VH-IVUS and OCT Evidences of In-Stent Neoatherosclerosis

A Mechanism of Stent Failure

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Disclosure

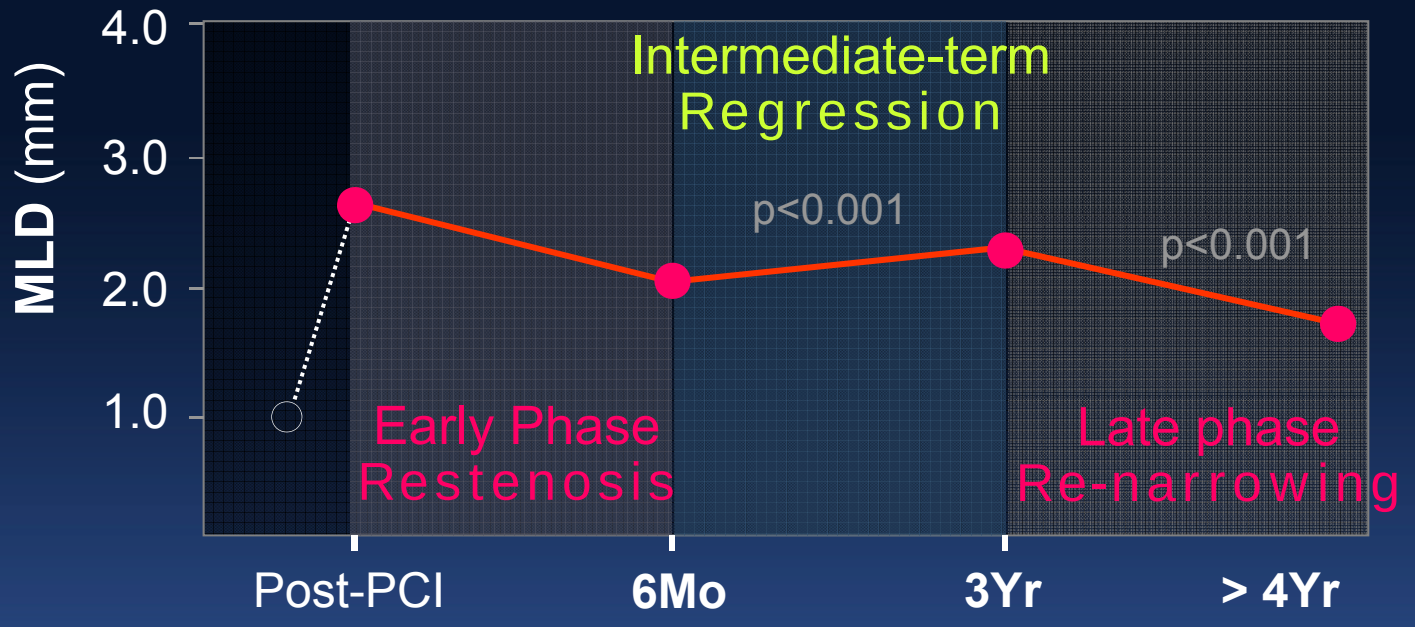
I have nothing to disclose

Evidences of Neoatherosclerosis

As a Mechanism of

Late In-stent Restenosis

Tri-phasic Luminal Response of BMS Extended Follow-up Study

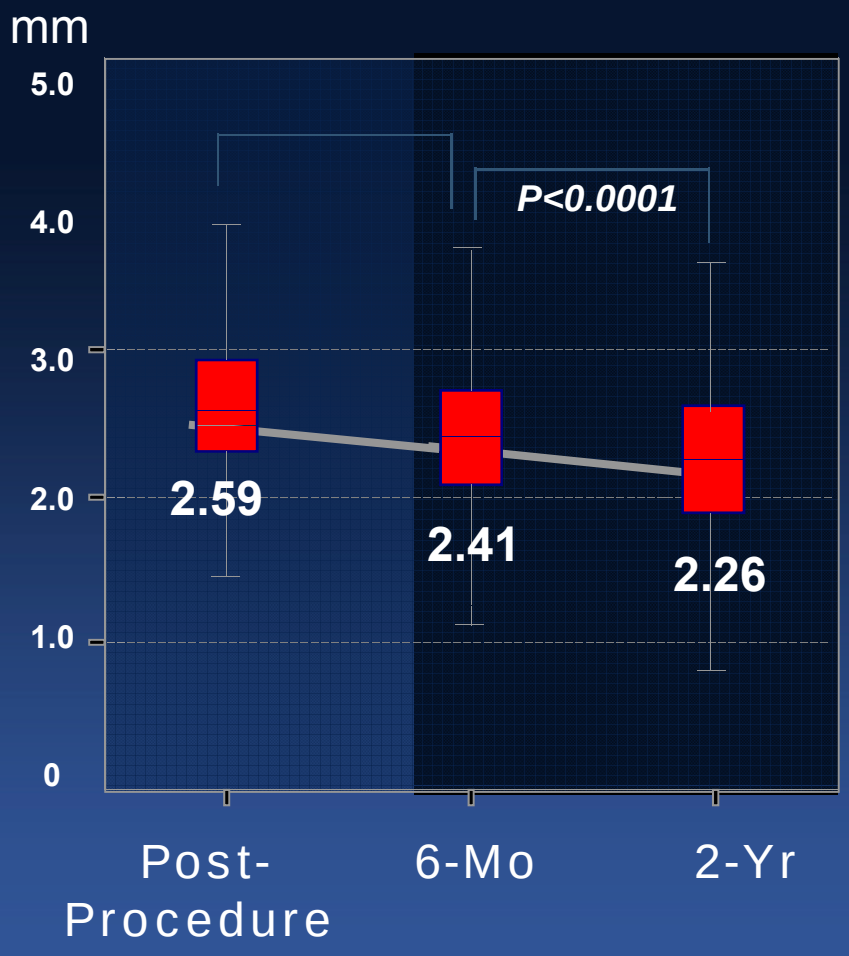


late phase re-narrowing likely related to neoatherosclerosis beyond 3 years

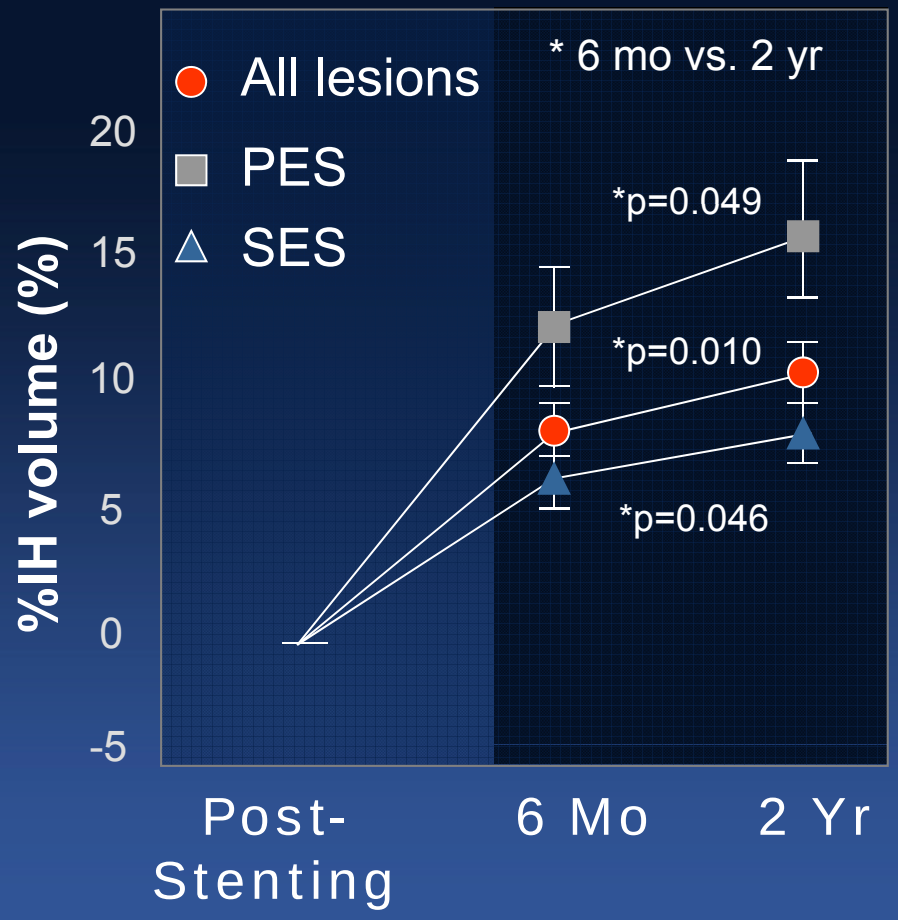
Kimura et al. N Engl J Med 1996;334:561-6
Kimura et al. Circulation 2002;105:2986-91

"Late Catch-up" in DES

Serial F/U of MLD



Serial F/U %IH Volume

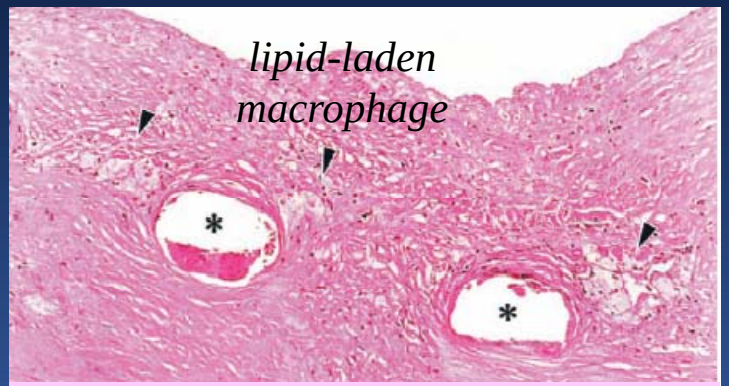


Park et al. Int J Cardiol. 2010 Sep in press

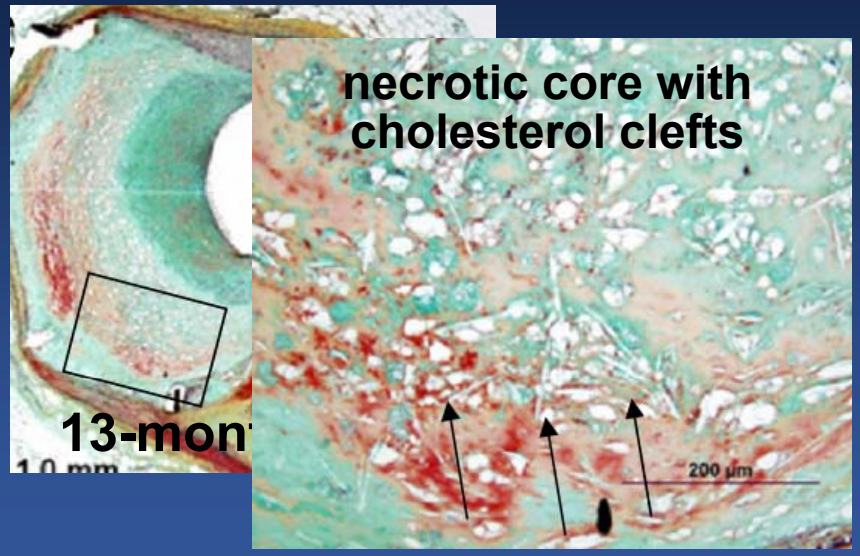
Kang et al. Am J Cardiol 2010;105:1402-8

Pathologic Definition of "Neoatherosclerosis"

Peri-strut foamy macrophage clusters with or without calcification, fibroatheroma, and ruptures with thrombosis in neointima, but no communication with underlying native atheroma



5-year f/u Palmaz–Schatz



13-mon

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

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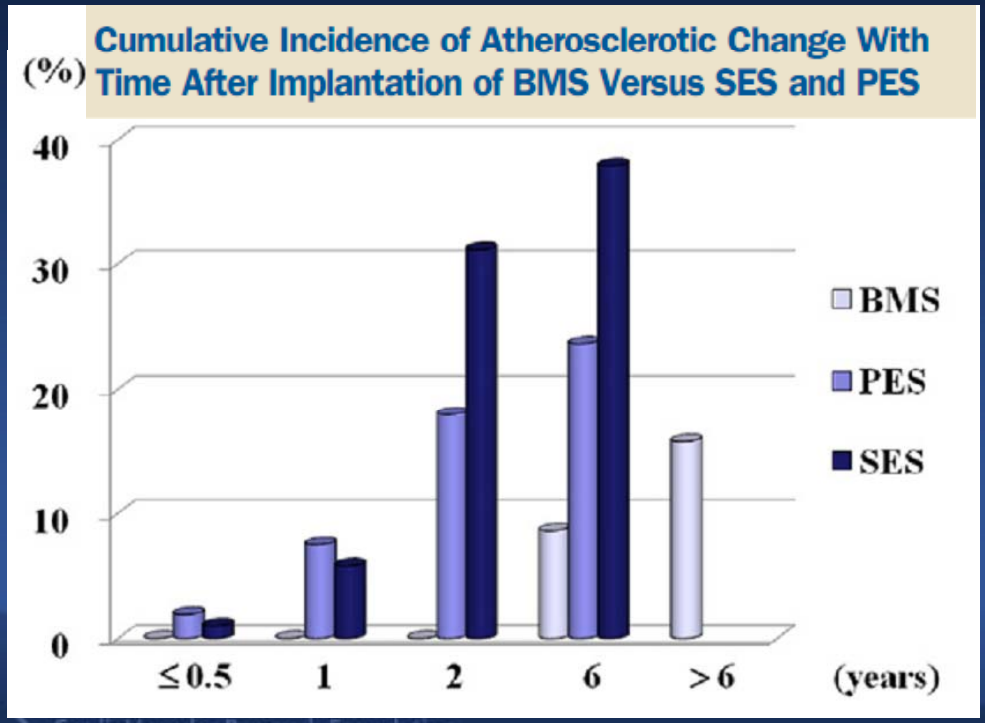
doi:10.1016/j.jacc.2011.01.011

EXPEDITED PUBLICATIONS

The Pathology of Neoatherosclerosis in Human Coronary Implants

Bare-Metal and Drug-Eluting Stents

Gaku Nakazawa, MD,* Fumiyuki Otsuka, MD,* Masataka Nakano, MD,* Marc Vorpahl, MD,* Saami K. Yazdani, PHD,* Elena Ladich, MD,* Frank D. Kolodgie, PHD,* Aloke V. Finn, MD,† Renu Virmani, MD*



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

Neoatherosclerosis **in DES** is more frequent and occurs earlier

Nakazawa et al. JACC 2011;57:1314–22

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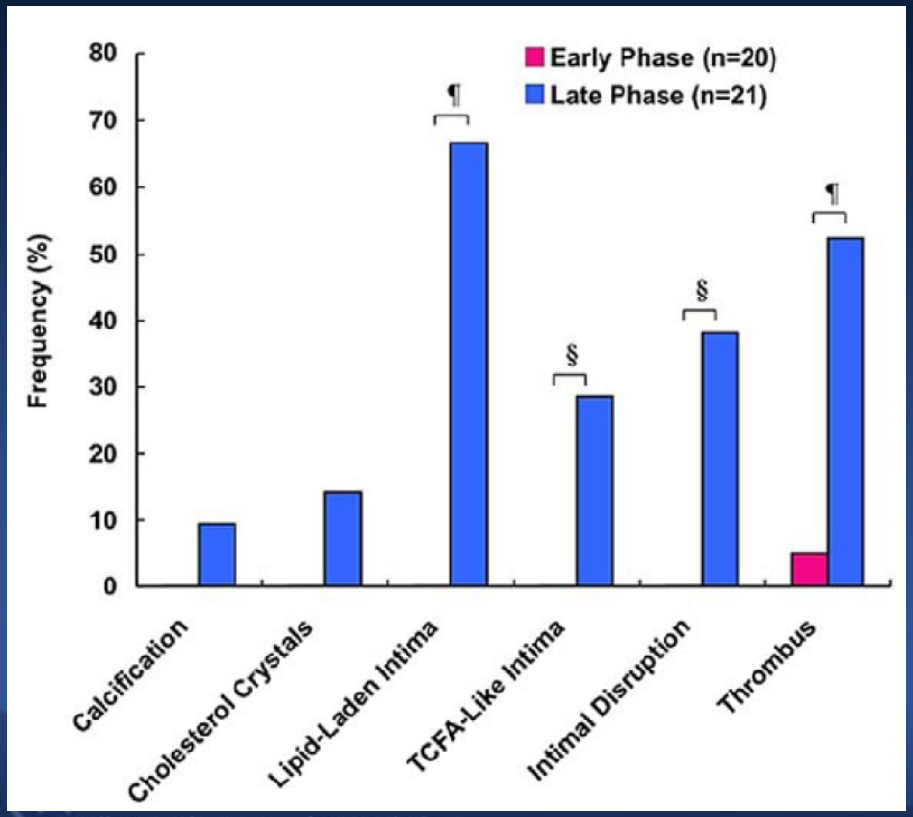
doi:10.1016/j.jacc.2009.08.032

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 late phase after BMS
- Lipid-laden intima frequently has intimal disruption, thrombi and neovascularization

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

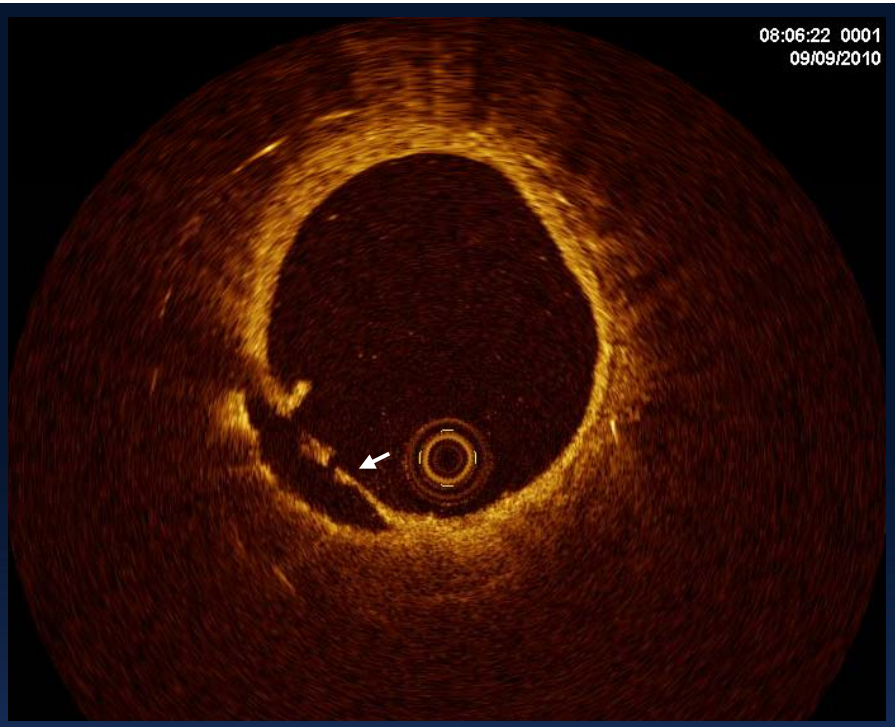
Early vs. Very late BMS-ISR

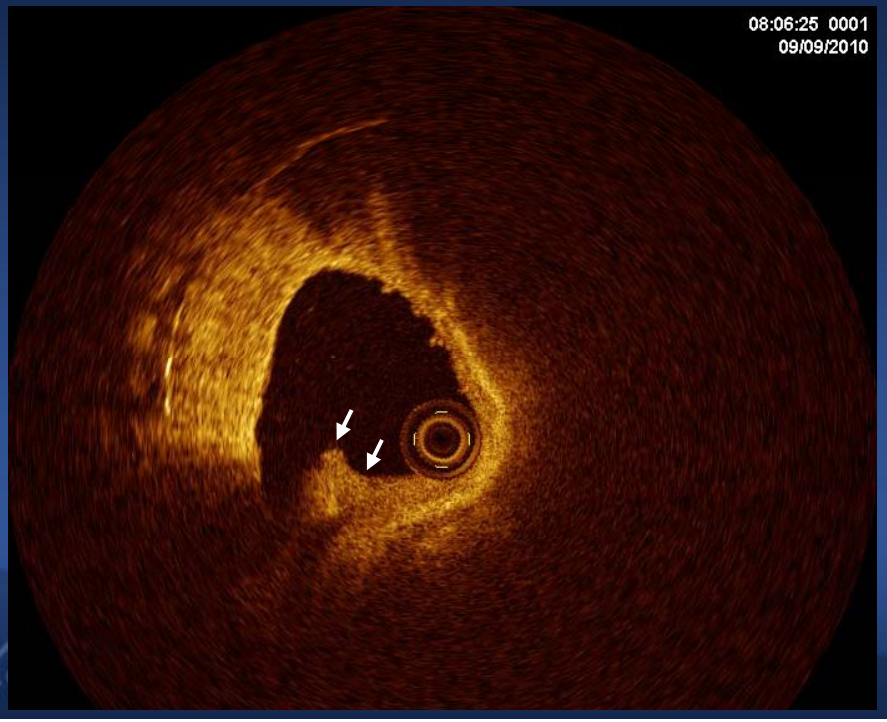
	Very late ISR	Early ISR
F/U duration	> 5 years	< 1year
MLA, mm^2	3.8±1.3	4.7±2.4
%IH area	58.6±10.3	55.6±13.4
Disrupted intima with cavity	18.6%	0%
Intraluminal material		
With shadowing	16.2%	0%
Without shadowing	4.7%	2.6%

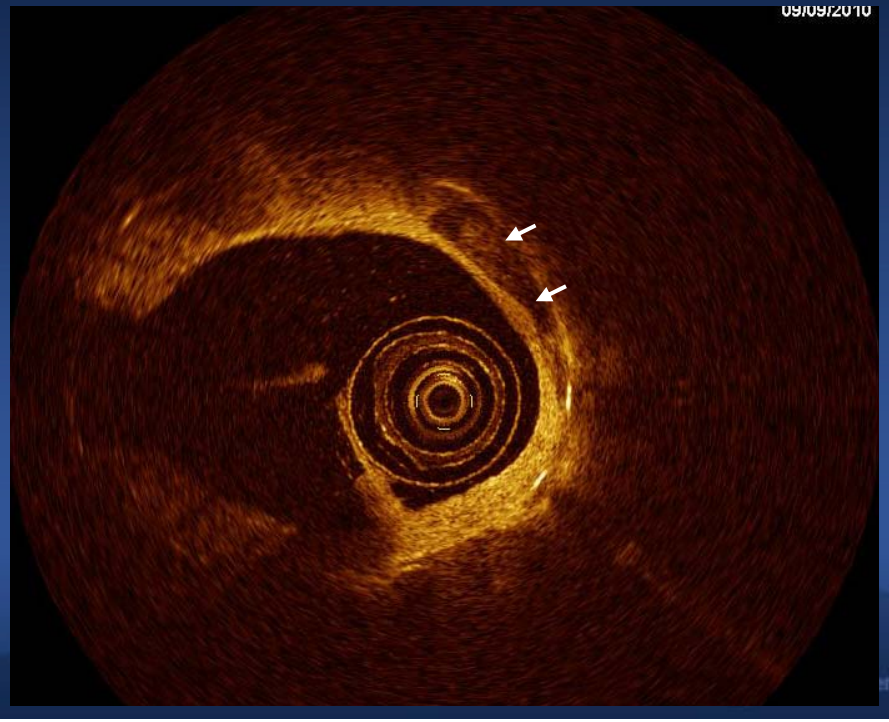
Progression of atherosclerotic process within neointima may be associated with very late BMS-ISR

Habara et al. Circ Cardiovasc Interv 2011;4:232-8

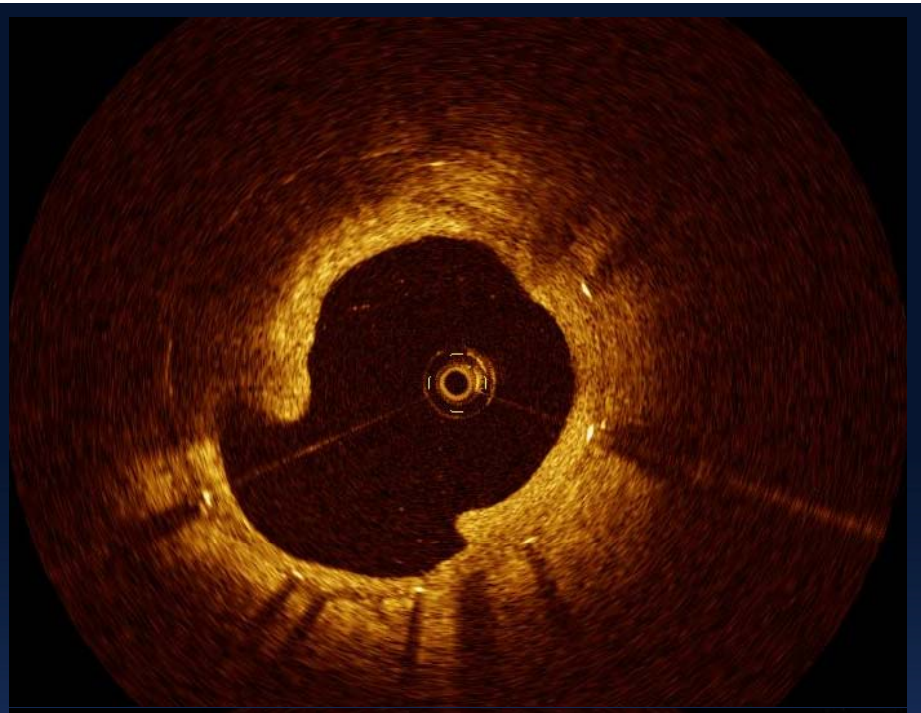
M/63 Stable angina
s/p BMS 10 years ago

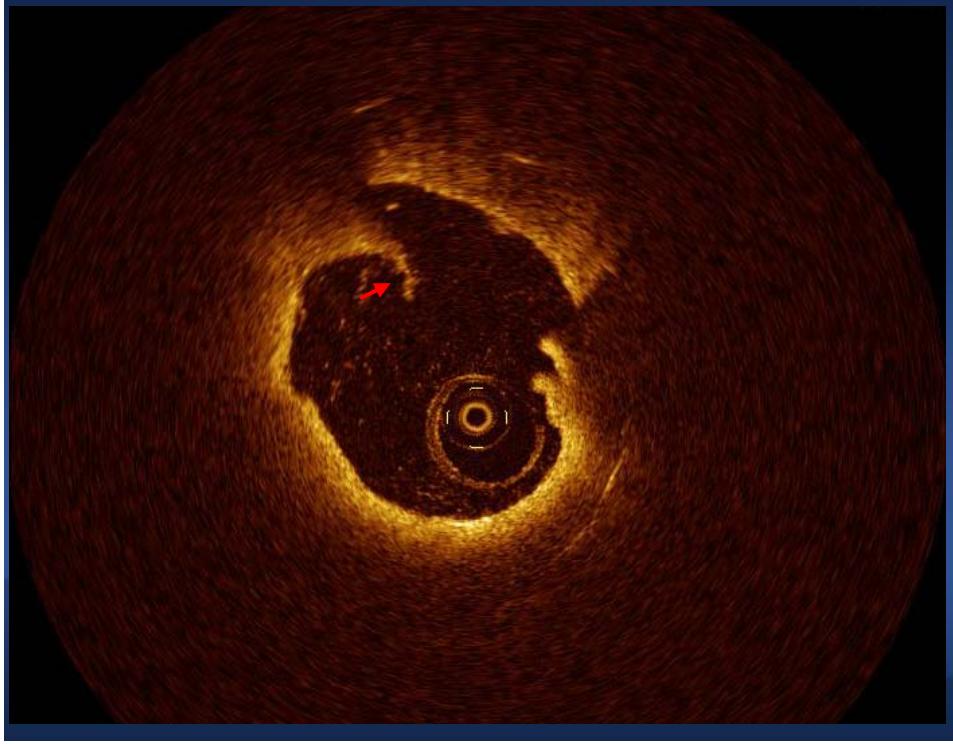


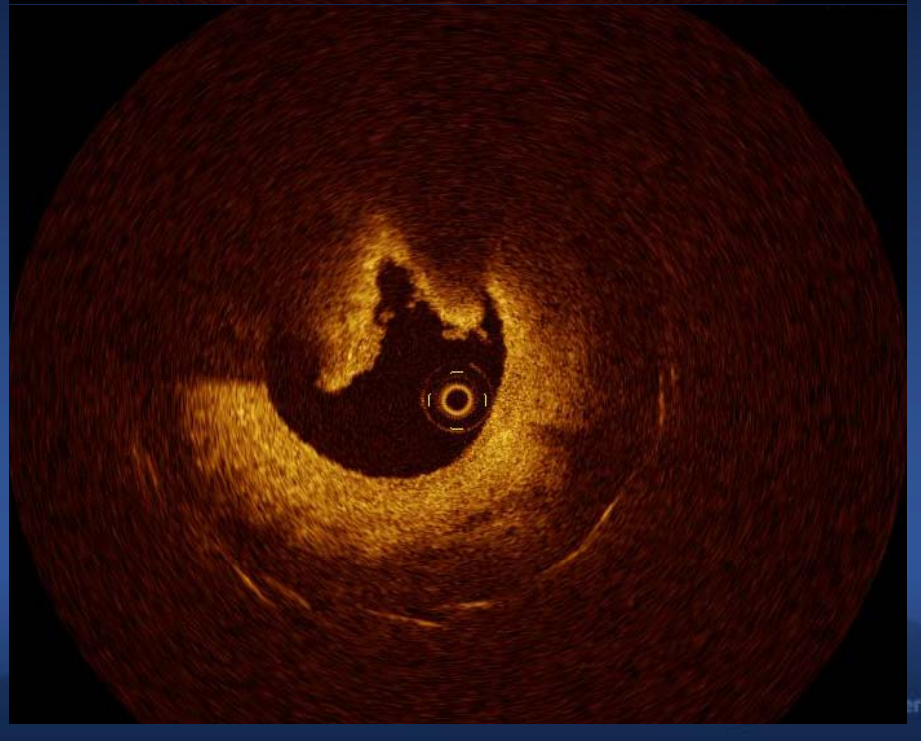




M/77 Unstable angina
s/p BMS 13 years ago







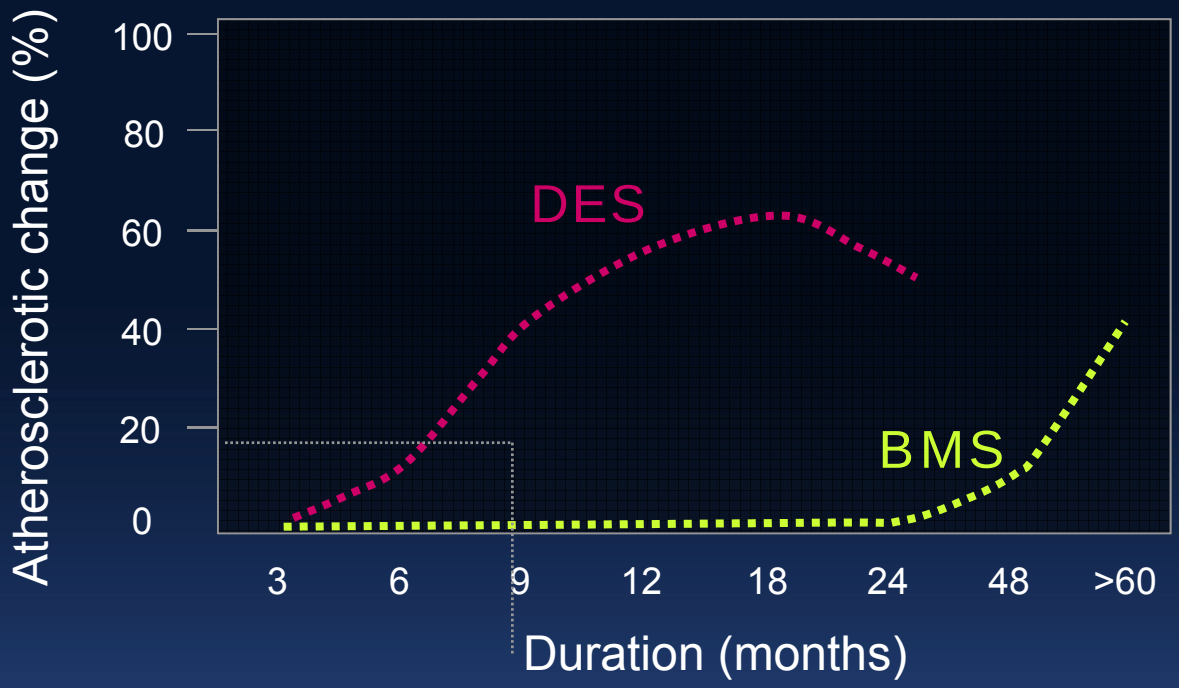
OCT Findings of BMS-ISR at 10-Year F/U

IH is a general mechanism of 22 very late BMS-ISR requiring clinically-driven TLR (Median F/U time 10.7 years)

Lipidic neointima	100%
Calcium-containing	32%
Thickness of fibrous cap	50 μm (IQR 50–60 μm)
TCFA-containing neointima	68%
TCFA at MLA site	55%
Intimal disruption	86%
Neointimal rupture with cavity	59%
Thrombi	77%
Red thrombi	75% in UA vs. 30% in SA
All 3 findings (TCFA, intimal rupture and thrombi)	50%

AMC data

Different Timing of Neoatherosclerosis

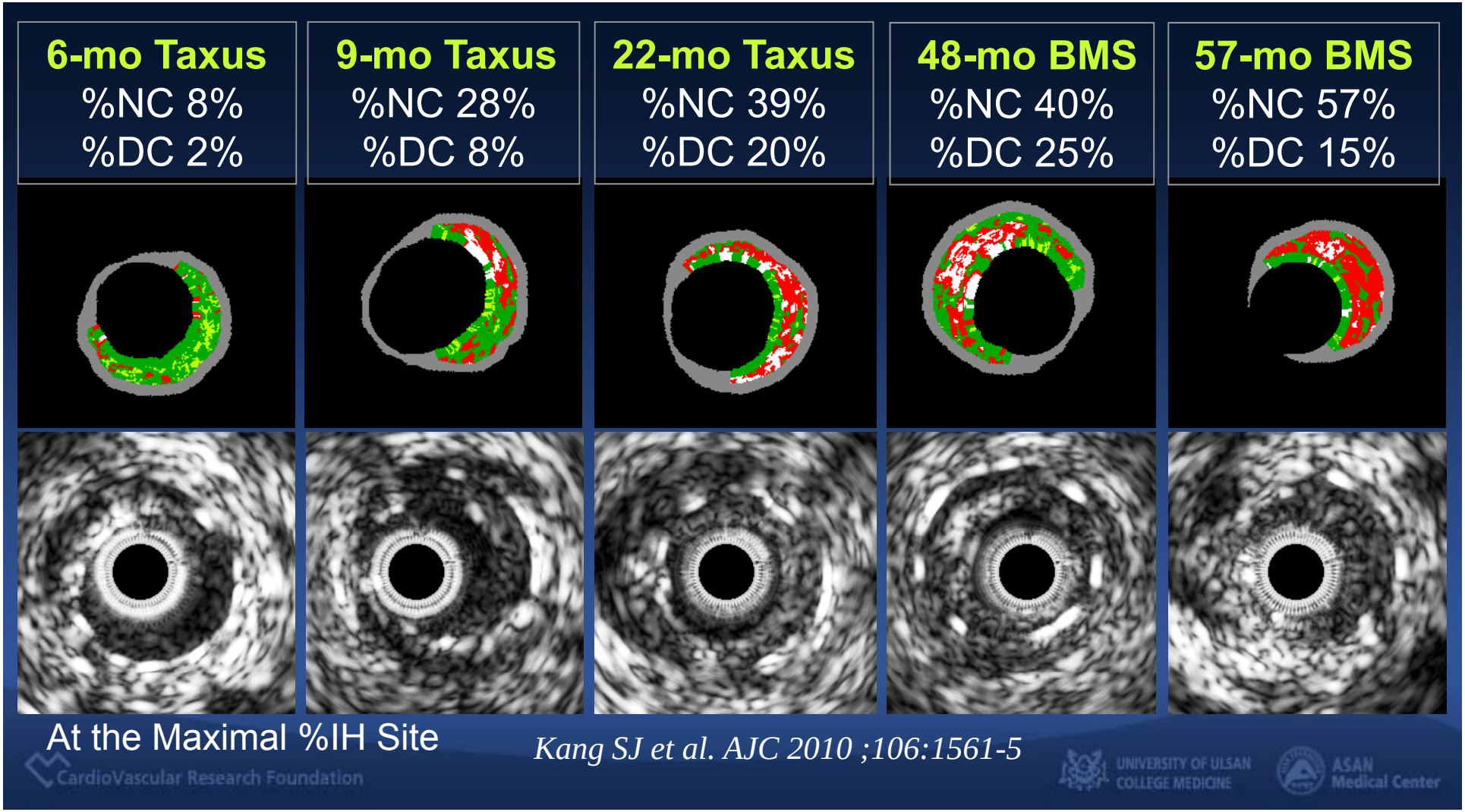


	<2 years		2-6 years	
	DES	BMS	DES	BMS
Neoatherosclerosis	29%	0%	41%	22%
Foamy mø clusters	14%	0%	19%	3%
Fibroatheroma (NC)	13%	0%	22%	15%

Nakazawa et al. JACC Cariovasc Imaging 2009;2:625-8

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

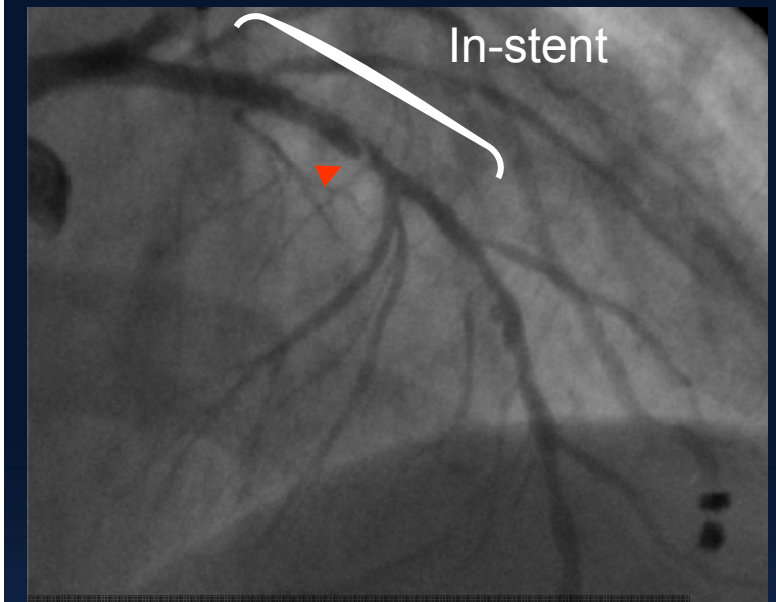
Soo-Jin Kang, MD[a], Gary S. Mintz, MD[b], Duk-Woo Park, MD[a], Seung-Whan Lee, MD[a], Young-Hak Kim, MD[a], Cheol Whan Lee, MD[a], Ki-Hoon Han, MD[a], Jae-Joong Kim, MD[a], Seong-Wook Park, MD[a], and Seung-Jung Park, MD[a,*]



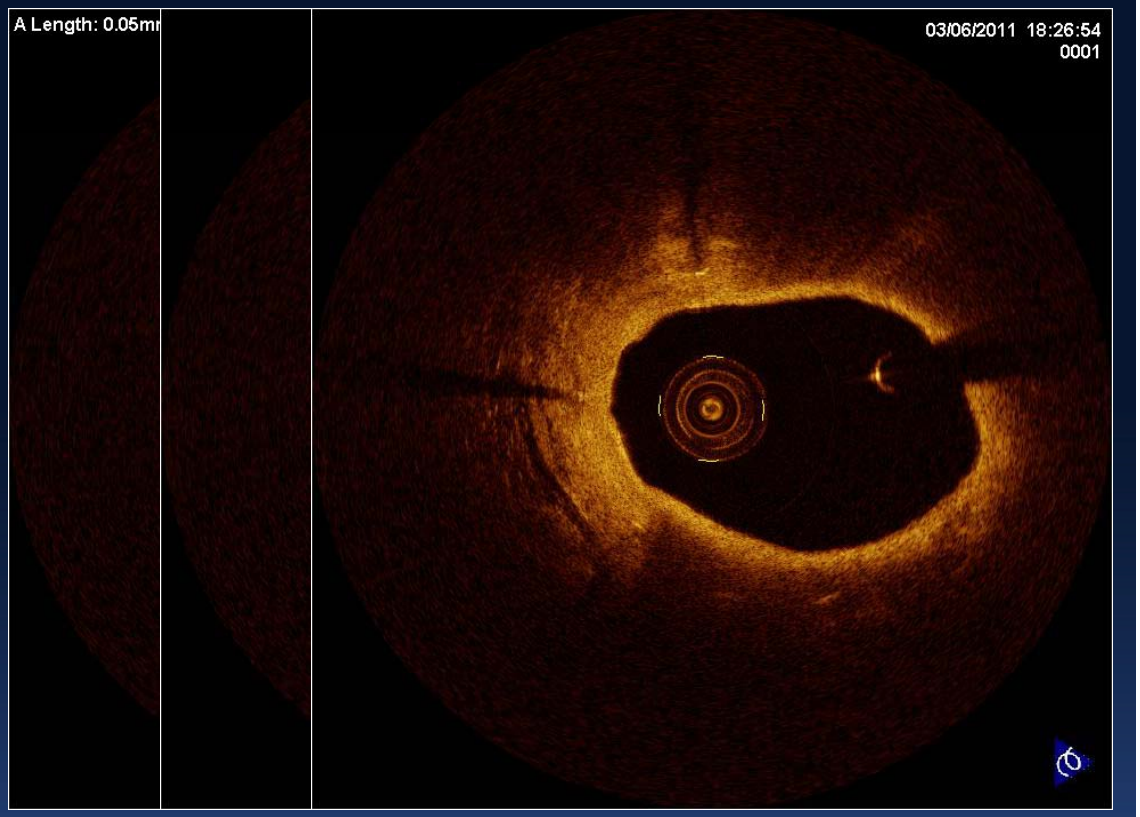
Neointimal Composition at Various FU Time
117 ISR Lesions (BMS and DES) with %IH>50%

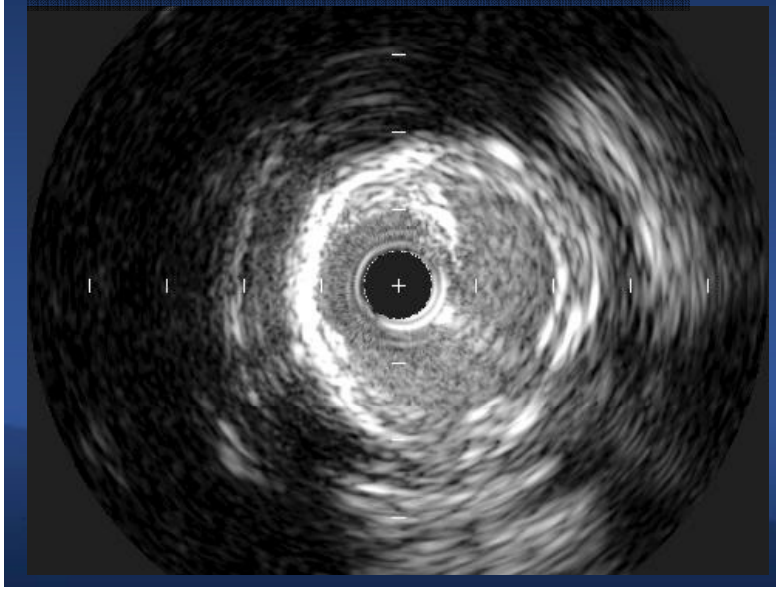
Neoatherosclerosis degeneration increases intimal vulnerability with extended follow-up period

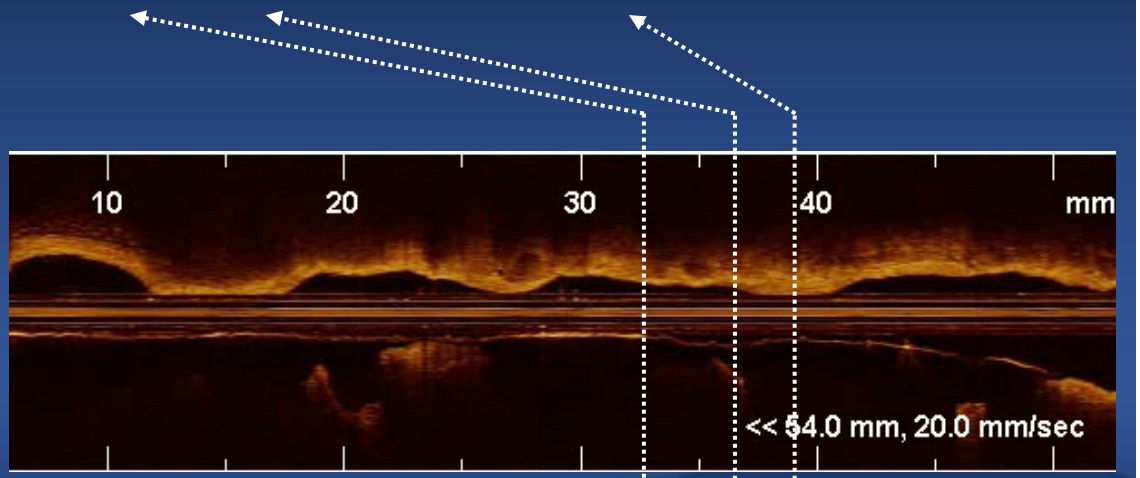
Kang SJ et al. AJC 2010 ;106:1561-5



M/68 Unstable angina
7YA s/p DES
2YA follow-up; patent







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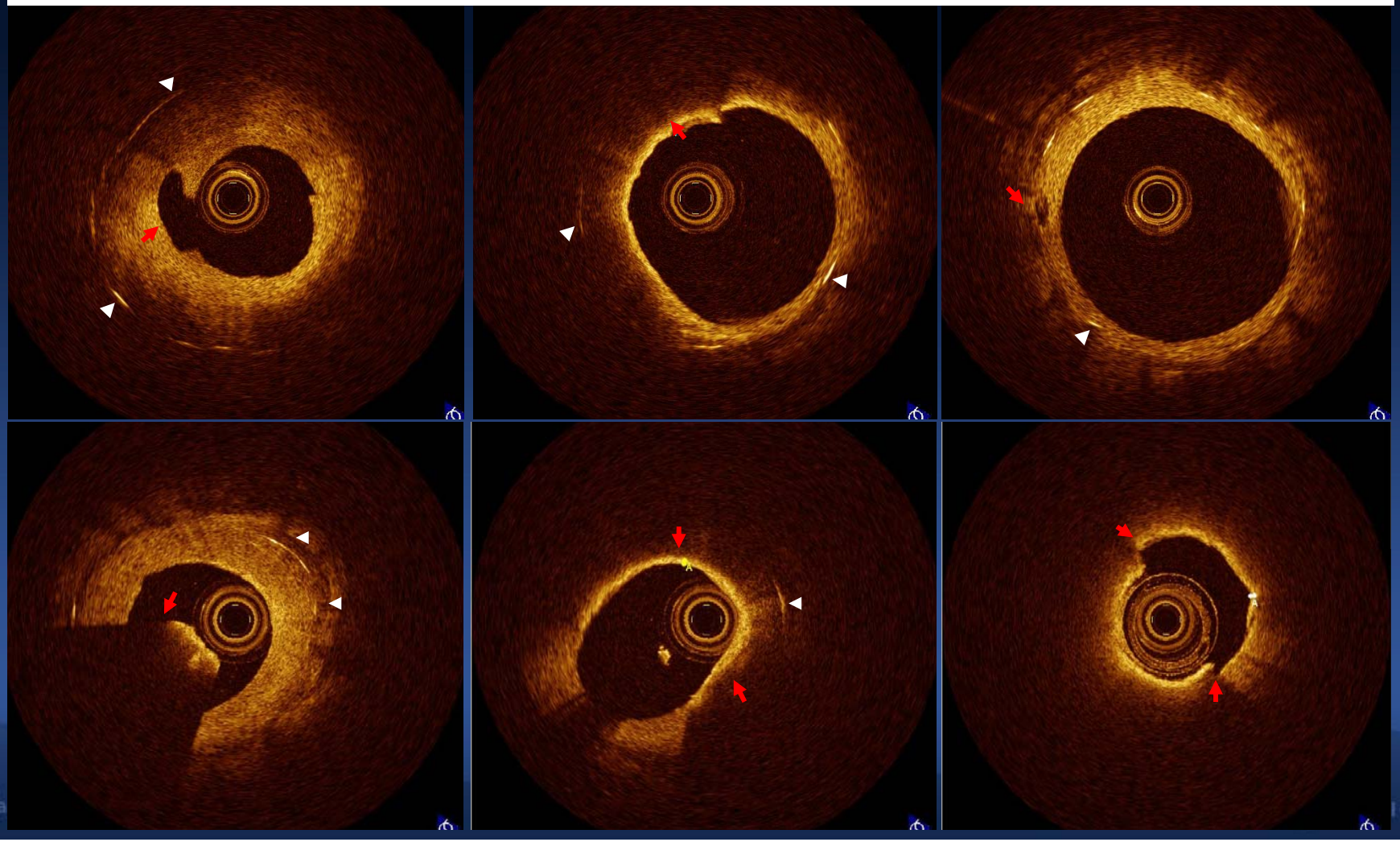
ASAN Medical Center

Optical Coherence Tomographic Analysis of In-Stent Neoatherosclerosis After Drug–Eluting Stent Implantation

Soo-Jin Kang, MD; Gary S. Mintz, MD; Takashi Akasaka, MD, PhD; Duk-Woo Park, MD, PhD; Jong-Young Lee, MD; Won-Jang Kim, MD; Seung-Whan Lee, MD, PhD; Young-Hak Kim, MD, PhD; Cheol Whan Lee, MD, PhD; Seong-Wook Park, MD, PhD; Seung-Jung Park, MD, PhD

Circulation 2011;123:2954-63



In-Stent Neoatherosclerosis

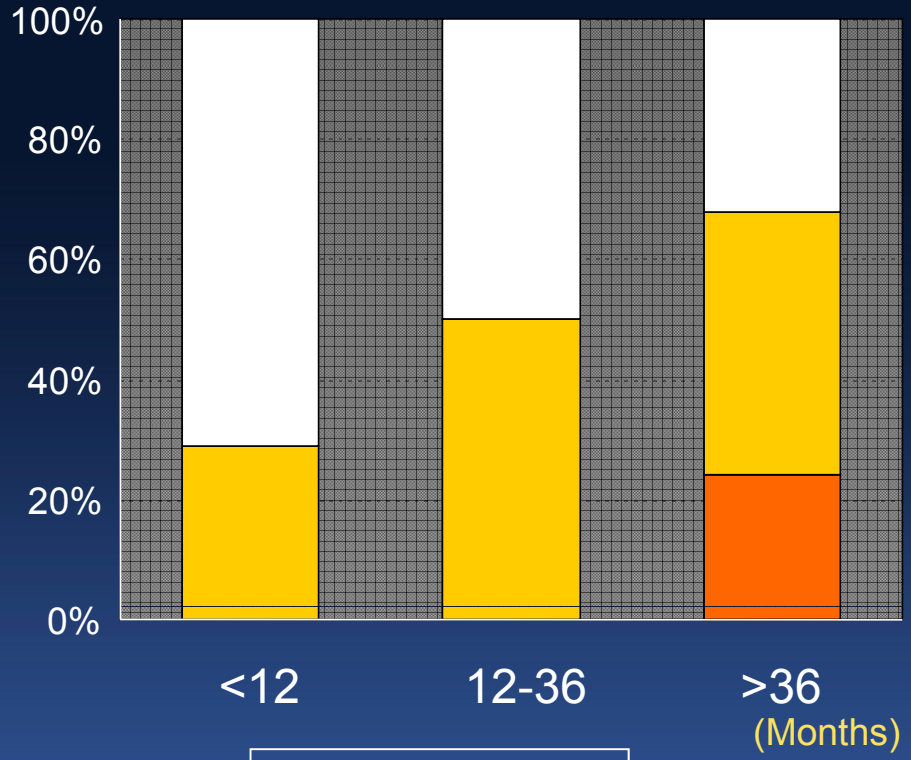
OCT Analysis in 50 DES-ISR Lesions with %IH>50%

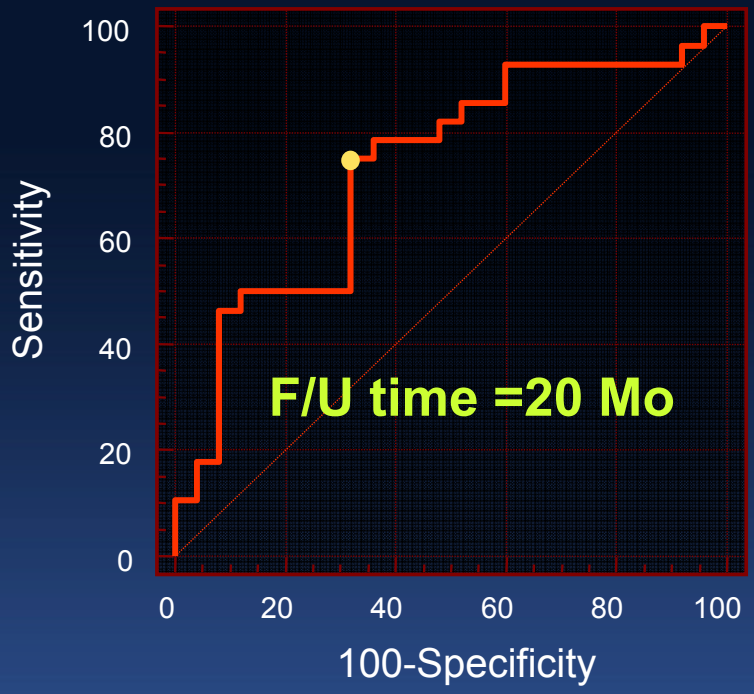
	Total N=50	Stable N=30	Unstable N=20	P
Follow-up (months)	32 (9-52)	14 (8-51)	41 (16-56)	0.178
Lipid neointima	45 (90%)	25 (83%)	20 (100%)	0.067
Fibrous cap thickness, μm	60 (50-162)	100 (60-205)	55 (42-105)	0.006
Incidence of thrombi	29 (58%)	13 (43%)	16 (80%)	0.010
Incidence of red thrombi	7 (14%)	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. Circulation 2011;123:2954-63

DES Follow-up >20 Months

Best Cut-Off to Predict **TCFA-Containing Neointima**

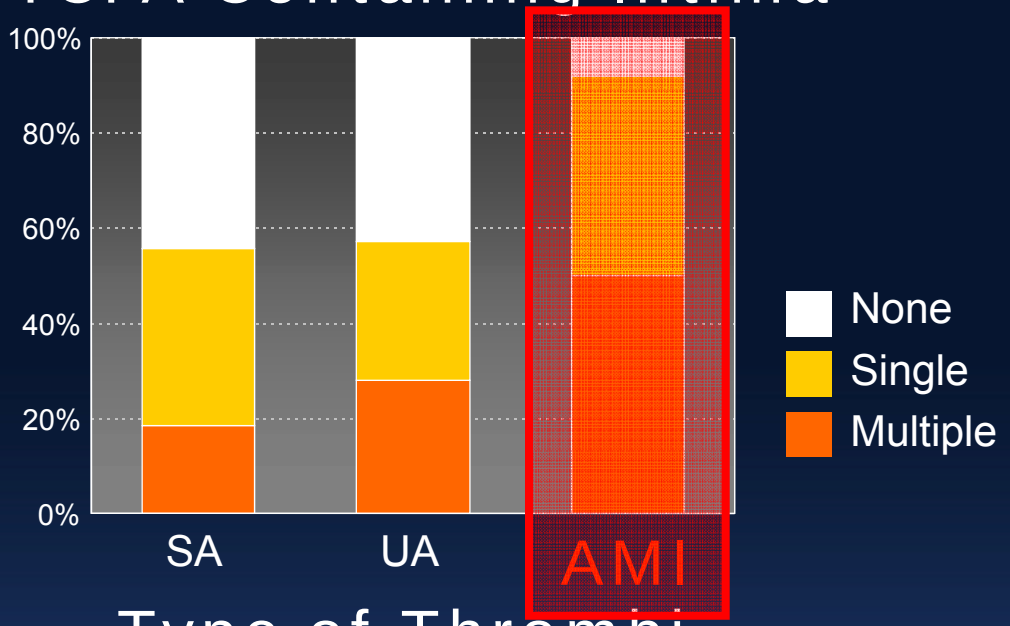




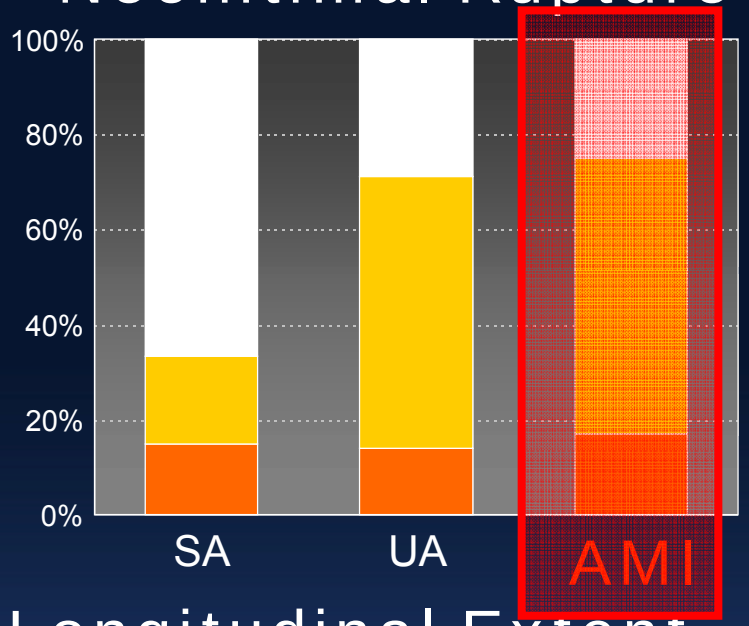
AUC=0.73
Sensitivity 75%
Specificity 68%

Kang et al. Circulation 2011;123:2954-63

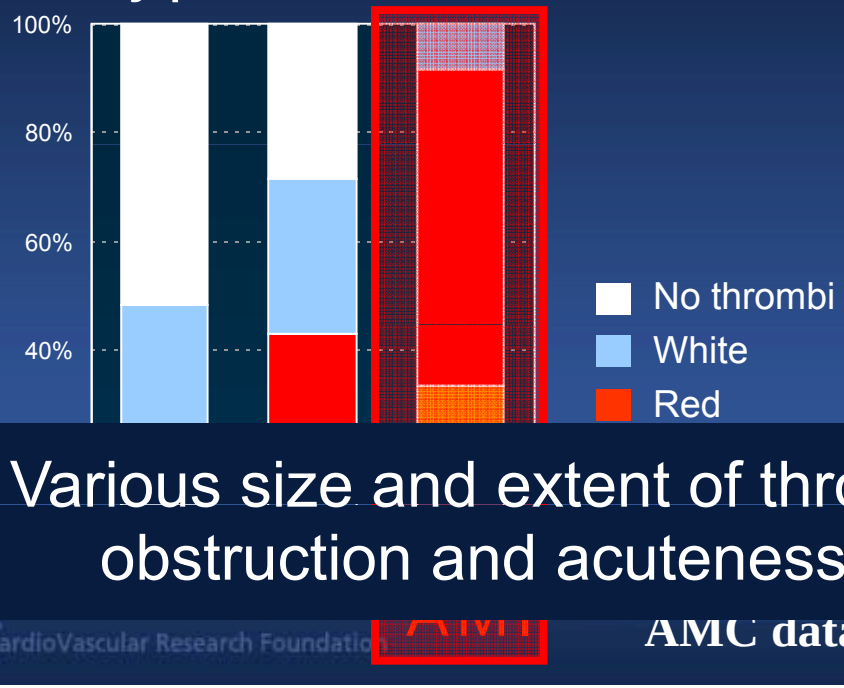
TCFA-Containing Intima



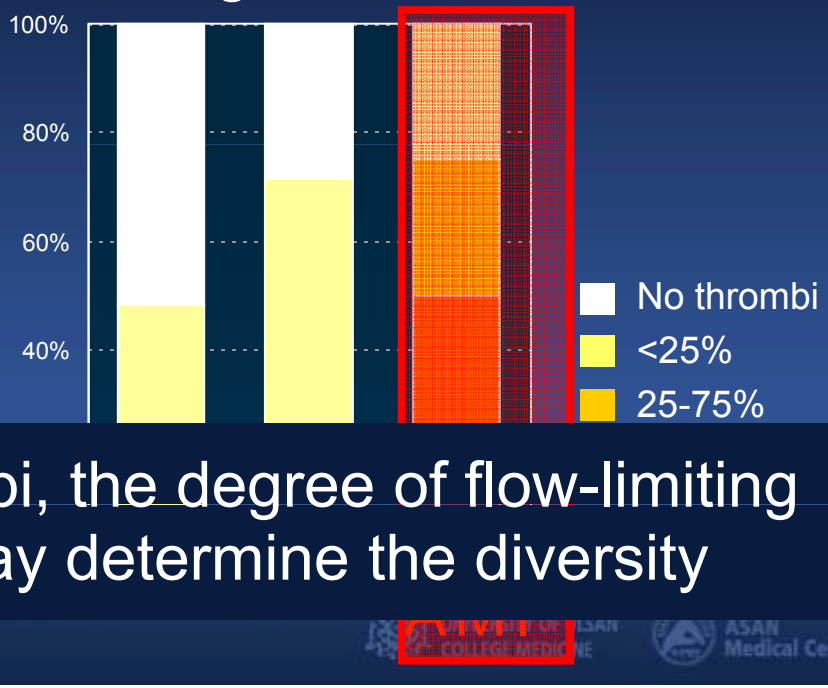
Neointimal Rupture



Type of Thrombi



Longitudinal Extent



Various size and extent of thrombi, the degree of flow-limiting obstruction and acuteness may determine the diversity

AMC data

Comparison between OCT vs. VH-IVUS

To identify TCFA-containing neointima

- 78% agreement between VH-IVUS and OCT
- Using OCT as a gold standard, VH had a sensitivity 60%, specificity 94%, PPV 90% and NPV 73%
- The lesions with VH-TCFA containing neointima showed much thinner fibrous cap than the lesions without VH-TCFA (OCT-measured thickness 50μm vs. 120μm]

	OCT-defined TCFA		p
	(+)	(-)	
%NC at the MLA	**25.2%** [8.6–30.0%]	**4.7%** [1.3–11.4%]	<0.001
Maximal %NC	**33.2%** [27.5–42.5%]	**12.8%** [6.0–24.2%]	<0.001
%DC	**5.5%** [2.4–8.5%]	**0.6%** [0.0–1.7%]	<0.001

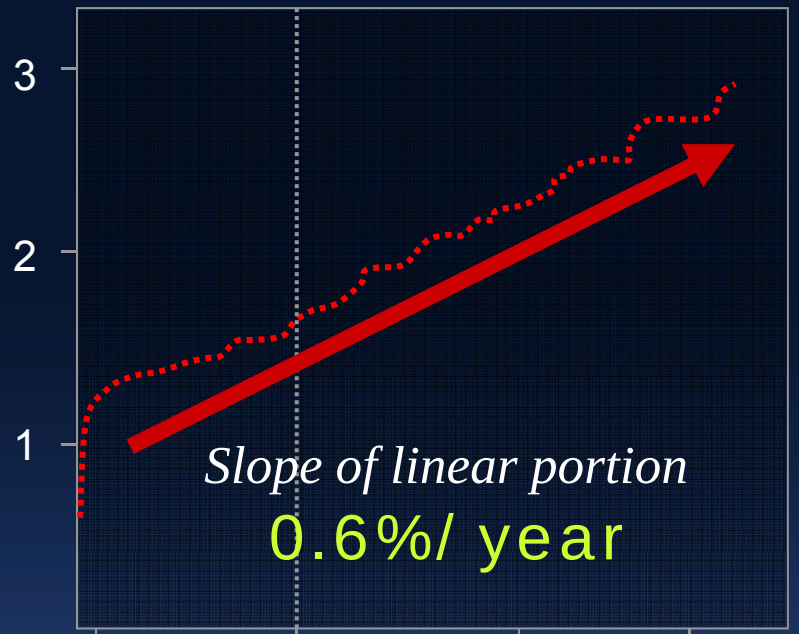
Kang et al. Circulation 2011;123:2954-63

Evidences of Neoatherosclerosis

As a Mechanism of

Very Late Stent thrombosis

Cumulative Incidence of DES Thrombosis

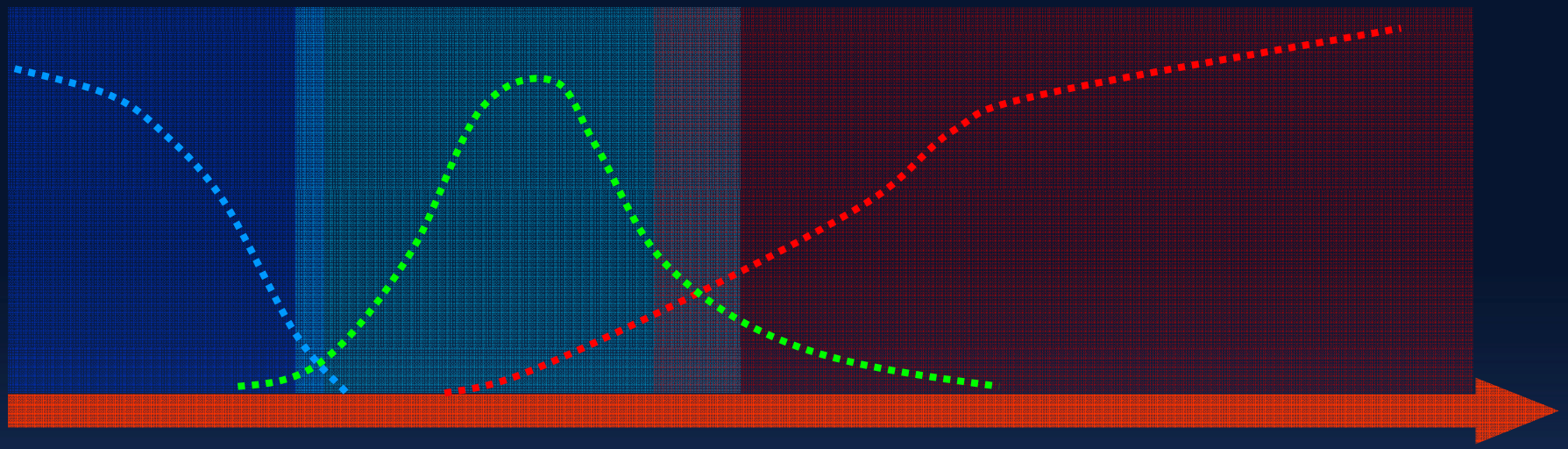


Cumulative incidence	**1.2%**	**1.7%**	**2.3%**	**2.9%**

Although the majority of DES showed good stent coverage with neointima beyond 1 year, a steady increase in late stent thrombosis (0.6% per year) have demonstrated thereafter

Daemen et al. Lancet 2007;369:667—78

Timing and Mechanism of DES Thrombosis



Early (<30d)	Late (1-12 Mo)	Very late (>12 Mo)
Procedural	Delayed healing	Abnormal vascular response
Underexpansion Edge dissection Residual plq rupture Medial fracture	Uncovered struts Fibrin deposition	Hypersensitivity Extensive fibrin deposition Late malapposition? "Neoatherosclerosis"

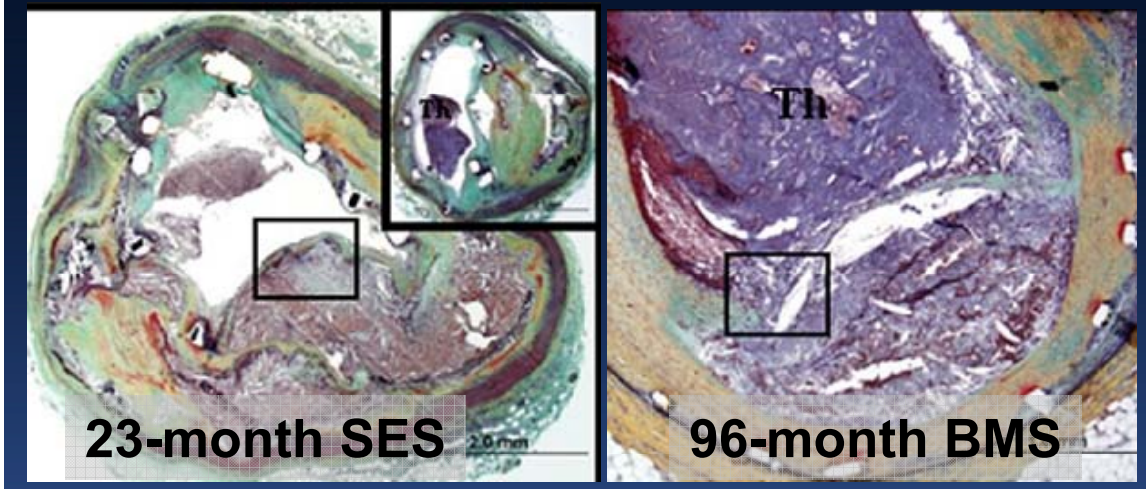
Nakazawa et al. J Cardiol 2011;58:84-91

More Advanced Neoatherosclerosis

TCFA-Containing Neointima

Intimal rupture

Thrombosis



"Unstable Neointima"

>5 years in BMS

≤2 years in DES

Although uncovered struts as a marker of incomplete endothelialization remains the primary cause of DES-VLST, neoatherosclerosis is added as another factor

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

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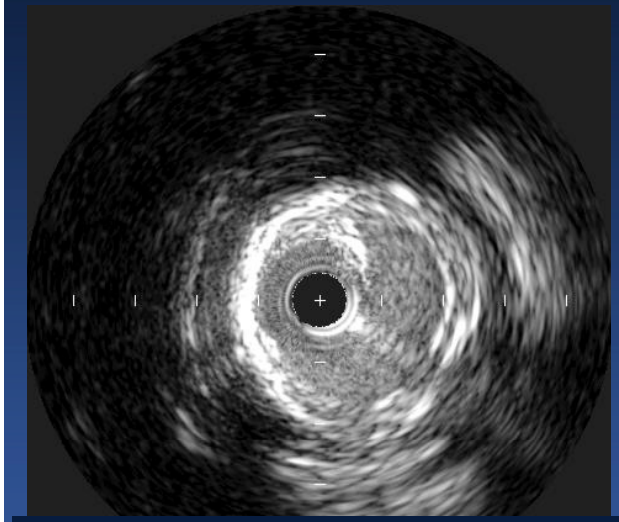
Intravascular Ultrasound Findings in Patients With Very Late Stent Thrombosis After Either Drug-Eluting or Bare-Metal Stent Implantation

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

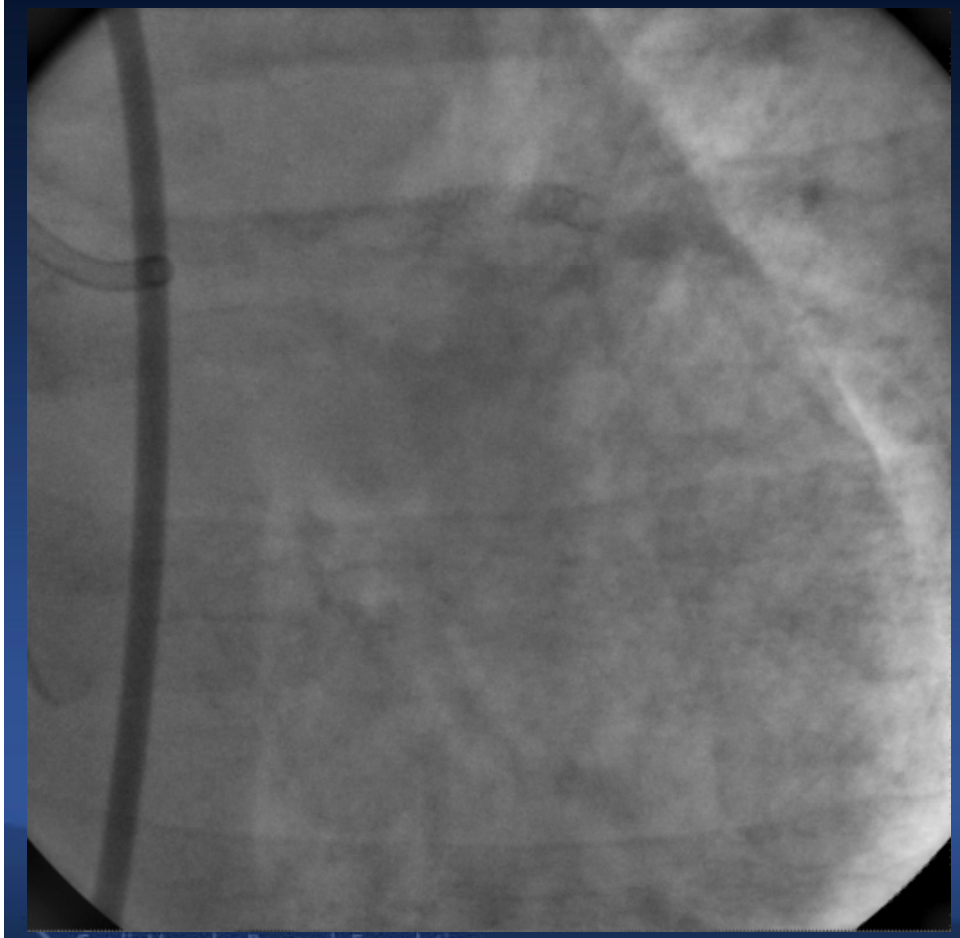


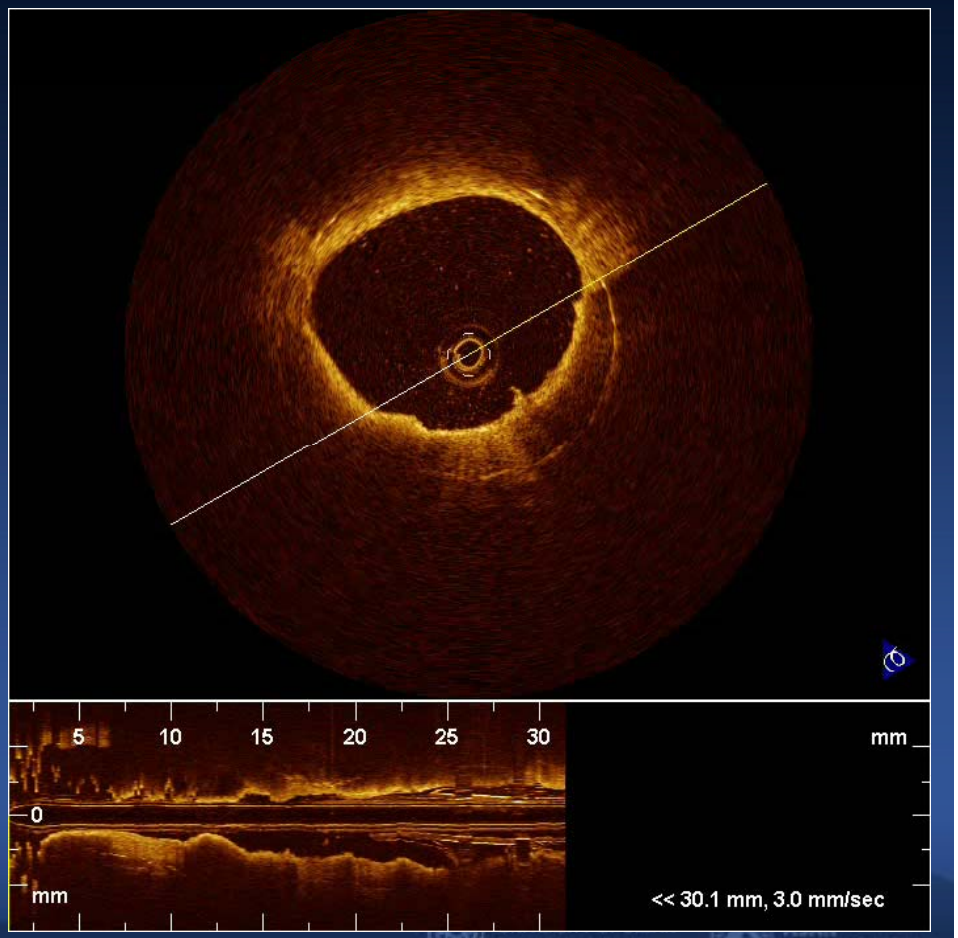
	DES (n=23)	BMS (n=7)
Mean EEM CSA, mm^2	19.5±6.0	18.3±4.1
Mean Lumen CSA, mm^2	4.2±1.4	4.7±4.6
Mean Neointima, mm^2	3.0±1.1	5.0±1.7*
Minimal stent CSA, mm^2	6.1±1.5	7.4±3.7
Neointima rupture	**10 (44%)**	**7 (100%)***

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

71 Year-Old Female

- 8YA s/p BMS at mLAD
- 7YA diffuse ISR→ triple anti-platelet
- Resting chest pain→ New ST depression, V4-6

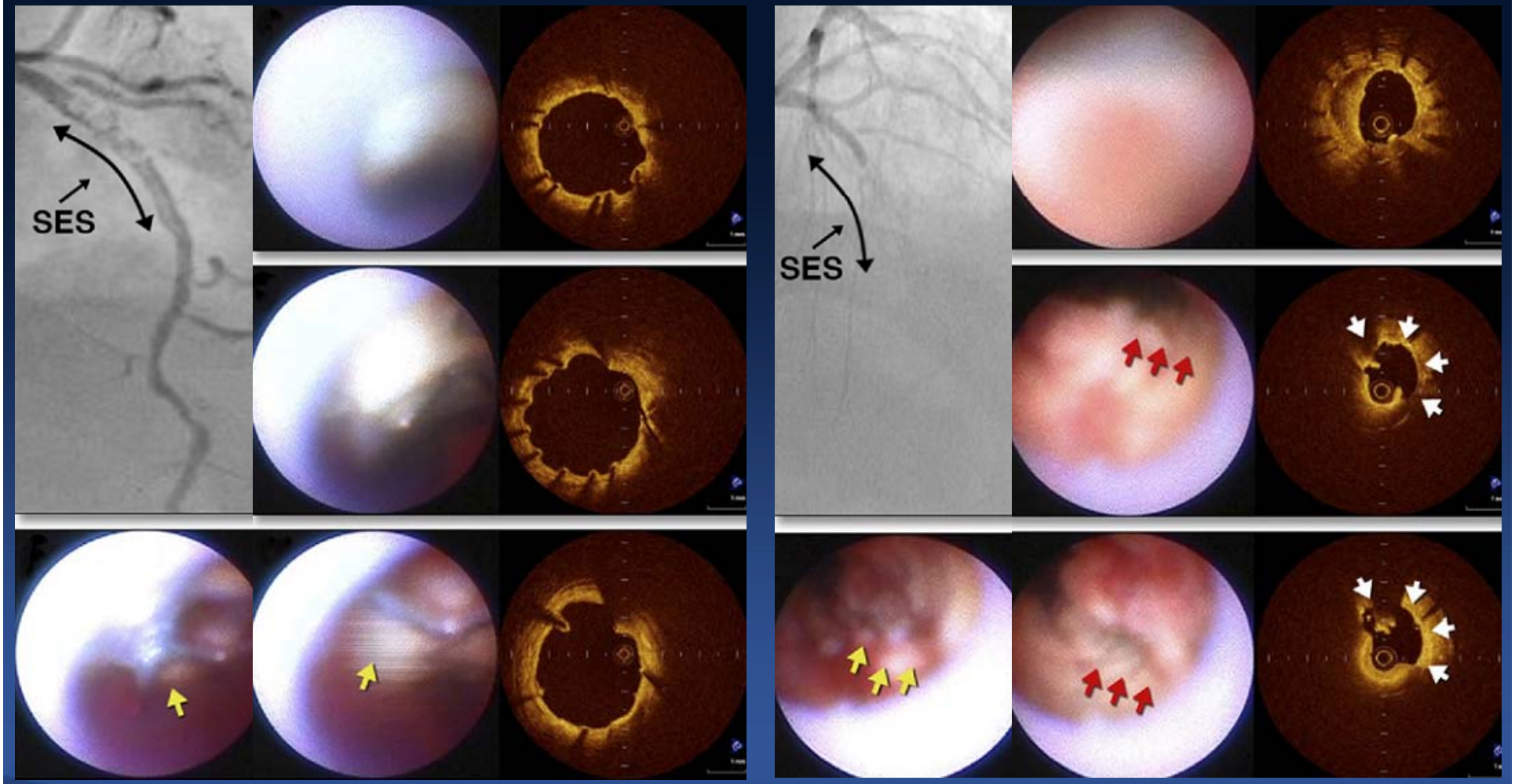




Different Mechanisms of DES-VLST

VLST of 34-month SES

VLST 54-month SES

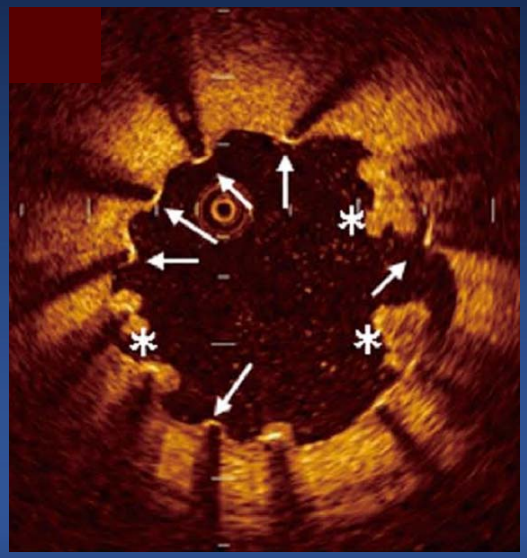


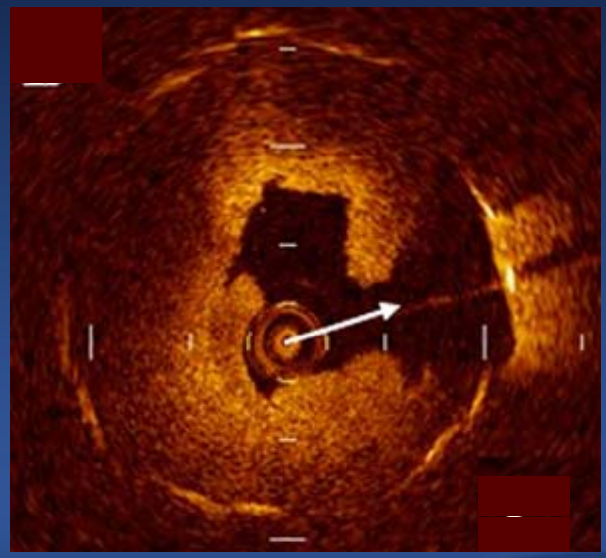
Ikenaga et al. JACC Cardiovasc Imaging 2011;4:1217-9

In Vivo OCT of DES-VLST

Table 3. Details of VLST Cases

Patient no.	Age (years)/ Gender	Duration (days)	Lesion location	Stent type (mm)	Procedure before OCT	Uncovered strut proportion		Malapposed strut proportion		Lipid-laden-like neointima with disruption
						Strut (%)	Frame (%)	Strut (%)	Frame (%)	
1	61/M	829	LAD, Seg 7	SES, 2.5×33	Thrombectomy +POBA	20.8	64.5	23.5	58.1	(–)
2	81/F	949	RCA, Seg 3	SES, 2.5×28	Thrombectomy +POBA	46.3	93.8	9.3	31.3	(–)
3	67/F	987	LCX, Seg 13	SES, 2.5×28	Thrombectomy	2.2	10.0	0	0	(+)
4	59/M	1,093	RCA, Seg 3	PES, 3.0×12	None	52.3	100	5.4	33.3	(–)
5	60/M	1,497	LCX, Seg 13	SES, 2.5×28	None	48.5	100	5.4	32.0	(–)
6	70/M	1,340	LAD, Seg 7	SES, 2.5×18	Thrombectomy	4.9	15.8	0	0	(+)

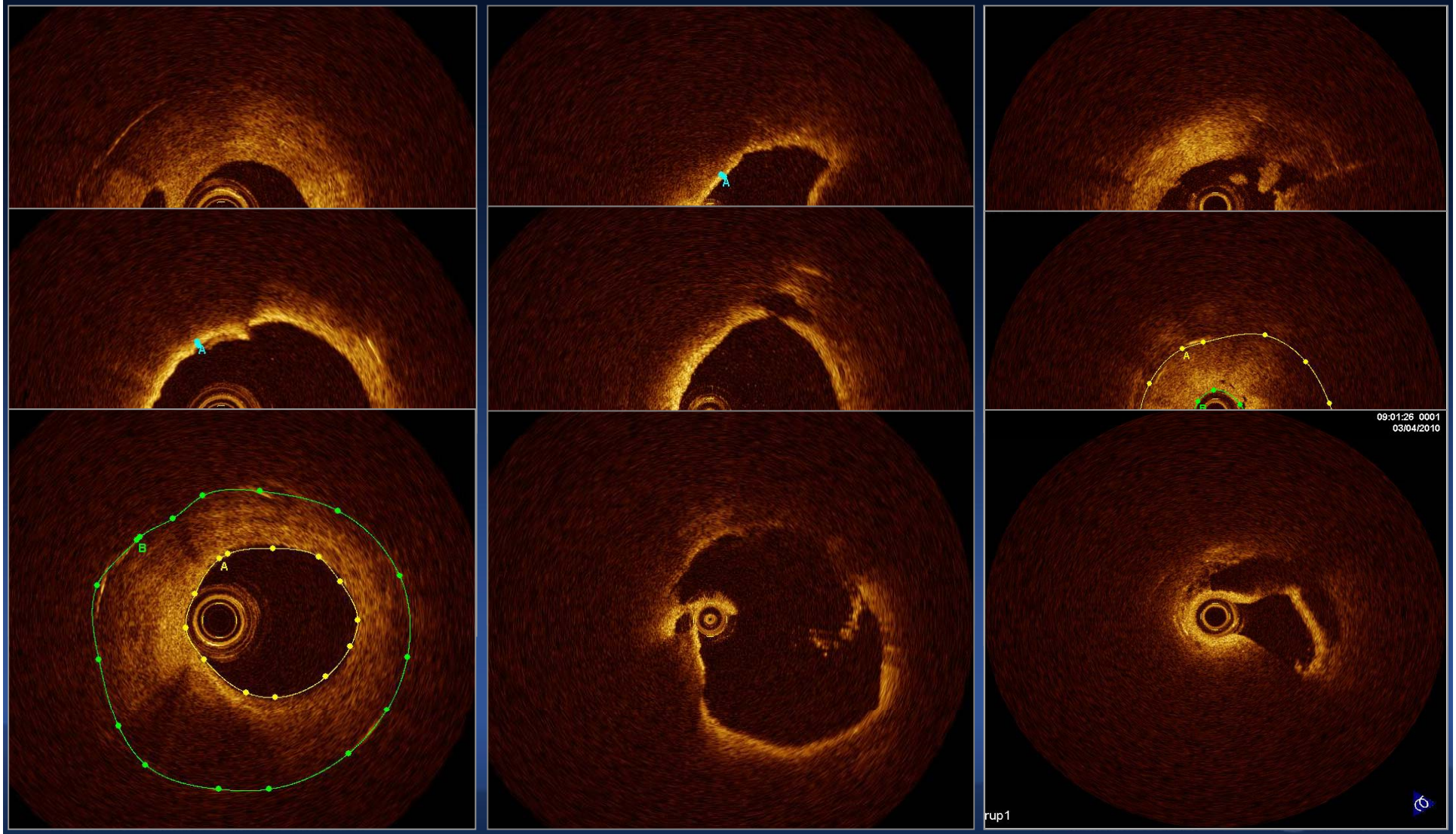


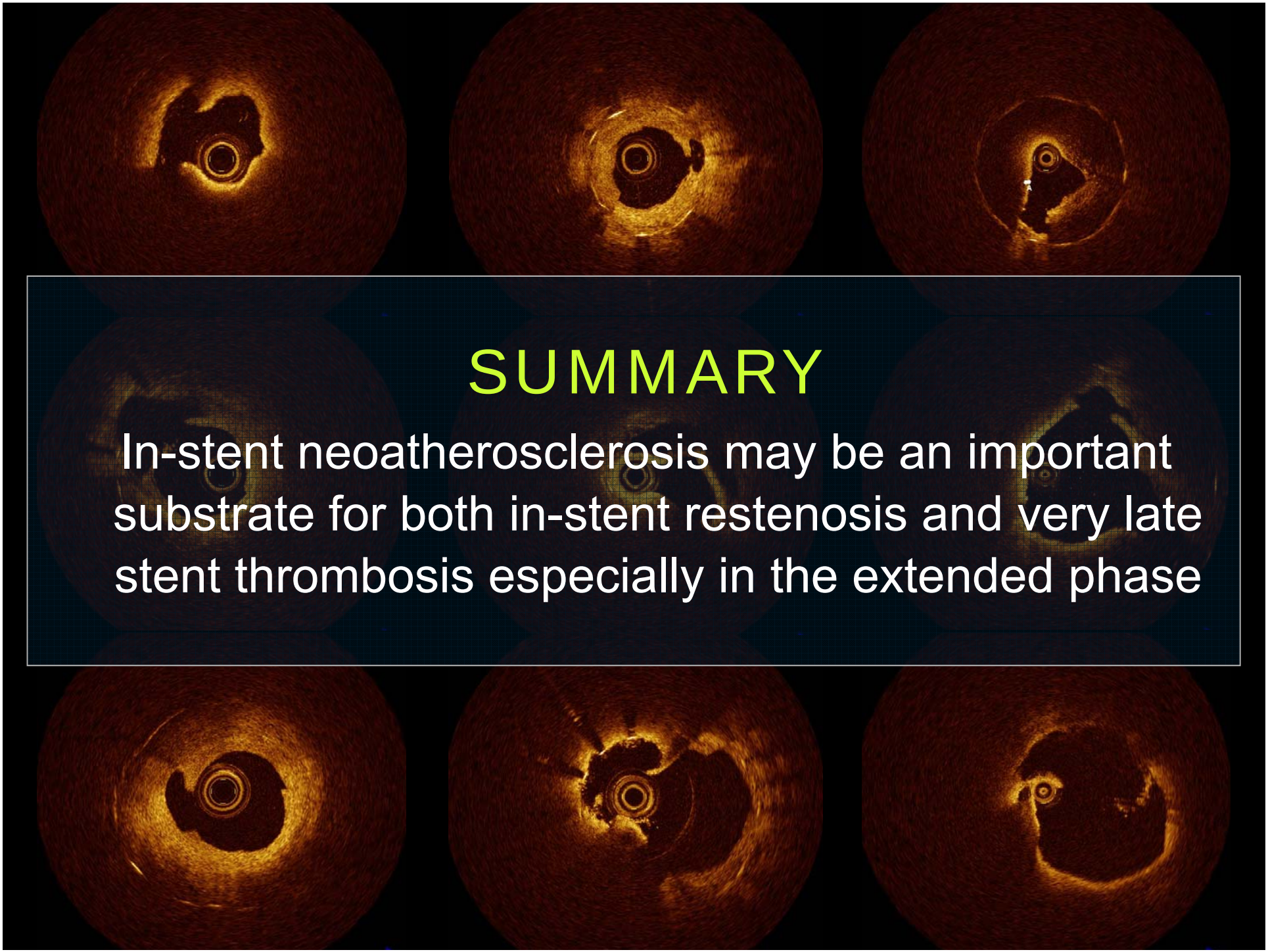


Miyazaki et al. Circulation J 2011 (in press)

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





SUMMARY

In-stent neoatherosclerosis may be an important substrate for both in-stent restenosis and very late stent thrombosis especially in the extended phase