In-Stent Neoatherosclerosis as a Mechanism of Stent Failure

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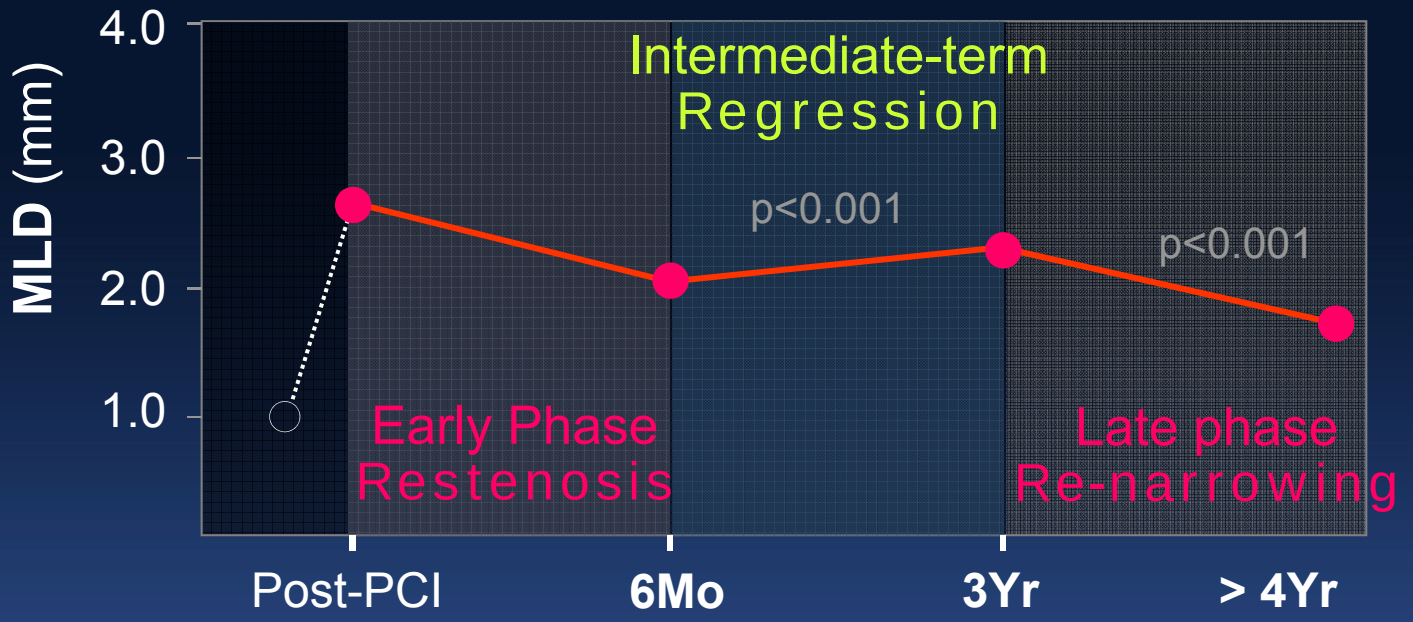
Disclosure

I have nothing to disclose

Evolving Neointima after BMS Implantation

Histologic and Angioscopic Evidences

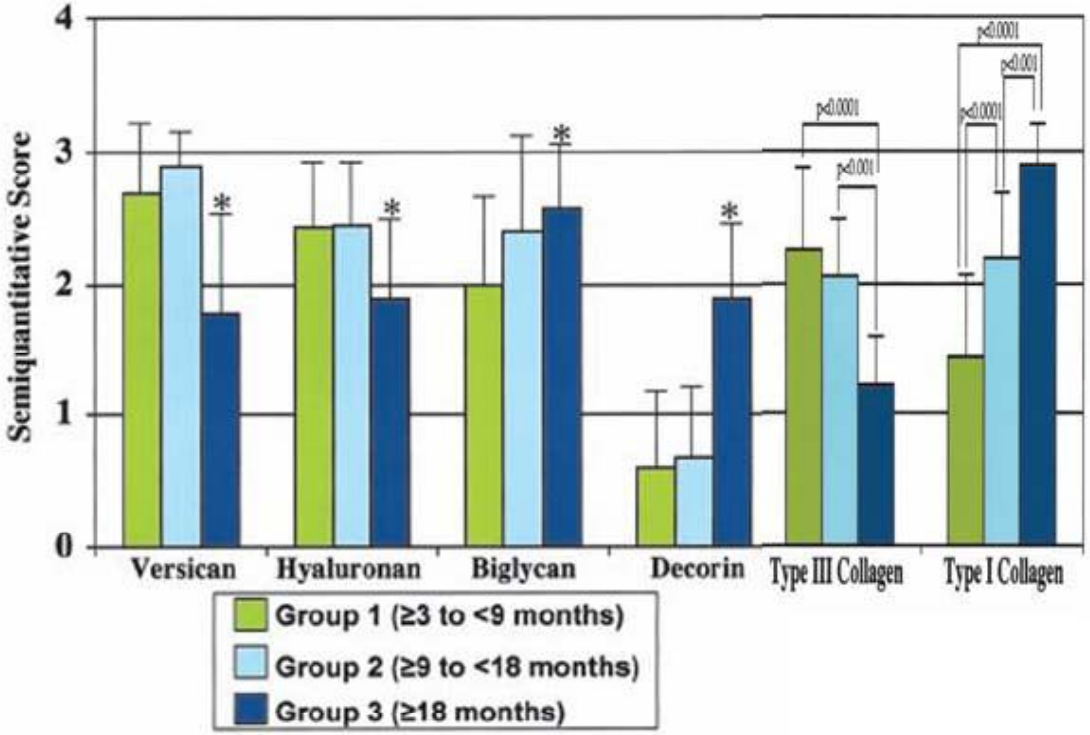
Tri-phasic Luminal Response Extended Follow-up Study 7-10 years



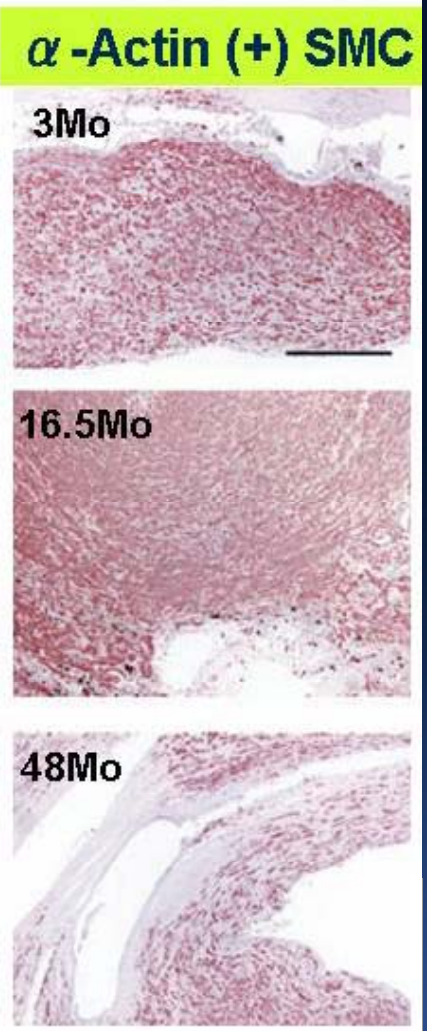
Traditionally, intimal hyperplasia has been believed to be stable with an early peak and a late quiescent period

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

Extracellular Matrix Changes in In-Stent Neointima



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

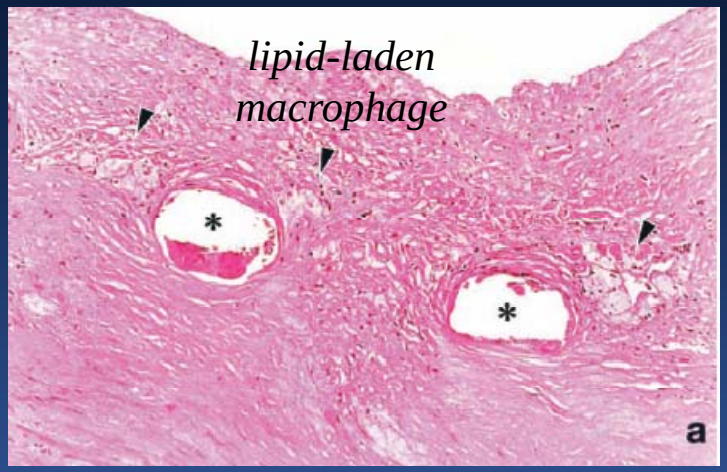


Pathologic mechanism	Proteoglycan-rich SMC proliferation	* Proteoglycan↓ * Cellularity↓ * Neointimal thinning	de-novo neoatherosclerosis

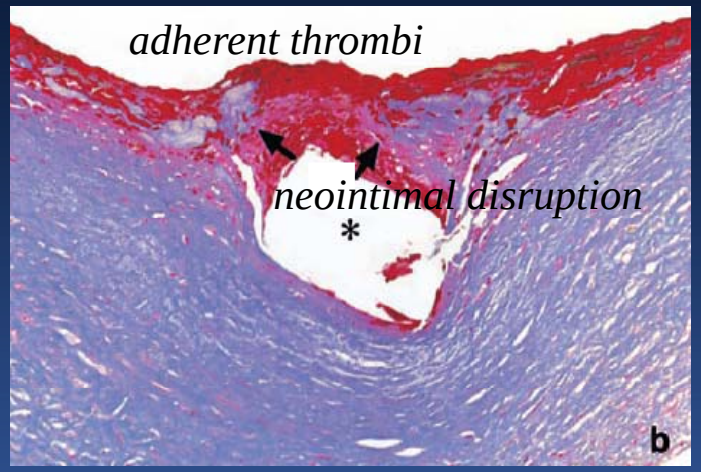
Farb et al. Circulation 2004;110:940-7

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

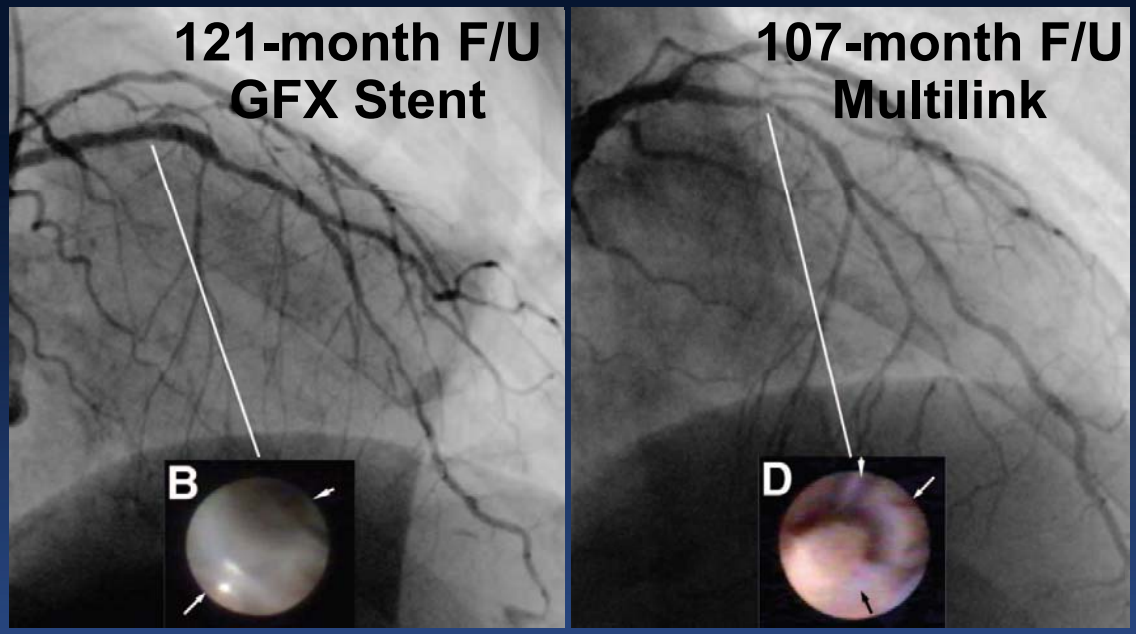


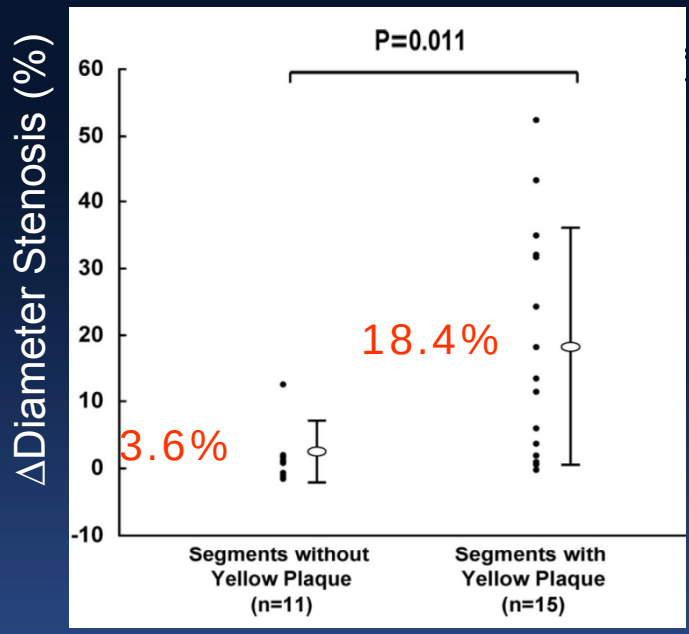
3-year f/u of Palmaz–Schatz

Hasegawa et al. Cathe 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





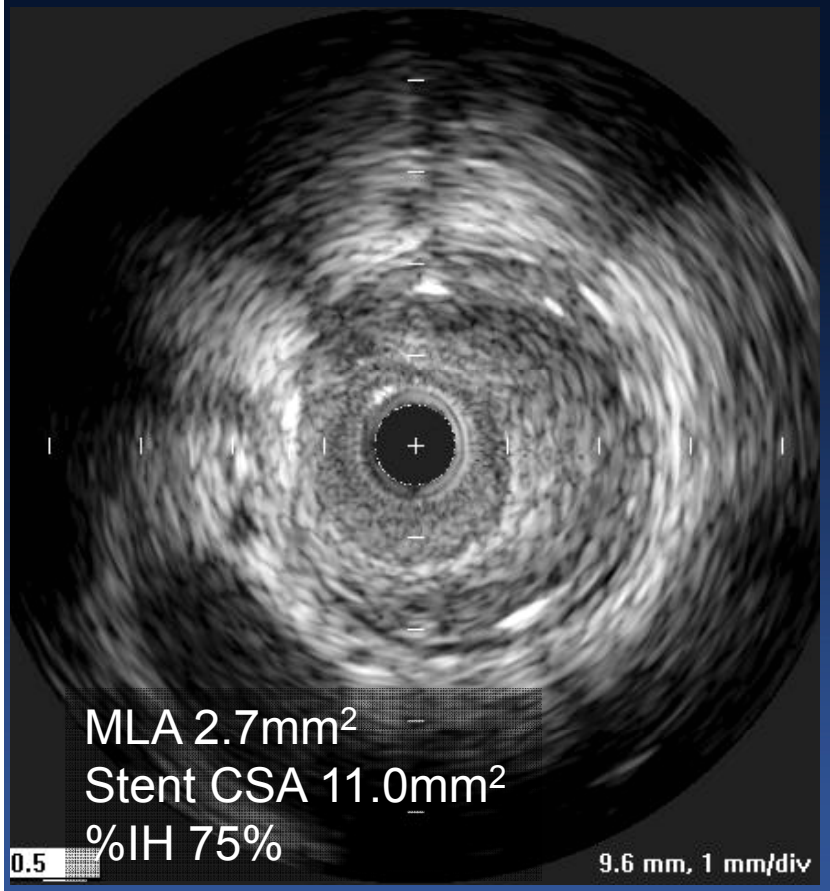
Atherosclerotic degeneration represented as yellow plaque contributed to the late luminal narrowing as well as rupture with thrombotic events

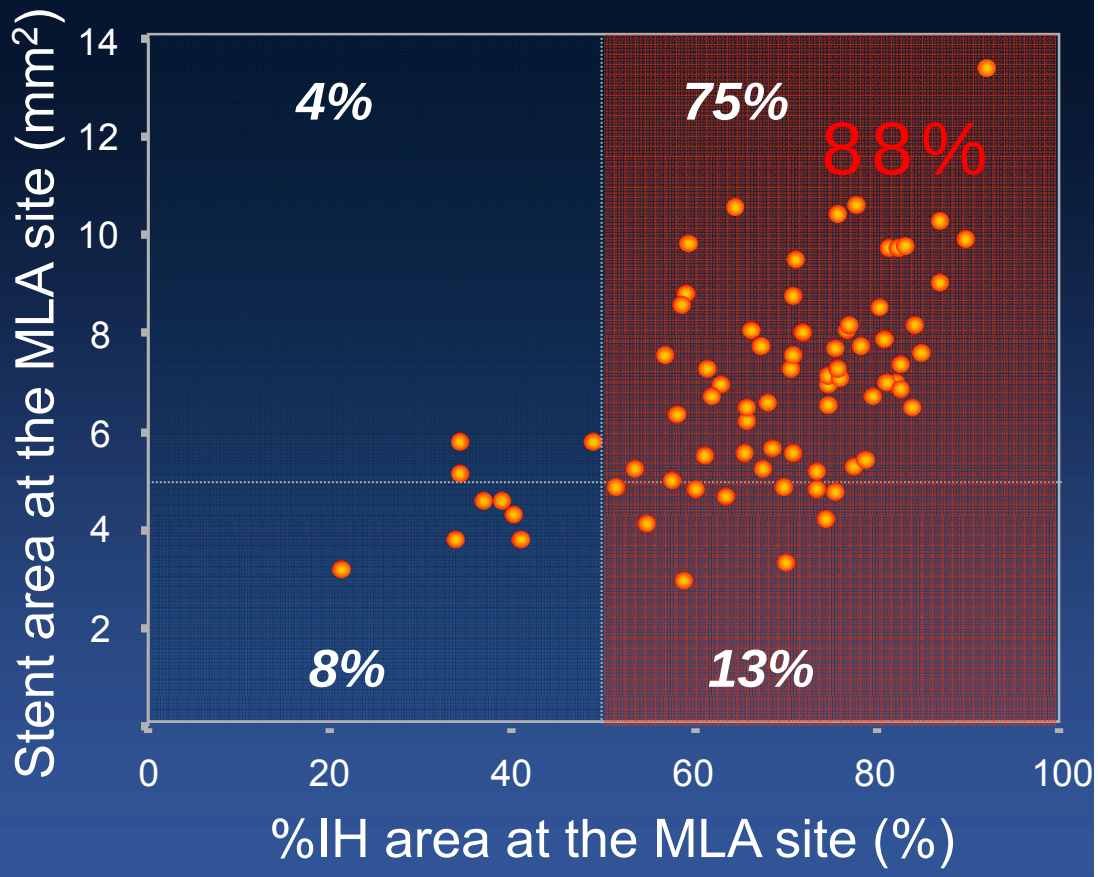
Yokoyama et al. Circ Cardiovasc Interv 2009;2:205-12

Intimal Hyperplasia after DES Implantation

Histologic and Angioscopic Evidences

Dominant IH
As a General Mechanism of DES-ISR

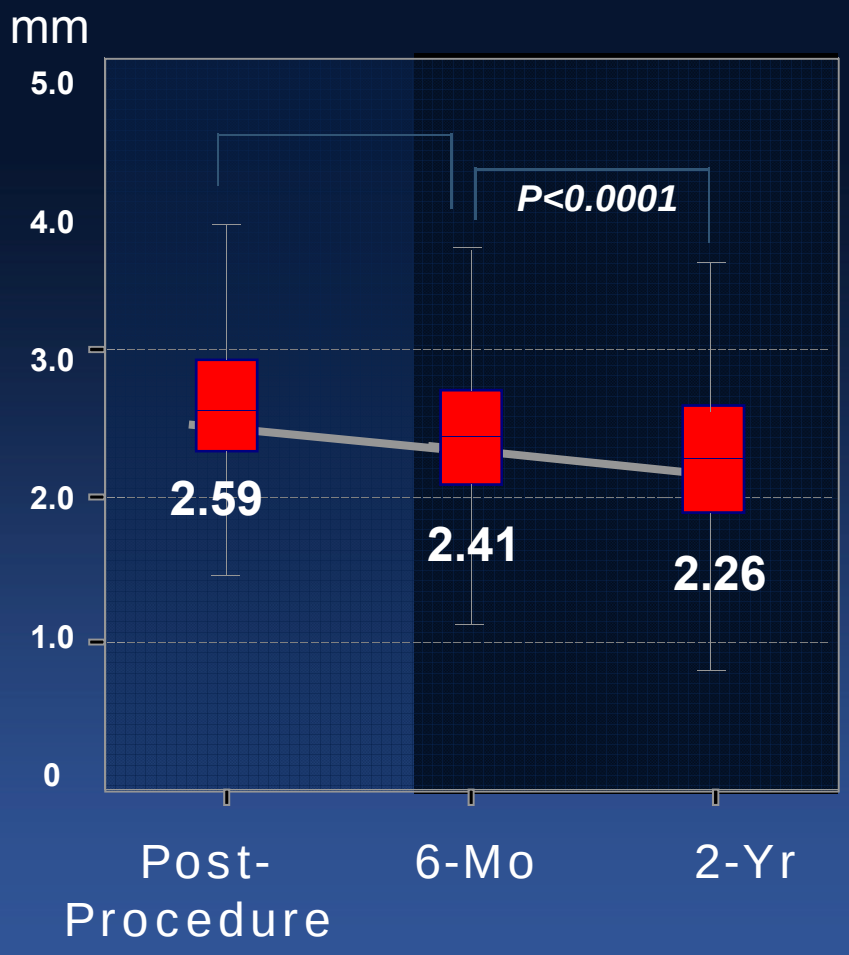




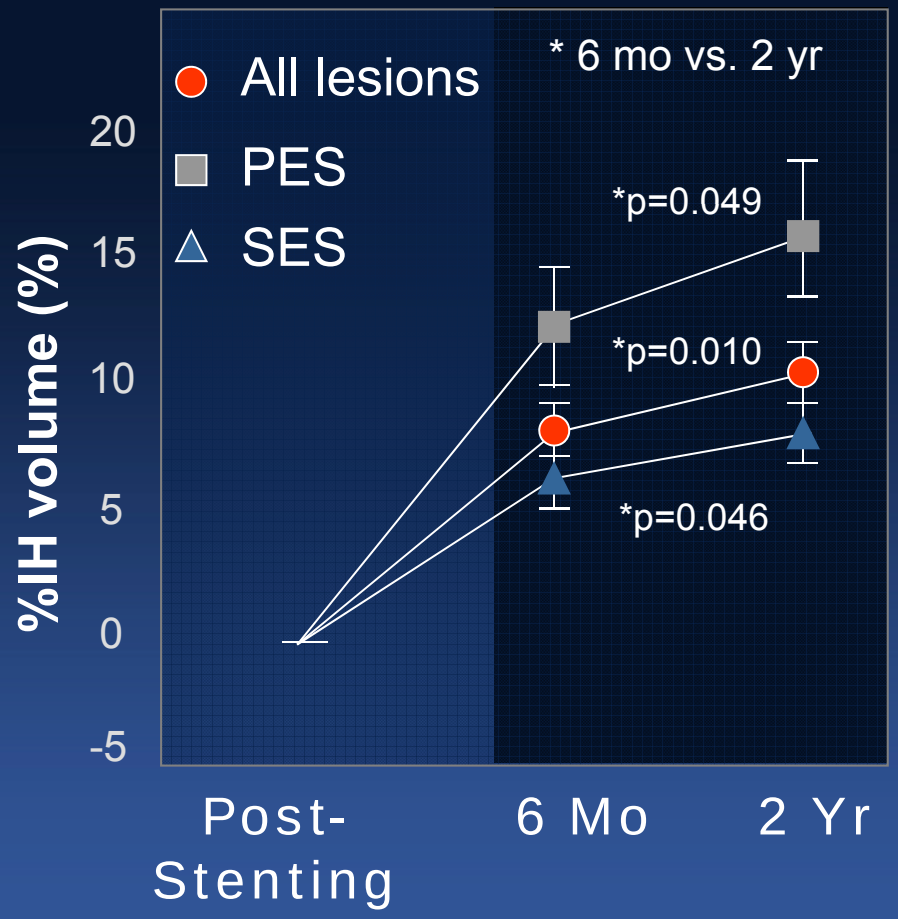
Kang et al. Circ Cardiovasc Interv 2011;4:9-14

"Late Catch-up" in DES

Serial F/U of MLD



Serial F/U %IH Volume



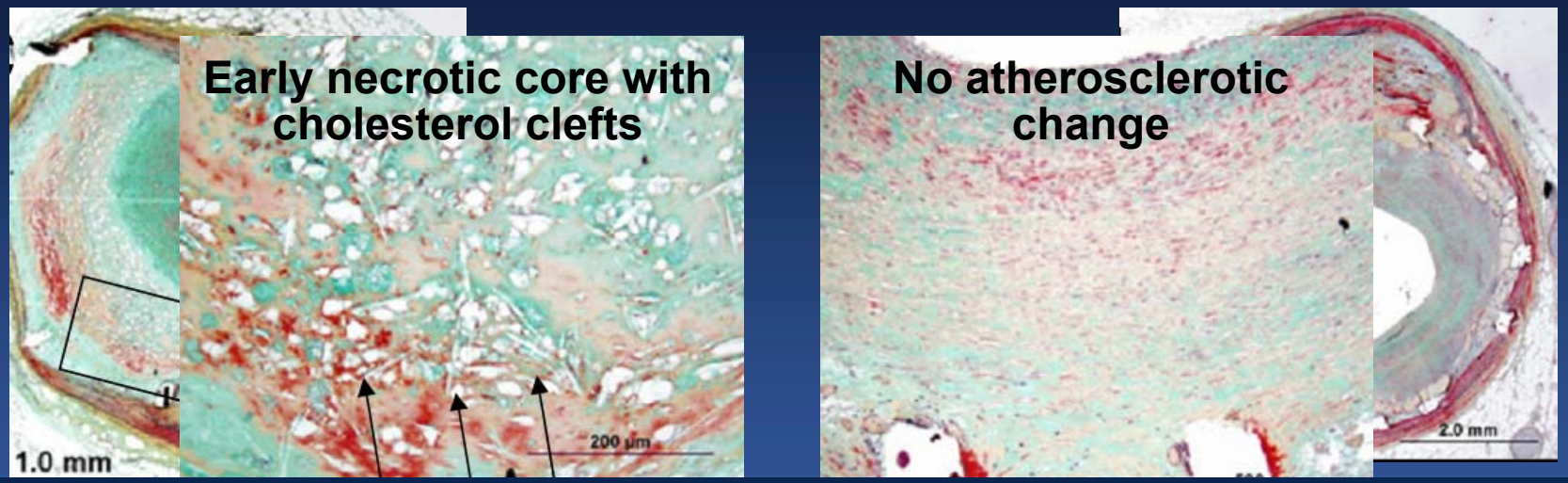
Park et al. Int J Cardiol. 2010 Sep in press

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

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

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

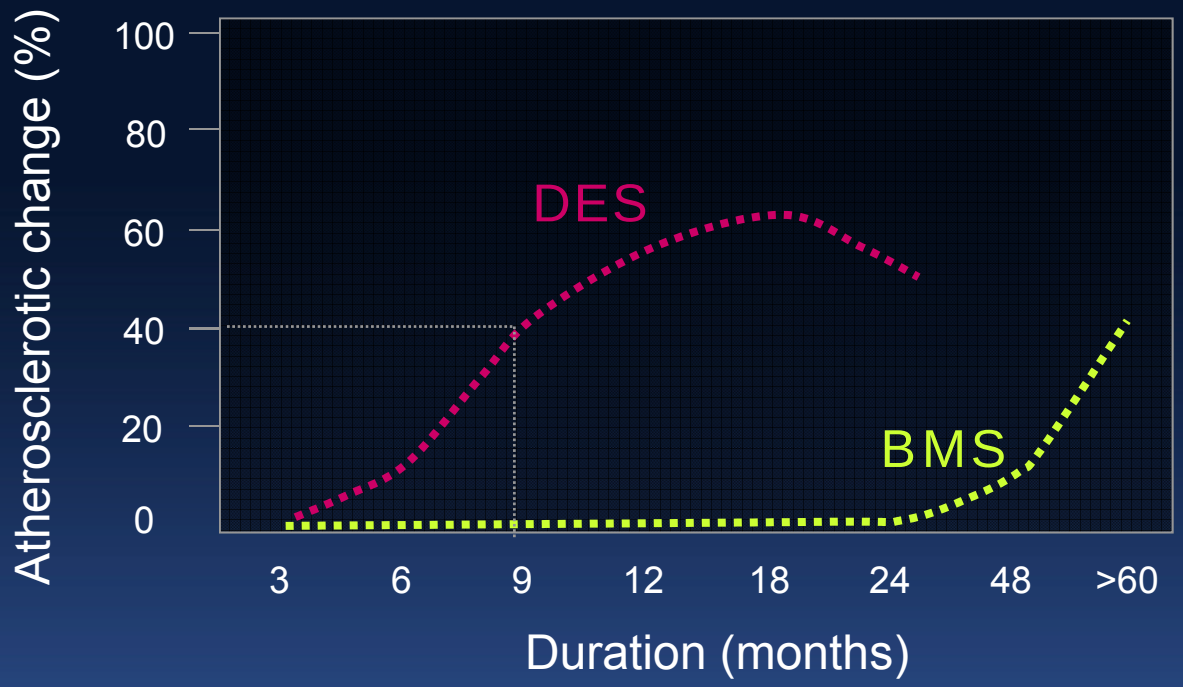
Chieffo et al. Am J Cardiol 2009;104:1660–7



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 Cariovasc Imaging 2009;2:625-8

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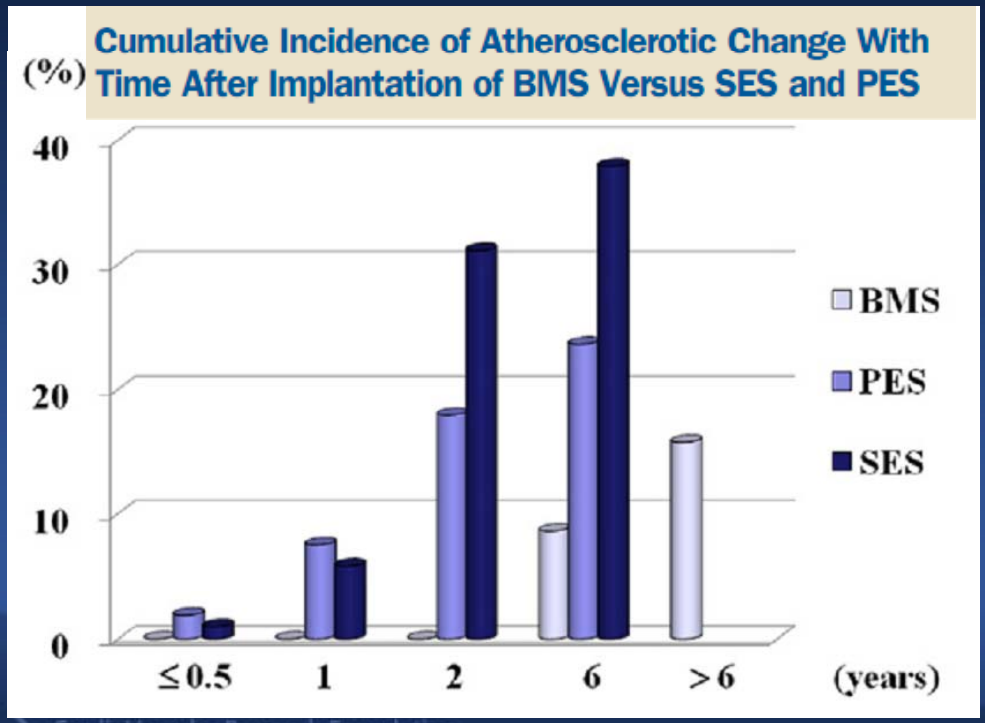
doi:10.1016/j.jacc.2011.01.011

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*



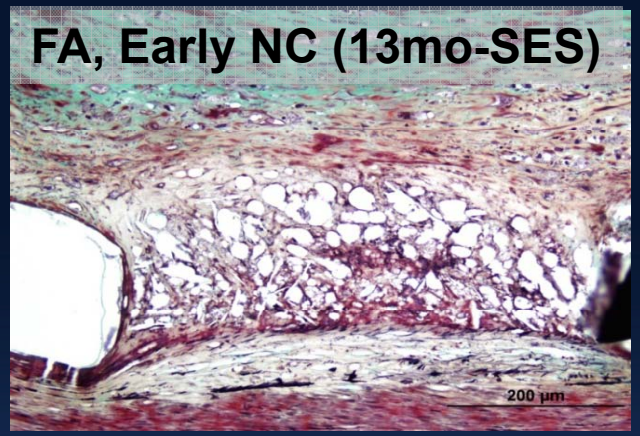
Neoatherosclerosis

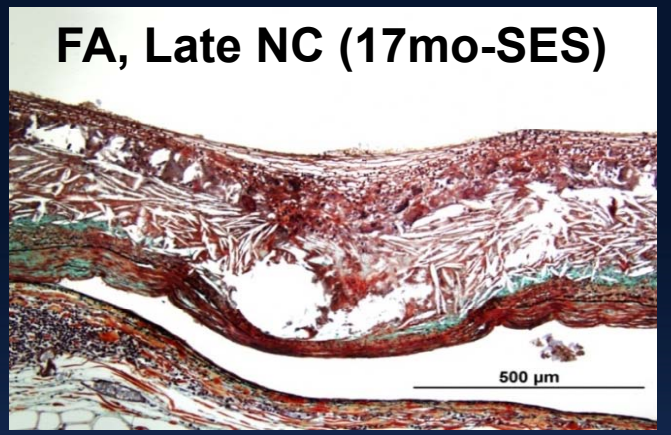
	DES	BMS
Incidence	31%	16%
Median F/U time point	14 Mo	72 Mo

Nakazawa et al. JACC 2011;57:1314–22

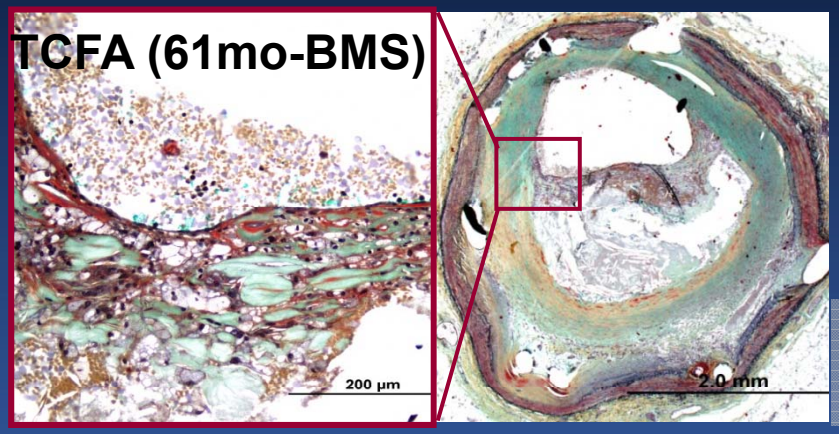
Various Stages of Neoatherosclerosis

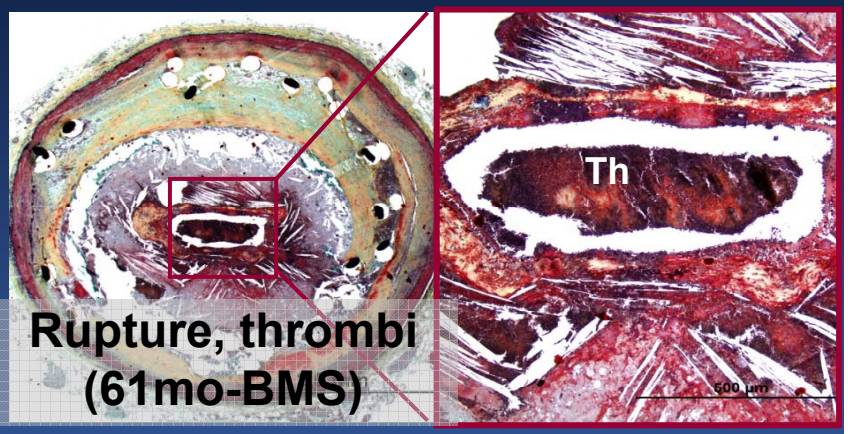
DES





BMS





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

Independent Risk Factors for Neoatherosclerosis

	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

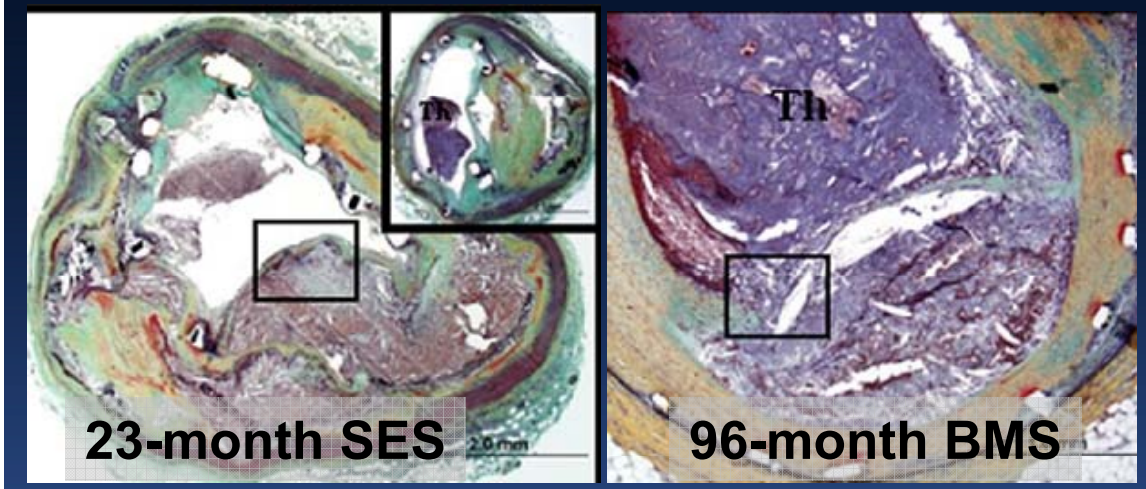
Nakazawa et al. JACC 2011;57:1314–22

More Advanced Neoatherosclerosis

TCFA-Containing Neointima

Intimal rupture

Thrombosis



"Unstable Neointima"

>5 years in BMS

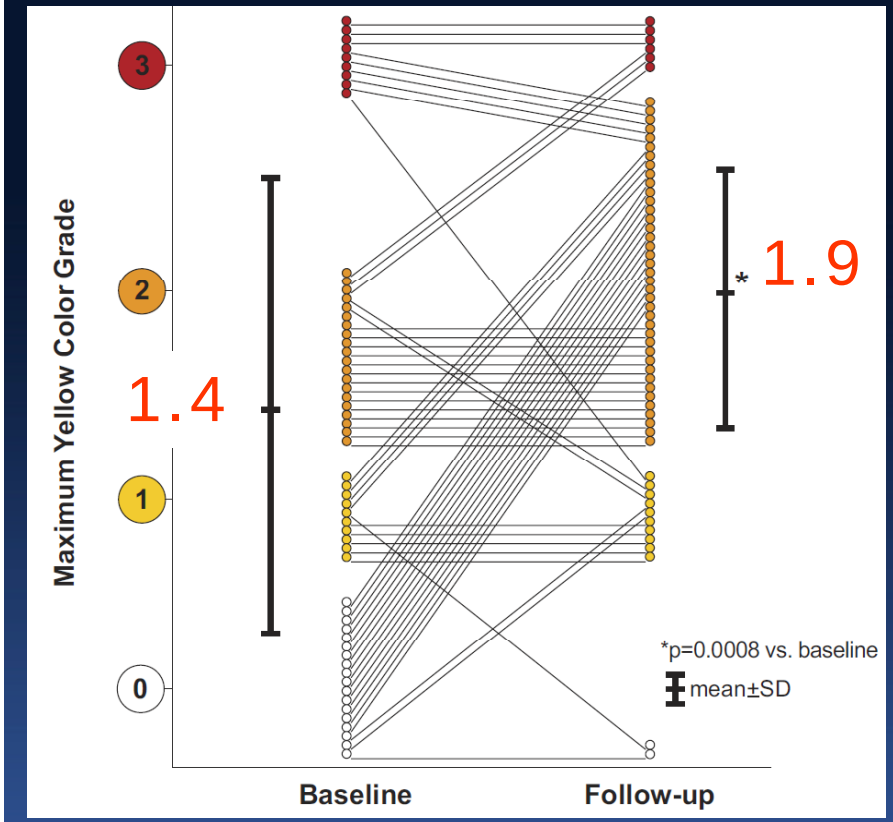
≤2 years in DES

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

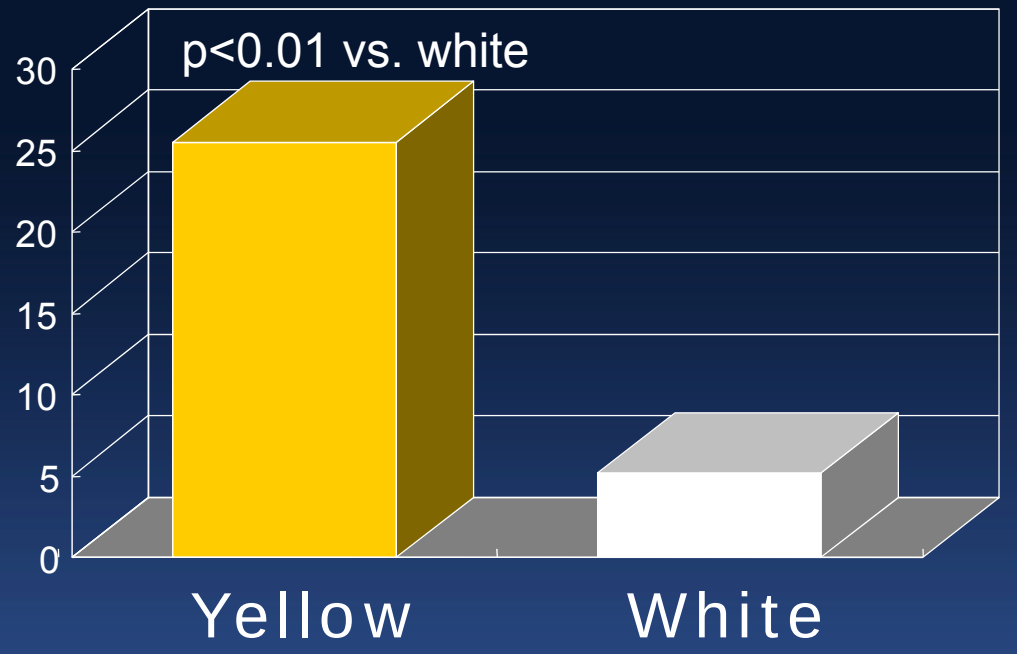
Nakazawa et al. JACC 2011;57:1314-22

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**

Higo et al. JACC Cardiovasc Imaging 2009;2:616-24

Neoatherosclerosis

Contributing Mechanism of Stent Failure

Broad Spectrum of Clinical Presentations

from In-Stent Restenosis
to Very Late Stent Thrombosis

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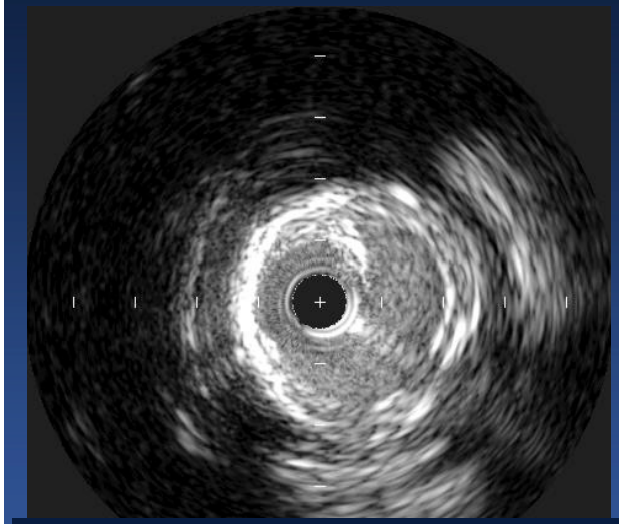
doi:10.1016/j.jacc.2009.10.077

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)

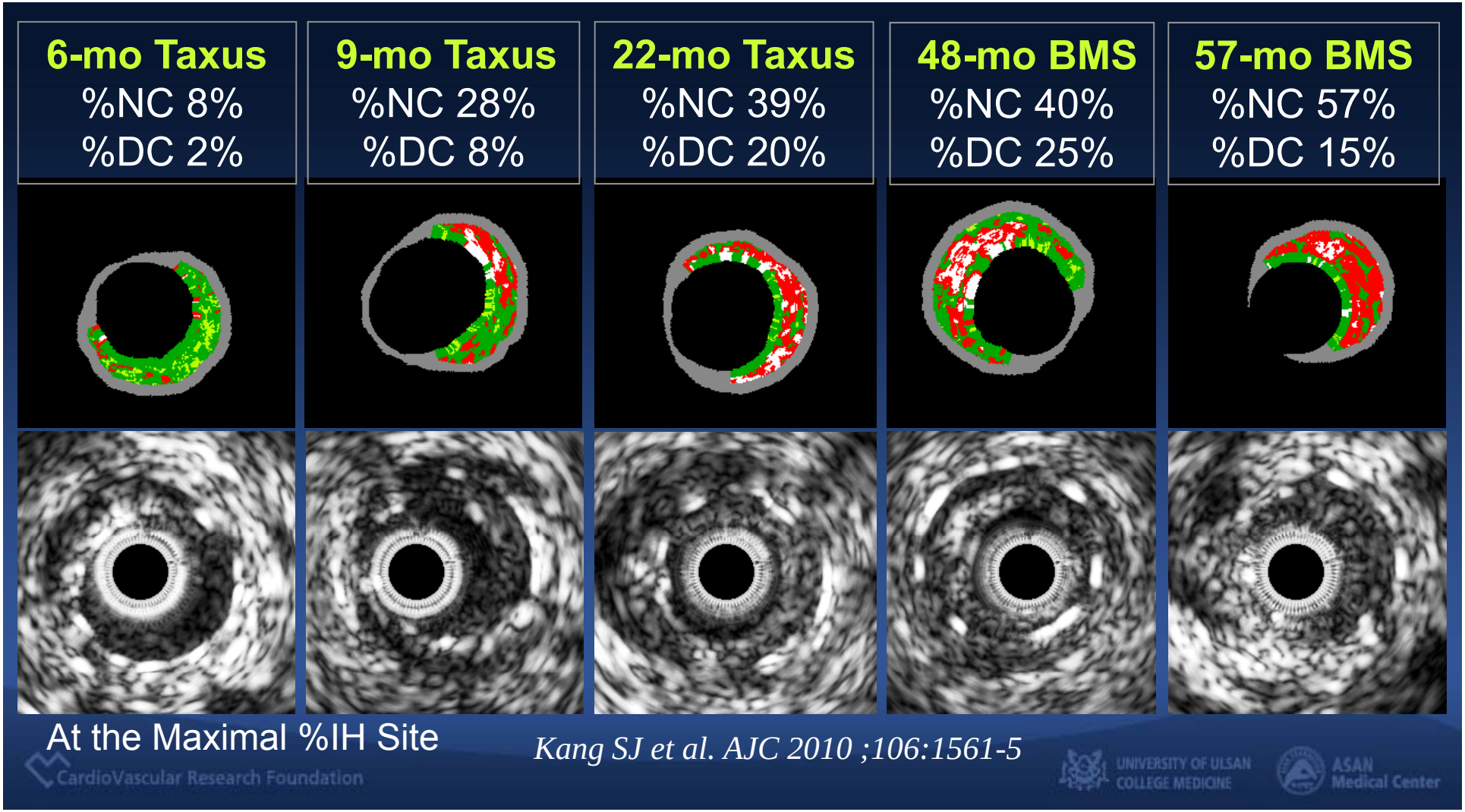


	DES (n=23)	BMS (n=7)
Mean EEM CSA, mm^2	19.5±6.0	18.3±4.1
Mean Lumen CSA, mm^2	4.2±1.4	4.7±4.6
Mean Neointima, mm^2	3.0±1.1	5.0±1.7*
Minimal stent CSA, mm^2	6.1±1.5	7.4±3.7
Neointima rupture	**10 (44%)**	**7 (100%)***

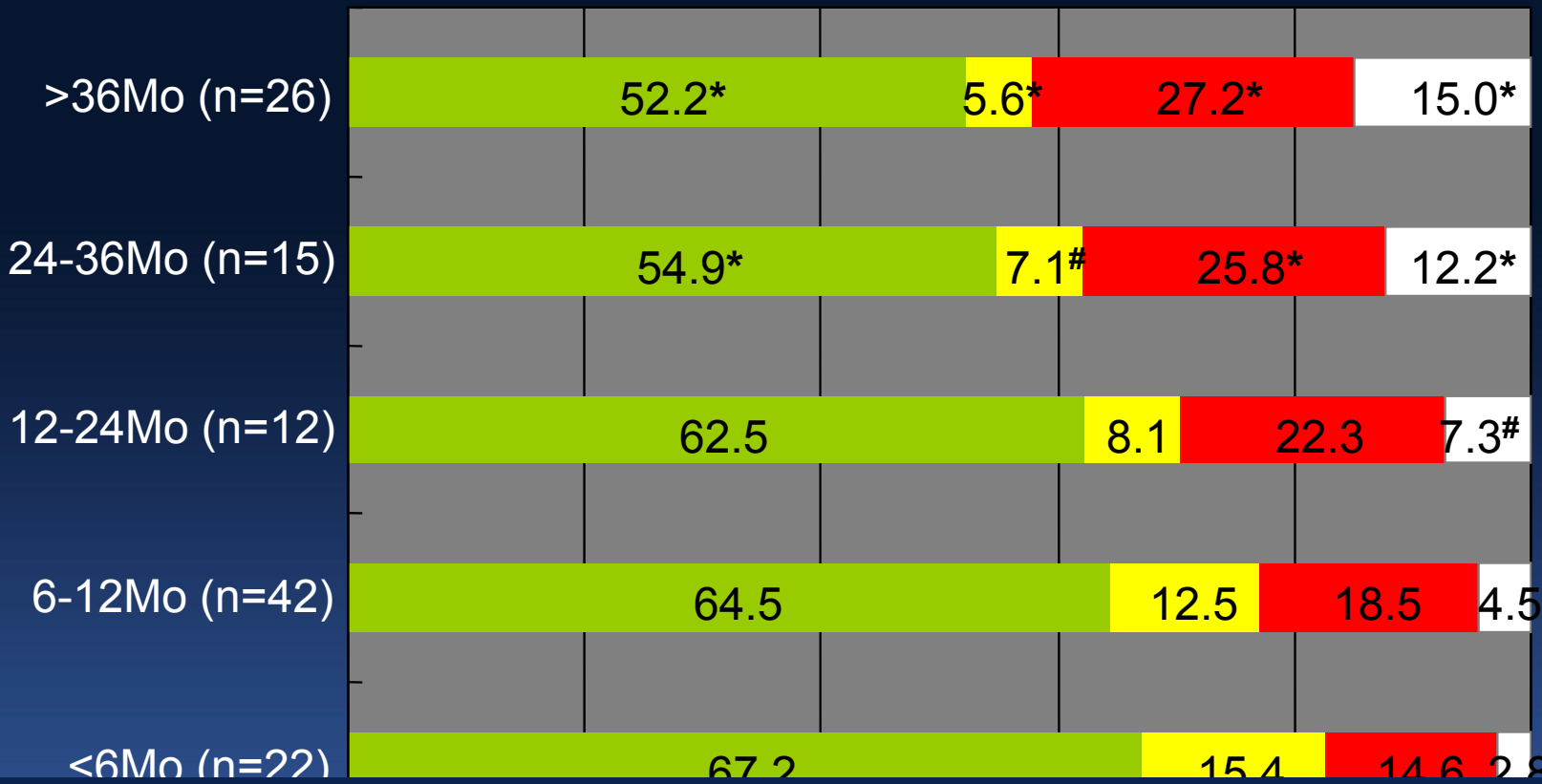
Neoatherosclerosis may contribute to the development of VLST as a common mechanism in BMS and DES

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

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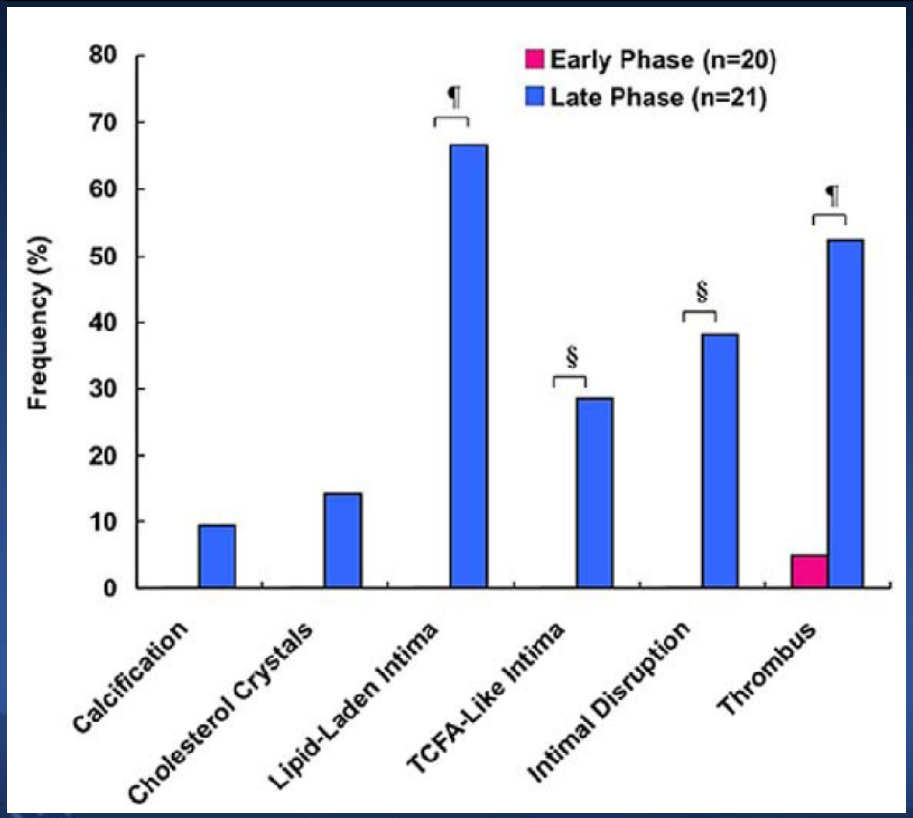
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.08.032

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

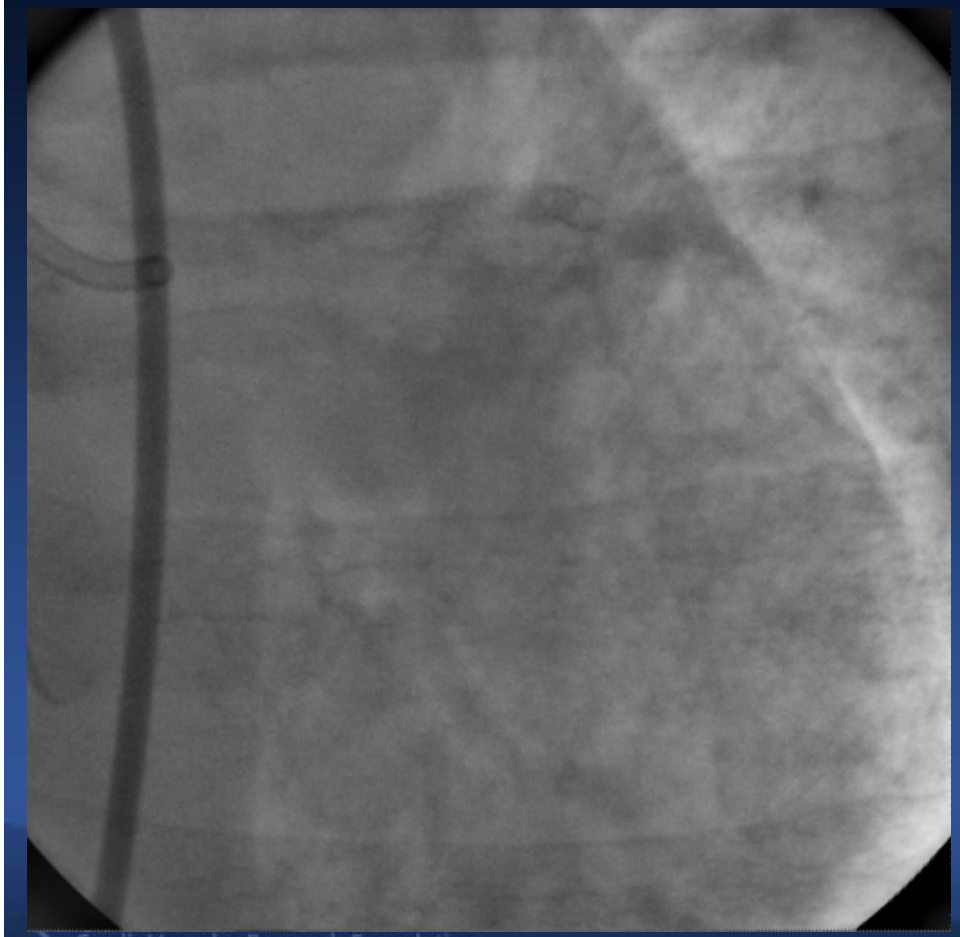


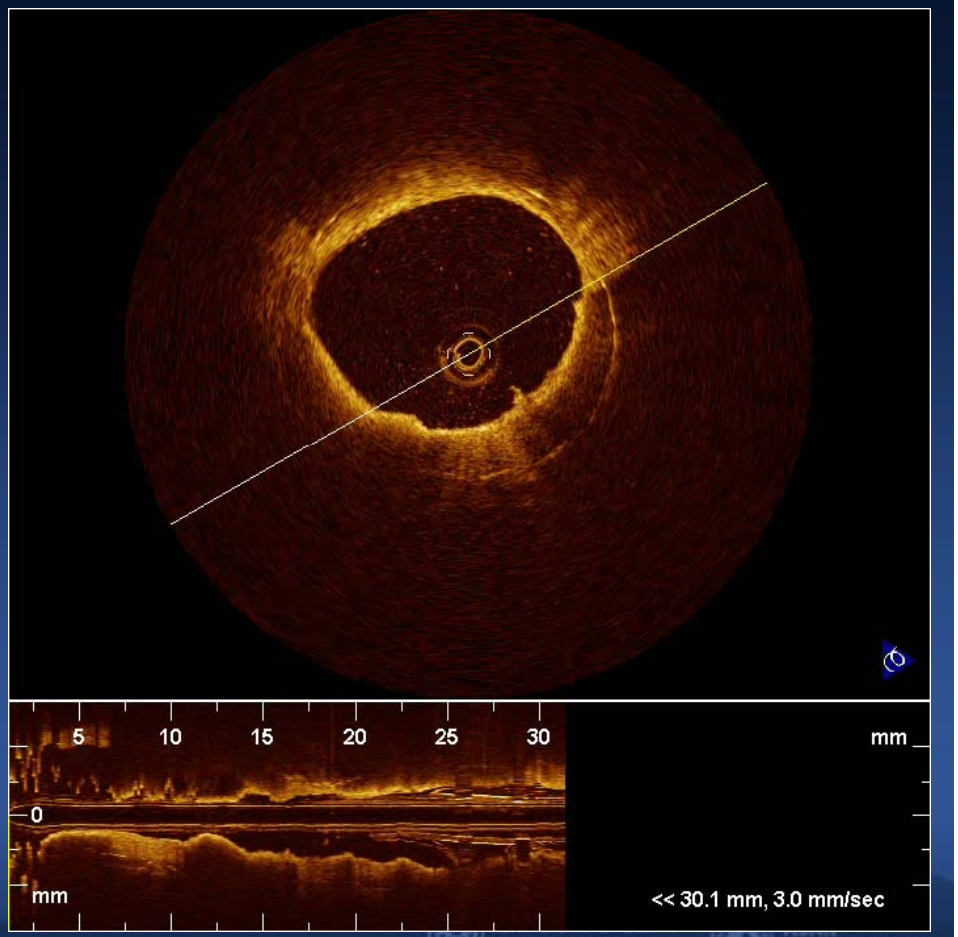
- Neointima transforms into lipid-laden atherosclerotic tissue in late phase after BMS
- Lipid-laden intima frequently has intimal disruption, thrombi and neovascularization

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

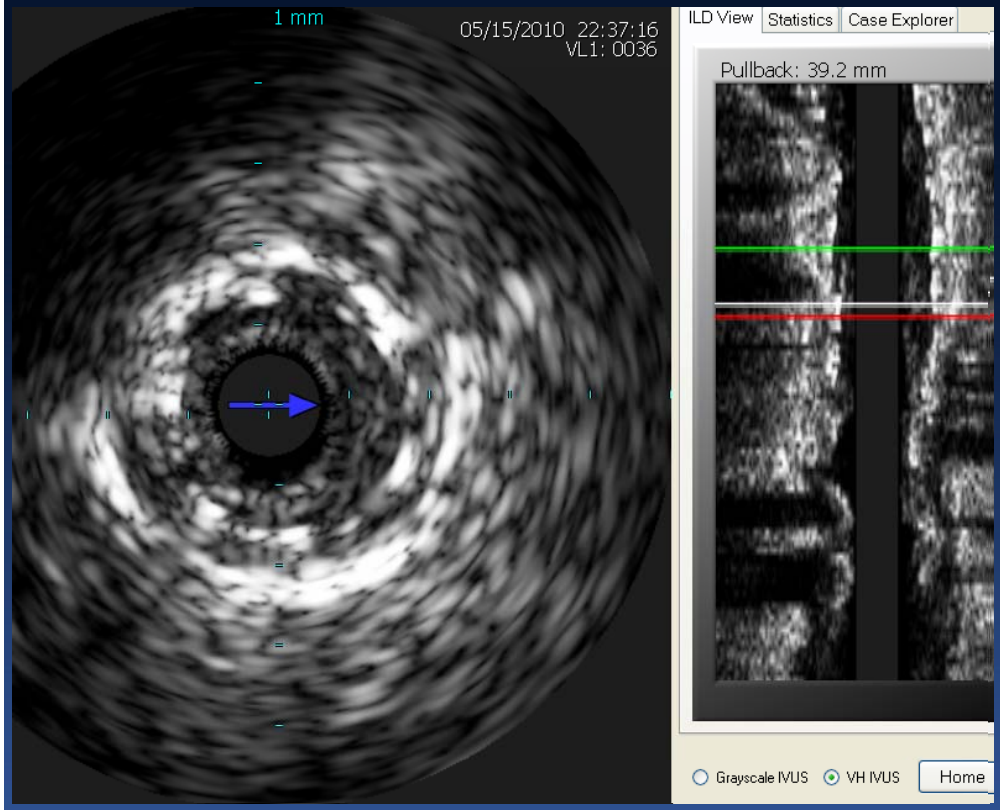
71 Year-Old Female

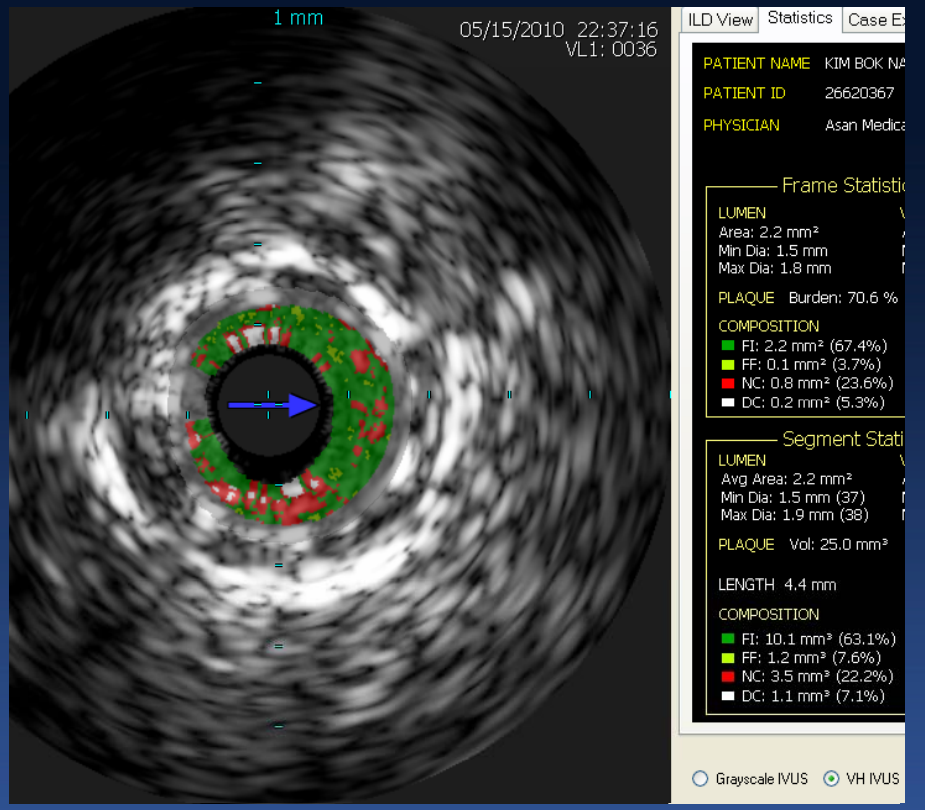
- 8YA Stable angina →s/p BMS at pRCA and mLAD
- 7YA mLAD diffuse ISR → triple anti-platelet
- Resting chest pain → "***Unstable Angina***"





Virtual Histology





In-Stent Neoatherosclerosis

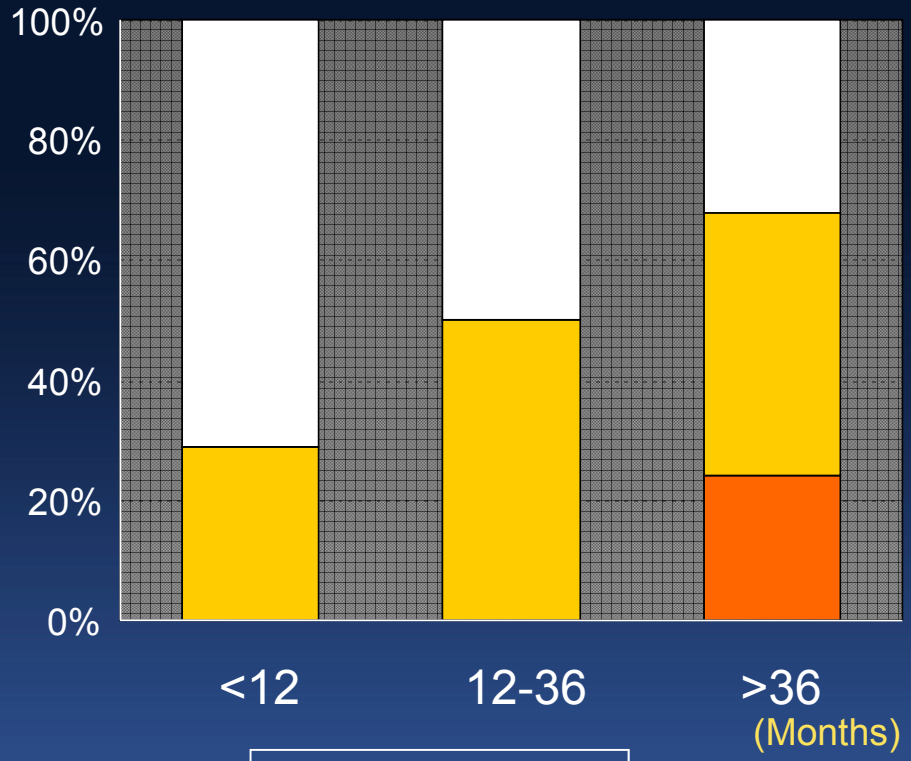
OCT Analysis in 50 DES-ISR Lesions with %IH>50%

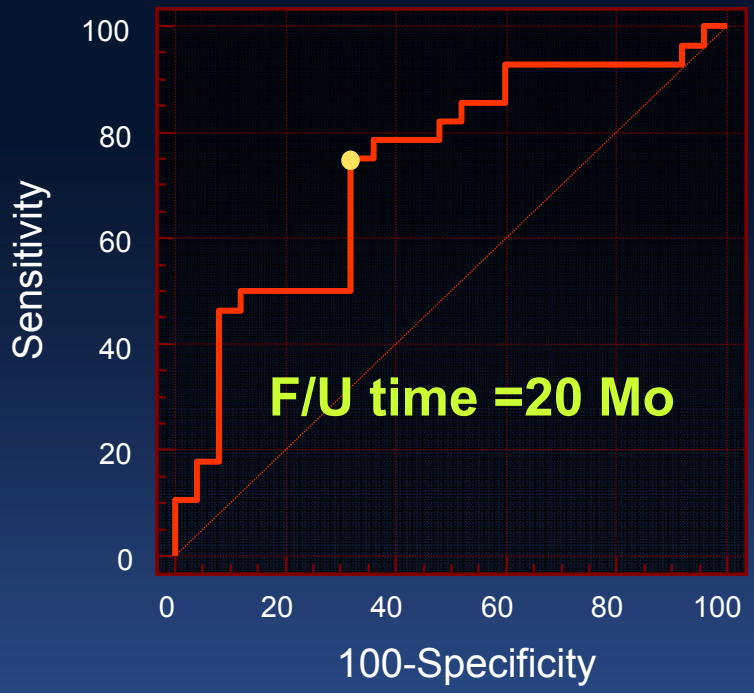
	Total N=50	Stable N=30	Unstable N=20	P
Follow-up (months)	32 (9-52)	14 (8-51)	41 (16-56)	0.178
Lipid neointima	45 (90%)	25 (83%)	20 (100%)	0.067
Fibrous cap thickness, μm	60 (50-162)	100 (60-205)	55 (42-105)	0.006
Incidence of thrombi	29 (58%)	13 (43%)	16 (80%)	0.010
Incidence of red thrombi	7 (14%)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

DES Follow-up >20 Months

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

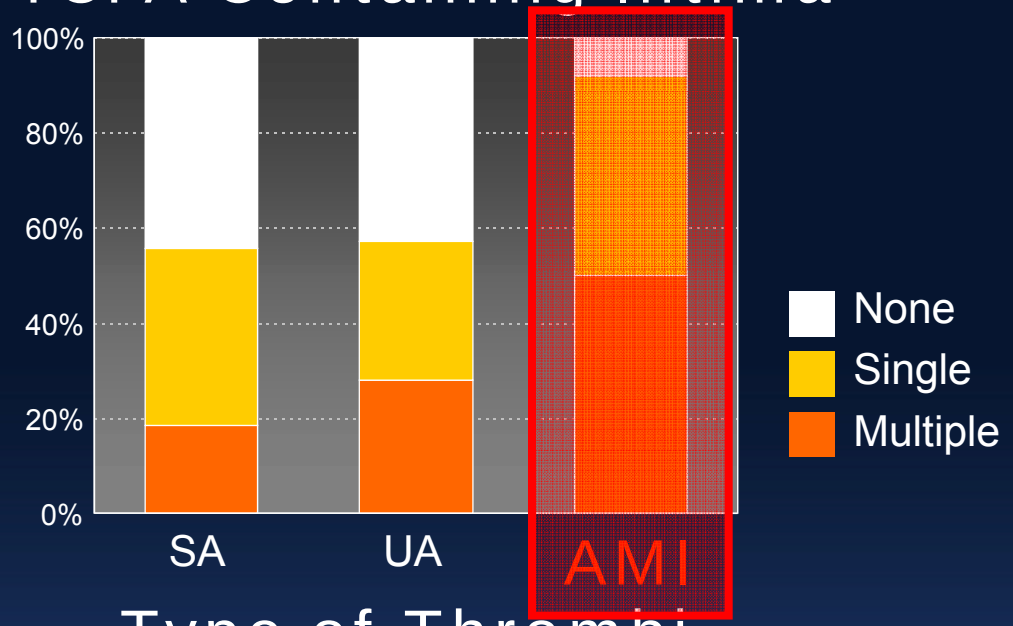




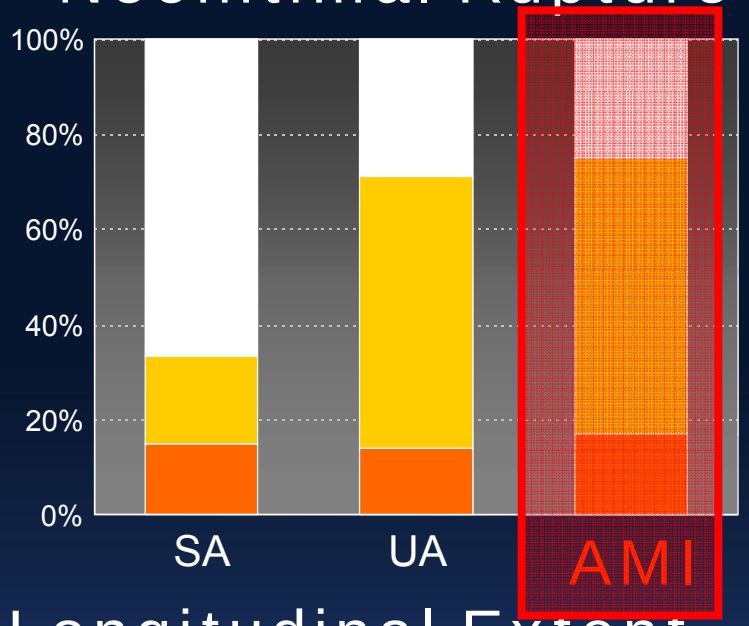
AUC=0.73
Sensitivity 75%
Specificity 68%

Kang et al. Accepted in Circulation 2011

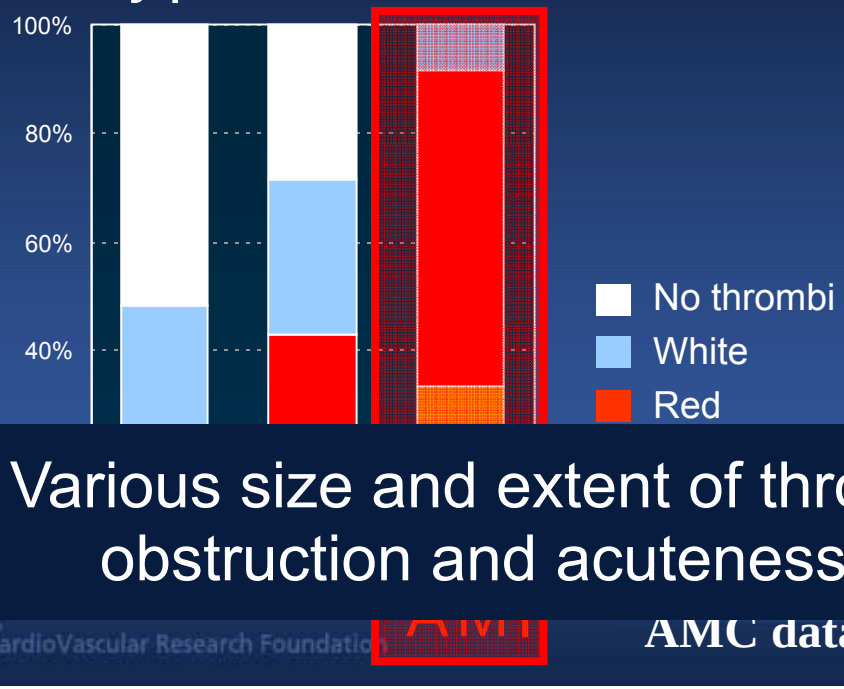
TCFA-Containing Intima



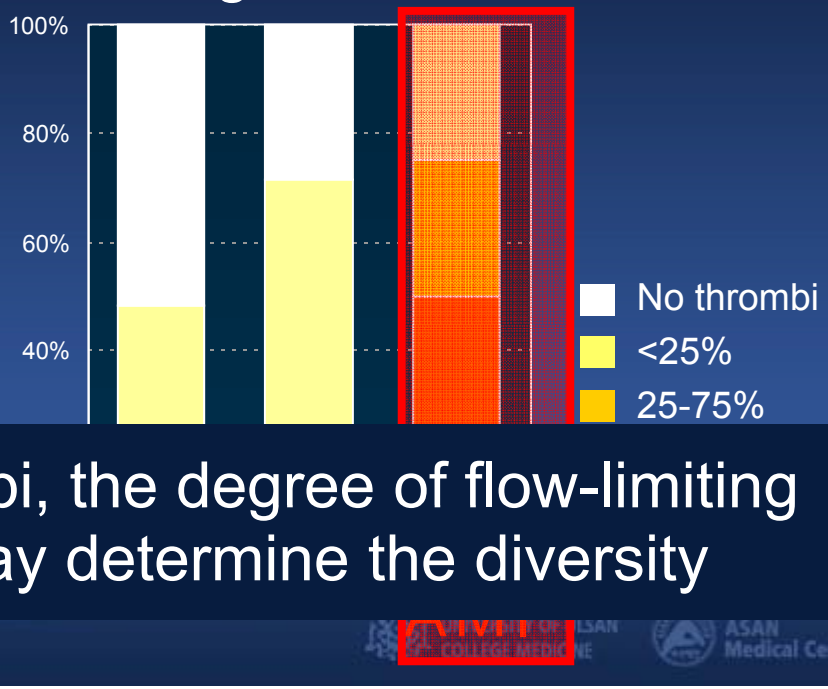
Neointimal Rupture



Type of Thrombi

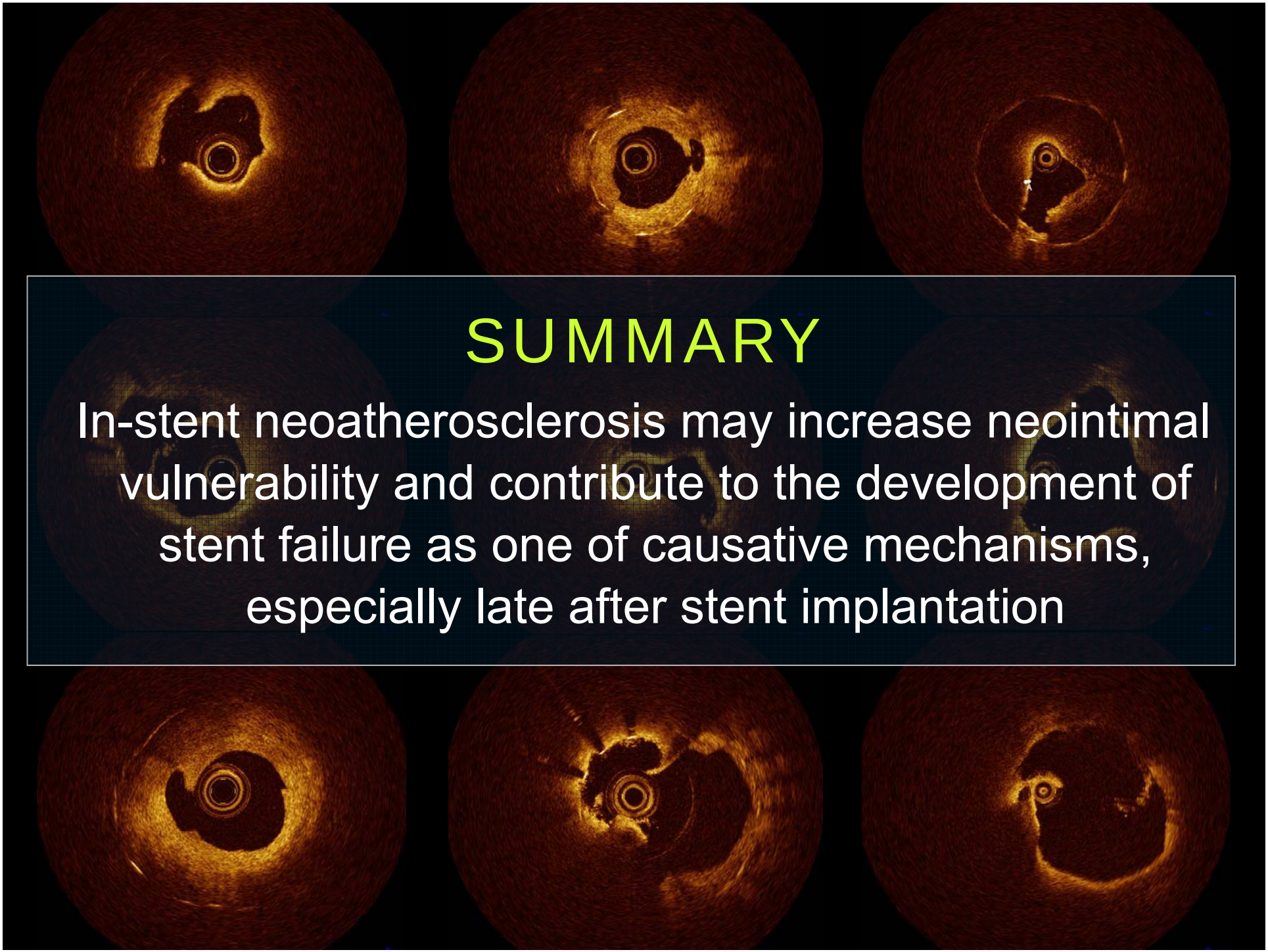


Longitudinal Extent



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

AMC data



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