

In-Stent Neoatherosclerosis as a Mechanism of Stent Failure

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Disclosure

I have nothing to disclose

CASE 68 Year-Old Male

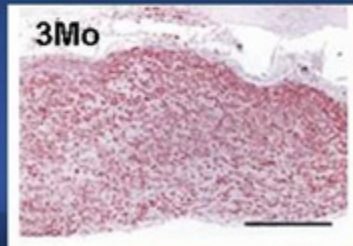
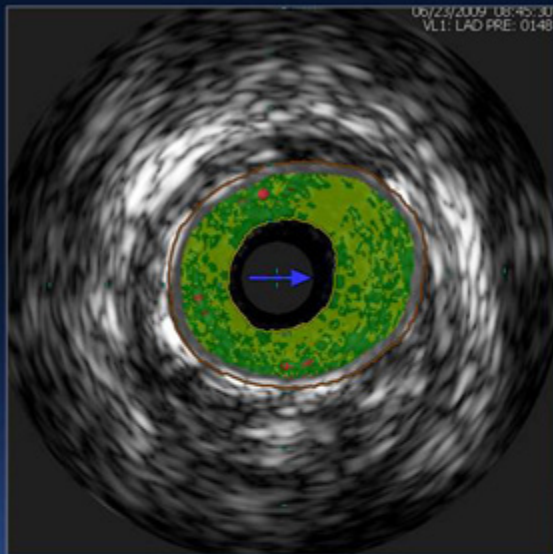
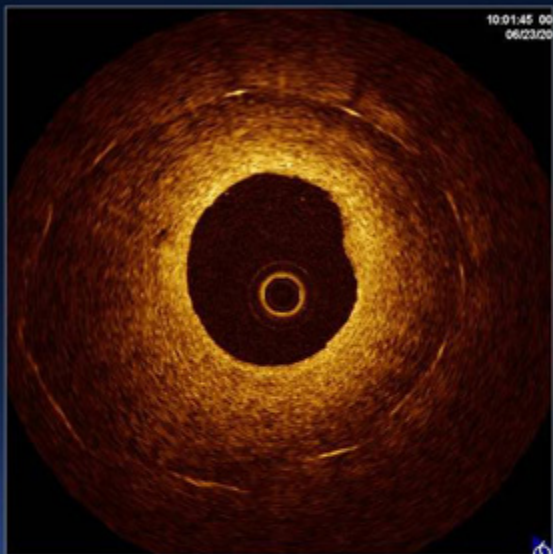
Present illness

- 6MA Stable angina → Taxus 4.0(20) mm at mLAD
- Asymptomatic ISR

Risk factors

- Smoking (+) Hypertension(+)





Proteoglycan-rich SMC proliferation

CASE 68 Year-Old Male

Chief complaint

- Chest pain

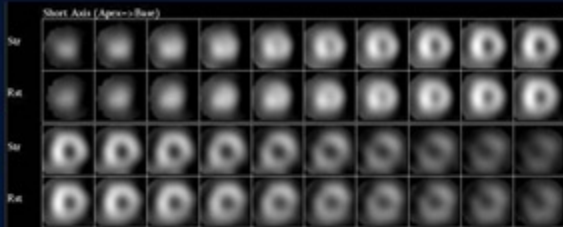
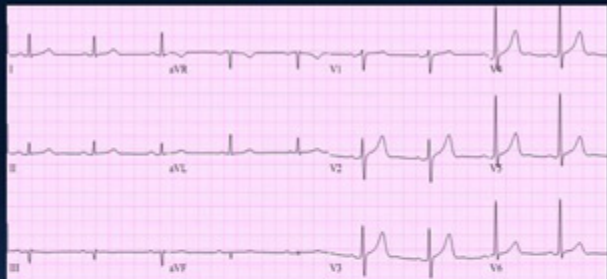
Present illness

- 7YA s/p DES implantation at p-mLAD
- 3YA Unstable angina → s/p Taxus at pRCA, dLCX
- 2MA Frequent, minimal effort-related chest pain

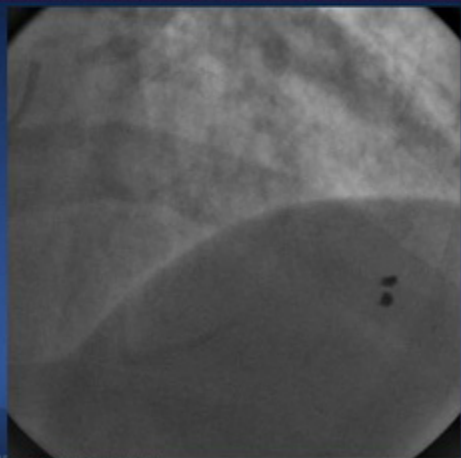
Risk factors

- Hypertension(+)

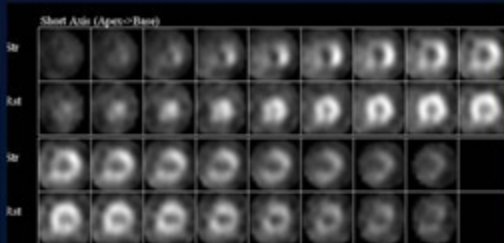
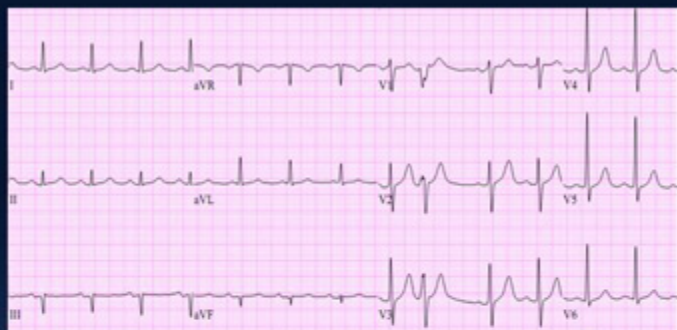
Last F/U Studies 2 years ago



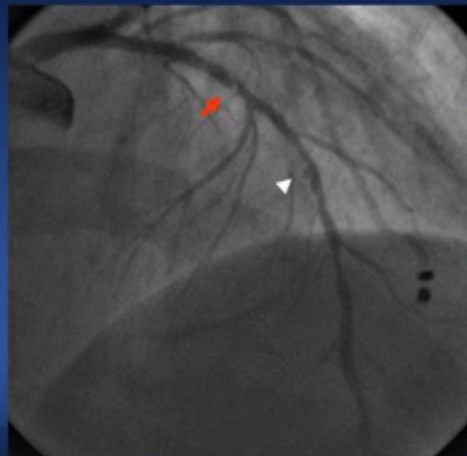
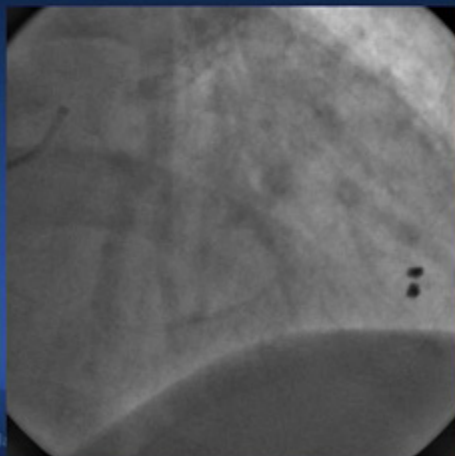
Fixed small sized perfusion
defect in basal inferolateral wall



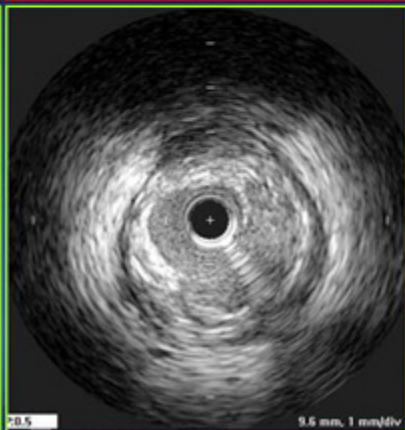
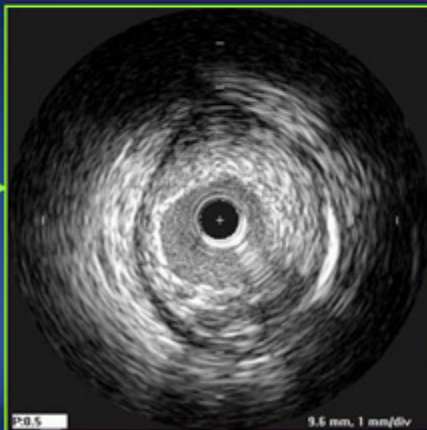
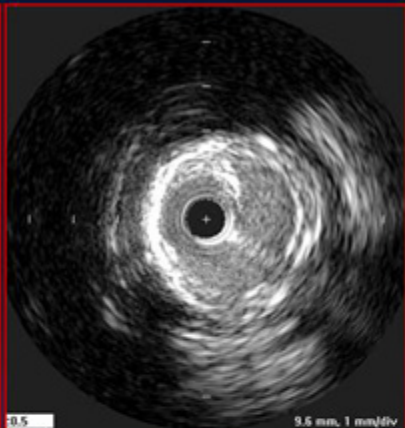
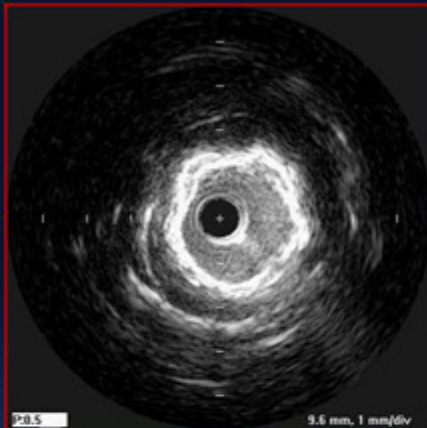
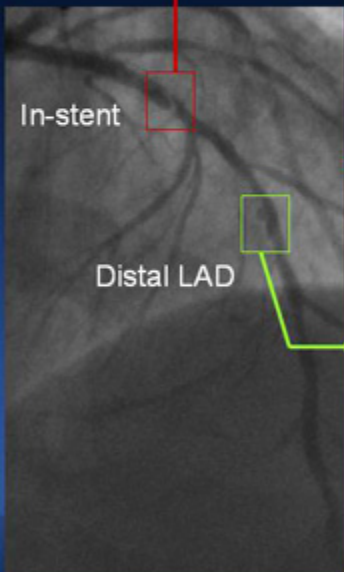
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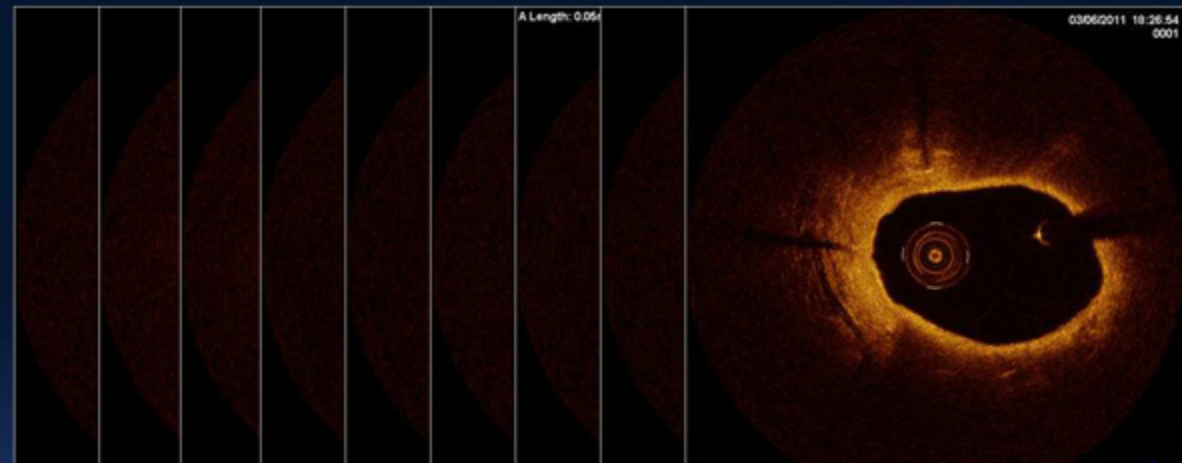


Reversible large sized
perfusion defect in
extensive LAD territories

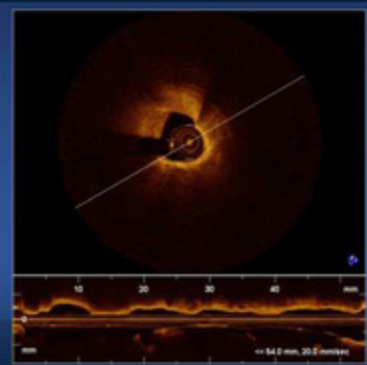
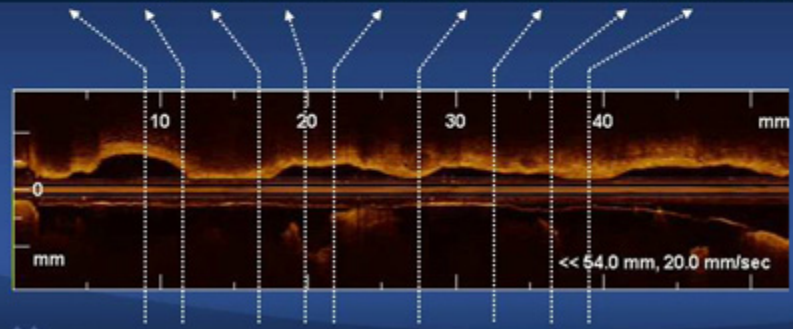


Grayscale IVUS

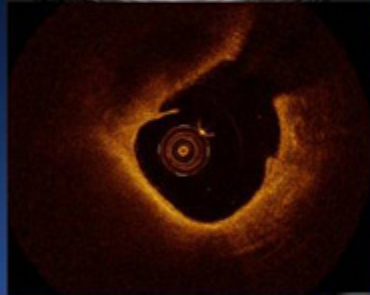




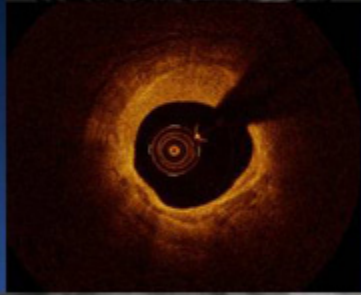
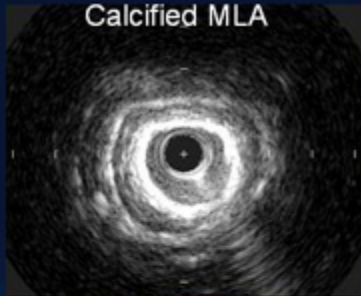
In-Stent Neo-atherosclerosis with Vulnerable Intima



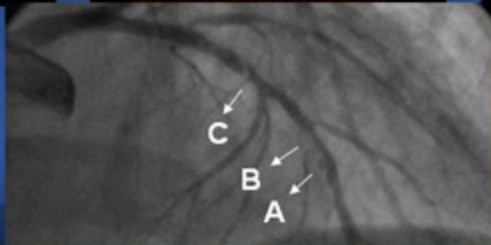
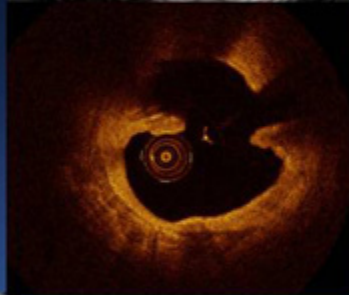
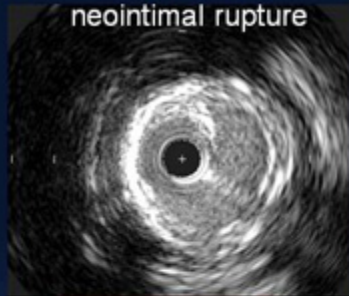
A. Distal LAD
plaque rupture



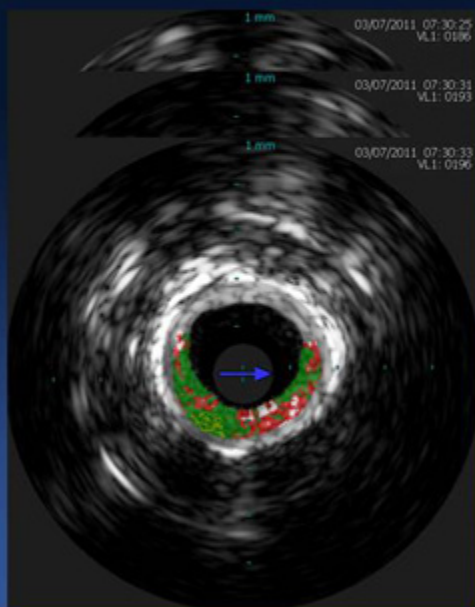
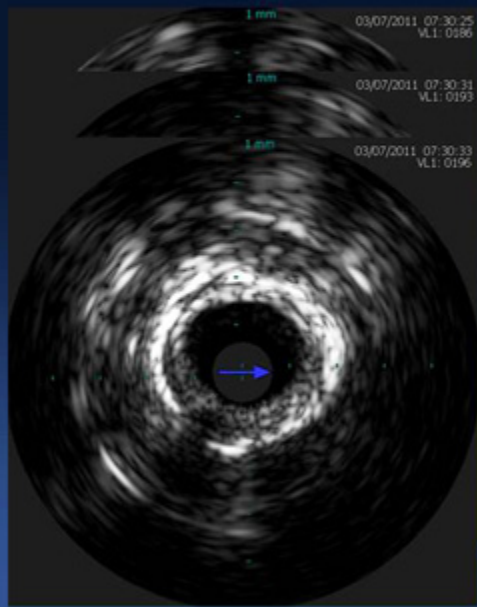
B. Distal LAD
Calcified MLA



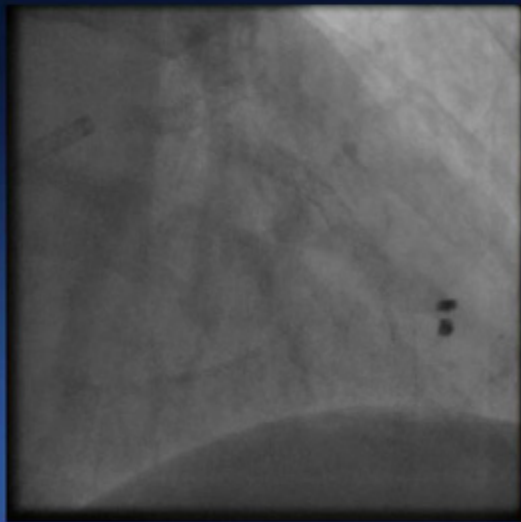
C. In-stent
neointimal rupture



Virtual Histology



- **NOBORI 3.0 (28)mm at distal LAD**
- **NOBORI 3.5 (18)mm, 3.5 (28)mm at mid LAD**



Evolving Neointima after BMS Implantation

Histologic and Angioscopic Evidences

MLD (mm)

4.0

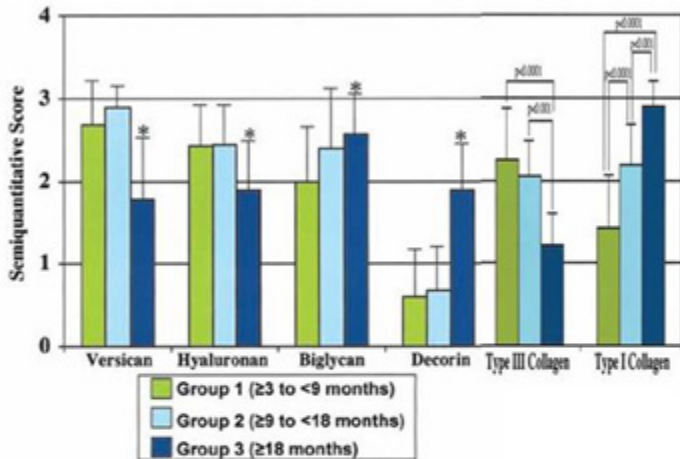
3.0

2.0

1.0

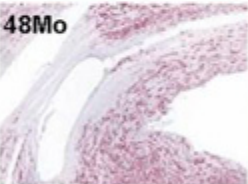
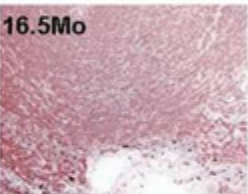
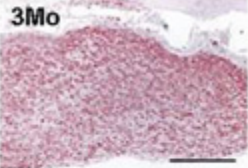
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Extracellular Matrix Changes in In-Stent Neointima



ECM modulates developing neointima with SMC proliferation, migration, growth factor expression, and remodeling

α -Actin (+) SMC



Pathologic mechanism

Proteoglycan-rich SMC proliferation

- * Proteoglycan ↓
- * Cellularity ↓
- * Neointimal thinning

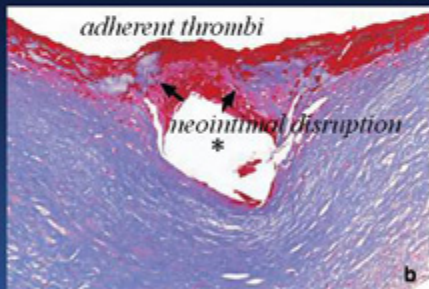
de-novo neoatherosclerosis

Pathologic Definition of “Neoatherosclerosis”

Peri-strut **foamy macrophage clusters** with or without calcification, fibroatheroma, and ruptures with thrombosis in in-stent neointima



5-year f/u of Palmaz-Schatz

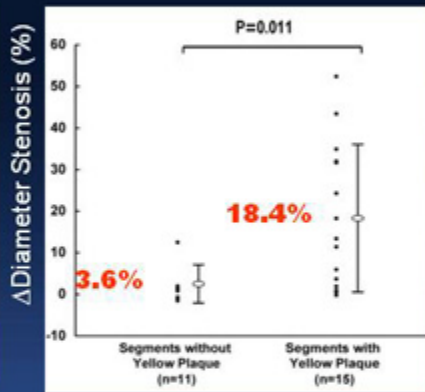
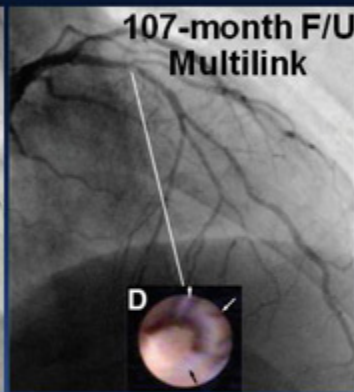
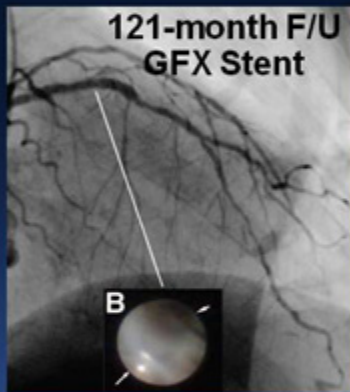


3-year f/u of Palmaz-Schatz

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

Atherosclerotic Transformation after BMS Implantation

Serial Angioscopic Observation at Extended Follow-Up



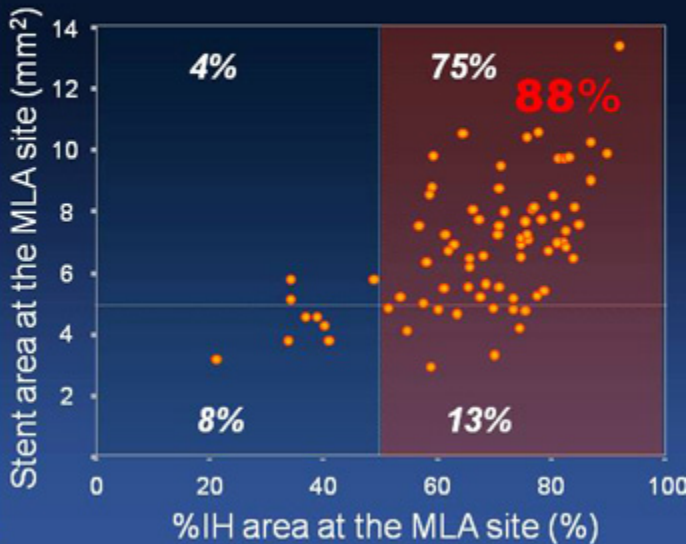
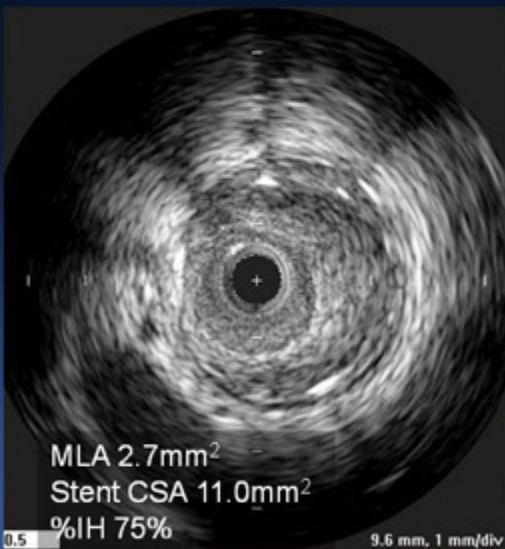
- White neointima often changes into yellow plaque over time
- Late luminal narrowing ($\Delta\%DS$) between early (6-12 mo) and late (≥ 4 yr) follow-up is greater in segments with yellow plaque

Intimal Hyperplasia after DES Implantation

Histologic and Angioscopic Evidences

Dominant IH

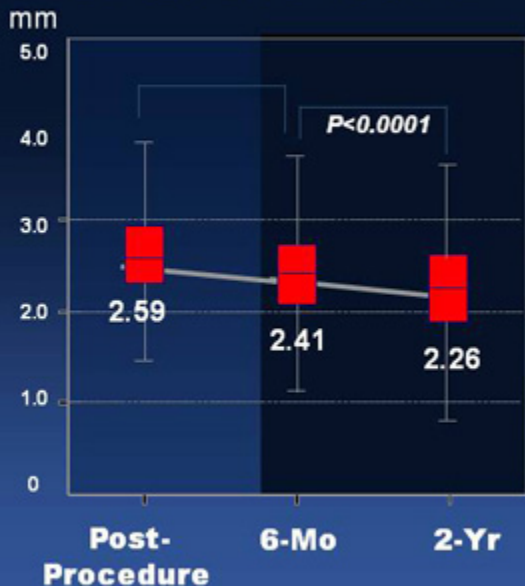
As a General Mechanism of DES-ISR



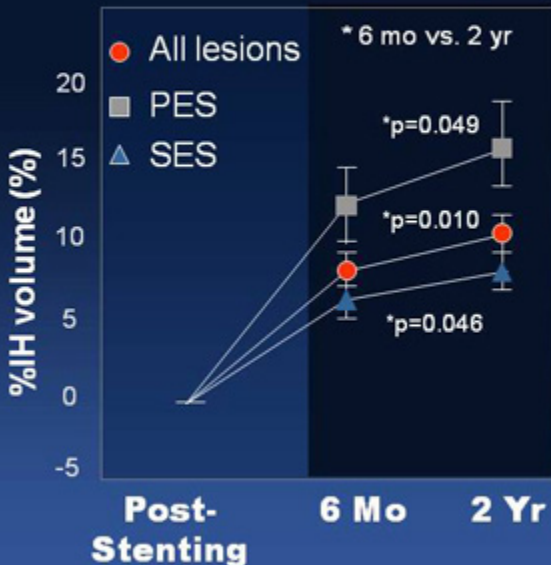
Kang et al. *Circ Cardiovasc Interv* 2011;4:9-14

“Late Catch-up” in DES

Serial F/U of MLD



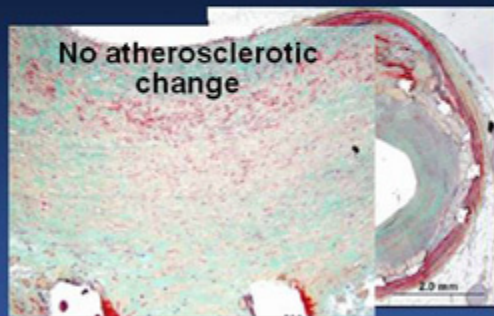
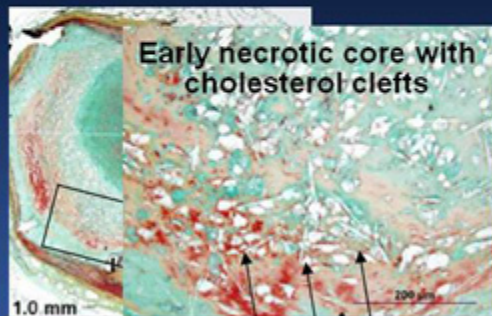
Serial F/U %IH Volume



Early Histopathologic Findings within 1 year between BMS- vs. DES-ISR

Restenotic neointima was composed of proteoglycan-rich SMC with different phenotypes and fibrolipid

Chieffo et al. Am J Cardiol 2009;104:1660-7



Neoatherosclerosis was more frequent in DES-lesions (DES 35% vs. BMS 10%) and occurs earlier

Different Timing of Neoatherosclerosis BMS vs. DES



In addition, the earliest necrotic core formation in DES was observed at 9 months, which was earlier than BMS lesions developed at 5 years

Nakazawa et al. JACC Cardiovasc Imaging 2009;2:625-S

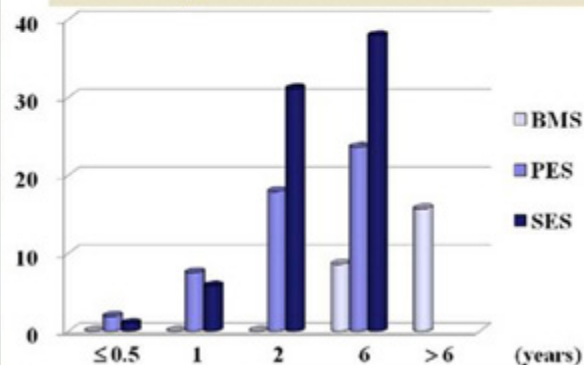
EXPEDITED PUBLICATIONS

The Pathology of Neoatherosclerosis in Human Coronary Implants

Bare-Metal and Drug-Eluting Stents

Gaku Nakazawa, MD,* Fumiya Otsuka, MD,* Masataka Nakano, MD,* Marc Vorpaahl, MD,*
Saami K. Yazdani, PhD,* Elena Ladich, MD,* Frank D. Kolodgie, PhD,* Alok V. Finn, MD,†
Renu Virmani, MD*

Cumulative Incidence of Atherosclerotic Change With Time After Implantation of BMS Versus SES and PES



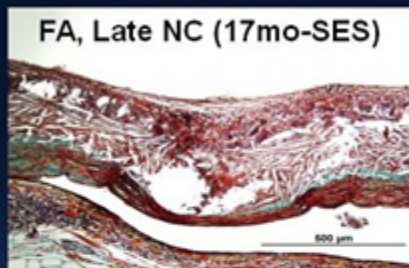
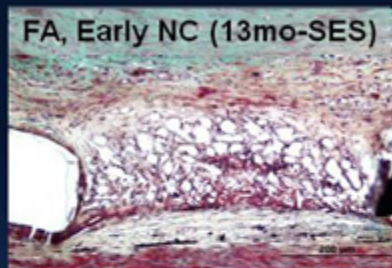
Neoatherosclerosis

	DES	BMS
Incidence	31%	16%
Median F/U time point	14 Mo	72 Mo

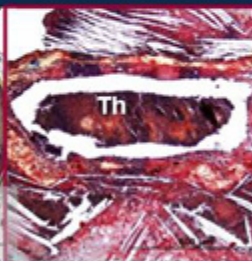
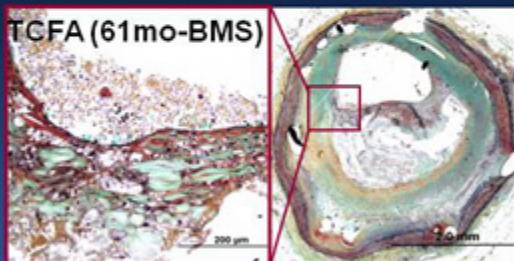
Nakazawa et al. JACC 2011;57:1314-22

Various Stages of Neointimal Hyperplasia

DES



BMS



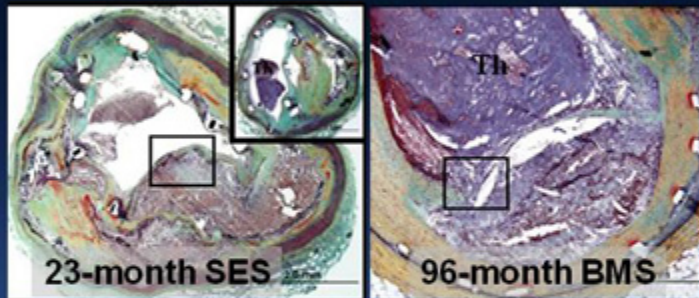
Nakazawa et al. JACC 2011;57:1314-22

Independent Risk Factors for Neointimal Hyperplasia

	OR	95% CI	p
Age, /year	0.963	0.942-0.983	<0.001
Stent duration (/month)	1.028	1.017-1.041	<0.001
SES usage	6.534	3.387-12.591	<0.001
PES usage	3.200	1.584-6.469	0.001
Underlying unstable lesion (rupture, TCFA)	2.387	1.326-4.302	0.004

Nakazawa et al. JACC 2011;57:1314-22

More Advanced Neointimal TCFA-Containing Neointima Intimal rupture Thrombosis



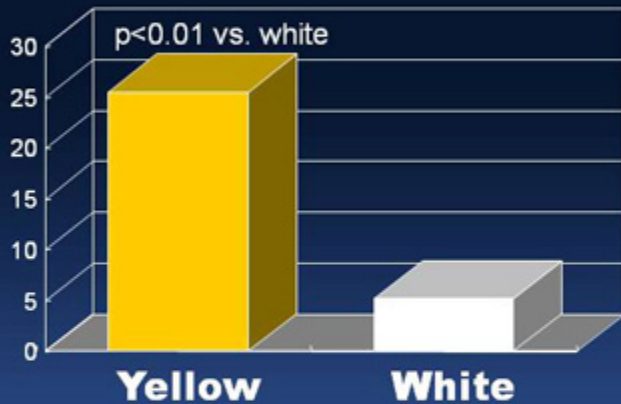
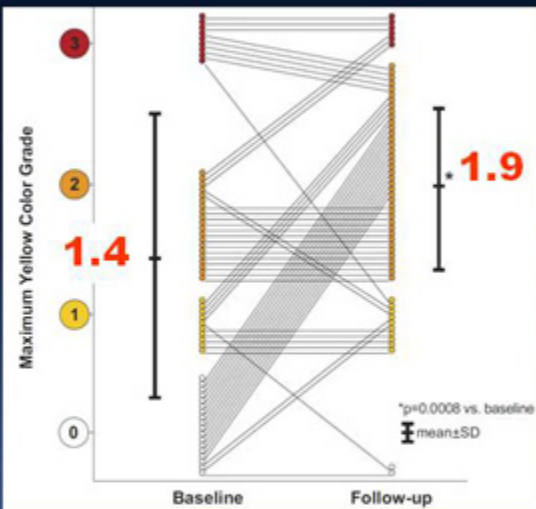
“Unstable Neointima”
>5 years in BMS
≤2 years in DES

Although uncovered struts remains the primary cause of DES-VLST, neointimal rupture may be added as another risk factor

Angioscopic DES Follow-Up at 10 Months

Yellow Grade Changes

Prevalence of Thrombi



The development of atherosclerotic **yellow** plaques may be a possible substrate for **late stent thrombosis**

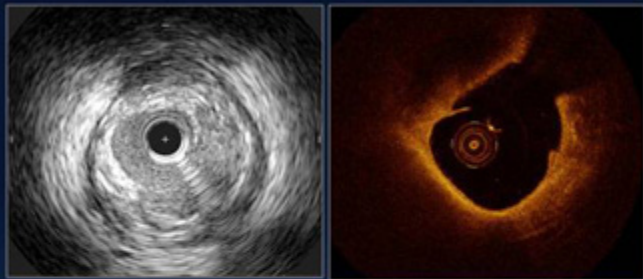
Neoatherosclerosis

Contributing Mechanism of Stent Failure

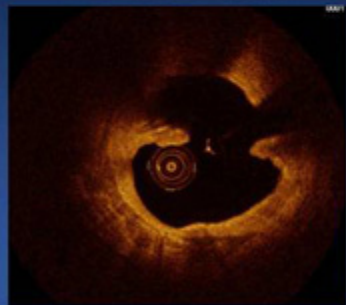
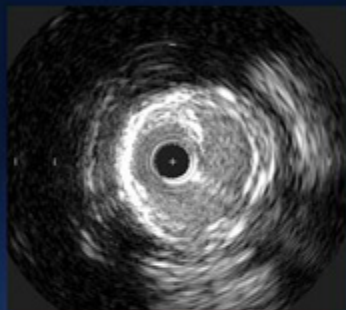
Broad Spectrum of Clinical Presentations

*from In-Stent Restenosis
to Very Late Stent Thrombosis*

Distal LAD plaque rupture

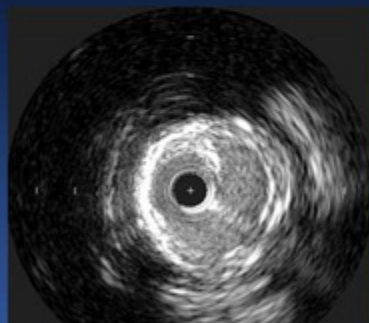


In-stent neointimal rupture



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

30 AMI with VLST (Mean F/U **33 Mo** in DES, **108 Mo** in BMS)



	DES (n=23)	BMS (n=7)
Mean EEM CSA, mm ²	19.5±6.0	18.3±4.1
Mean Lumen CSA, mm ²	4.2±1.4	4.7±4.6
Mean Neointima, mm ²	3.0±1.1	5.0±1.7*
Minimal stent CSA, mm ²	6.1±1.5	7.4±3.7
Neointima rupture	10 (44%)	7 (100%)*

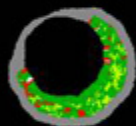
Neoatheroclerosis may contribute to the development of VLST as a common mechanism in BMS and DES

Tissue Characterization of In-Stent Neointima Using Intravascular Ultrasound Radiofrequency Data Analysis

Soo-Jin Kang, MD^a, Gary S. Mintz, MD^b, Duk-Woo Park, MD^a, Seung-Whan Lee, MD^a,
Young-Hak Kim, MD^a, Cheol Whan Lee, MD^a, Ki-Hoon Han, MD^a, Jae-Joong Kim, MD^a,
Seong-Wook Park, MD^a, and Seung-Jung Park, MD^{a,*}

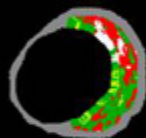
6-mo Taxus

%NC 8%
%DC 2%



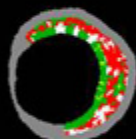
9-mo Taxus

%NC 28%
%DC 8%



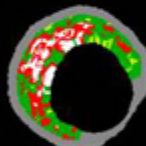
22-mo Taxus

%NC 39%
%DC 20%



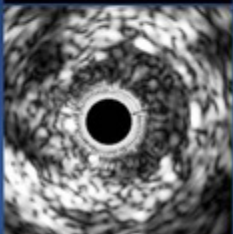
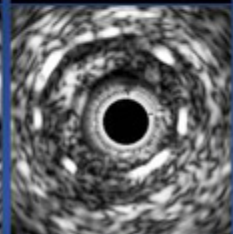
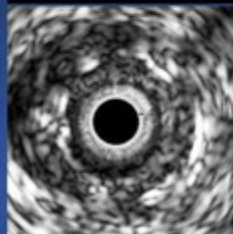
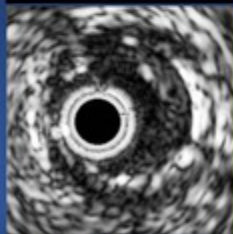
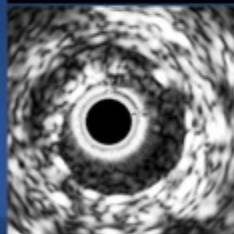
48-mo BMS

%NC 40%
%DC 25%



57-mo BMS

%NC 57%
%DC 15%

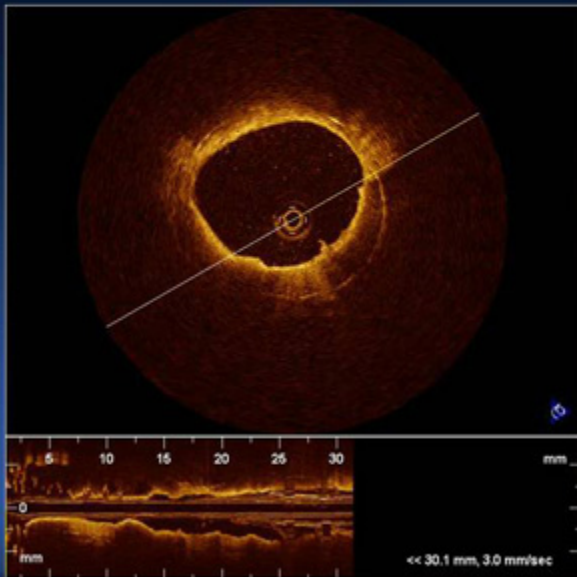
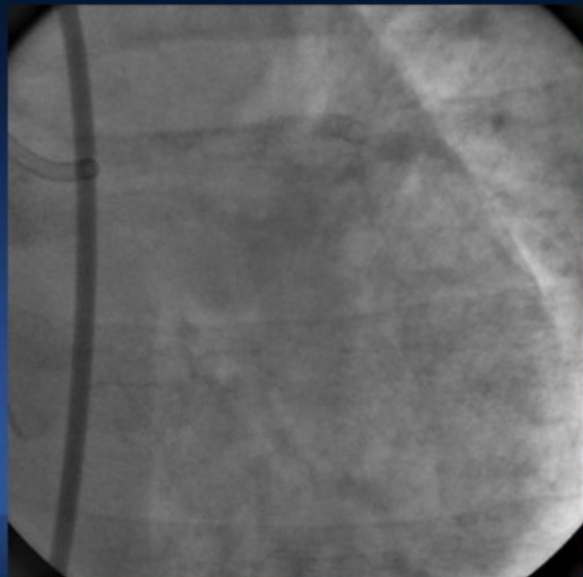


At the Maximal %IH Site

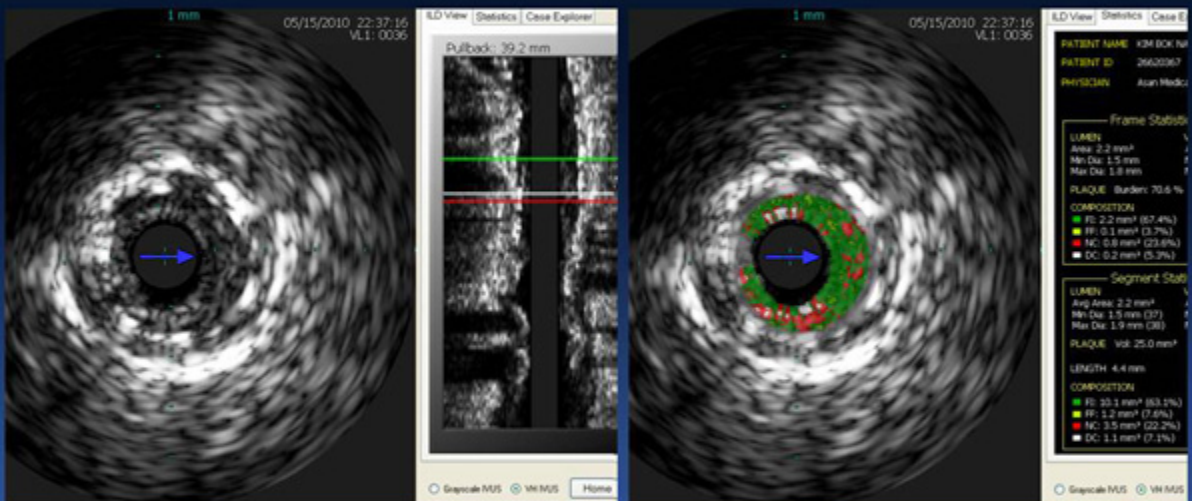
Kang SJ et al. *AJC* 2010;106:1561-5

71 Year-Old Female

- 8YA Stable angina → s/p BMS at pRCA and mLAD
- 7YA mLAD diffuse ISR → triple anti-platelet
- Resting chest pain → “**Unstable Angina**”



Virtual Histology



In-Stent Neointimal Hyperplasia

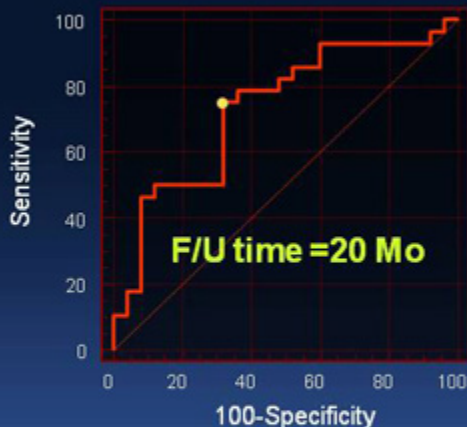
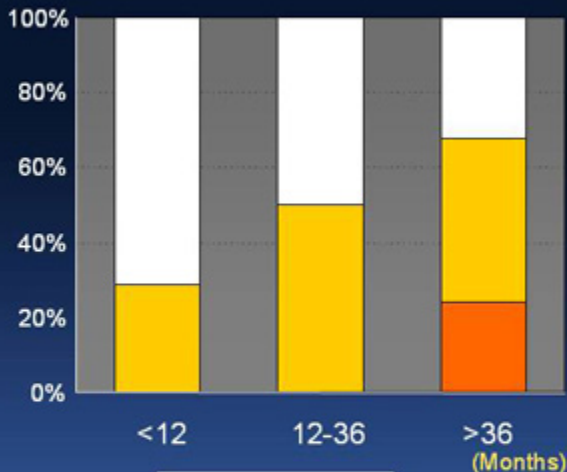
OCT Analysis in 50 DES-ISR Lesions with %IH>50%

	Total N=50	Stable N=30	Unstable N=20	P
Follow-up (months)	32 (9-52)	14 (8-51)	41 (16-56)	0.178
Lipid neointima	45 (90%)	25 (83%)	20 (100%)	0.067
Fibrous cap thickness, μm	60 (50-162)	100 (60-205)	55 (42-105)	0.006
Incidence of thrombi	29 (58%)	13 (43%)	16 (80%)	0.010
Incidence of red thrombi	7 (14%)	1 (3%)	6 (30%)	0.012
Incidence of rupture	29 (58%)	14 (47%)	15 (75%)	0.044
Incidence of TCFA	26 (52%)	11 (37%)	15 (75%)	0.008
Neovascularization	30 (60%)	15 (50%)	15 (75%)	0.069

Kang et al. Accepted in Circulation 2011

DES Follow-up >20 Months

Best Cut-Off to Predict TCFA-Containing Neointima



AUC=0.73

Sensitivity 75%

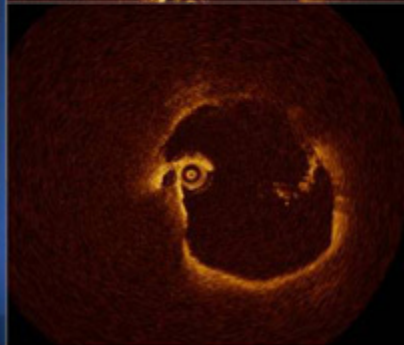
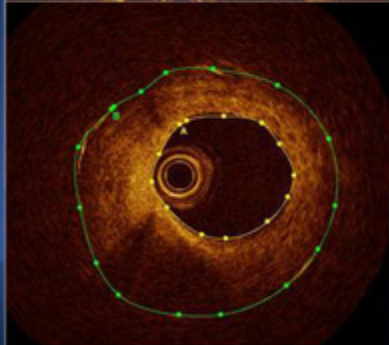
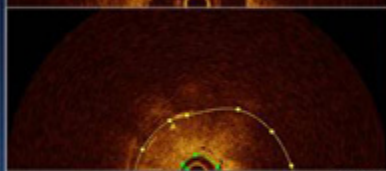
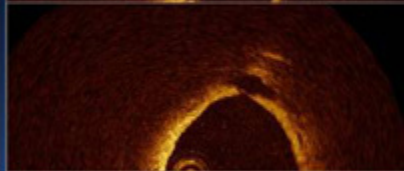
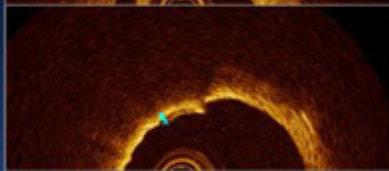
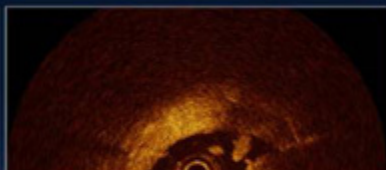
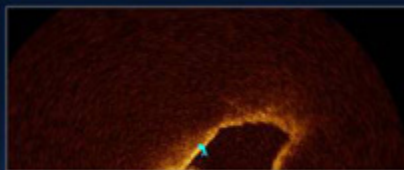
Specificity 68%

Diverse Clinical Features of Neoatherosclerosis

71/M, **Stable Angina**
5YA DES at RCA

37/M, **Unstable Angina**
8YA BMS at LAD

60/M, **NSTEMI**
7YA DES at RCA



The image consists of six circular OCT cross-sectional views of a coronary artery containing a stent. The images are arranged in two rows of three. The top row shows the stent with some plaque accumulation. The middle row, which is partially obscured by a text box, shows more significant plaque buildup. The bottom row shows the stent with extensive, irregular plaque accumulation, particularly in the inter-stent regions, illustrating the progression of in-stent neoatherosclerosis.

SUMMARY

In-stent neoatherosclerosis may increase neointimal vulnerability and contribute to the development of stent failure as one of causative mechanisms, especially late after stent implantation