Assessment of In-Stent Restenosis Using Gray-Scale IVUS, VH and OCT

Mechanism of ISR and Tissue Characterization

Based on the Data from AMC IVUS Core Lab

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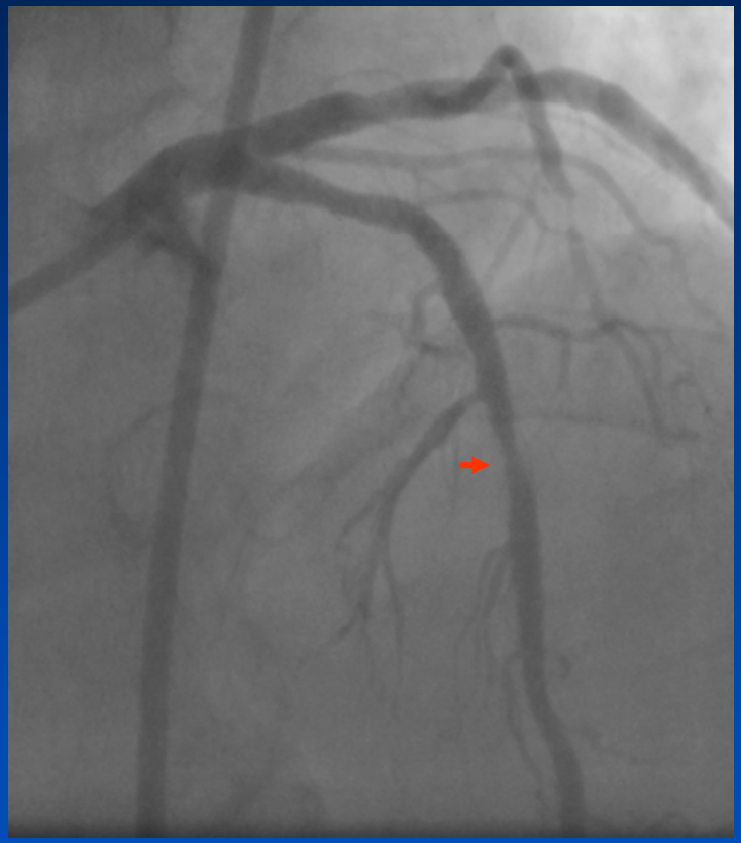
Two Different Mechanisms of ISR
Stent Underexpansion

56 Year-Old Male

- 9MA Primary PCI for STEMI

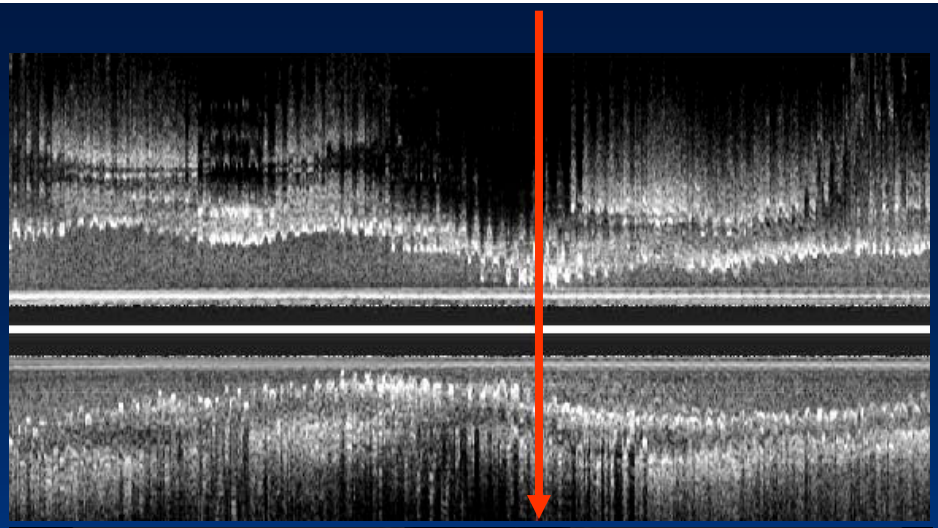
→TAXUS 3.0 (28) mm and
3.5(28) mm at the mLAD

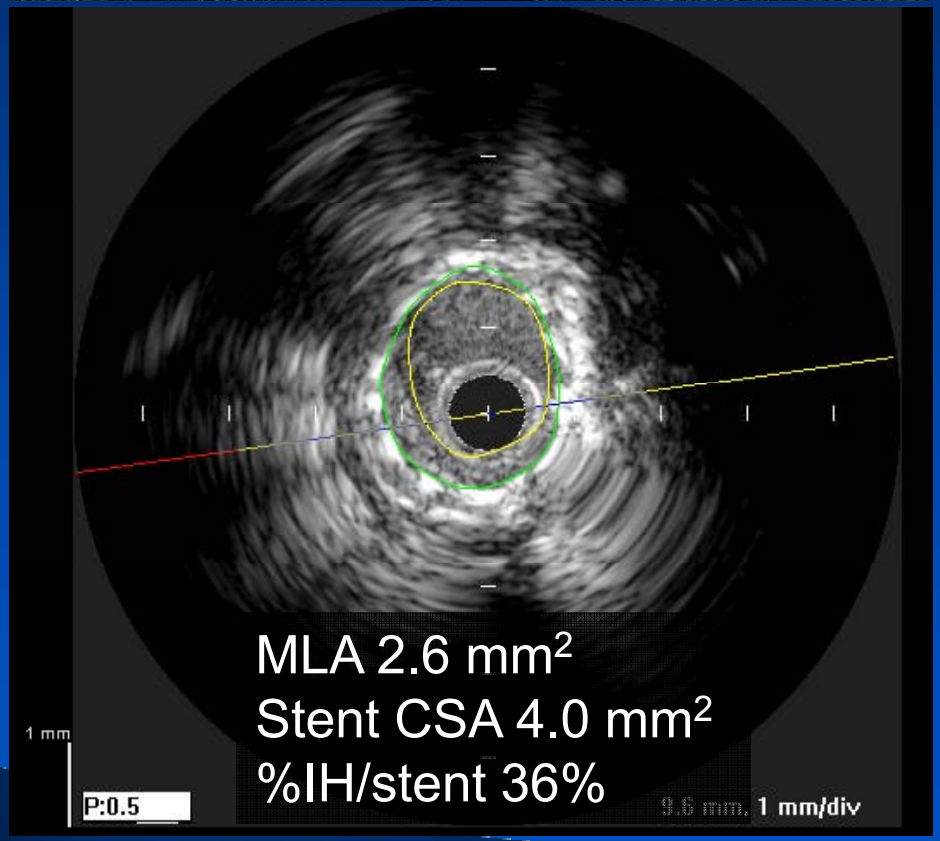
- 9-month F/U angiography

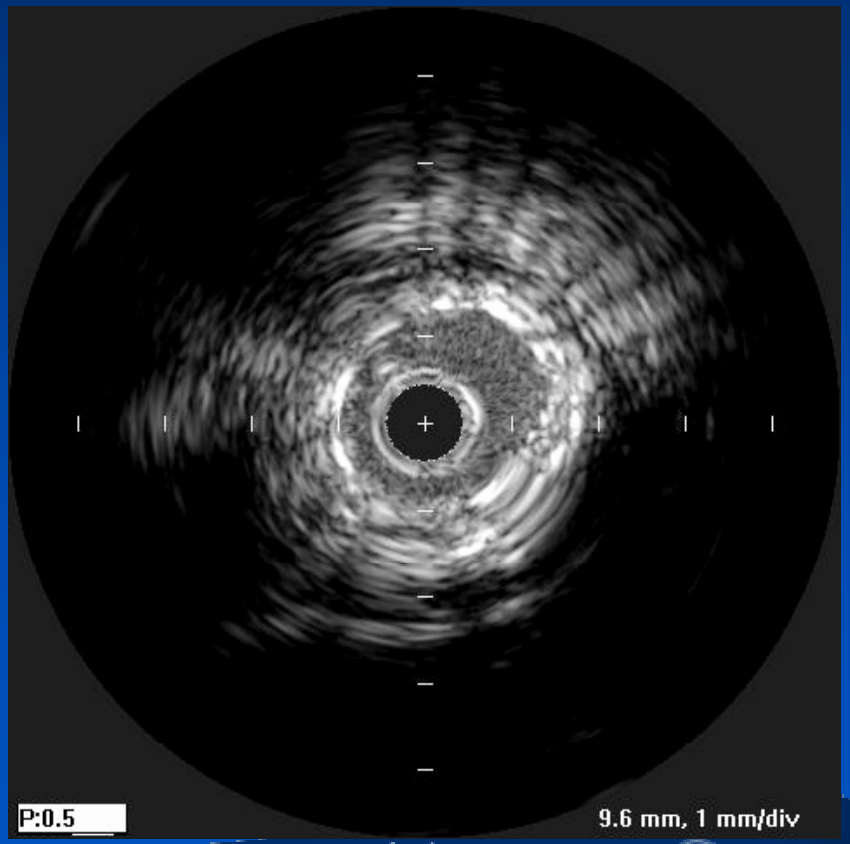


Main Mechanism of ISR at the MLA site

Underexpansion







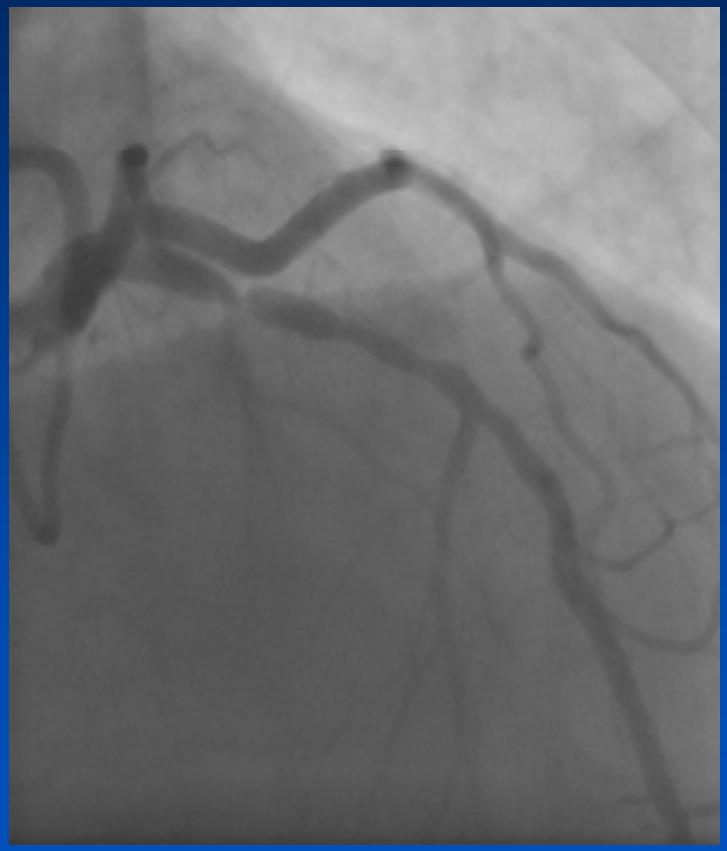
Two Different Mechanisms of ISR
Intimal Hyperplasia

68 Year-Old Female

- 1YA stable angina

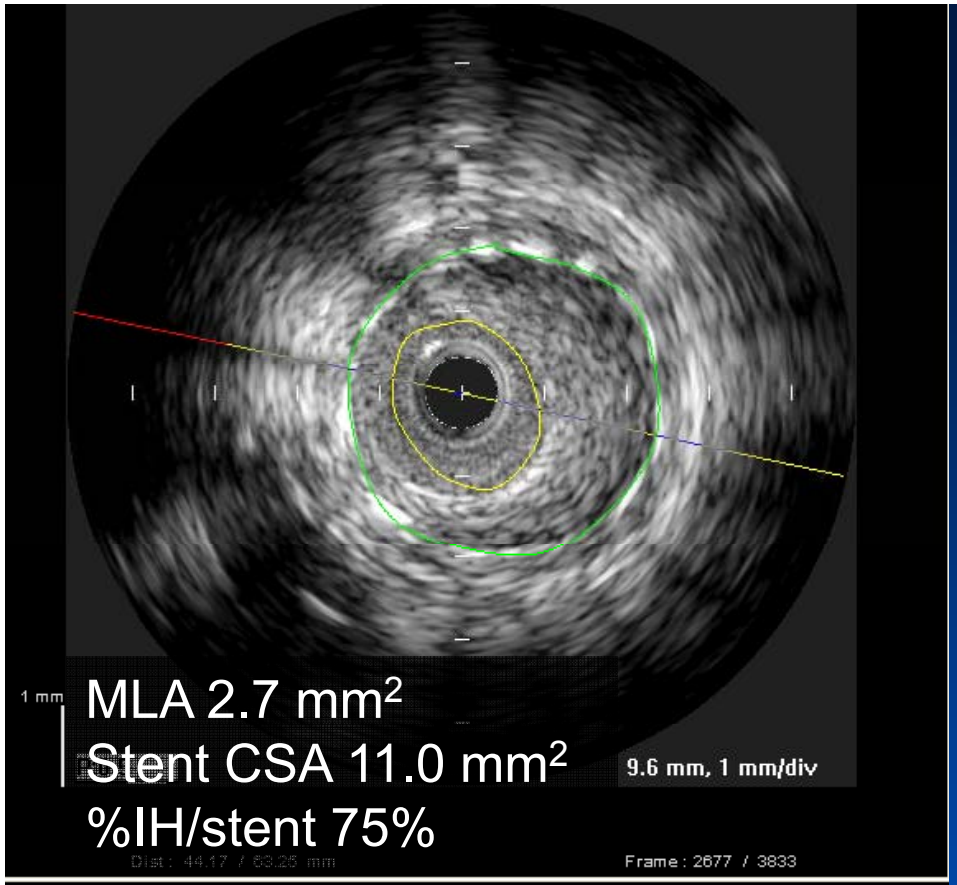
→Taxus 3.5 (20) mm at mLAD

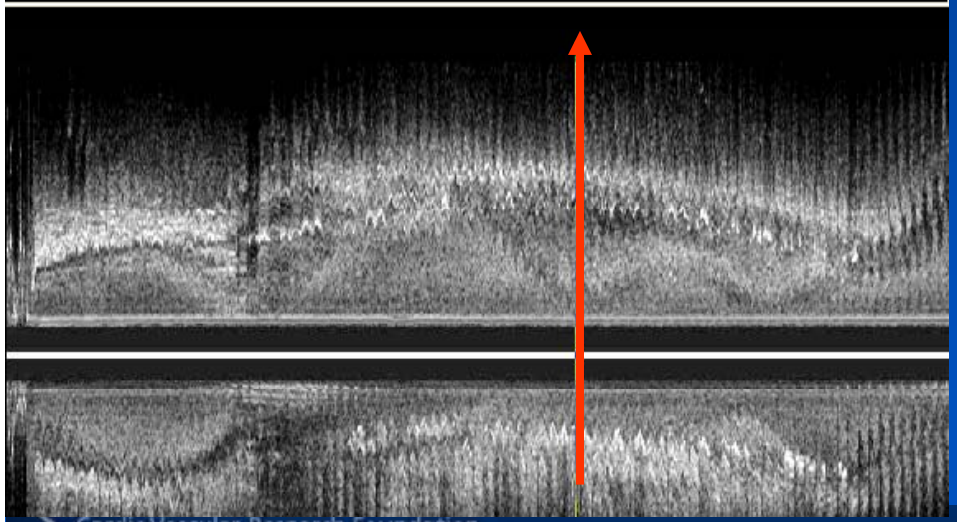
- 5MA effort-related chest pain
- 1-year F/U angiography

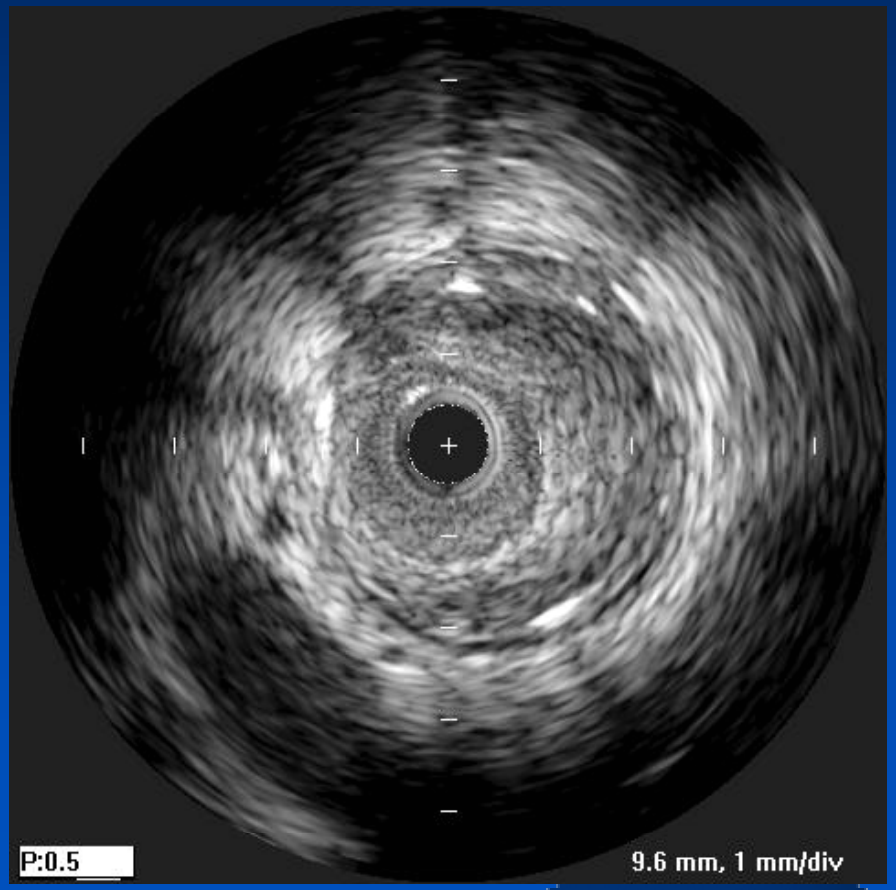


Main Mechanism of ISR at the MLA site

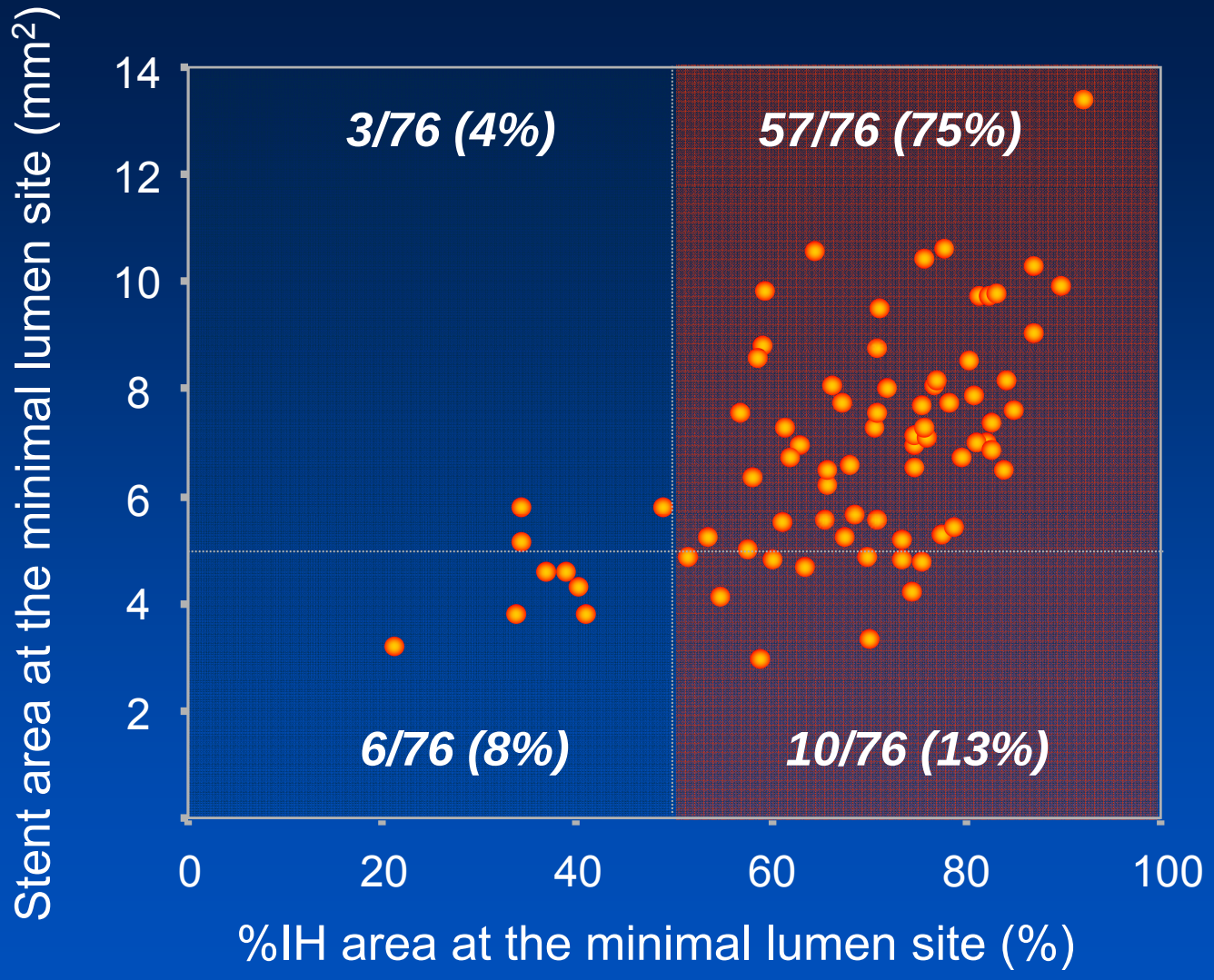
Dominant IH





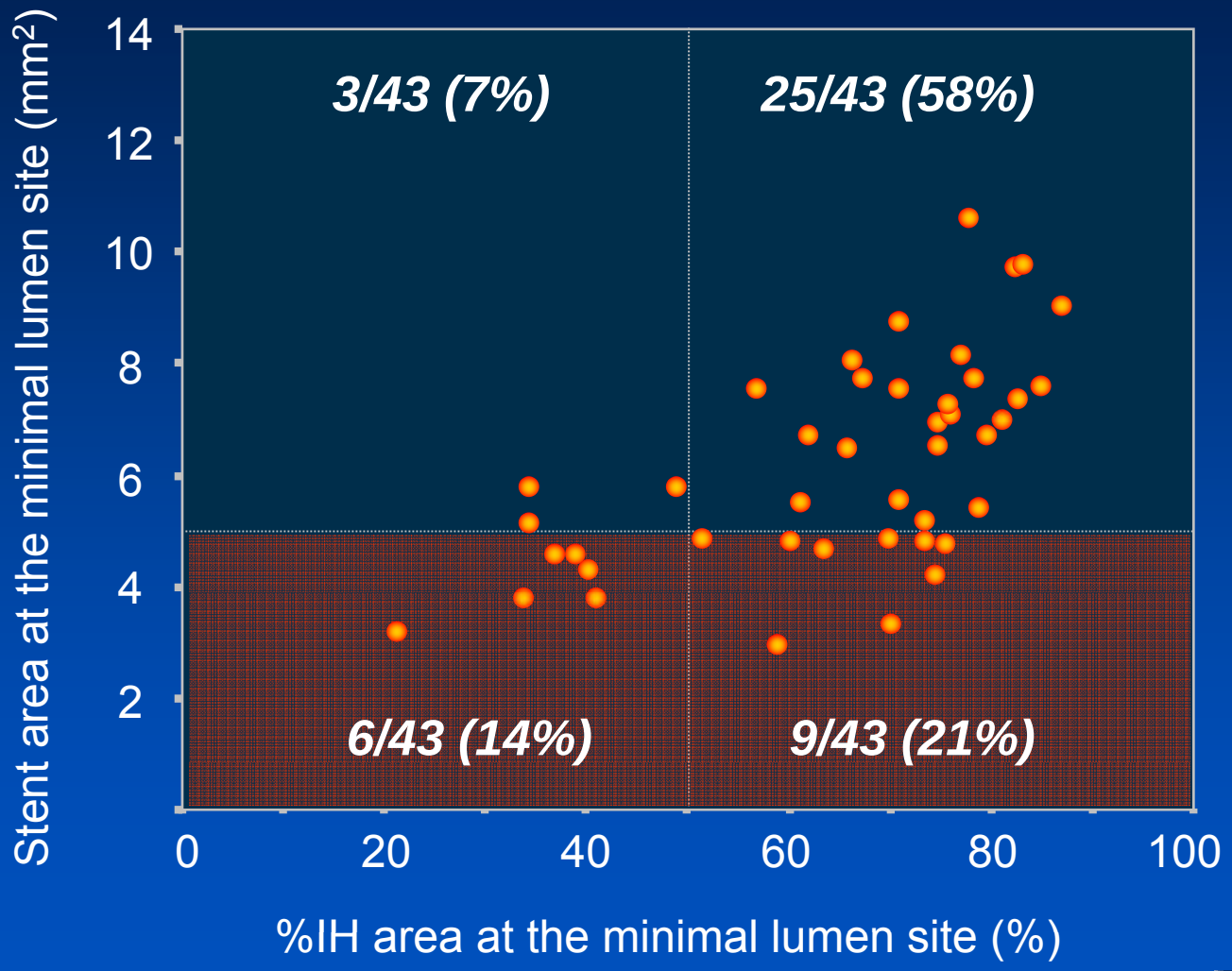


Mechanism of DES-ISR at the MLA Site

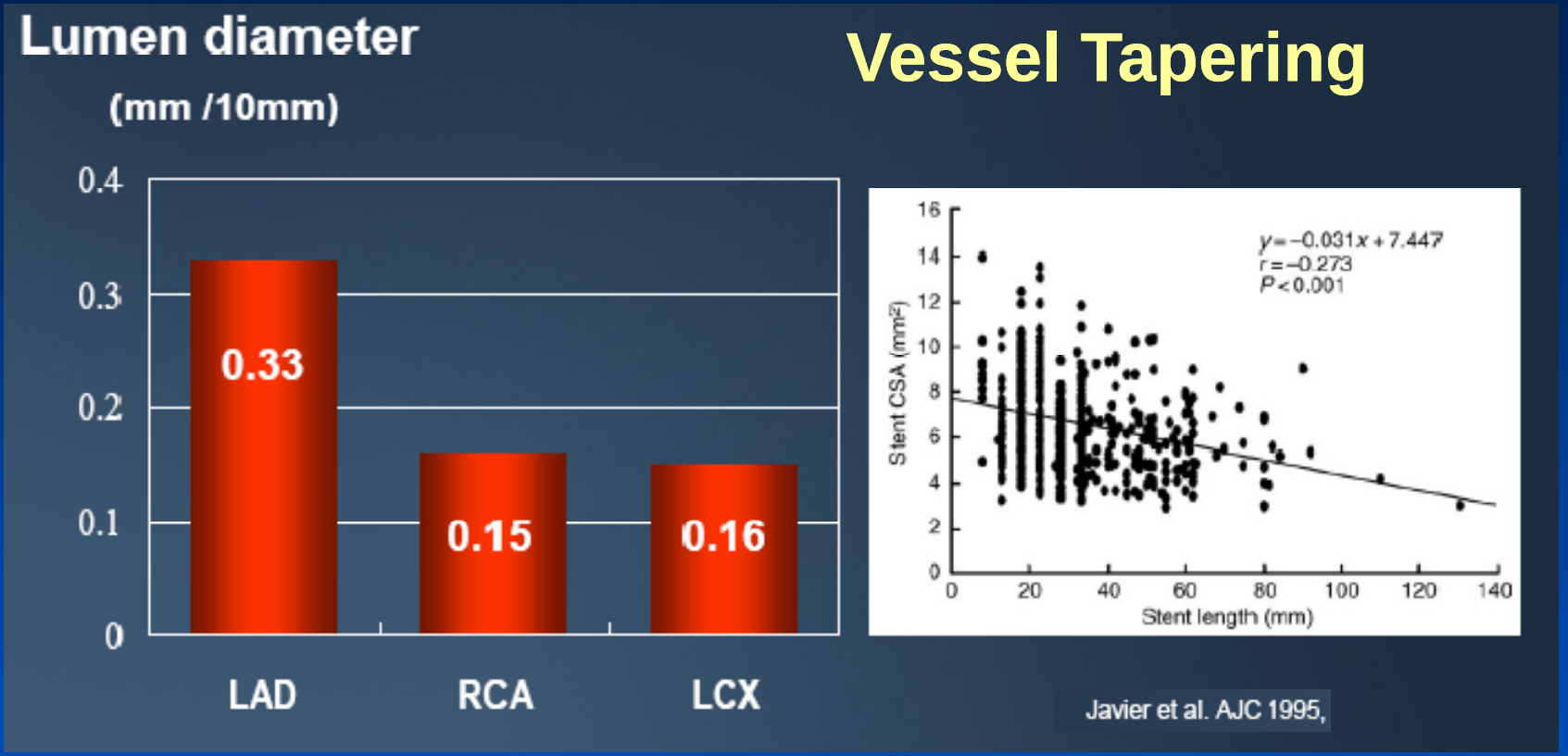


Intimal hyperplasia contributed to DES-ISR in 88%

Mechanism of DES-ISR at the MLA Site in the subgroup with Total Stent Length >28 mm

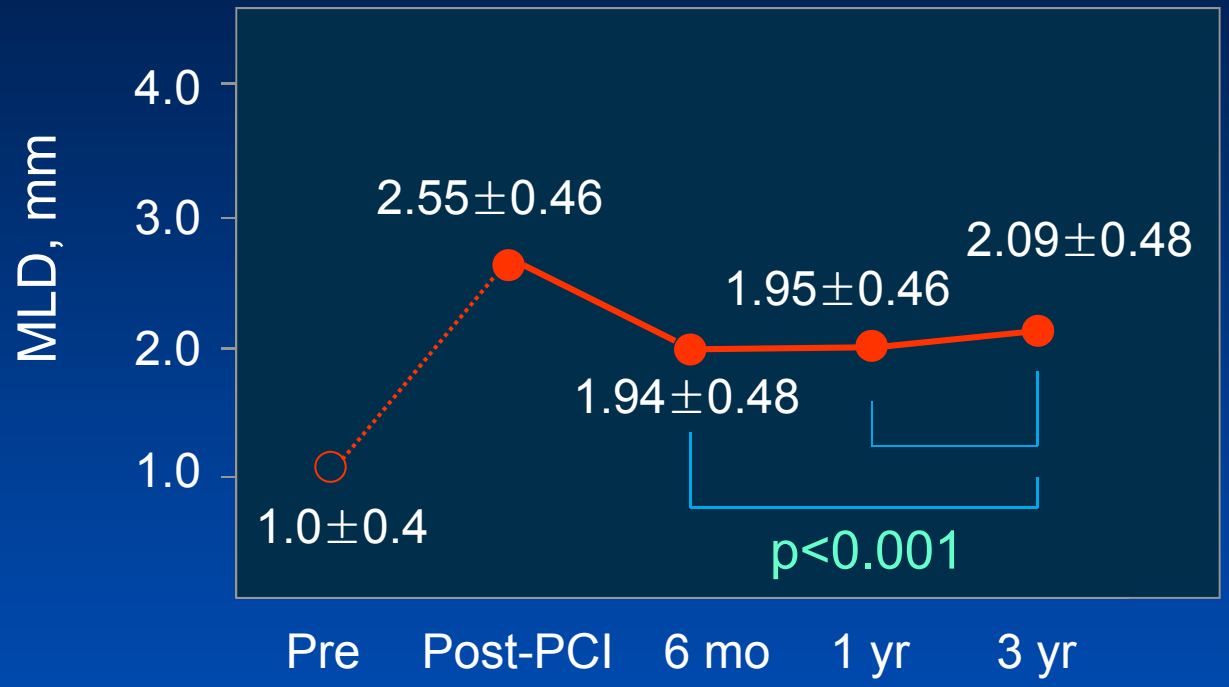


Higher Rate of Underexpansion in Lesions with Longer Stent



- The property of vessel tapering especially in LAD
- A greater possibility for “occult” focal underexpansion

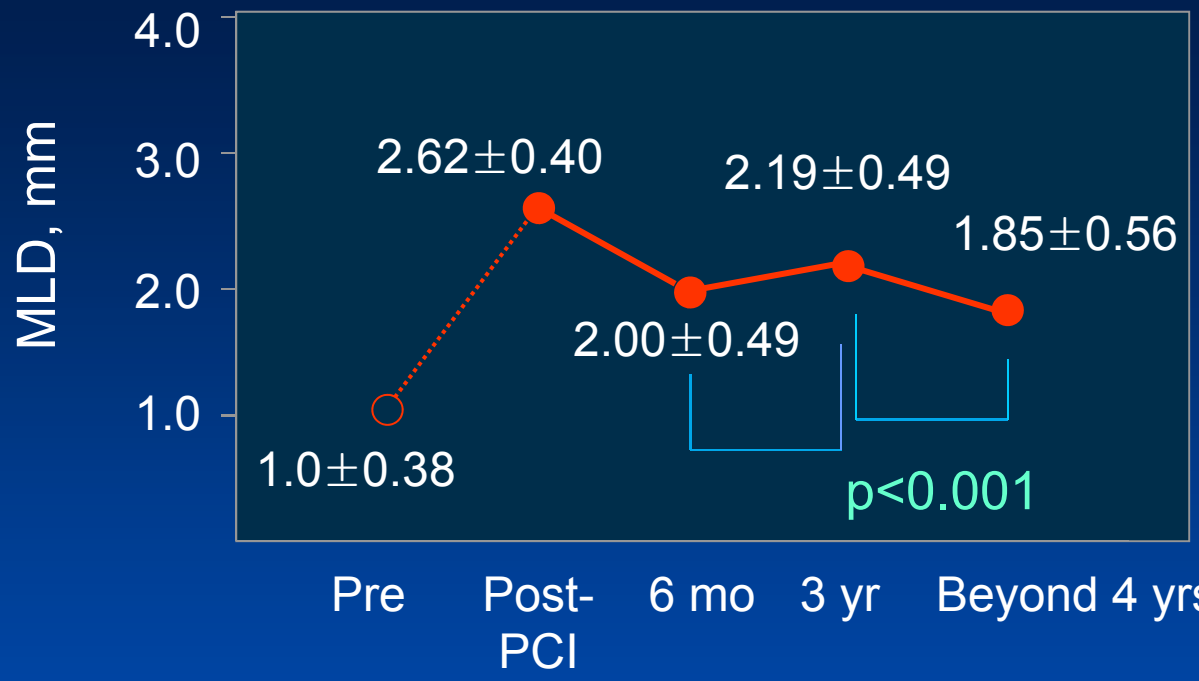
Serial MLD Changes in 72 Lesions Over 3 Years after BMS Implantation



Early lumen loss at 6 months and subsequent improvement in MLD

Kimura et al. N Engl J Med 1996;334:561-6

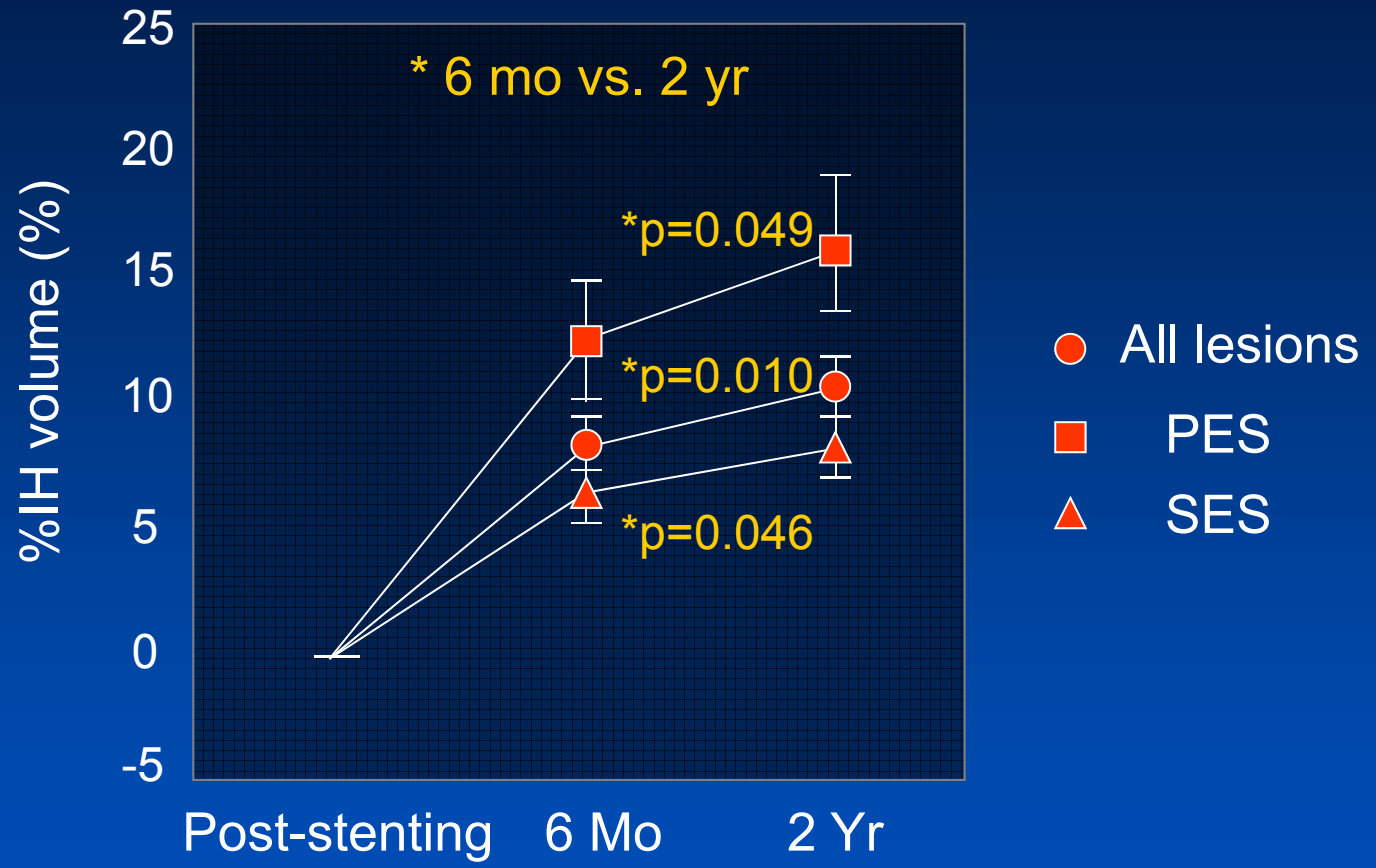
Tri-phasic MLD Response



Early restenosis phase until 6 months
intermediate-term regression phase
late re-narrowing phase beyond 3 years

kimura et al. Circulation 2002;105:2986-91

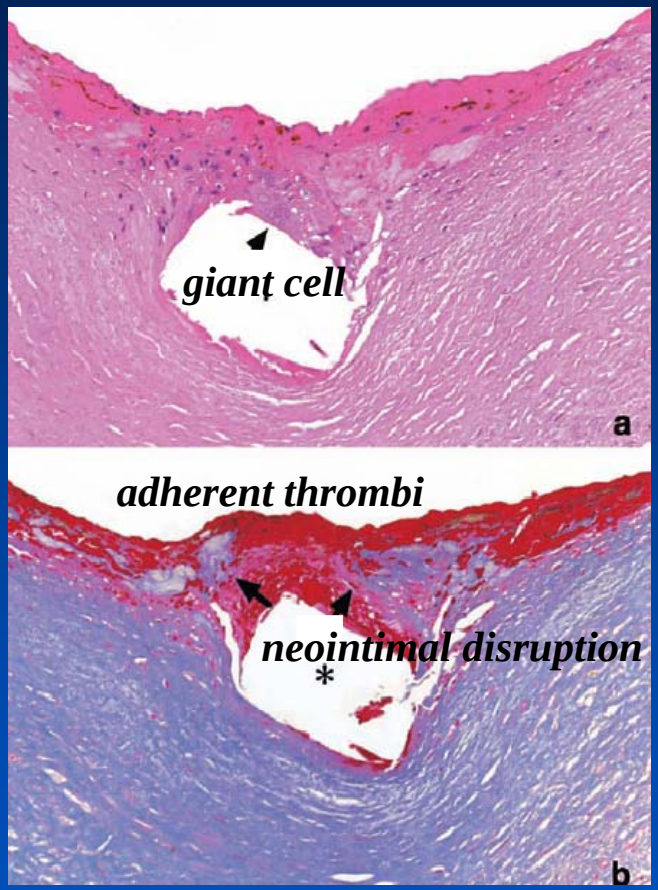
Serial Changes in %IH Volume over 2 Years



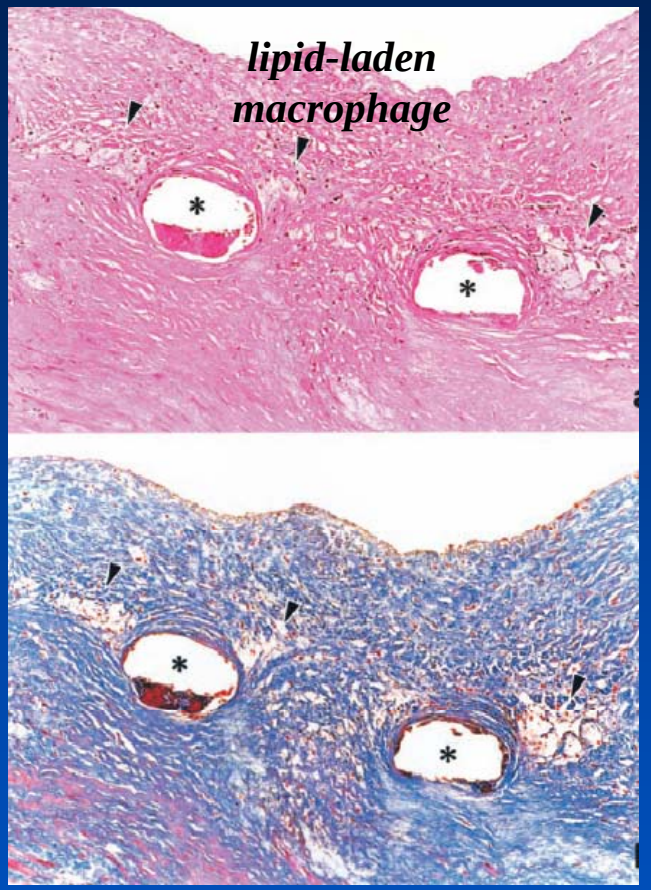
Even though the rate of IH attenuated over time, IH continued to increase beyond 6 months in both DES groups with a modest late catch-up

Late De-Novo Neo-Atherosclerosis

5-year f/u of Palmaz–Schatz



3-year f/u of Palmaz–Schatz



Hasegawa et al. Cathe and Cardiovasc Interv 2006;68:554–8
Inoue et al. Cardiovascular Pathology 2004;14:109–15

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Intravascular Ultrasound Findings in Patients With Very Late Stent Thrombosis After Either Drug-Eluting or Bare-Metal Stent Implantation

30 AMI patients with VLST

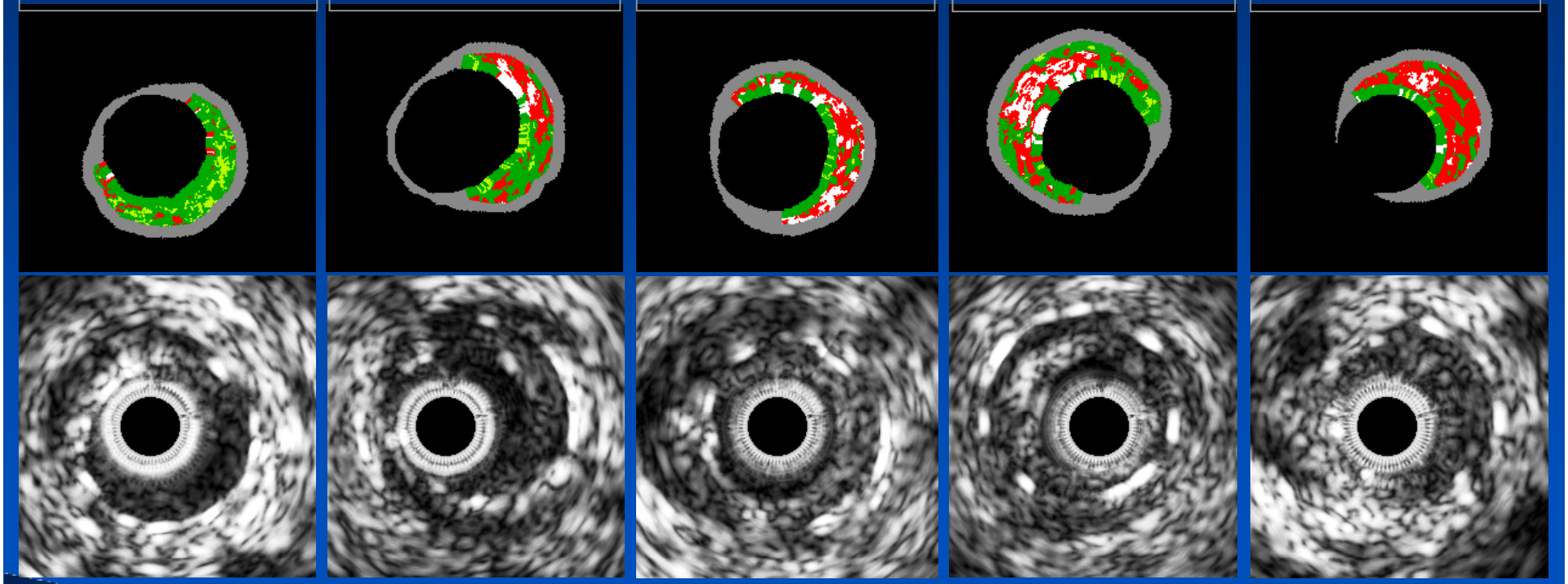
	DES (n=23)	BMS (n=7)	*p*-value
Mean EEM CSA, mm^2	19.55±6.07	18.31±4.17	0.774
Mean Lumen CSA, mm^2	4.20±1.40	4.73±4.64	0.564
Mean Neointima, mm^2	3.07±1.15	5.03±1.78	0.014
Minimal stent CSA, mm^2	6.15±1.58	7.42±3.77	0.413
Neointima rupture	**10 (43.7%)**	**7 (100%)**	**0.010**

Lee CW et al. J Am Coll Cardiol 2010;55:1936-42

Tissue Characterization of Neointima in In-Stent Restenosis Using VH-IVUS

Neointimal VH Composition at the Maximal %IH Site

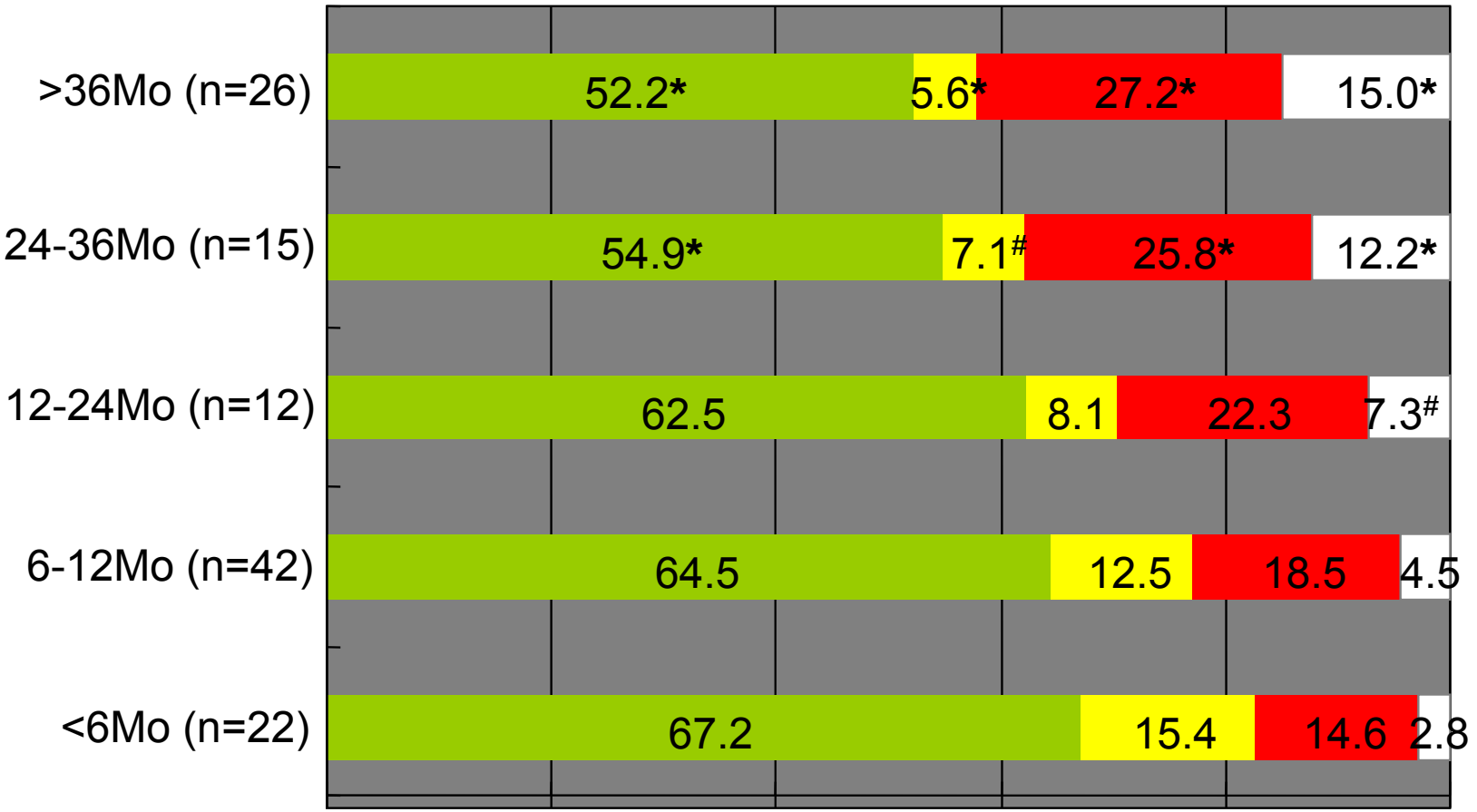
6-mo Taxus	9-mo Taxus	22-mo Taxus	48-mo BMS	57-mo BMS
%NC 8%	%NC 28%	%NC 39%	%NC 40%	%NC 57%
%DC 2%	%DC 8%	%DC 20%	%DC 25%	%DC 15%



Kang SJ et al. AJC 2010 Accepted

Neointimal Composition at Various FU Time

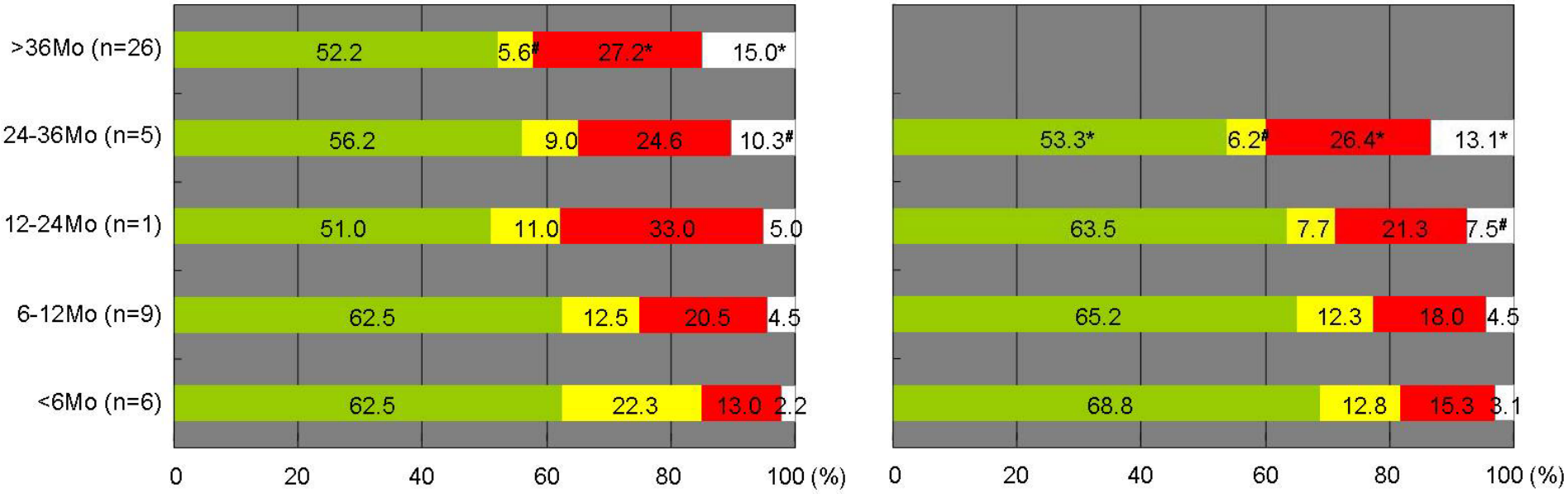
Overall 117 ISR Lesions with both BMS and DES



Neointimal content of %NC and %DC significantly increased over time, suggesting neo-atherosclerosis in extended follow-up period

47 BMS-treated ISR

70 DES-treated ISR



*p<0.01 and #p<0.05, vs. lesions at follow-up time <6 months

Kang SJ et al. AJC 2010 Accepted

Multivariable Analysis

- Longer follow-up time (β=0.938, p=0.001)
- Older age (β=0.300, p=0.023)
- Male gender (β=5.238, p=0.028)

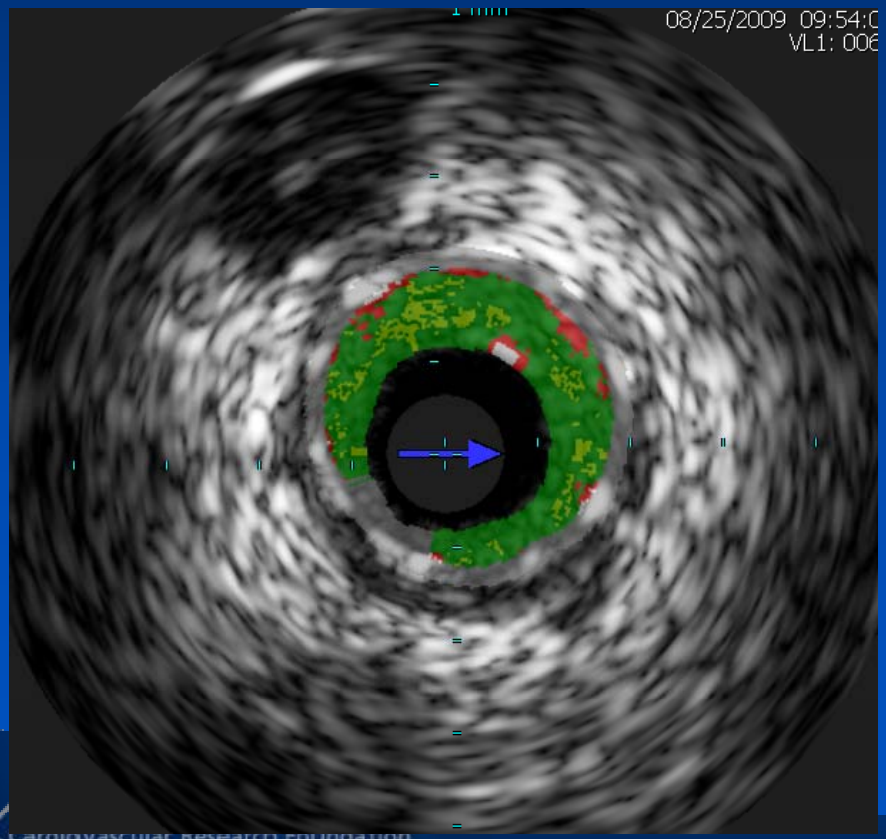
→ *associated with %NC at the max %IH sites*

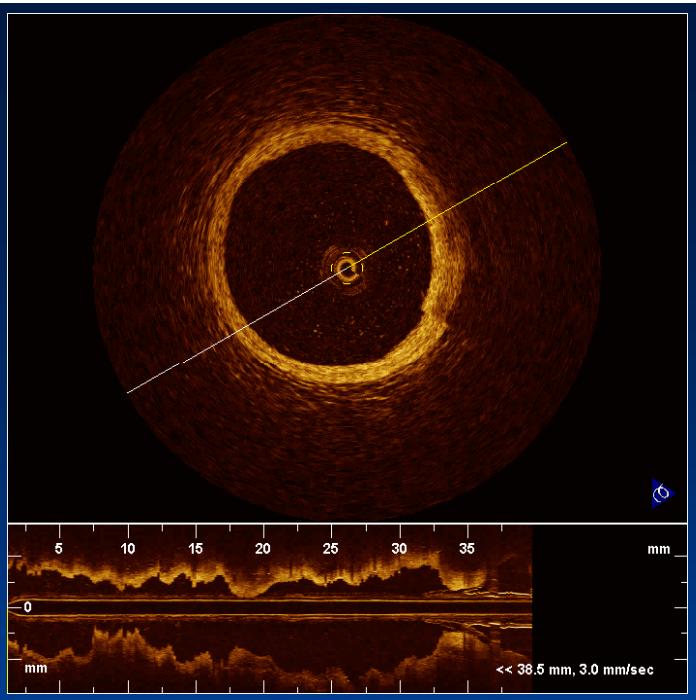
Neo-atheromatous degeneration and increase in vulnerability with aging of stent

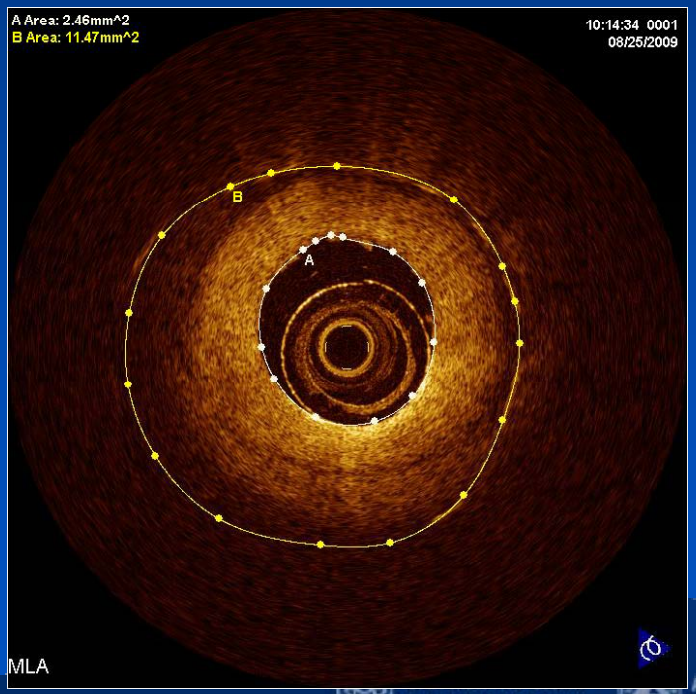
Kang SJ et al. AJC 2010 Accepted

54/Male
ISR with Stable Angina

- 8MA DES at mLAD





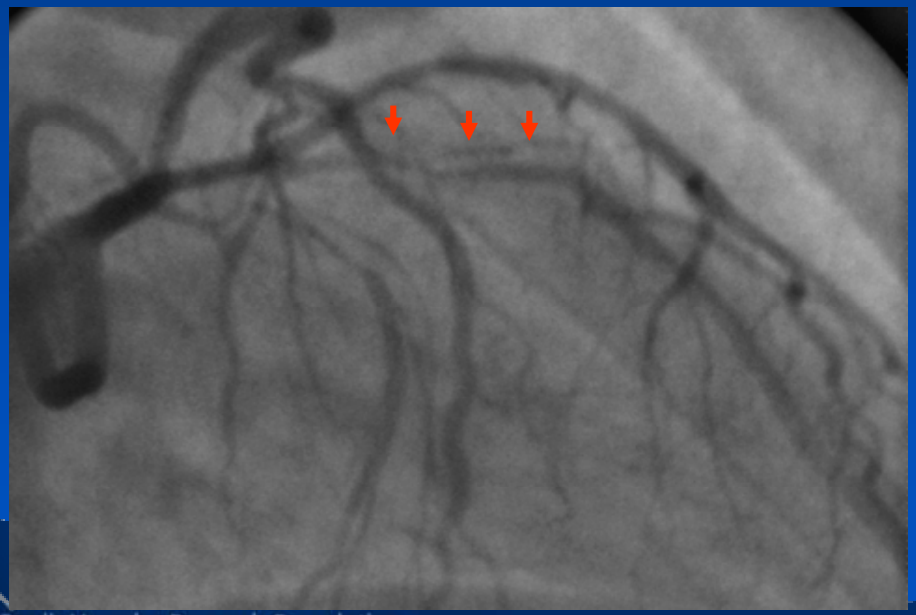


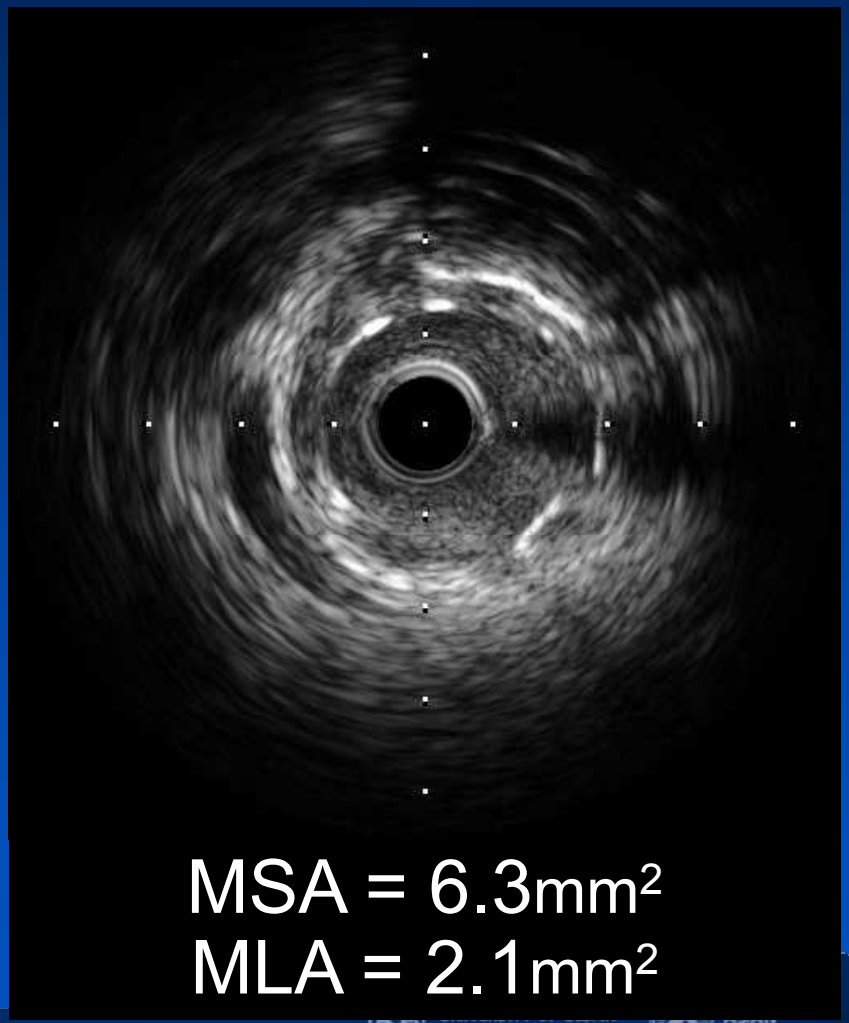
71 Year-Old Female

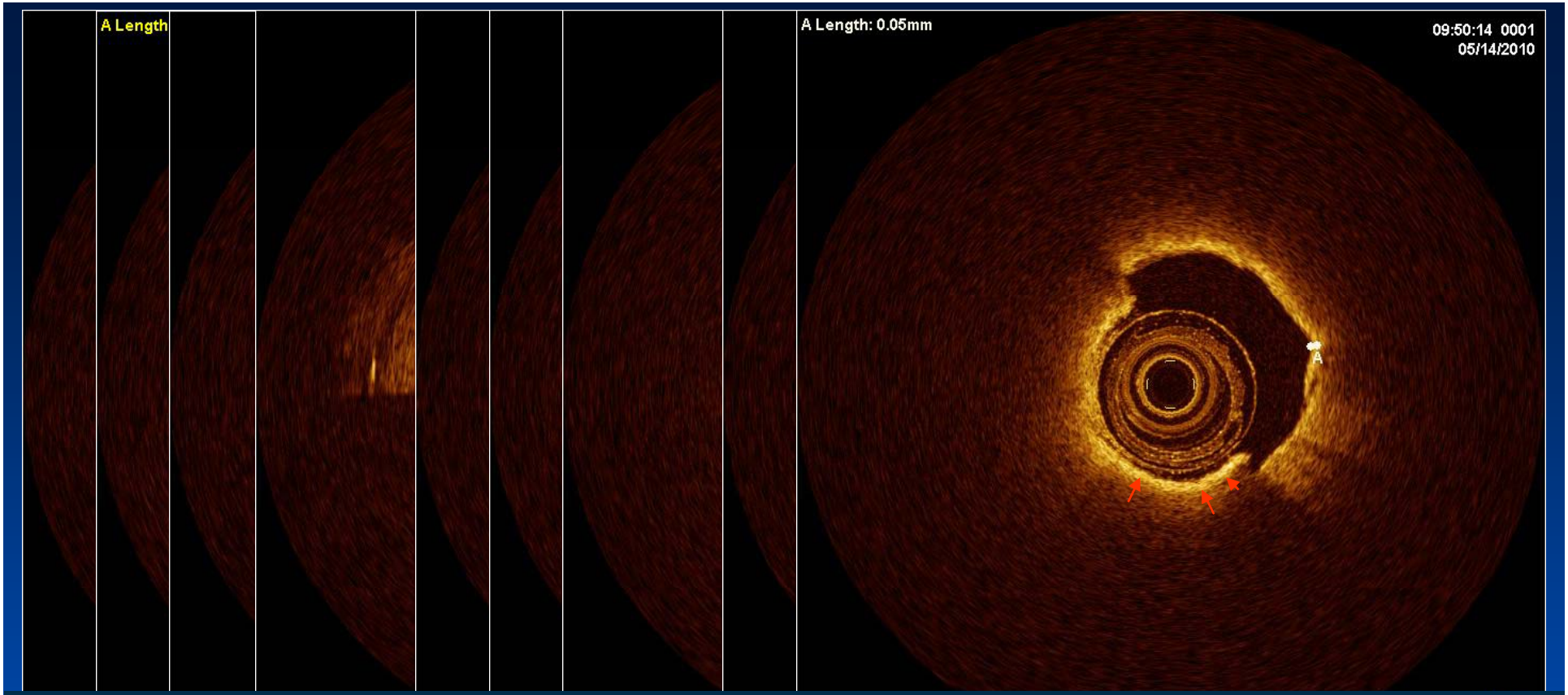
- 8YA Stable angina →s/p BMS at mLAD
- 7YA mLAD diffuse ISR → triple anti-platelet
- 1WA resting chest pain
- Cardiac enzyme: normal

Clinical Diagnosis

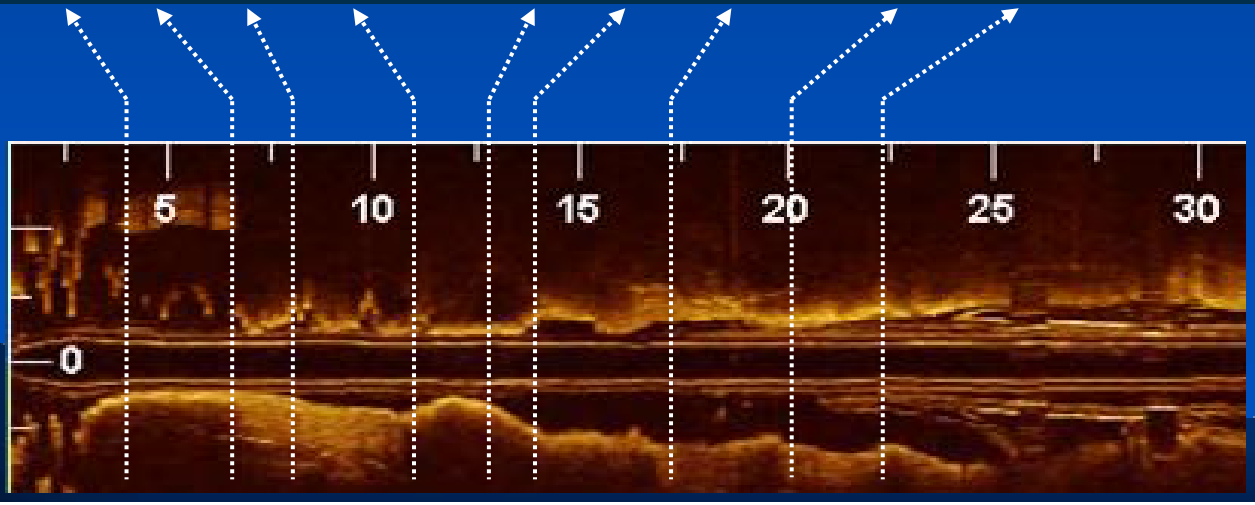
- **Unstable Angina**







In-Stent Neo-atherosclerosis with Vulnerable Intima



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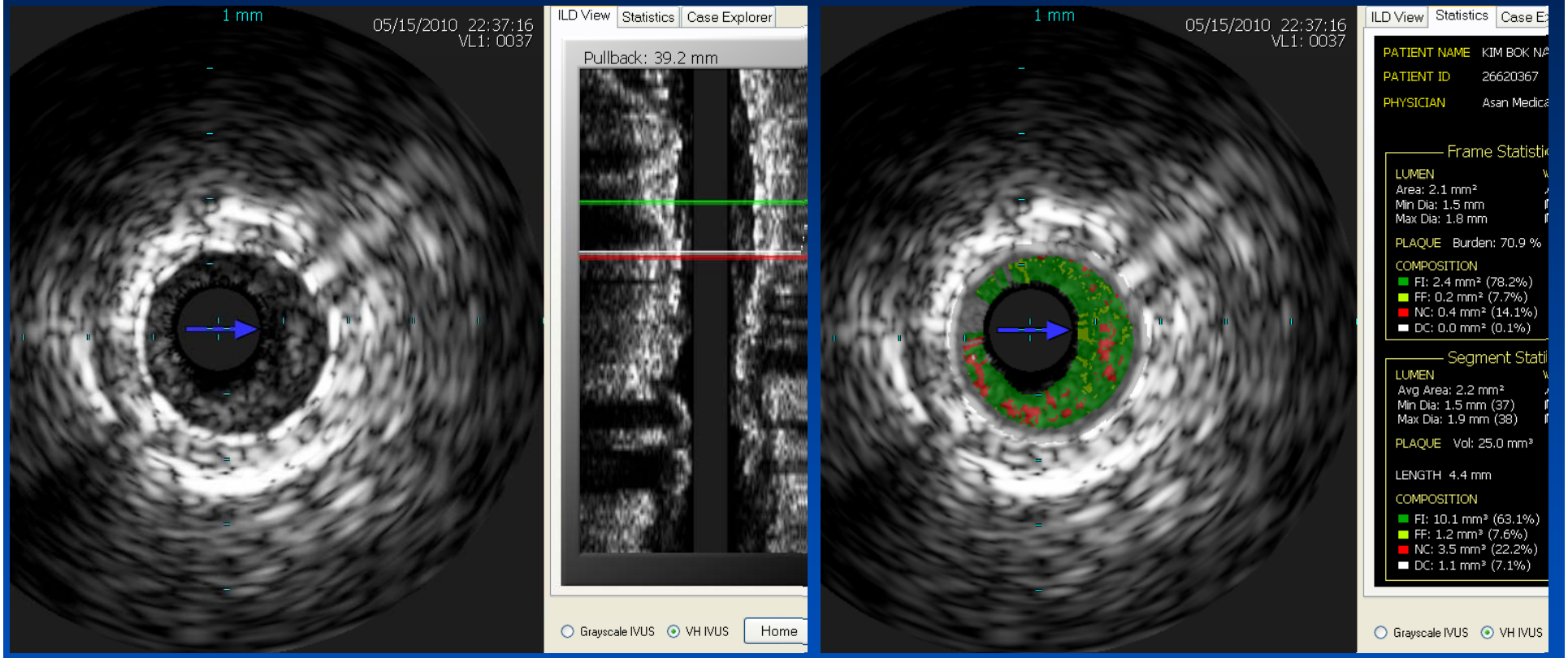
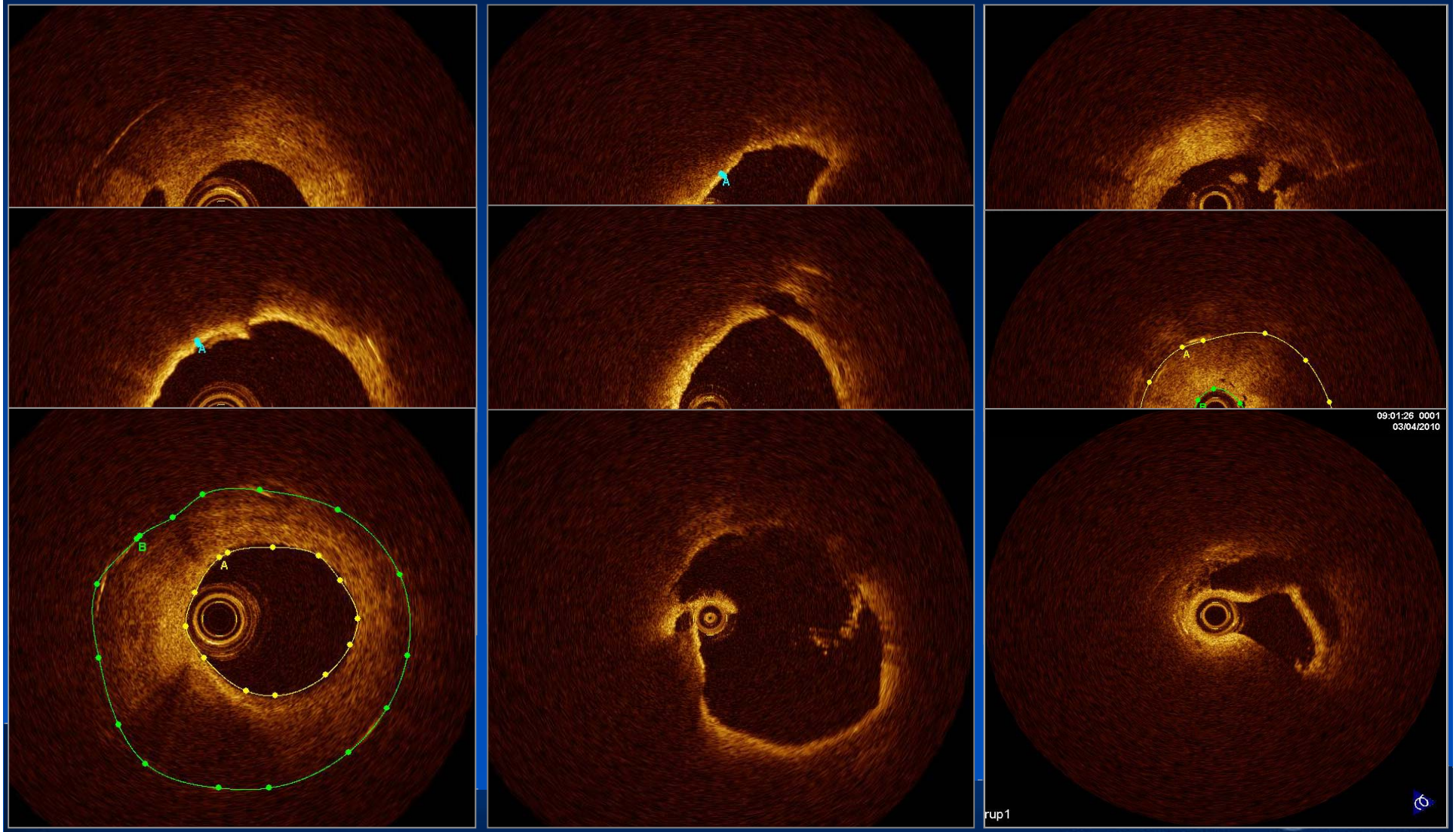
Virtual Histology



Tissue Characteristics in DES-Failure

71/M, **Stable Angina**	37/M, **Unstable Angina**	60/M, **NSTEMI**
5YA DES at RCA	8YA BMS at LAD	7YA DES at RCA



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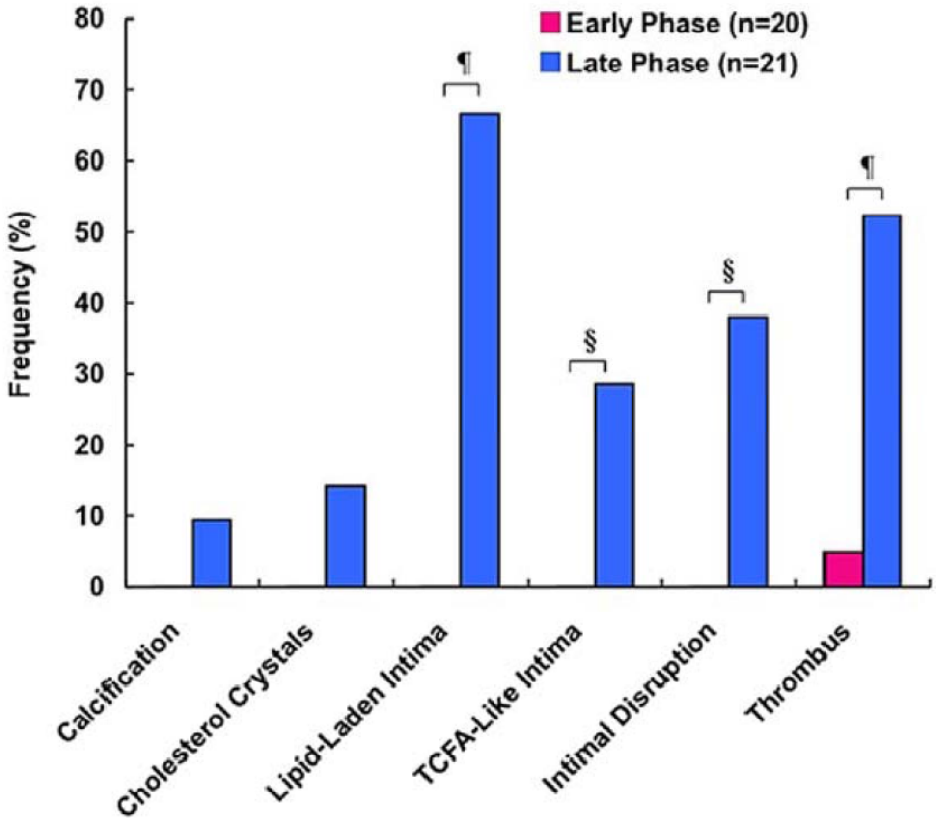
CLINICAL RESEARCH — Interventional Cardiology

Appearance of Lipid-Laden Intima and Neovascularization After Implantation of Bare-Metal Stents

Extended Late-Phase Observation by Intracoronary Optical Coherence Tomography



- Neointima transforms into lipid-laden atherosclerotic tissue in extended phase
- Lipid-laden intima frequently has intimal disruption, thrombi and neovascularization

Takano et al. J Am Coll Cardiol 2009;55:26-32

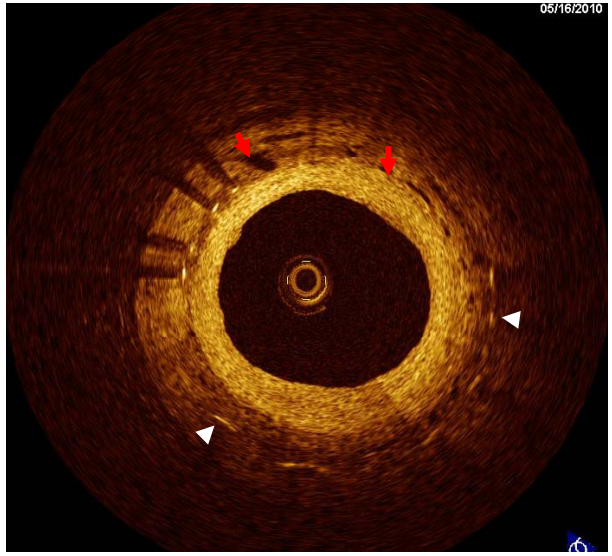
Optical Coherent Tomographic Analysis of In-stent Neo-atherosclerosis in Patients with DES Failure: From In-Stent Restenosis to Very Late Stent Thrombosis

- The aim of the study was to assess OCT findings of in-stent neointima in DES-treated restenotic lesions with significant intimal tissue (%IH>50%)

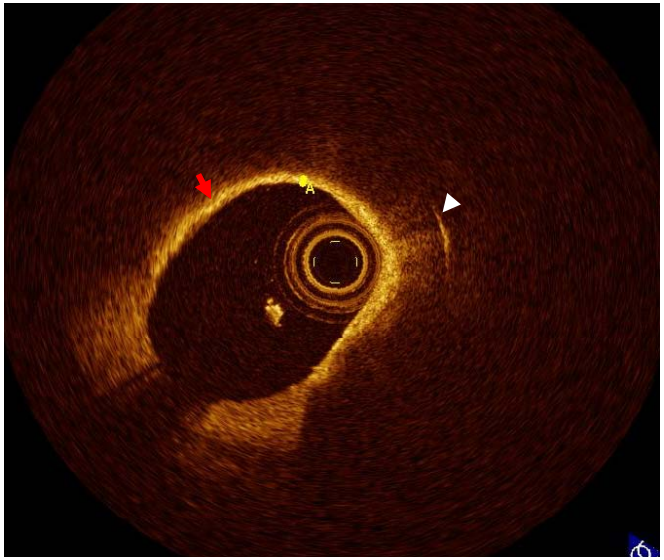
Exclusion : hemodynamic instability, inability of OCT-wire to cross the lesion due to tight stenosis or tortousity, LM or SVG, or angiographically visible thrombi with embolic risk, thrombotic occlusion without intima, ISR with dominant underexpansion

Methods : OCT Definition

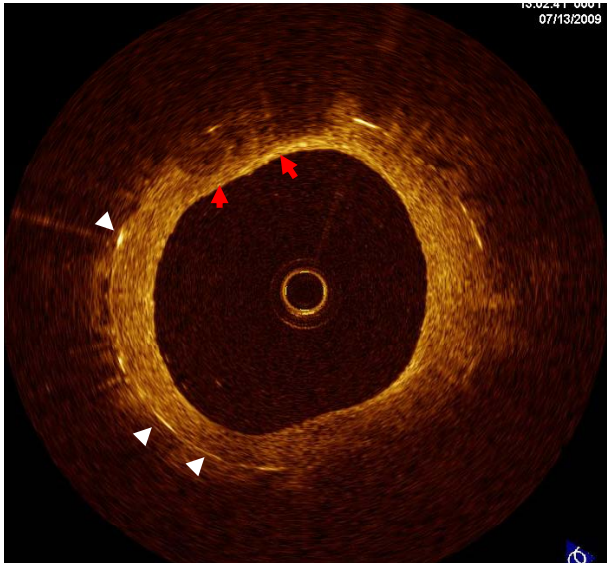
Microvessel



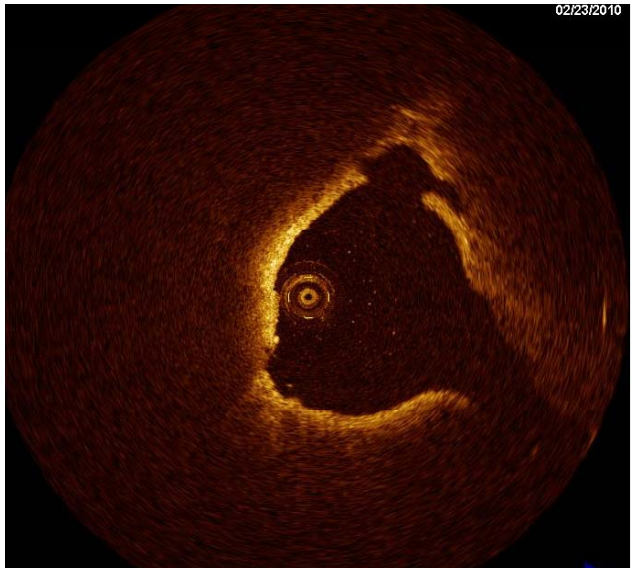
TCFA-like neointima

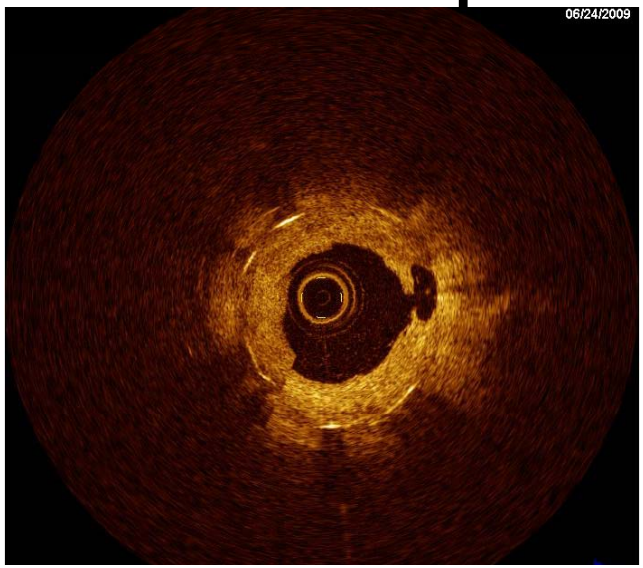


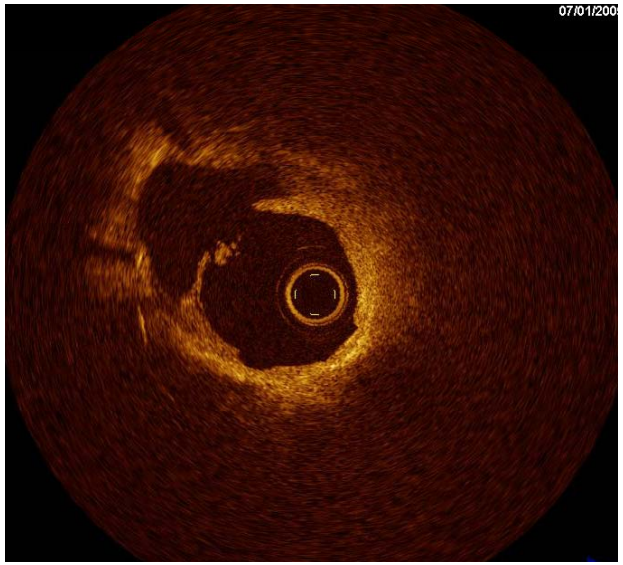
Calcium



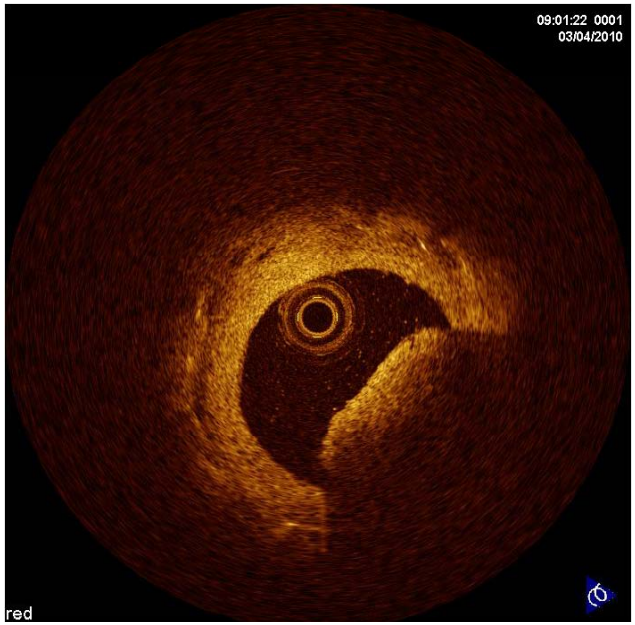
Neointimal rupture

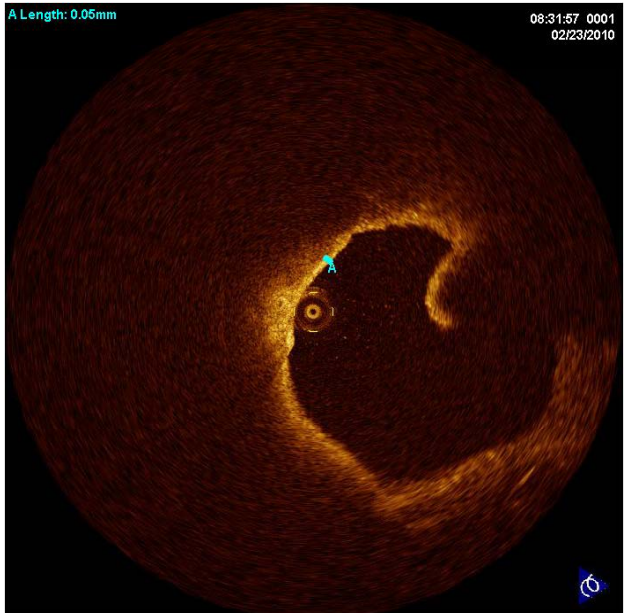


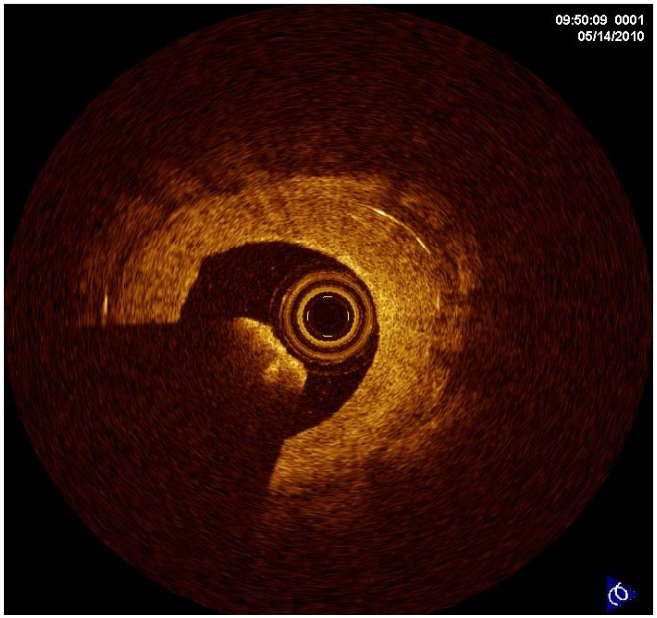




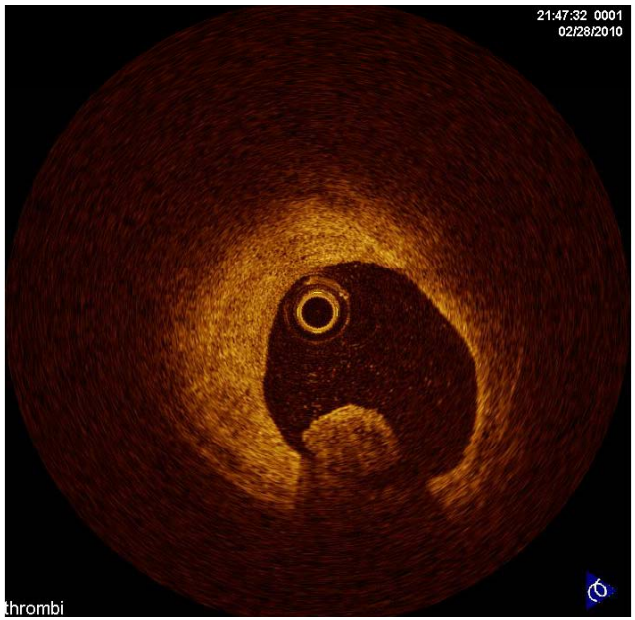
Red thrombus

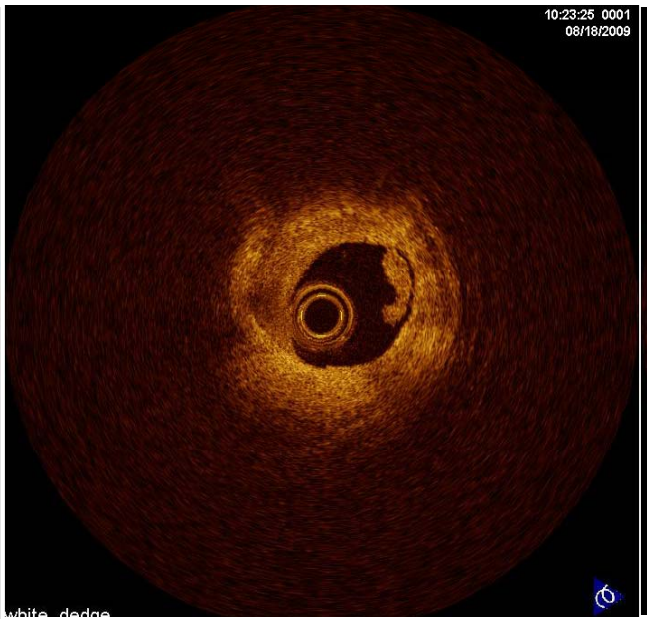


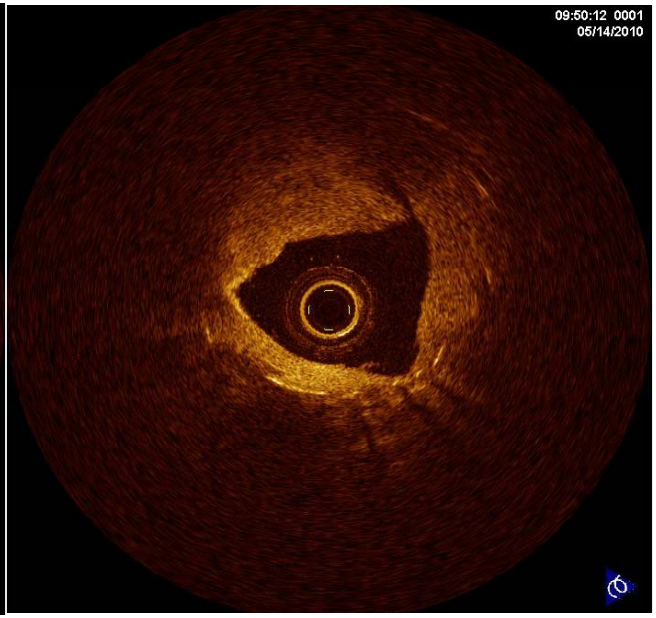




White thrombus







Results

- All 53 lesions with angiographic restenosis after DES implantation contained significant intima (%IH>50%)
- Follow-up time: 35.5±25.3 months (4.1-80.3 months)

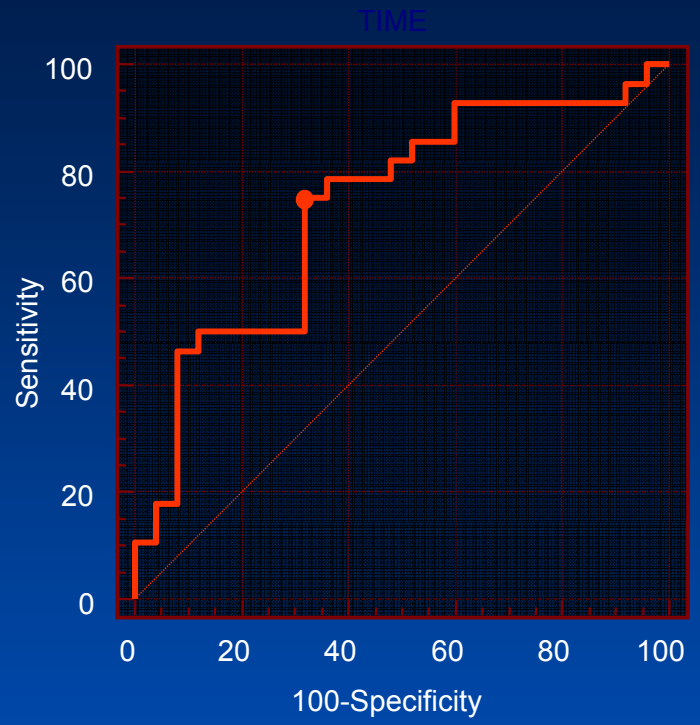
Clinical presentation

- Stable angina in 27 (51%)
- Unstable angina in 14 (26%)
- NSTEMI in 4 (8%)
- STEMI in 8 (15%)

DES Restenosis

Very Late Stent Thrombosis
(AMI>12 months after stenting)

TCFA-Like Intima in 28 (53%) Lesions



The best cut-off value of follow-up duration to predict TCFA was **19.5 months** (AUC=0.73)

Sensitivity 75%, Specificity 68%, PPV 72%, NPV 71%

OCT Findings According to Clinical Presentation

	Total	Clinical presentation		
		Non-ACS	ACS	P value†
N	53	27	26	
Lipid-containing neointima, N (%)	48 (91%)	23 (86%)	25 (96%)	0.187
Calcium, N (%)	6 (11%)	2 (7%)	4 (15%)	0.316
Min. thickness of fibrous cap, μm*	107.3±79.5	110(60-200)	60(50-85)	0.028
Incidence of thrombi, N (%)	35 (66%)	13 (48%)	22 (85%)	<0.001
Incidence of red thrombi, N (%)	20 (38%)	3 (11%)	17 (65%)	<0.001
Maximal area of thrombi, mm^2 *	1.6±1.5	0.4 (0.3-0.9)	1.7 (1.0-3.6)	0.001
Intimal rupture, N (%)	34 (64%)	15 (56%)	19 (73%)	0.148
Multiple ruptures, N (%)	15 (28%)	5 (19%)	10 (39%)	0.095
Incidence of TCFA, N (%)	28 (53%)	9 (33%)	19 (73%)	0.004
Multiple TCFA, N (%)	8 (15%)	4 (15%)	4 (15%)	0.626

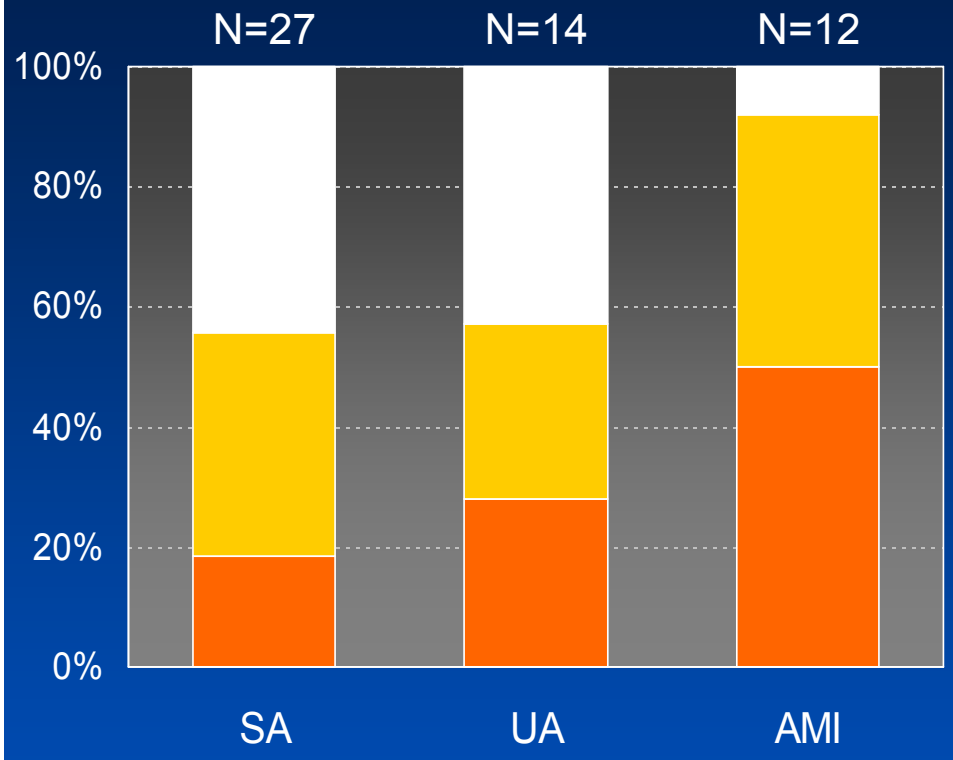
* Median value (inter-quartile range)
†Non-parametric, Mann-Whitney test

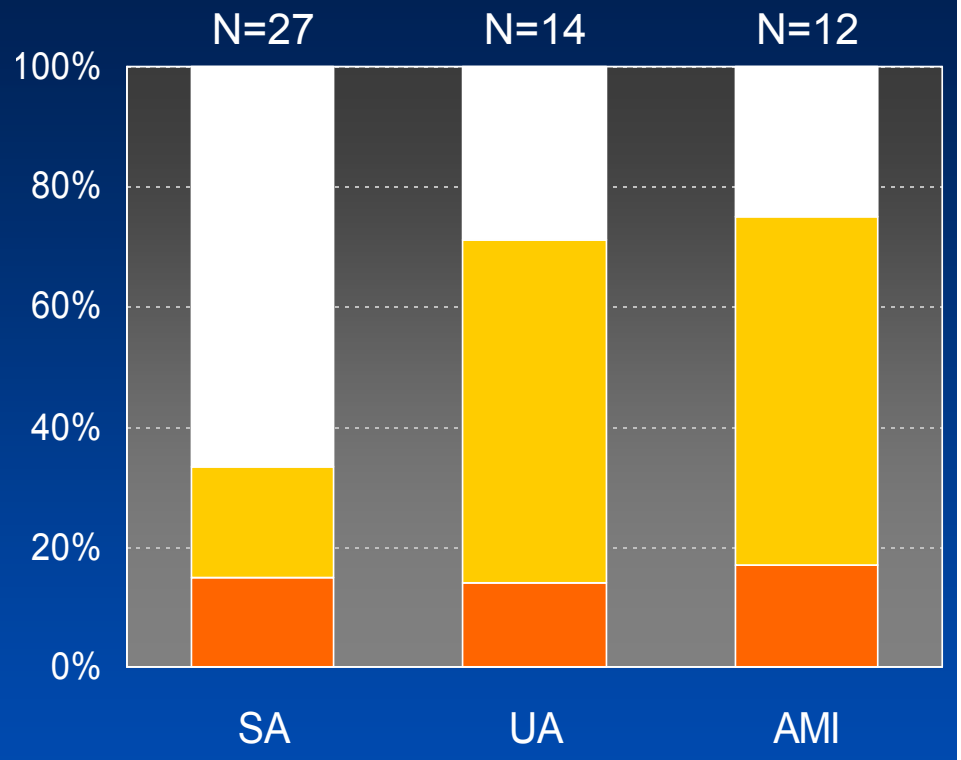
OCT Findings According to Follow-up Time

	Total	Follow-up time		
		<19.5 months	≥19.5months	P value†
N	53	24	29	
Lipid neointima, N (%)	48 (91%)	21 (87%)	27 (93%)	0.409
Calcium, N (%)	6 (11%)	1 (4%)	5 (17%)	0.145
Min. thickness of fibrous cap, μm*	107.3±79.5	110 (60-220)	60 (50-98)	0.016
Incidence of thrombi, N (%)	35 (66%)	13 (54%)	22 (76%)	0.031
Incidence of red thrombi, N (%)	20 (38%)	5 (21%)	15 (52%)	0.017
Maximal area of thrombi, mm^2 *	1.6±1.5	0.6 (0.3-1.0)	1.5 (0.7-3.6)	0.020
Incidence of intimal rupture, N (%)	34 (64%)	13 (54%)	21 (72%)	0.168
Multiple ruptures, N (%)	15 (28%)	4 (17%)	11 (38%)	0.079
Incidence of TCFA, N (%)	28 (53%)	7 (29%)	21 (72%)	0.002
Incidence of multiple TCFA, N (%)	8 (15%)	1 (4%)	7 (24%)	0.043

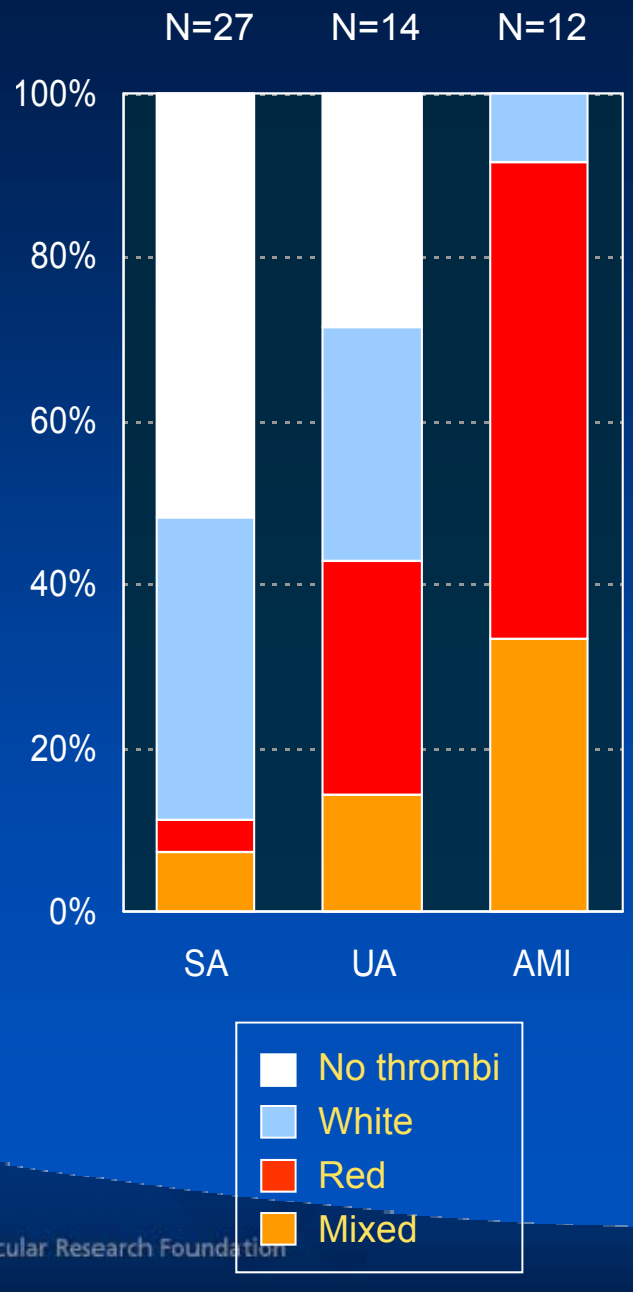
* Median value (inter-quartile range)
†Non-parametric, Mann-Whitney test

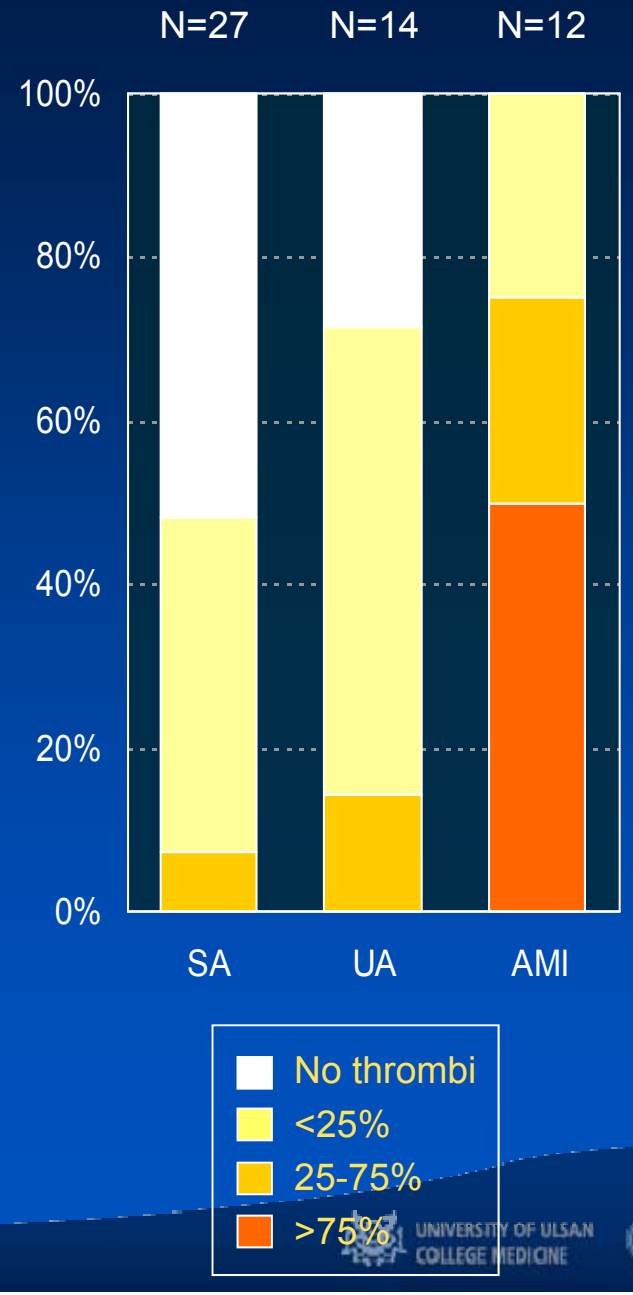
Frequency of TCFA-Like Intima and Intimal Rupture
According to the Clinical Presentation





Frequency of Thrombi





Summary

- TCFA-like neointima, intimal rupture and thrombi were frequent OCT findings in the DES-treated lesions with either ISR or VLST
- In-stent neo-atherosclerosis with highly vulnerable intima over time may be an important common mechanism of DES failure with a broad spectrum of clinical presentations from stable angina to AMI