

# Drug Eluting Stent

## DES Pathology Update – What we know, what we do not know

13<sup>th</sup> Summit TCT Asia  
25<sup>th</sup> April 2008

Renu Virmani, MD.  
CVPath Institute Inc.  
Gaithersburg, MD

## Disclosure Statement of Financial Interest

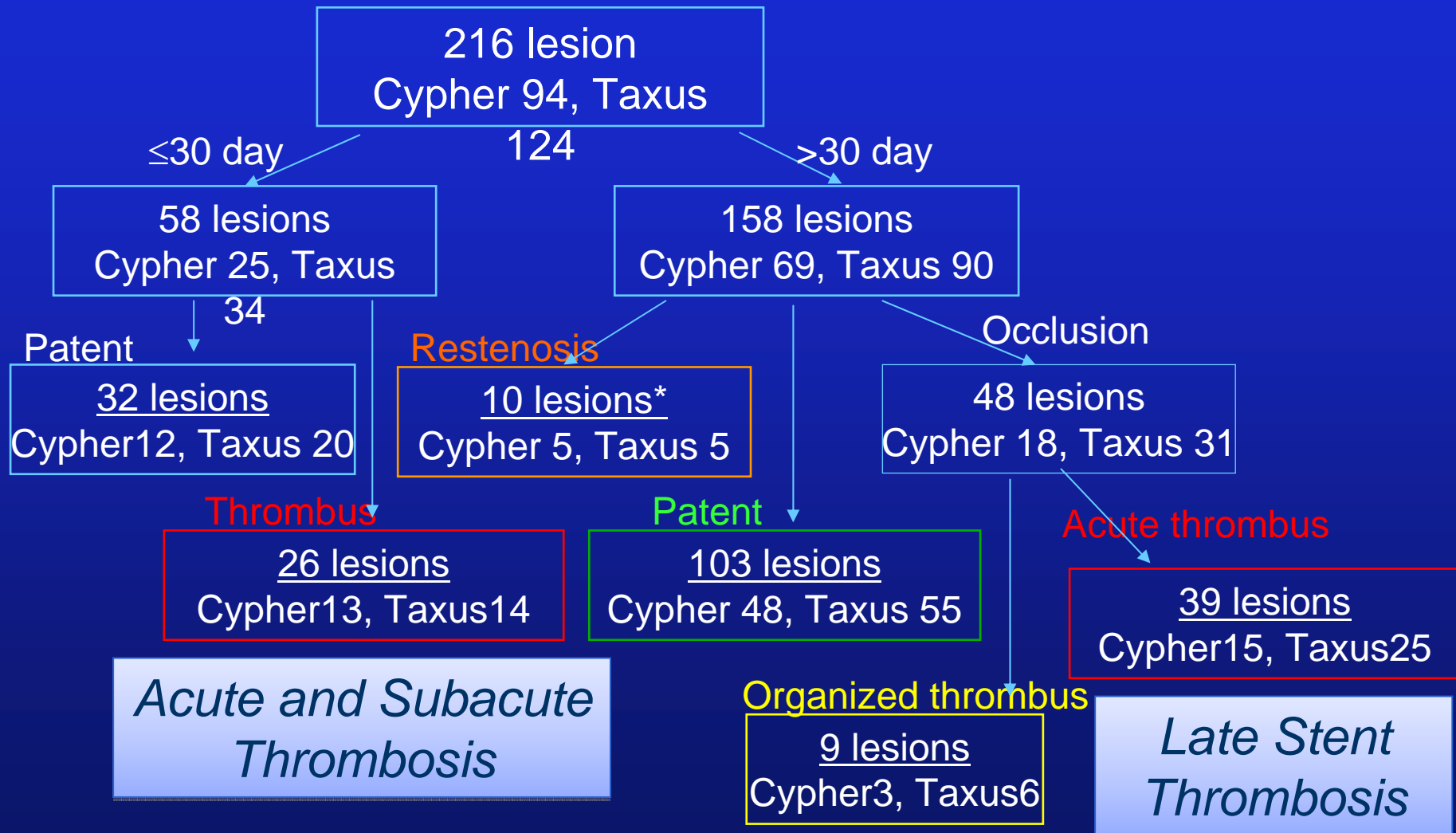
Within the past 12 months, I or my spouse/partner have had a financial interest /arrangement or affiliation with the organizations listed below.

Affiliation/Financial Relationship                      Company

**Grant/ Research Support:** Medtronic AVE; Abbott Vascular; GE Healthcare Bio-Sciences; Atrium Medical Corp.; ev3; Conor Medsystems; TopSpin Medical (Israel) Ltd.; Paracor Medical Inc.; OrbusNeich; Terumo Corp.; Vascular Therapies, LLC; CardioKinetix; Cardiovascular Research Foundation; Osiris Therapeutics, Inc.; Bard Peripheral Vascular, Inc.; Edwards Life Sciences; Biomerix; Nitinol Device and Components; Sorin Biomedica Cardio S.r.l; 3F Therapeutics; Hancock Jaffee Labs, Inc.; Cardiovascular Device Design; Angel Medical Systems, Inc.; Biotegra; Cardica, Inc.; Concentric Medical; Cordis Corporation; Cryo Vascular Systems, Inc.; CVRx; diaDexus; InfraReDx; InterVascular/Datascope; Kensey Nash Corp.; Medeikon Corp.; MedNova USA, Inc.; Microvention, Inc.; Oregon Medical Laser Center; Spectranetics Corp.; Takeda Pharmaceuticals North America; Toray Industries, Inc.; Vascular Concepts; Volcano Therapeutics, Inc.; BioSensors International; and Alchimer S.A.

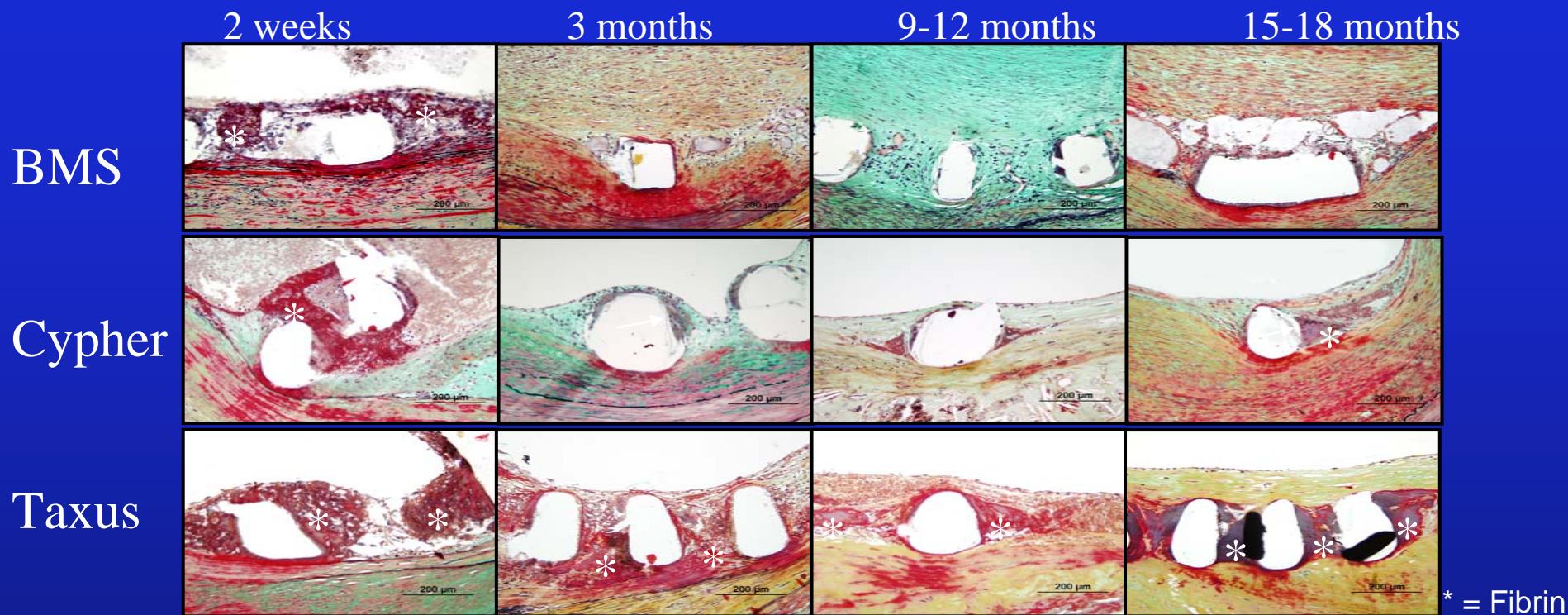
**Consultant:** Medtronic AVE; Abbott Vascular; W.L. Gore; Volcano Therapeutics Inc.; Prescient Medical; CardioMind, Inc.; Direct Flow and Atrium Medical Corp.

# Detail of DES CVPPath Registry



\* 3 of 10 restenosis had also thrombus

# Healing of DES (Cypher and Taxus) vs. BMS in Man

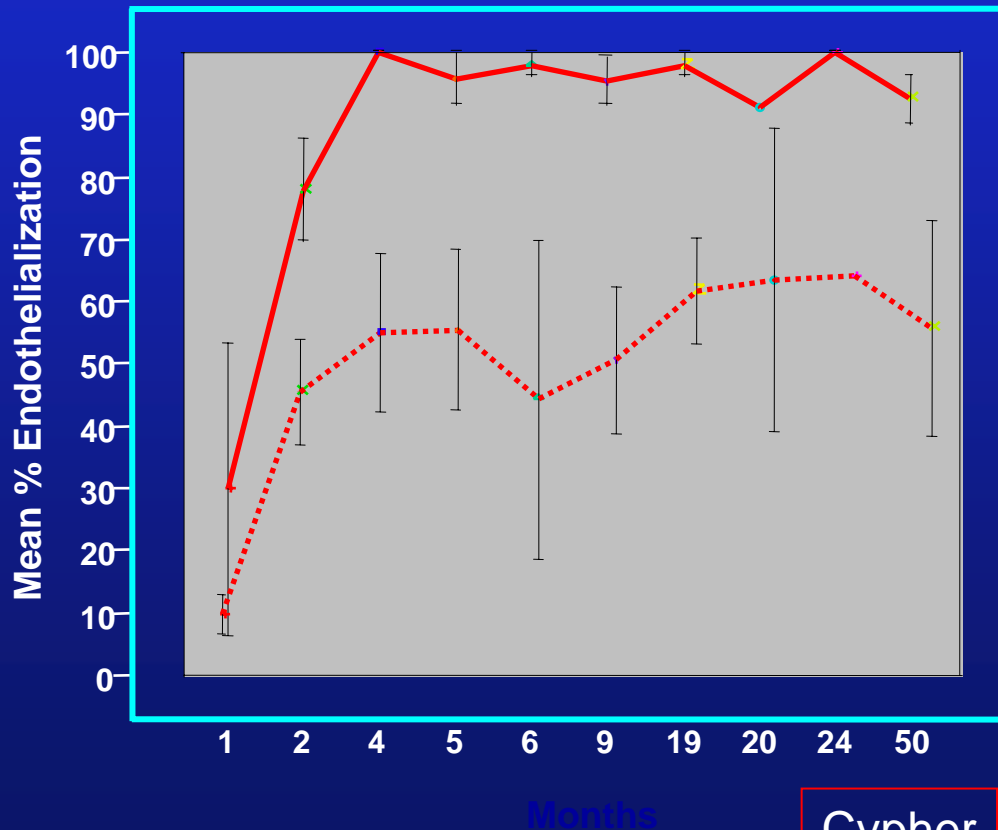


<i>Group</i>	<i>Mean Duration (days)</i>	<i>Stent Length (mm)</i>	<i>Neointimal Area~ (mm<sup>2</sup>)</i>	<i>X-sectional Area Stenosis %</i>	<i>Fibrin score</i>	<i>% Struts endothelialized</i>
DES n = 32	223±253	32.1±17	2.8±1.1	51.4±22	2.3±1.1	55.8±26.5
BMS n = 36	299±360	20.2±12	4.9±3.0	66.5±22	0.9±0.8	89.8±20.9
p-value	ns	0.01	0.0003	0.01	0.0001	0.0001

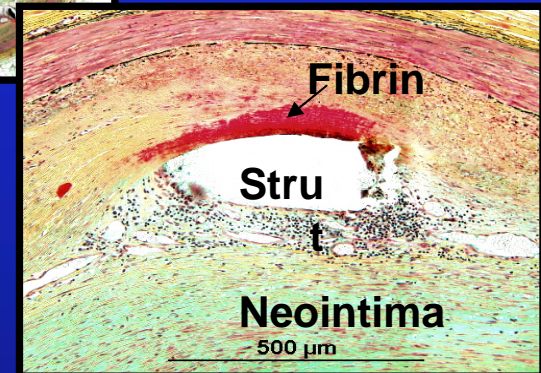
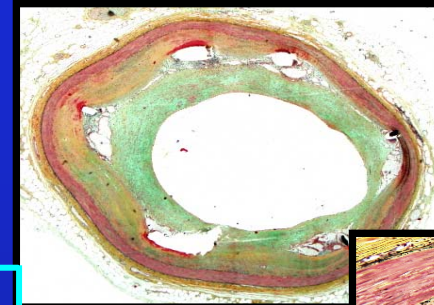


# Delayed Arterial Healing in DES

BxVelocity

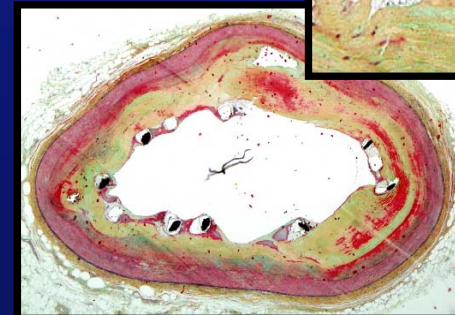
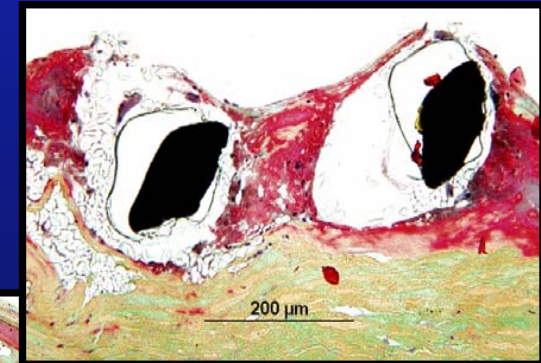


Cypher



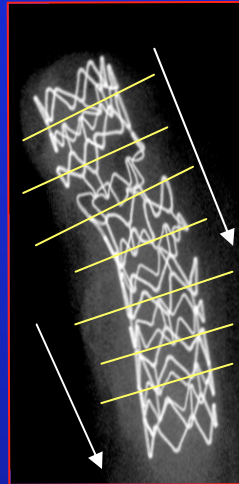
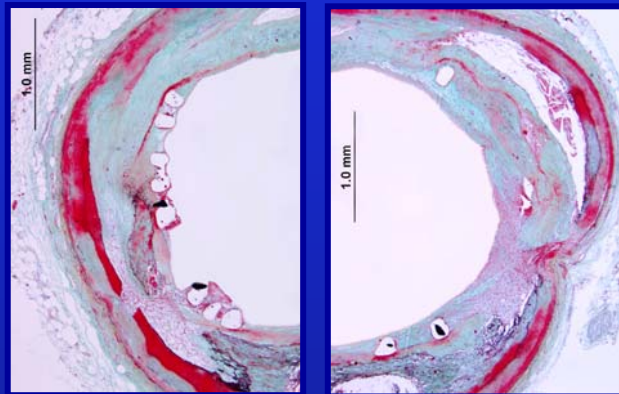
— BMS

... DES

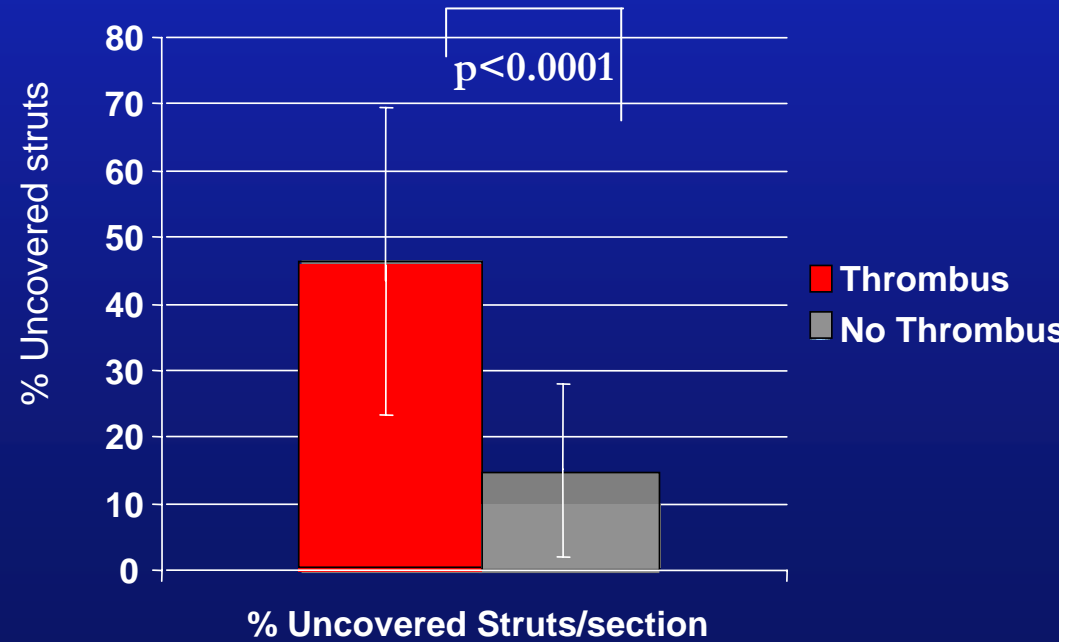
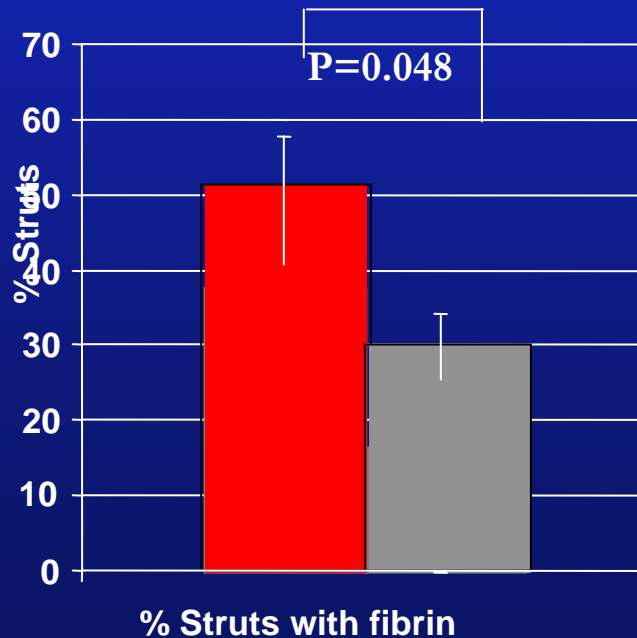
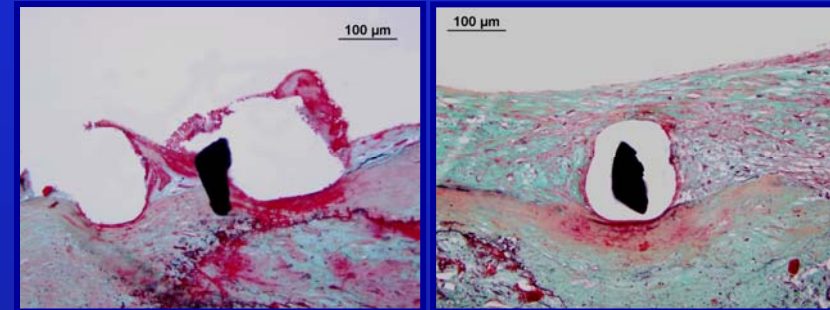


# Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization.

> 30 days implants  
uncovered      covered



> 30 days implants  
uncovered      covered





# Multiple Linear Regression Analysis to Find Significant Correlations Between Endothelialization and Morphometric Parameters

	No. of uncovered struts/section	Ratio uncovered/total strut	Interstrut Distance	Stent Length w/o Neointima	Fibrin Score
Multiple Linear Regression	$r^2=0.64$	$r^2=0.86$	$r^2=0.15$	$r^2=0.20$	$r^2=0.32$
P-value	0.0001	0.0001	0.002	0.0005	0.0005

$$r^2 = 0.9$$

Significant multivariable correlates of endothelialization

Since the most powerful morphometric predictor of endothelialization was RUTSS (ratio of uncovered to total stent struts per section), univariate logistic regression to analyze the probability of thrombosis: OR for late stent thrombosis in lesions having RUTSS of >30% is 9.0[95% CI: 3.5-22]

*Finn AV, Joner M, et al. Circulation 2007*

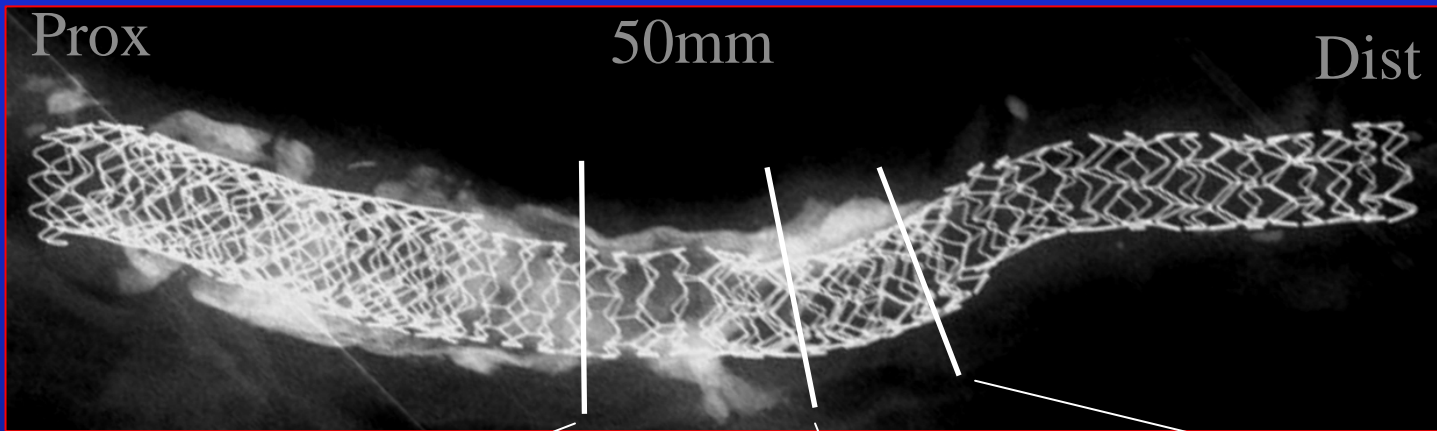
# Main Causes of DES failure

- Uncovered struts (focal, delayed healing)
- Long stents, overlapping stents
- Malapposition
- Hypersensitivity
- Bifurcation stenting
- Acute myocardial infarction/vulnerable plaque
- Restenosis with or without atherosclerosis



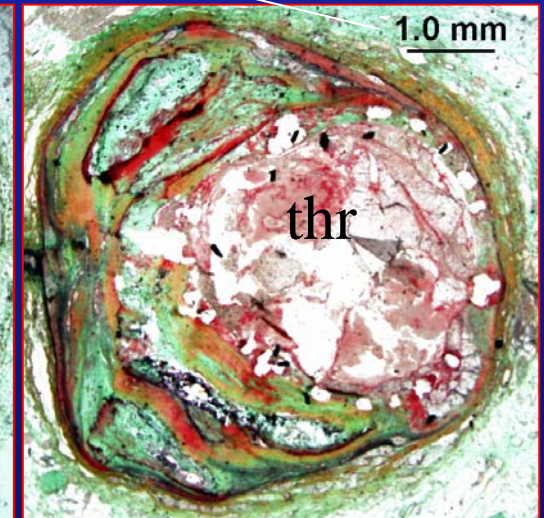
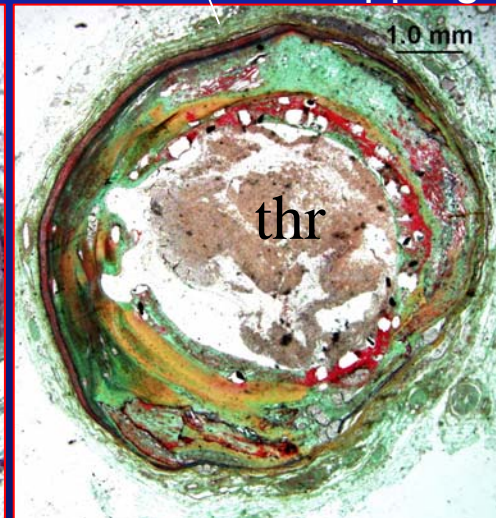
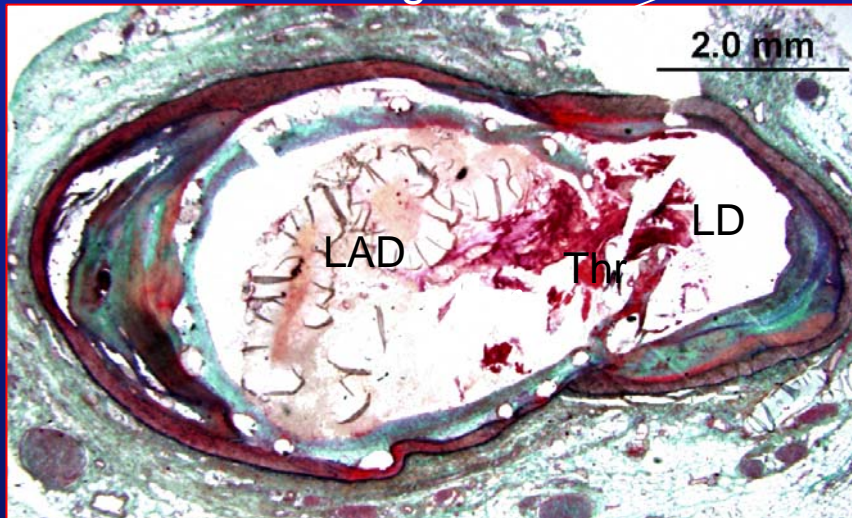
# Long lesion length and overlapping stents

9 months following *Taxus* stents implantation in LAD



Single

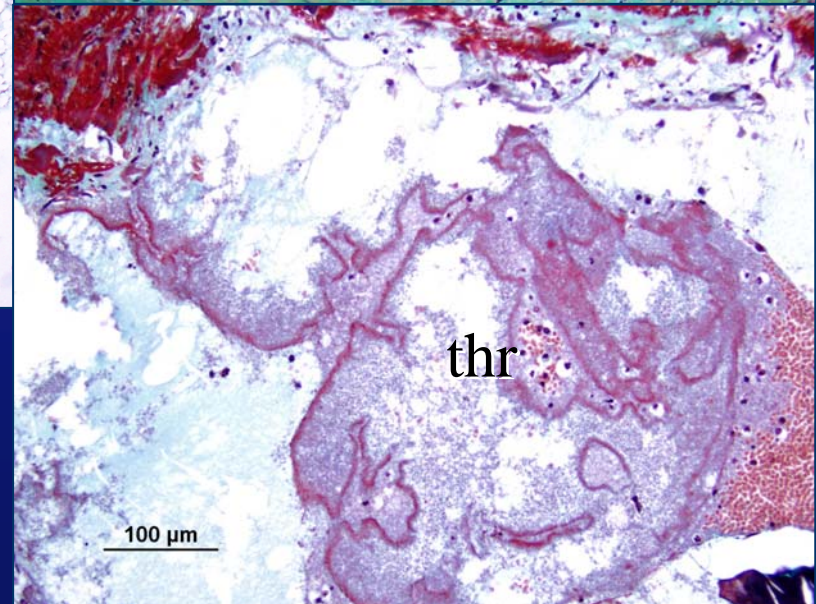
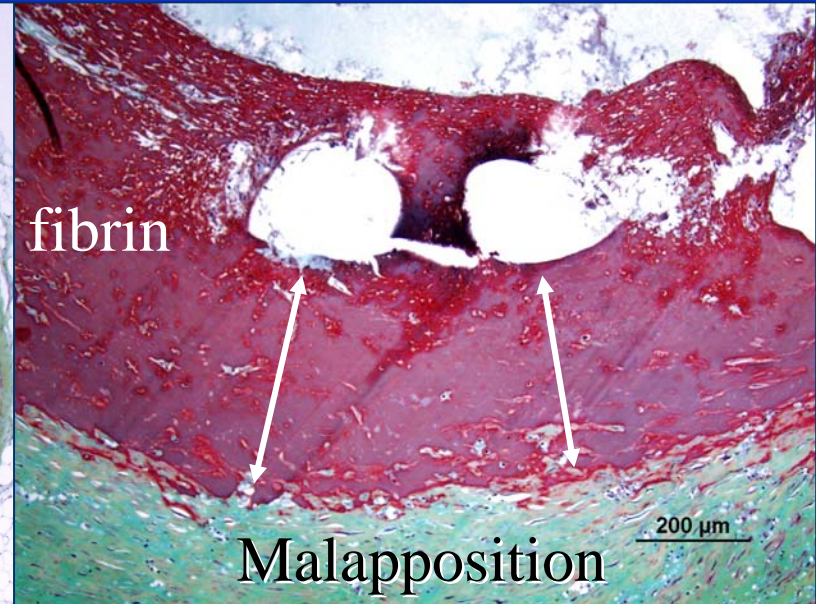
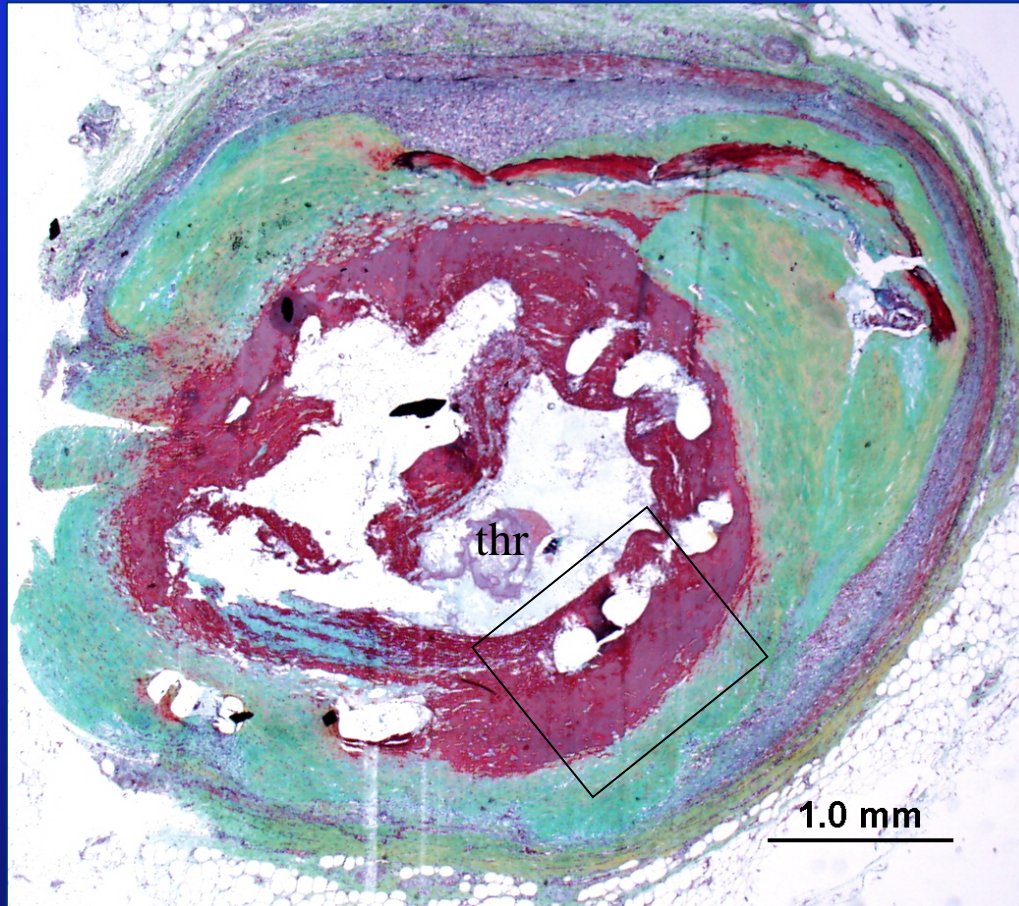
Overlapping stents





# Stent Malapposition

*9 months following Taxus stents implantation*



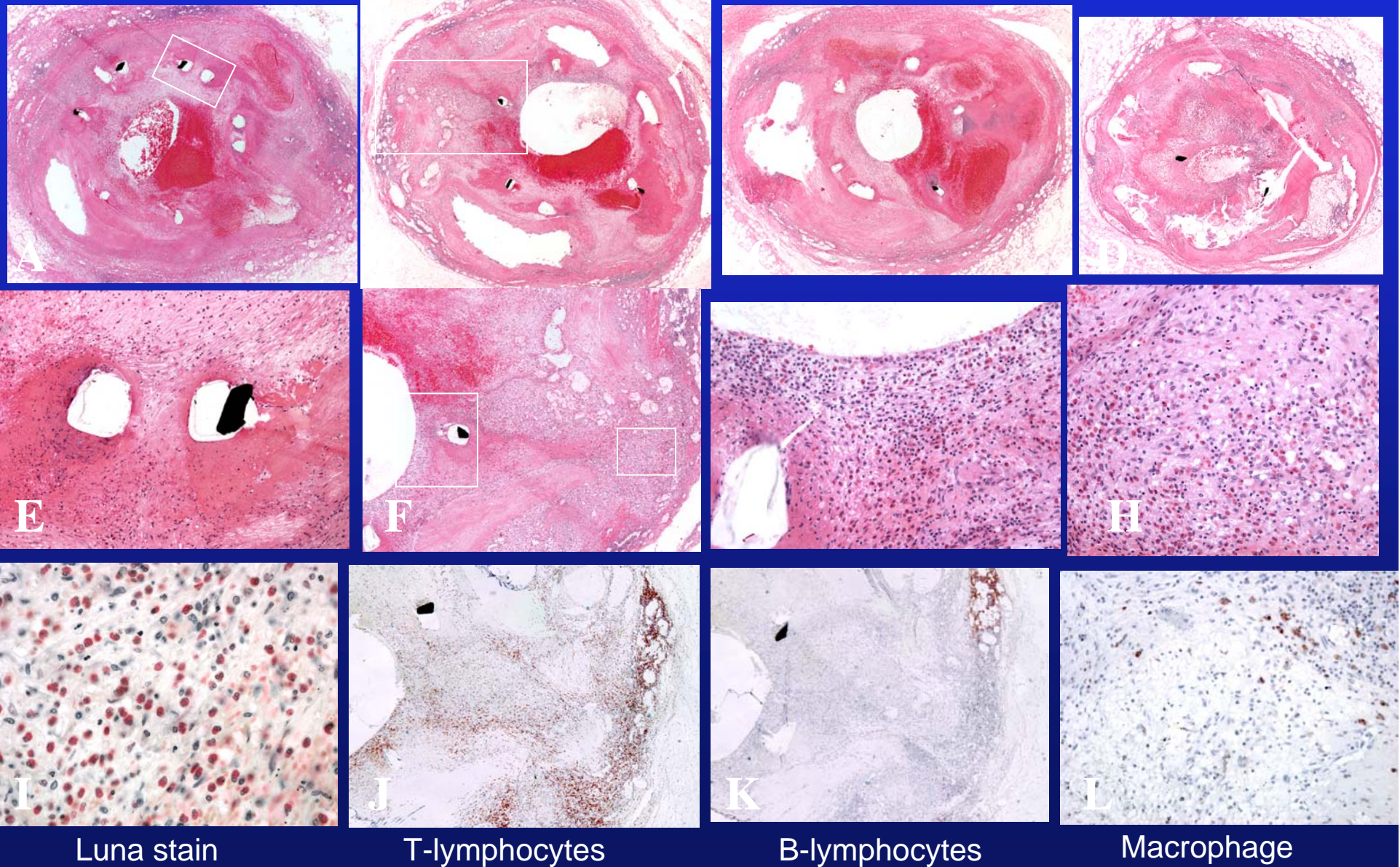
# Patients with Hypersensitivity Reaction (5 of 129 cases)

Age years	Indication for PCI	Type of DES	Duration (days)	No. of stents	Length of stent	Cause of death
58M	UAP	Cypher	504	2x LCX	27	AMI, Cardiac rupture
61M	AP	Cypher	112	1x PDA	18	SCD
46M	AMI	Cypher	940	2x RCA, 1x LAD	30, 23	AMI
40F	AMI	Cypher	510	1x LAD, 1x RCA	27, 25	SCD
63F	CAD	Cypher	720-1080	3x LAD	23, 23, 18 OL	Removed surgically



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.

## Distal Stent

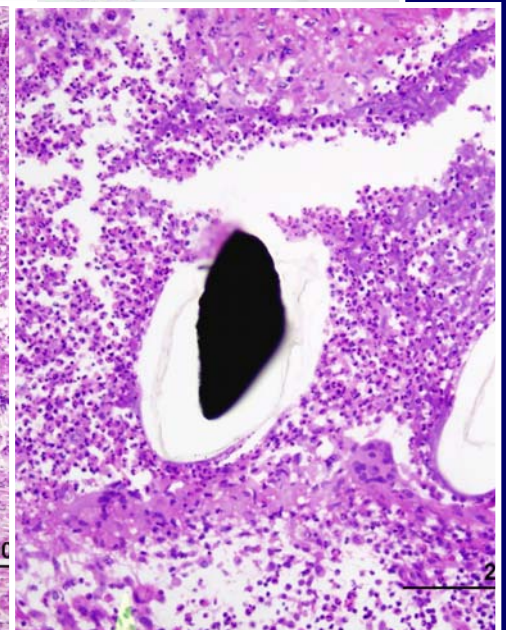
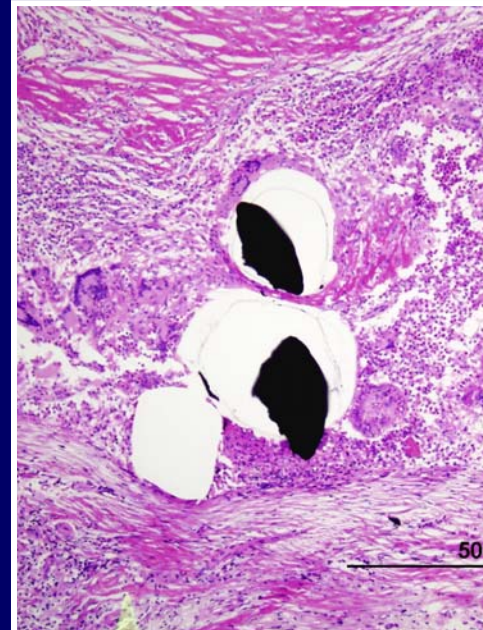
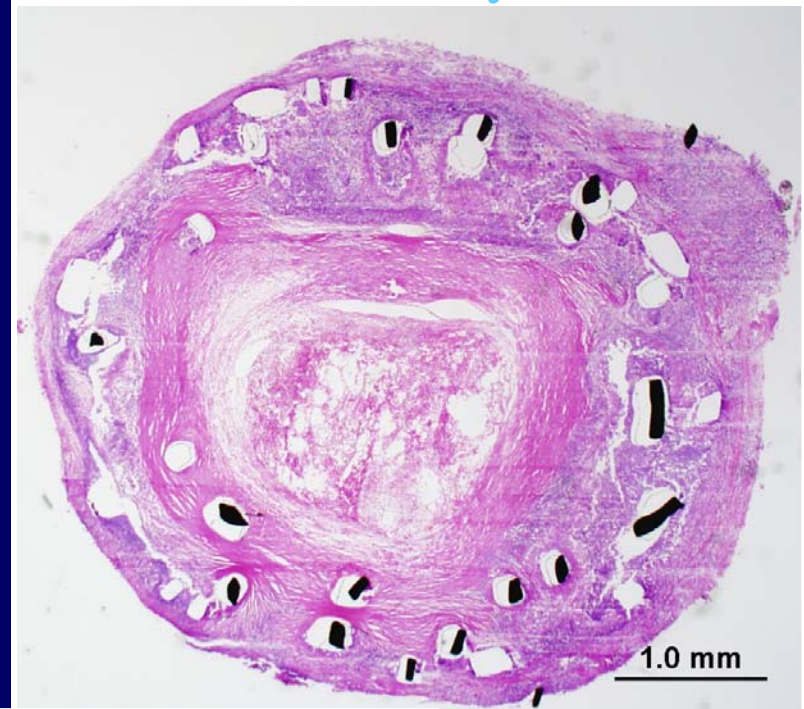
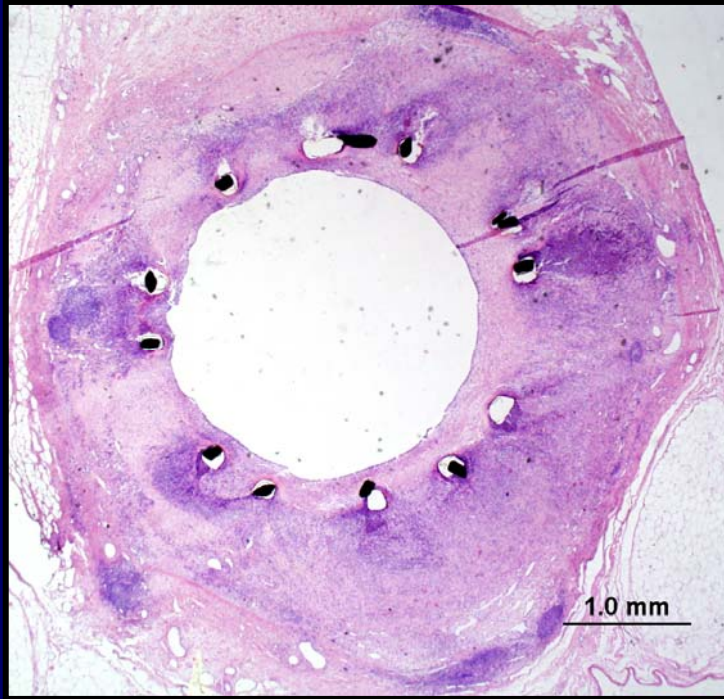




Porcine 3 months

CYPHER

Human 2-3 years

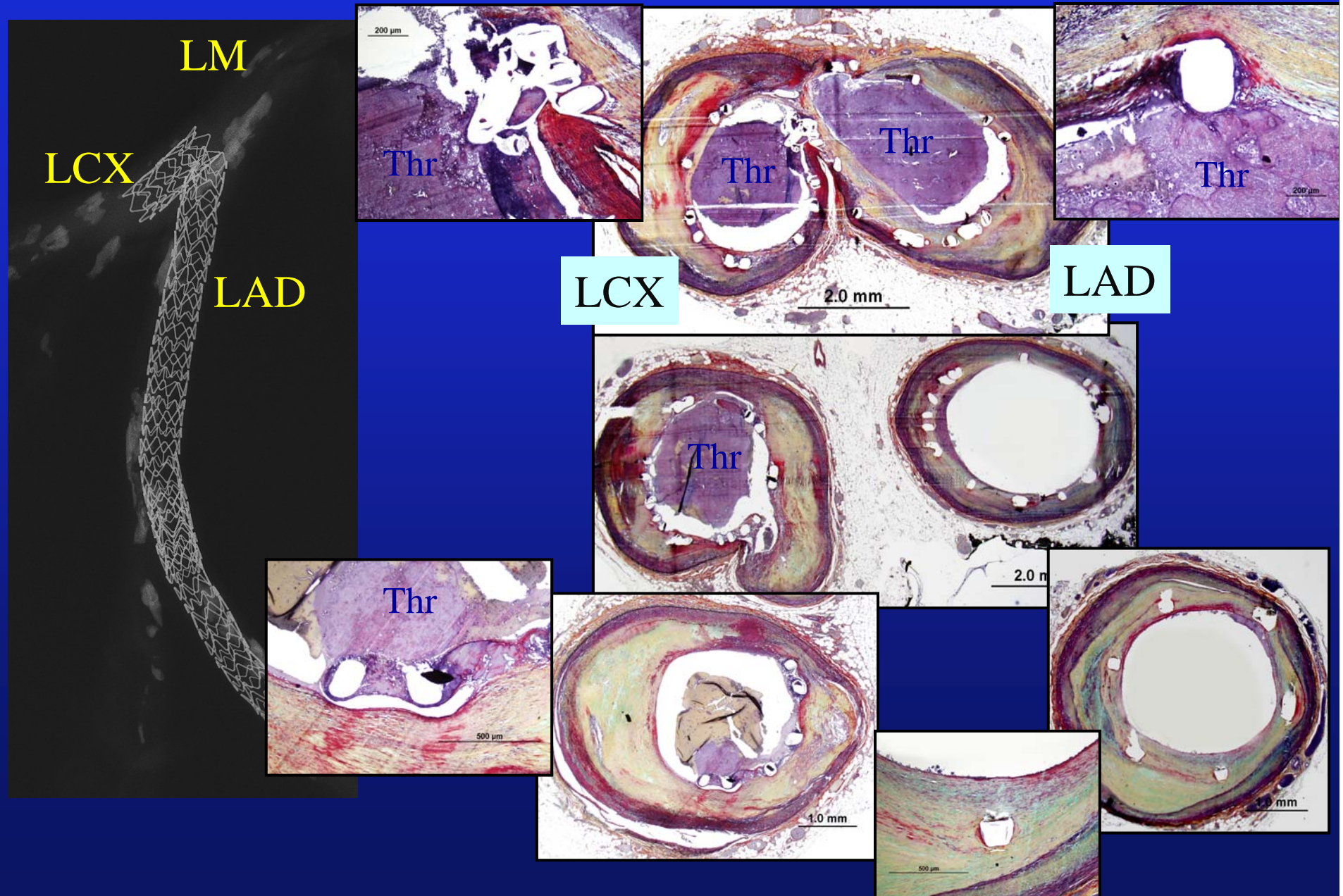


# Bifurcation Stenting DES vs. BMS

	DES n=18	BMS n=20	p value
Age (yrs)	62 ±16	57 ±15	0.33
Male Gender (%)	14 (78)	13 (65)	0.48
Mean duration (day)	228 ± 258	160 ± 220	0.38
>30 days (%)	11 (61)	13 (65)	>0.99
<u>Technique</u>			
1 stent	10	9	0.32
2 stent, T/ V/ Crush	4/ 2/ 2	8/ 3/ 0	
<u>Number of stents</u>			
	1.9 ± 0.8	1.8 ± 0.8	0.58
<u>Restenosis</u>			
MV (%)	1 (6)	6 (30)	0.09
SB (%)	3 (17)	5 (25)	0.7
<u>Thrombosis</u>			
Total			
MV (%)	11 (61)	8 (40)	0.33
SB (%)	7 (39)	6 (30)	0.73
> 30 days			
MV (%)	8 (73)	5 (38)	0.12
SB (%)	4 (36)	2 (15)	0.35
<u>Stent related death (%)</u>			
	11 (61)	8 (40)	0.33
<u>Procedure related death (%)</u>			
	1 (6)	2 (10)	>0.99

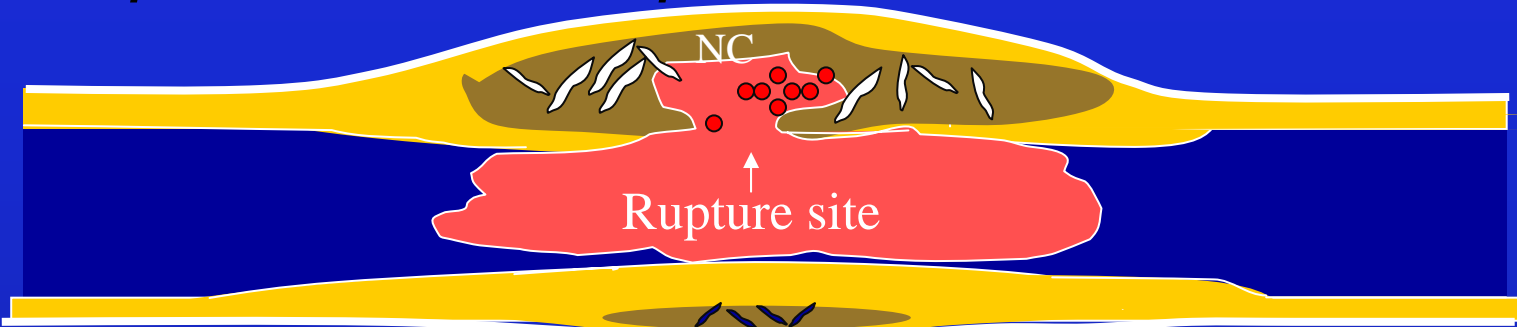


55M, Taxus stents implantation in Distal LM (LAD/CX), presented 2 years after PCI for AP and stress test positive, died suddenly

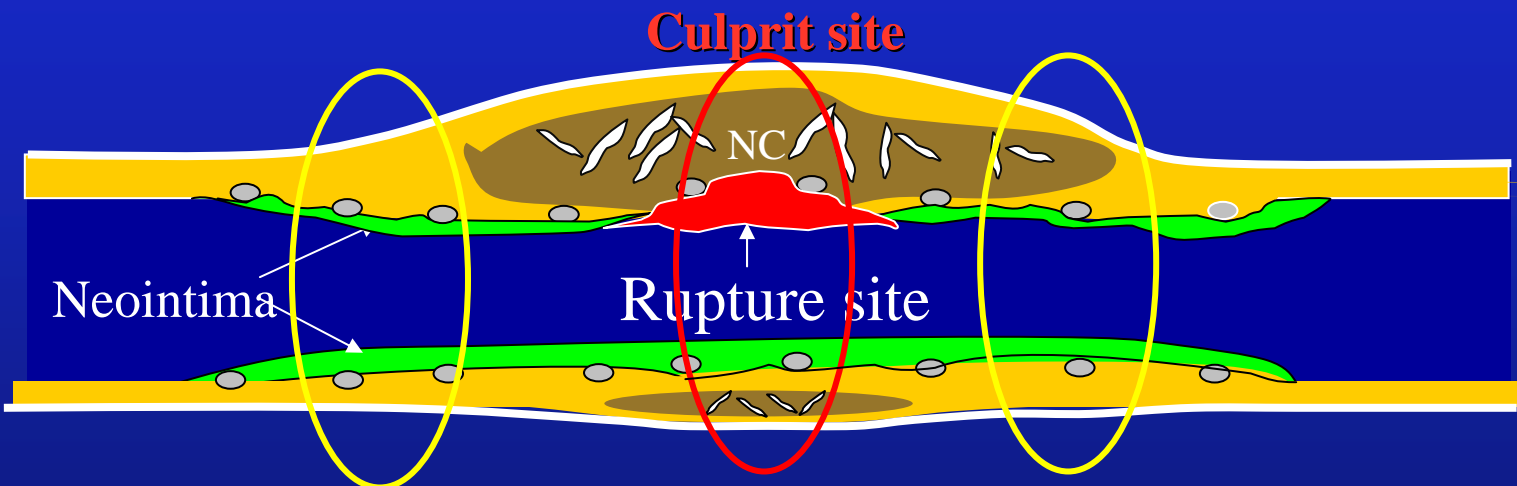


# Definition; Culprit and Non-culprit sites in AMI and stable

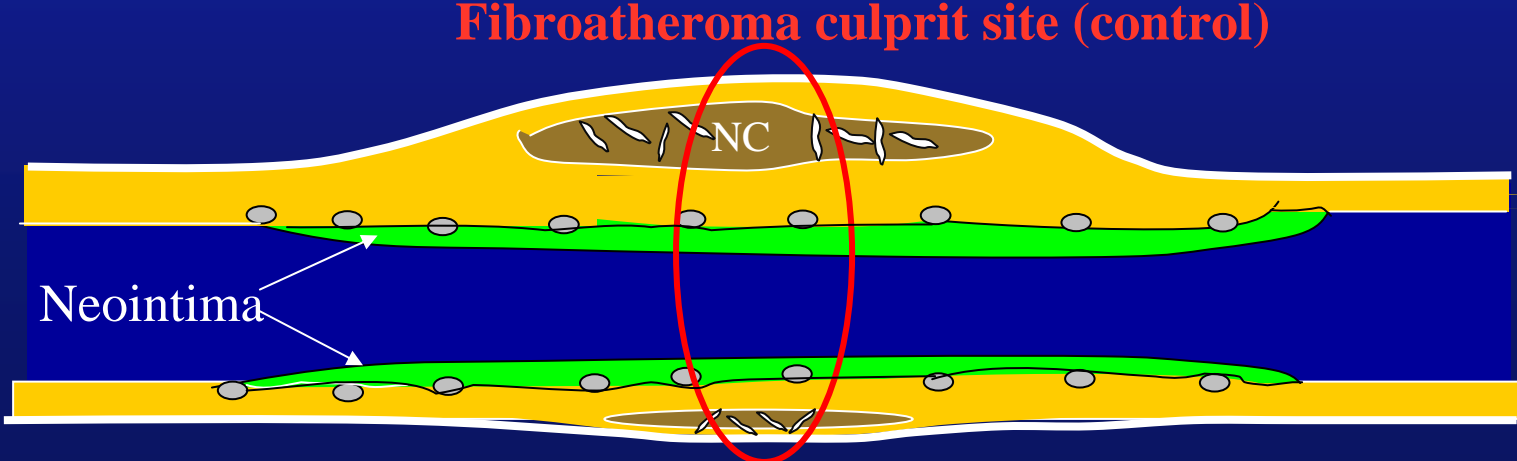
AMI lesion



AMI lesion  
Post stent



Stable lesion  
Post stent



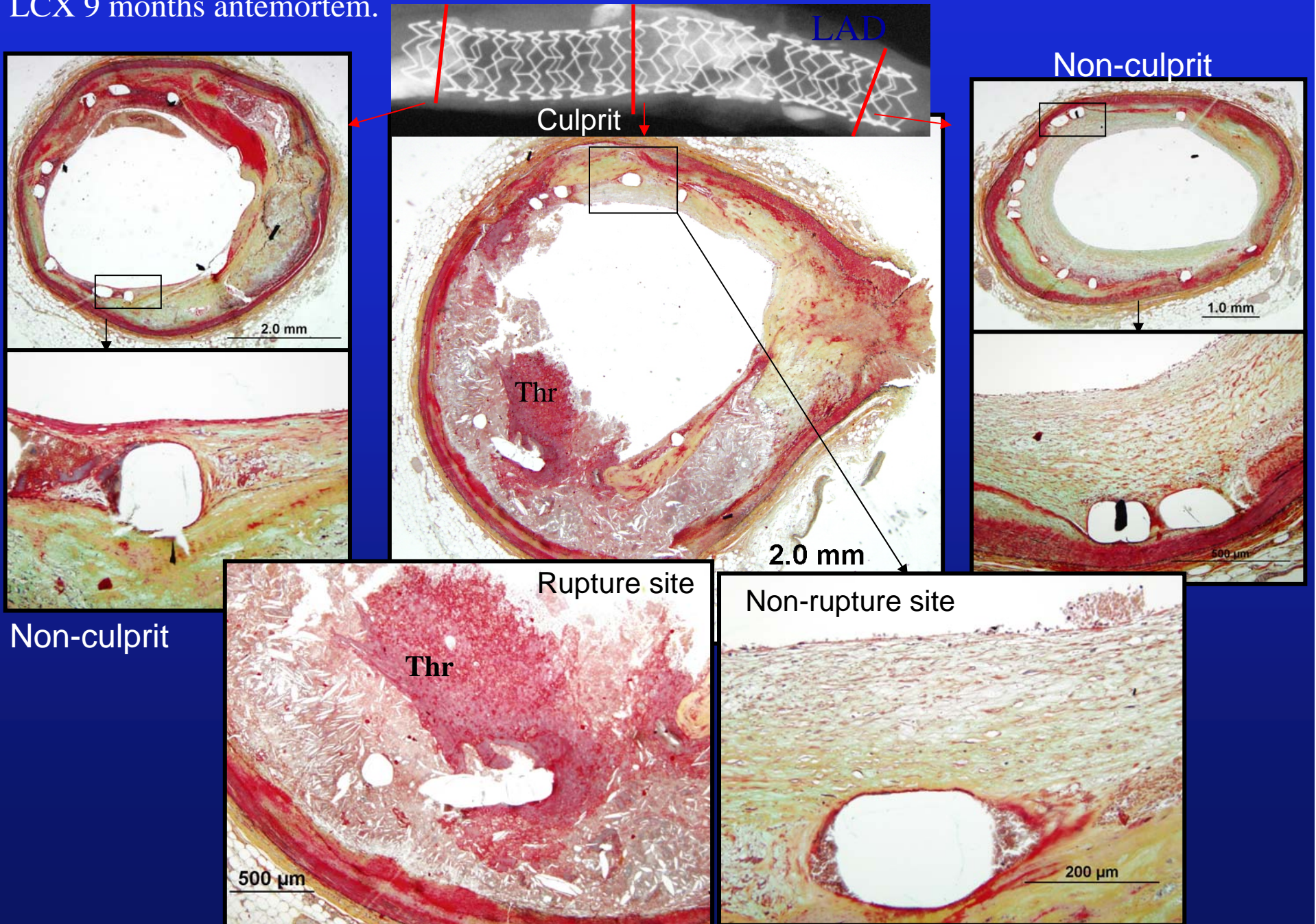


## *Morphometry and Pathologic Assessment (AMI vs. stable lesion at culprit sites)*

	AMI lesions with PR or TCFA (n=14)	Stable lesions with Fibroatheroma (n=13)	p value AMI vs. Stable (Culprit)
<b>Neointimal thickness, mm</b>	0.05±0.04	0.12±0.10	<u><b>0.03</b></u>
<b>Strut with fibrin deposition, %</b>	67.2±24.7	41.8±29.4	<u><b>0.02</b></u>
<b>Strut with inflammation, %</b>	54.7±36.4	17.8±15.9	<u><b>0.03</b></u>
<b>Uncovered strut, %</b>	33.6±19.6	23.8±27.4	<u><b>0.02</b></u>

*PR = plaque rupture; TCFA=thin cap fibroatheroma*

65 yrs old male, presenting acute coronary syndrome, stent (Taxus) implantation in the LAD and LCX 9 months antemortem.



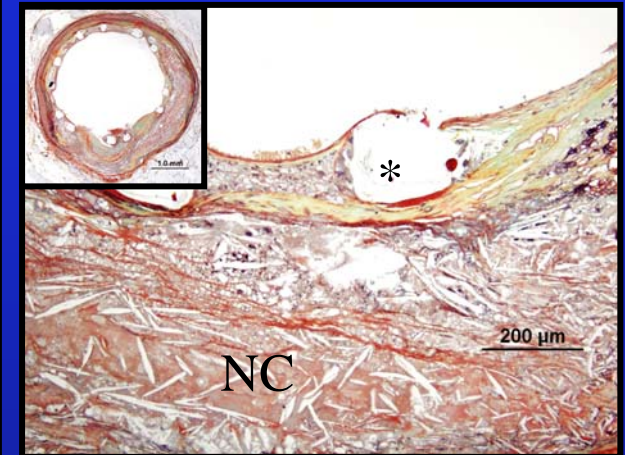
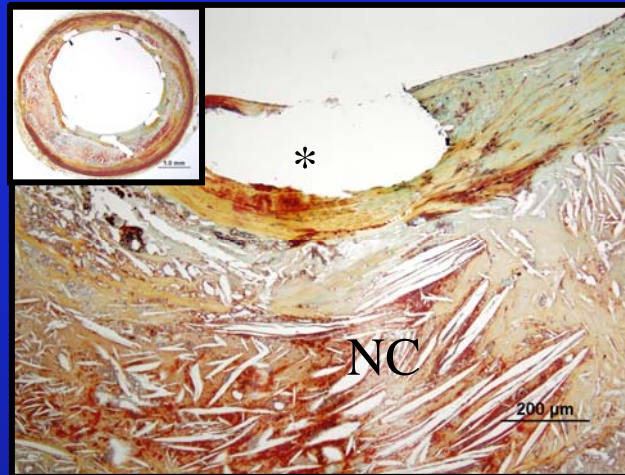
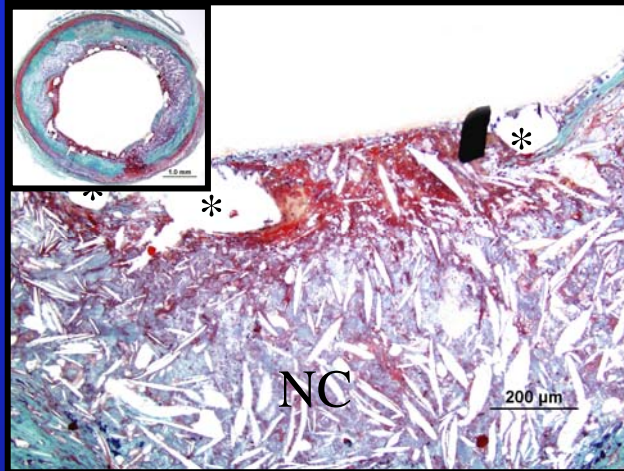


*AMI lesions (with Plaque Rupture)*

9 months  
Taxus

13 months  
Cypher

24 months  
Cypher

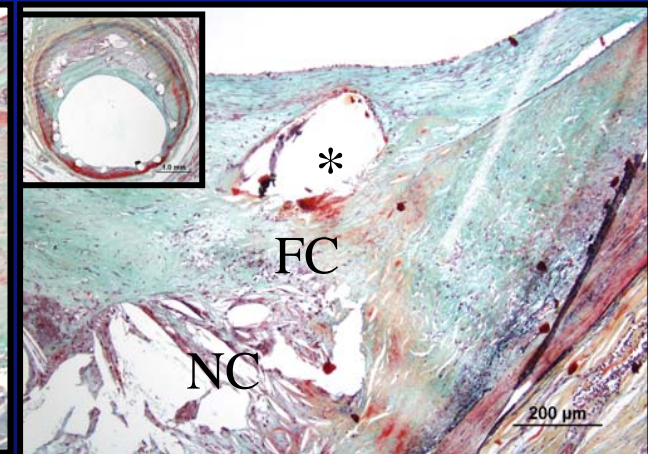
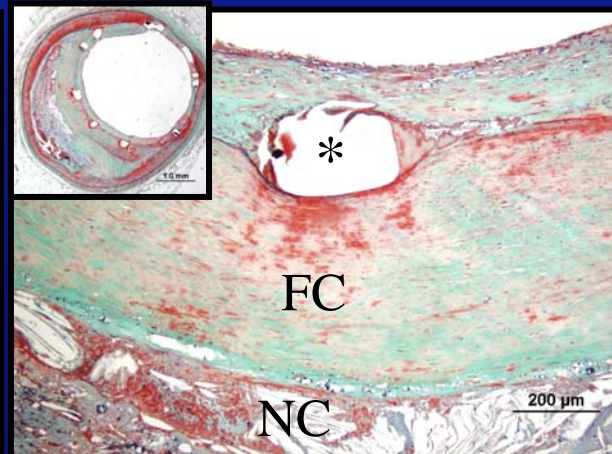
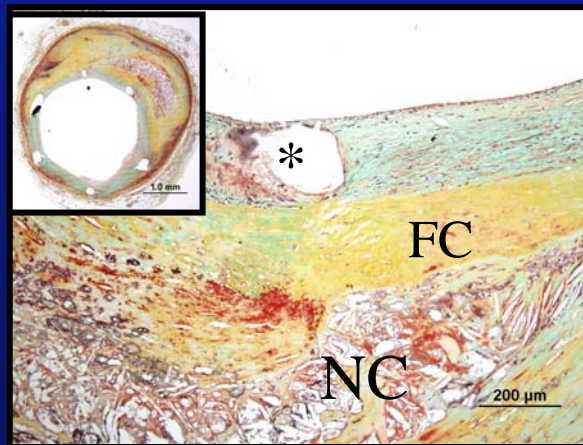


*Stable Lesions (with Fibroatheroma and thick cap)*

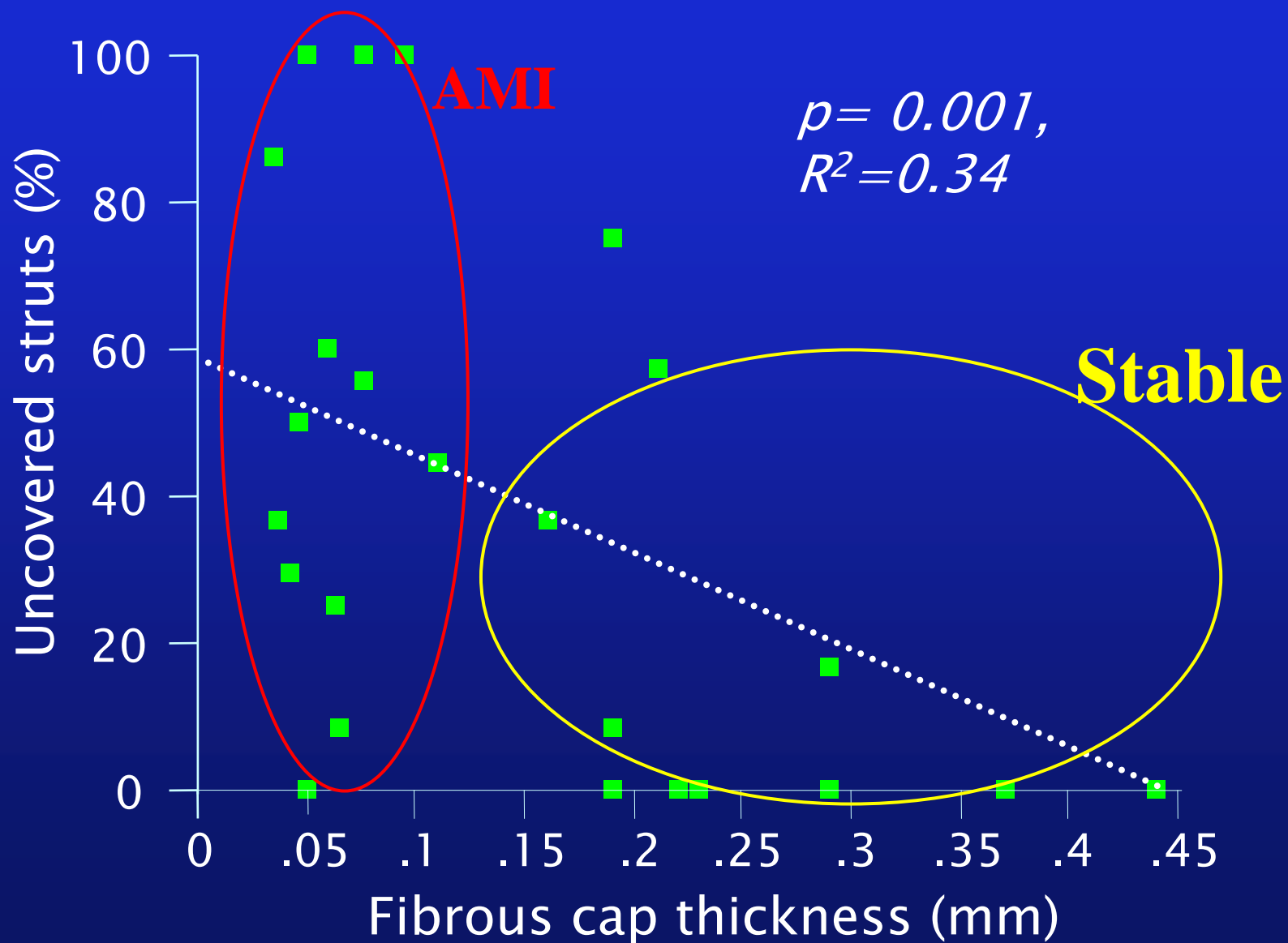
7 months  
Cypher

18 months  
Taxus

19 months  
Cypher



# Influence of underlying “Fibrous Cap thickness” on the percentage of “Uncovered struts”

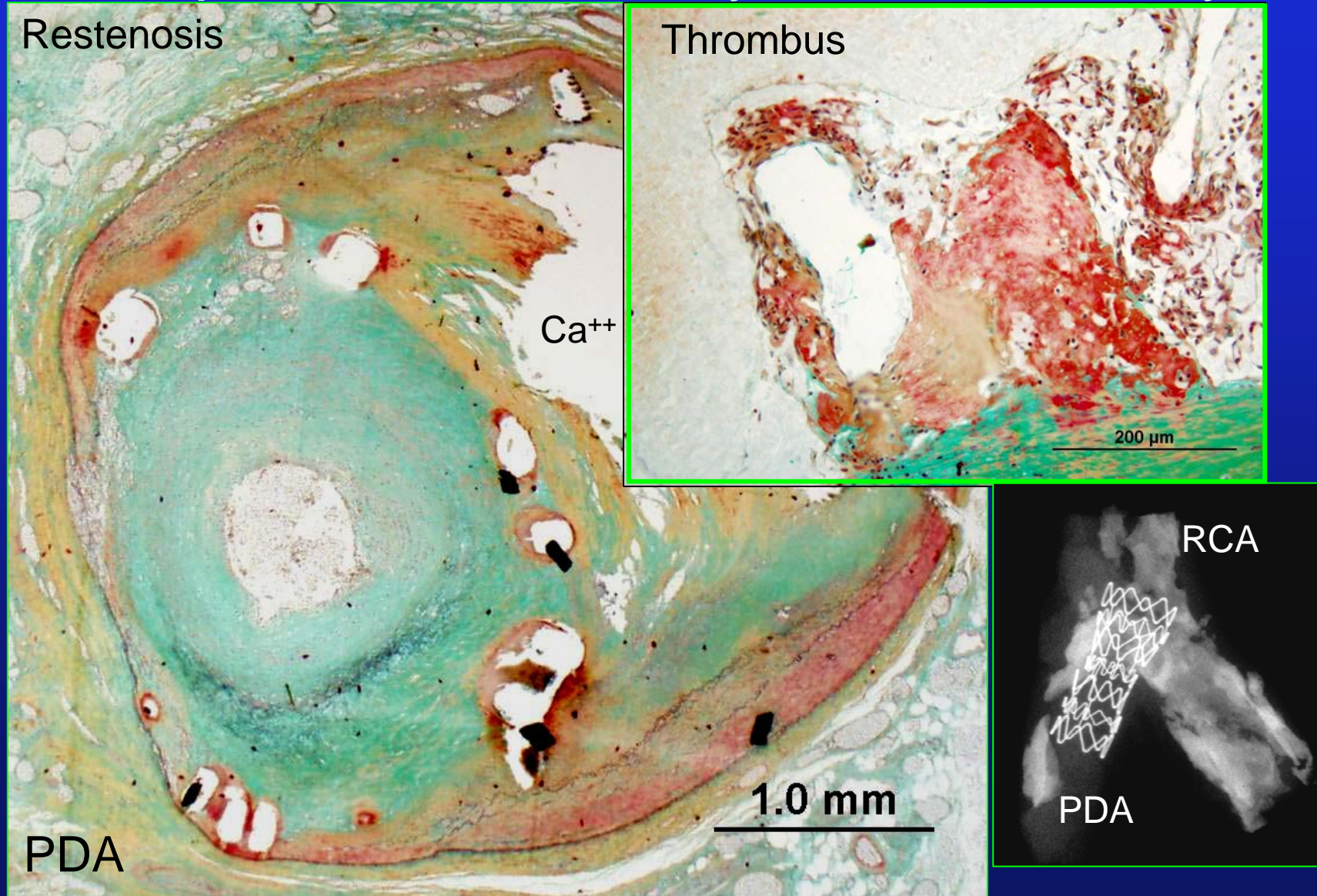




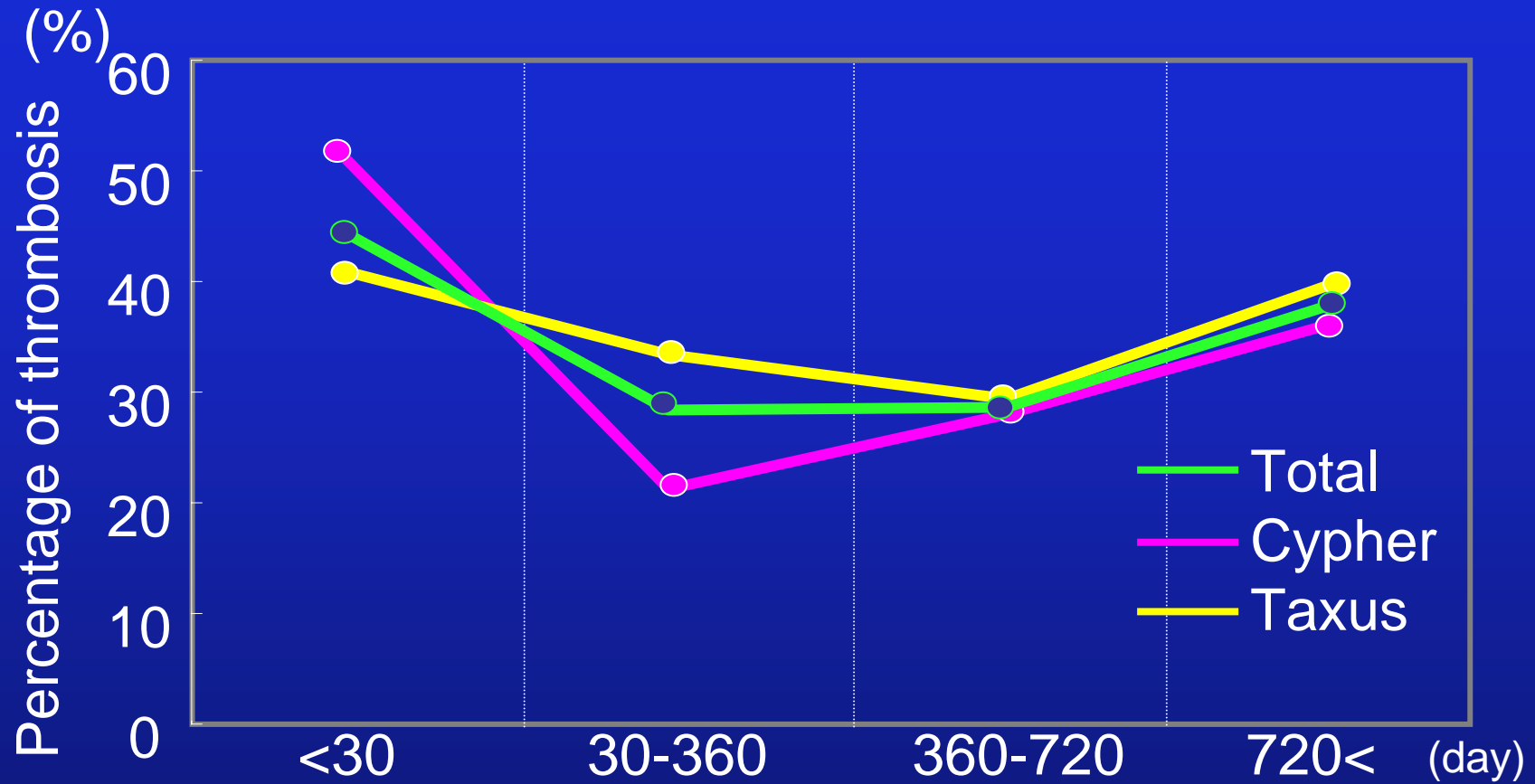
# Patients with Restenosis (10 of 180)

Age Sex	Indication for PCI	Type of DES	Duration (days)	No.of stents	Length of stent	Cause of death
75M	AMI	Cypher	120	1x RCA 1x LCX	18 mm 18 mm	SCD
47F	AMI	Cypher	270	1x LAD	18 mm	SCD
68F	SAP	Cypher	172	1x LOM	25 mm	AMI (LST in other stent)
75M	SAP	Taxus	330	1x PDA	9 mm	SCD Thrombus
60M	SAP	Taxus	200	2x LAD	28, OL	SCD
70F	AMI	Taxus	210	2x LAD	25, OL	SCD
44M	AMI	Cypher	360	1x RI	18 mm	AMI Unrelated to stent
60M	SAP	Taxus	270	1x LCX 1X RCA	30 mm 14 mm	CHF

# 75-year old man with Taxus stent (RCA-PDA) implanted for 330-days, died suddenly

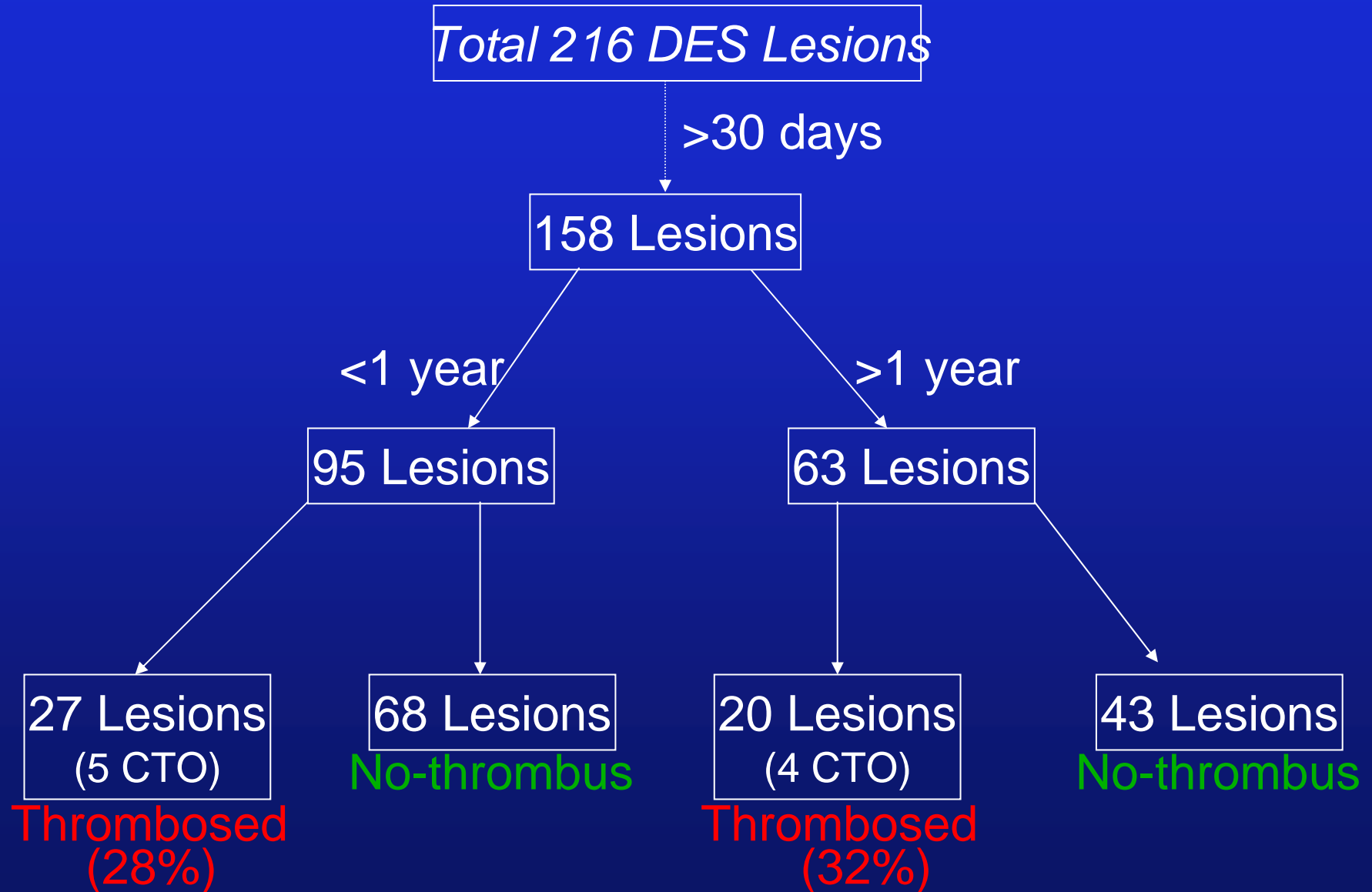


# Incidence of thrombosis at autopsy



Total lesion #	58	95	42	21
Thrombosis	26	27	12	8

# CVPath DES Registry





# Comparison between Very Late vs. Late Lesions

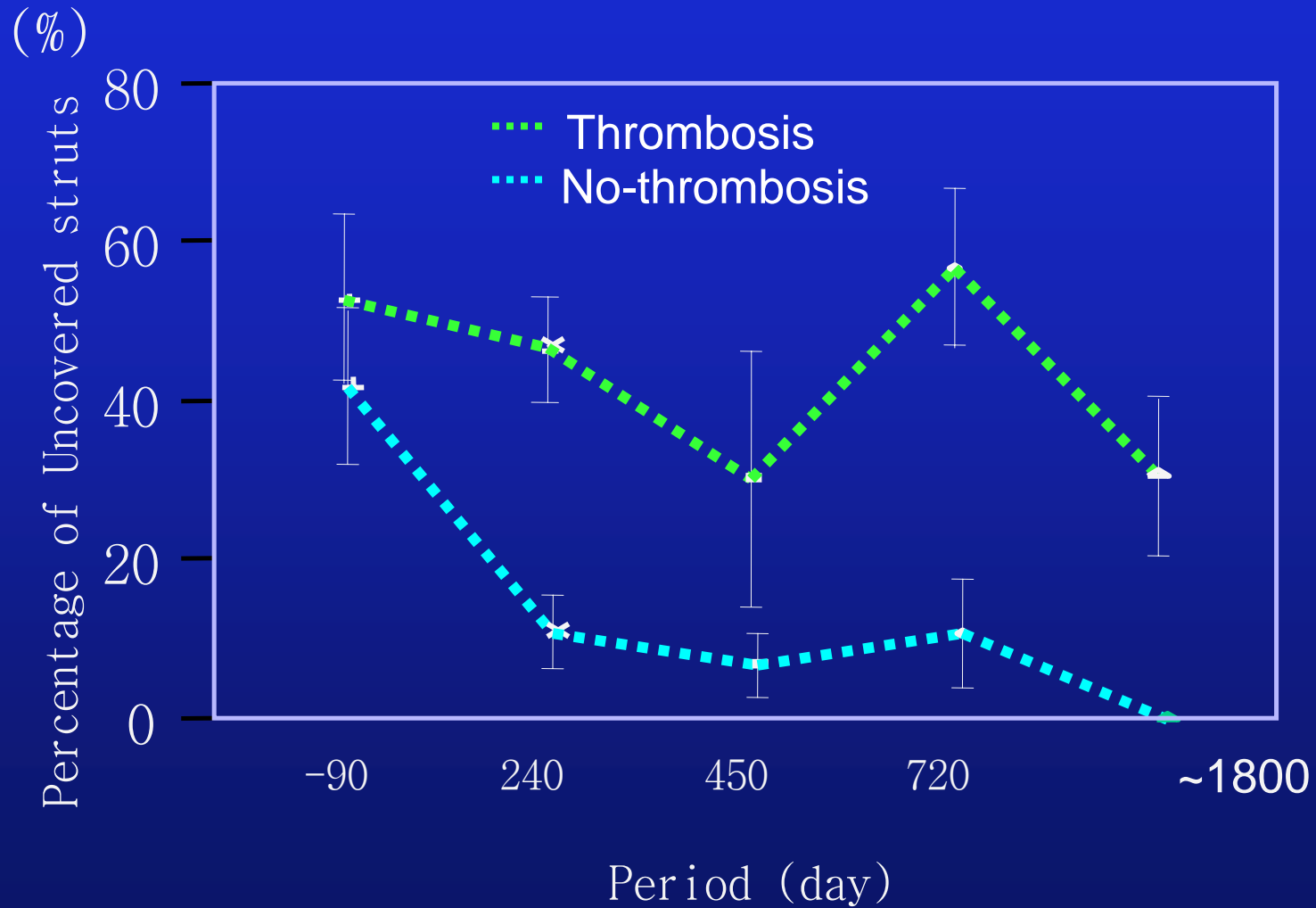
	Non-Thrombosis		p value	Thrombosis		p value
	Late	Very Late		Late	Very Late	
Duration, day	142 ± 94	706 ± 345	<0.0001	145 ± 80	587 ± 173	<0.0001
Stent length, mm	20.5 ± 9.6	23.5 ± 14.7	0.24	27.4 ± 12.3	28.5 ± 13.3	0.79
EEL, mm <sup>2</sup>	13.0 ± 5.8	14.2 ± 4.7	0.31	17.5 ± 4.3	15.6 ± 4.4	0.18
Stent Area, mm <sup>2</sup>	6.8 ± 3.5	7.1 ± 2.5	0.56	8.0 ± 2.2	7.0 ± 1.2	0.11
Neointimal thickness, mm	0.14 ± 0.1	0.16 ± 0.1	0.49	0.13 ± 0.1	0.12 ± 0.0	0.90

# Comparison between Very Late vs. Late Lesions

	Non-Thrombosis		p value	Thrombosis		p value
	Late	Very Late		Late	Very Late	
Inflammation Score	1.1 ± 1.0	1.2 ± 0.8	0.92	1.1 ± 1.2	2.6 ± 2.1	0.02
% Strut Giant Cell	20 ± 23	19 ± 20	0.92	8 ± 14	13 ± 21	0.41
Fibrin score	1.3 ± 1.2	0.8 ± 0.9	0.04	2.7 ± 1.0	1.6 ± 1.2	0.006
% Struts Fibrin	46 ± 27	29 ± 28	0.01	61 ± 23	49 ± 21	0.14
% Uncovered struts	27 ± 29	10 ± 12	0.0018	60 ± 32	47 ± 27	0.21



# Uncovered Struts in DES Thrombosis vs No-Thrombosis



## What we do not know?

We cannot easily translate what we have learnt at the autopsy table to clinical practice .e.g., although AMI patients do not benefit from DES. The interventionalists consider autopsy as only representing the dead and are convinced that it cannot be applied to the living (or to their practice)!!

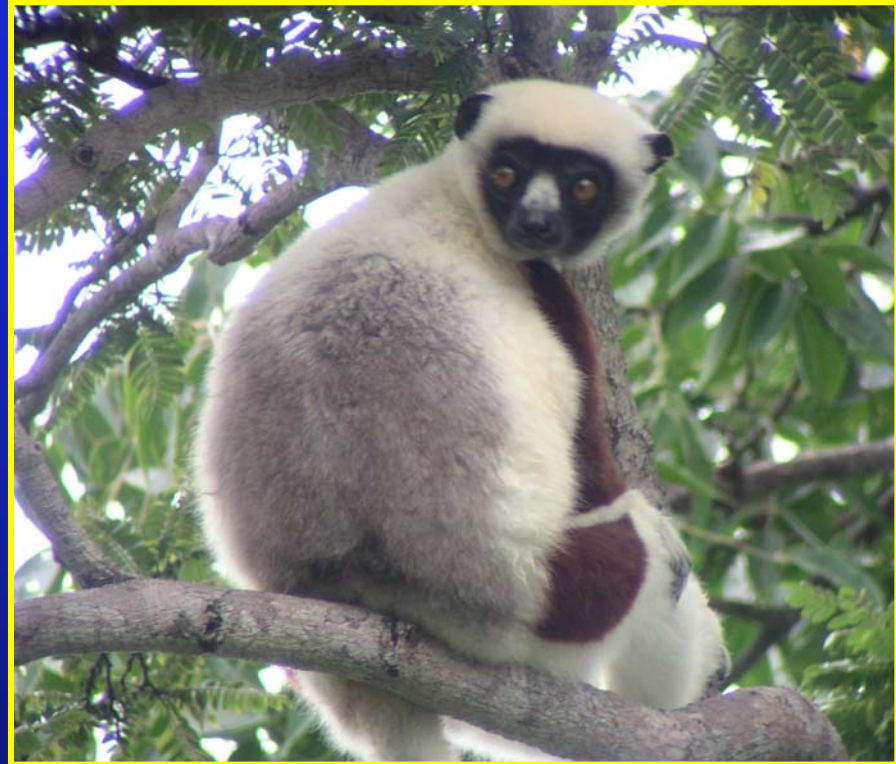
Stable AP patients benefit from DES with fewer cases of late stent thrombosis. Lesion morphology is important for LST

LM, SVBG, bifurcation lesions, long lesion etc – role of DES not proven as yet studies are needed for better understanding - both clinical and pathology



- Frank Kolodgie, Ph.D.
- Gaku Nakazawa, M.D.
- Alope Finn, M.D.
- Elena Ladich, M.D.
- Michael Joner, M.D.
- Andrew Farb, M.D.
- Ed Campado, D.V.M.
- Robert Kutz, M.S.
- You-hui Liang, M.D.
- Hedwig Avallone
- Lila Adams
- Russ Jones
- Rosellin Mathew

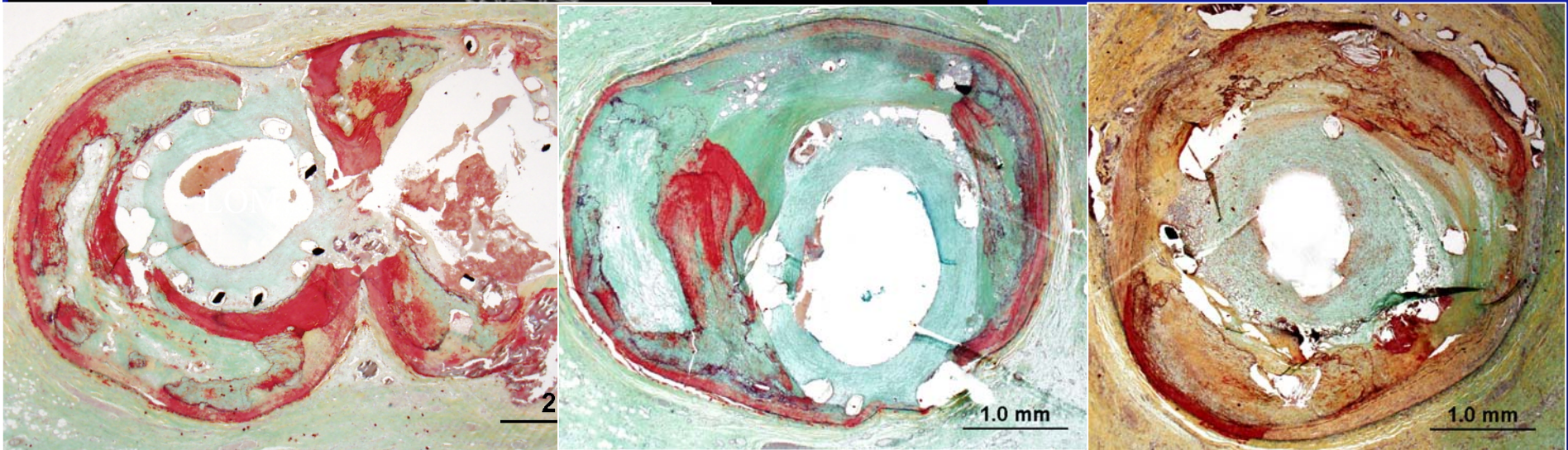
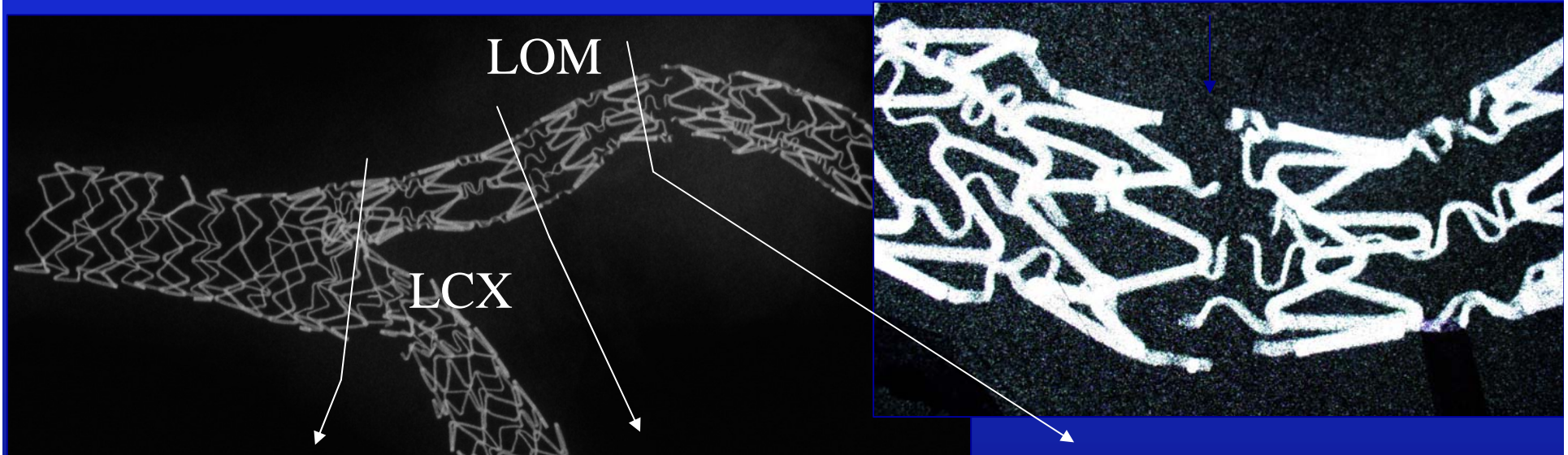
## Acknowledgments



Madagascar, 2003.  
Photograph by R Virmani



# Case 3; 68F died of late stent thrombosis 6 months following DES implantation in the bifurcation lesion



restenosis

## Procedural Factors

- Incomplete apposition
- Excessive stent length
- Overlapping Stents

With Current FDA  
Approved DES  
LST remains a  
Risk factor

## Device Factors

- Hypersensitivity reaction
- Uneven distribution of drug
- Incomplete apposition due to positive remodeling

# **Increased Risk For Late Stent Thrombosis**

## Lesions Factors

- Penetration of necrotic core or Pre-existing thrombus with necrotic core (AMI)
- Bifurcation/ Ostial stenting
- Long lesion
- Uncovered struts
- Late malapposition (inflammation)

## Patient Factors

- Diabetes
- Renal failure
- Low EF
- Not a candidate for long term anti-platelet therapy?
- Premature discontinuation of antiplatelet therapy



# Thrombosis Distribution

