"Vulnerable Plaque"

Detected by IVUS and OCT

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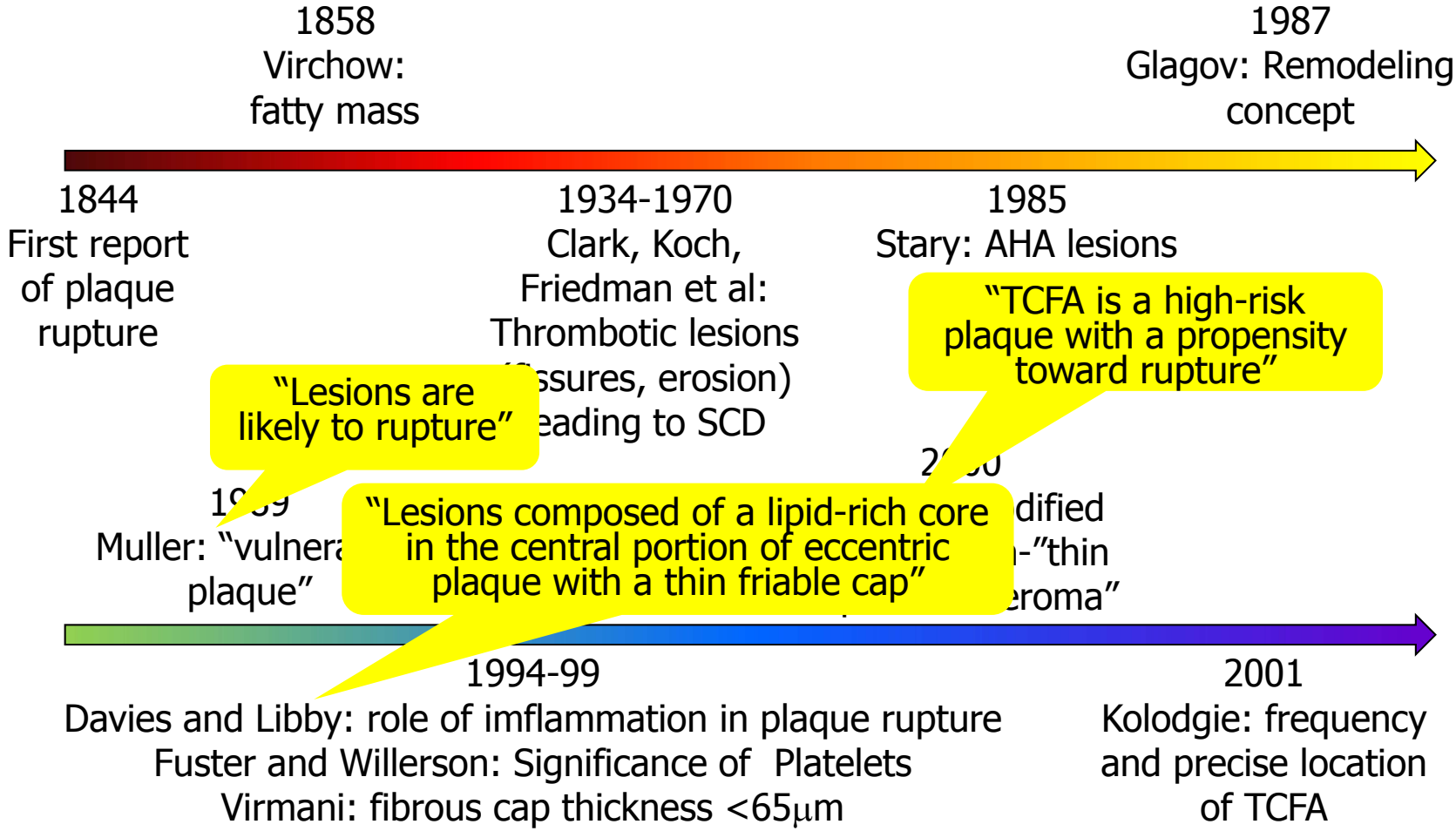
Questions About Vulnerable Plaques

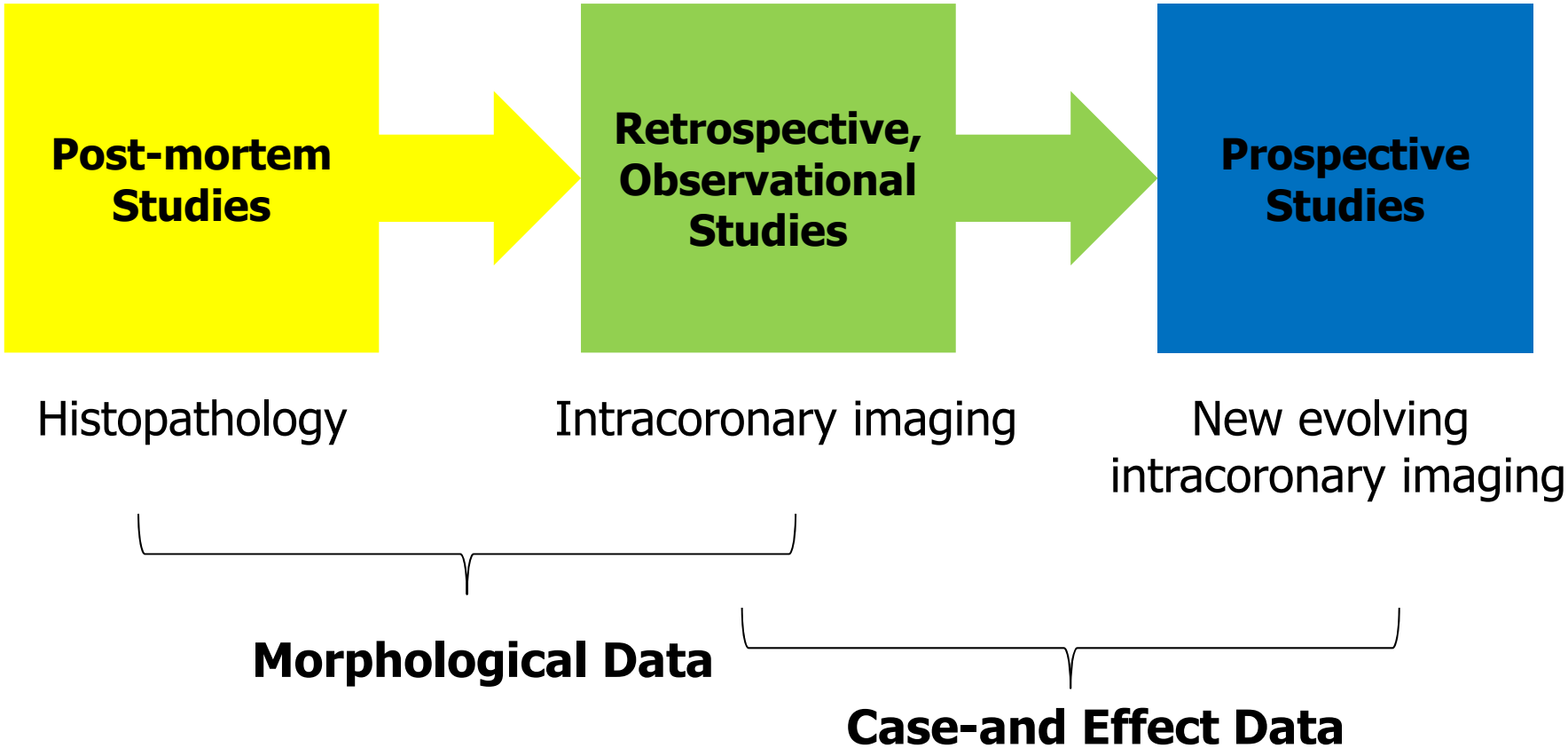
- Dose vulnerable plaque really exist?
- Should we find out vulnerable plaque?
- Which modality is the best for searching vulnerable plaque?
- What can we do for vulnerable plaque?

History of Vulnerable Plaque



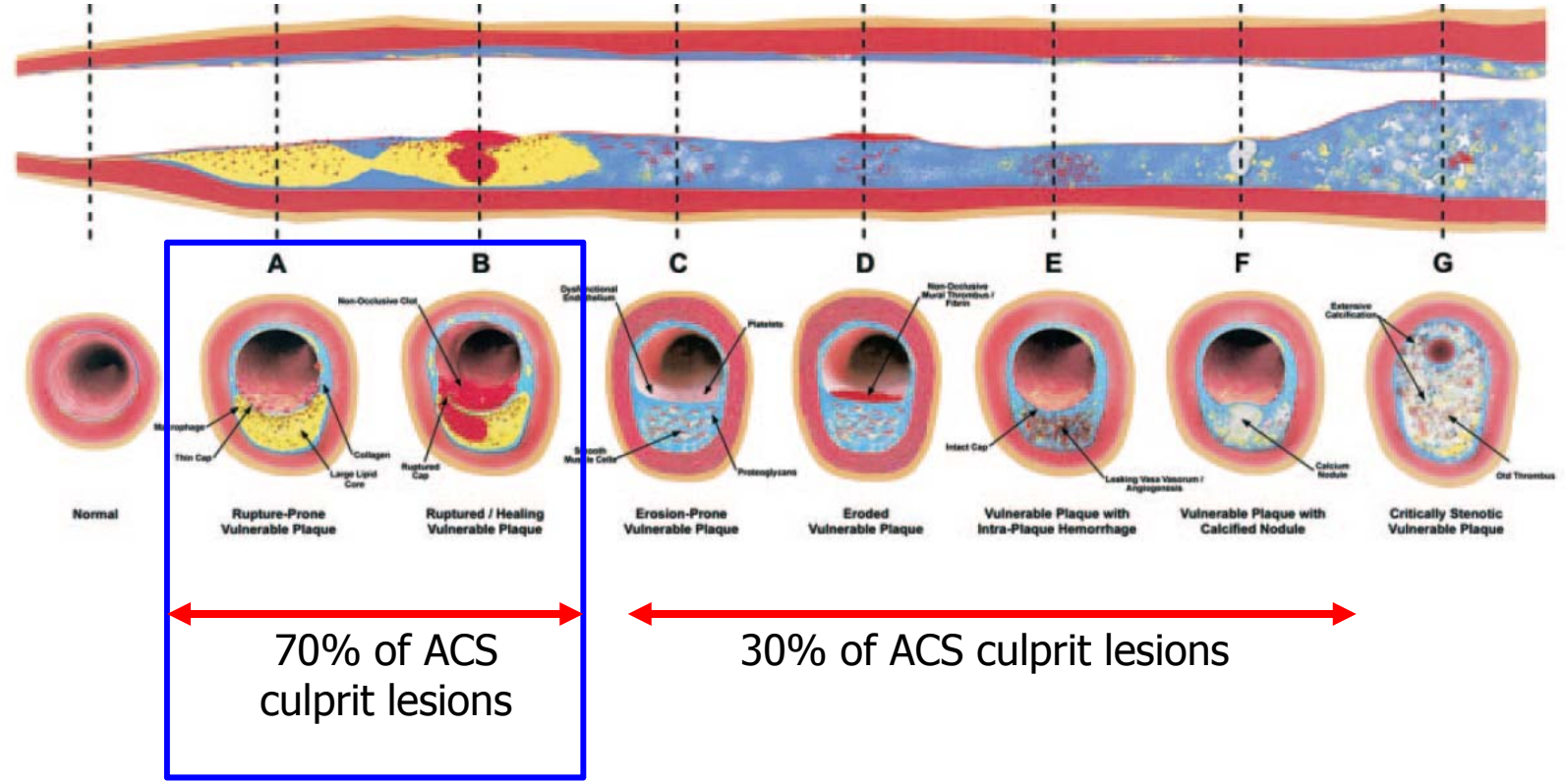
Finn AV, Virmani R, Arterioscler Thromb Vasc Biol. 2010;30:1282-92

Study Paradigm of Vulnerable Plaque



Different Types of Vulnerable Plaques

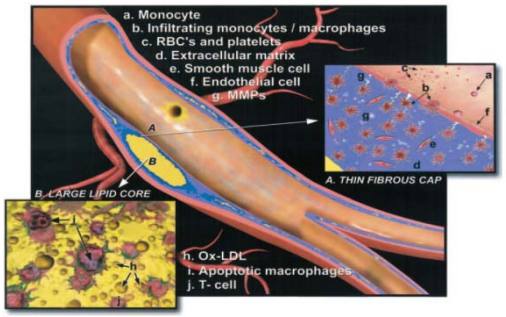
"Vulnerable plaque"=plaque not only prone to thrombosis/rupture but also at risk for rapid progression



Naghavi M , Libby P, Circulation. 2003;108:1664-1672

Criteria for Defining Vulnerable Plaque

Based on previously presented autopsy studies



The vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, and large lipid core.

Naghavi M , Libby P, et al. Circulation. 2003;108:1664-1672

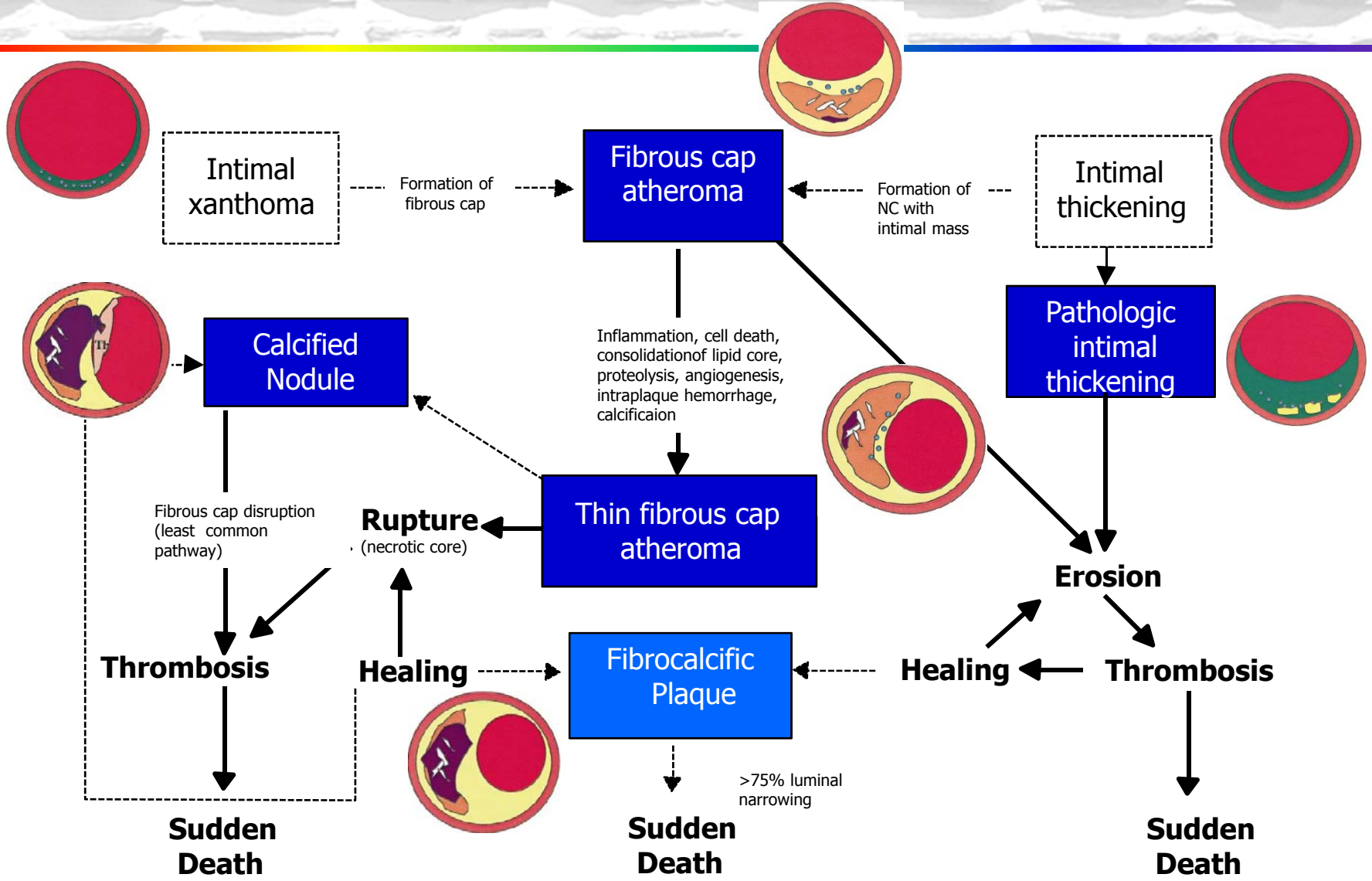
Major criteria

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

Minor criteria

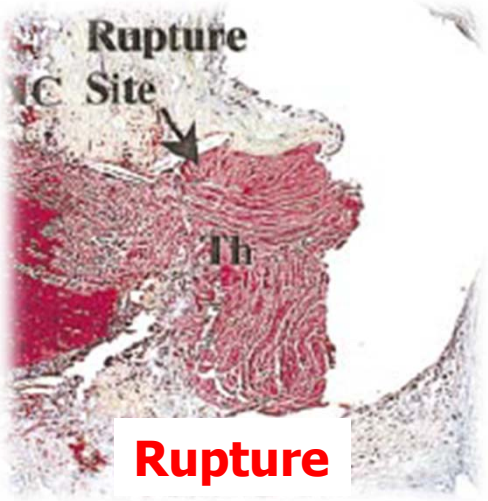
- **Superficial calcified nodule**
- **Glistening yellow**
- **Intraplaque hemorrhage**
- **Endothelial dysfunction**
- **Outward (positive) remodeling**

Scheme for AS Plaques Related to SCD



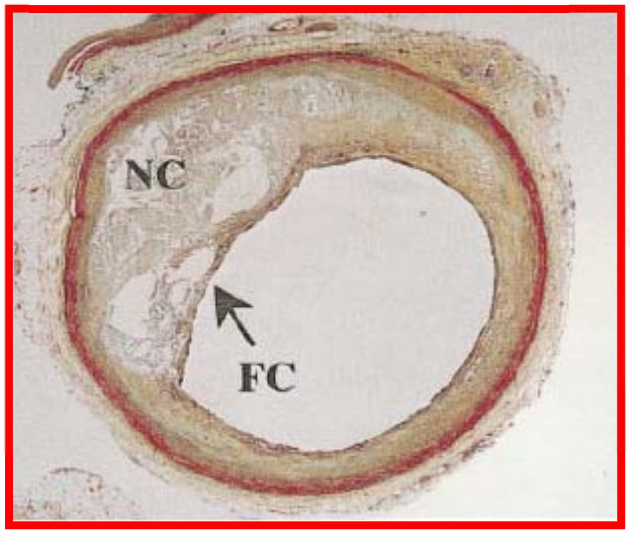
Distribution of Culprit Plaques by Sex and Age in 241 Cases of SCD
Virmani R et al, Arterioscler Thromb Vasc Biol 2000;20;1262-1275

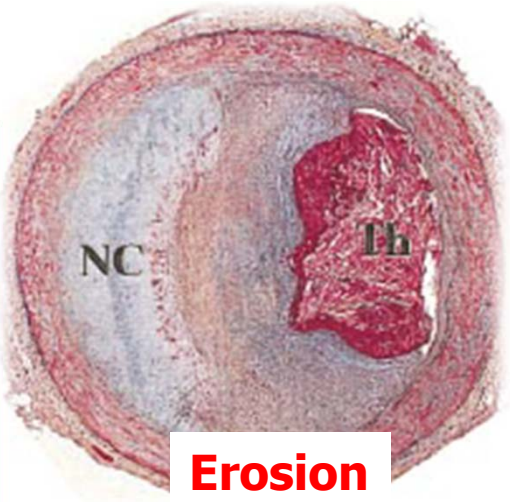
Thin Cap Fibroatheroma: TCFA



Rupture

TCFA





Erosion

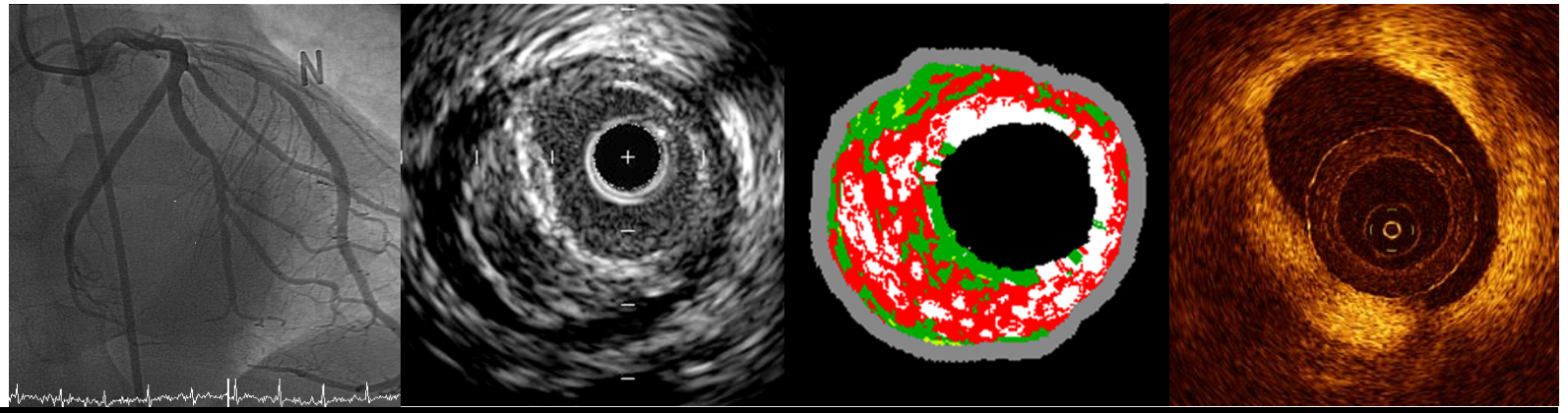
Lipid Core	Fibrous Cap	Intimal Inflammation
>10% area of the plaque 3mm2 in 75% of case Length:2-17mm (mean 8mm)	<65 μm Mean cap thickness ±2SD of ruptured plaque	Macrophage infiltration >25 cell/0.3mm diameter

Burke AP et al. N Engl J Med 1997;336:1276-82
Virmani R et al. J Interv Cardiol 2003;16:267-72
Virmani R et al. JACC 2006;47:C13

What we learned from pathologic studies…

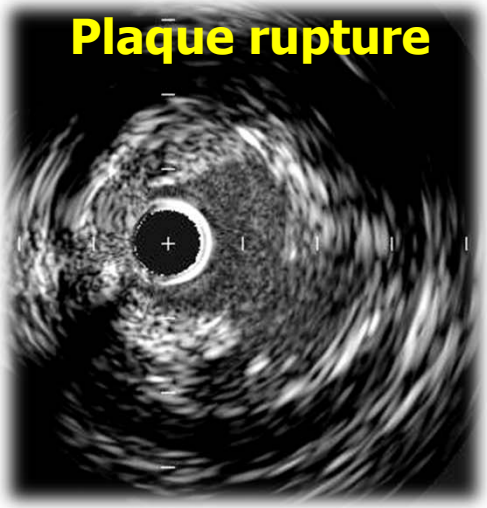
- Vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and large lipid core.
- 1) Abluminal expansion of the arterial wall and 2) subclinical plaque rupture of hemodynamically insignificant lesions are involved in the growth of advanced plaque.
- 2/3 of lesions showed <75% cross sectional luminal narrowing (<50% DS).
- Vulnerable plaque has pre-dominant lesion location. ½ of the TCFAs occur in the proximal portions of the major coronary arteries (LAD>LCX>RCA).

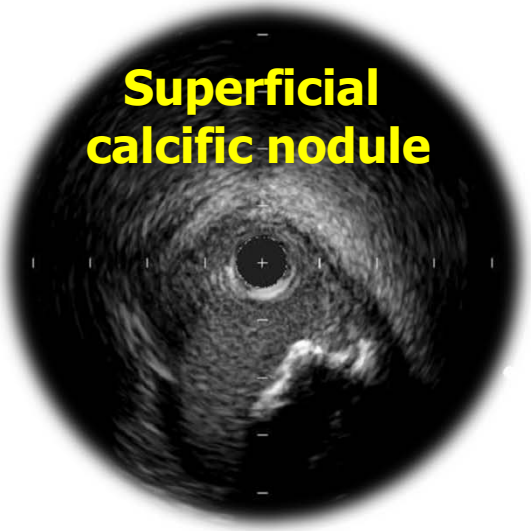
Imaging Modalities in Cath Lab

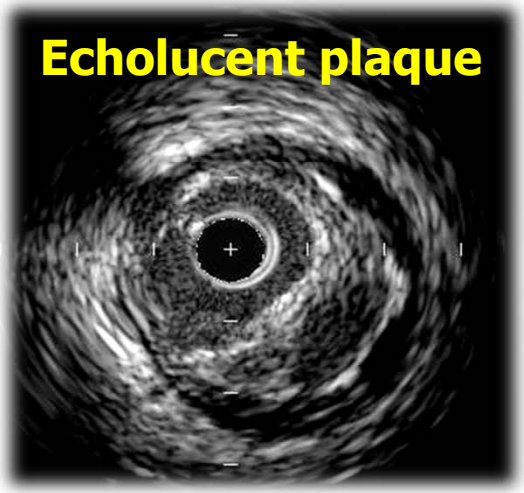


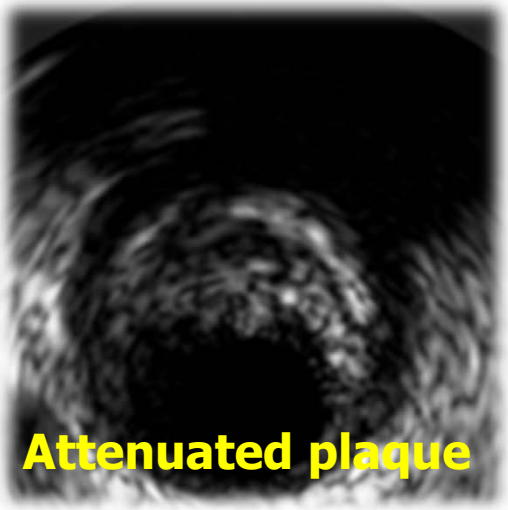
	Angiography	IVUS	VH-IVUS	OCT
Type of source	X-ray	Ultrasound	Ultrasound (RF)	Near-IR light
Resolution (μm)	100-200	80-120	80-120	10-40
Probe size (mm)	n/a	0.7	0.7	0.14
Scan area	n/a	10-15mm	10-15mm	6-7mm
Other	Images blood flow "luminogram"	Subsurface tomogram	Subsurface tomogram	Subsurface tomogram

Vulnerable Plaque로 생각되는 동맥경화반은?



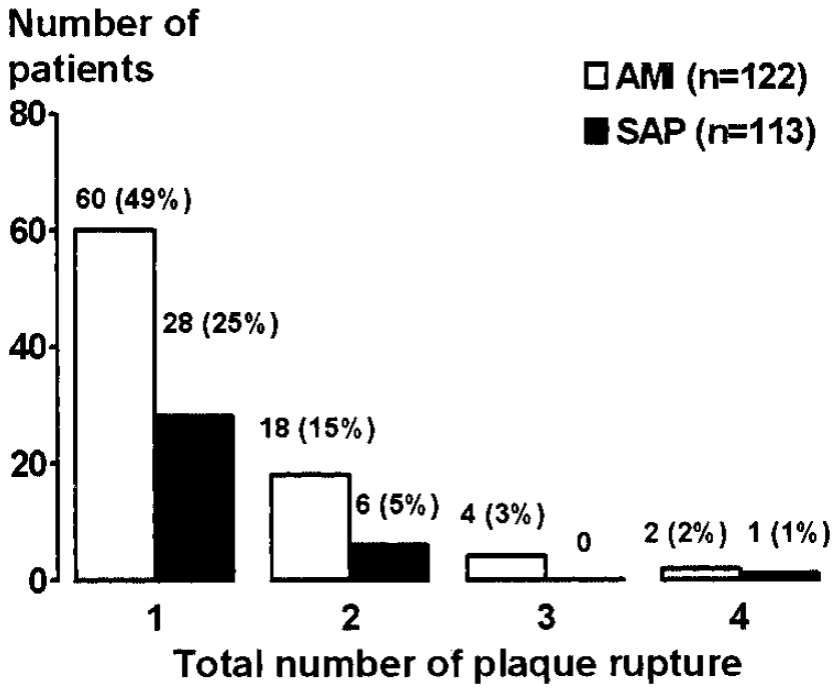






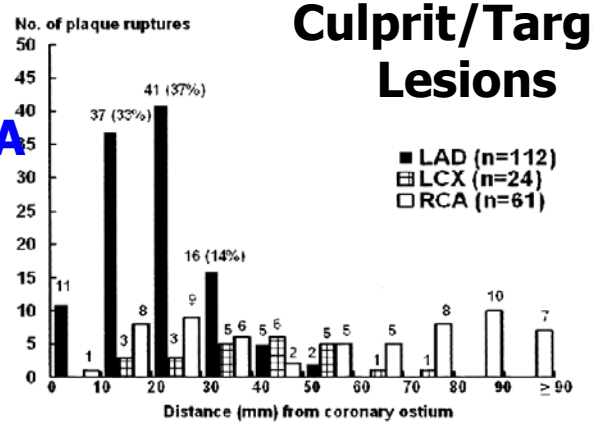
PRs: Three-vessel IVUS studies

122 AMI vs 113 SA
Culprit PR: 66% in AMI, 27% in SA
Non-culprit PR: 17% in AMI, 5% in SA

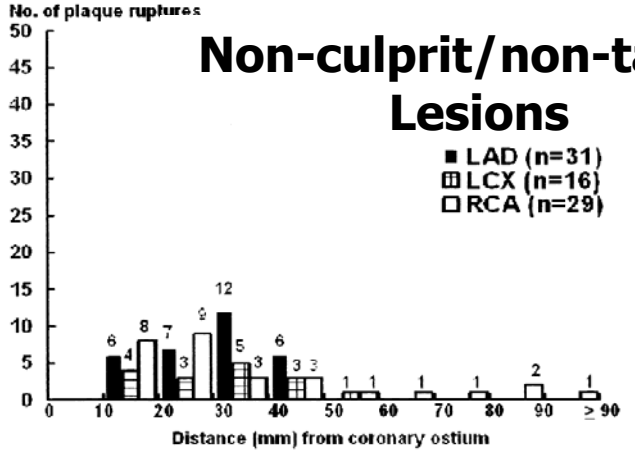


Hong MK et al.,
Circulation. 2004;110:928-933

Culprit/Target Lesions



Non-culprit/non-target Lesions

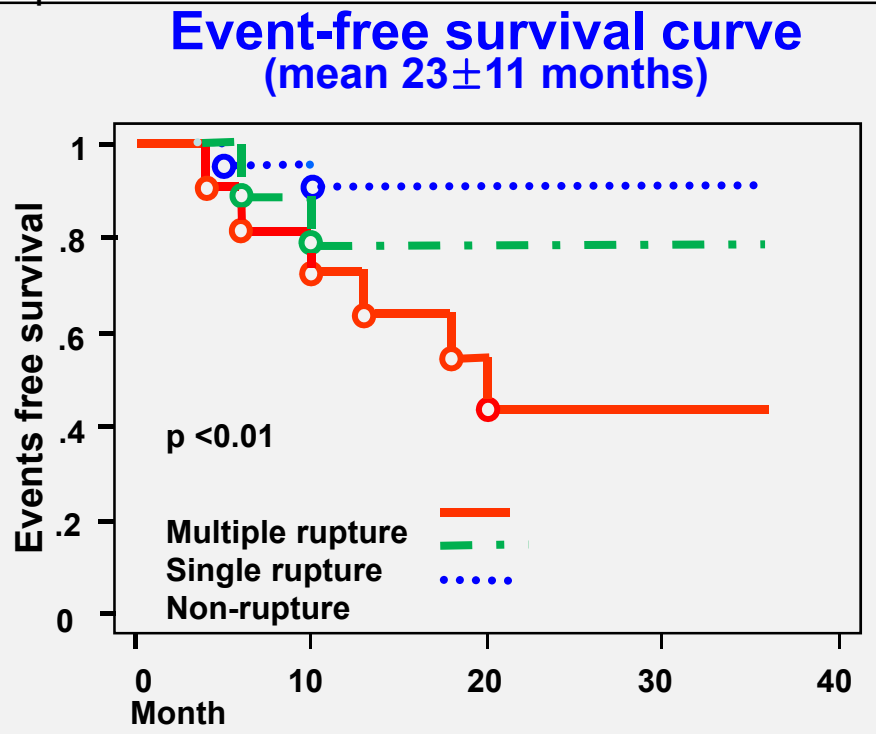


Hong MK et al.,
J Am Coll Cardiol. 2005;46:261-265.

Multiple plaque rupture and C-reactive protein in acute myocardial infarction

45 infarct-related arteries and another 84 major coronary arteries in 45 AMI patients.
PR at the culprit site: 47%, Multiple PRs: 24% of patients.

- Multiple risk factors were more frequently found in multiple-PR patients compared with single-rupture or non-rupture patients (82% vs. 40% vs. 29%, p = 0.01).
- Hs-CRP levels had a positive correlation with the number of PRs (p < 0.01).



Conclusion: Multiple PR is associated with systemic inflammation, and patients with multiple PR can be expected to show a poor prognosis.

Tanaka A, Akasaka T, et al. J Am Coll Cardiol. 2005;45:1594-9.

IVUS Assessment of PR
ACS Culprit vs ACS non-culprit vs Non-ACS

- 80 PRs in 74 patients
- 35 ACS culprit vs 19 ACS non-culprit vs 26 Non-ACS

	ACS culprit	ACS non-culprit	Non-ACS	P Value
Thrombus, %	**60**	**32**	**8**	**0.001**
Proximal location of rupture, %	**80**	**74**	**50**	**0.04**
MLA, mm^2	**3.5±1.5**	**5.3±2.6**	**6.0±3.0**	**<0.001**
Lumen CSA at PR, mm^2	**4.6±1.7**	**6.6±2.8**	**7.3±3.3**	**<0.001**
Plaque burden, %	**76±17**	**68±9**	**65±13**	**<0.001**
Remodeling index	**1.26±0.21**	**1.22±0.23**	**1.09±0.05**	**0.002**

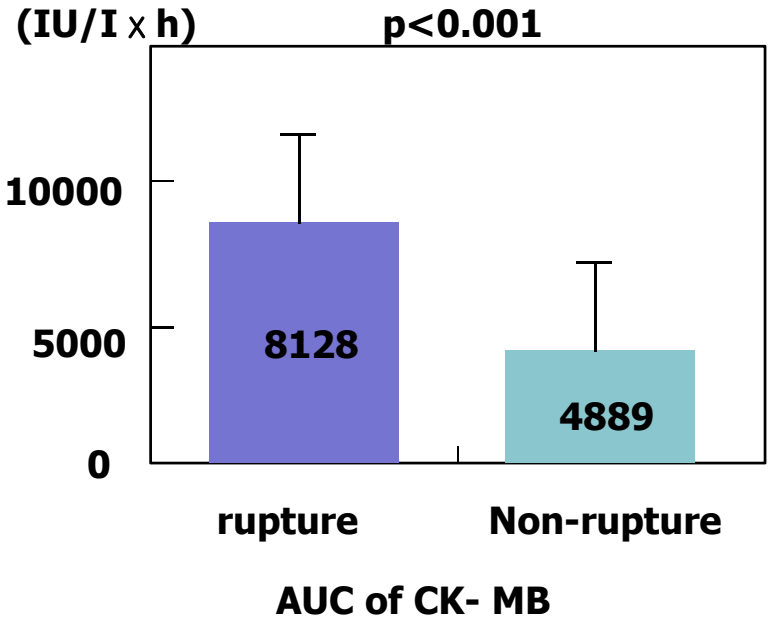
Multivariate analysis identified a smaller minimum lumen area (p=0.01) and presence of thrombus (p=0.01) as independent predictors of ACS.

Fujii et al., Circulation. 2003;108:2473-2478.

PRs associated with poor outcomes after PCI

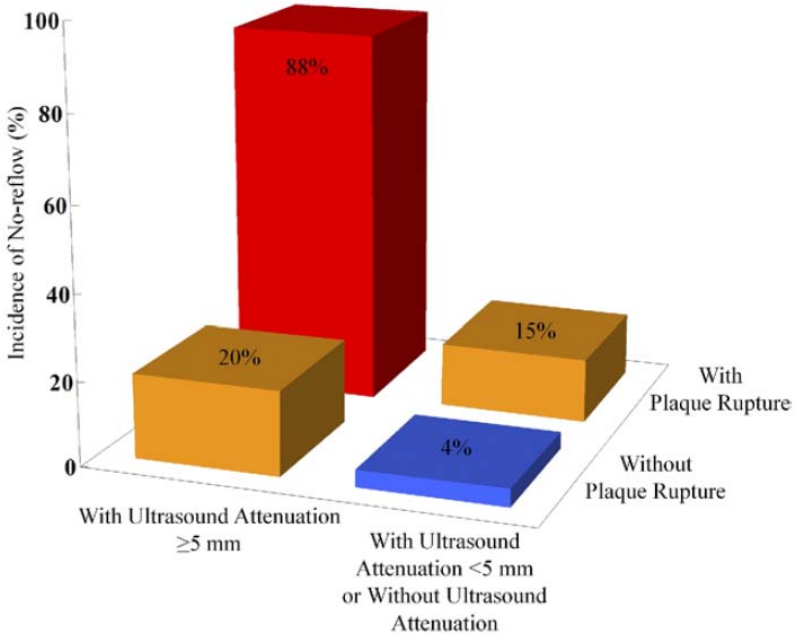
Infarct Size

91 patients with acute STEMI
54 with PR vs 37 without PR



No Reflow

170 patients with acute STEMI
underwent PCI within 12 h



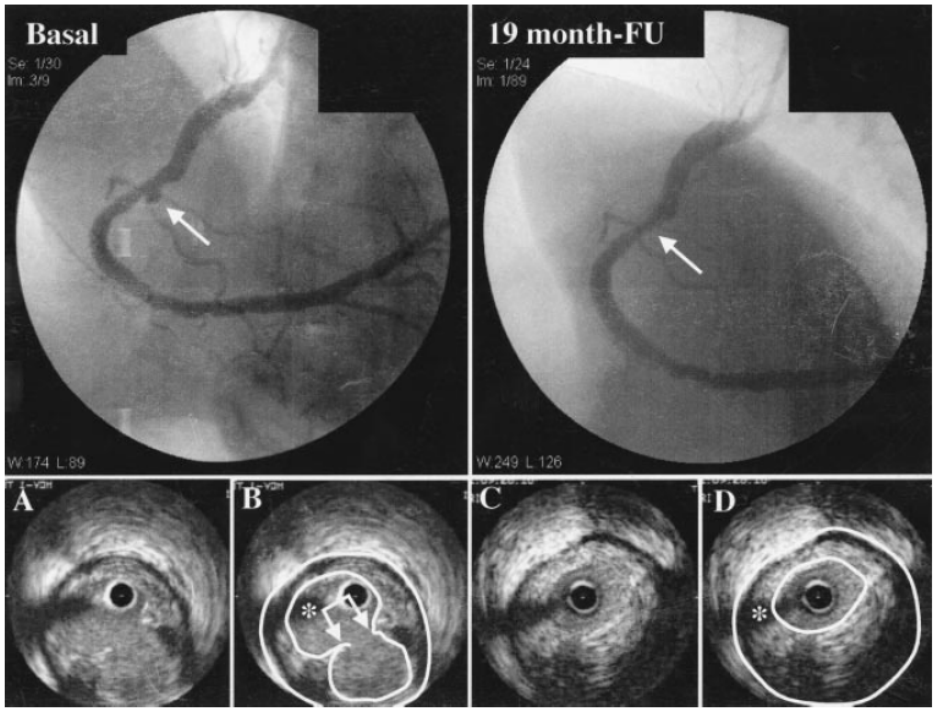
Kusama et al., J Am Coll Cardiol. 2007;50:1230-1237

Endo et al., J Am Coll Cardiol Intv 2010;3:540 –549

ACS PR without significant stenosis healed with medication

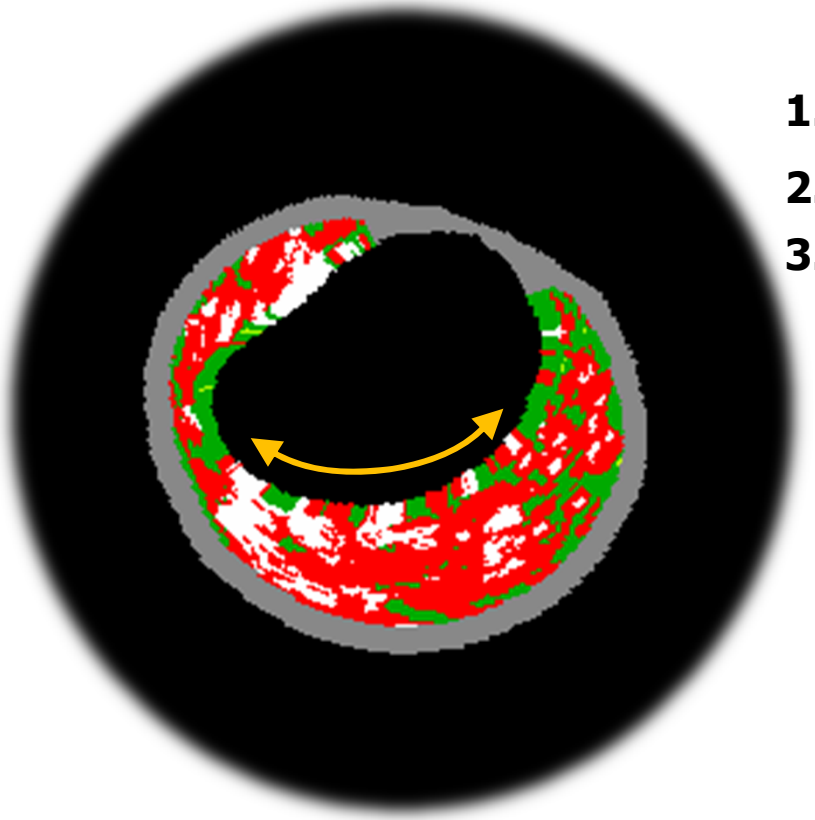
14 patients with 28 distinct PRs without significant stenosis
22 months (median) follow-up with 40mg statin and antiplatelet agent (clopidogrel and aspirin for 9 months)

- **No clinical event related to the lesion under study occurred.**
- **On final IVUS, 50% PRs had healed, and the degree of stenosis tended to diminish (stenosis, 22±17% vs 29±17% at baseline; *P=0.056).***
- ***No healing-prediction criterion could be identified.***



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

VH-Thin cap fibroatheroma (VH-TCFA)



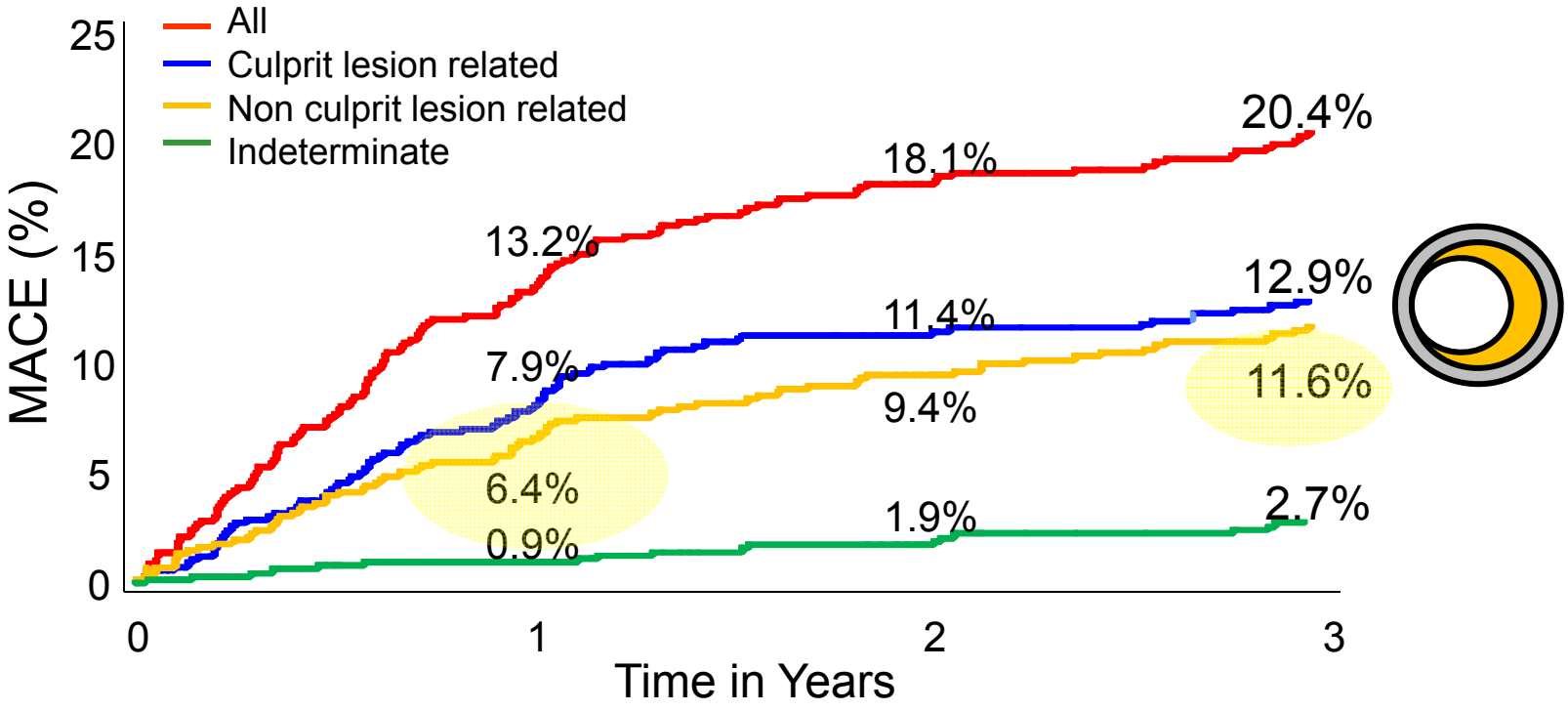
1. Confluent NC>10%
2. 30° NC abutting the lumen
3. 3 consecutive frames (=1.5mm in length)

Thin cap < 65 μm (less than the 200 μm resolution of IVUS)

Prospective Natural-Histology Study of Coronary Atherosclerosis

PROSPECT: MACE

697 patients with ACS underwent PCI and 3V imaging study

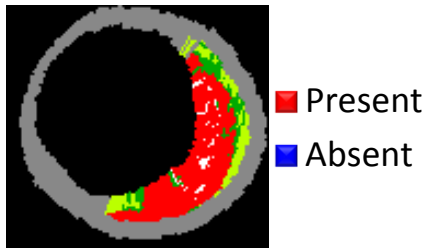


Stone GW et al. N Engl J Med. 2011;364(3):226-35.

Predictors of Events in Non-culprit Lesion

PROSPECT: Non-culprit Lesion Related Events

PB_{MLA} ≥70%	4.99 [2.54, 9.79]	<0.0001
VH-TCFA	3.00 [1.68, 5.37]	0.0002
MLA ≤4.0mm^2	2.77 [1.32, 5.81]	0.007



Lesion HR	3.84 (2.22, 6.65)	6.41 (3.35, 12.24)	10.77 (5.53, 21.00)	10.81 (4.30, 27.22)
P value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence*	51.2%	17.4%	11.0%	4.6%

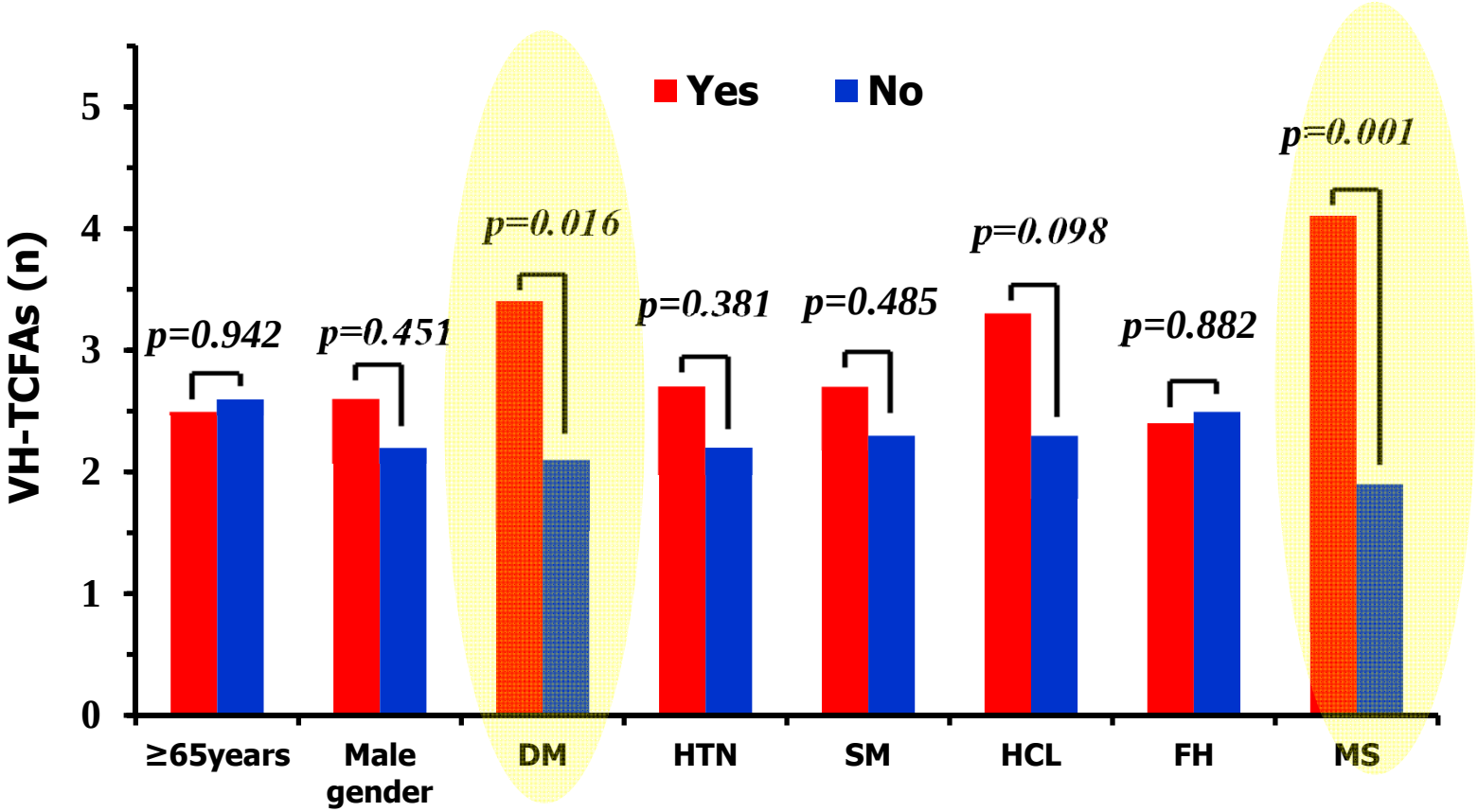
Stone GW et al. N Engl J Med. 2011;364(3):226-35.

Plaque Components and Risk Factors

A Three-Vessel VH-IVUS Analysis

"Whole vessel" VH-IVUS analysis was performed in 189 vessels of 63 patients.

VH-TCFAs in regard to being with or without risk factors

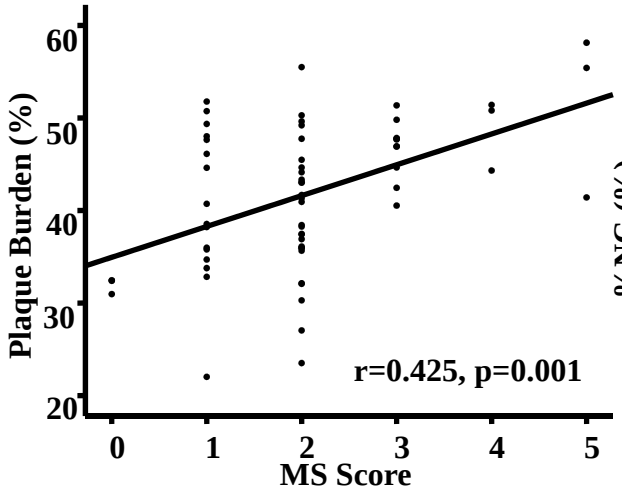


Zheng M, Choi SY et al., J Am Coll Cardiol Intv 2011;4:503–10

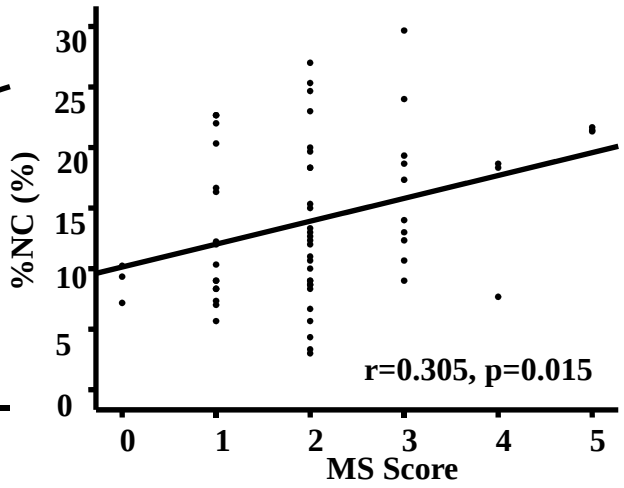
Plaque Components and Risk Factors

The correlation between the plaque components and the metabolic syndrome scores

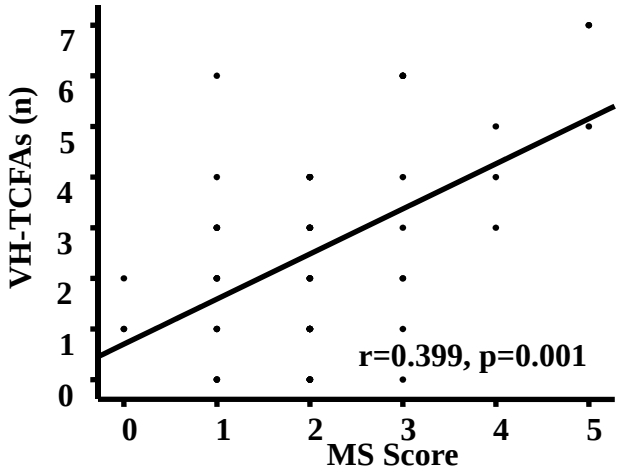
Plaque Burden (%)



% Necrotic Core (%)



VH-TCFAs (%)



Zheng M, Choi SY et al., J Am Coll Cardiol Intv 2011;4:503–10

Plaque Components and Risk Factors

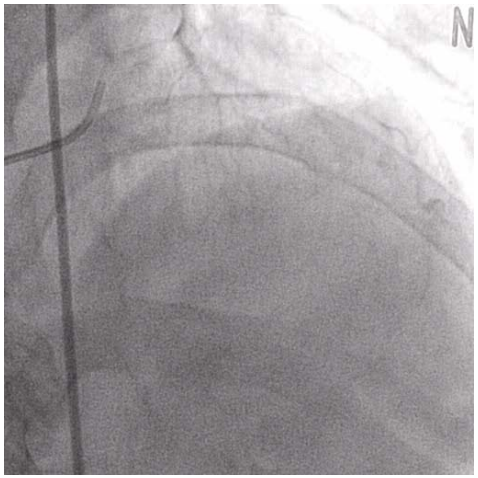
Multivariate predictors of the PB, the % NC and the VH-TCFAs

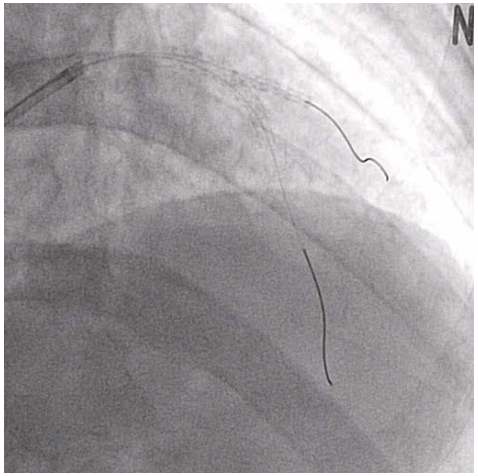
Parameters	B coefficient	95% CI	*p value*
Predictors of mean P+M			
≥65 years			***0.046***
Diabetes [illegible]			***[illegible]013***
Meta[illegible]			
Predic[illegible]			
Diabetes mel[illegible]			***0.014***
Metabolic syndrome* (Y/N)		[illegible]0.674	*0.094*
Predictors of VH-TCFAs			
Diabetes mellitus	0.699	-0.282-1.680	*0.159*
Metabolic syndrome* (Y/N)	2.230	1.269-3.192	***<0.001***

3V VH-IVUS analysis showed that DM and MS patients had a larger PB, larger amount of NC, and more frequent VH-TCFAs in coronary arterial trees implying greater plaque vulnerability in DM and MS patients.

Zheng M, Choi SY et al., J Am Coll Cardiol Intv 2011;4:503–10

Case: VP related with PCI complication

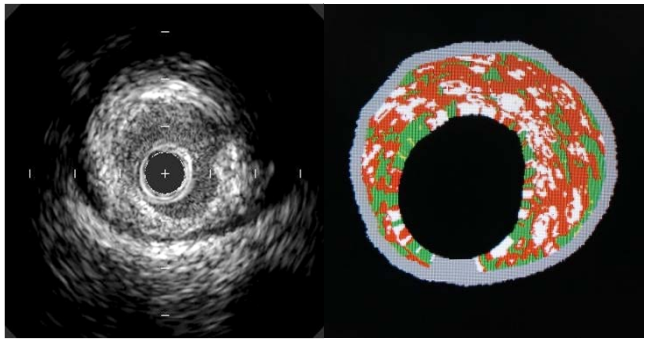




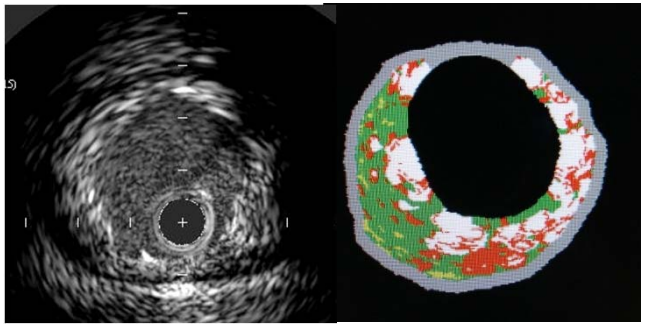
Two Cypher™ Select™ stents (3.5×33 mm in LAD and 2.5×18 mm in D1) with minimal crushing technique

M/65 with UA
CV RF: Smoking

Pre-intervention



Post-PCI

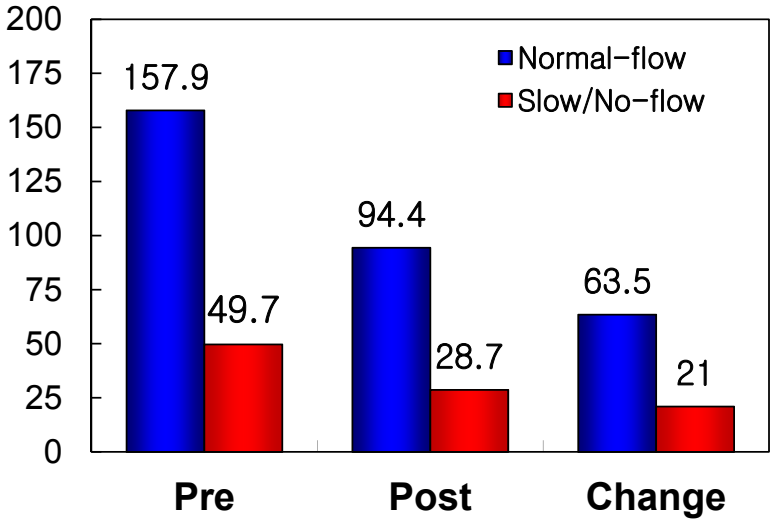


	Pre	Post	Change
Fibrous, mm^2(%)	171.9(37%)	176.3(43%)	4.4(6)
Fibrofatty, mm^2(%)	69.7(15%)	28.7(7%)	-41(-8)
Calcium, mm^2(%)	65.1(14%)	110.7(27%)	45.7(13)
Necrotic core, mm^2(%)	157.9(33%)	94.4(21%)	-63.5(12)

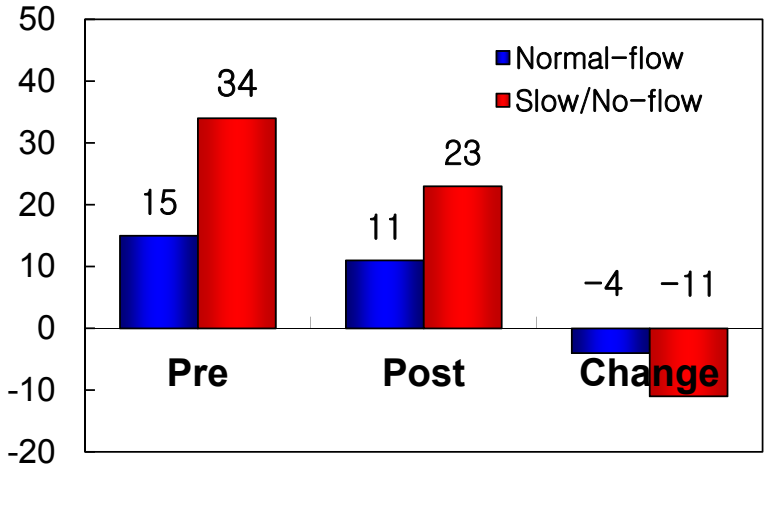
Change of Plaque Component Related to Slow-flow

VH plaque components in 64 lesions of 58 patients (ACS=27, SA=31)
Comparison between Normal-flow (n=47) vs Slow/No-flow (n=17)

Absolute volume of NC, mm³



% volume of NC, %

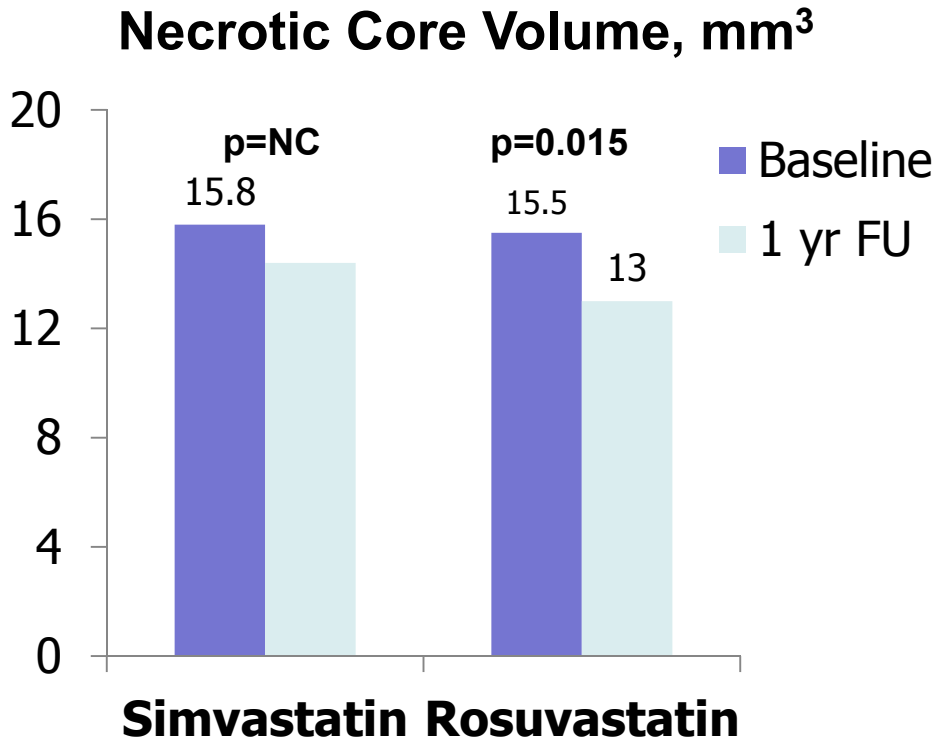


Reduction of absolute volume and % volume of necrotic core component of the plaque was related to microvascular injury after coronary stenting .

Choi SY et al., K Circ J 2007

Medial Tx reduces plaque vulnerability

100 patients, 12 month FU
50 simvastatin 20mg vs 50 rosuvastatin 10mg

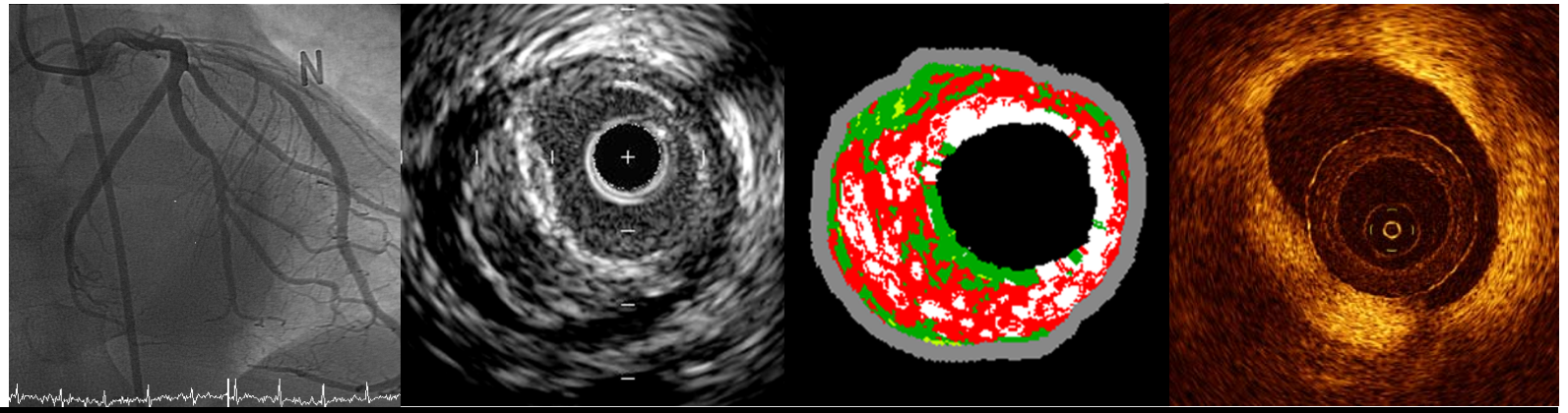


Hong MK et al,
JACC Cardiovasc Interv.
2009;2(7):679-88.

What we learned from IVUS studies…

- Intracoronary imaging served an understanding toward the natural history of the vulnerable plaque.
- Vulnerable plaque is predominant in ACS and might be a marker of the extensive inflammatory reaction of atherosclerosis. But VP could be also found in non-culprit lesions.
- Plaque with some vulnerable IVUS-features are at the risk of acute (or late) complication during PCI.
- PROSPECT provided prospective in vivo confirmation of the hypothesis that ACSs arise from atheromas with certain histopathological characteristics, and that these characteristics are not necessarily dependent on the degree of angiographic stenosis at that site.

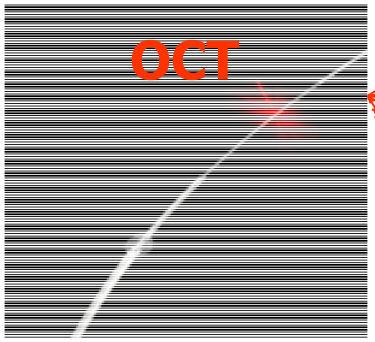
Imaging Modalities in Cath Lab



	Angiography	IVUS	VH-IVUS	OCT
Type of source	X-ray	Ultrasound	Ultrasound (RF)	Near-IR light
Resolution (μm)	100-200	80-120	80-120	10-40
Probe size (mm)	n/a	0.7	0.7	0.14
Scan area	n/a	10-15mm	10-15mm	6-7mm
Other	Images blood flow "luminogram"	Subsurface tomogram	Subsurface tomogram	Subsurface tomogram

Criteria for Defining Vulnerable Plaque

Based on the autopsy study



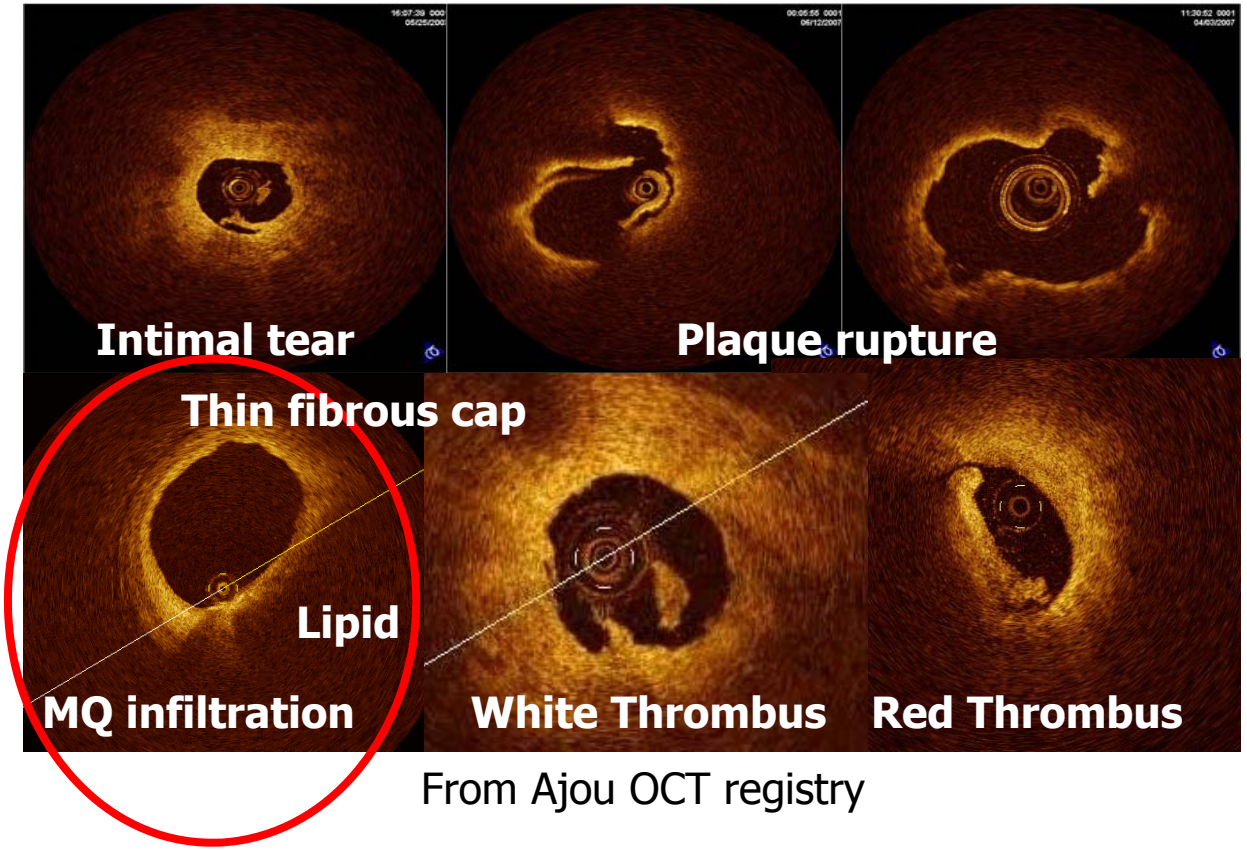
Major criteria

- Active inflammation (monocyte/macrophage and 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

Detection of VP in OCT

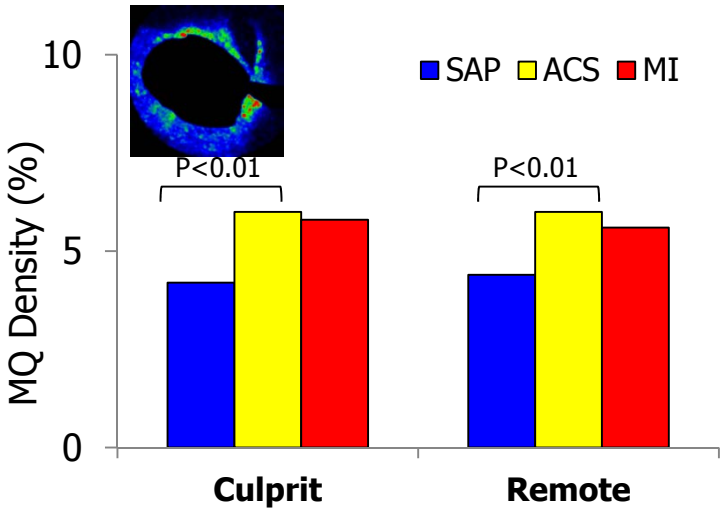


From Ajou OCT registry

Detection of VP in OCT

119 lipid rich plaques in 49 patients
49 AMI; 46 ACS; 24 SAP

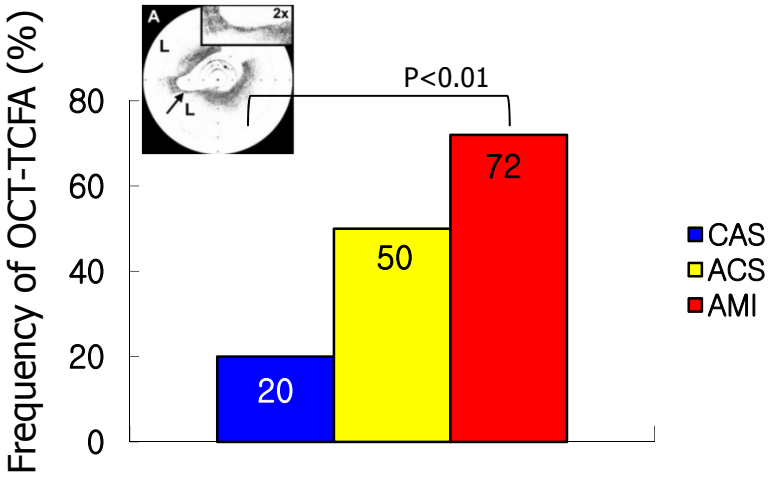
Macrophage Accumulation



Briain D et al. JACC 2004;44:972–9

57 patients: 20 AMI, 20 ACS, 17 SAP

Thin Fibrous Cap

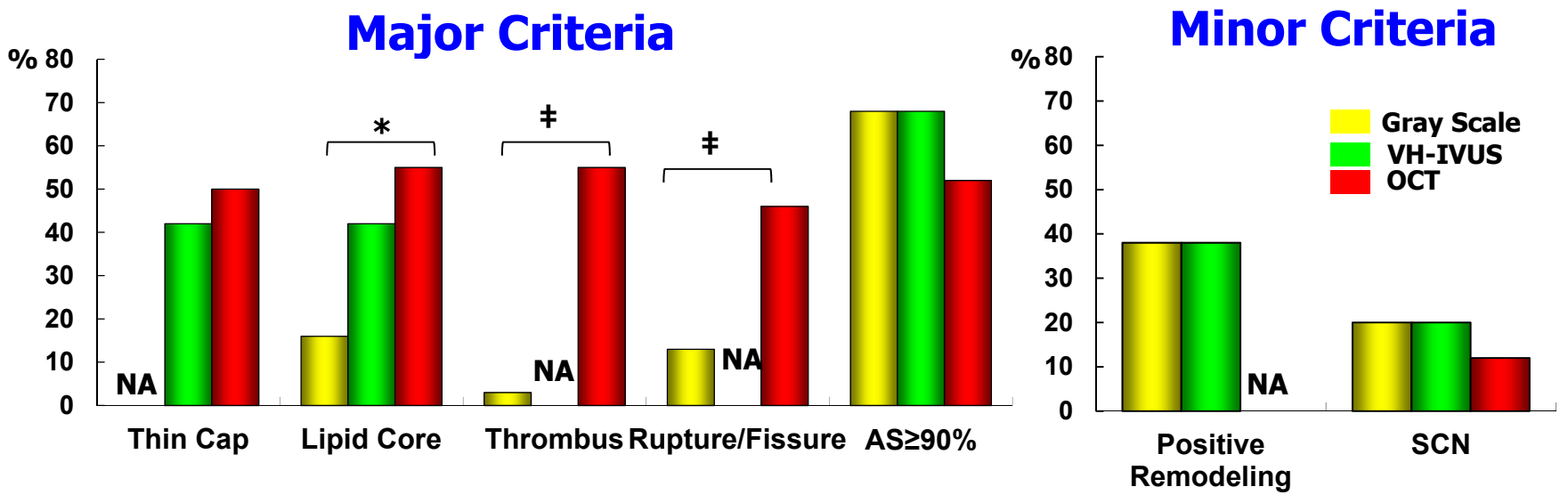


Jang IK et al. Circulation. 2005;111:1551-5

Ability of Detection for VP

IVUS vs. VH-IVUS vs. OCT

95 Patients (95 lesions) were enrolled and categorized according to their clinical presentation into SAP (n=31) and ACS (n=64).

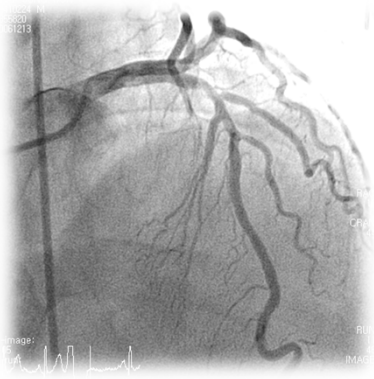


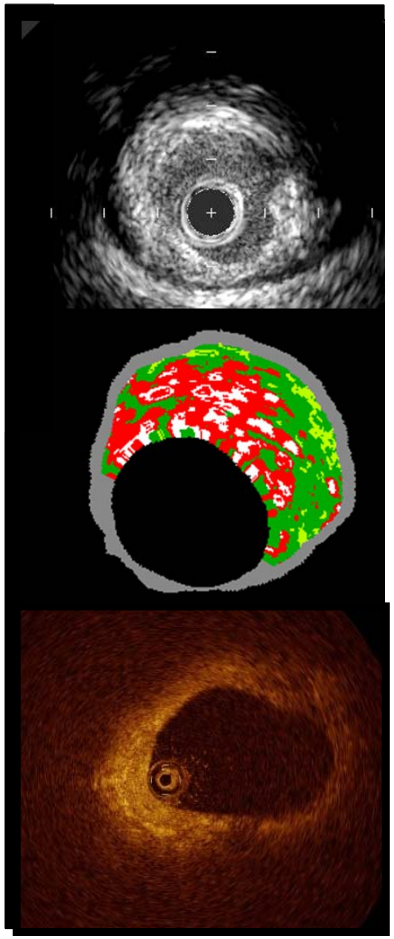
*p<0.05 among 3 modalities, †p<0.05 between GS vs. OCT, ‡p<0.05 between VH-IVUS vs. OCT

Choi SY et al, TCT 2008
Ajou OCT registry

Ability of Detection for VP

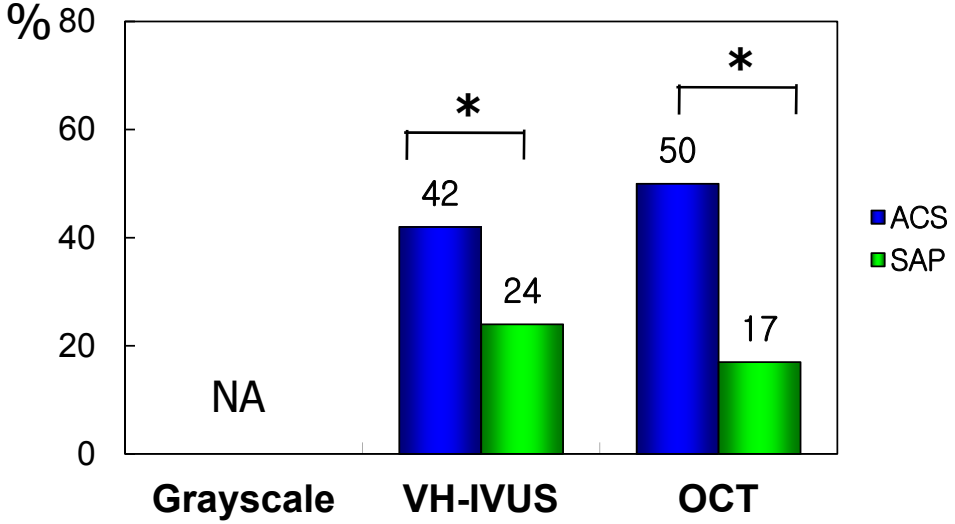
IVUS vs. VH-IVUS vs. OCT





The Incidence of TCFA

Comparison between ACS and SAP



*p<0.05 between ACS vs.SAP, †p<0.05 between VH-IVIS vs. OCT

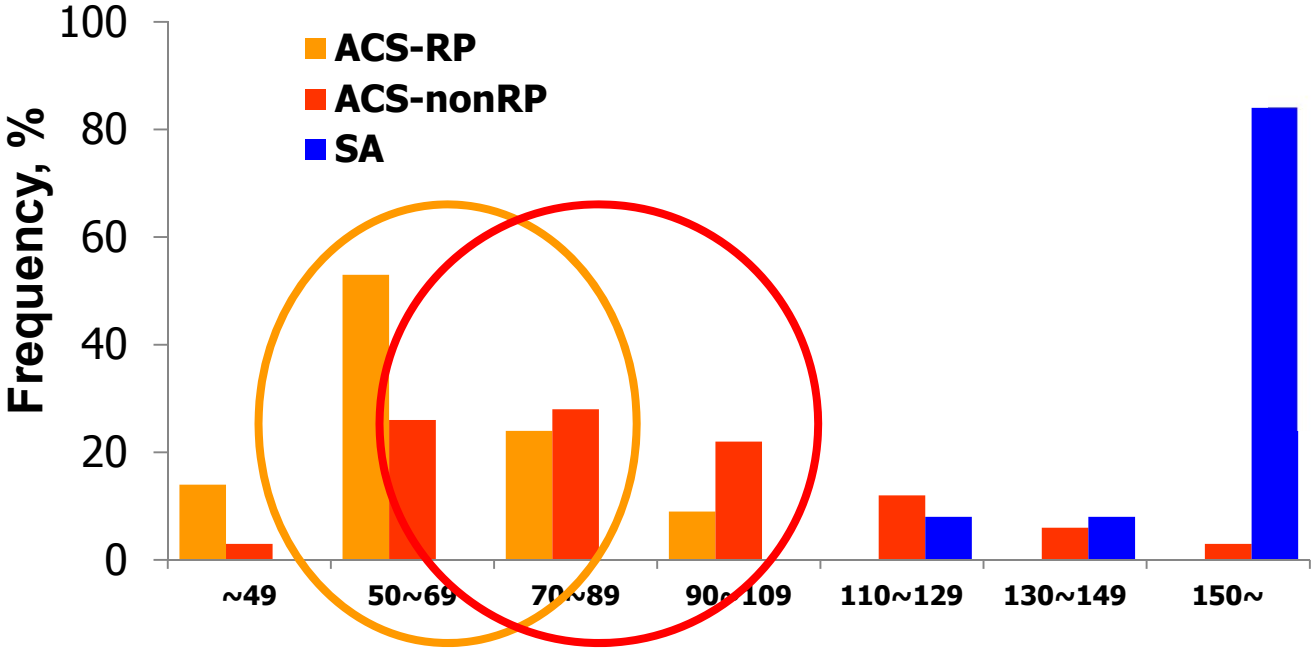
Choi SY et al, TCT 2008
Ajou OCT registry

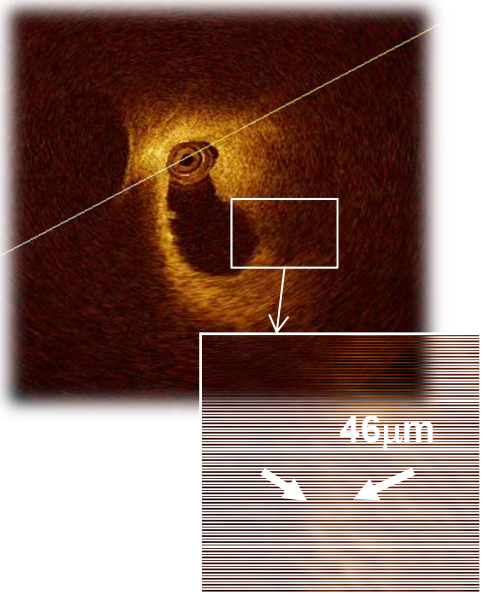
Ability of Detection for VP

Observation by OCT

ACS-Ruptured Plaque (n=43) vs ACS-Non ruptured plaque (n=21)
vs Stable plaque (n=31)

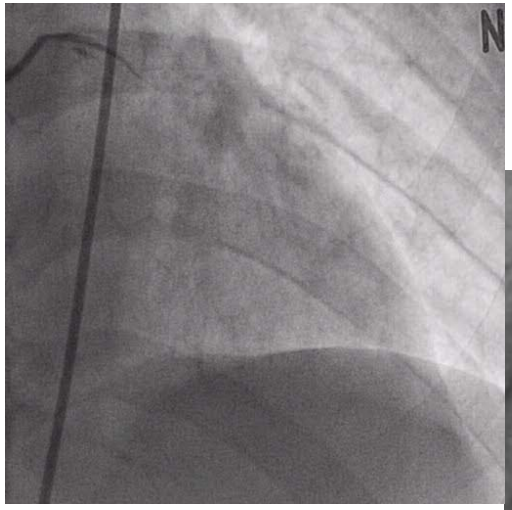
Fibrous Cap Thickness, μm



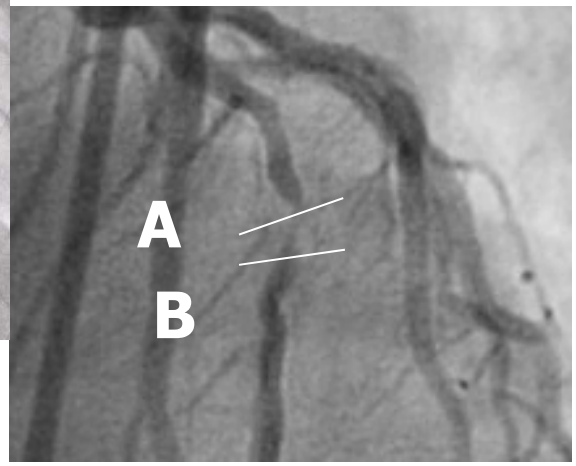


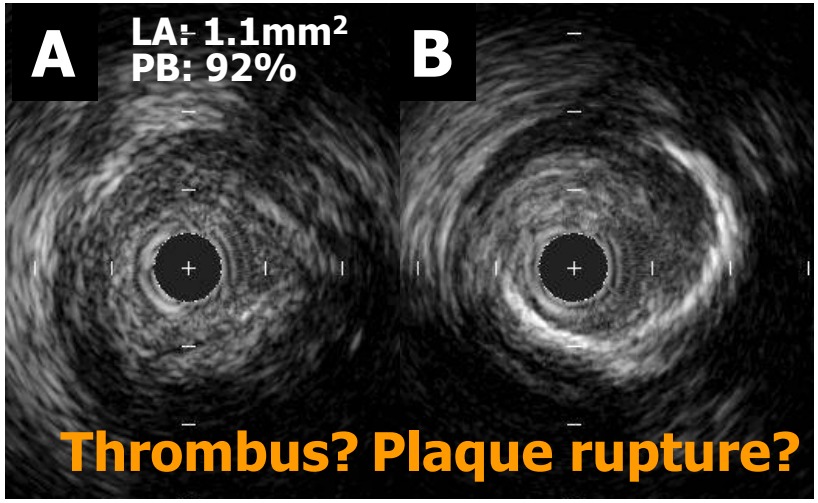
Choi SY et al, ACC2010
Ajou OCT registry

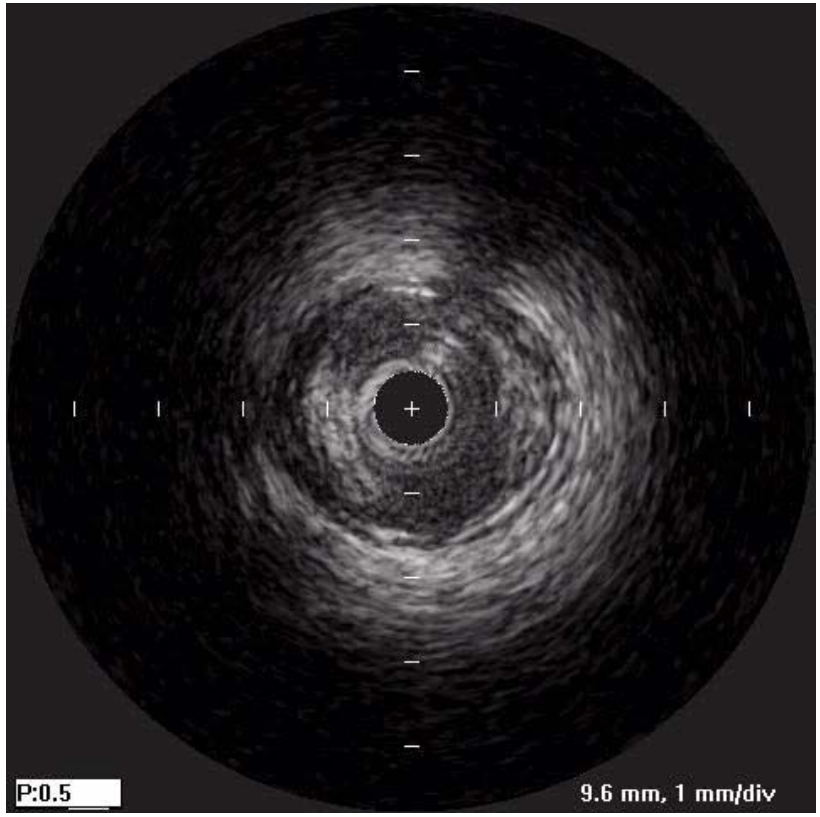
Case: OCT is the best tool for evaluation of VP I

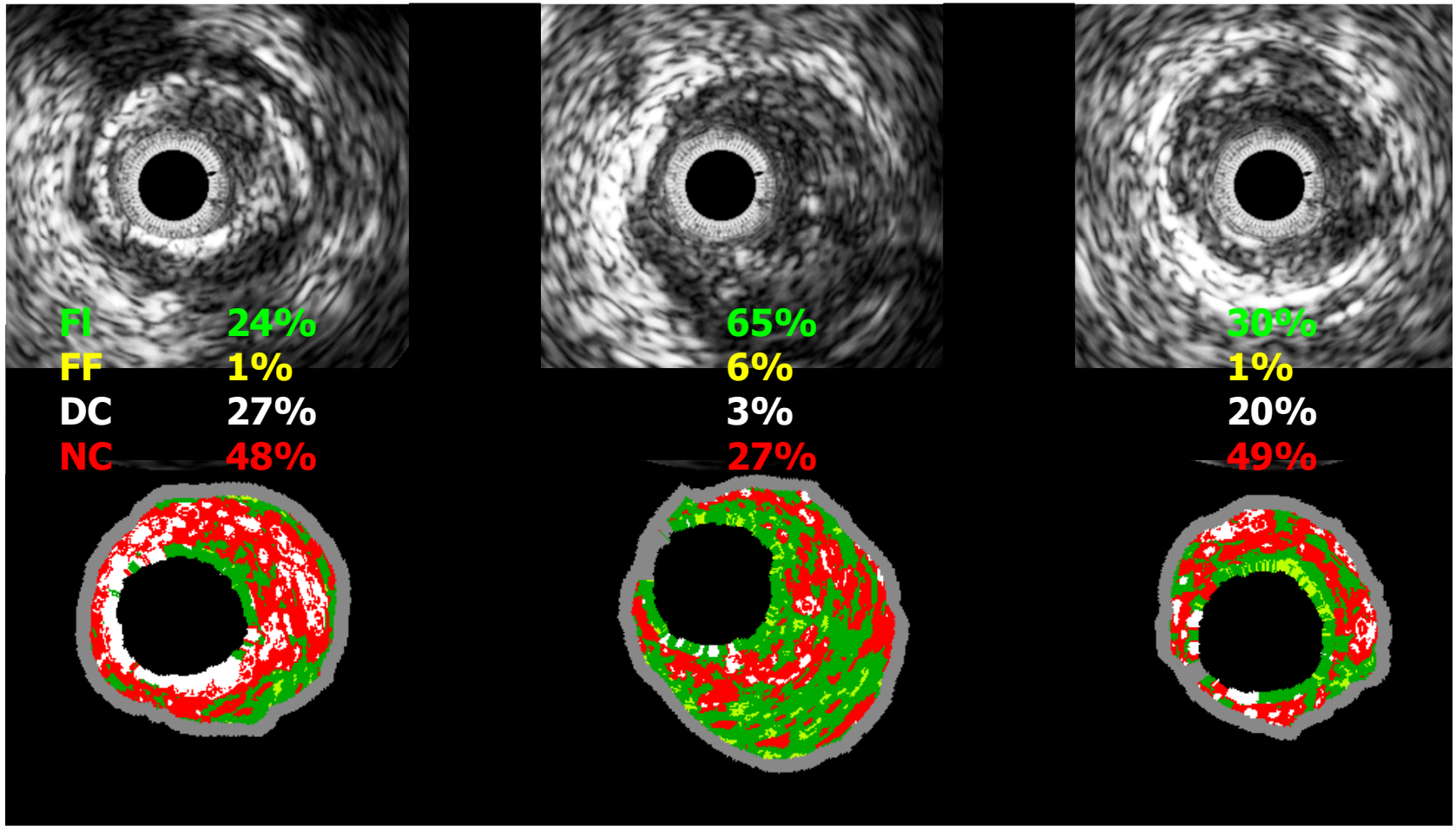


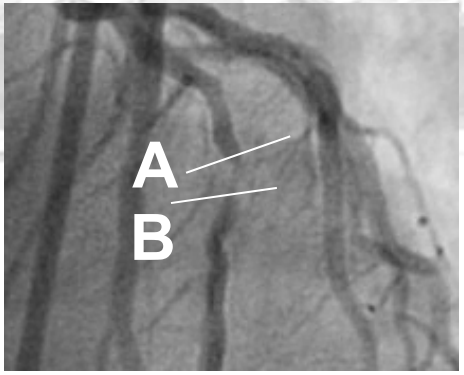
SJS, 46/M
NSTEMI, anterior

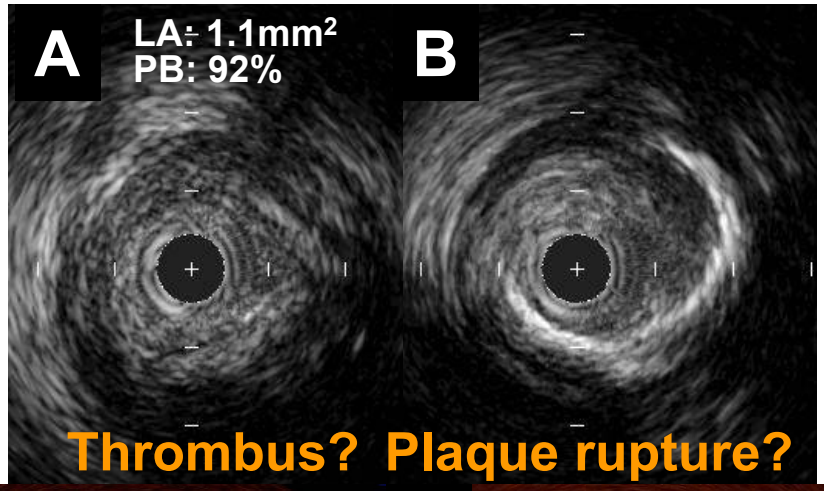


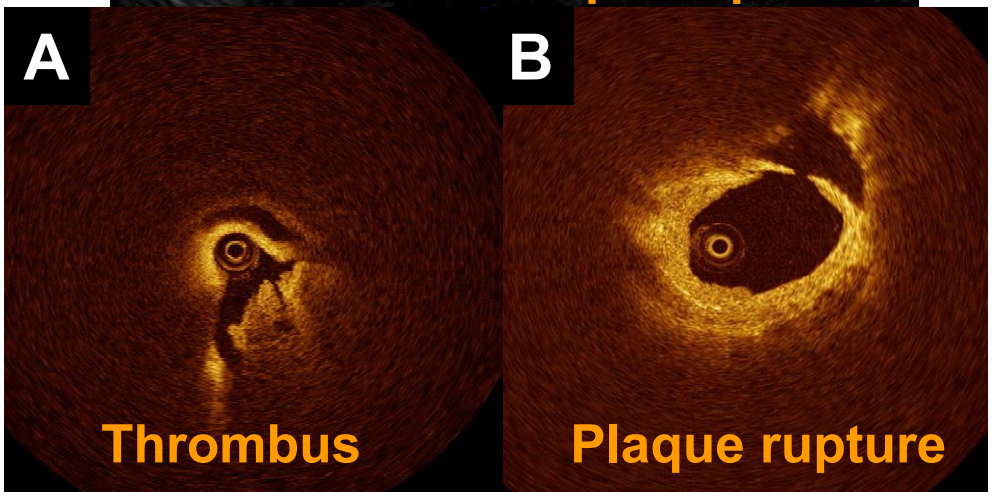


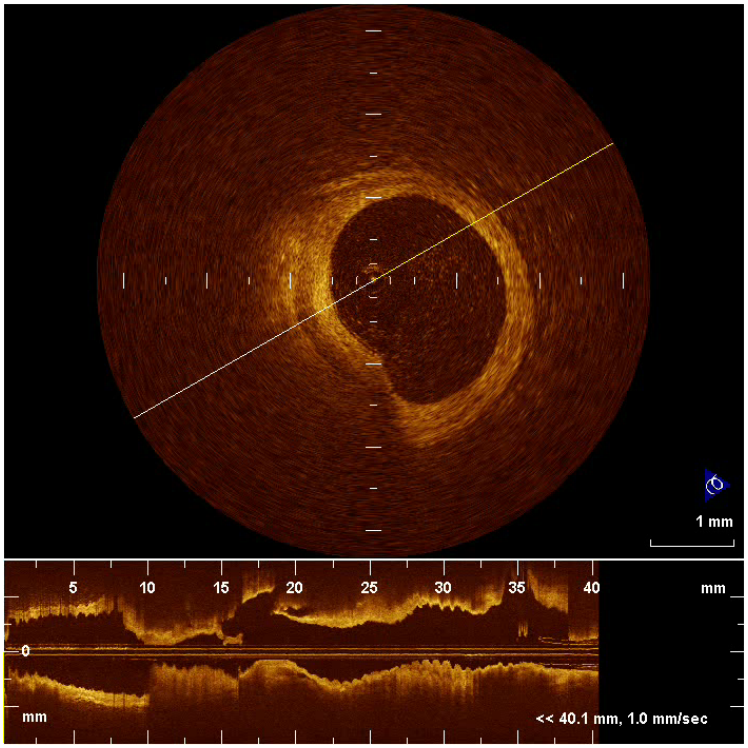



FI 24%
FF 1%
DC 27%
NC 48%
65%
6%
3%
27%
30%
1%
20%
49%


A
B

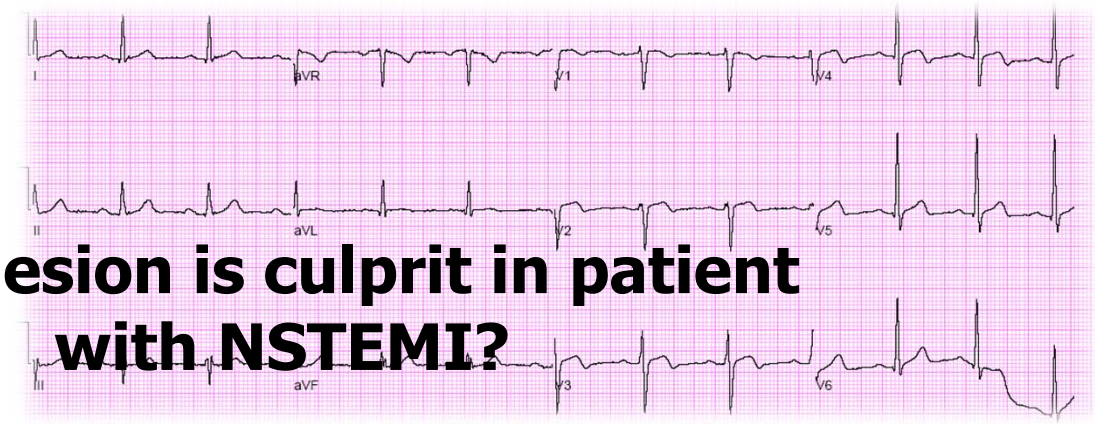

A
LA: 1.1mm²
PB: 92%
B
Thrombus? Plaque rupture?


A
Thrombus
B
Plaque rupture

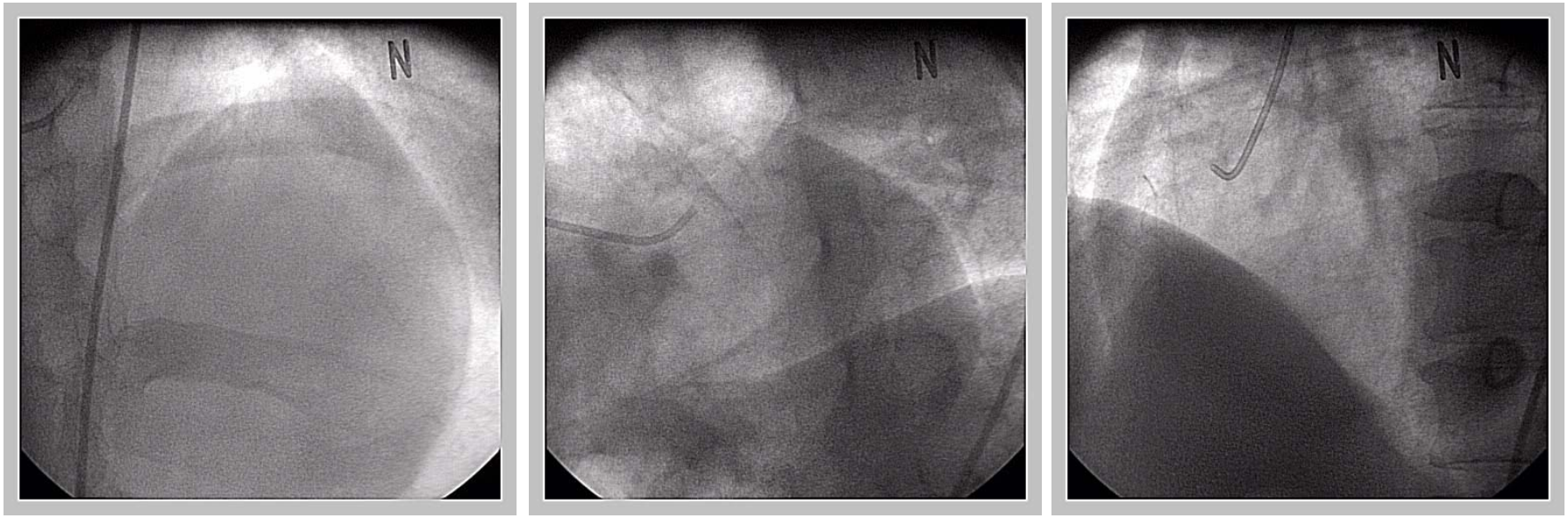

1 mm
5
10
15
20
25
30
35
40
mm
0
mm
<< 40.1 mm, 1.0 mm/sec

Case: OCT is the best tool for evaluation of VP II

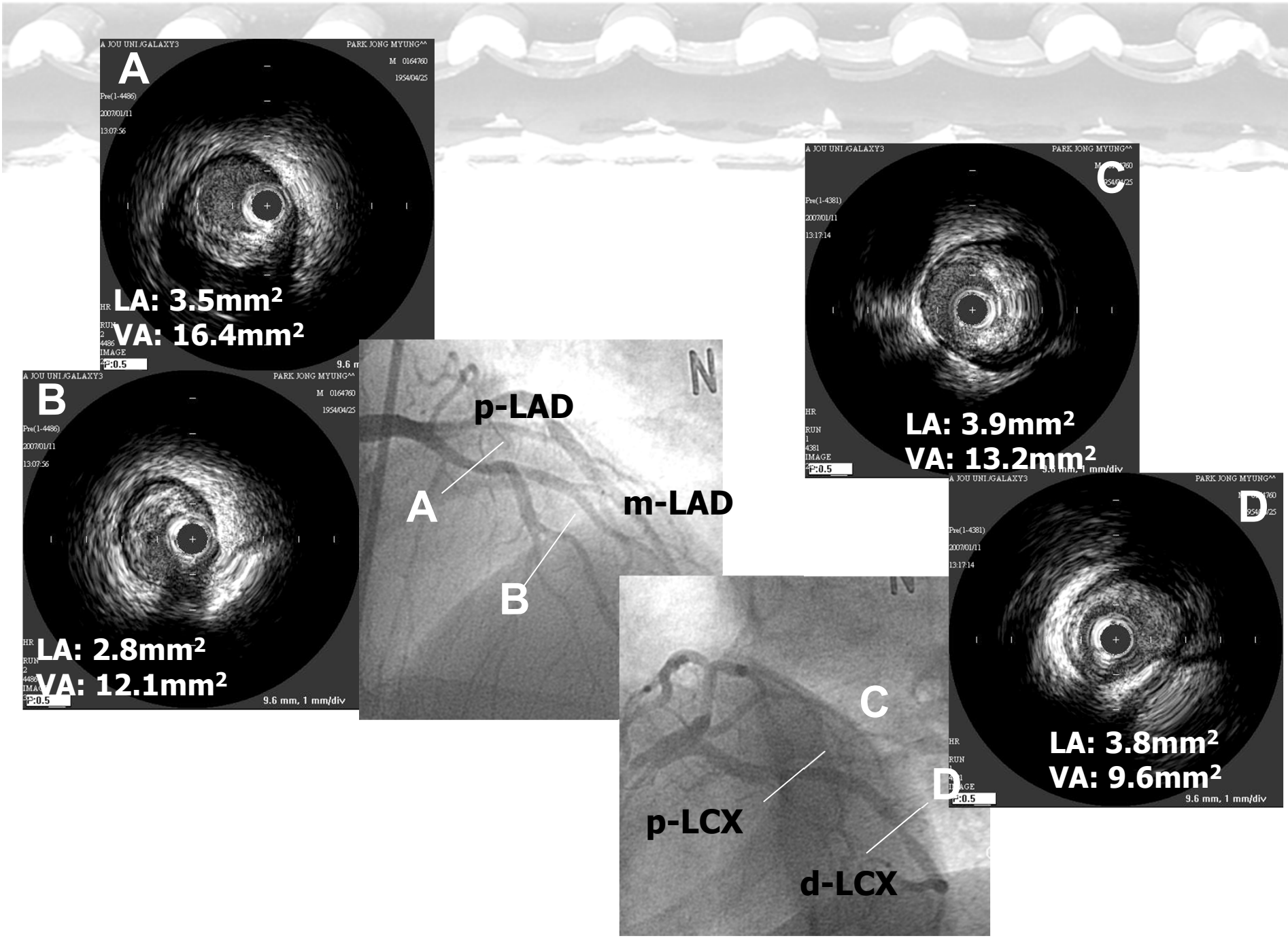
52/M with resting chest pain
Cardiac enzymes:
CK 481 U/L, CK-MB 8.49 ug/L, TnT 0.74 ng/mL

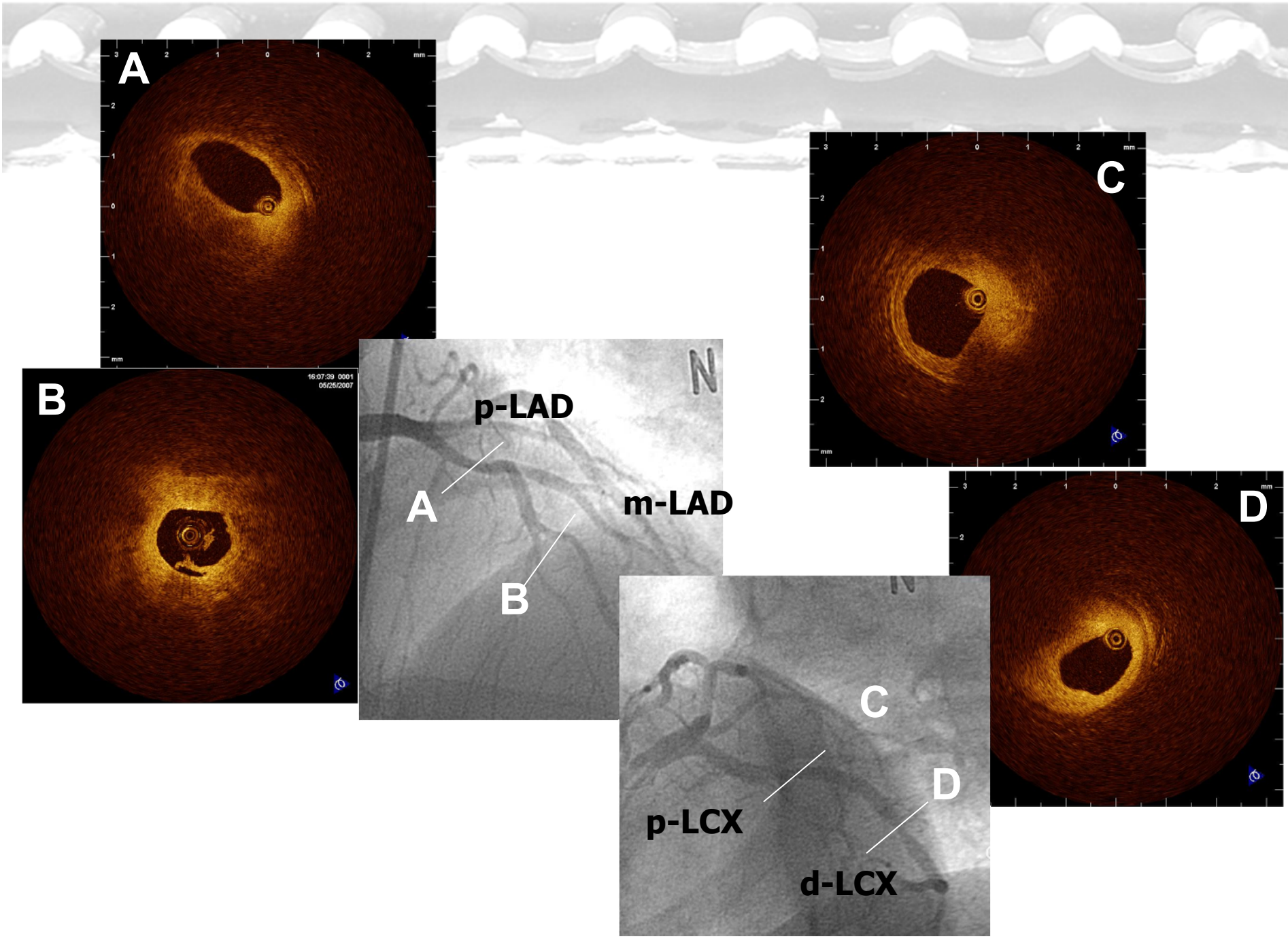


Which lesion is culprit in patient with NSTEMI?



Multiple stenoses at p-LAD, m-LAD, p-LCX and d-LCX

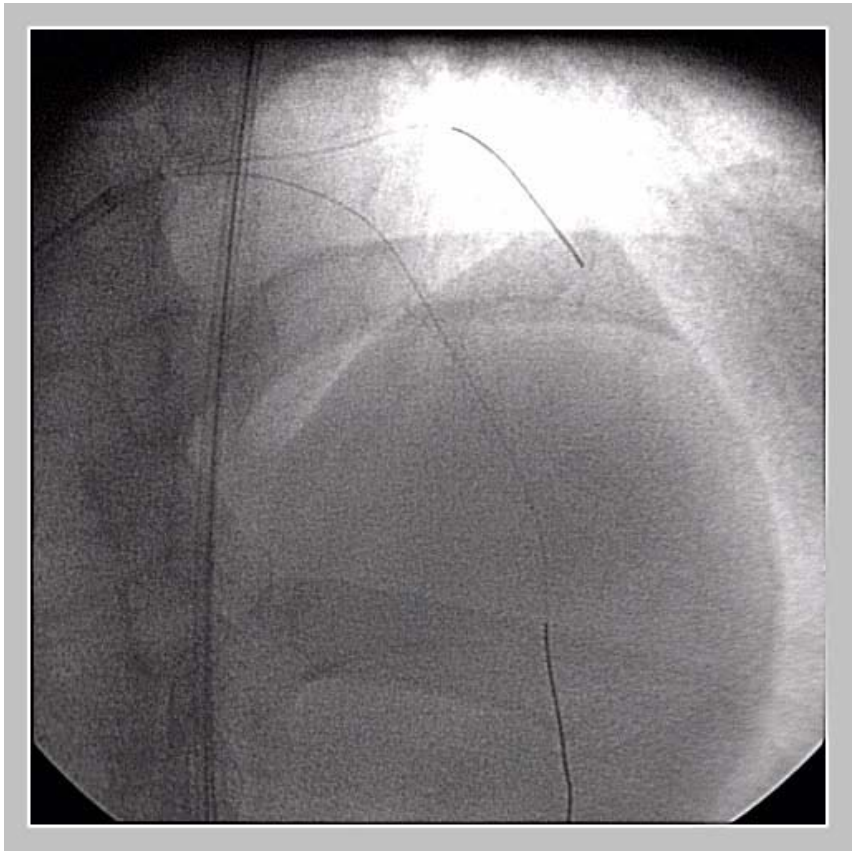

A
LA: 3.5mm²
VA: 16.4mm²
B
LA: 2.8mm²
VA: 12.1mm²
p-LAD
A
m-LAD
B
C
LA: 3.9mm²
VA: 13.2mm²
C
p-LCX
D
d-LCX
D
LA: 3.8mm²
VA: 9.6mm²


A
B
16:07:39 0001
05/25/2007
C
D
p-LAD
A
m-LAD
B
C
p-LCX
D
d-LCX

Procedure

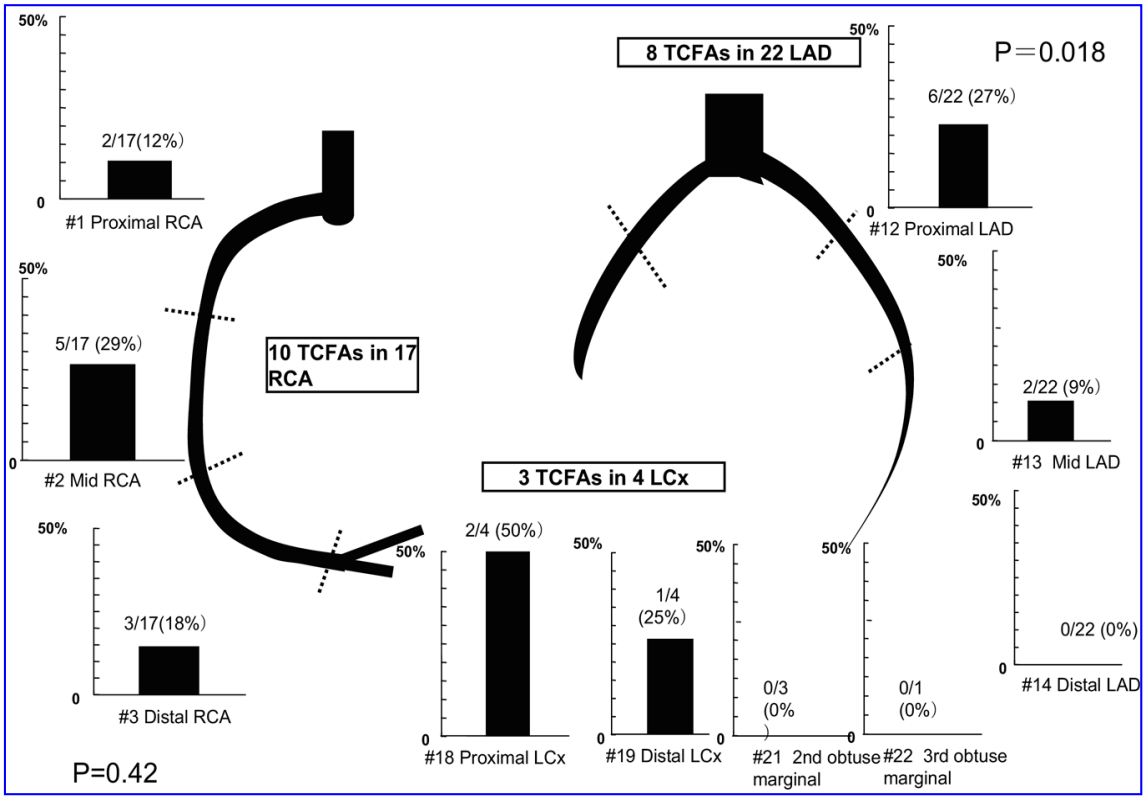
- Maveric2™ 2.5x20 mm
- Taxus™ Liberte™ 2.75x24 mm

Final angiogram



Distribution and Frequency of PR and OCT-TCFA

3V OCT studies in 43 patients with ACS

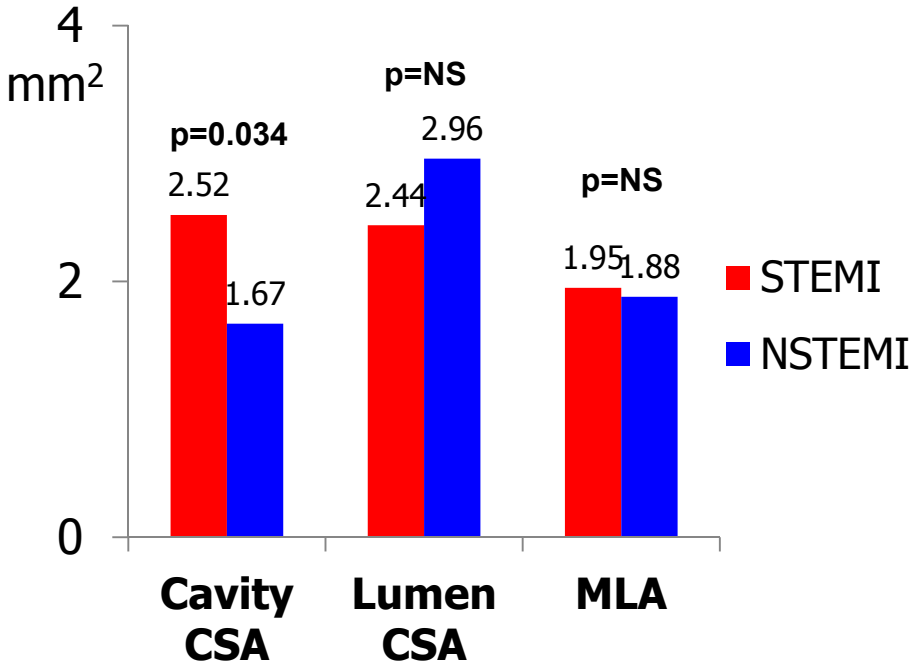


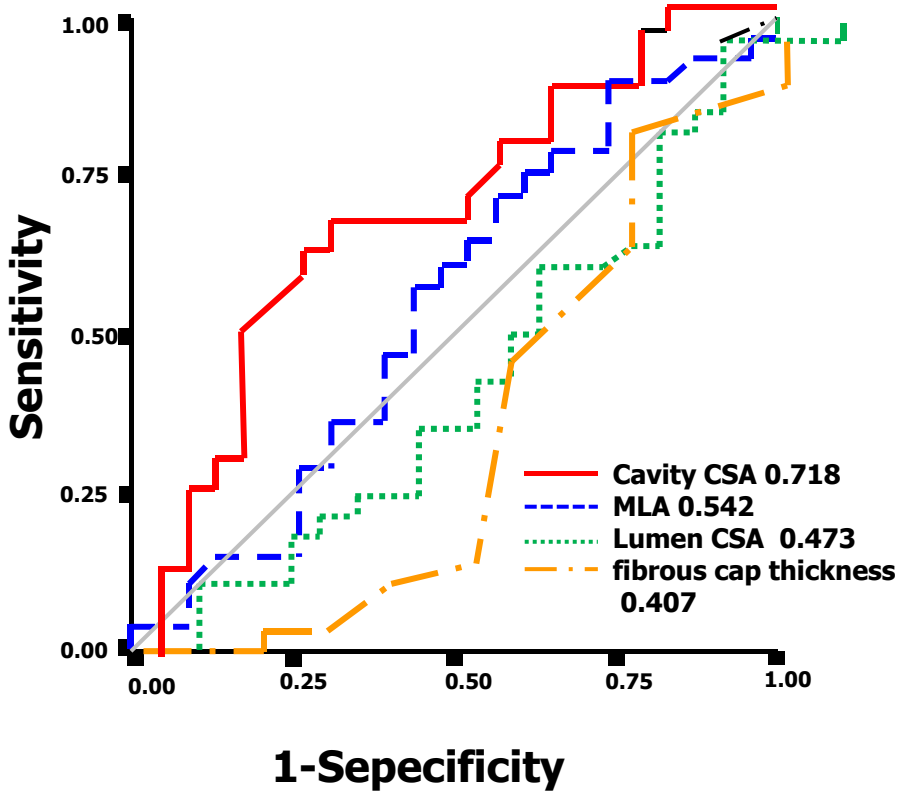
PR was found in 28 patients (65%) and multiple PRs in 5 patients (12%).
21 TCFA was found in 18 patients (42%) and multiple TCFAs were found in the same vessel in 3 patients (7%).

Tanaka A, Akasaka T et al. Am J Cardiol 2008;102:975–979

OCT Findings of PR STEMI vs NSTEMI

- 89 culprit lesions in 89 patients
- 40 STEMI vs 49 NSTEMI

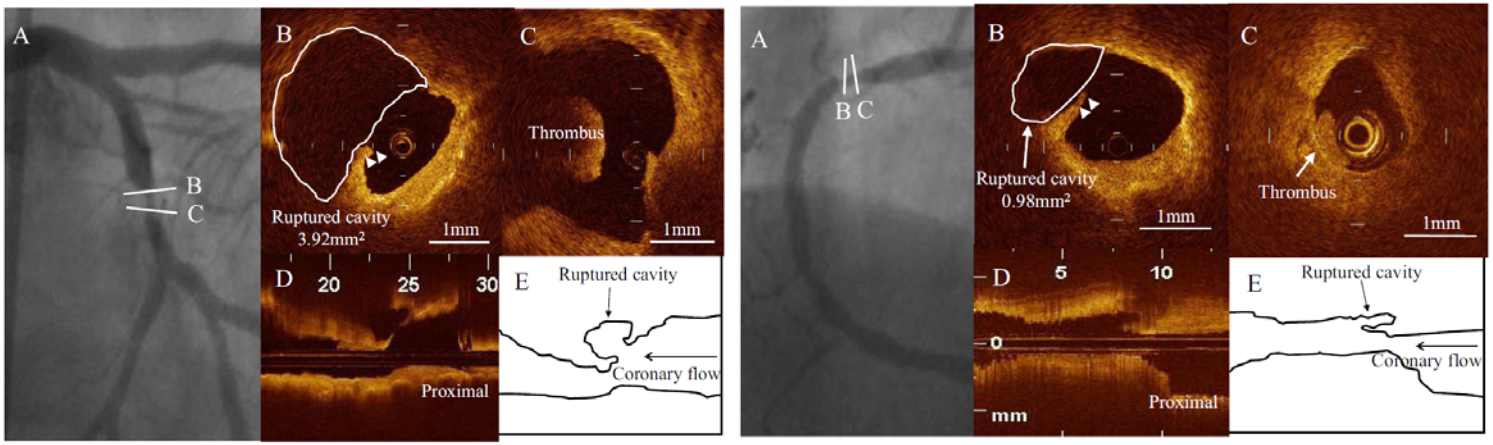




Ino et al., J Am Coll Cardiol Intv 2011;4:76–82

OCT Findings of PR STEMI vs NSTEMI

	STEMI	NSTEMI	P Value
Proximal location of ruptured cavity	**18 (64)**	**8 (35)**	**0.036**
Longitudinal morphological features of plaque rupture (proximal type)	**13 (46)**	**4 (17)**	**0.039**

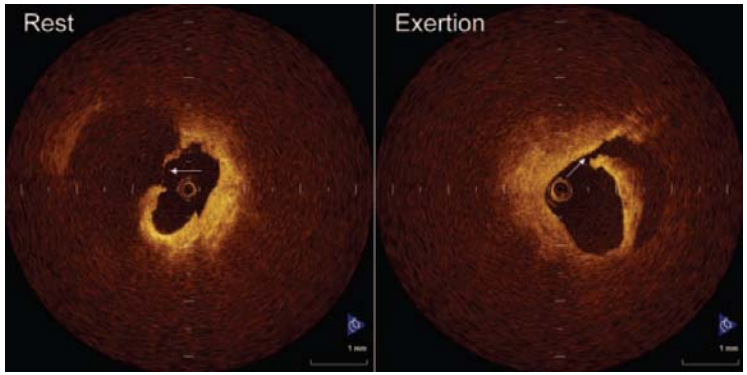


STEMI **NSTEMI**

Ino, et al., J Am Coll Cardiol Intv 2011;4:76–82

Exercise-triggered Plaque Rupture

43 consecutive ACS patients
Plaque rupture in 43 (60%)
Onset at Rest vs onset with exertion



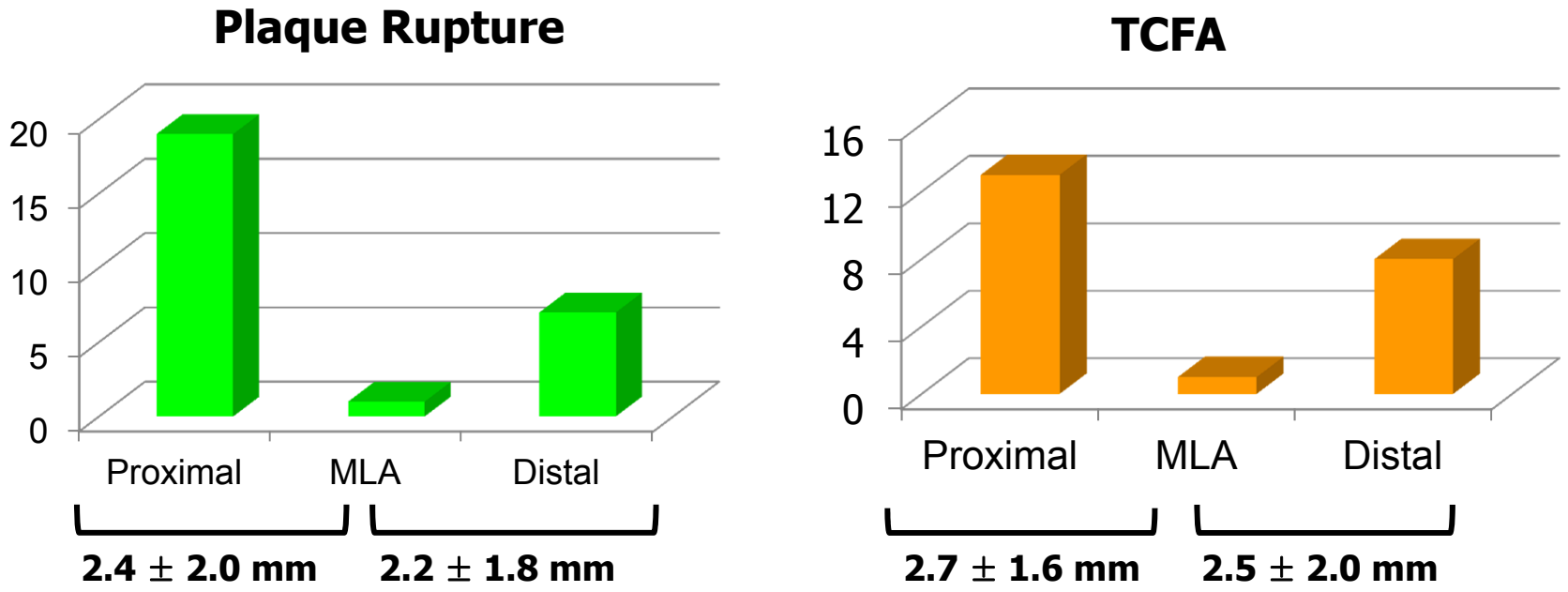
	Rest	Exercise	P
	n=28	**n=15**	
Thrombus	27 (96)	11(73)	0.04
Thin-cap fibroatheroma at culprit site	16 (57)	6 (40)	0.35
Broken at plaque shoulder	16 (57)	14 (93)	0.017
Thickness of broken fibrous cap, m	50 915)	90 (65)	0.0017

Conclusion: The morphologies of exertion-triggered and rest-onset ruptured plaques differ in ACS patients. some plaque rupture may occur in thick fibrous caps depending on exertion levels.

Tanaka A, Akasaka T et al. Circulation. 2008;118: 2368-2373.

Axial Distribution of PR and TCFA

48 culprit lesions in 48 patients with ACS

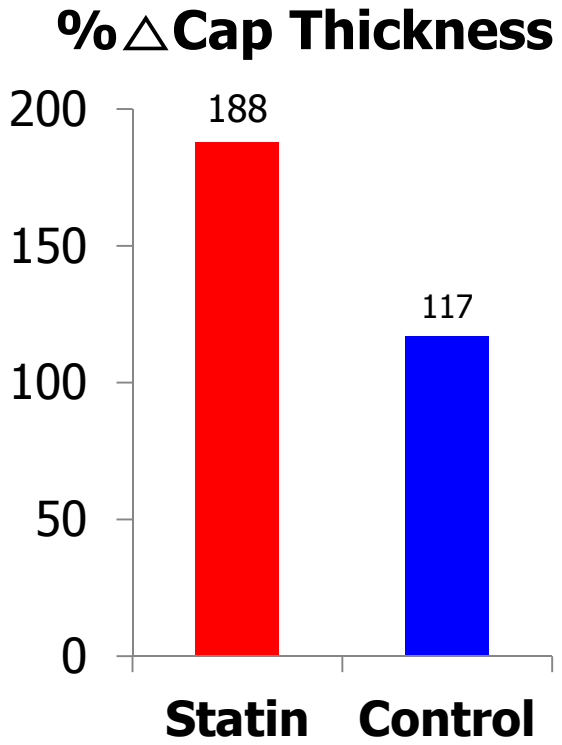


Conclusions: OCT showed that the MLA is rarely at the site of greatest instability (location of rupture and TCFA) and plaque instability sites are more common proximal to MLA site within the lesion in ACS.

Yang HM, Choi SY et al, TCT2009
Ajou OCT registry

Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome

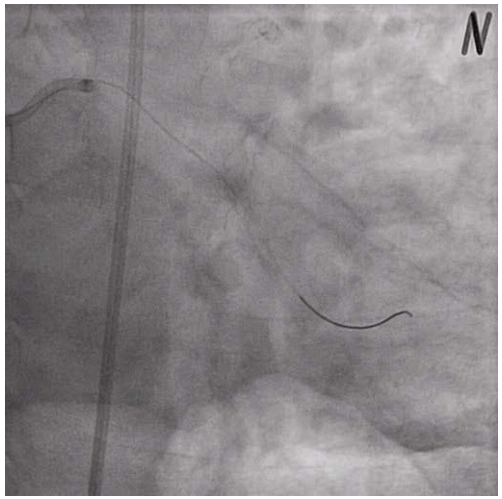
Forty AMI patients with hyperlipidemia were divided into statin treatment (n=23) vs control (n=17); serial OCT of a non-treated, lipid-rich lesion was performed at baseline and 9-month follow-up.



Conclusion: Statin therapy for 9 months after the onset of AMI increased fibrous-cap thickness in patients with hyperlipidemia.

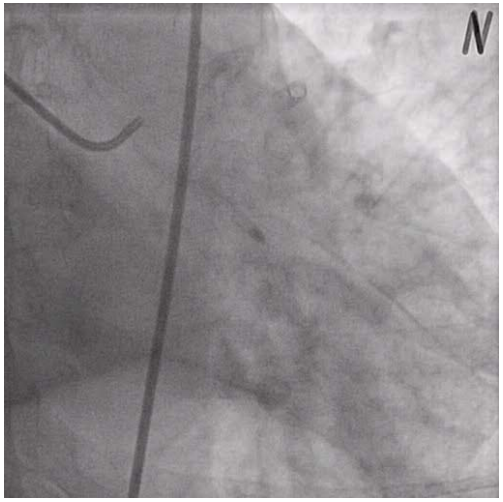
Takarada S, et al. Atherosclerosis 2009;202(2):491–497

Case: Neoatherosclerosis related with AMI

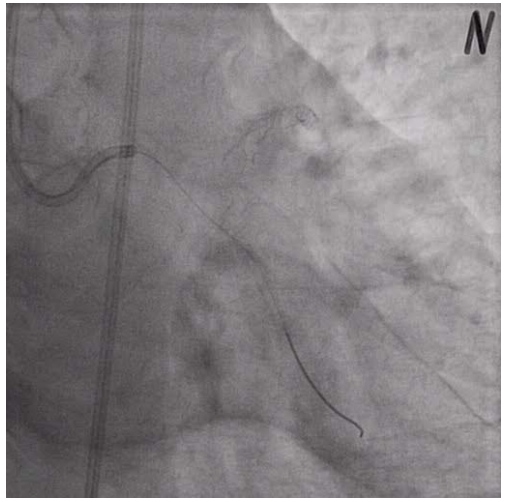


M/56 with AMI (lat)
PCI with Endeavor stent 2.75 x 12mm at OM 18 months ago

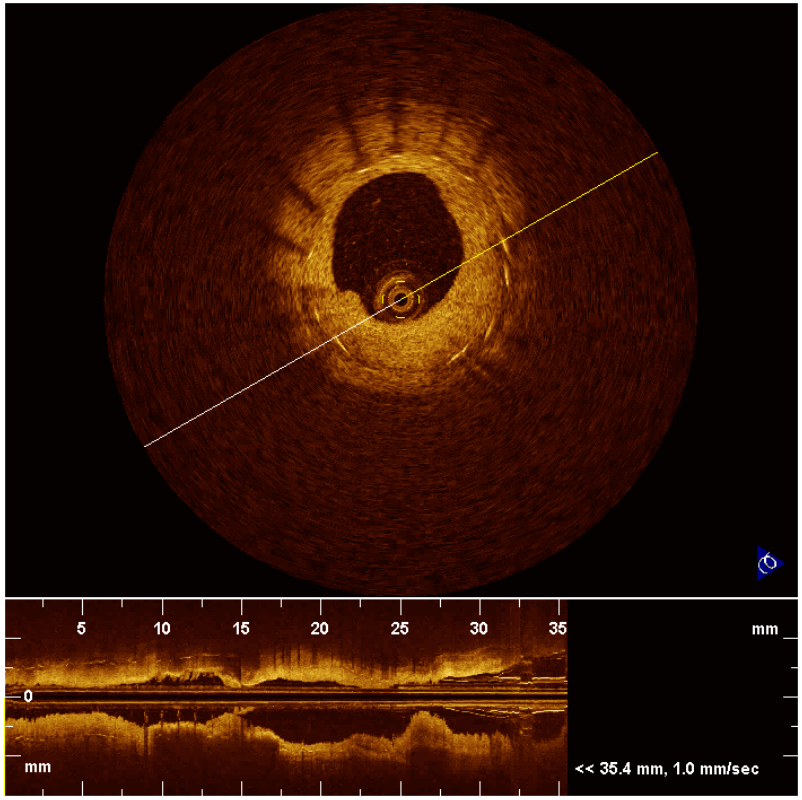
18mo ago

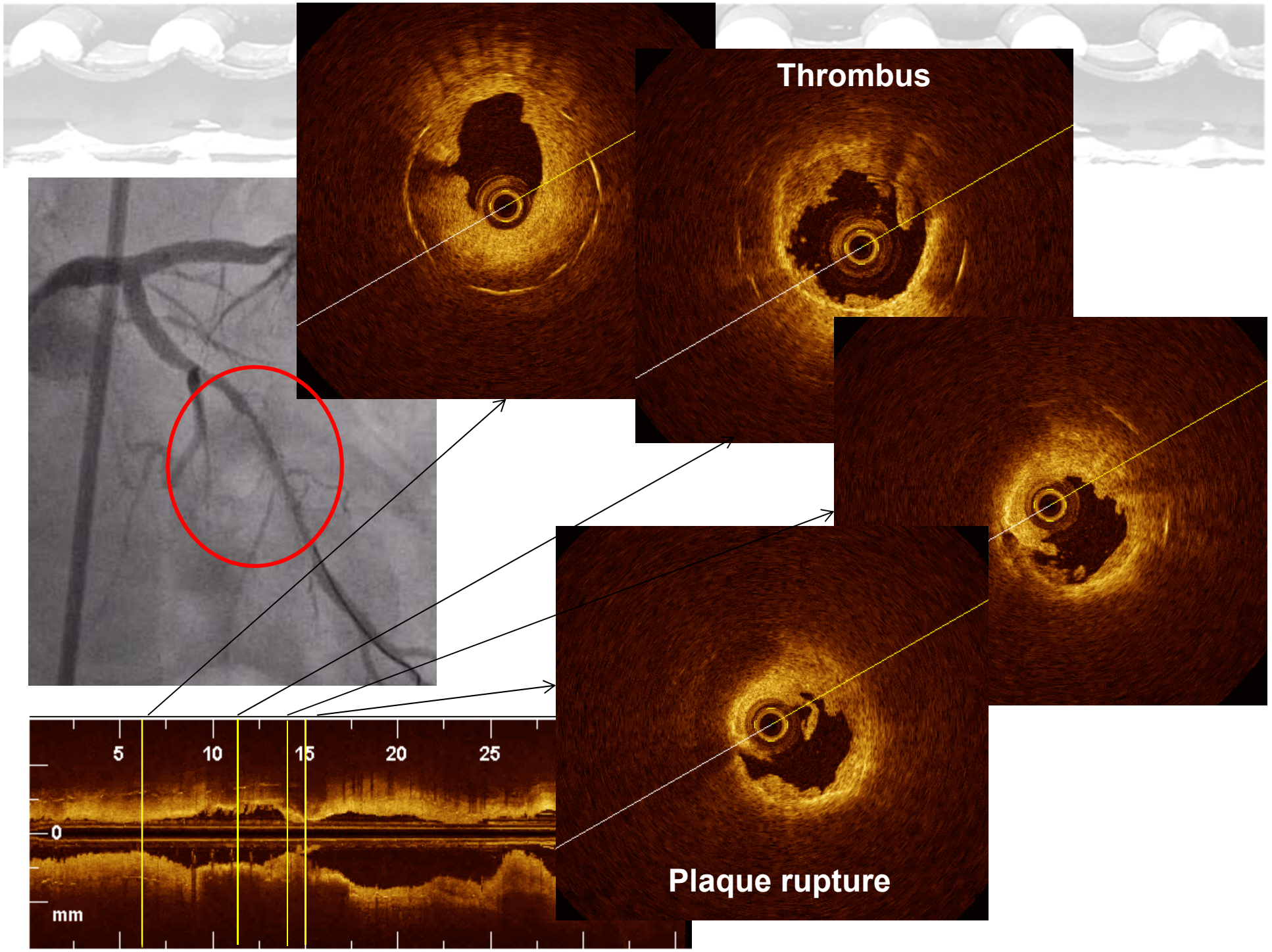


Baseline

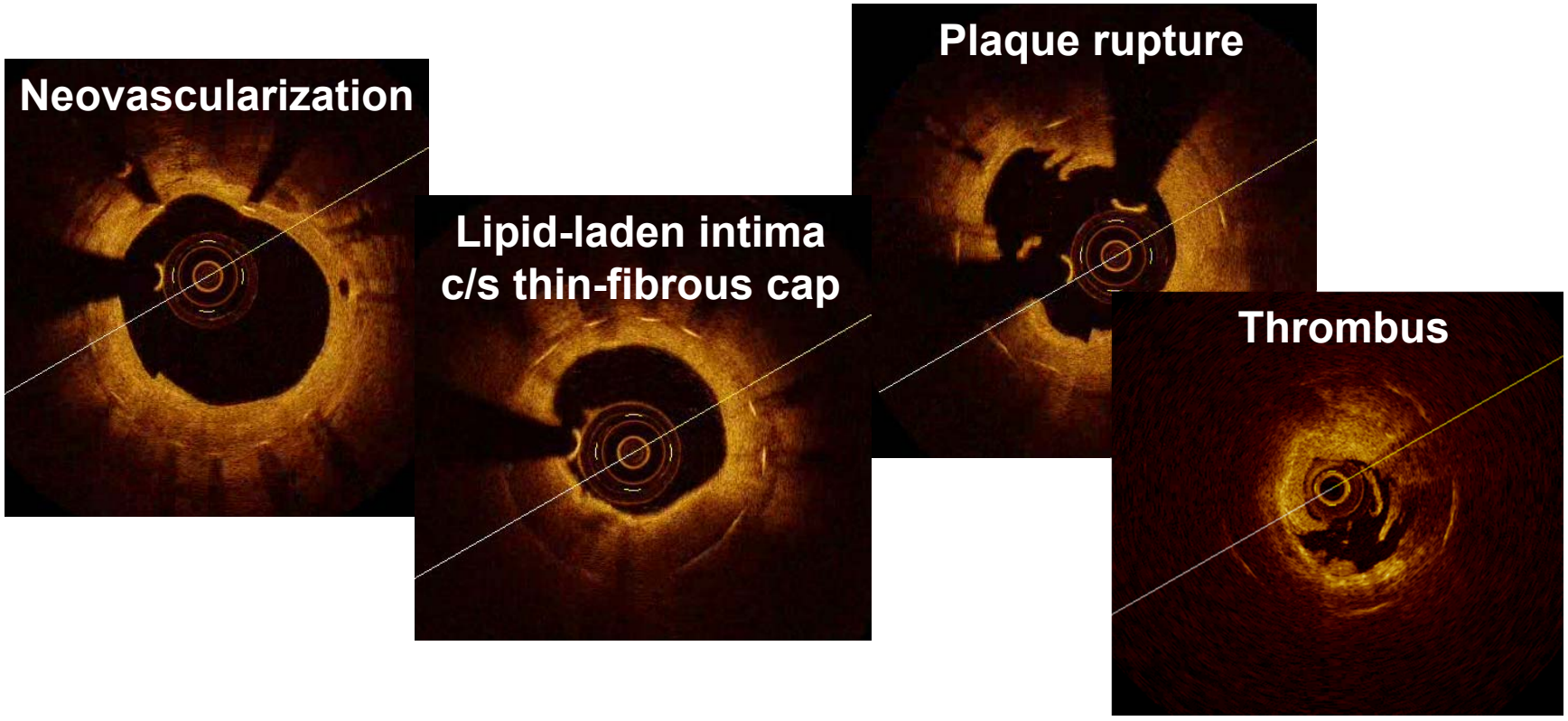


After thrombosuction



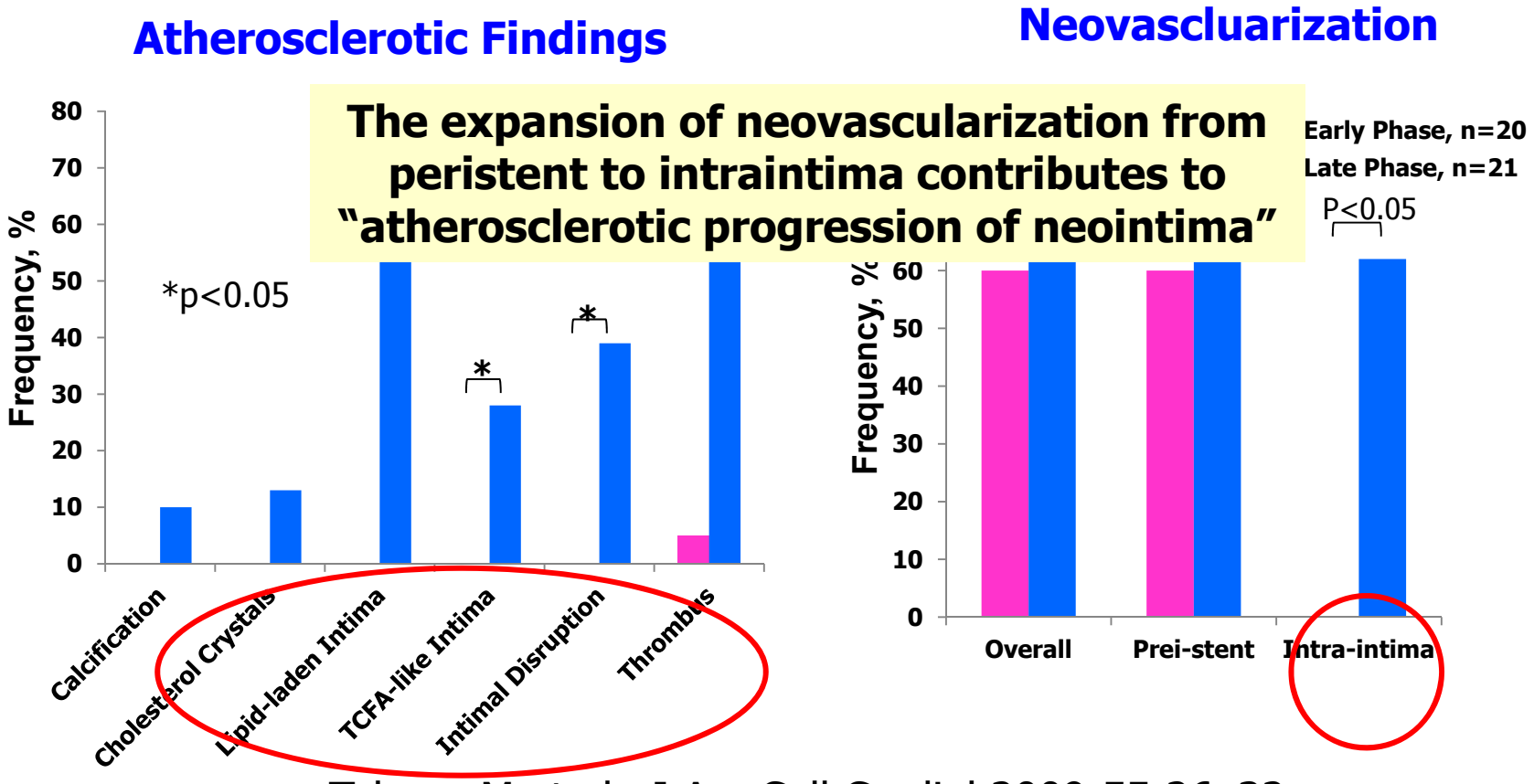

Thrombus
5
10
15
20
25
0
mm
Plaque rupture

OCT Findings of Neoatherosclerosis



Lipid-Laden Intima and Neovascularization After BMS

Early phase (<6mos, n=20) vs late phase (≥5 yrs, n=21) observation by OCT



Takano M et al., J Am Coll Cardiol 2009;55:26–32

Neointima in ISR lesion with DES

50 ISR lesions with DES implantation
Median follow-up time was 32.2 months

26 lesions (52%) had at least 1 OCT-defined in-stent thin-cap fibroatheroma (TCFA)–containing neointima and 29 (58%) had at least 1 in-stent neointimal rupture.

	Stable	Unstable	p
Fibrous cap thickness, μm	100 (60-205)	55 (42-105)	0.008
Intimal rupture	47%	75%	0.044
Thrombi	43%	80%	0.007
Red thrombi	3%	30%	0.012
Lipid neointima	83%	100%	0.067
TCFA	37%	75%	0.008
Neovascularization	50	75%	0.069

Kang SJ, Park SJ et al., Circulation. 2011;123:2954-2963.

Neoatheroma and VLST after DES or BMS

- 30 VLST patients with AMI (23 DES and 7 BMS)

	DES	BMS	p
Months after index procedure	33.2±12.5	108.4±26.5	<0.001
Stent length, mm	32.9±13.0	18.6±4.2	0.001
Minimum stent CSA, mm^2	6.2±1.6	7.4±3.8	0.413
Mean EEM CSA, mm^2	19.6±6.1	18.3±4.2	0.774
Malapposition, %	73.9	0	0.001
Neo-intimal rupture, %	43.5	100	0.010

Lee CW, Park SJ et al., JACC 2010;55:1936–42

What we learned from OCT studies…

- OCT has a potential benefit to identify vulnerable plaques-especially plaque rupture, thrombus, fibrous cap thickness, macrophage accumulation-rather than other intracoronary imaging modalities.
- OCT can provide better information for understanding the mechanism of disease progression in both native lesions and the lesion underwent therapeutic modification.
- Prospective clinical outcome date undergoing in the field of OCT studies might be helpful to achieve knowledge of vulnerable plaque nature.

Lessons from Current Experiences

- The current paradigm designation vulnerable plaques as a prelude rupture is primarily supported by autopsy findings, where definitive proof dose not exist because of a lack of prospective human data confirming a cause-and effect relationship.
- Potential morphological (and biological) processes that may be helpful for the identification and understanding of vulnerable plaque recognized by today's intracoronary imaging modalities; gray-scale IVUS, RF-IVUS and OCT.
- Advancing the field is required in furthering the development of novel imaging and therapeutic modalities.