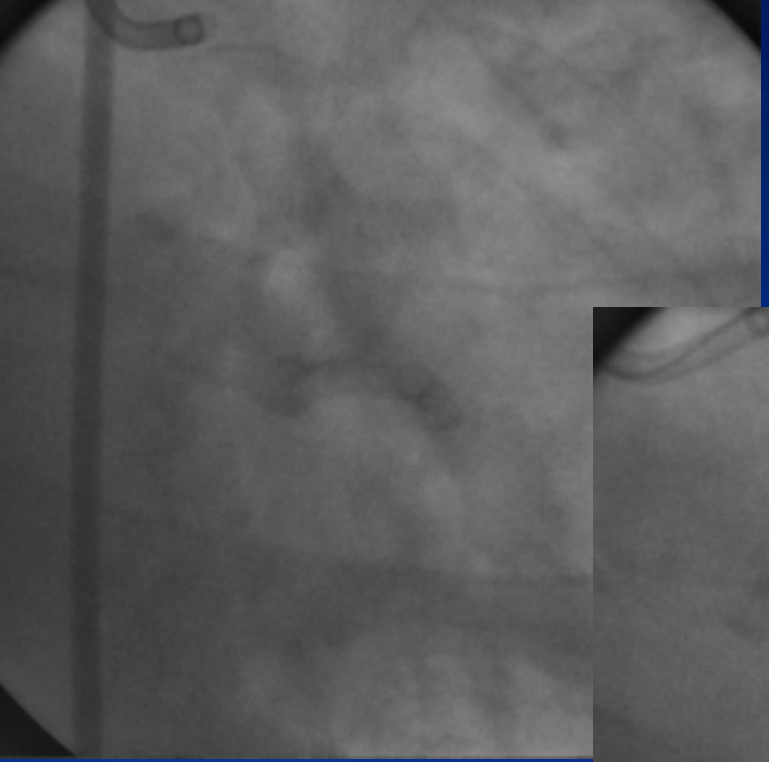


After stent

6-month
follow-up





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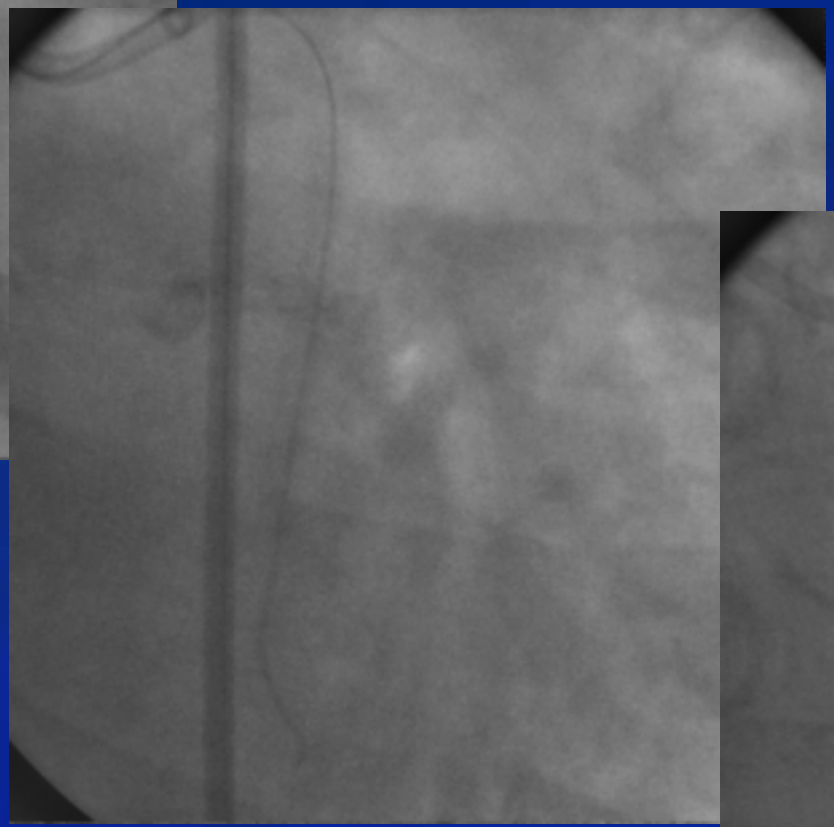
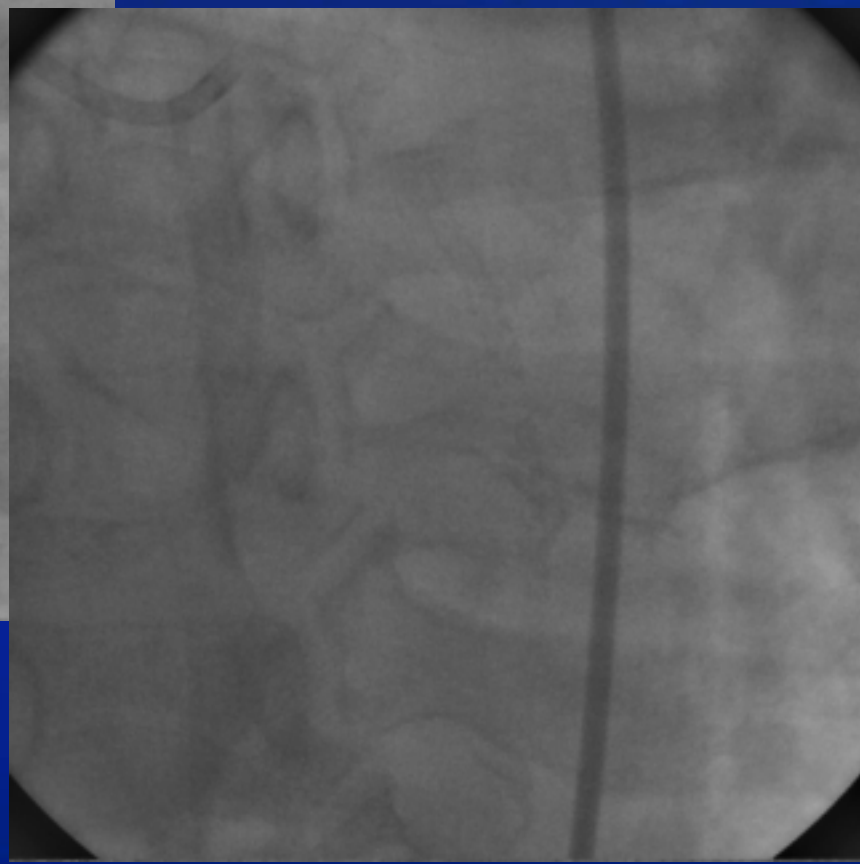
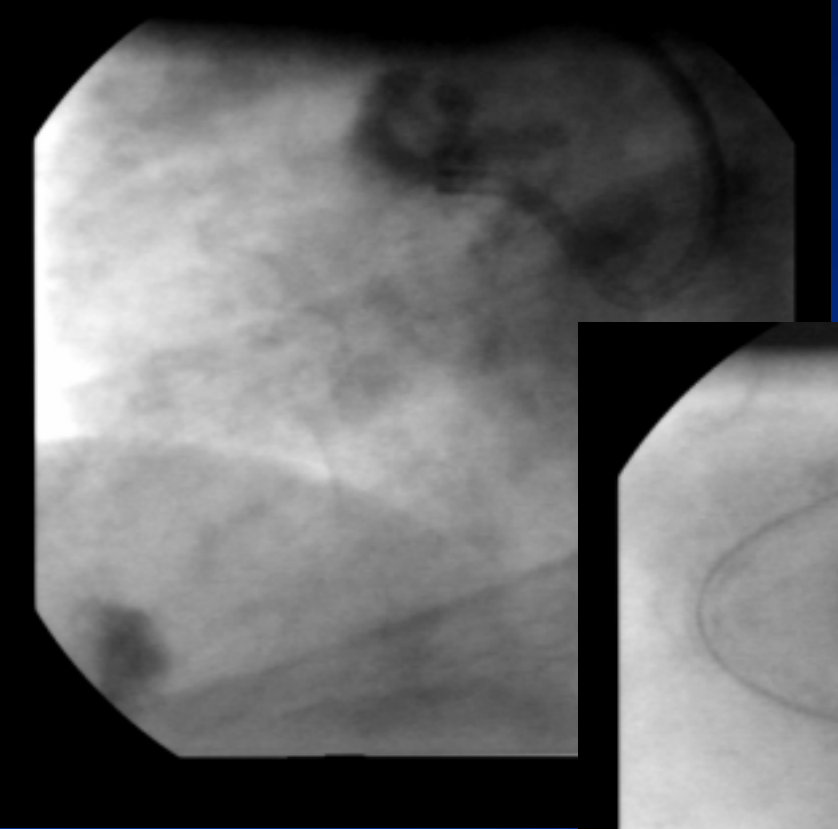


After stent

6-month
follow-up





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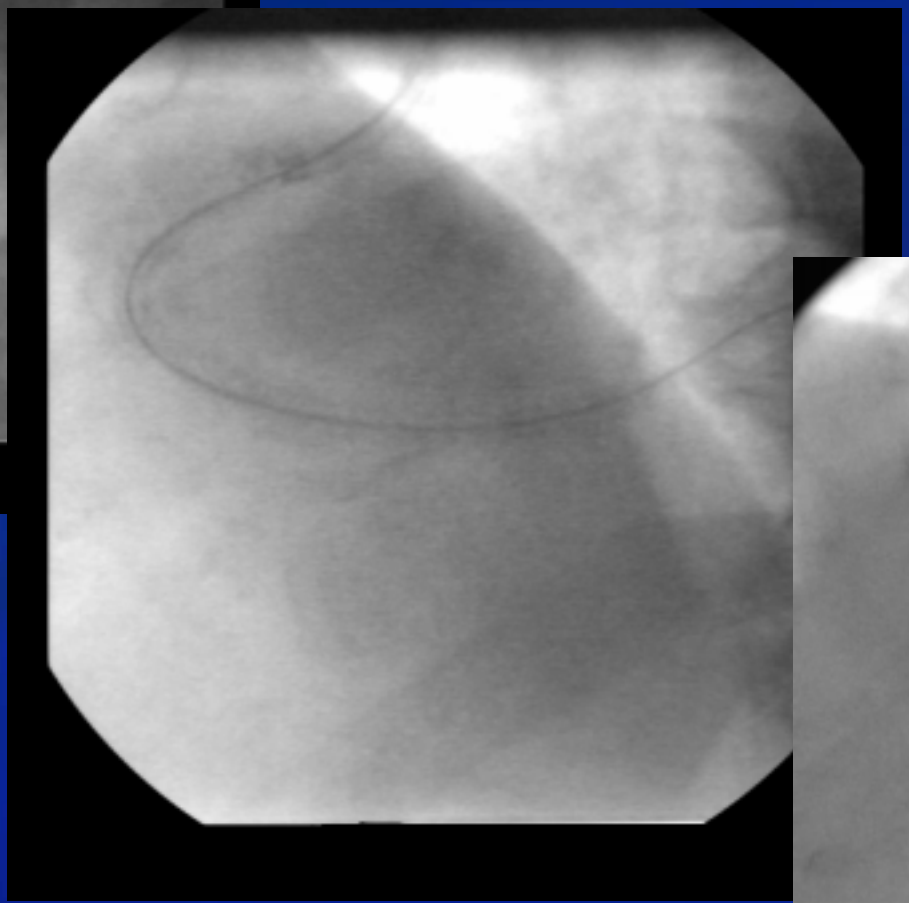
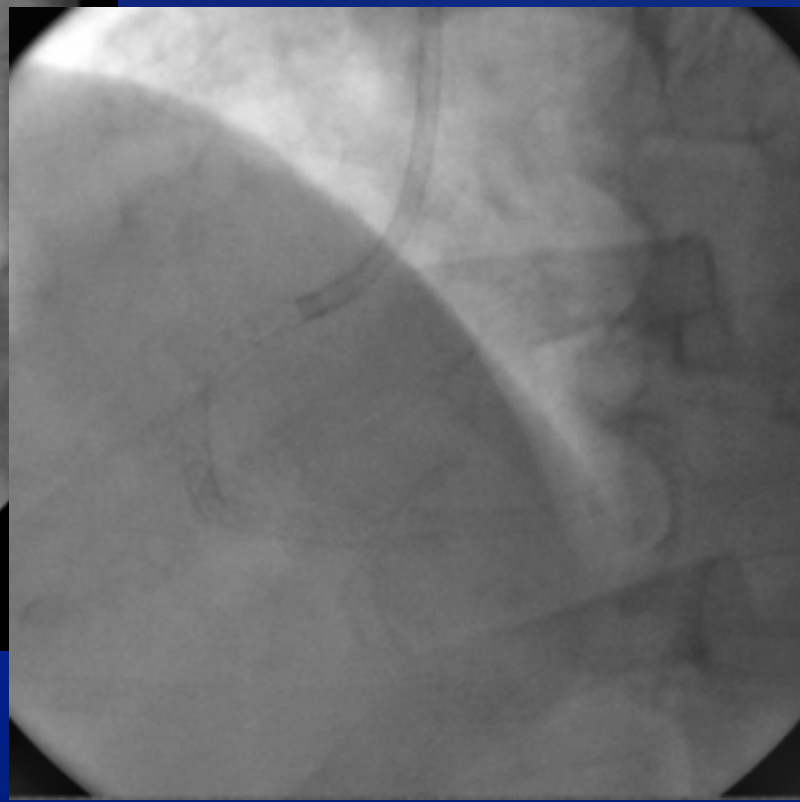


After stent

6-month
follow-up



In the previous era of bare metal stents

The proximal LAD lesion location was a risk factor for restenosis; therefore, strategies were developed to avoid unnecessary intervention.

In the current era of drug-eluting stents

- **The proximal LAD lesion location is no longer associated with a higher rate of restenosis.**

- **It may be time to evaluate the clinical efficacy of drug-eluting stent implantation in mild to moderate proximal LAD stenosis lesions with potentially vulnerable plaque.**

Concepts of Provisional DES implantation for vulnerable plaques

Transformation of the target plaque *from vulnerable plaque to scar tissue* without any increase of sudden death, AMI and restenosis.

여러분이 진료와 연구에 몰두하고 있는 이 시각에도 cardiac death와 fatal myocardial infarct은 여전히 줄지 않고 계속 발생하고 있읍니다.
Statin만 맹신하고 불안하게 지내시겠읍니까?
Drug-eluting stenting으로 불안한 마음을 떨치고 상쾌하게 지내시겠읍니까?

Statin ?

DES ?

Question 2: Limitations

- **Lack of control group**
- **Too small number of study patients to draw the conclusions in previously published data**
- **Need for randomized study to compare the efficacy between stent vs. statin with larger number of patients.**

Conclusion

Combination of

1) Need for systemic therapy (statin), and

2) Consideration of local interventional treatment, additionally and very aggressively


Thanks for
your attention