Main Mechanisms of DES In-stent Restenosis: **Underexpansion, Intimal Hyperplasia, Neoatherosclerosis, Stent Fracture and Malapposition**

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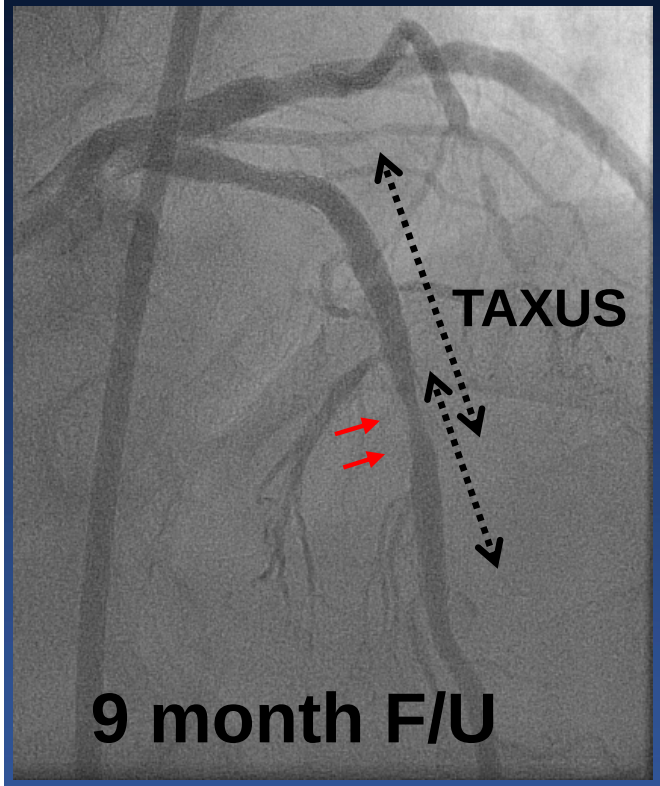
Disclosure

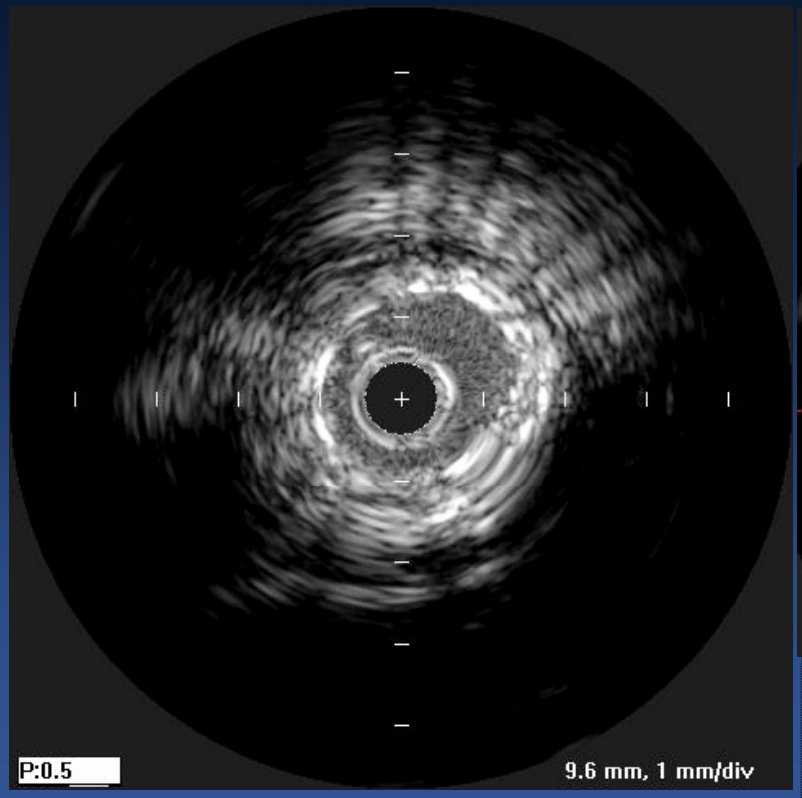
I have nothing to disclose

ISR – Underexpansion

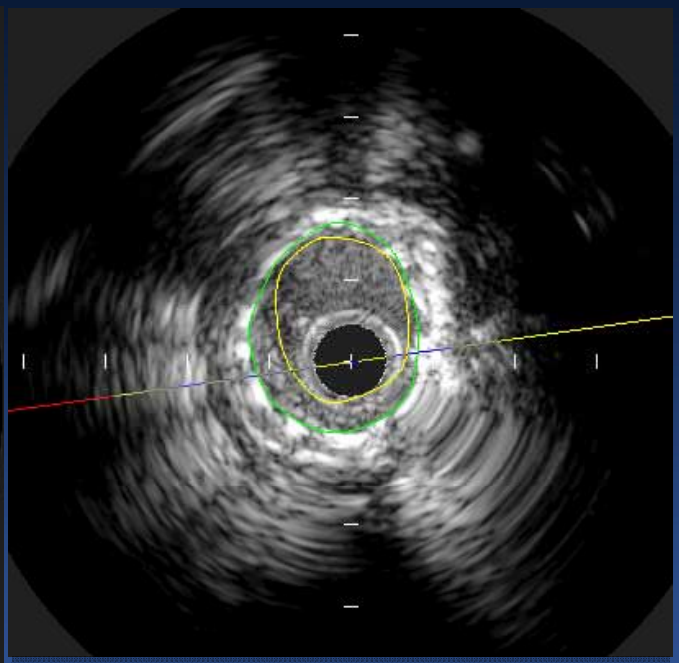
56-year old male

- Primary PCI for STEMI →TAXUS 3.0 (28) and 3.5 (28)
- After 9 months, effort-related chest pain





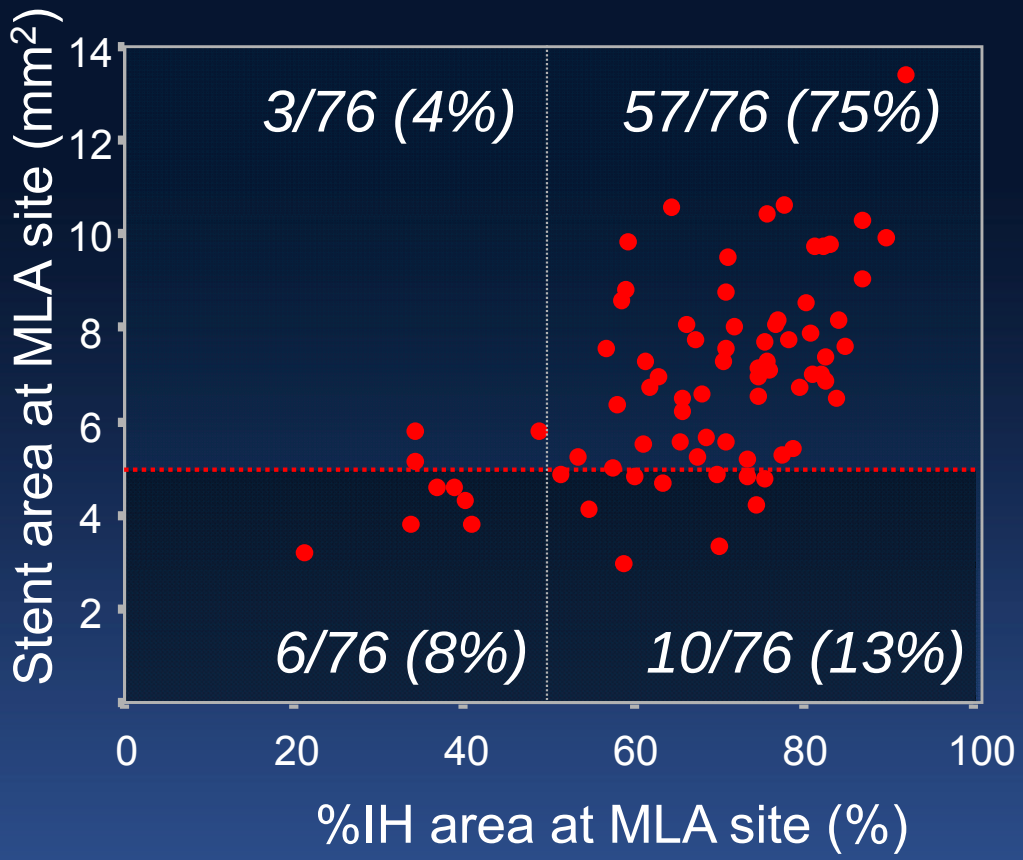
At the MLA site



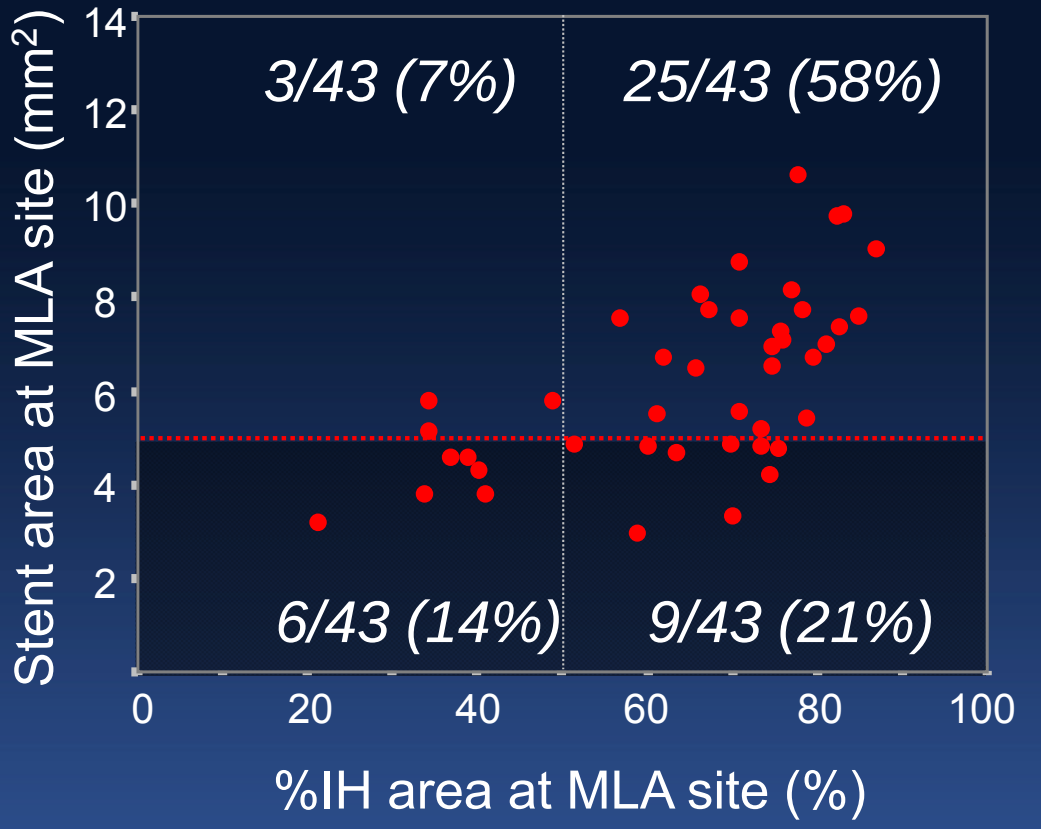
Stent CSA 4.0 mm^2
MLA 2.6 mm^2
%IH/stent 36%

Mechanism of DES-ISR

Overall lesions

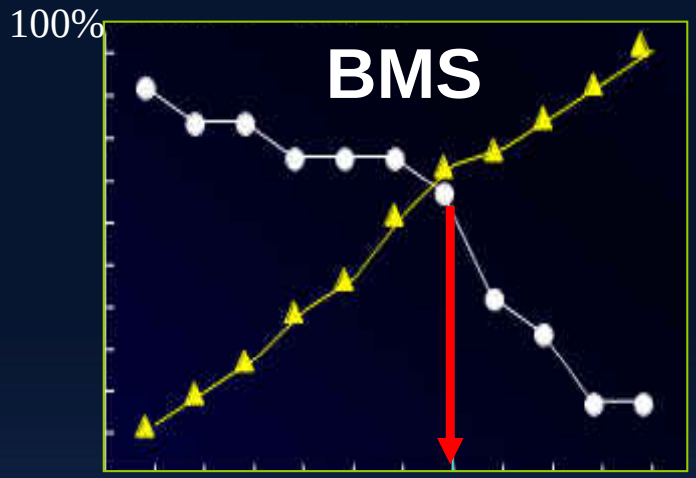


Stent length >28mm



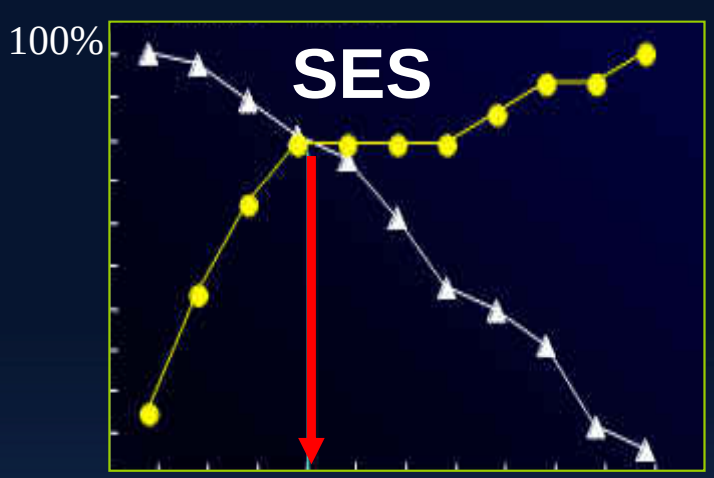
IVUS optimization is useful to correct stent underexpansion especially in the long lesion

Underexpansion Predicts DES Restenosis



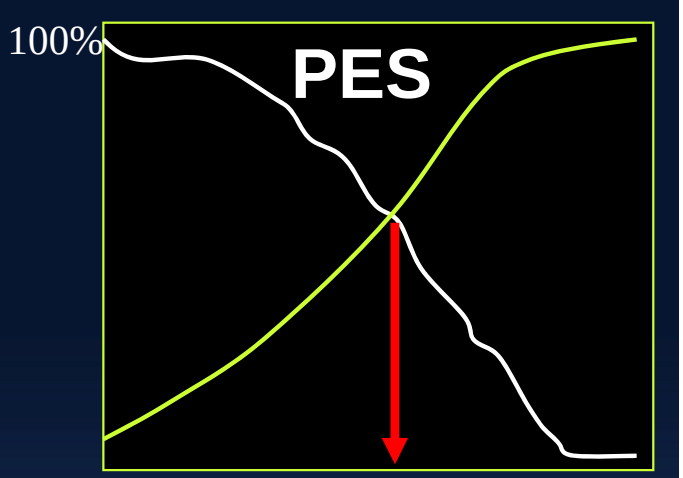
MSA 6.5mm²

Predictive value 56%



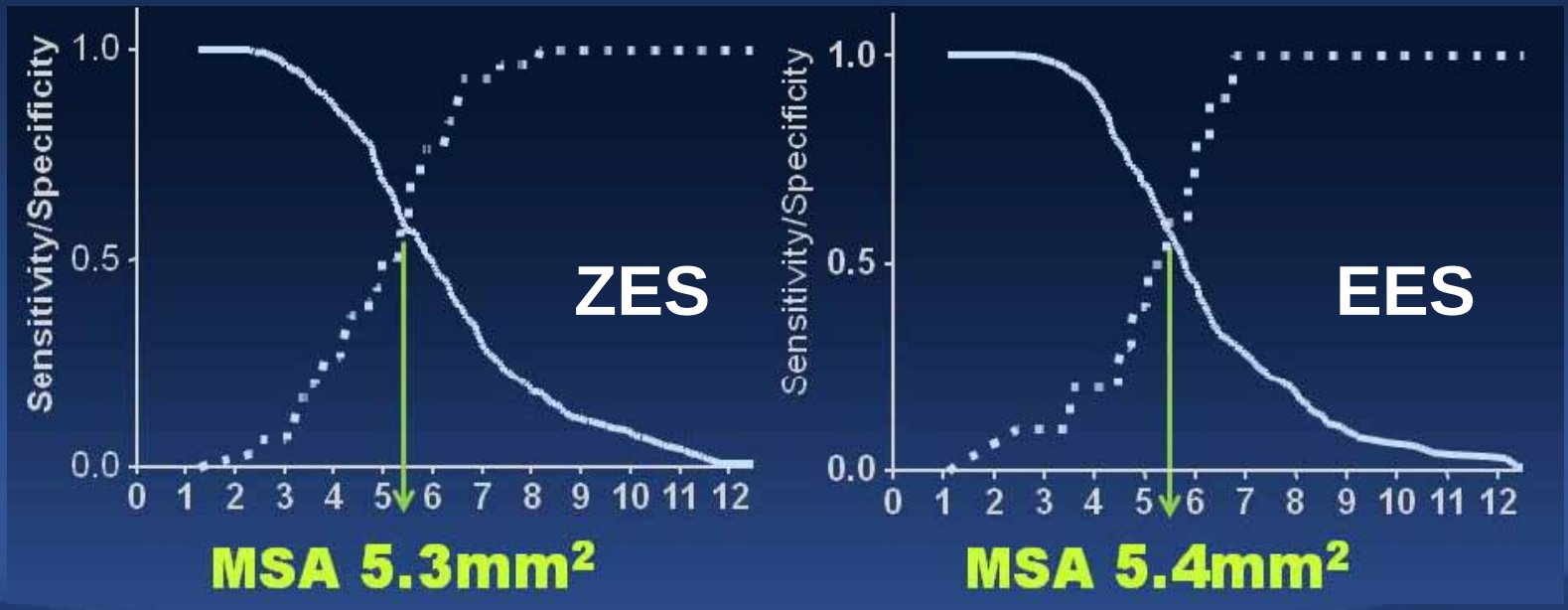
MSA 5.0mm²

Predictive value 90%



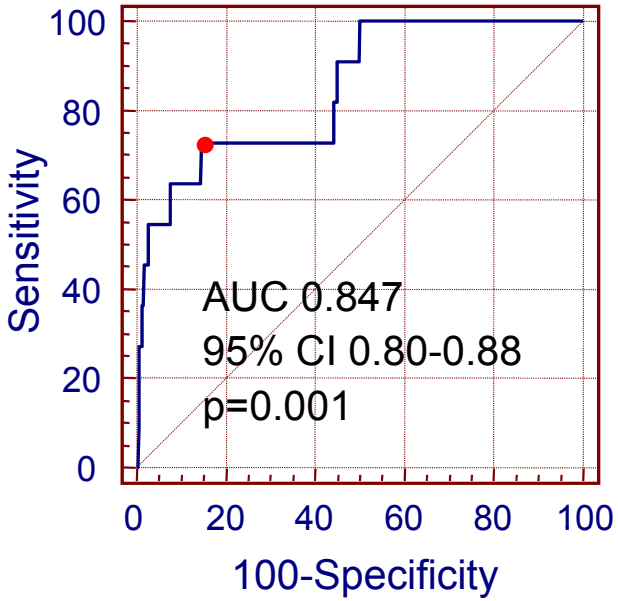
MSA 5.7mm²

Eur Heart J 2006;27:1305-10
JACC Interv 2009;2:1269-75



Song et al. Catheter Cardiovasc Interv 2012 (in press)

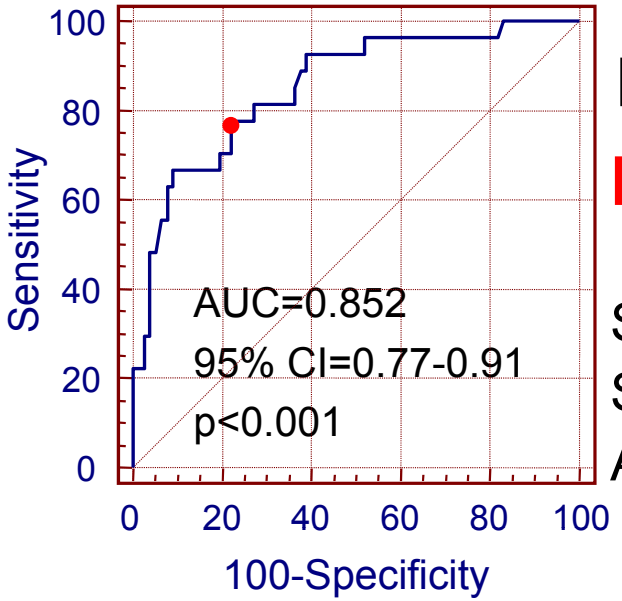
MSA Cut-offs Predicting 9-month ISR



LAD ostium

MSA 6.3mm²

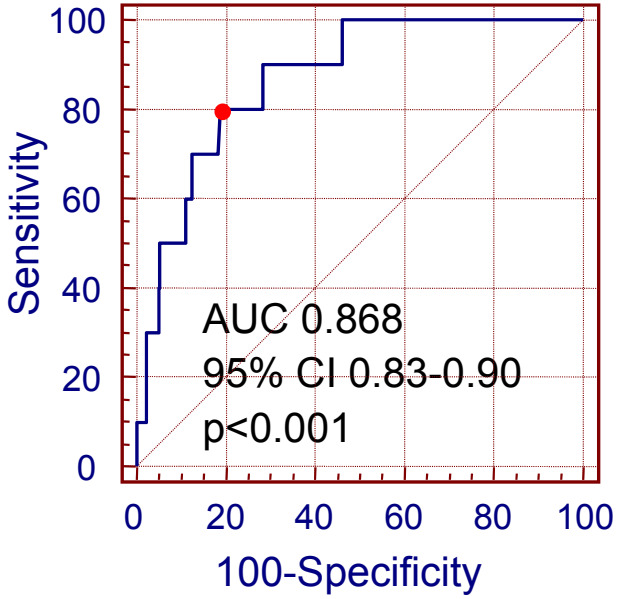
Sensitivity 73%
Specificity 85%
Accuracy 84%



LCX ostium

MSA 5.0mm²

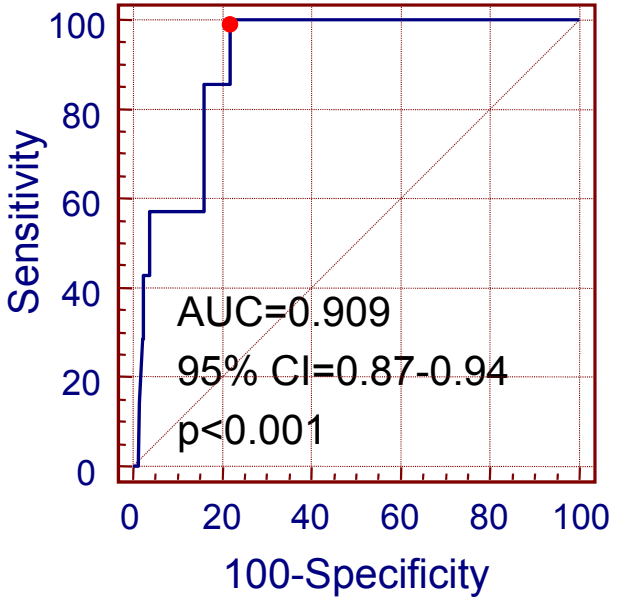
Sensitivity 78%
Specificity 78%
Accuracy 78%



Proximal LM

MSA 8.2mm²

Sensitivity 80%
Specificity 81%
Accuracy 81%



POC

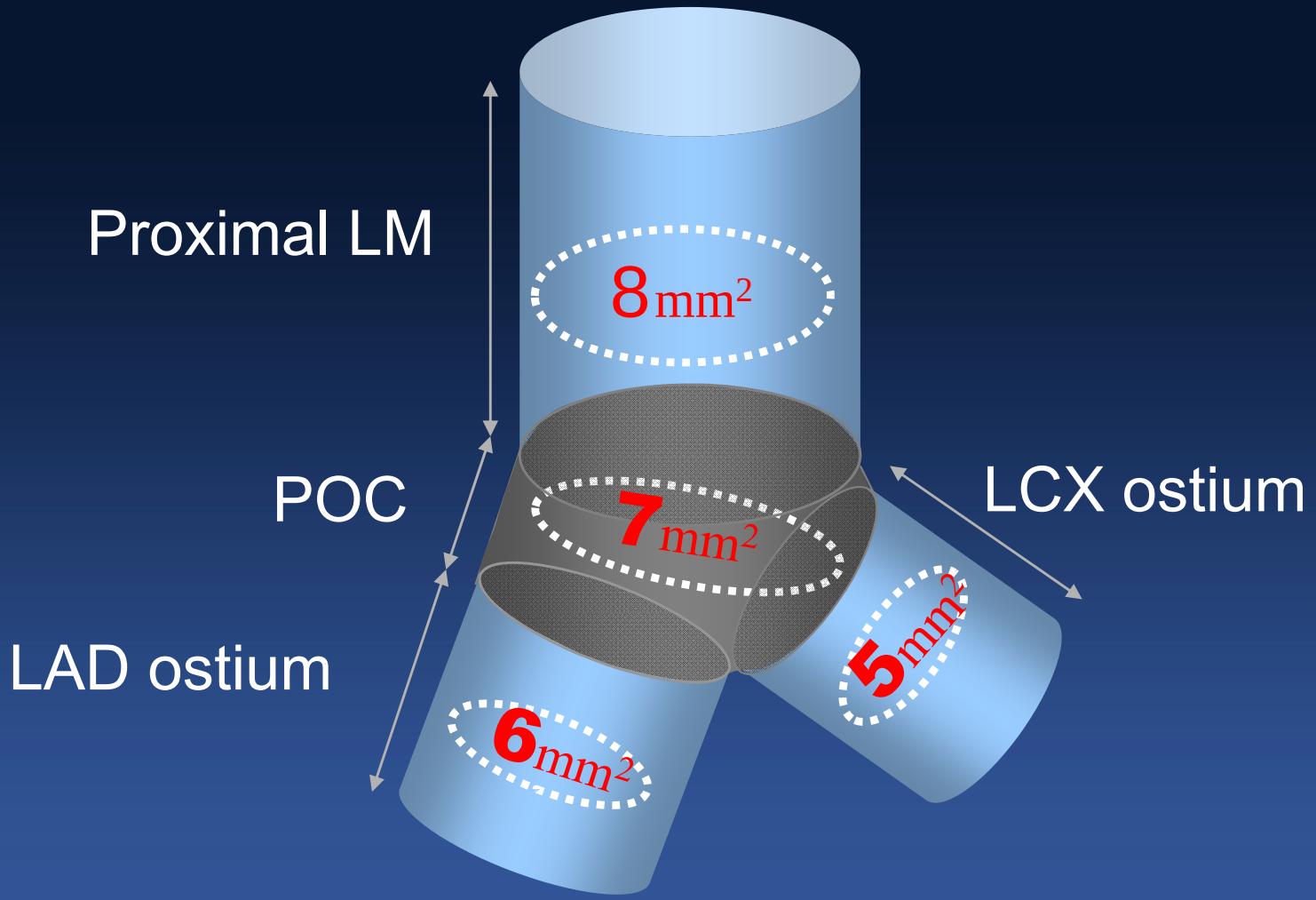
MSA 7.2mm²

Sensitivity 100%
Specificity 78%
Accuracy 80%

Kang et al. Circ Cardiovasc Interv 2011 2011;4:1168-74

LM Stent Optimization

on a segmental basis

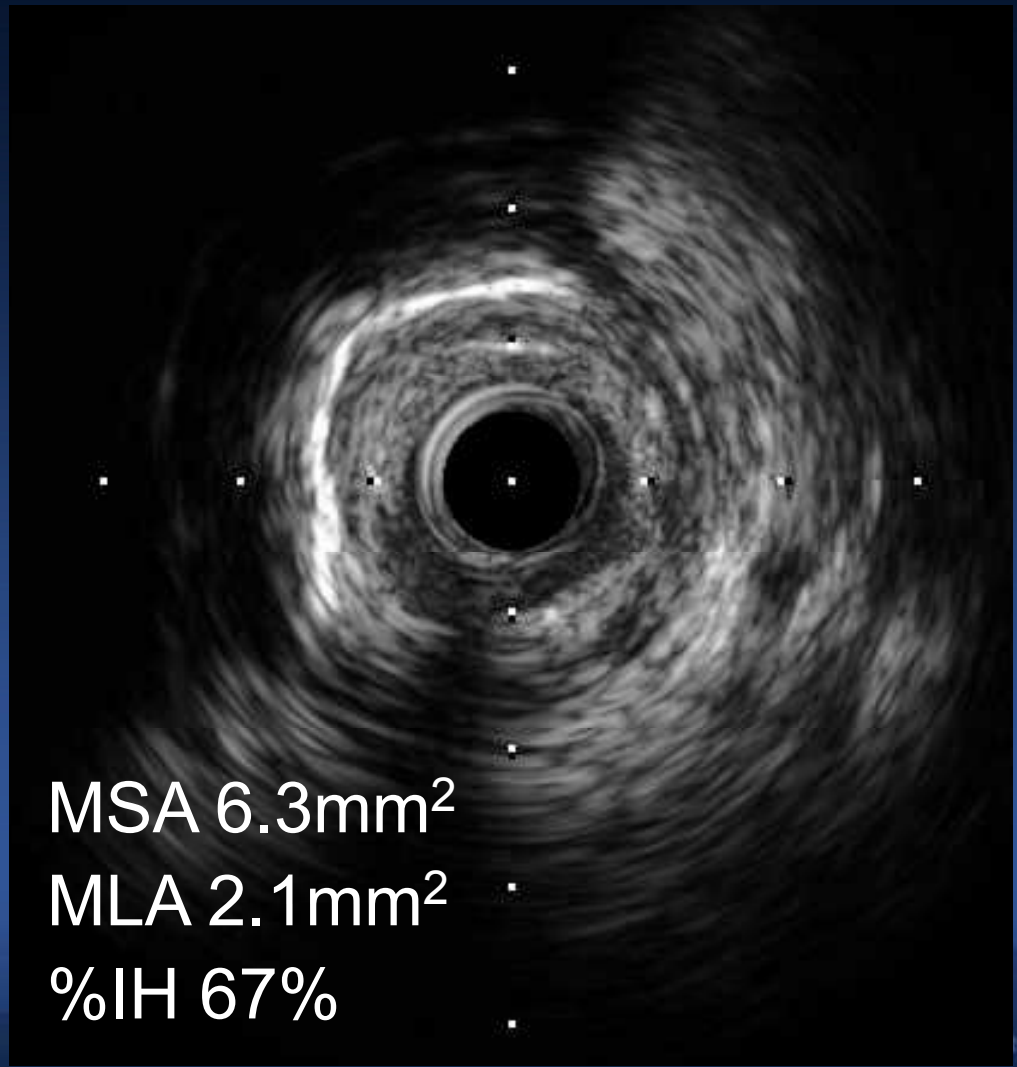


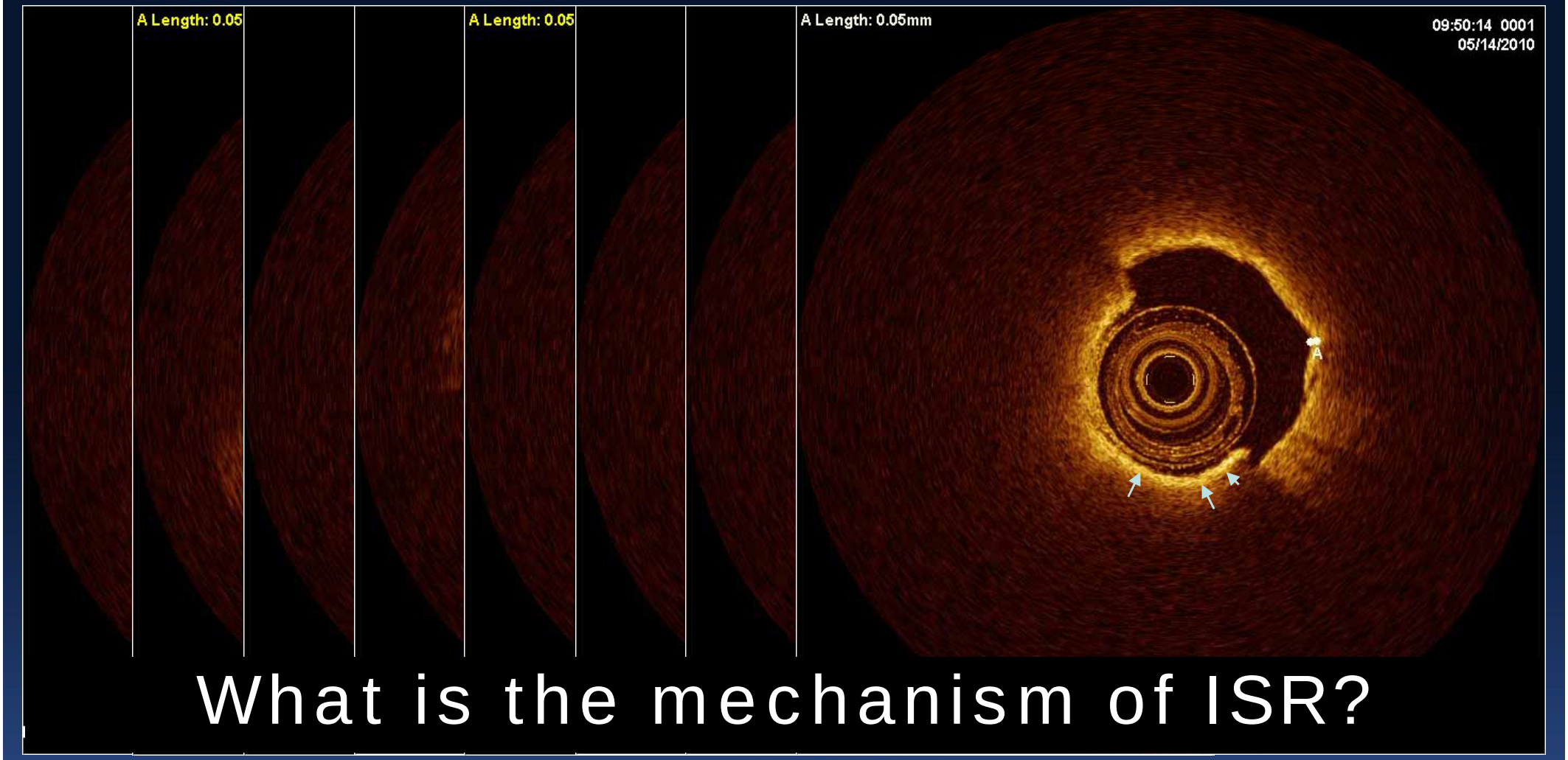
Kang et al. Circ Cardiovasc Interv 2011 2011;4:1168-74

ISR – Intimal Hyperplasia

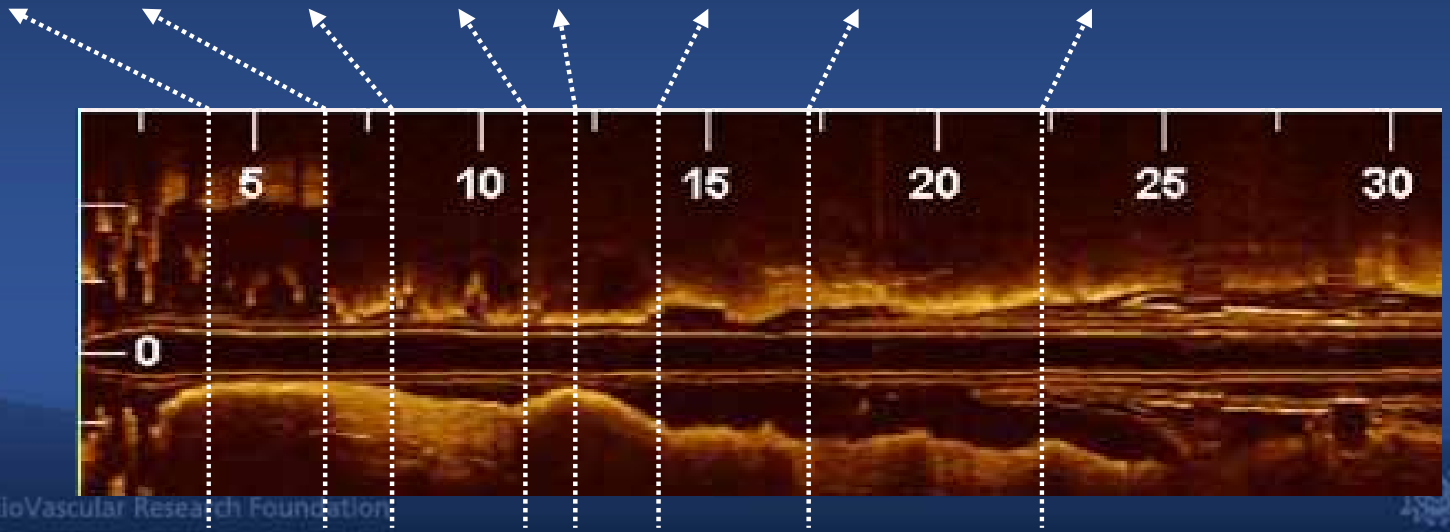
71 Year-Old Female, Unstable angina

- 8YA s/p BMS at pRCA and mLAD
- Hypertension, Diabetes



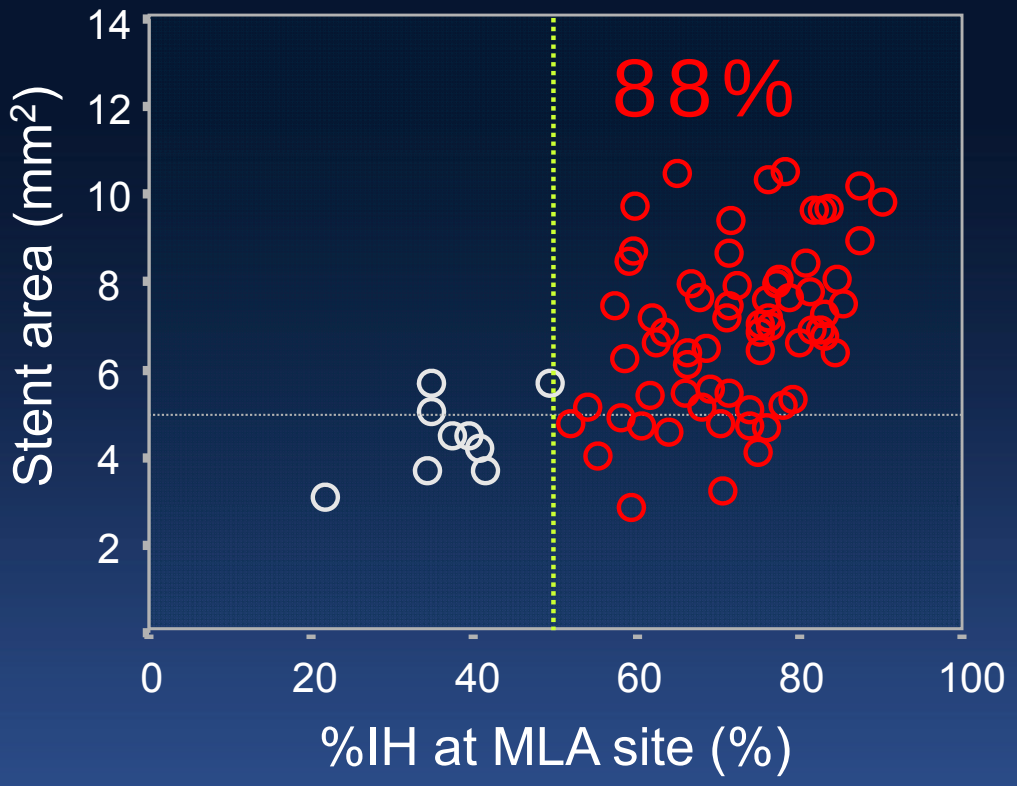


What is the mechanism of ISR?

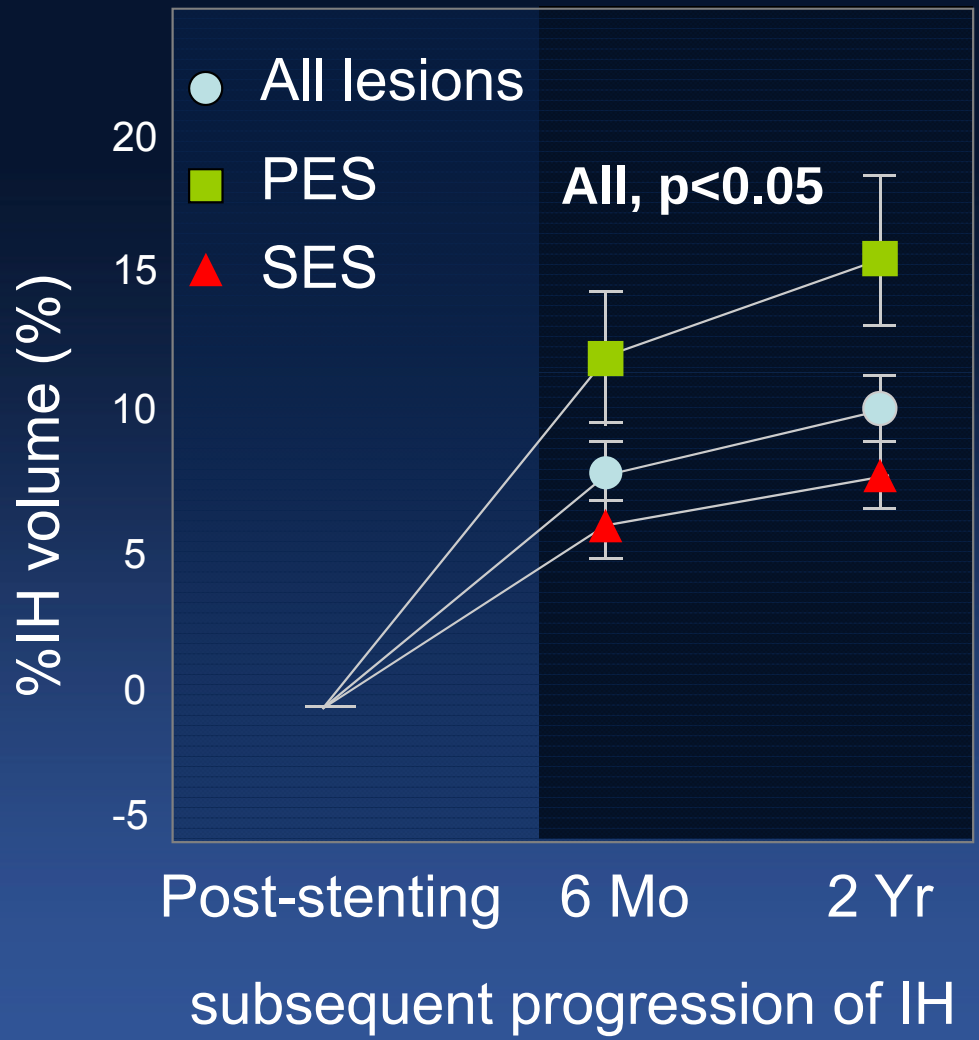


"Late Catch-up"

Mechanism of DES-ISR



Serial F/U %IH

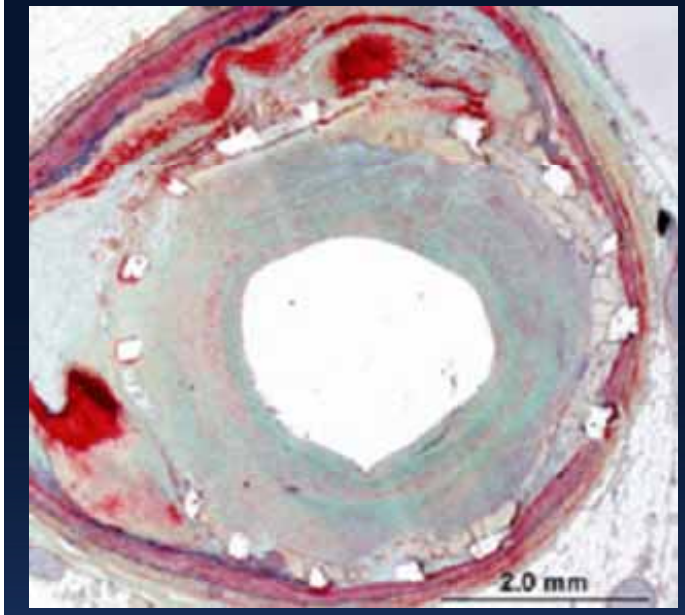


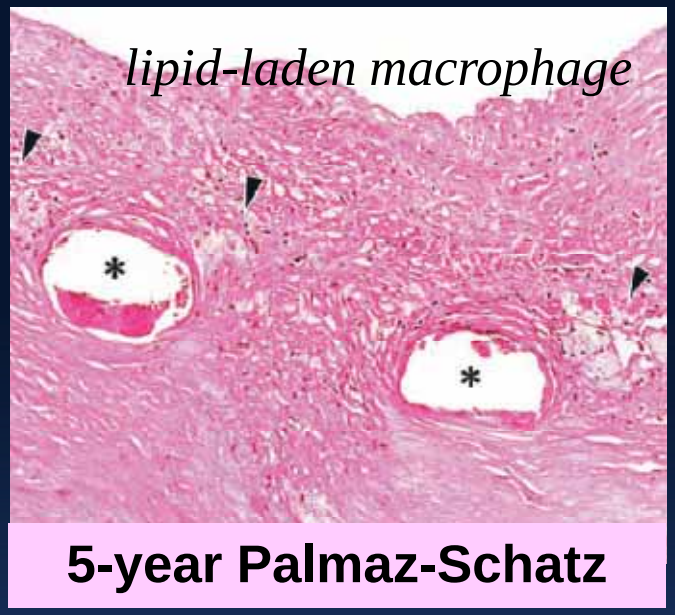
subsequent progression of IH

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

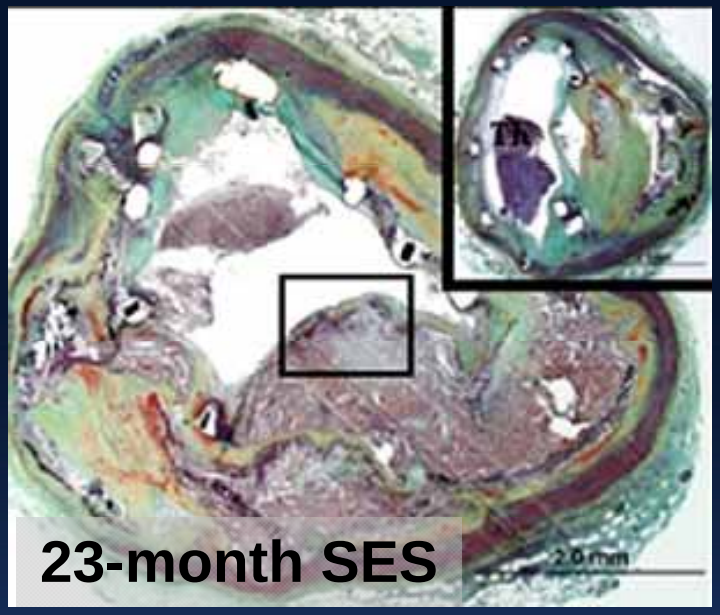
Kang et al. Am J Cardiol 2010;105:1402-8

Early Neointima → Neoatherosclerosis

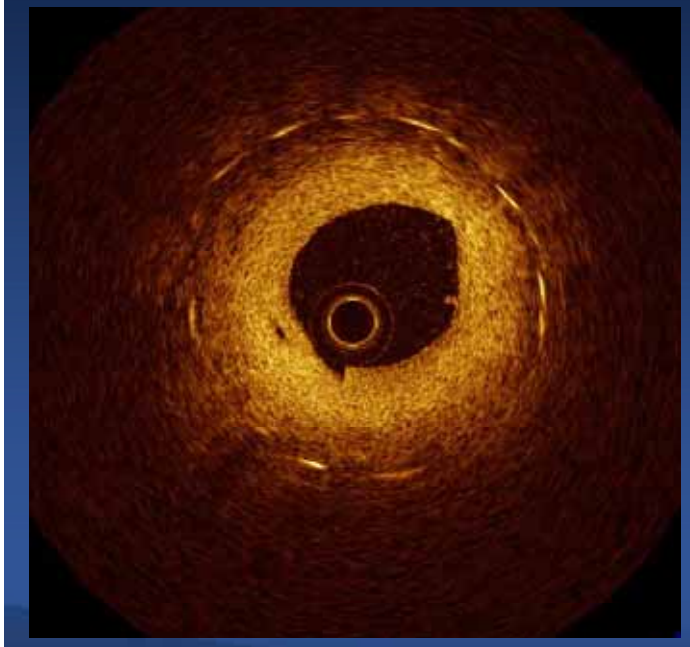


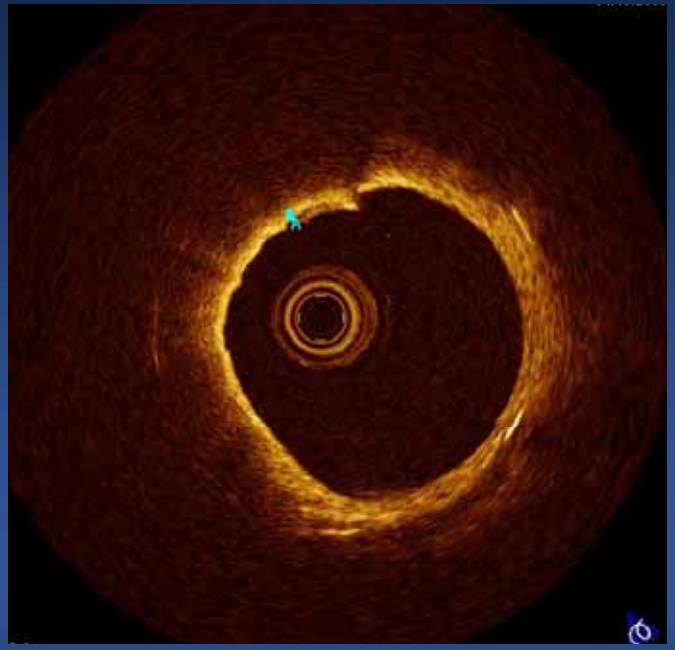


5-year Palmaz-Schatz



23-month SES





Chieffo et al. Am J Cardiol 2009;104:1660–7
Nakazawa et al. JACC Cariovasc Imaging 2009;2:625-8

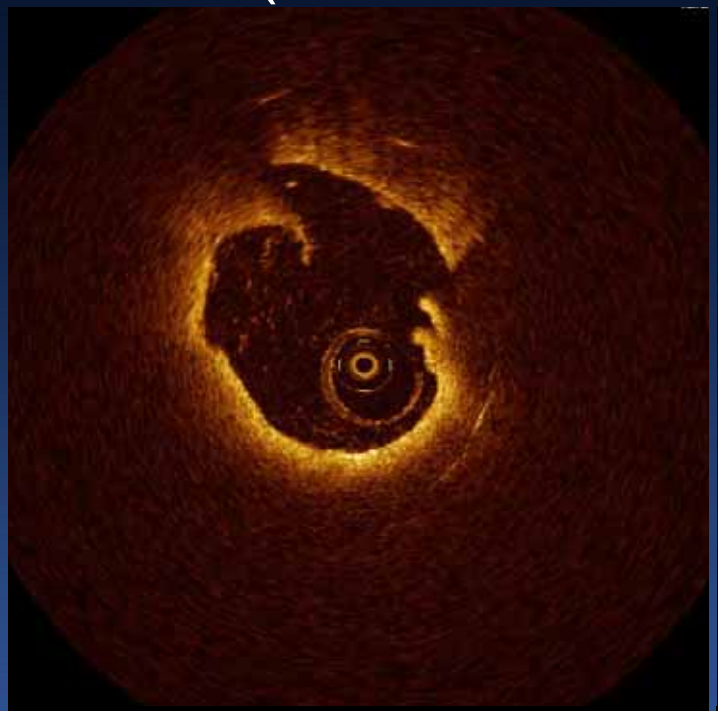
Nakazawa et al. JACC 2011;57:1314–22

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

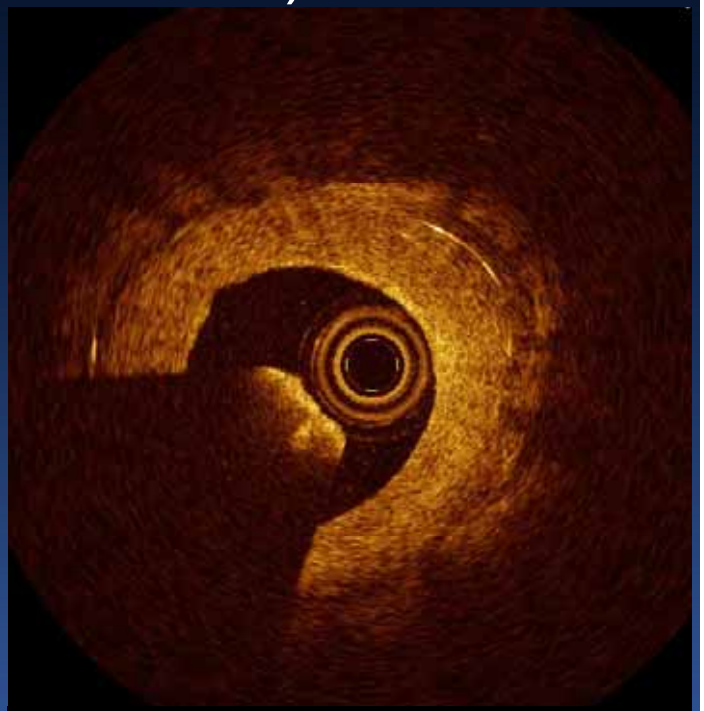
Soo-Jin Kang, MD; Gary S. Mintz, MD; Takashi Akasaka, MD, PhD; Duk-Woo Park, MD, PhD; Jong-Young Lee, MD; Won-Jang Kim, MD; Seung-Whan Lee, MD, PhD; Young-Hak Kim, MD, PhD; Cheol Whan Lee, MD, PhD; Seong-Wook Park, MD, PhD; Seung-Jung Park, MD, PhD

50 DES-ISR (Median F/U 32 months)

TCFA 52%



Rupture 58%



Thrombi 58%

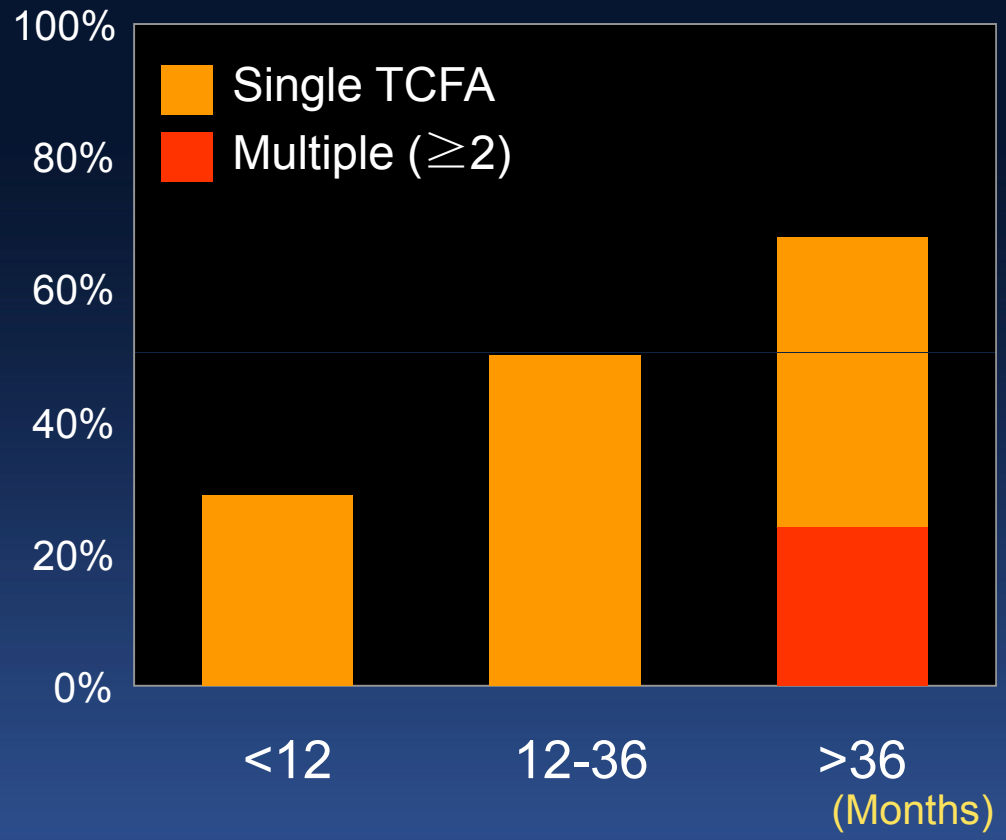
Kang et al. Circulation 2011;123:2954-63

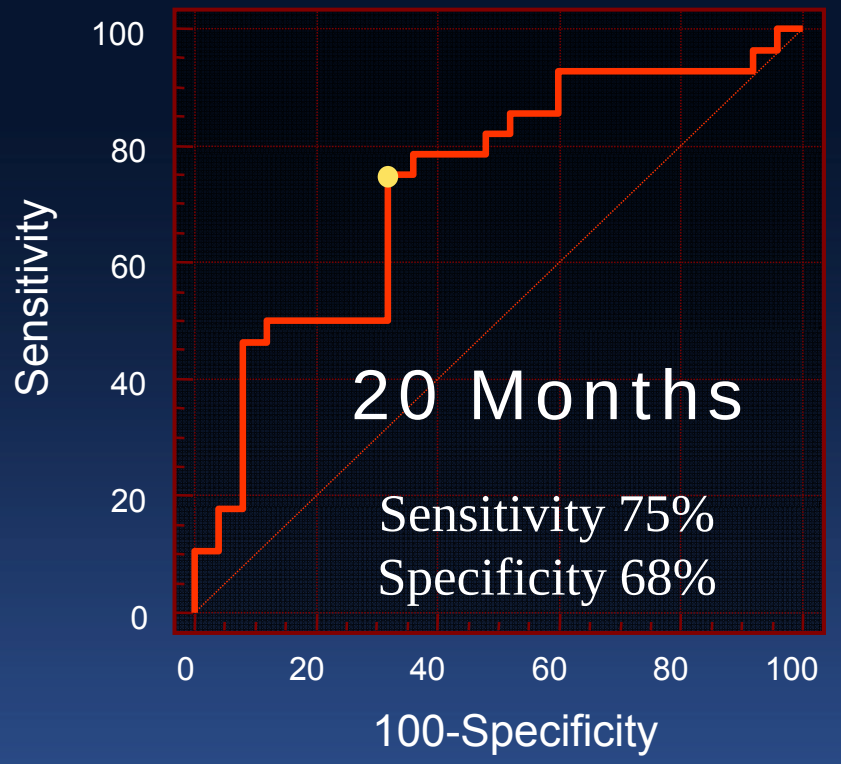
Stable vs. Unstable Angina

	Stable N=30	Unstable N=20	P
Fibrous cap thickness, μm	100 (60-205)	55 (42-105)	0.006
Incidence of thrombi	13 (43%)	16 (80%)	0.010
Incidence of red thrombi	1 (3%)	6 (30%)	0.012
Incidence of rupture	14 (47%)	15 (75%)	0.044
Incidence of TCFA	11 (37%)	15 (75%)	0.008

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

DES Duration >20 Months
Best Predict TCFA-Containing Neointima





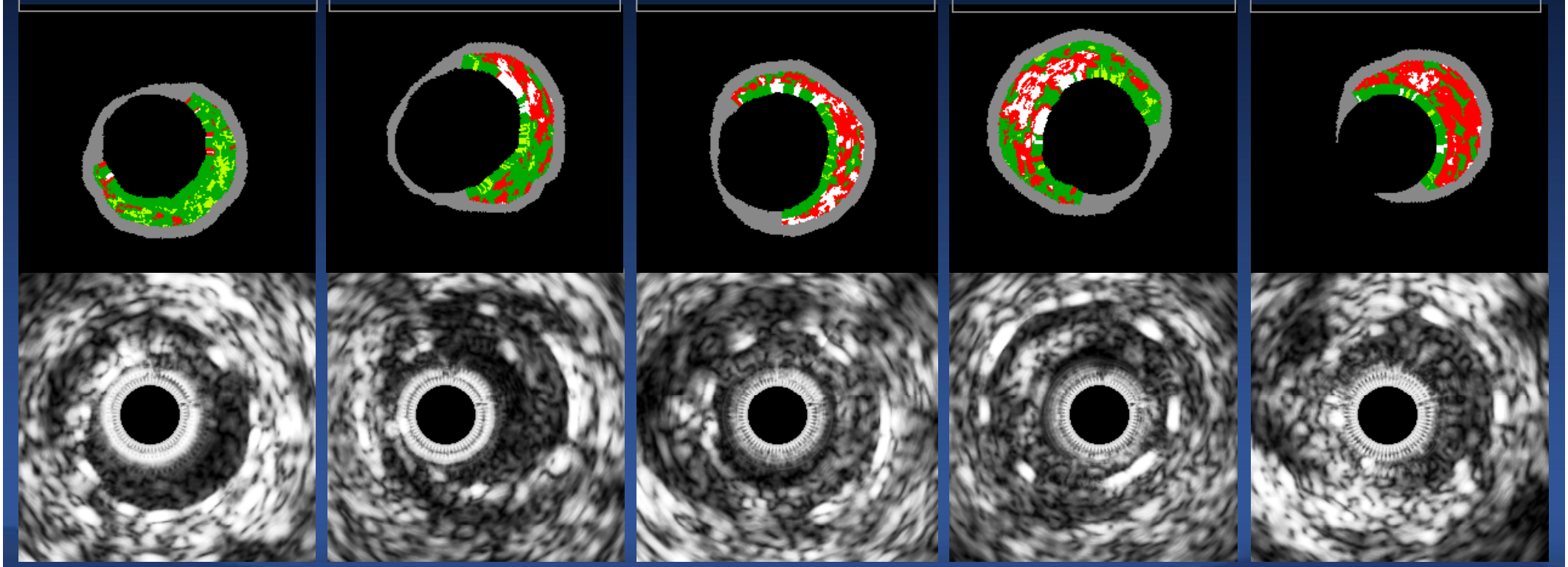
Kang et al. Circulation 2011;123:2954-63

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,*]

The longer f/u duration, the greater atherosclerotic change

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%



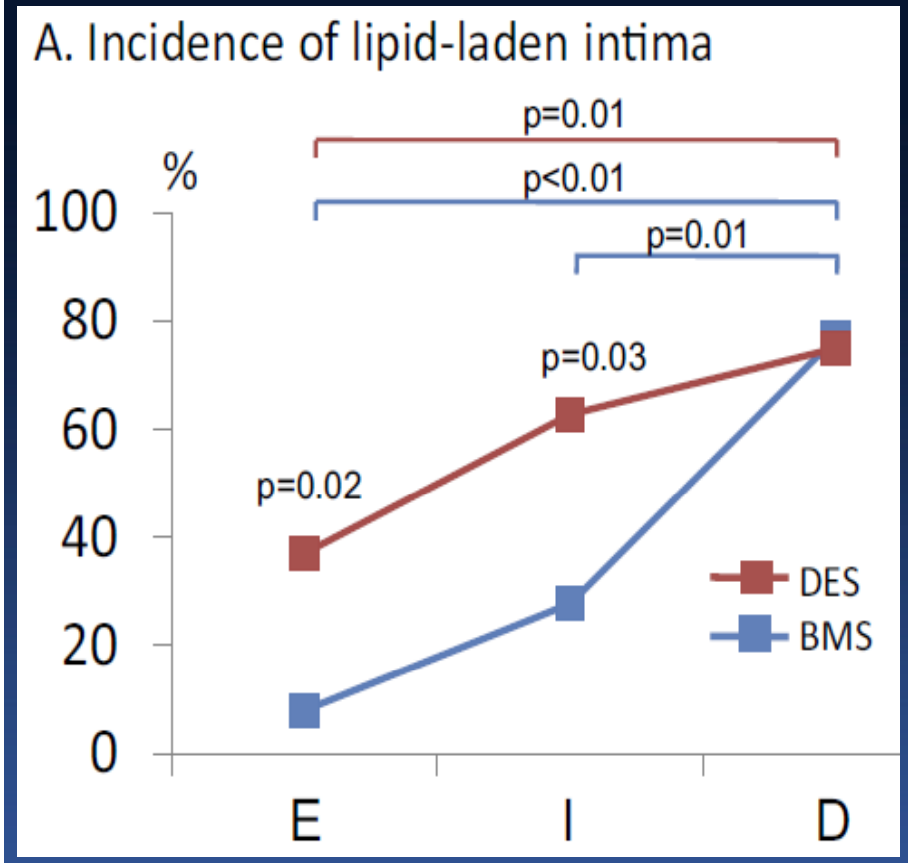
Kang SJ et al. AJC 2010 ;106:1561-5

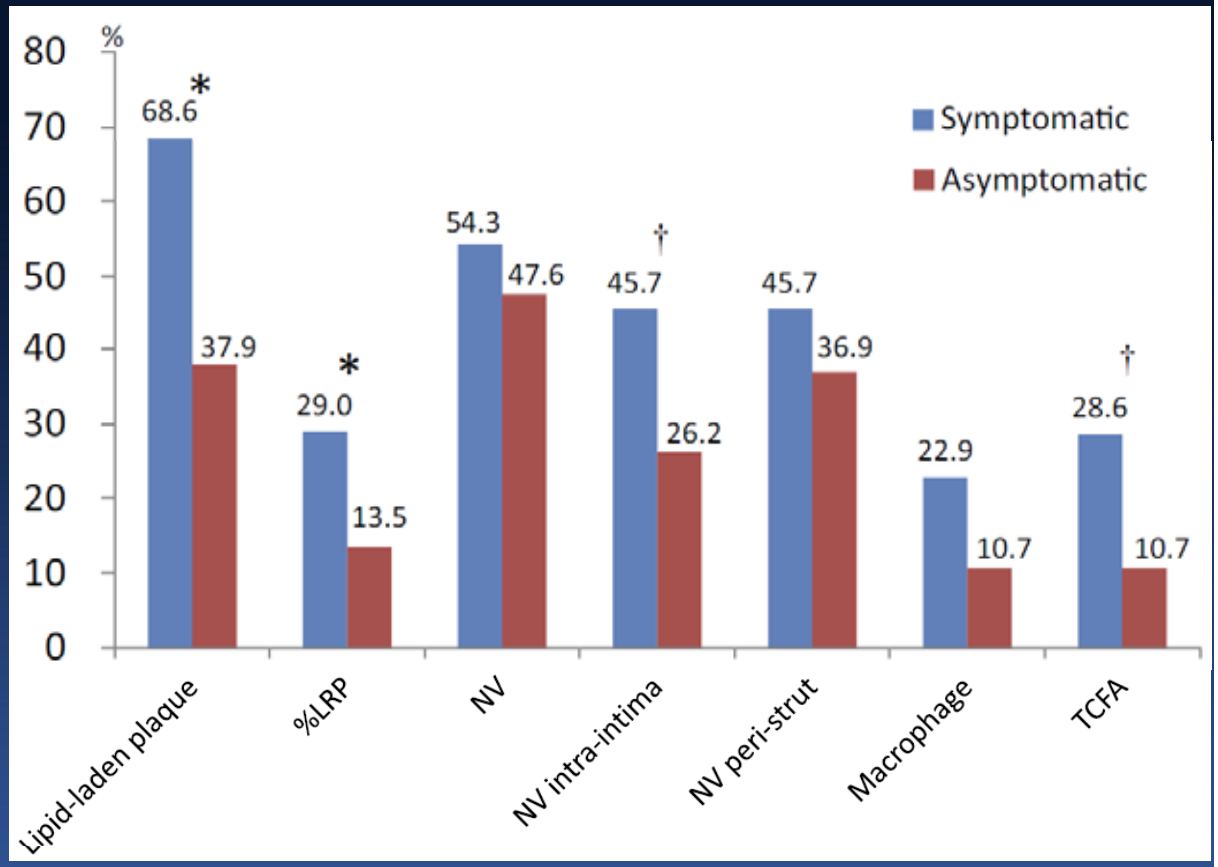
CardioVascular Research Foundation

UNIVERSITY OF ULSAN COLLEGE MEDICINE

ASAN Medical Center

Incidence and Time Course of Neoatherosclerosis; from MGH OCT registry



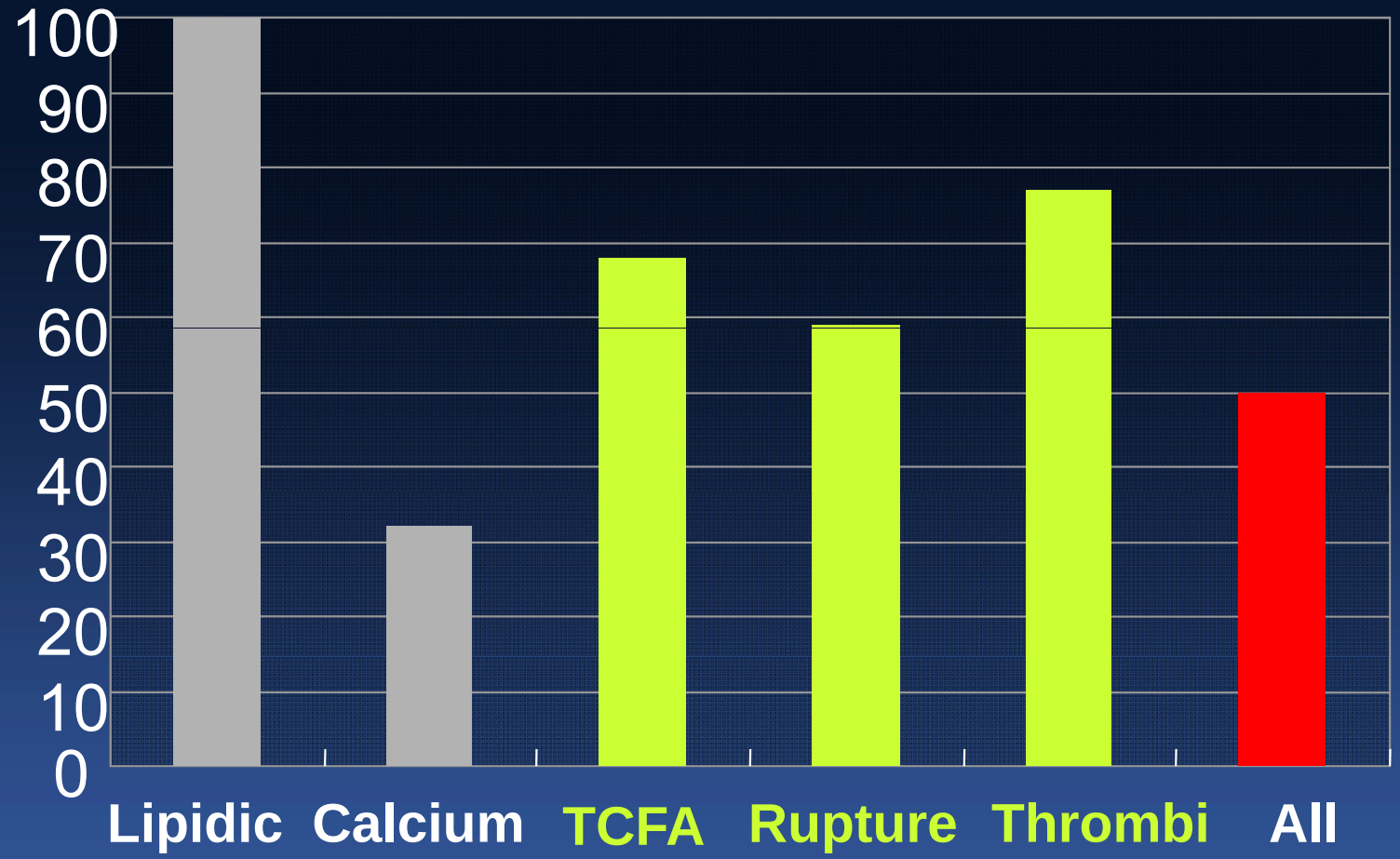


<9 mo 9–48 mo >48 mo

Yonetsu et al. Am J Cardiol 2012;110:933–9

OCT Findings of BMS-ISR at 10 Years

Clinically-driven TLR, Median F/U time 11 years



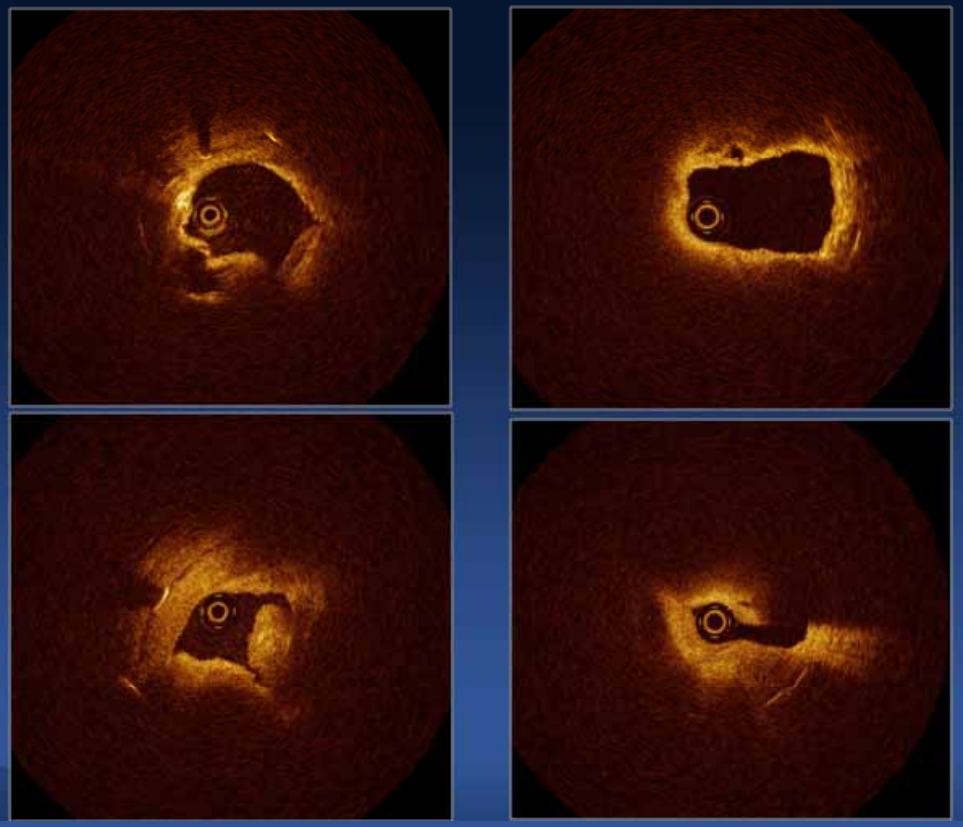
Kang et al. JACC Cardiovasc Imaging 2012;5:1267-8

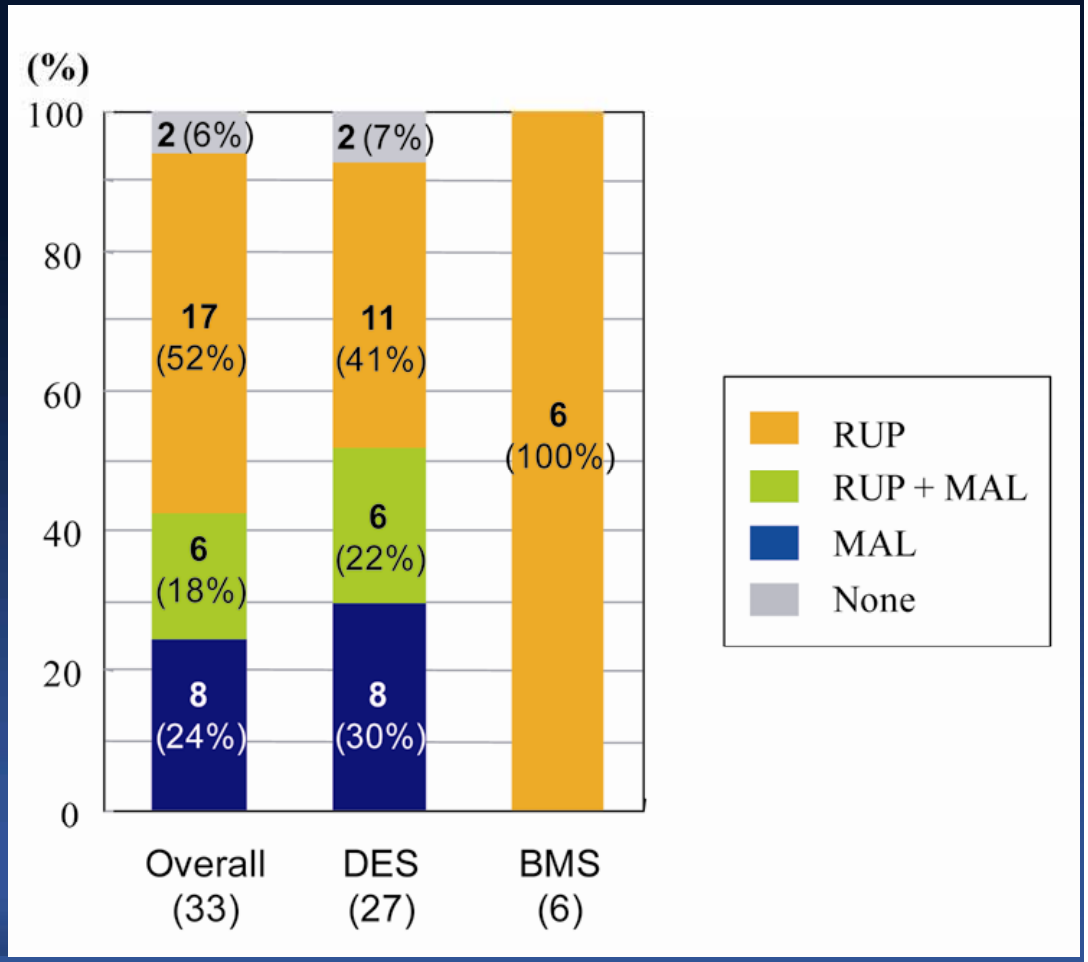
OCT Analysis in Patients with Very Late Stent Thrombosis

Definite VLST (27 DES, 6 BMS)

69/Male STEMI
165-month BMS

79/Male NSTEMI
60-month SES





Kang et al. JACC Cardiovasc imaging, 2013 in press

Predictors for Neoatherosclerosis

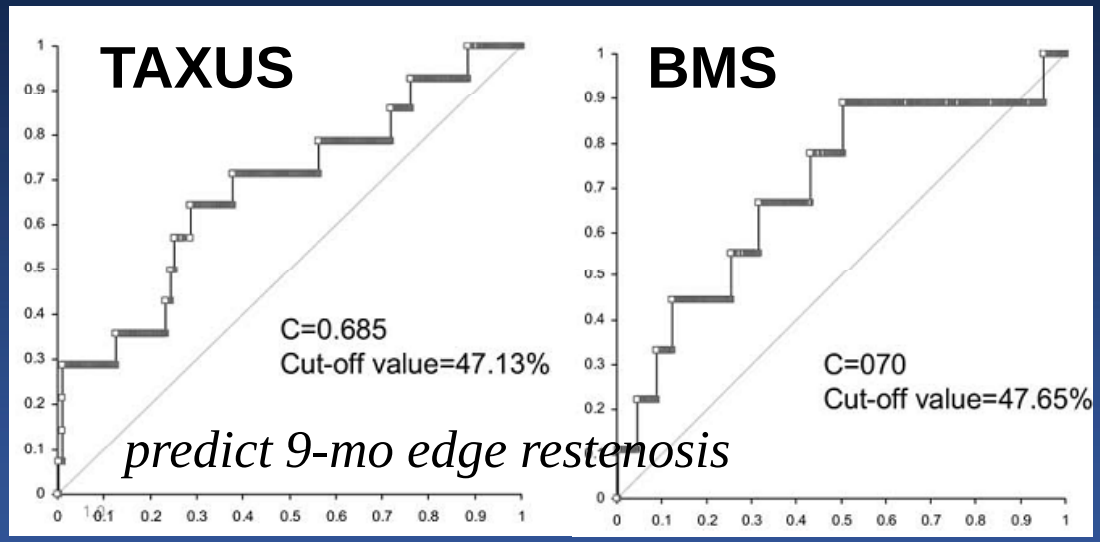
Retrospective Study from MGH OCT Registry

Multivariable Analysis			
	Adjusted OR	95% CI	p
SES	3.86	1.44 – 10.38	0.007
PES	24.17	6.02 – 97.02	<0.001
ZES	7.18	1.51 – 34.21	0.013
EES	6.46	1.65 – 25.34	0.007
Age >65 years	1.84	0.85 – 3.97	0.121
Stent age >48 months	10.45	3.71 – 29.41	<0.001
Current smoking	7.03	2.46 – 20.04	<0.001
Chronic renal disease	3.69	1.10 – 12.35	0.035
ACE-I / ARB use	0.39	0.17 – 0.91	0.028

Yonetu et al. Circ Cardiovasc Imaging 2012;5:660-6

Residual Plaque Predicts Edge Restenosis

	Population	DES	F/U time	Predictor
SIRIUS[1]	6 edge restenosis vs. 162 controls	SES	8 mo	**Ref segment PB** 60% vs. 41% (p<0.01)
TAXUS[2]	276 edge stenosis	PES	9 mo	**Ref segment PB 47%**



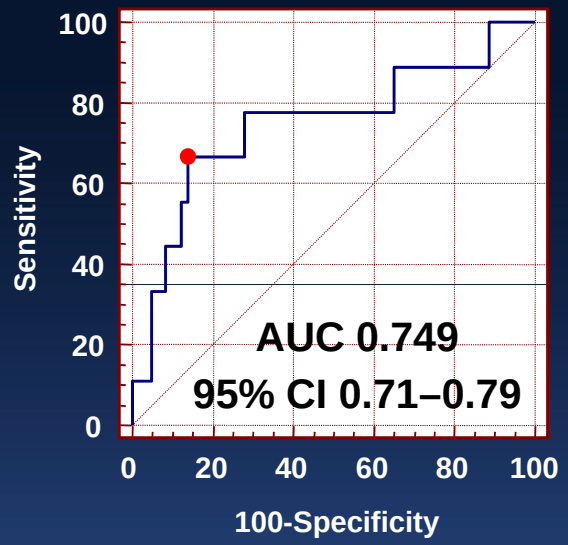
predict 9-mo edge restenosis

[1] *Am J Cardiol 2005;96:1251-3*

[2] *Liu et al. Am J Cardiol 2009;103:501-6*

Intravascular Ultrasound Predictors for Edge Restenosis After Newer Generation Drug-Eluting Stent Implantation

433 E-ZES

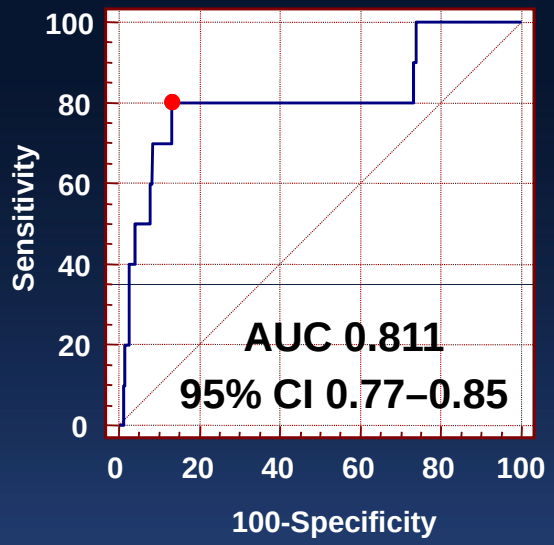


PB 56.3%

Sensitivity 67%

Specificity 86%

422 R-ZES

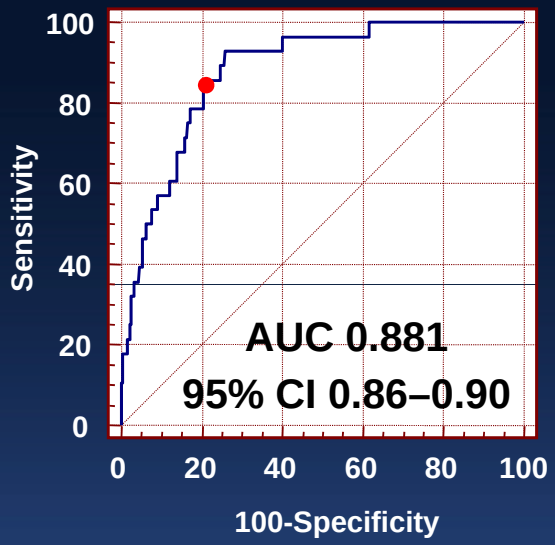


PB 57.3%

Sensitivity 80%

Specificity 87%

813 EES



PB 54.2%

Sensitivity 86%

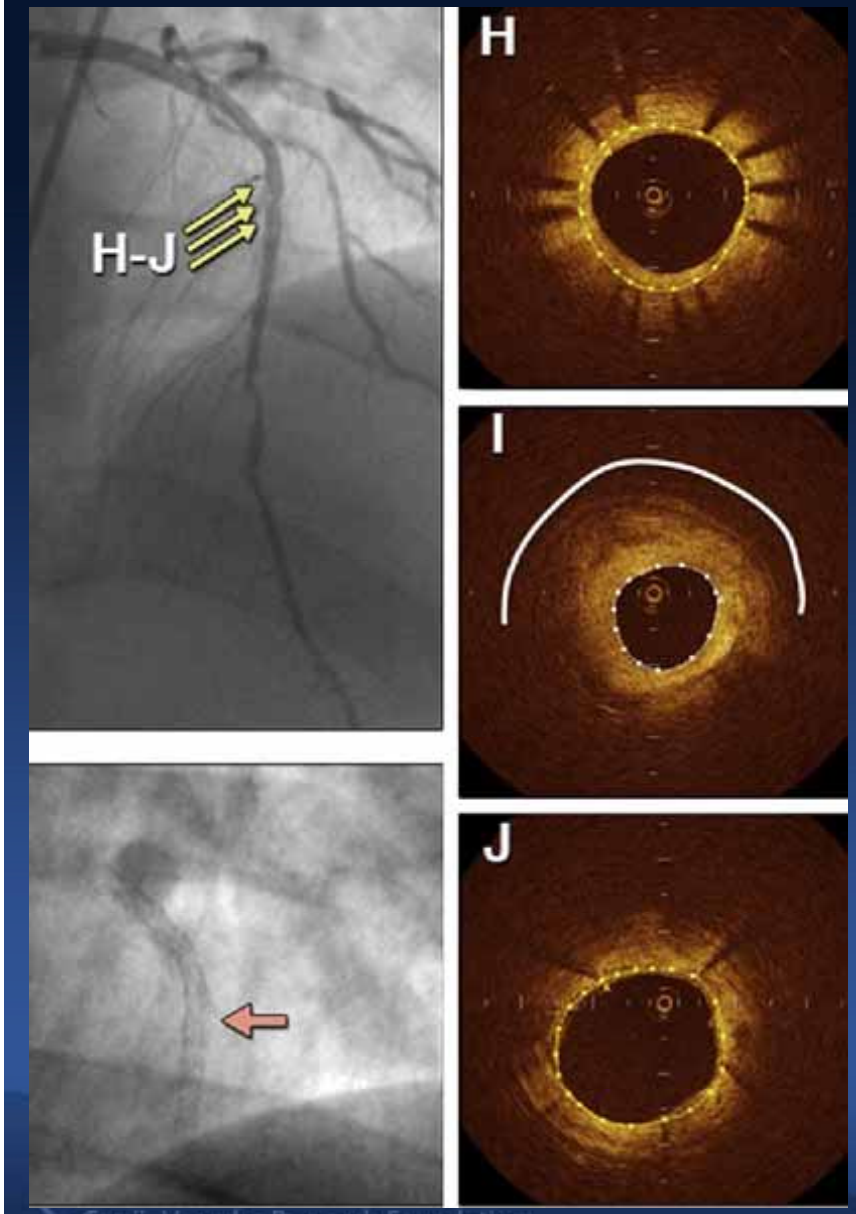
Specificity 80%

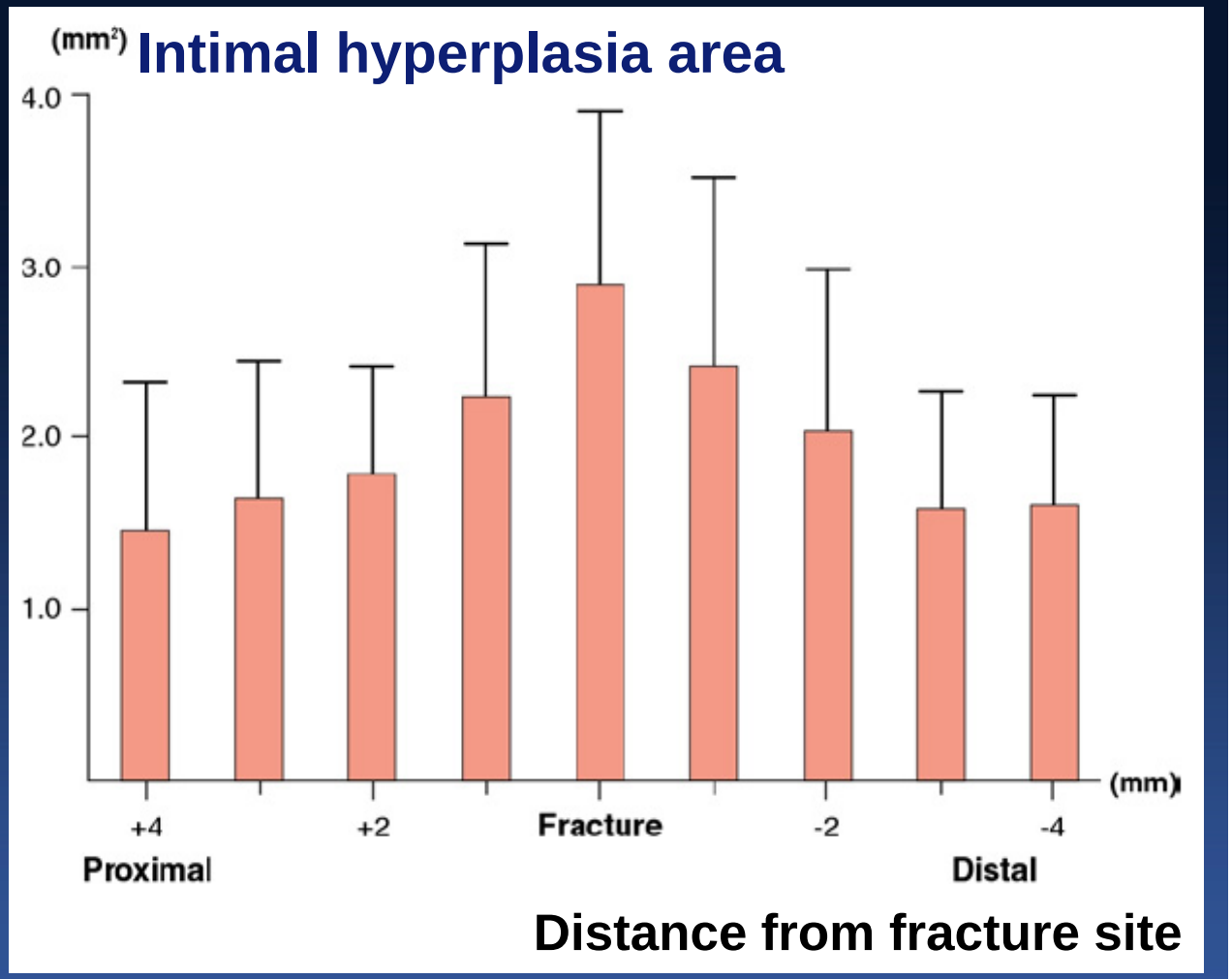
Reference segment residual PB<55% may be useful to determine the optimal landing zone of stent deployment

Kang et al. Am J Cardiol 2013 in press

DES Fracture

Increased intimal hyperplasia at the fracture site



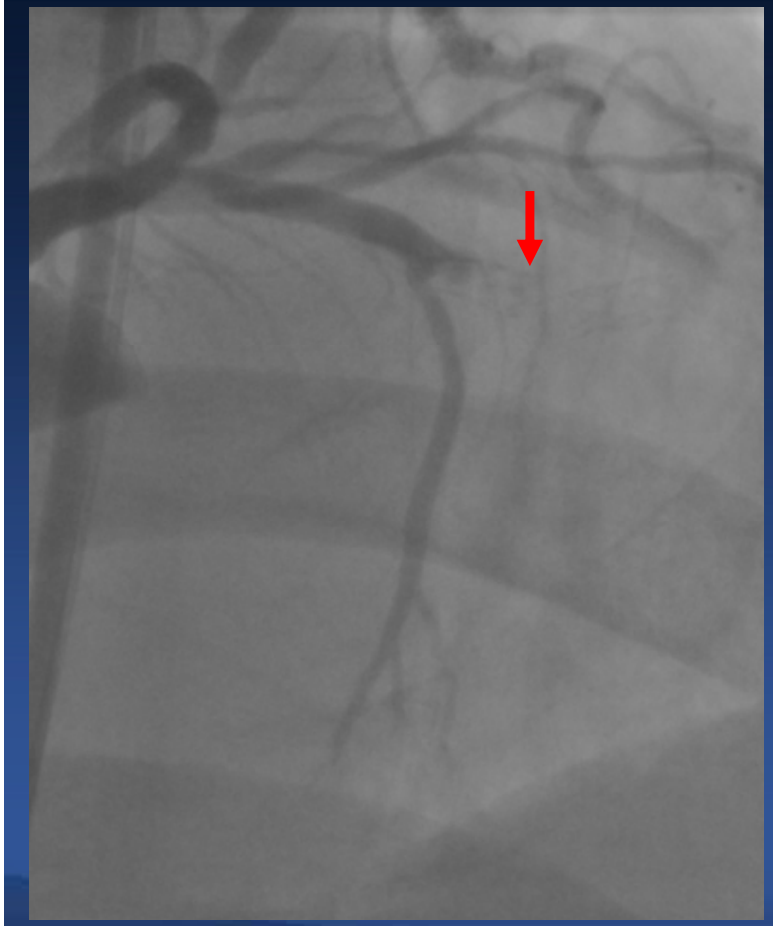


Kashiwagi et al. JACC Cardiovasc Img 2012;5:232-3

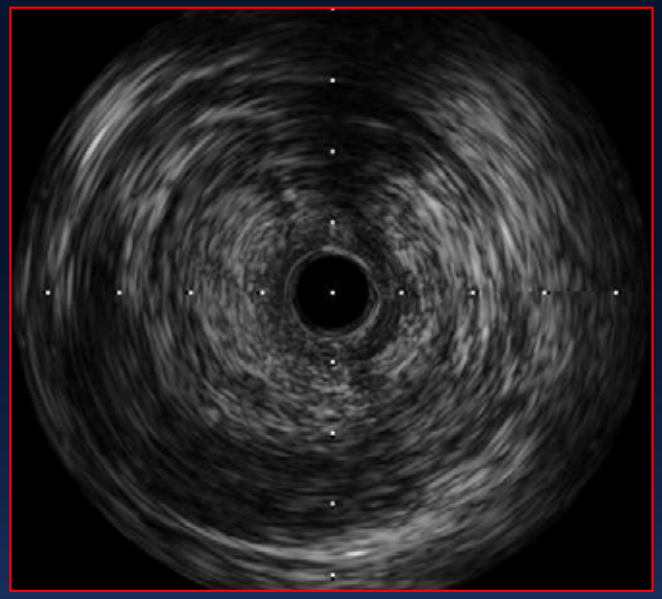
Stent Fracture in DES-VLST

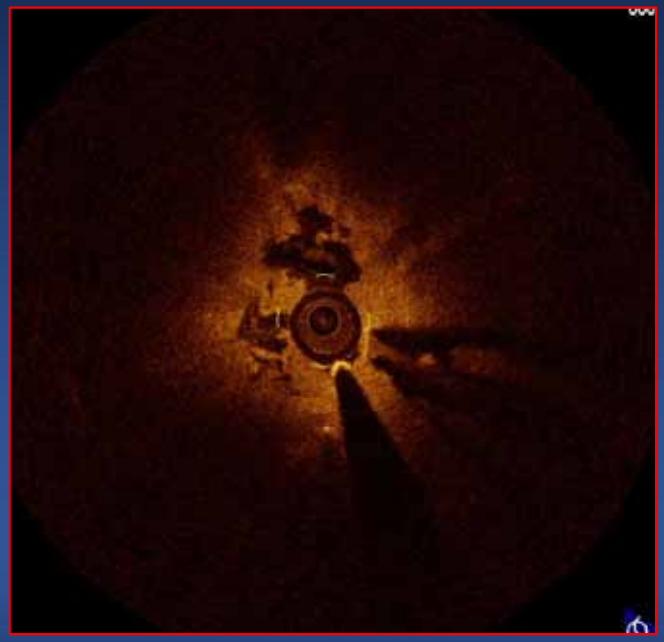
55/male

- SES 7 years ago
- VLST with STEMI

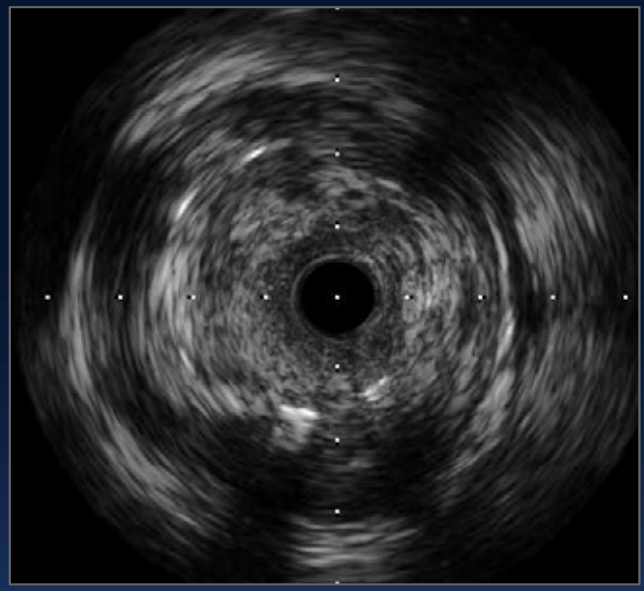


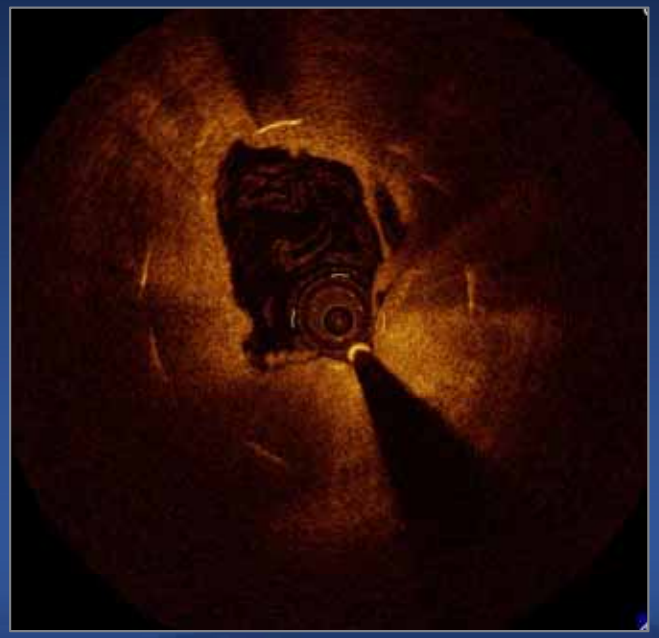
At fracture site





Adjacent intimal rupture





Kang et al. JACC Cardiovasc Imaging 2013 in press

Acute Stent Malapposition (ASM)

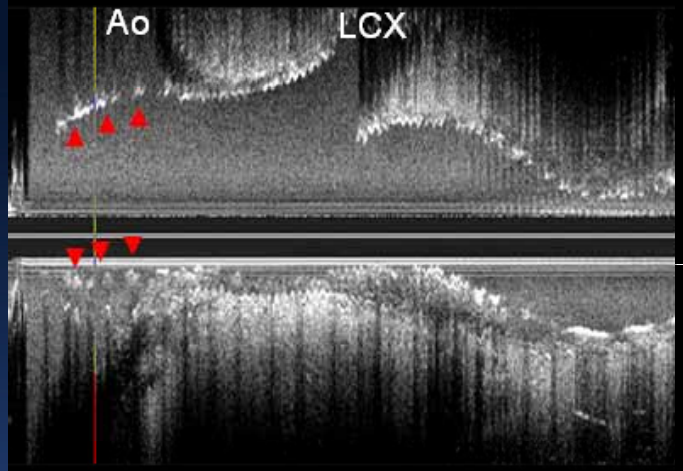
Little Evidence Linking ASM to MACE

Study	ASM frequency	Clinical outcomes
HORIZON-AMI[1]	34% of PES 39% of BMS	39% resolved by negative remodeling No difference in 13-month MACE
TAXUS IV,V,VI[2]	9.7% of PES 7.2% of BMS	No difference in 9-mo MACE between ASM vs. control (12% vs. 9%, p=0.45)
Hong et al.[3]	7.2% of DES	No MACE or TLR at 6 months
Kimura et al.[4]	18% of SES	25% of ASM resolved at 6 months No ISR or ST

[1]*Guo et al. Circulation 2010;122:1077-84*
[2]*Steinberg et al. JACC interv 2010;3:486-94*
[3]*Hong et al. Circulation 2006;113:414-9*
[4]*Kimura et al. Am J Cardiol 2006;98:36-42*

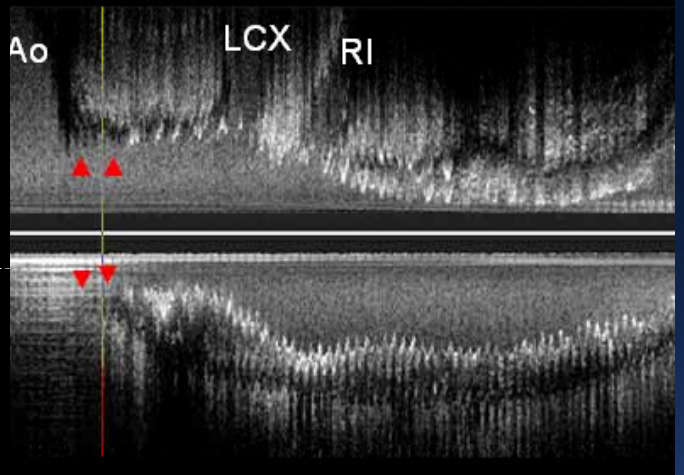
Intravascular Ultrasound Assessment of Drug-Eluting Stent Coverage of the Coronary Ostium and Effect on Outcomes

Strut protrusion



- LMCA 68% (length 3.4±1.7mm)
- RCA 59%
- LAD 53%

Incomplete coverage



- LMCA 23%
- RCA 28%
- LAD 33% (residual PB 42±11%)

Ostial Restenosis Rate

- with vs. without strut protrusion (3.2% vs. 2.3%), p=NS
- incomplete vs. complete coverage (2.4% vs. 3.0%), p=NS

Kang et al. Am J Cardiol 2013 in press

Summary

- IVUS provides new insights for mechanisms of restenosis
- Intimal hyperplasis is a general mechanism of DES-ISR. In-stent neoatherosclerosis is an important mechanism of the late restenosis
- As preventable mechanisms, underexpansion and large reference residual plaque should be corrected to avoid stent failure