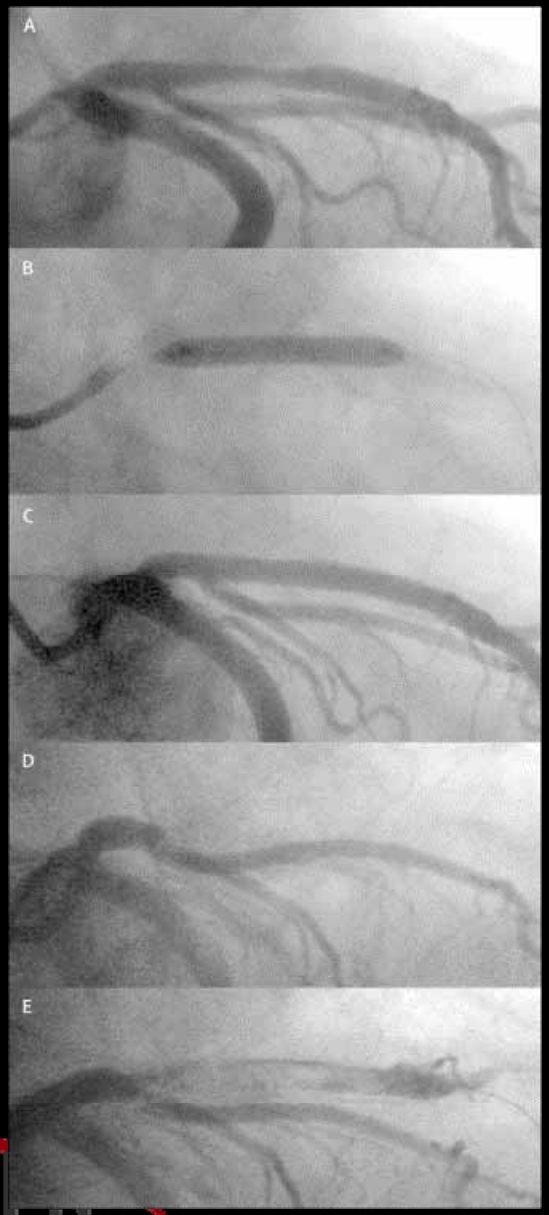
Pathology Insights of DES from Human Specimens

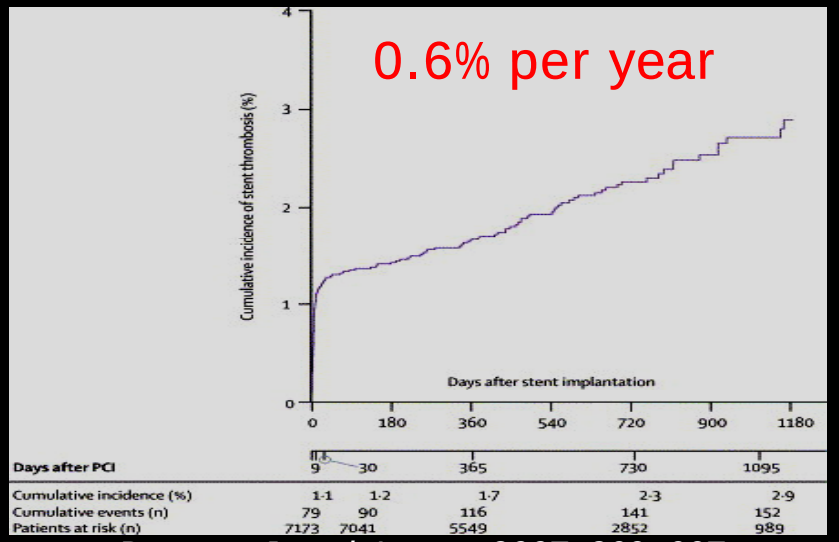
G Nakazawa

Tokai Univ.

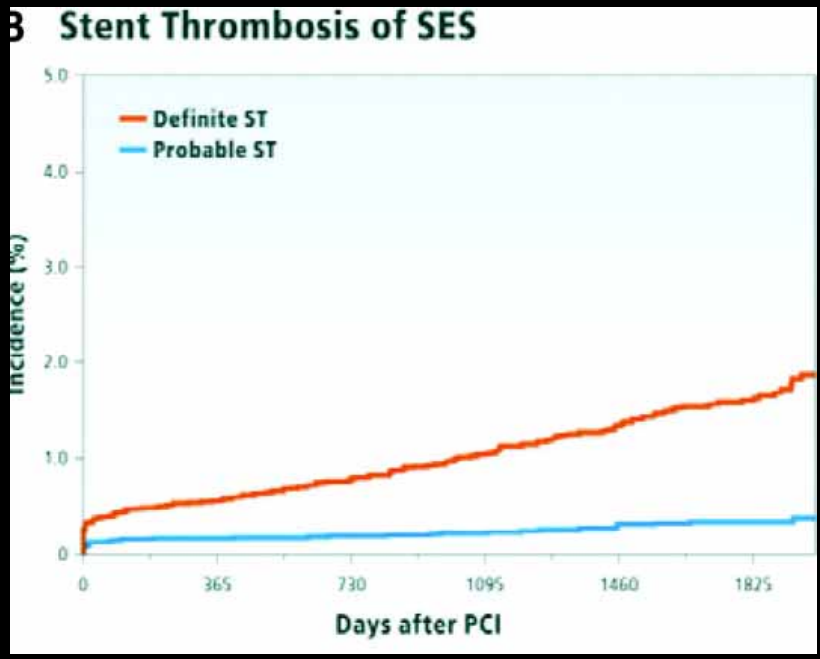
Late Stent Thrombosis (LST)



McFadden E et al. Lancet 2004



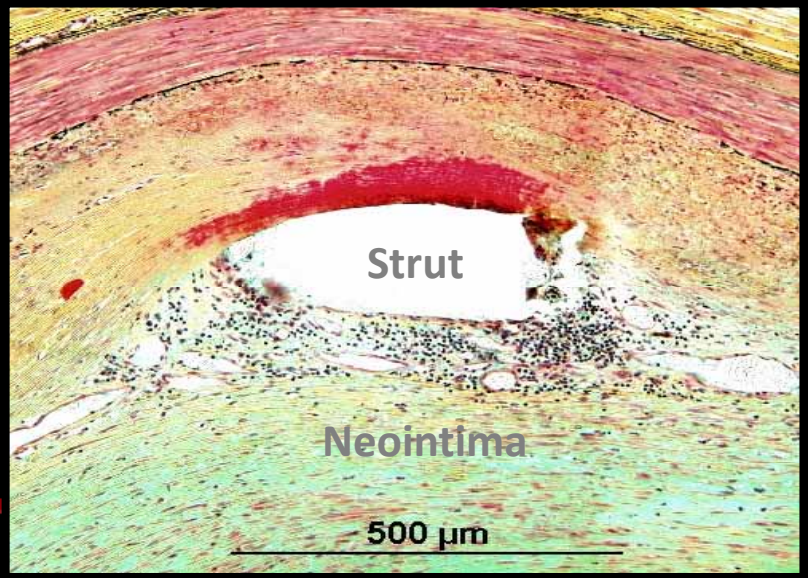
Daemen J et al. Lancet 2007; 369: 667



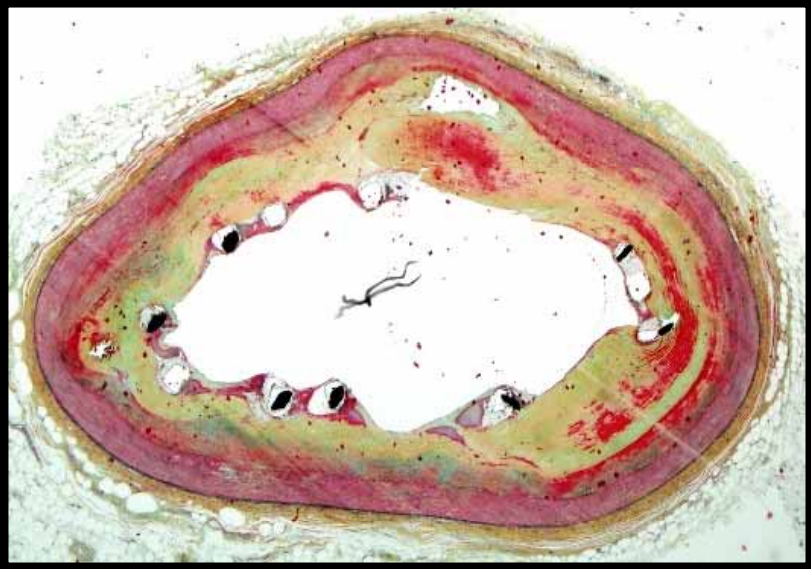
Kimura T et al. Circulation 2012;125:584-591

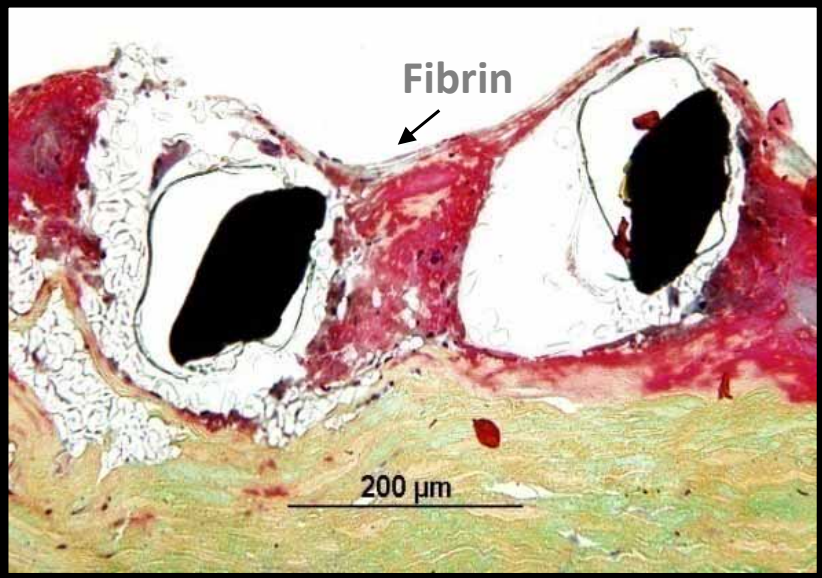
Delayed Arterial Healing in DES

BxVelocity (BMS)



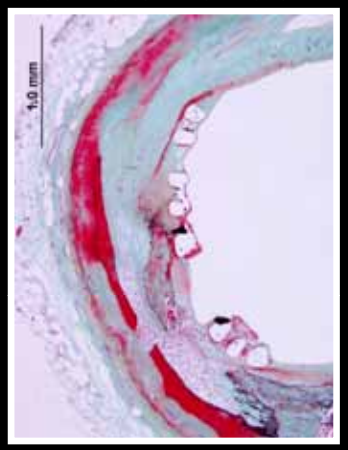
Cypher (DES)

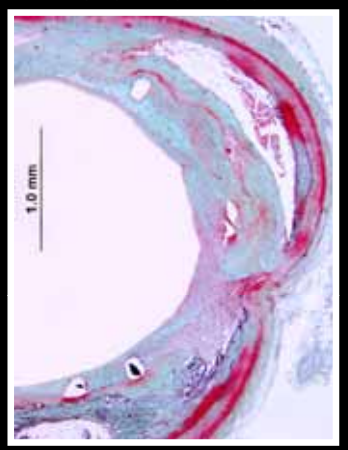


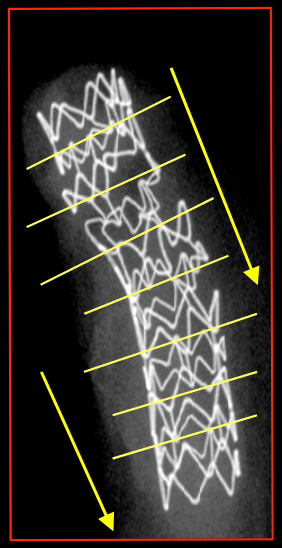


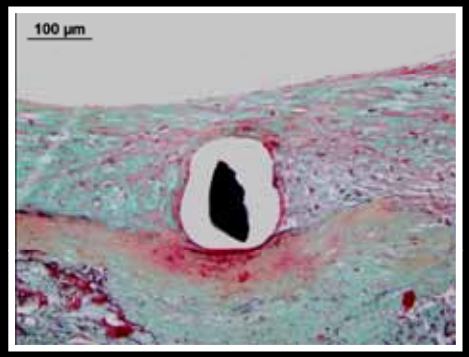
Joner M & Finn AV. J Am Coll Cardiol. 2006;48(1):193-202.

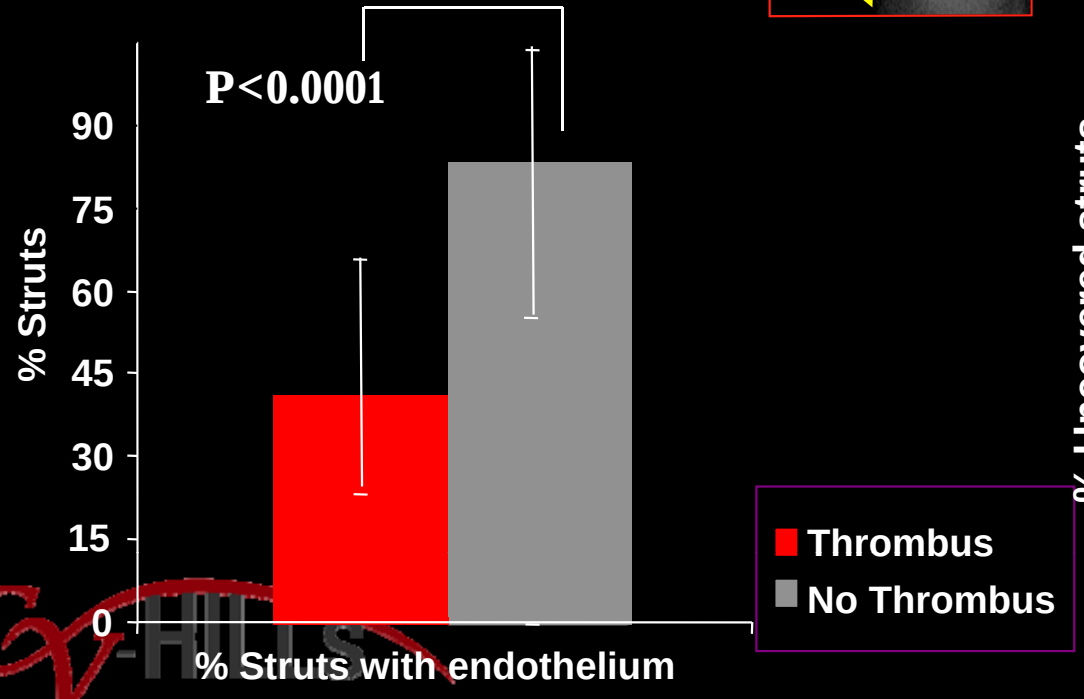
Strut Coverage is a Marker of Endothelialization

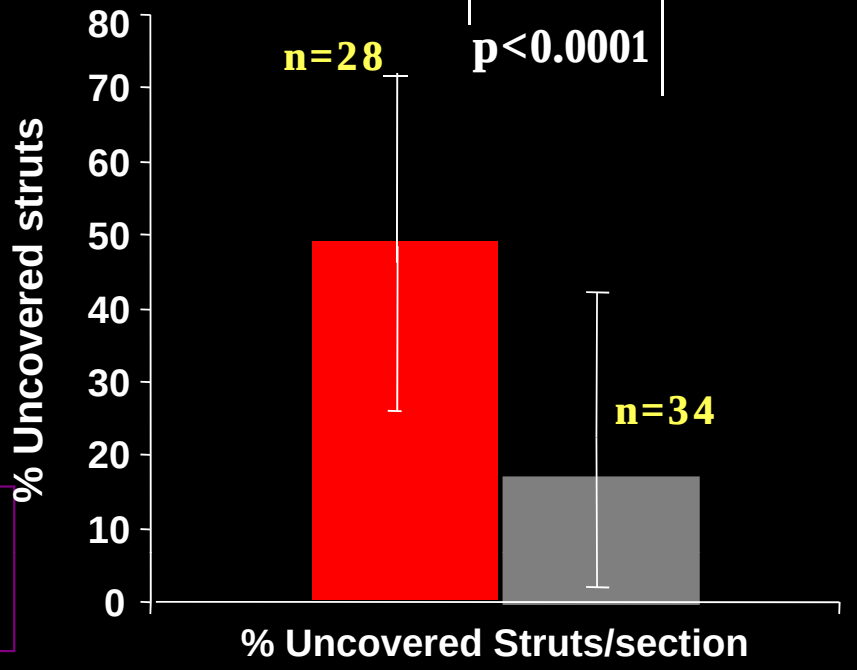






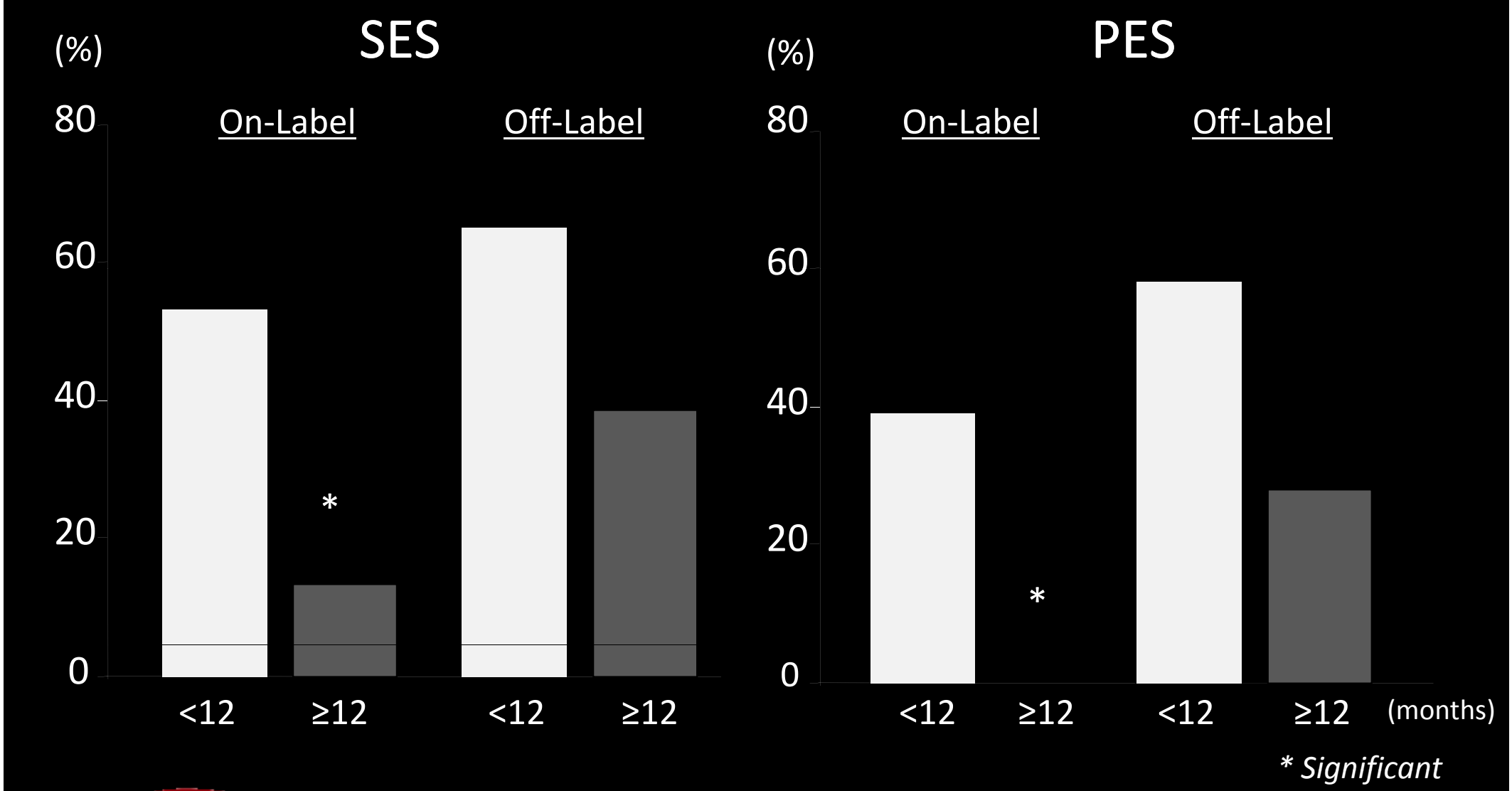






Finn AV, et al., Circulation 2007;115:2435-2441

Prevalence of Unhealed Stents (>30% of uncovered struts)



Nakazawa, G et al. J Am Coll Cardiol 2011: 57(4).390-8

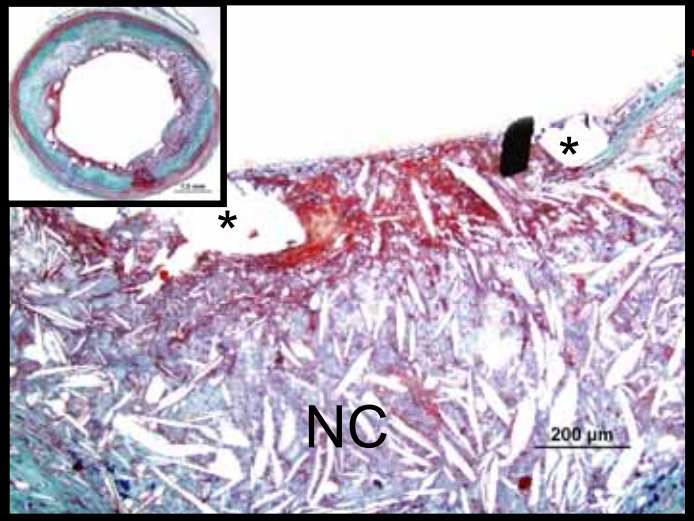
Delayed Arterial Healing and Increased Late Stent Thrombosis at Culprit Sites After Drug-Eluting Stent Placement for Acute Myocardial Infarction Patients

An Autopsy Study

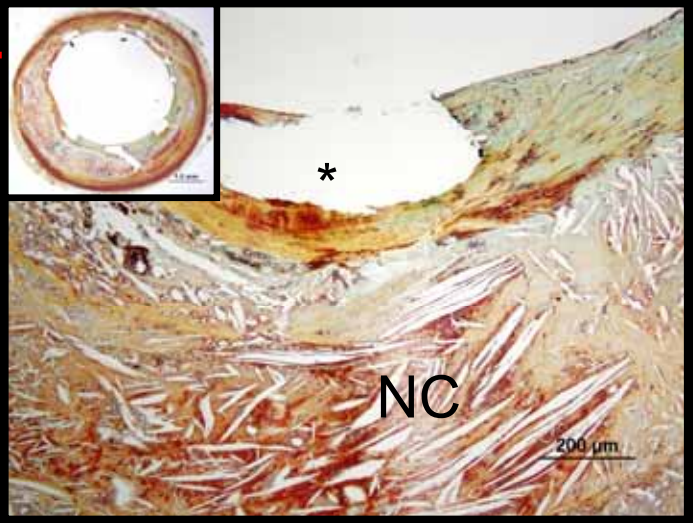
Gaku Nakazawa, MD; Aloke V. Finn, MD; Michael Joner, MD; Elena Ladich, MD; Robert Kutys, MS; Erik K. Mont, MD; Herman K. Gold, MD†; Allen P. Burke, MD; Frank D. Kolodgie, PhD; Renu Virmani, MD

AMI lesions (with Plaque Rupture)

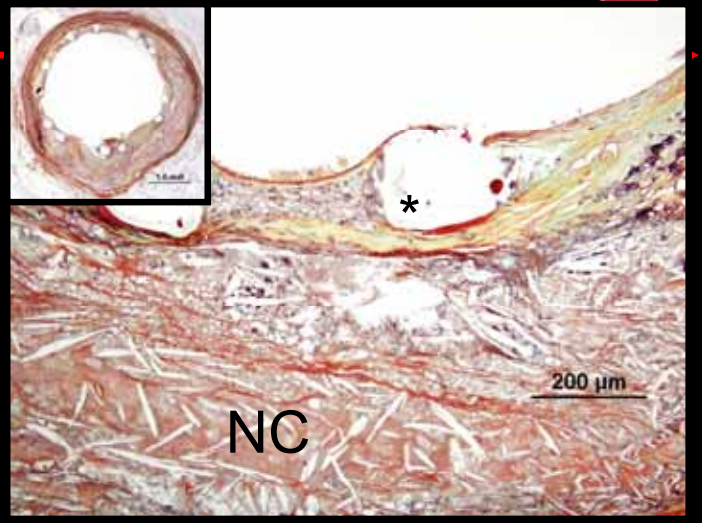
9 months (Taxus)



13 months (Cypher)

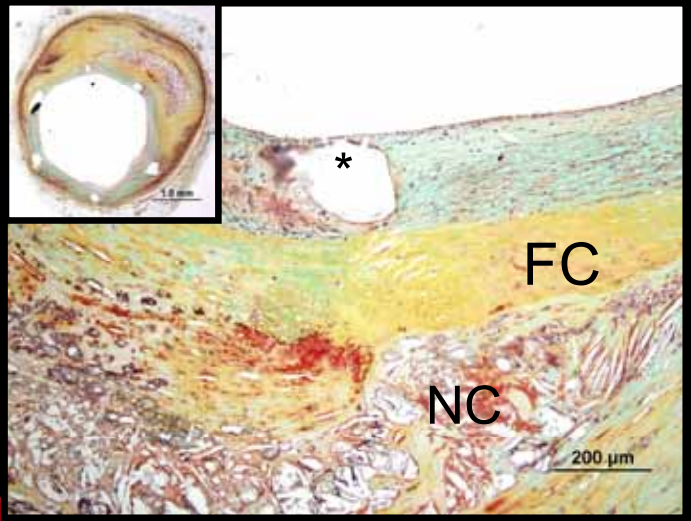


24 months (Cypher)

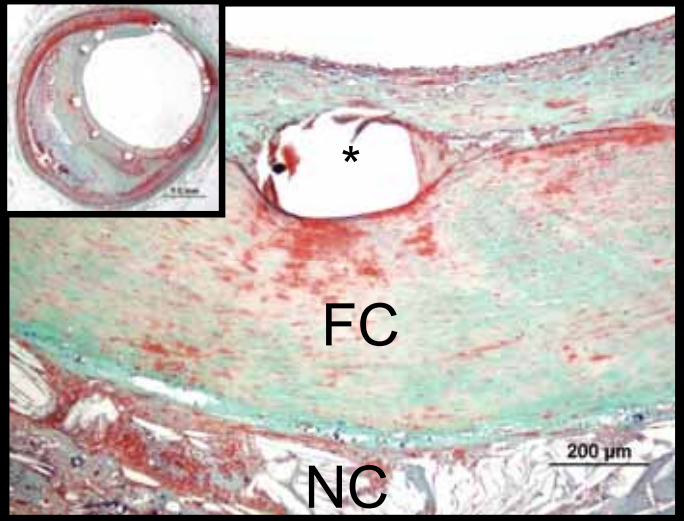


Stable Lesions (with Fibroatheroma and thick cap)

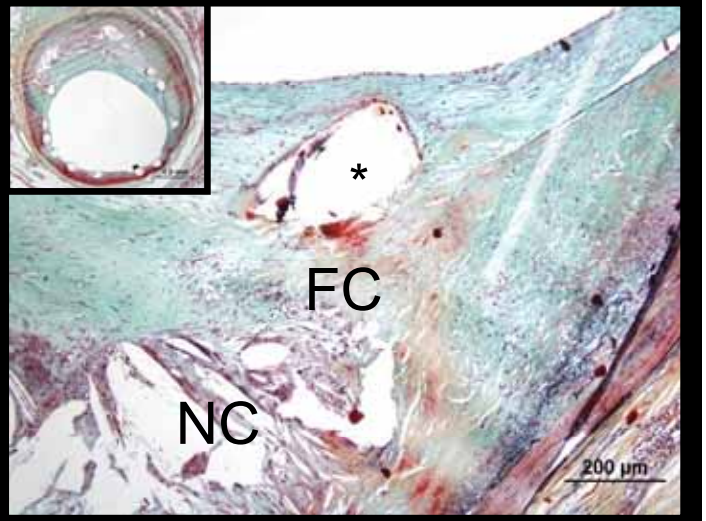
7 months (Cypher)



18 months (Taxus)



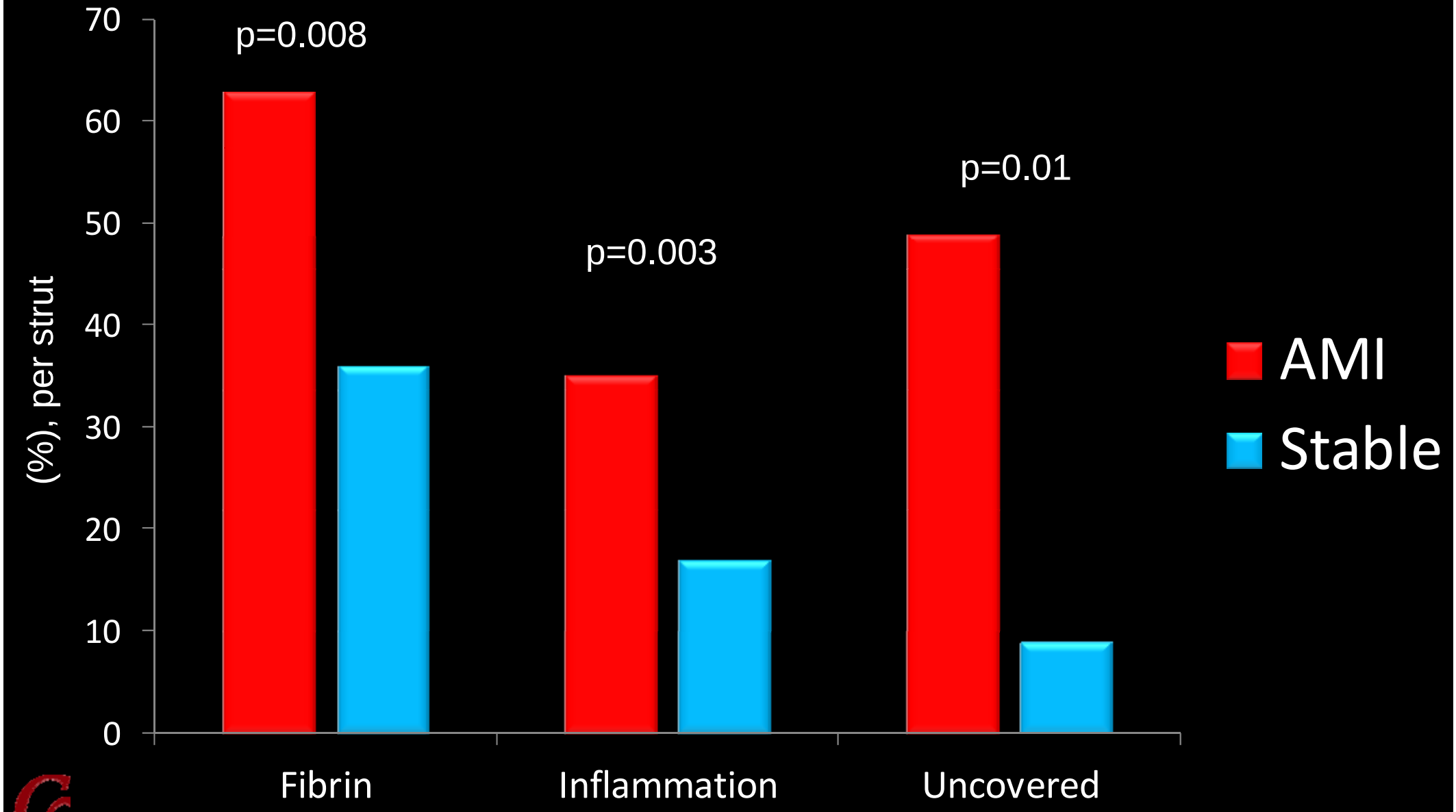
19 months (Cypher)



V-HILLS

Nakazawa, G et al. Circulation 2008; 118:1138-

Morphometry and Pathologic Assessment at Culprit Site (AMI vs. stable patients)



Nakazawa, G et al. Circulation 2008; 118:1138-

Stent Healing at 9 months Assessed by OCT in Stable and Unstable AP patients

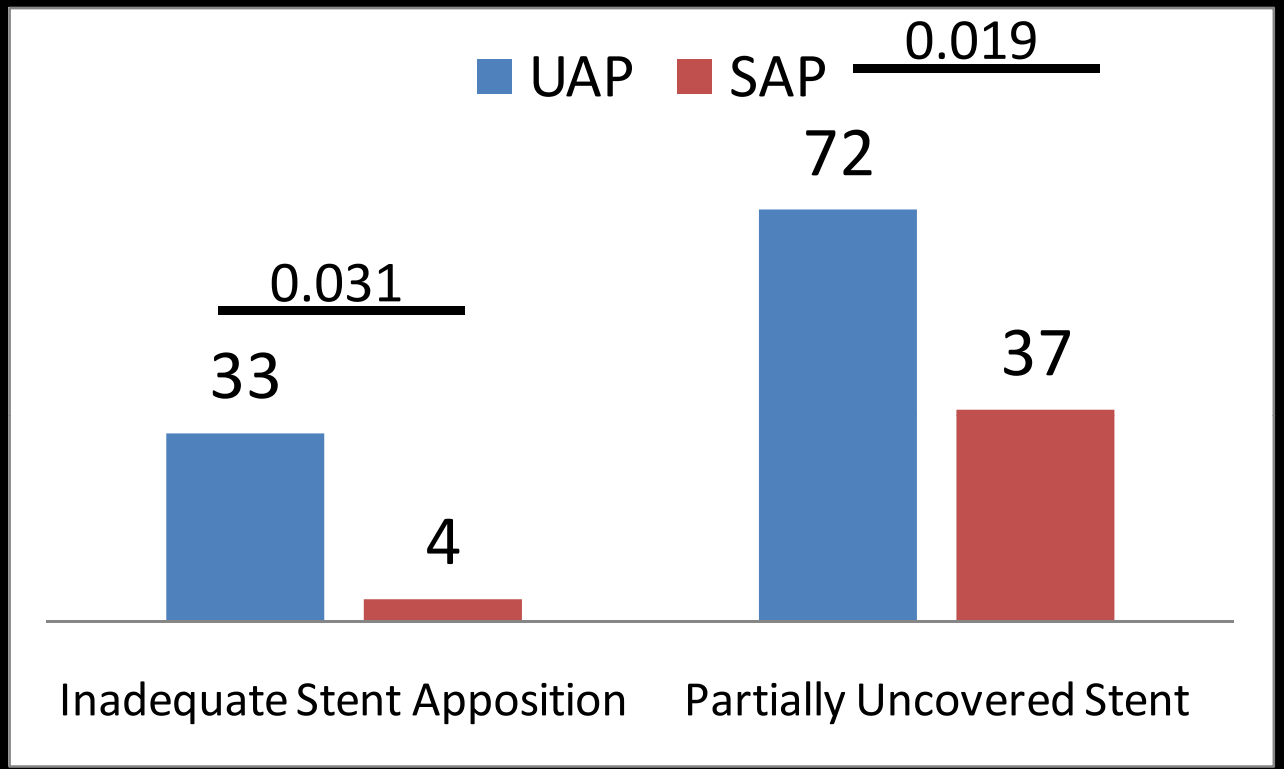


Table 5. OCT Assessment for Neointimal Coverage of Stent Struts at 9 Months' Follow-Up in UAP and SAP Patients

	UAP (n = 18)	SAP (n = 27)	p Value
No. of struts with neointimal coverage	145.2 ± 38.5	160.0 ± 35.1	0.189
No. struts without neointimal coverage			
Well-apposed struts	19.0 ± 18.1	6.6 ± 11.3	0.007
Inadequately-apposed struts	4.0 ± 6.7	0.2 ± 1.2	0.006

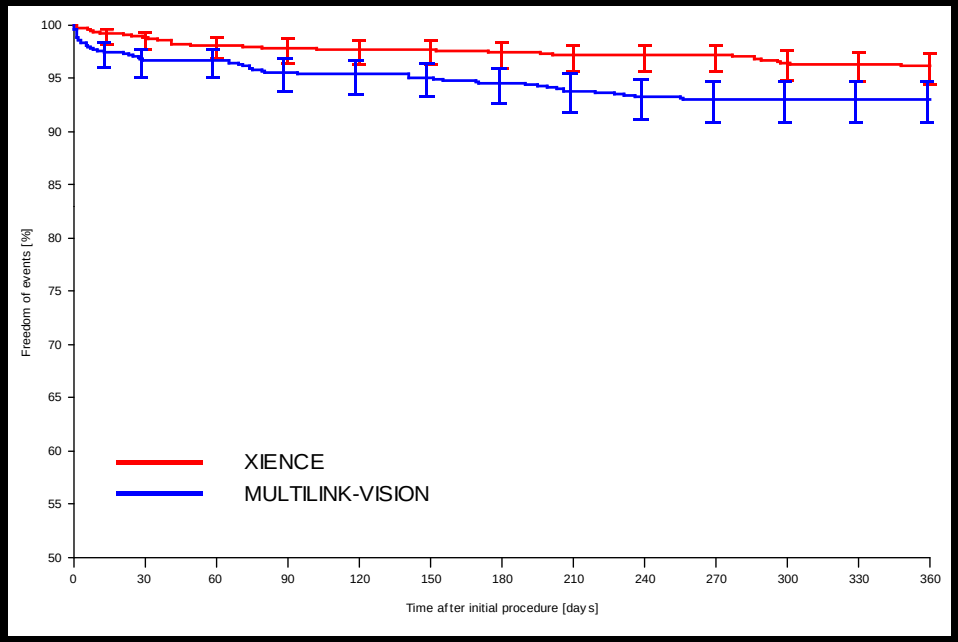
Values are given as mean ± SD.
Abbreviations as in Tables 1 and 2.

Kubo, T et al. J Am Coll Cardiol Img 2008; 1:475-84

No Difference in ST with low TVR in EES

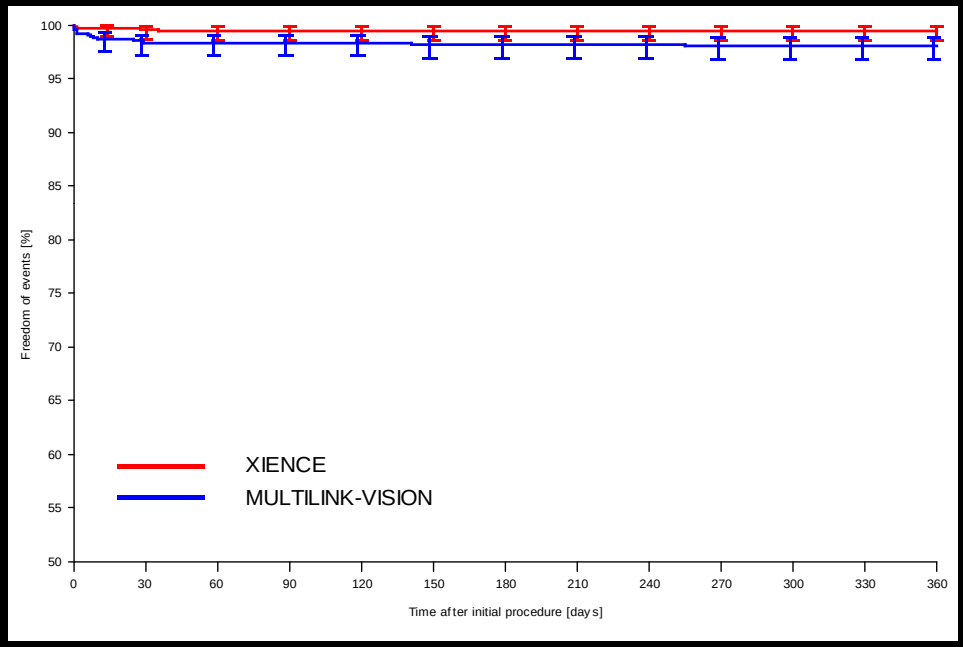
EXAMINATION trial

TVR



	Xience-V	Vision	Log-Rank P-value
Freedom from event, %	96.1	93.0	0.007

Definite Stent Thrombosis



	Xience-V	Vision	Log-Rank P-value
Freedom from event, %	99.5	98.1	0.01

CLINICAL RESEARCH Interventional Cardiology

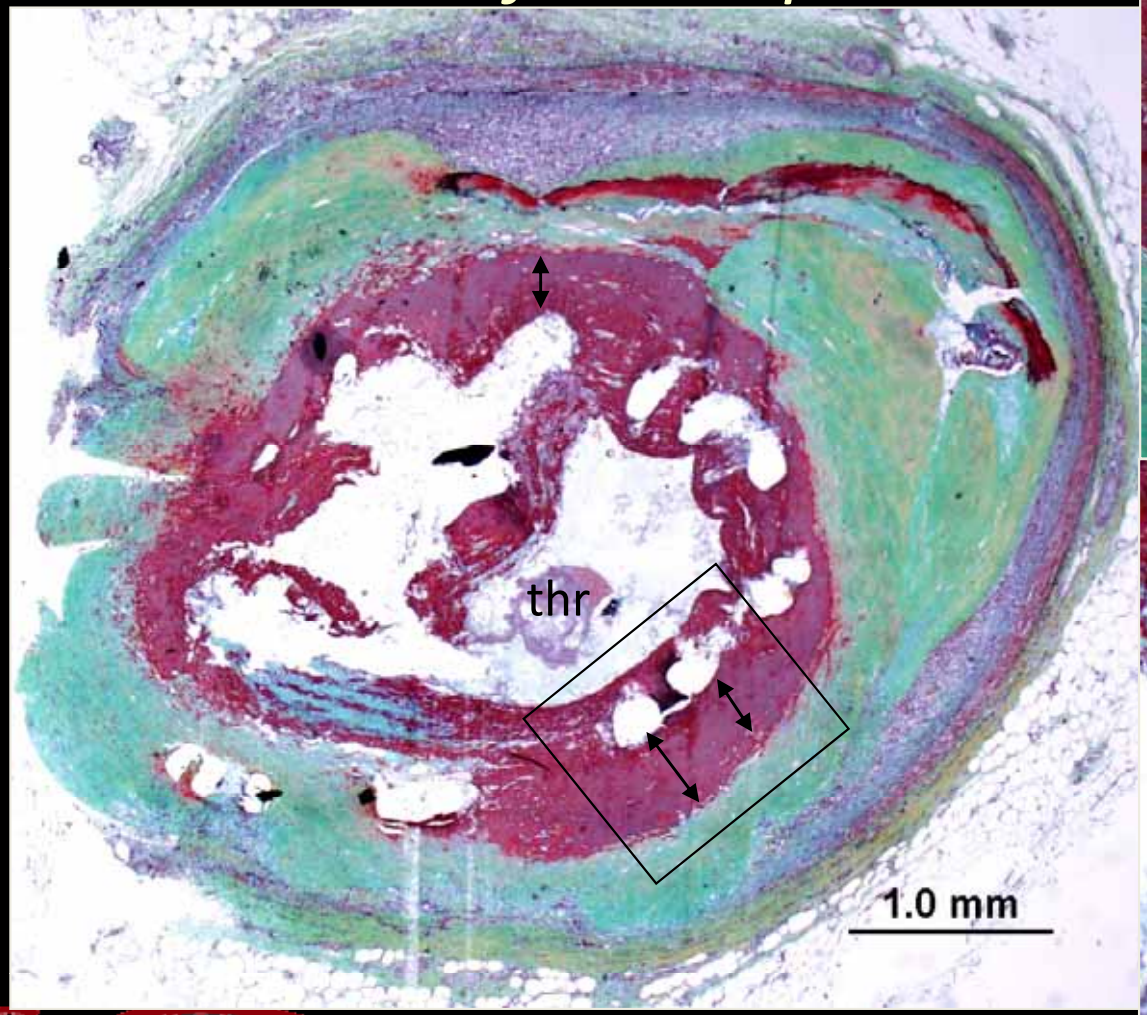
Coronary Responses and Differential Mechanisms of Late Stent Thrombosis Attributed to First-Generation Sirolimus- and Paclitaxel-Eluting Stents

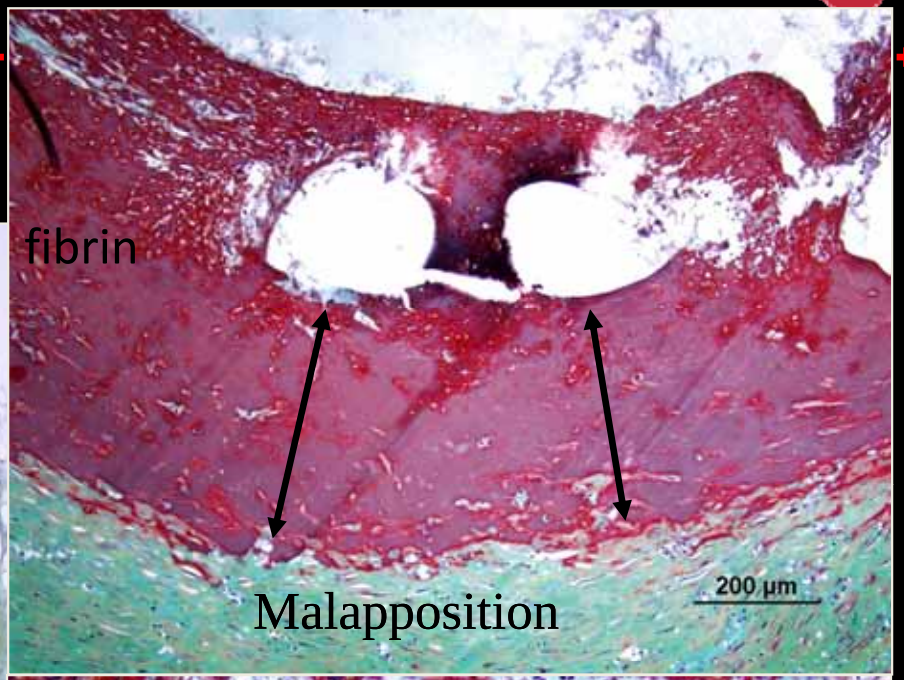
Gaku Nakazawa, MD,* Aloke V. Finn, MD,† Marc Vorpahl, MD,* Elena R. Ladich, MD,* Frank D. Kolodgie, PHD,* Renu Virmani, MD*

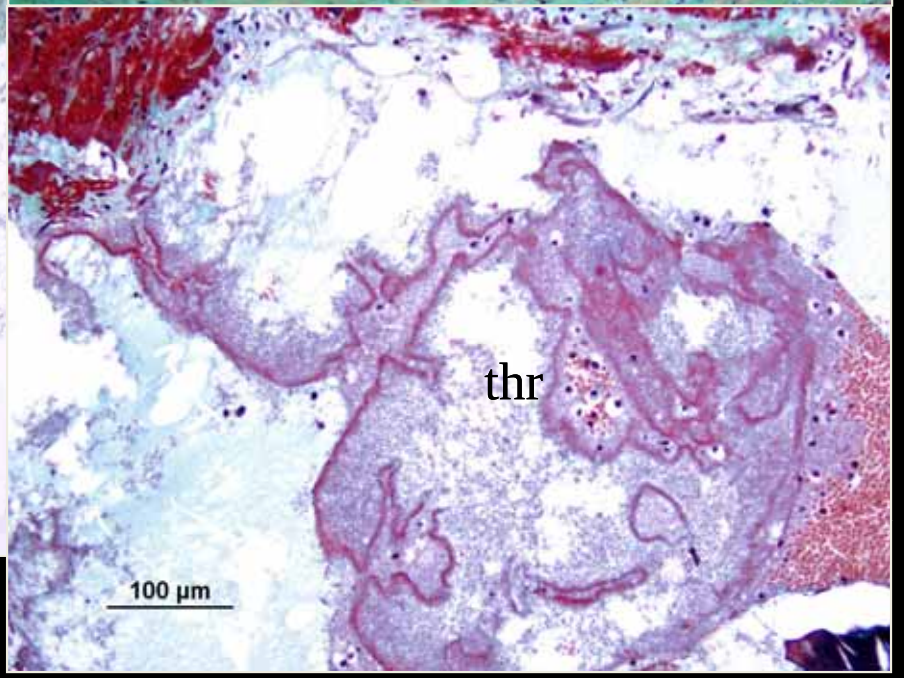
Gaithersburg, Maryland; and Atlanta, Georgia

Late Stent Thrombosis in TAXUS stent

Stent Malapposition with extensive fibrin deposition





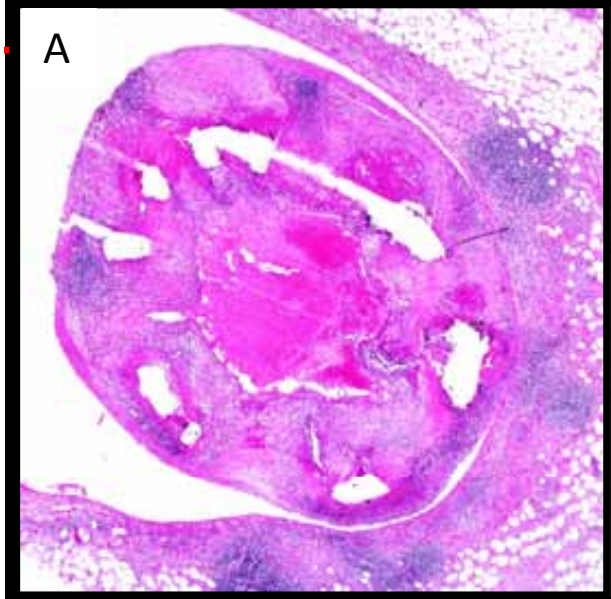


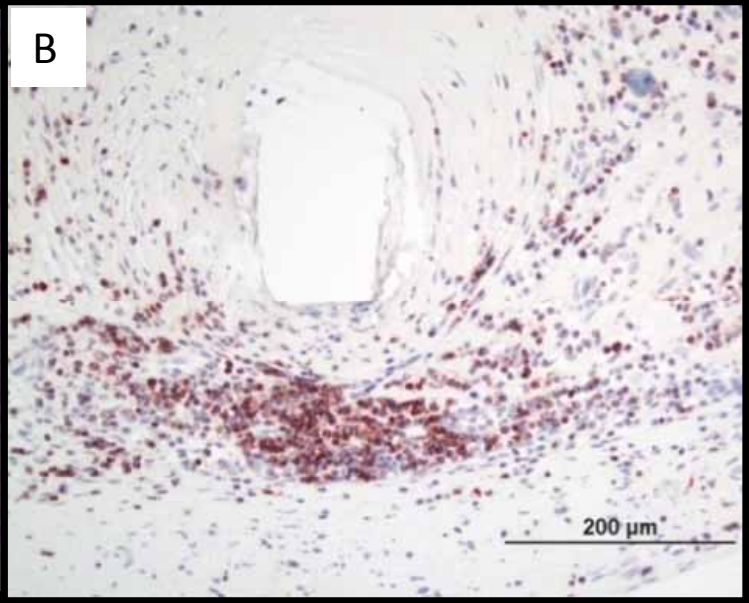
9 months following Taxus stents implantation

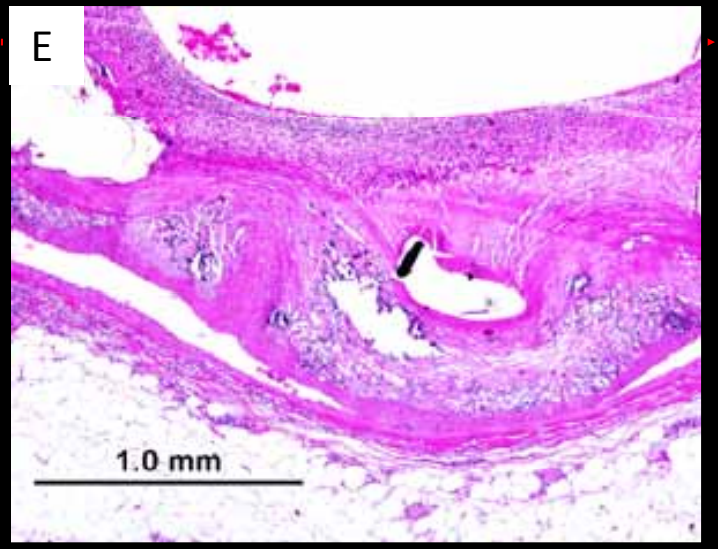
Localized Hypersensitivity Reaction in Cypher

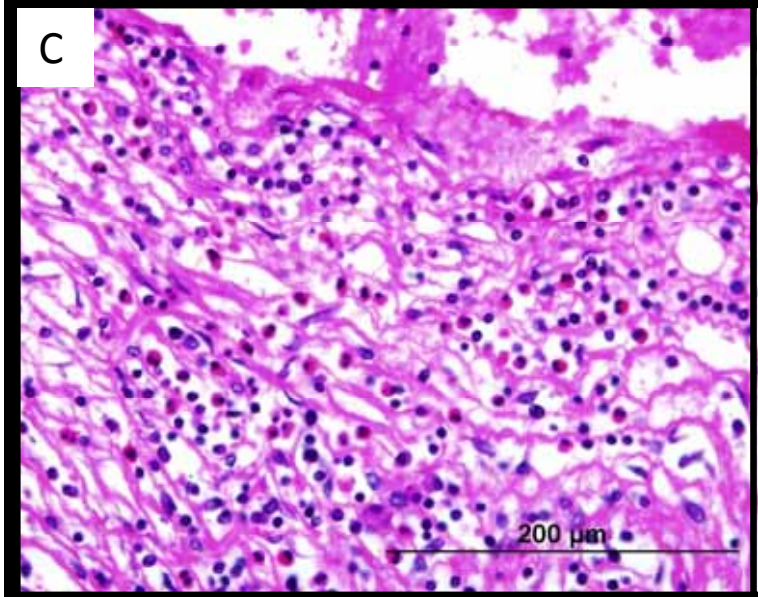
LAD: Cypher (17months)

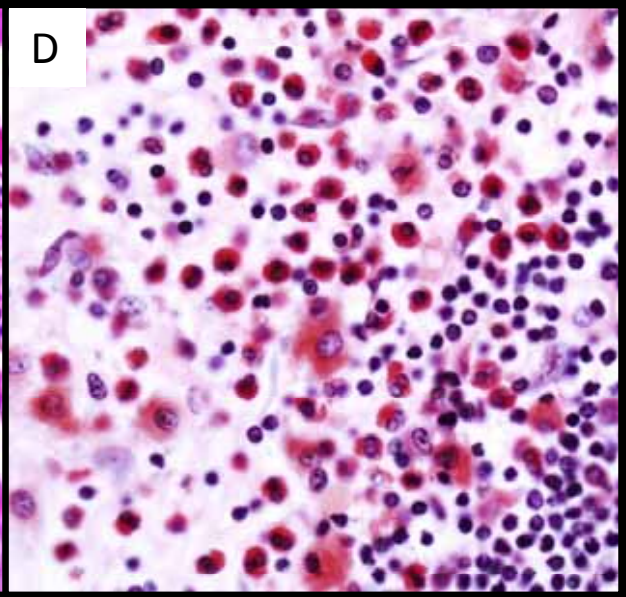
RCA: Cypher (17months)

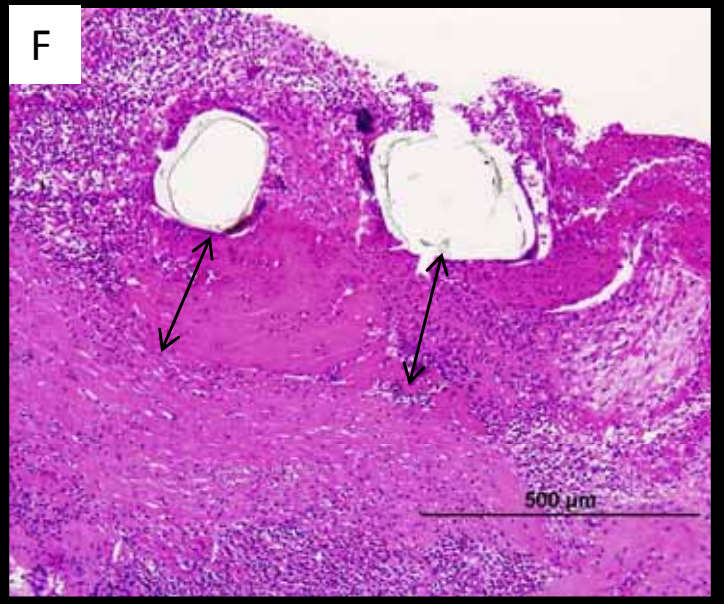






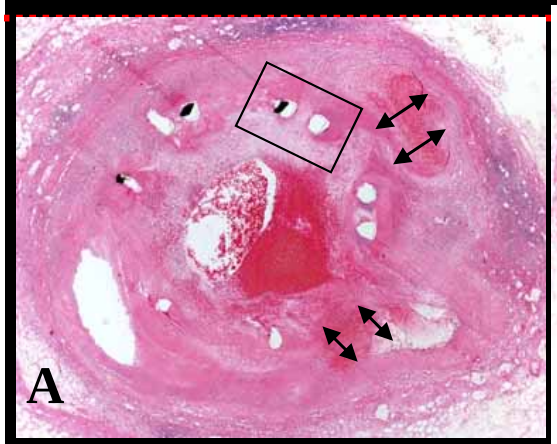


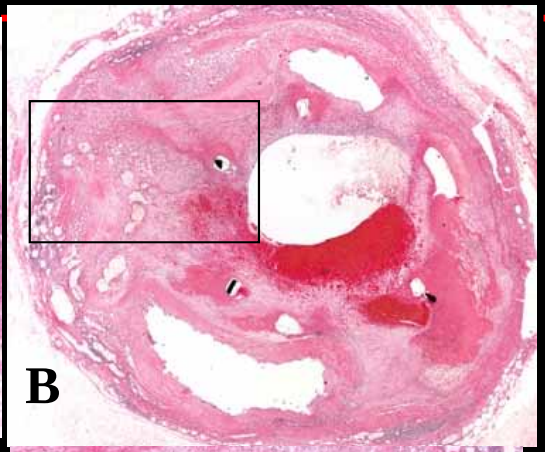


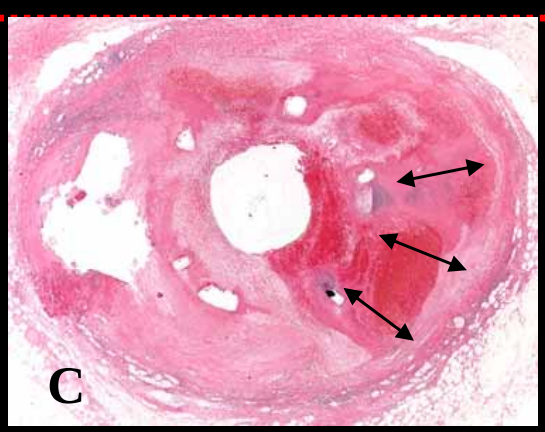


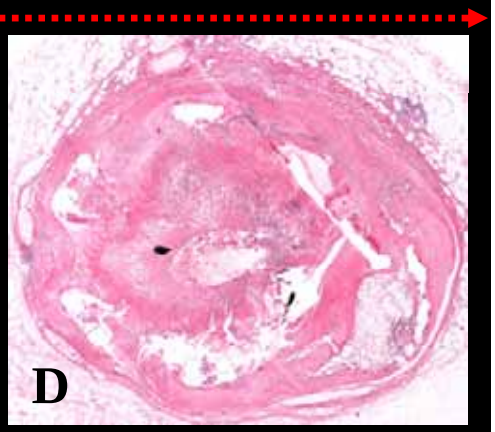
Nakazawa, G et al. J Am Coll Cardiol 2011: 57(4).390-8

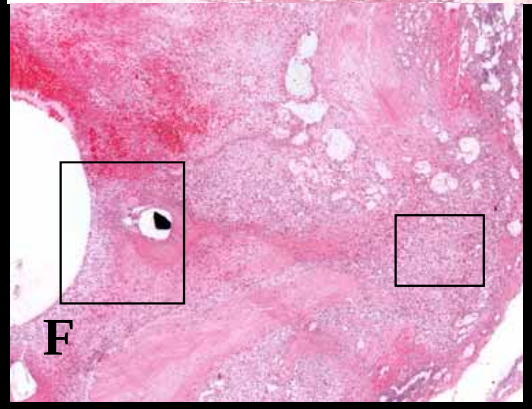
58-years old male who died of late stent thrombosis. A Cypher stent had been placed in the LCx for UAP 18-months prior to onset of CP.

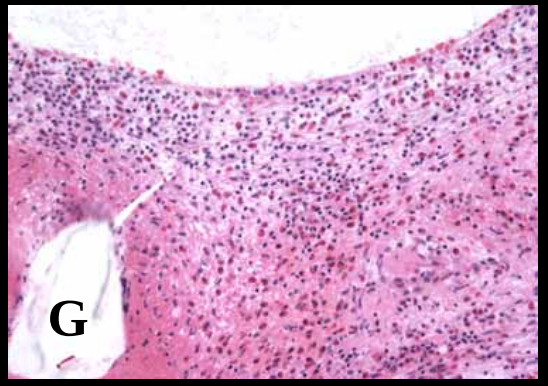


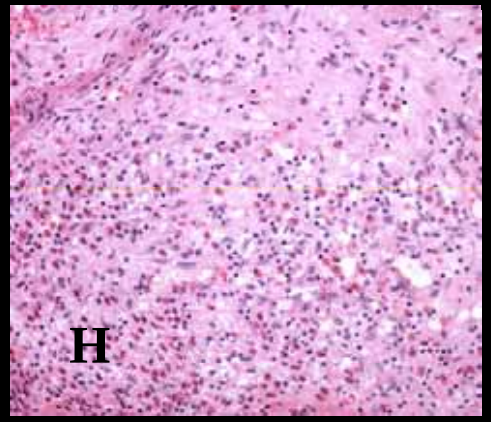


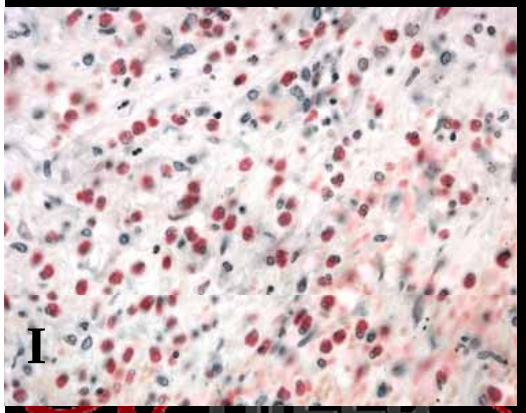




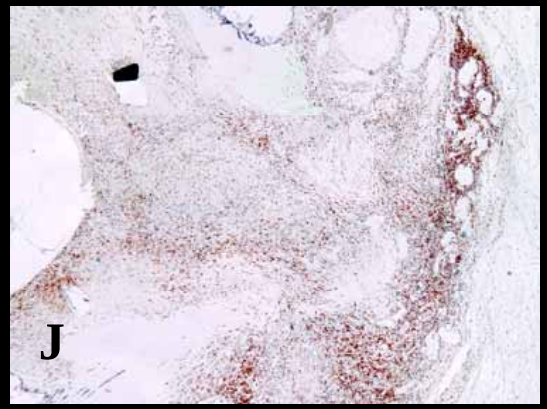




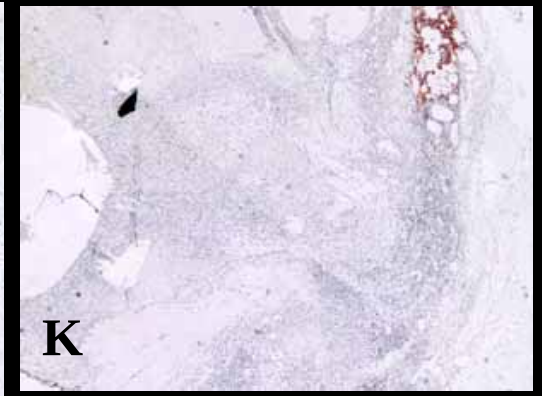




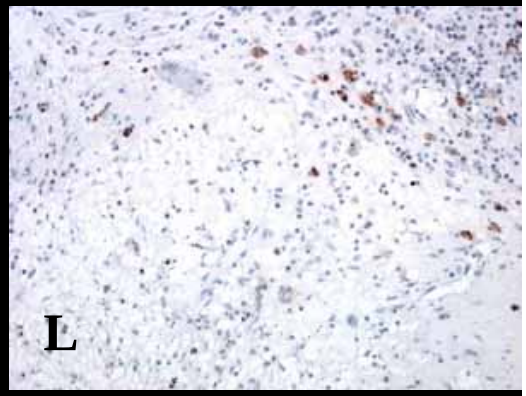
Luna stain



T-lymphocytes



B-lymphocytes



Macrophage

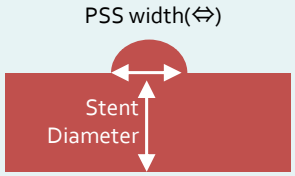
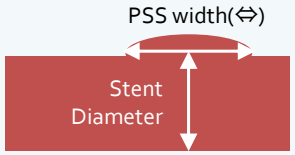
Definition & Morphological Classification
Peri-Stent contrast Staining(PSS)

Maximum contrast staining outside the stent > 20% of stent diameter at the same site

Definition*:

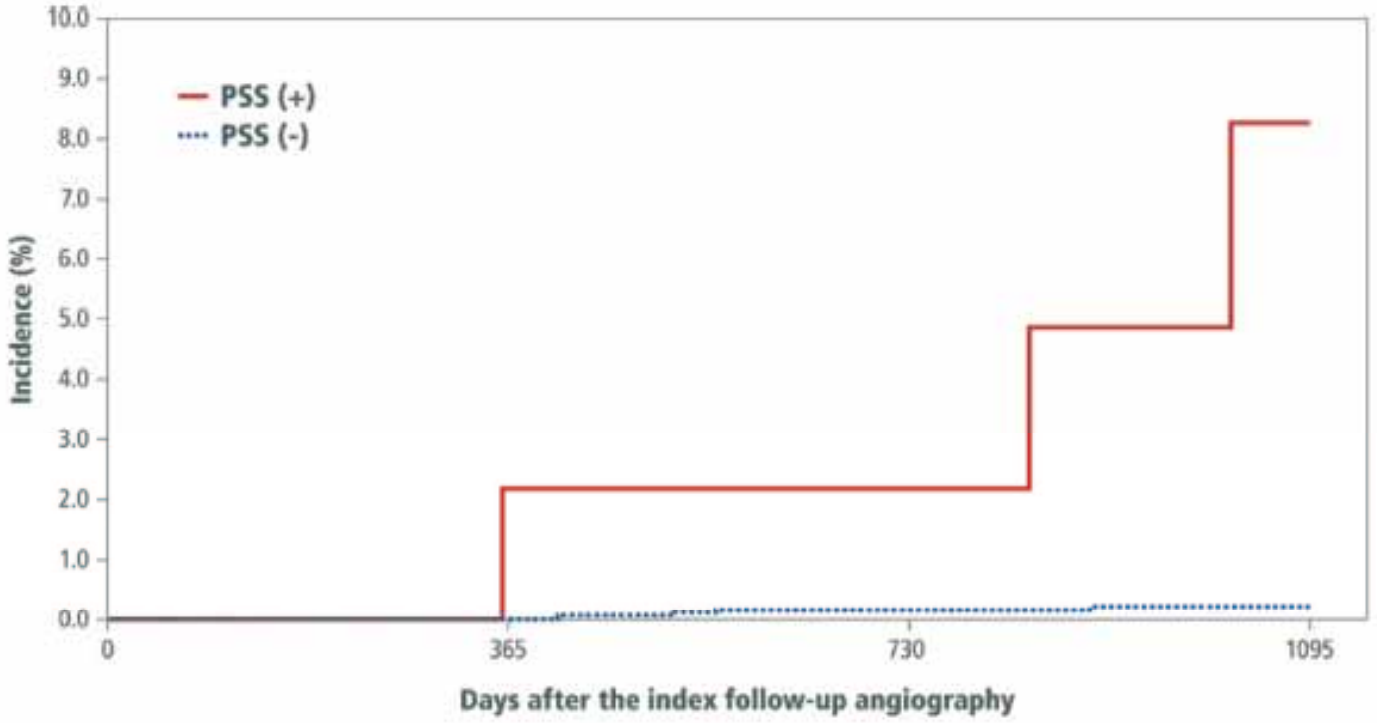
PSS was defined as contrast staining outside the stent extending to ≥20% of stent diameter

Example:
If measured stent diameter at the site of maximum contrast staining was 3.0mm, PSS was defined as contrast staining outside the stent ≥ 0.6mm (20%).

Classification of PSS Morphology		Definition
Focal		PSS width ≤ Stent diameter
Mono-focal		Single focal PSS at the stented segment
Multi-focal		Multiple focal PSS at the stented segment
Segmental**		PSS width > Stent diameter
Irregular-contour***		Segmental PSS with irregular contour
Smooth-contour		Segmental PSS with smooth contour

*:including aneurysm **:including coexisting focal type PSS ***:including coexisting smooth contour type

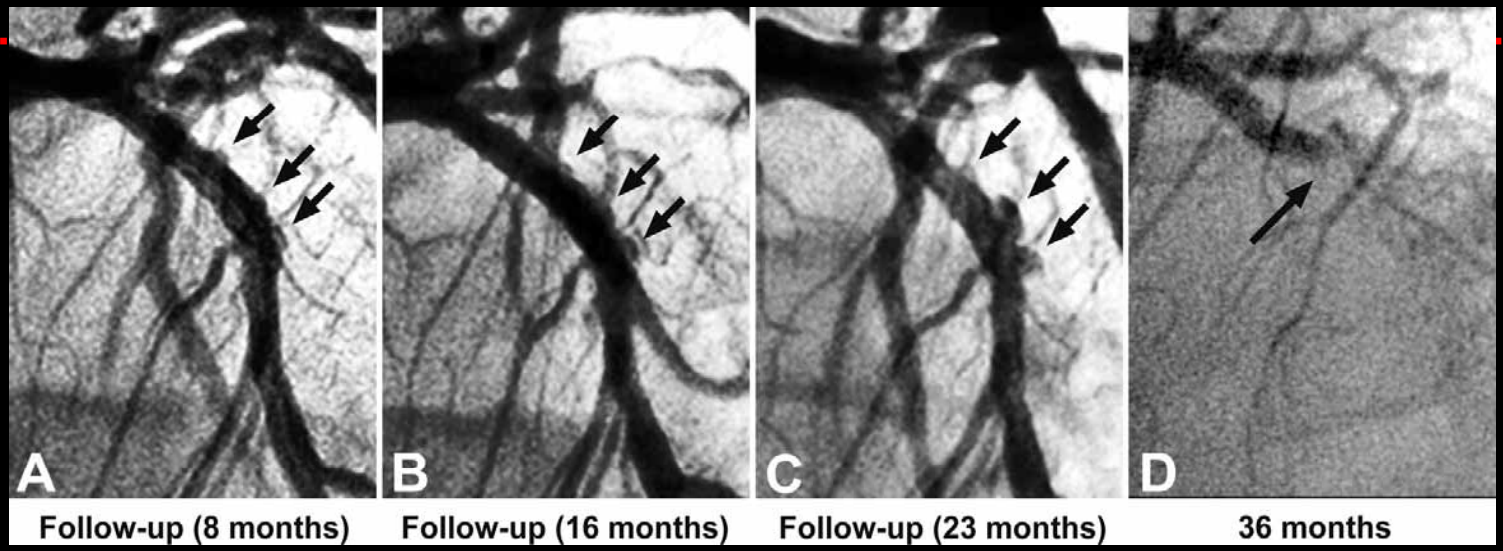
PSS predicts a risk for LST

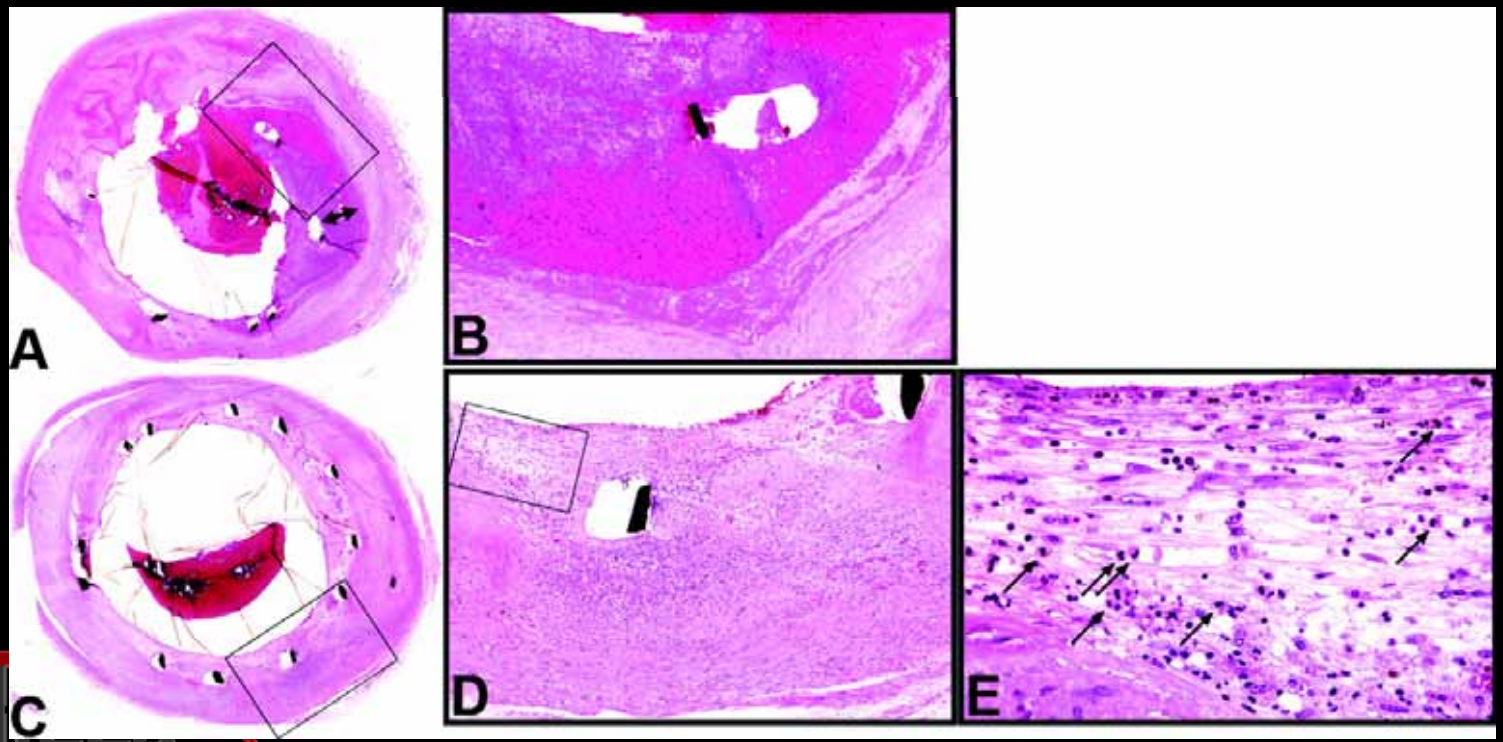


Days	0	365	730	1095
PSS (+) N of lesions at risk	51	46	40	26
N of lesions with events	0	1	1	3
Cumulative incidence	0%	2.1%	2.1%	8.2%
PSS (-) N of lesions at risk	2761	2532	1847	580
N of lesions with events	0	0	3	4
Cumulative incidence	0%	0%	0.13%	0.2%

Imai M, et al. Circulation. 2011;123:2382-2391

PSS & Hypersensitivity Vacuities





Kon H et al. Circ Cardiovasc Interv 2011;4:e1-e3

EXPEDITED PUBLICATIONS

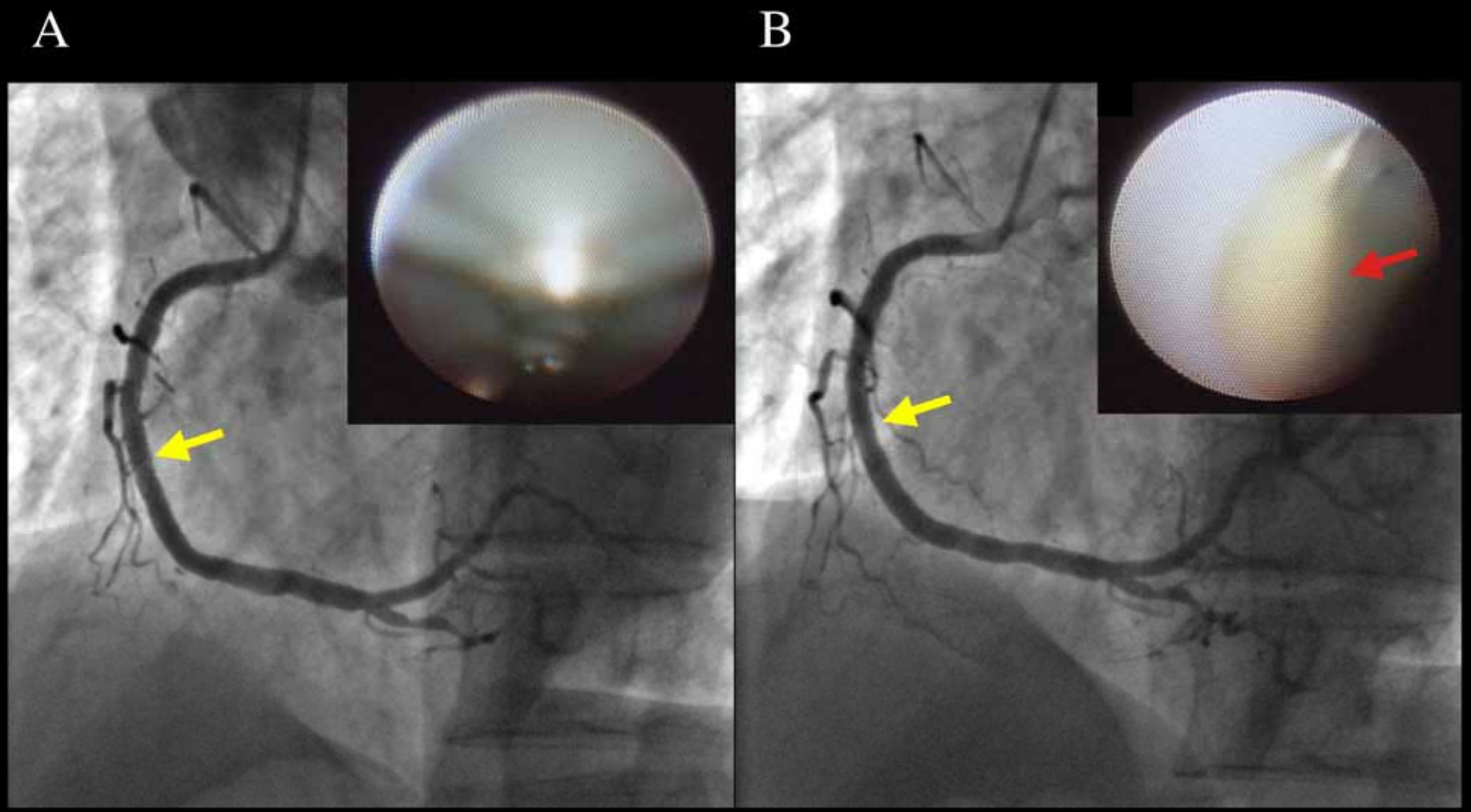
The Pathology of Neoatherosclerosis in Human Coronary Implants

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*

Gaithersburg, Maryland; and Atlanta, Georgia

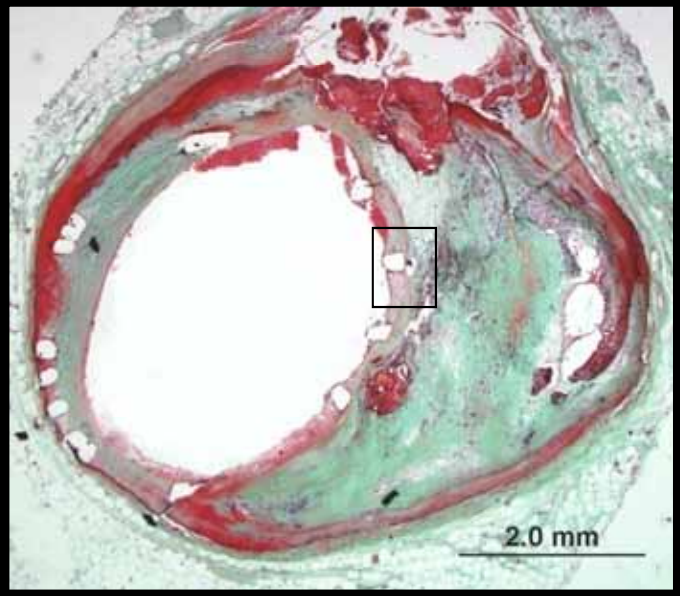
Newly formed “Yellow Neointima” in SES

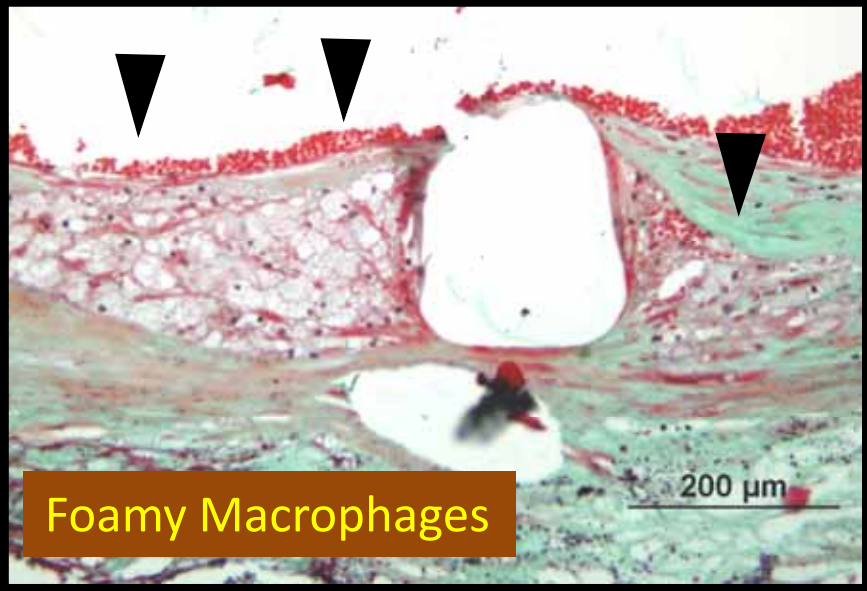


Higo et al. JACC Cardiovasc Imaging, 2009 May;2(5):616-24

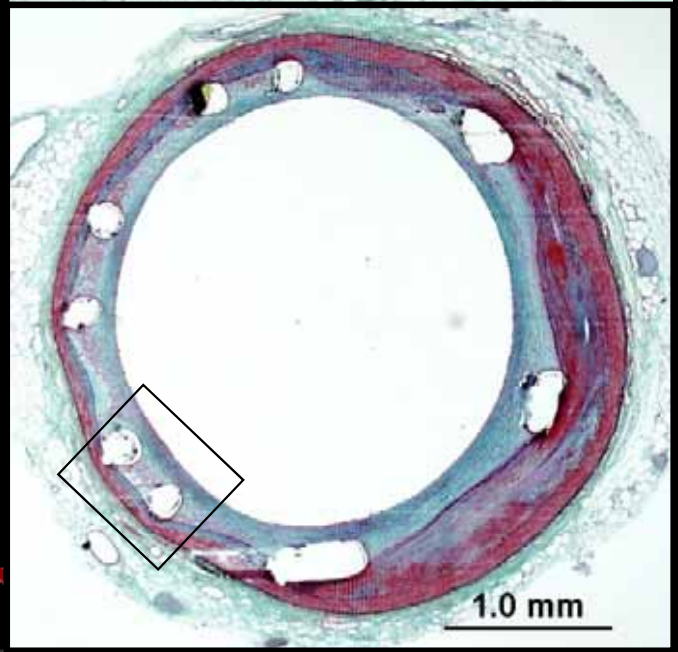
Early Atherosclerotic Change in DES

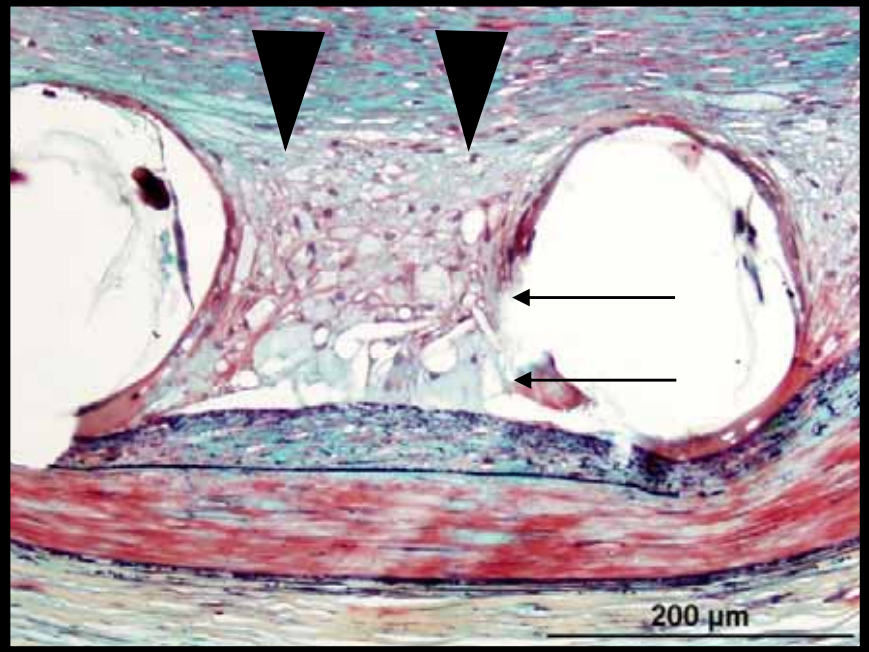
Taxus 7monts





Cypher 12monts

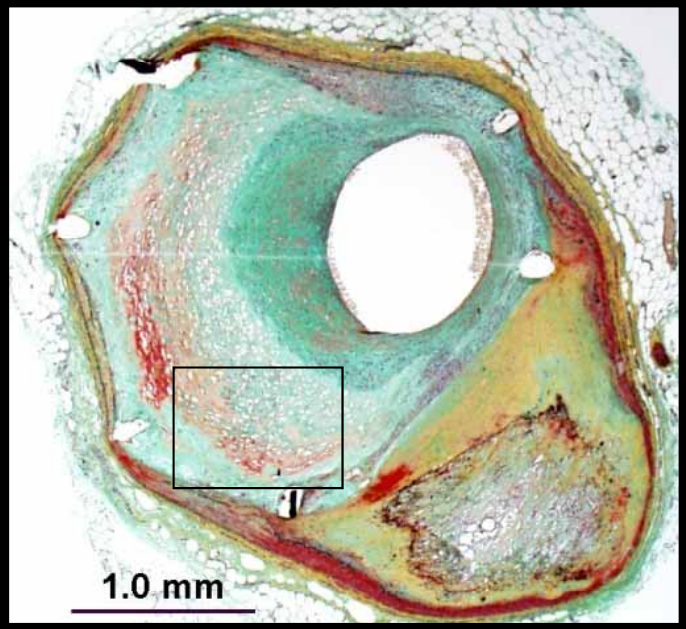




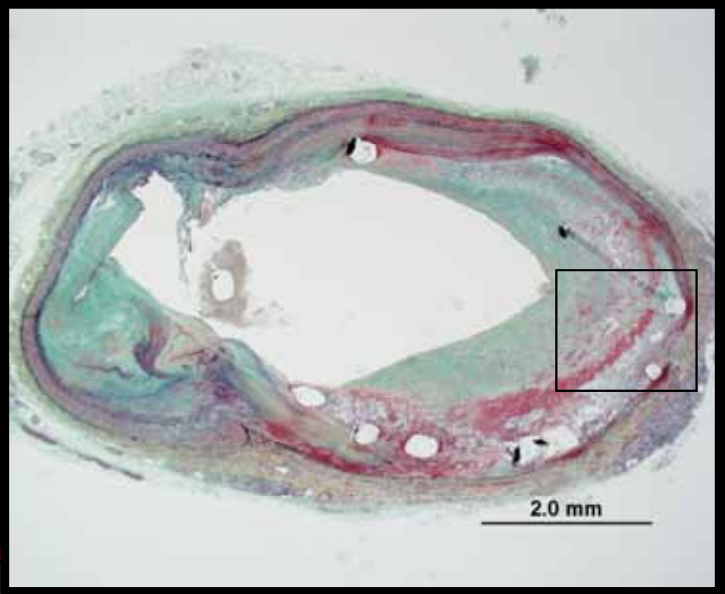
Nakazawa, G et al. J Am Coll Cardiol. 2011 Mar 15;57(11):1314-22.

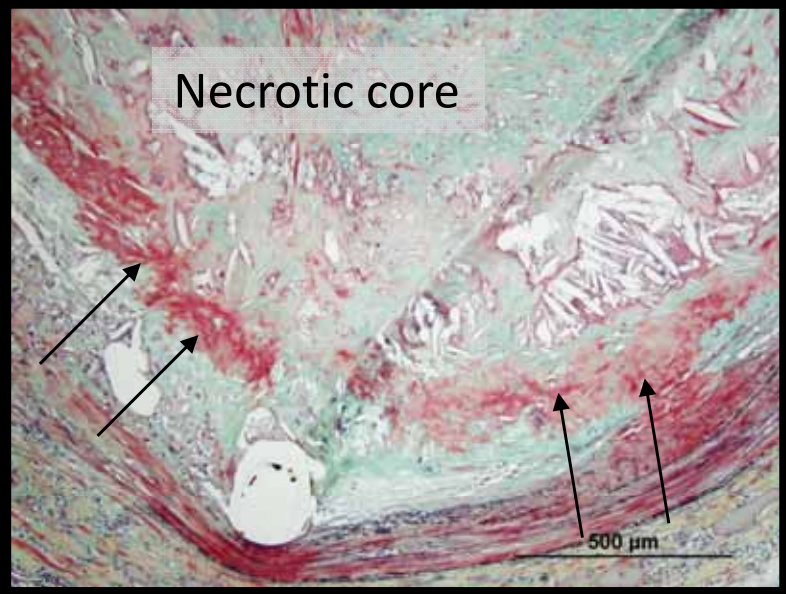
Late Atherosclerotic Change in DES

Cypher 13months



Taxus14months

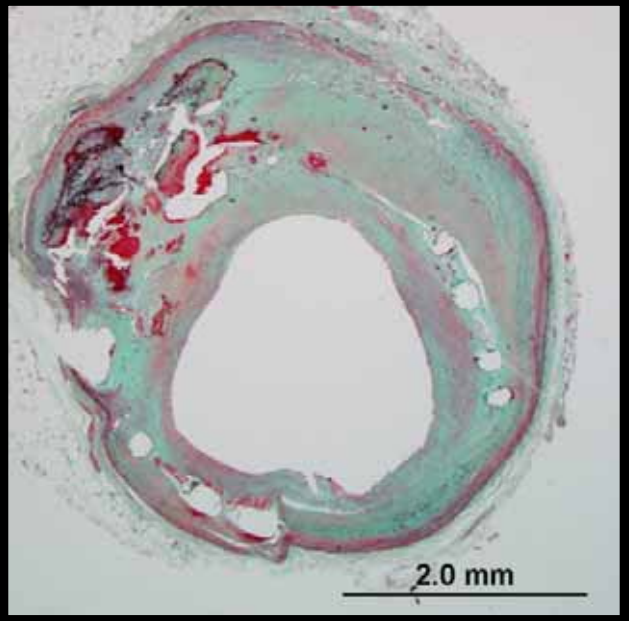


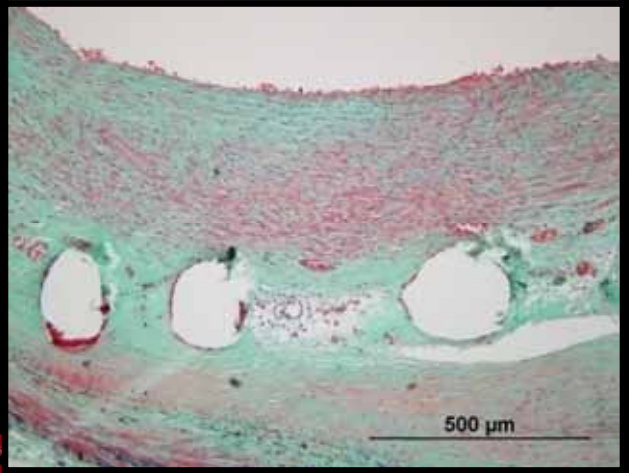


Nakazawa, G et al. J Am Coll Cardiol. 2011 Mar 15;57(11):1314-22.

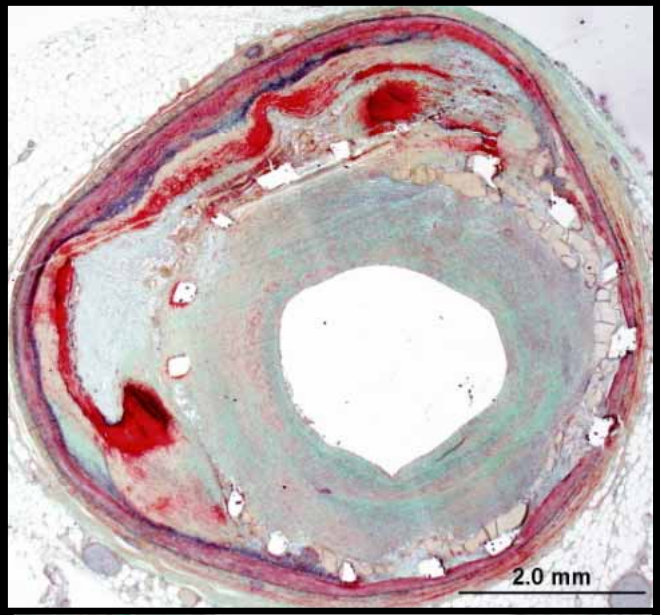
Typical neointima following BMS implantation

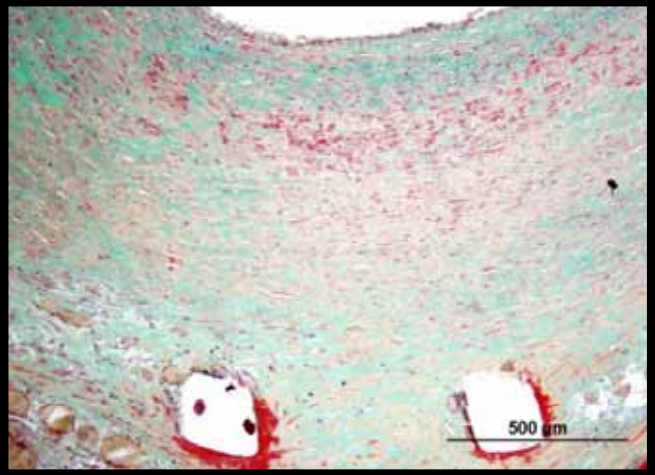
BMS 7months



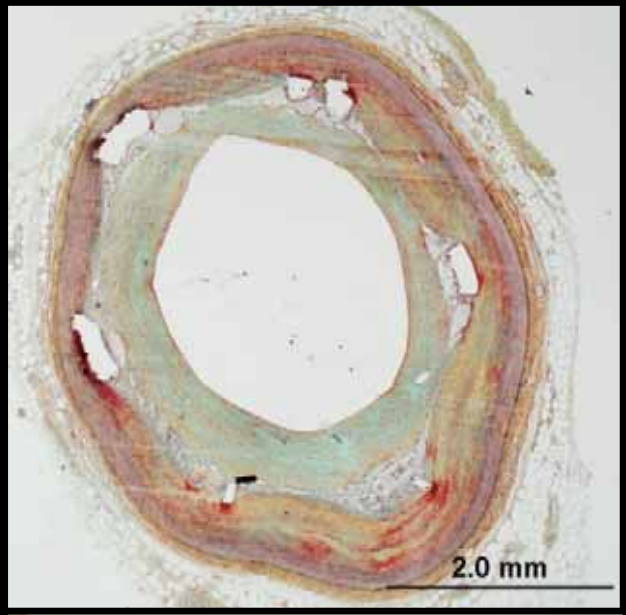


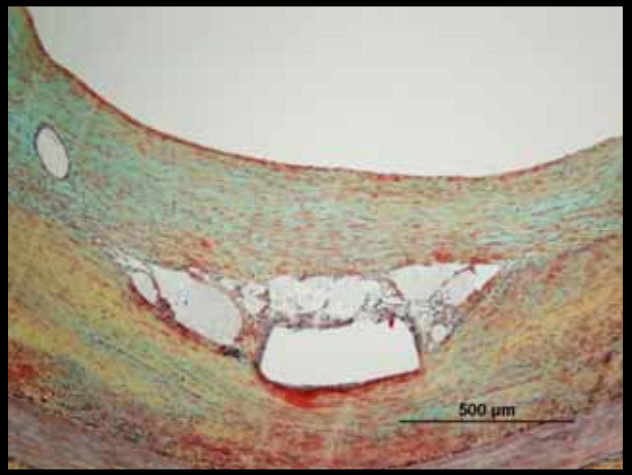
BMS 13months



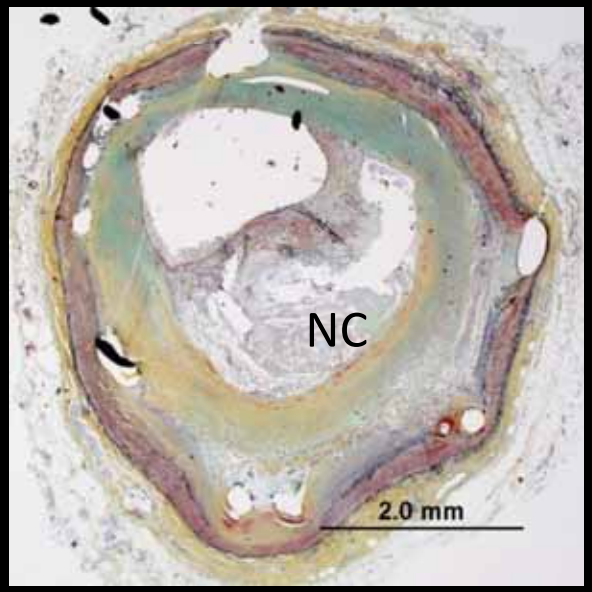


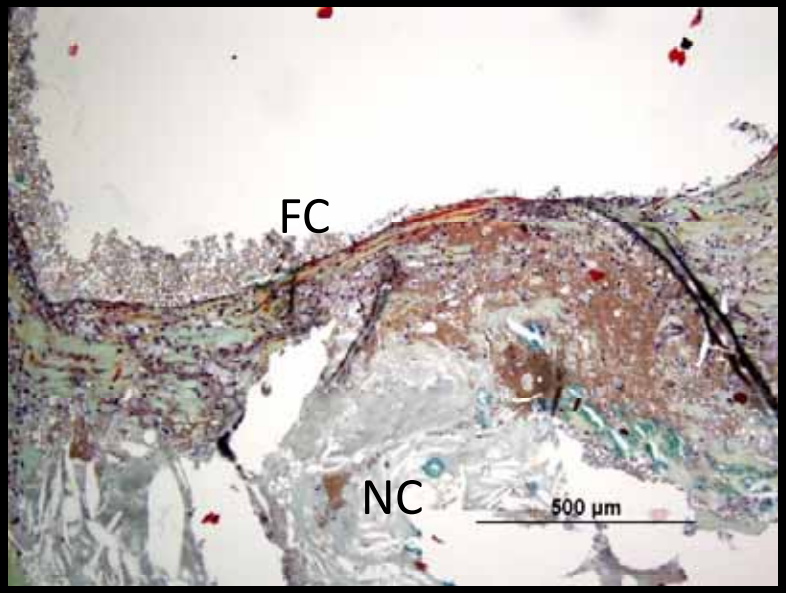
BMS 15months

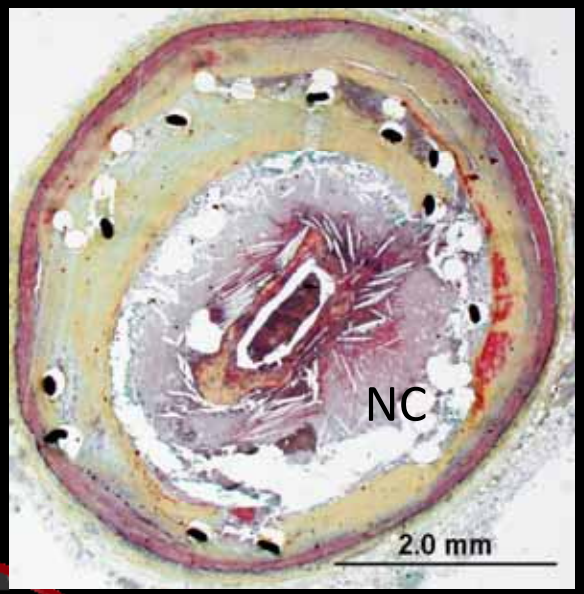


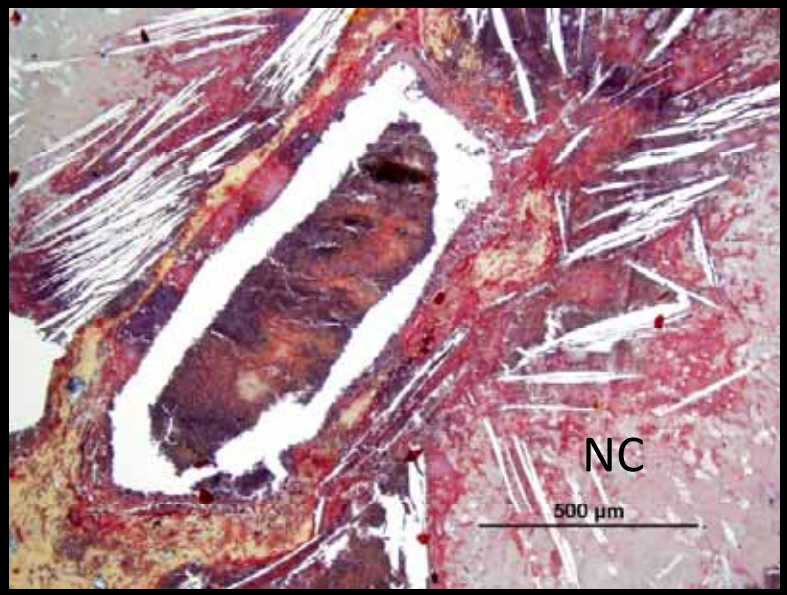


Plaque Rupture secondary to newly formed atherosclerosis within the stent



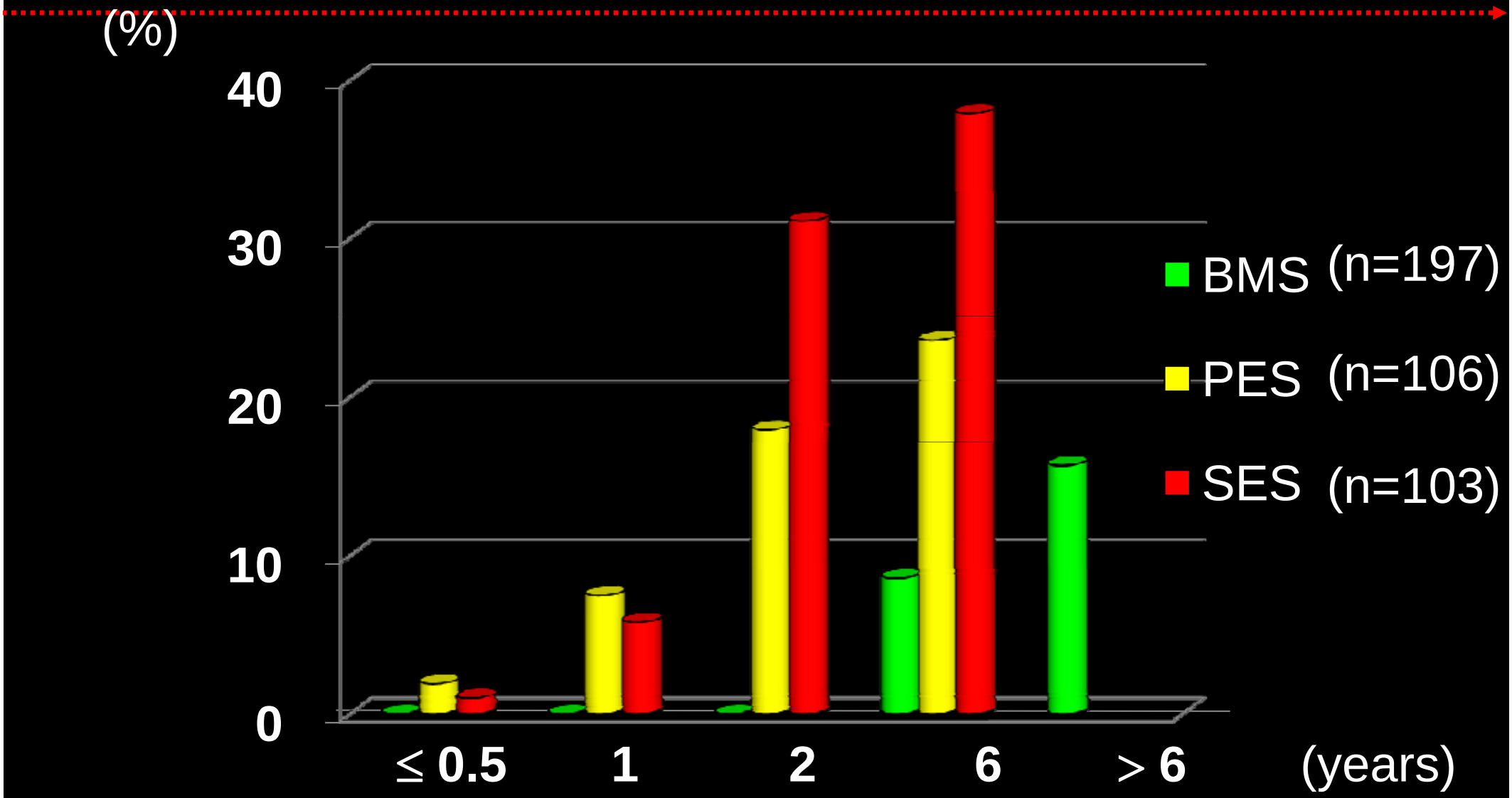






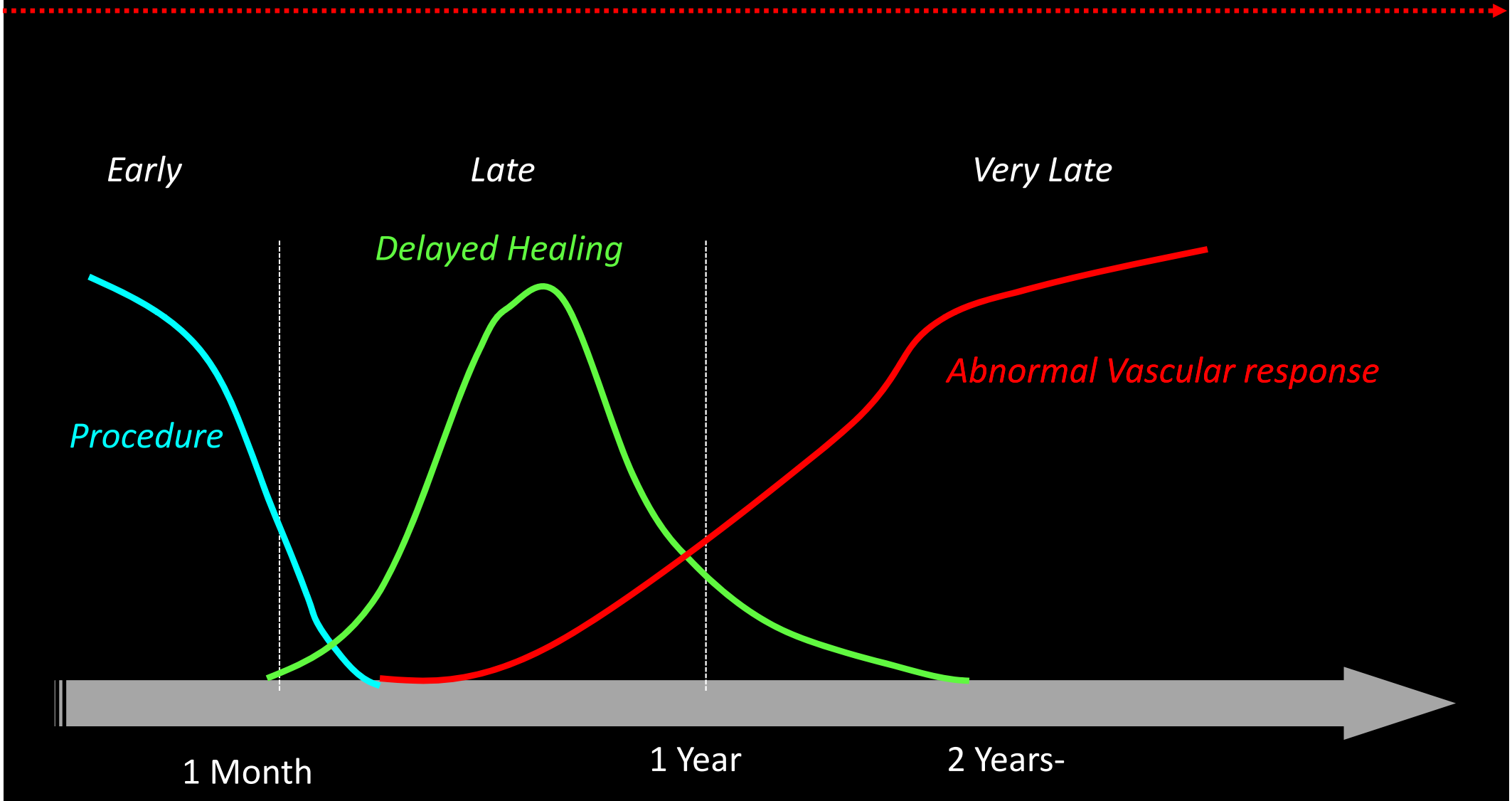
BMS implantation >5 years antemortem, Died suddenly

Cumulative Incidence of Neoatherosclerosis



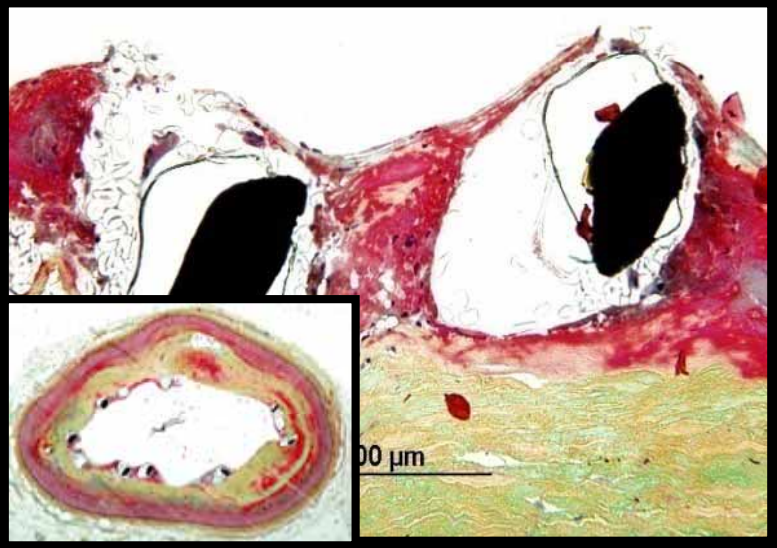
Cumulative Number of Lesions		≤ 0.5	1	2	6	> 6
	BMS	34	53	88	164	197
	PES	32	62	90	106	NA
	SES	26	41	87	103	NA

Mechanisms of Stent Thrombosis in DES era

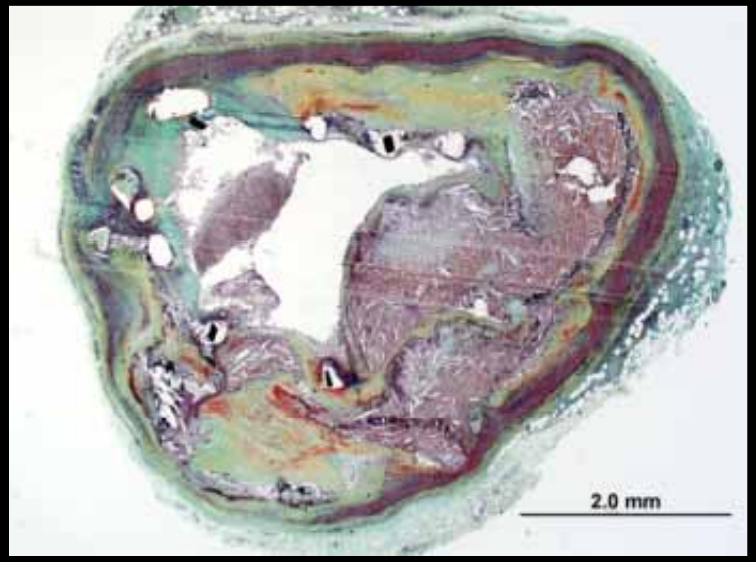


Major Causes of 1st Gen DES thrombosis

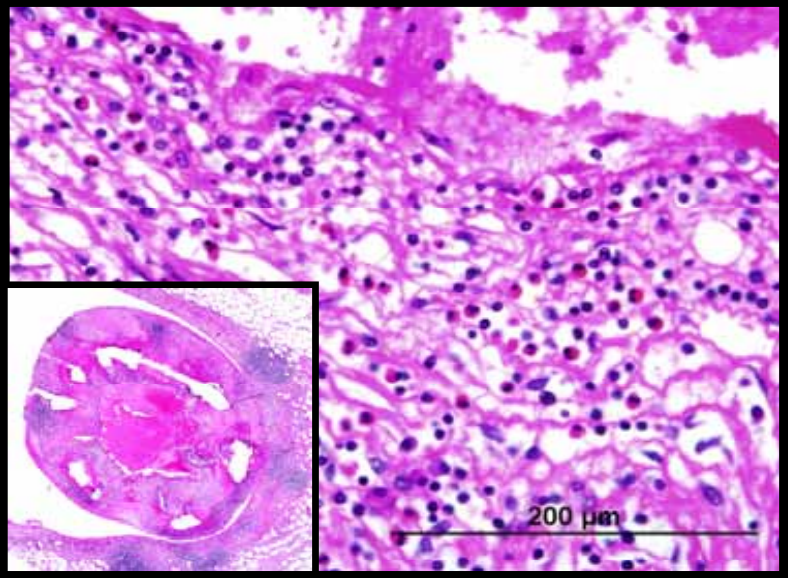
Delayed Healing



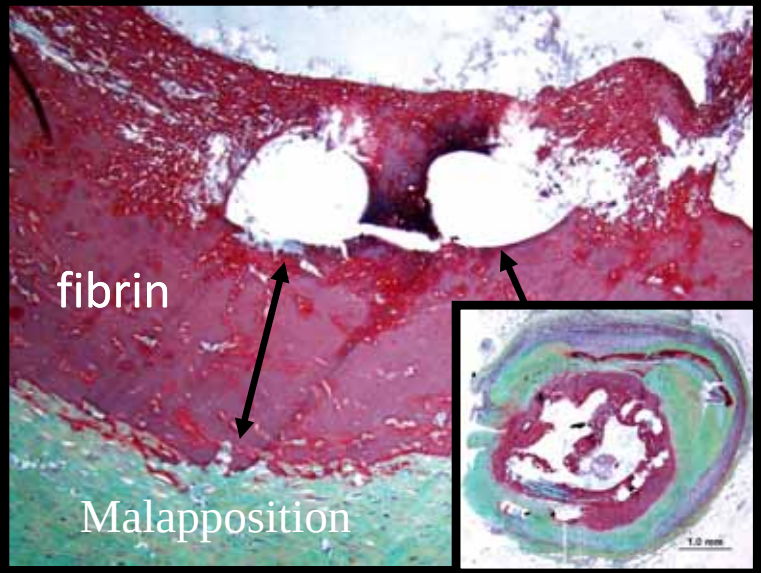
Neoatherosclerosis



Hypersensitivity



Severe Fibrin with malapposition



Joner, J et al. J Am Coll Cardiol. 2006;48(1):193-202.
Nakazawa, G et al. J Am Coll Cardiol 2011:57(4).390-8
Nakazawa, G et al. J Am Coll Cardiol. 2011:57(11):1314-22.

Representative Images of 2nd- vs. 1st-generation DES in Human Coronary Arteries

1st-generation DES

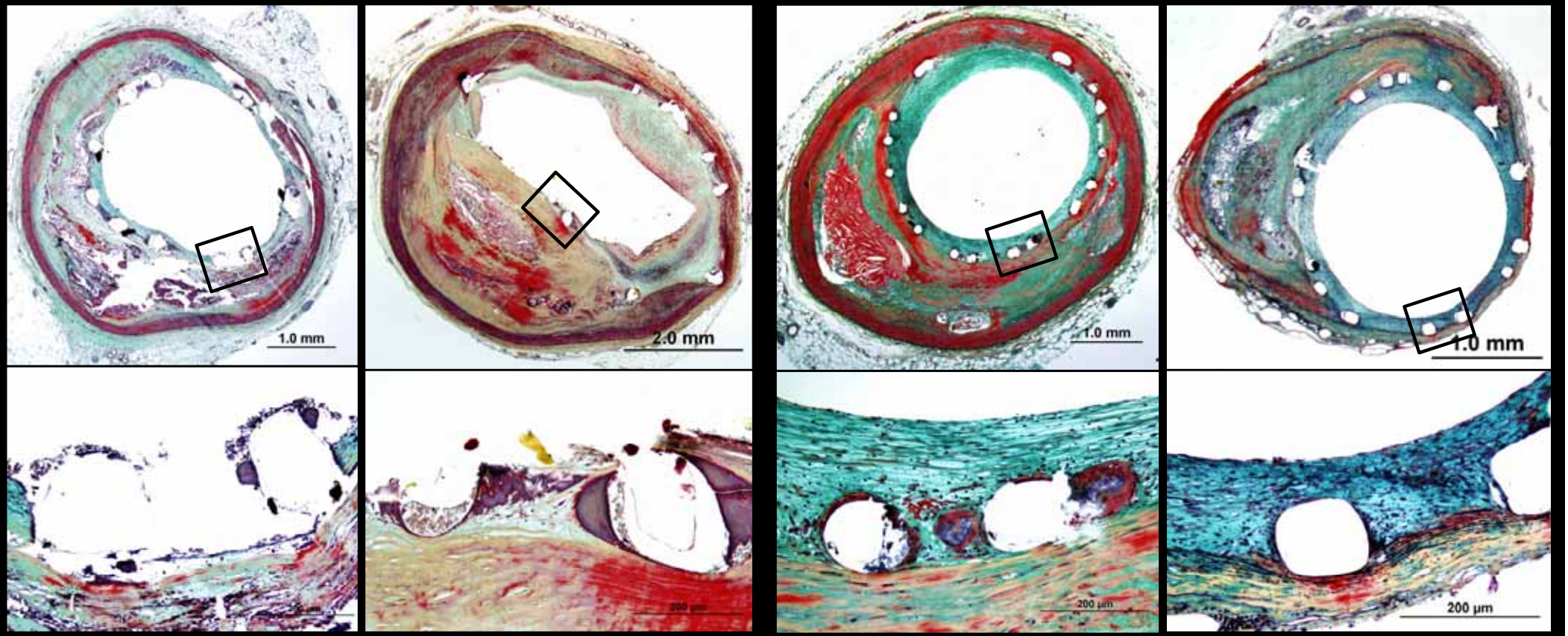
2nd-generation DES

SES 13 months

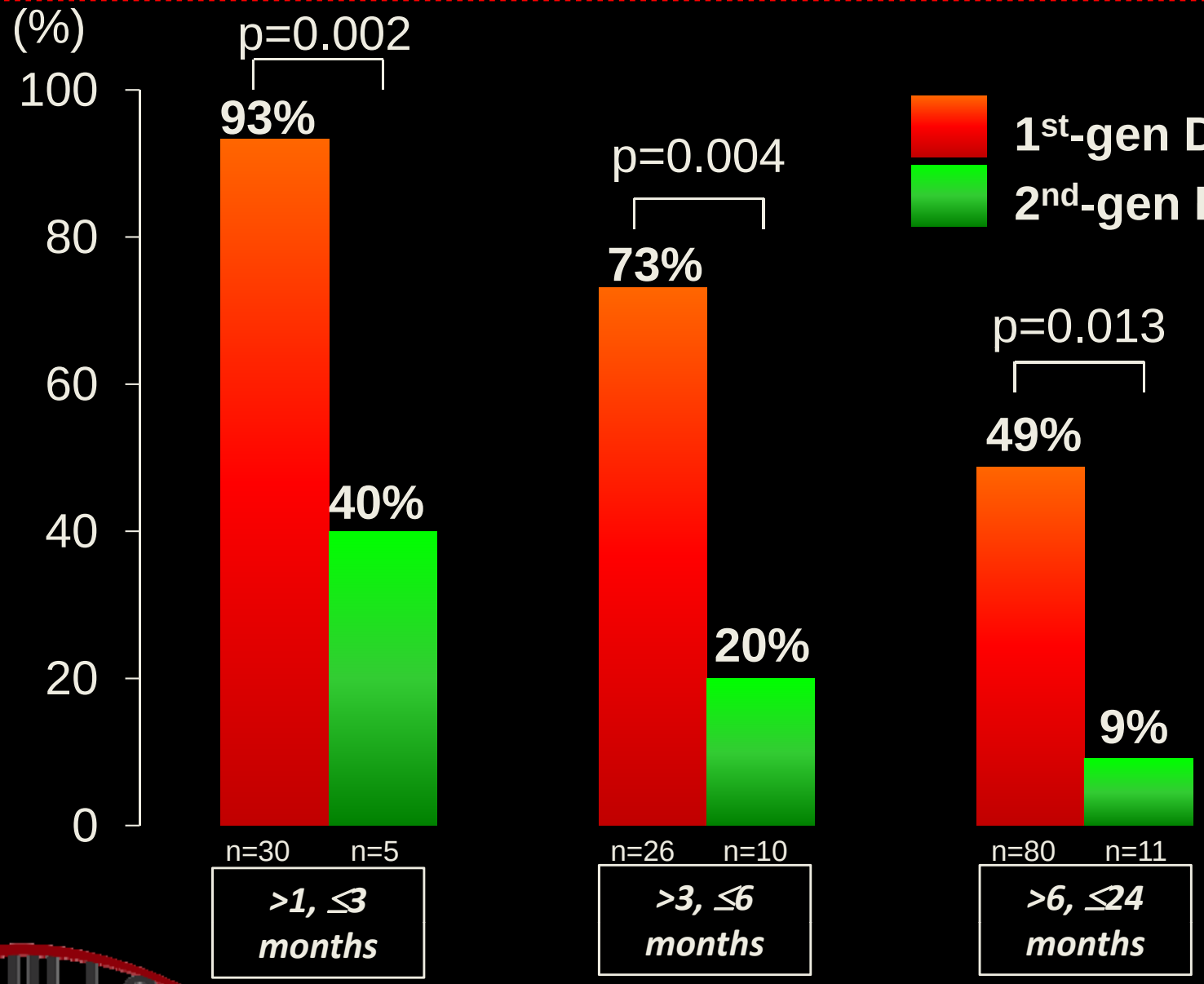
PES 11 months

ZES 3 months

EES 6 months



Prevalence of Unhealed Struts* Stratified by Duration of Implant

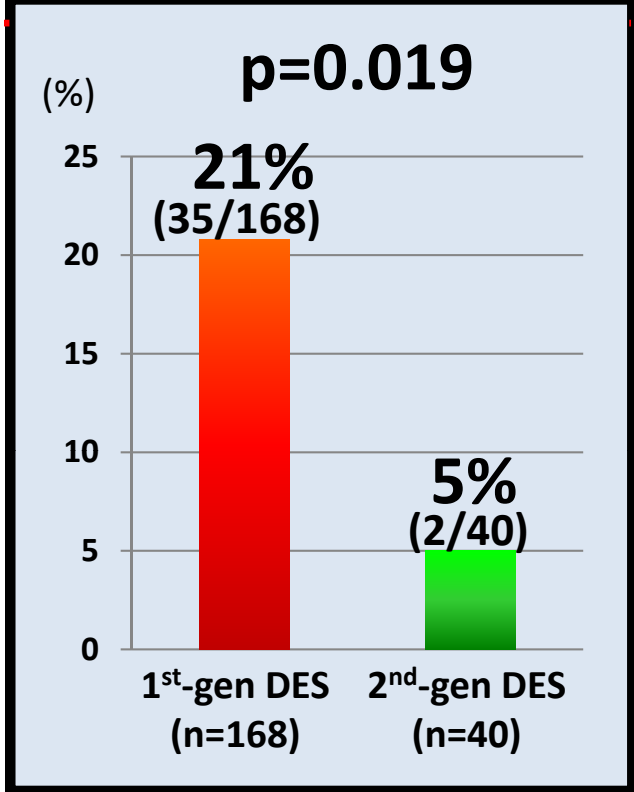


Presented by R. Virmani@TCT2011

* An unhealed strut was defined as >30% ratio of uncovered-to-total stent struts per cross section. *(Finn AV, et al. Circulation 2007;115:2435-41.)*

LST/VLST in 2nd-generation DES

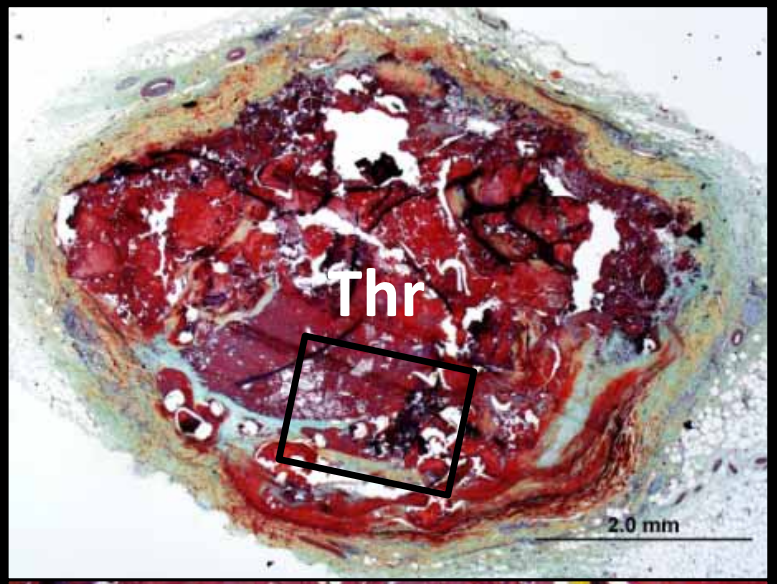
Incidence of LST/VLST

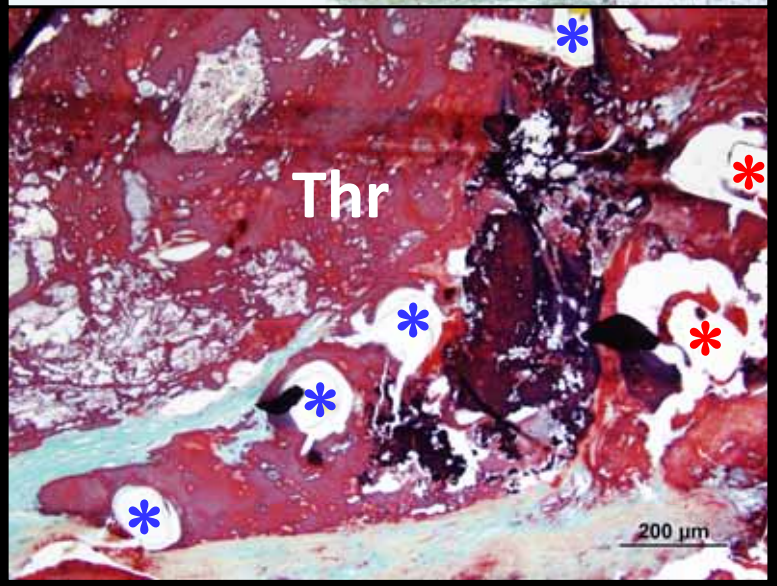


Cypher: 15/77 (19%)
Taxus: 20/91 (22%)
Endeavor: 0/6 (0%)
Resolute: 0/1 (0%)
Xience V: 2/33 (6%)

Duration of implant was matched. (>30 days, ≤3 years)

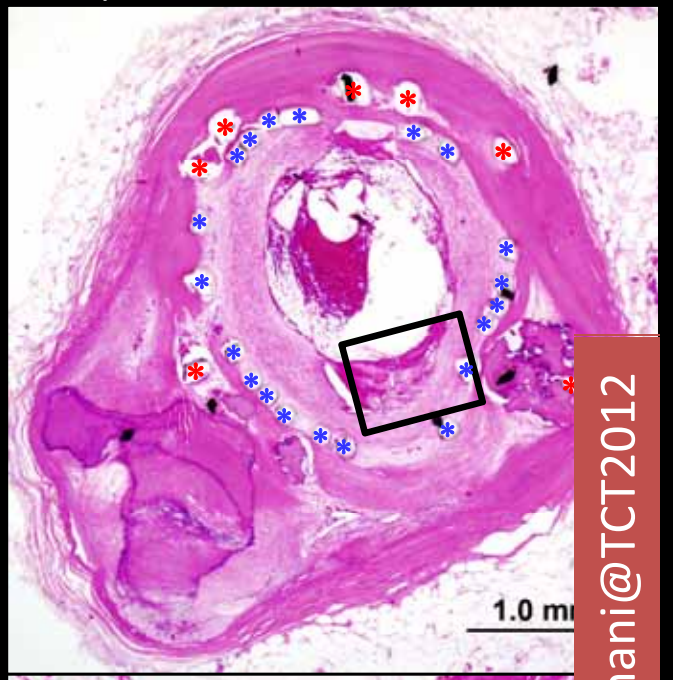
55M, EES implanted within PES in RCA 6 months antemortem, died suddenly.

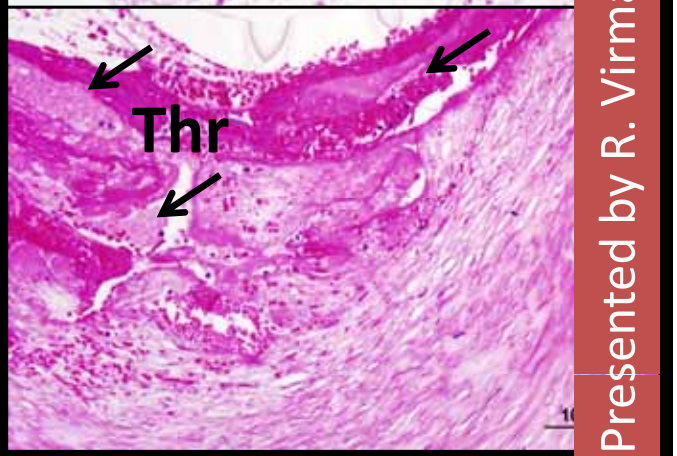




EES struts PES struts

72F, EES implanted within PES in LAD for 7 months , presented acute MI from EES restenosis, underwent balloon angioplasty which resulted in rupture of LAD.



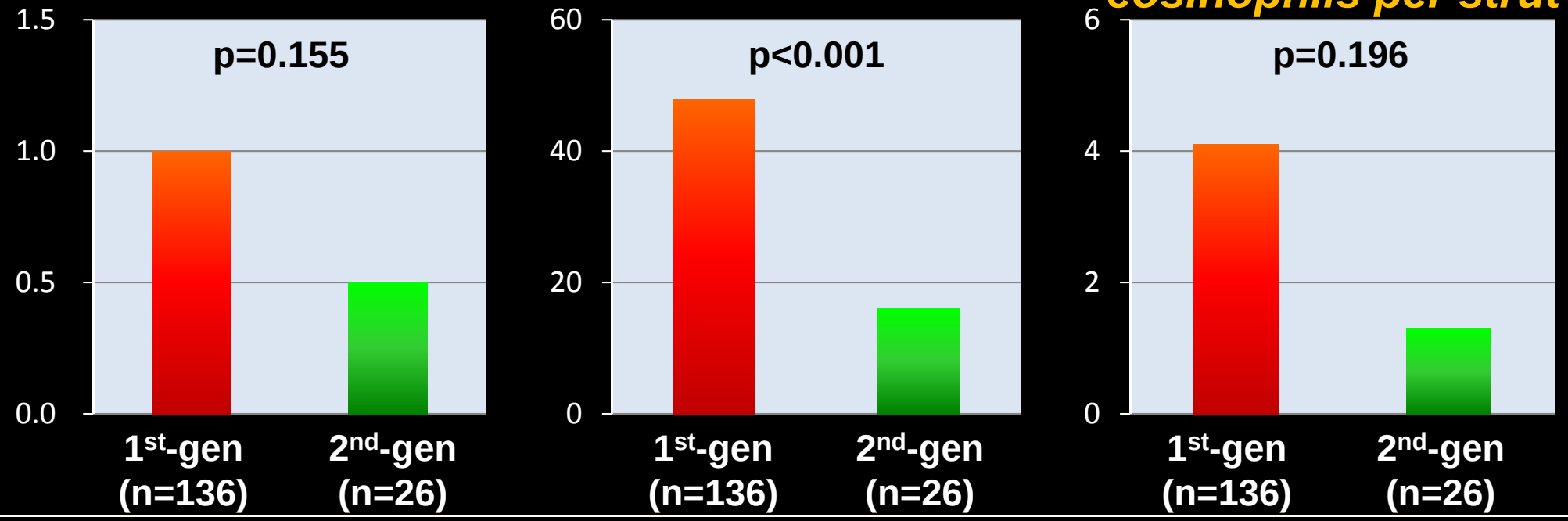


EES struts PES struts

Presented by R. Virmani@TCT2012

Morphometric Analysis

2nd- vs. 1st-generation DES



	1st-gen DES (n=136 lesions; SES=61, PES=75)	2nd-gen DES (n=26 lesions; ZES=6, EES=20)	p value
Inflammation score	1.0 (0.5, 1.5)	0.5 (0.1, 1.6)	0.155
Struts with fibrin (%)	48 (21, 65)	16 (0, 31)	<0.001
Maximum number of eosinophils per strut	4.1 ± 11.1	1.3 ± 3.1	0.196

Values are expressed as medians (interquartile range) or means ± SD. Bar graph shows median or mean values.

Lesson from Autopsy

- Delayed healing is the principle cause of late drug-eluting stent thrombosis
- Very late stent thrombosis is related to the abnormal vascular response such as hypersensitivity reaction, severe fibrin deposition with malapposition, and neoatherosclerosis
- New generation DESs likely show better safety profile

CV-HILLS