

# DES Pathobiology Considerations: What We Know and What We Don't Know Can Hurt US!



*Siberia*

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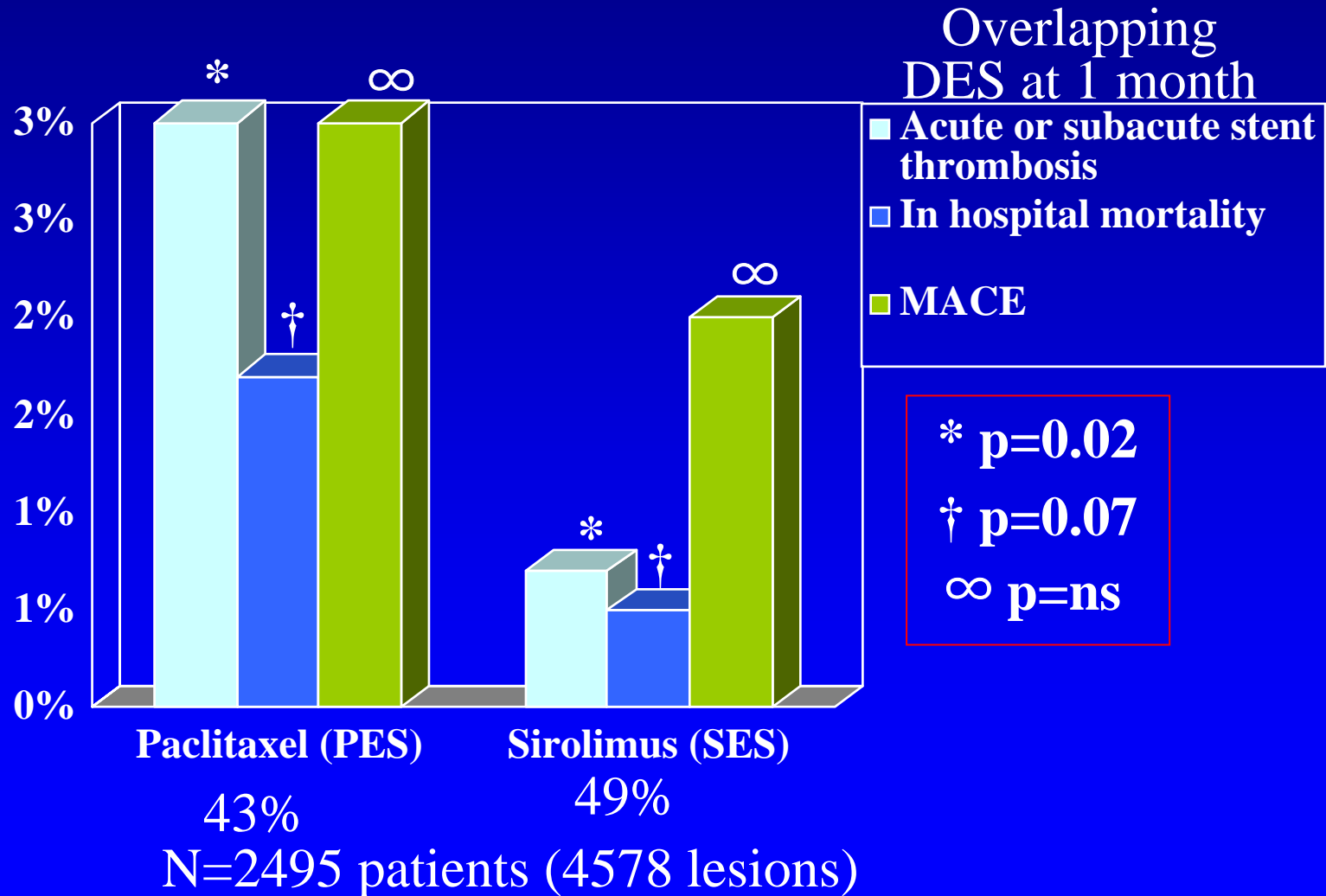
Gaithersburg, MD



# Are the current DES stents (CYPHER and TAXUS) doing their job - prevent restenosis?

- Current DES stents (non-overlapped) prevent restenosis at 6 and 12-months (Cypher >36 months) in highly select patient population
- DES stents have been shown to cause greater subacute thrombosis especially in overlapping stents vs. BMS
- Hypersensitivity reactions have been reported following CYPHER
- TAXUS stents have had problems with deflation of the balloon (4 voluntary recalls?). ↑Subacute thrombosis and excessive inflammation (neutrophils and eosinophilic) are also seen with TAXUS stent >90 days

# Increased Risk of Sub-acute Thrombosis After Overlapping With DES: An analysis from Real-world Eluting Stent Comparative Italian Retrospective Evaluation (RECIPE) Study



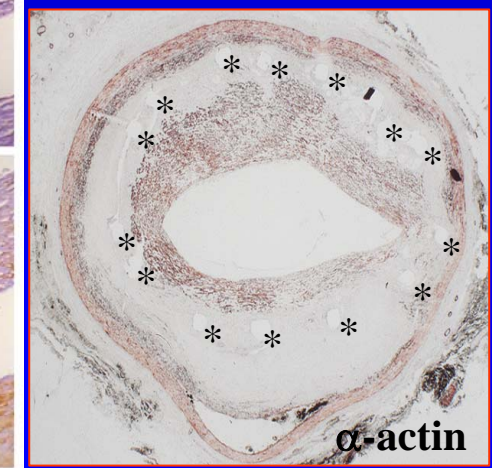
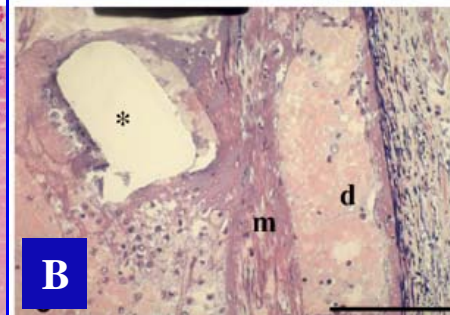
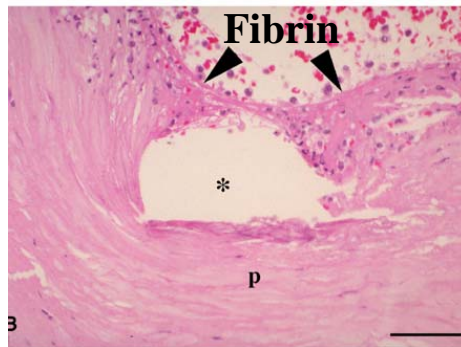
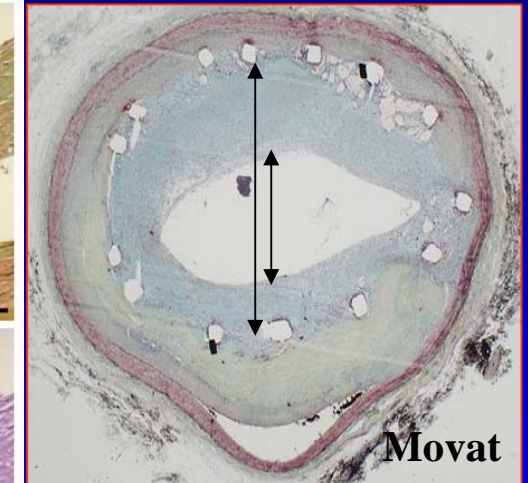
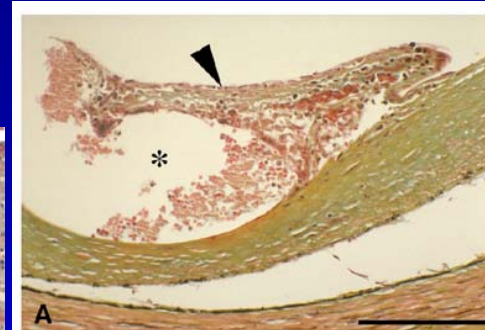
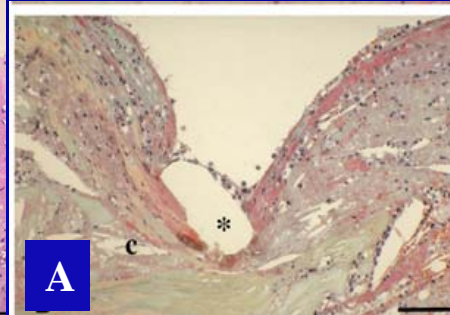
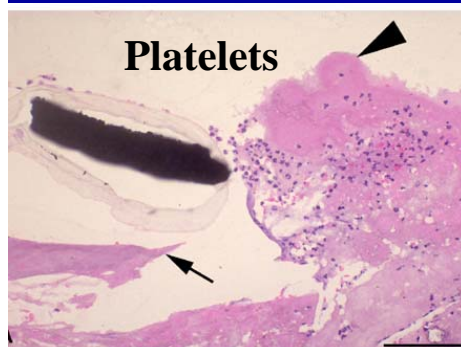
# Balloon Expandable Stainless Steel Stent Healing in Man

Granulation tissue

Smooth muscle cells  
and matrix

Thrombus

Inflammation



1-30 days

1-30 days

14 - 90 days

$\geq$  4 months

Endothelialization is complete in 3-4 months

## *Taxus Stents With Total Subacute Occlusive Thrombosis*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
45 M	SAP	LAD	>30 days	Sudden death	<i>Occlusive</i>	Focal persistent
52 M	SAP	LCX, RCA	Unknown	Sudden death	<i>Occlusive</i>	Giant cell reaction
74 F	SAP	LCX	~ 6 months	Sudden death	<i>Occlusive</i>	Focal mild
47 M	AP	LAD	1 month	AMI	<i>Occlusive</i>	Mild

## *TAXUS Stents: Non-occlusive Thrombus and minimal inflammation*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
49 M	AP	PDA	6 days	Sudden death	<i>Minimal luminal</i>	mild
56 M	AMI	RCA	Same day	Sudden death	<i>Focal minimal</i>	Large calcification

## ***TAXUS Stents With Acute Inflammatory Reaction***

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
45 M	AP	RCA	Few days	Sudden death	<i>Moderate</i>	Acute inflam, eosinophils
40 F	AMI	LAD	3 days	Sudden death	<i>Moderate</i>	Acute inflammation
59 F	SAP	LAD	18 weeks	Sudden death	<i>Surface thrombus</i>	Moderate, eosinophils
81 F	AMI	RCA	Same day	AMI	<i>Superimposed</i>	Acute inflammation

## ***TAXUS Stents With Mild Inflammation***

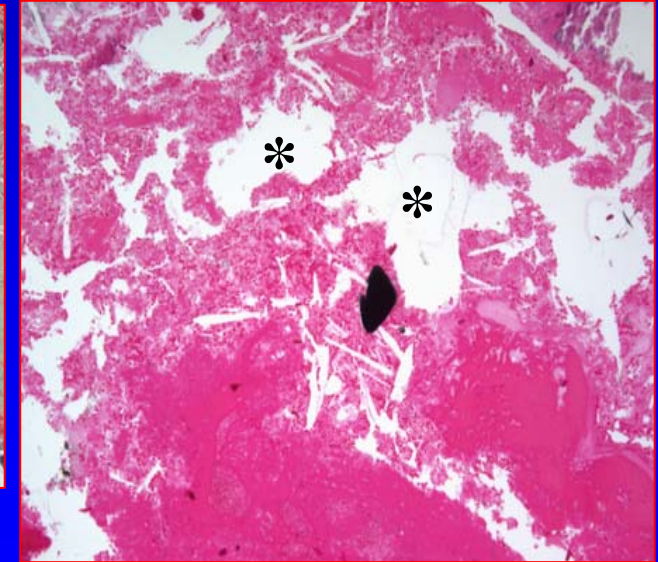
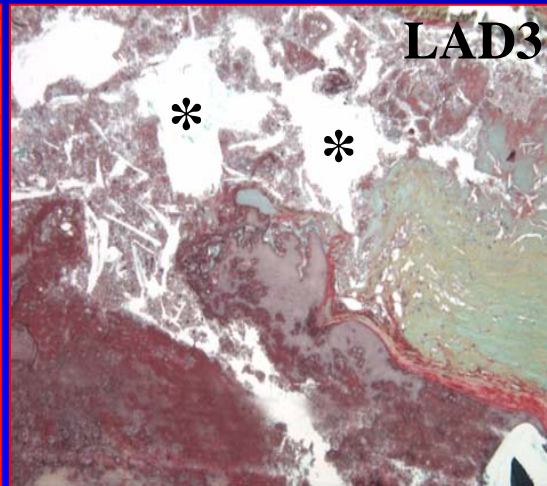
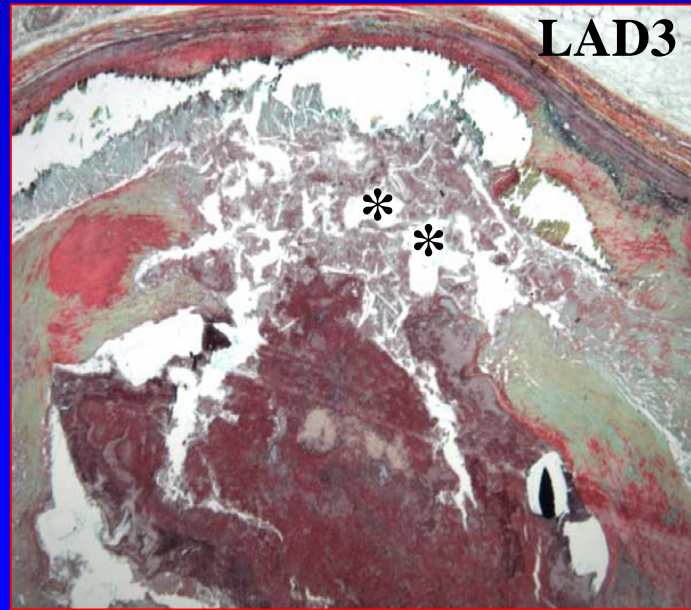
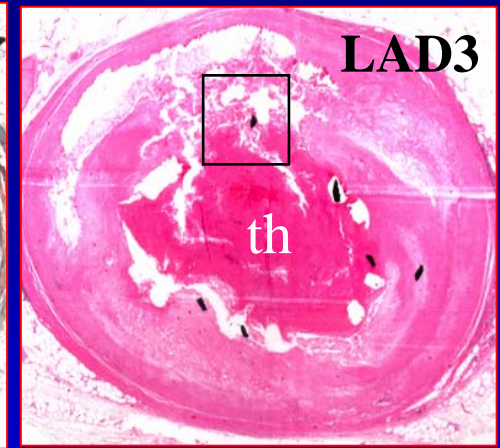
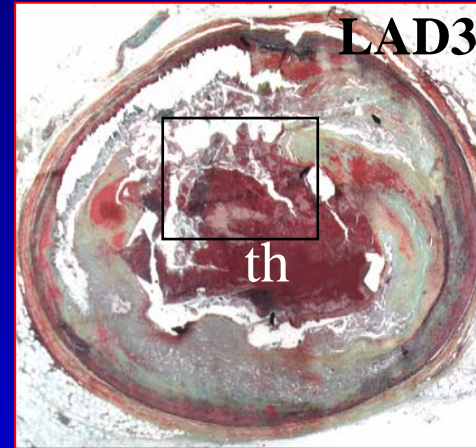
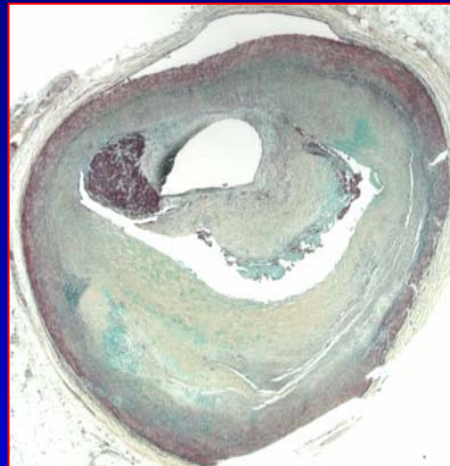
71 F	SAP	LAD	57 days	Sudden death	<i>Focal minimal</i>	Minimal inflammation
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## ***TAXUS Stents With Restenosis***

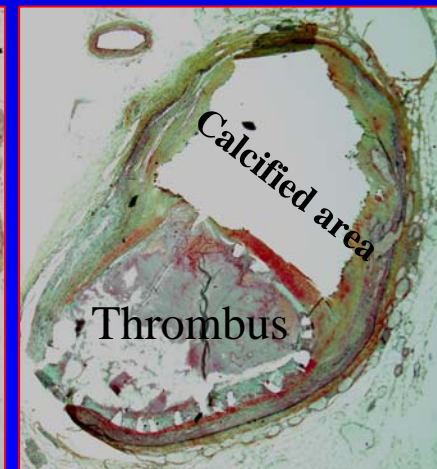
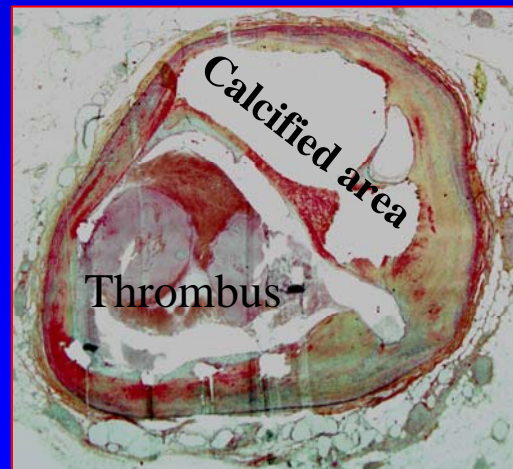
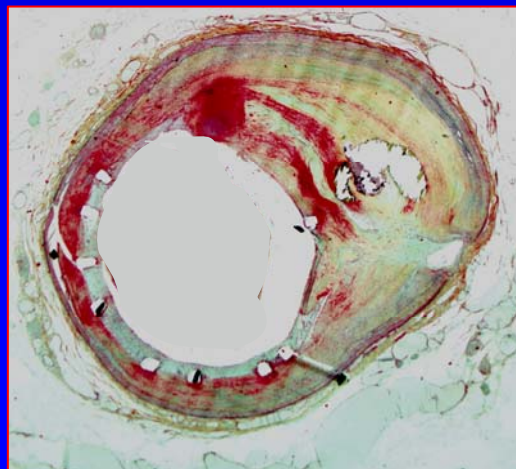
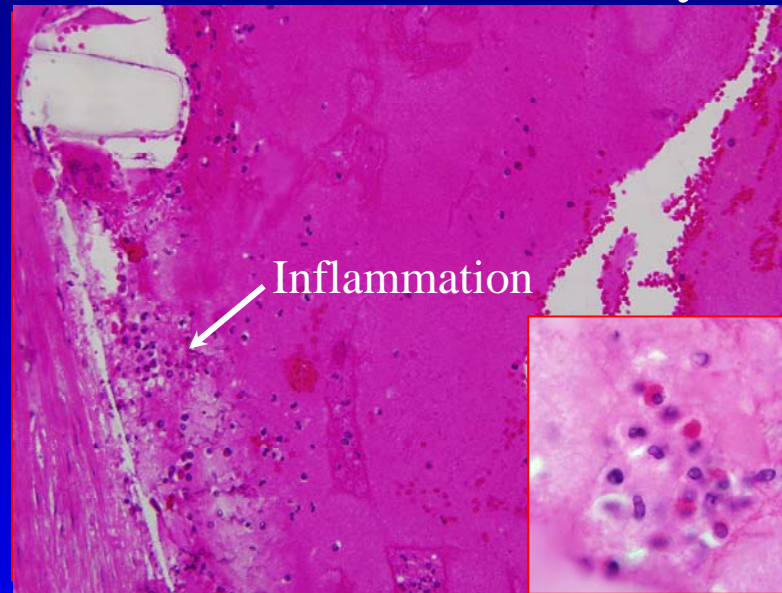
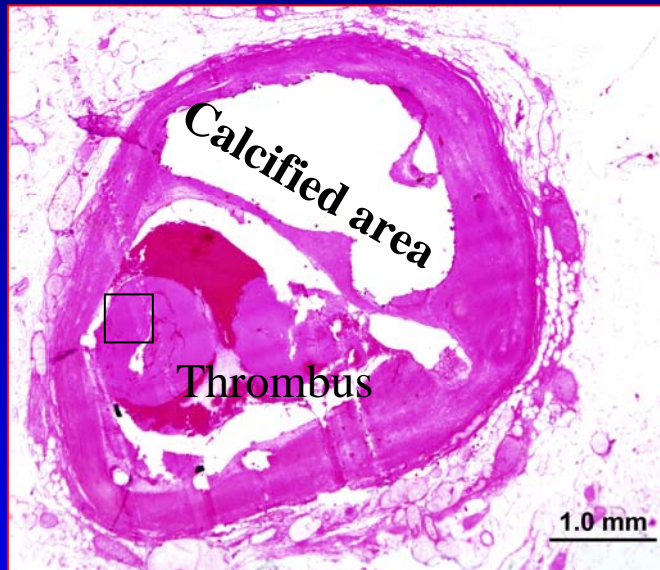
Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
70 M	AMI	LAD	6 months	MI	<i>Organizing</i>	Mild

# Taxus Stent Thrombosis in a 47-year-old M at 41 days

Proximal to stent

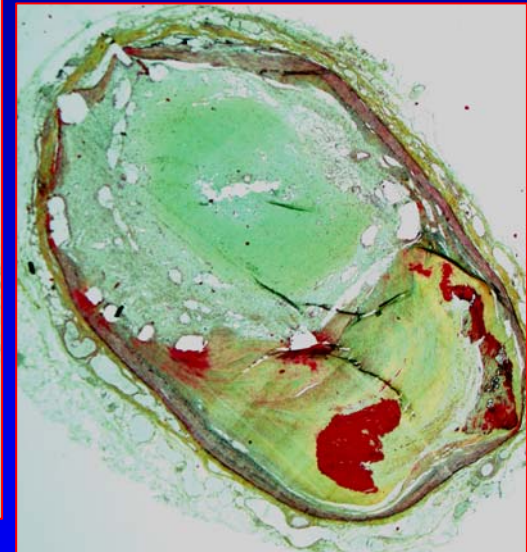
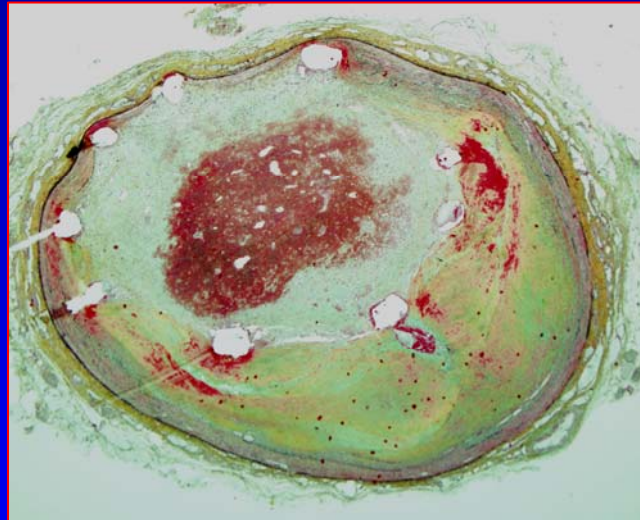
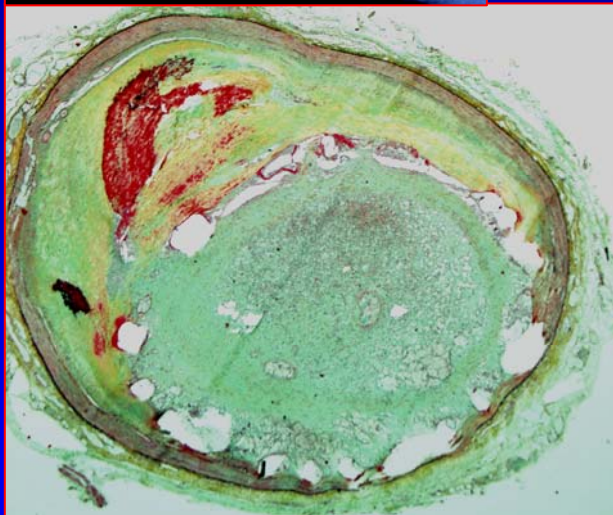
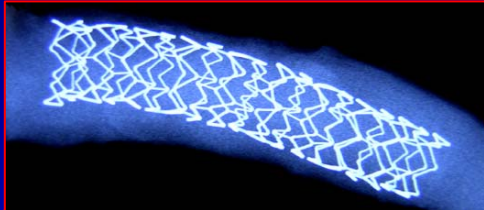


# 74-year old man with TAXUS Stent placed in LAD 2 weeks prior to † Acute thrombotic occlusion of the stented artery



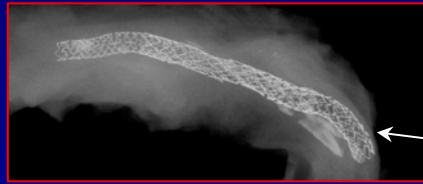


**74-year old female with CAD had  
TAXUS stent placed ~ 6 months prior  
to death**



**Total occlusion from organizing thrombus**

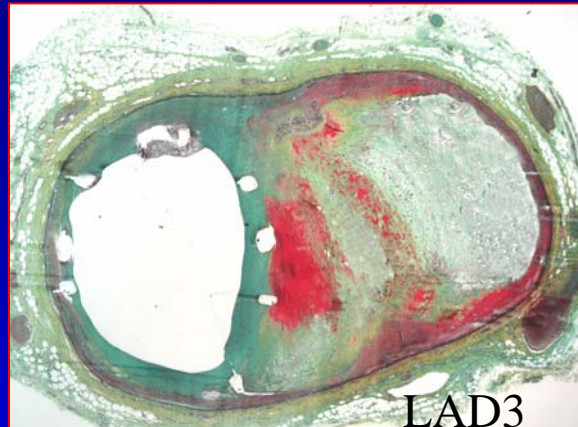
# 59- year old Female with TAXUS stent deployed in the LAD for 130 days



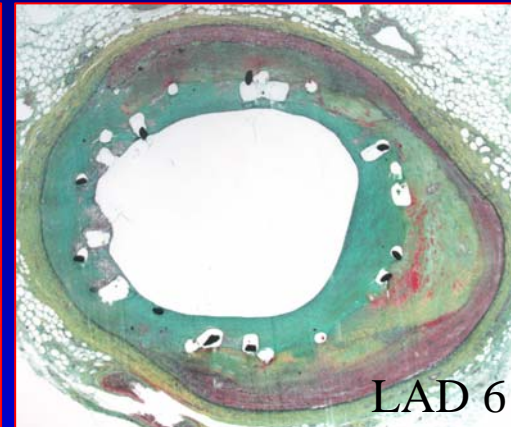
TAXUS



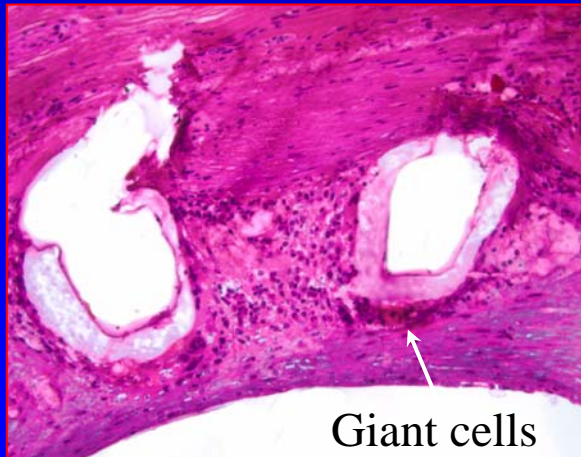
LAD1



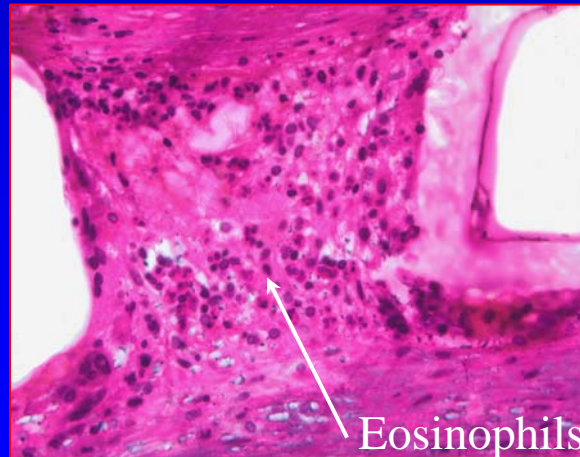
LAD3



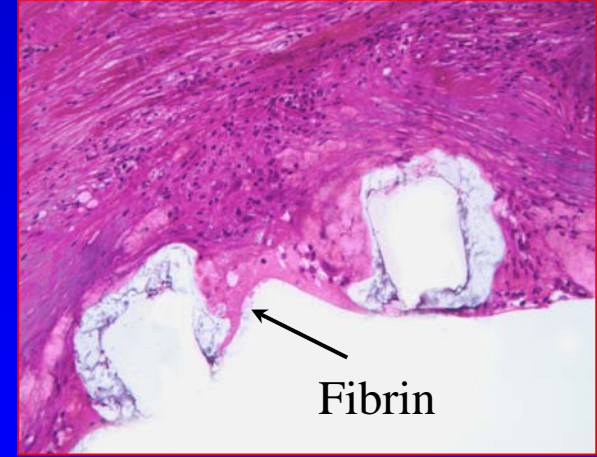
LAD 6



Giant cells



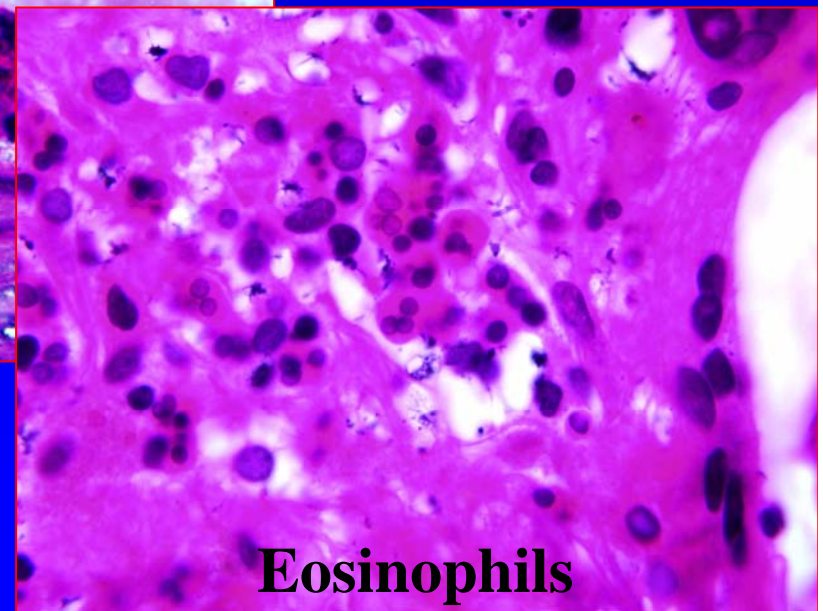
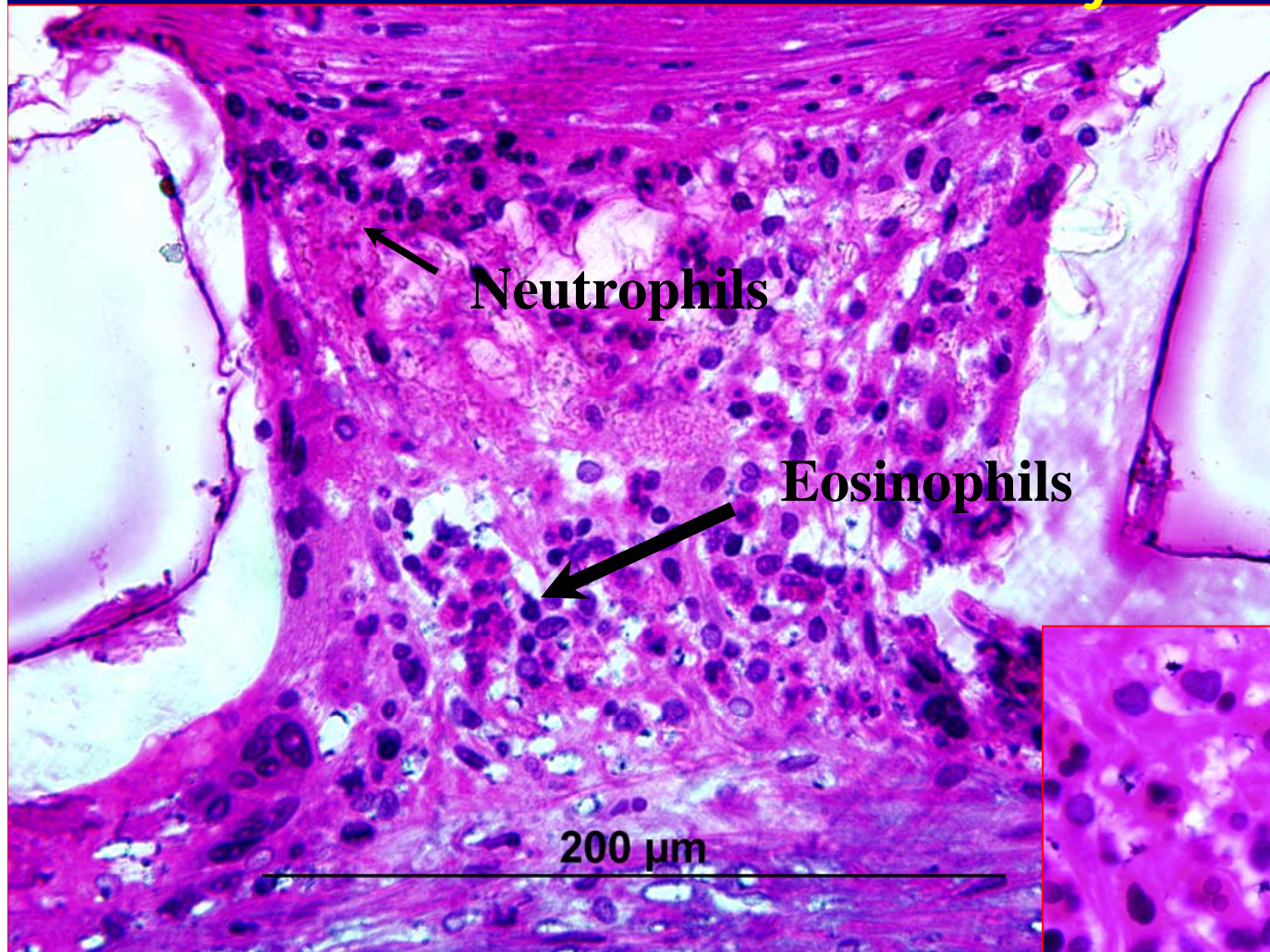
Eosinophils



Fibrin

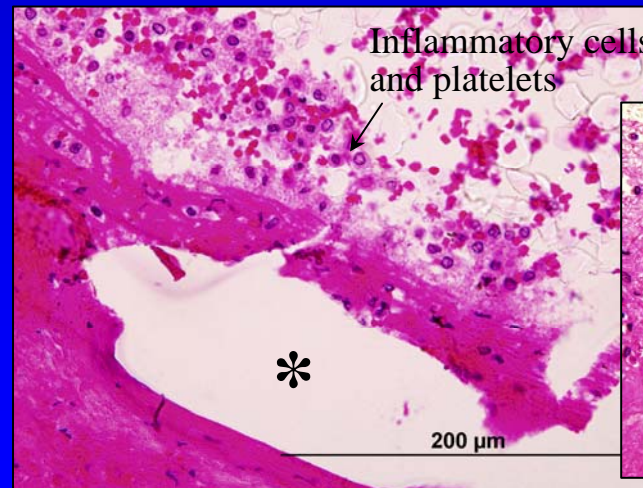
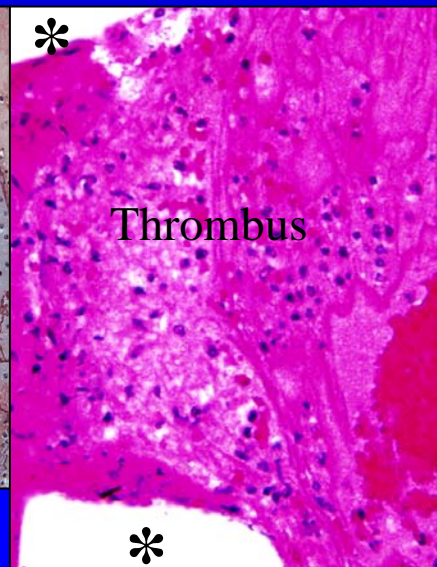
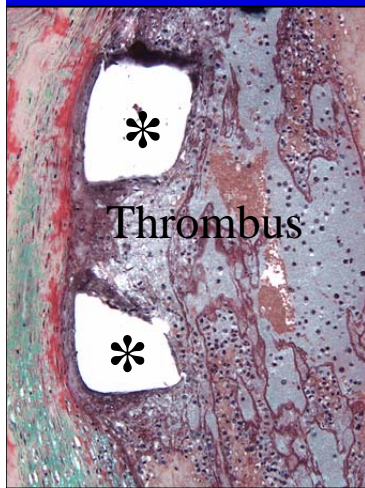
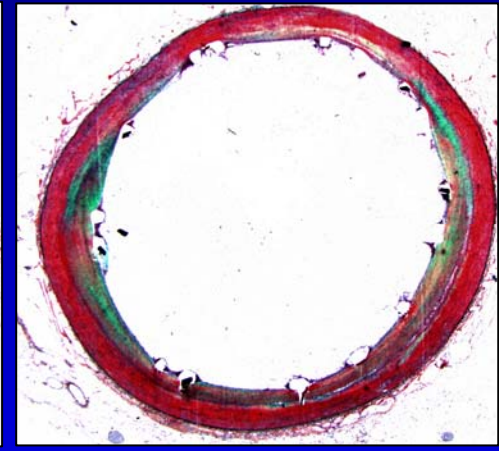
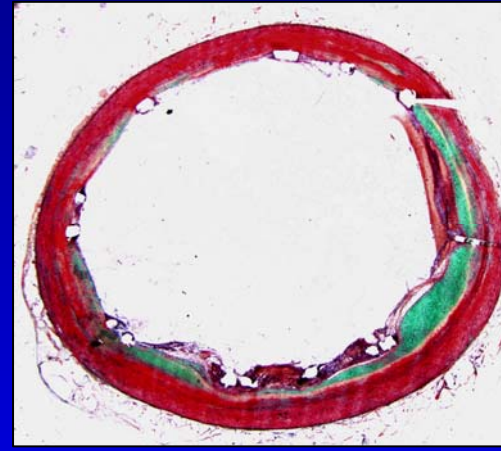
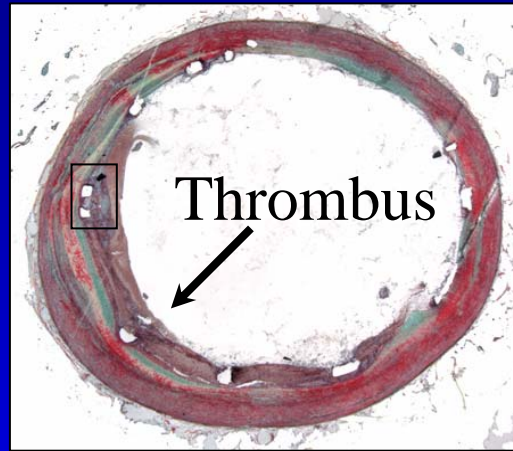
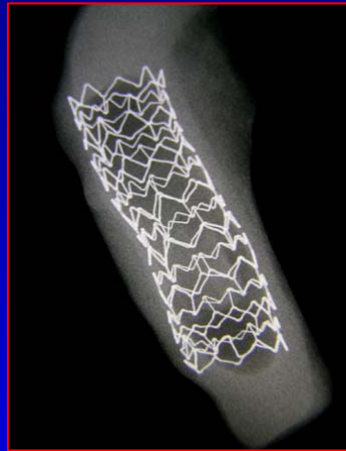
70% Surface Endothelialized

**59- year old Female with TAXUS stent deployed in the LAD for 130 days**

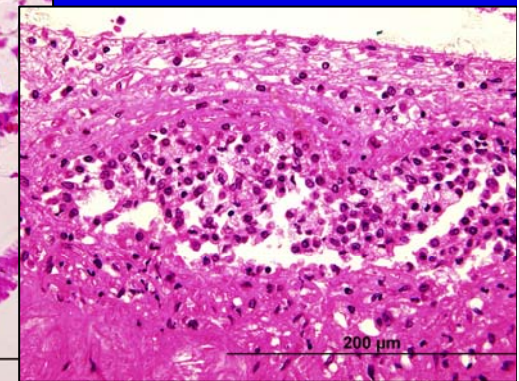


# 45-year old man with hypertension and recent (~7 days) TAXUS stent placed in RCA

Minimal underlying atherosclerotic luminal narrowing (diffuse dilatation of CA)



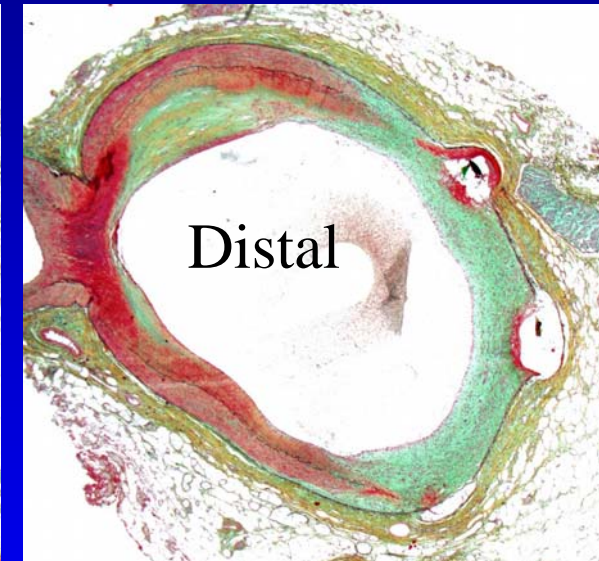
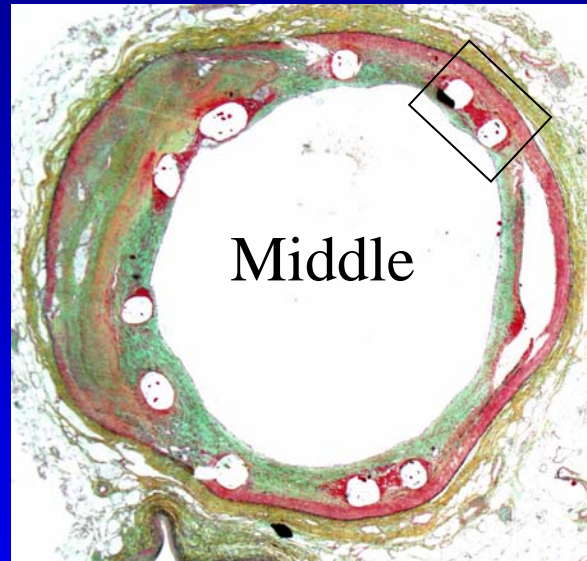
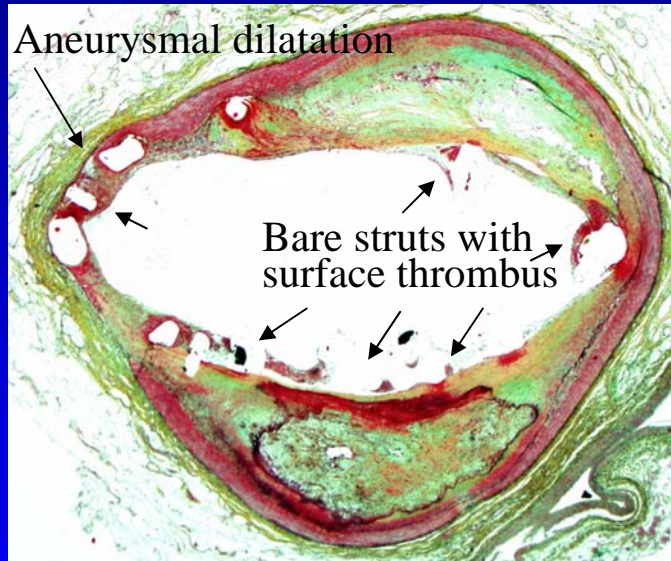
Acute inflammation, within thrombus



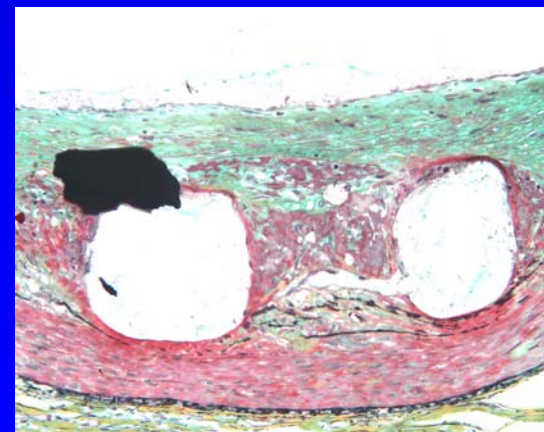
\* Stent struts

# 71-year old female with CAD had TAXUS stent (3x23) placed 3-months prior to death

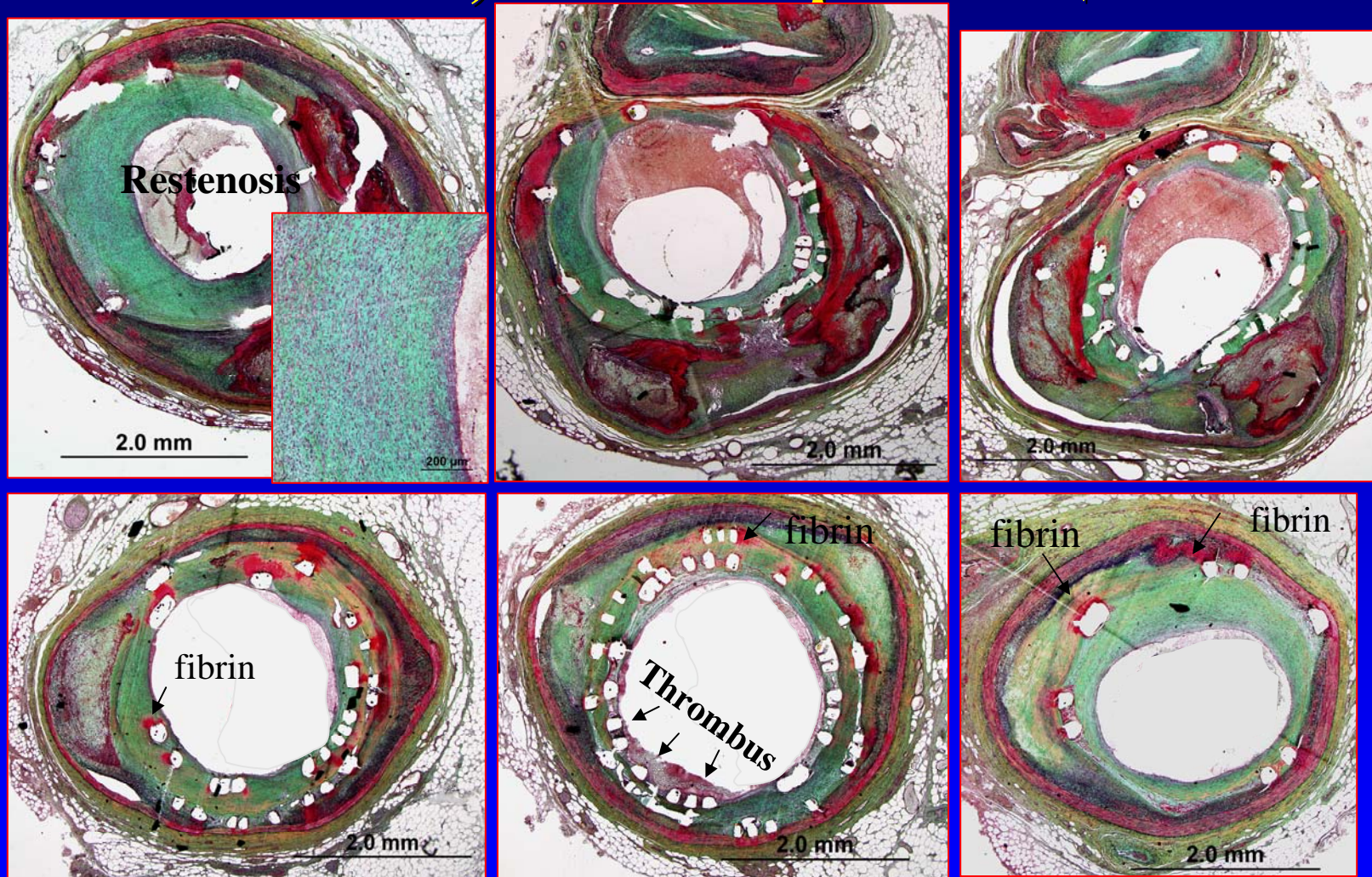
Proximal



60% surface endothelialized



# Taxus stent: 1<sup>st</sup> stent 10 months, 2<sup>nd</sup> stent placed for AMI, 6 months prior to †



70-year-old woman with CAD presented 10 months prior to death with AMI had TAXUS stent placed returned; 4 months later presented with MI 2<sup>o</sup> to stent thrombosis, second TAXUS stent placed and patient expired 6 months later. ( **Diagnosis; delayed healing with luminal thrombus** )

## *Cypher stents with Subacute Occlusive Thrombosis*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	<i>Thrombus</i>	Inflammation
37 F	MI (non-Q)	LAD/LOM & LCx	7 days	AMI	<i>Occlusive</i>	Minimal
58 M	UAP	LM+LAD	11 and 6 days	AMI	<i>Occlusive</i>	Mild, dissection
65 M	AMI recent	LAD	38 days	Stroke+ AMI	<i>Occlusive</i>	None
70 M	AMI	LCX & LAD	6 days	AMI	<i>Occlusive</i>	Moderate

## *Cypher stents: Mild Non-occlusive Thrombus and inflammation*

51 M	AP with in-stent restenosis	LCx & distal RCA*	10 days	SD -CAD	Minimal	Occasional
60 M~	AP	Cypher mid LAD†	2 months	AMI	Mild	Mild
79 M	AMI	LD	1 day	AMI +	Mild	Moderate

\* Diffuse disease, 51 year old had documented vasospasm and had diffuse narrowing.

~ UAP has in-stent restenosis receives brachytherapy and Cypher stent in the mid LAD: presents 9 days later with CP -50 to 70% narrowing of proximal LAD S7 stent placed; patient admitted 2 months later with CP, catheterization slow flow to LAD Ballooned, arrests and dies after by-pass surgery. At autopsy diffuse disease.

## *Cypher with Hypersensitivity Reaction*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
61 M	AMI	LCx/ PD	4 months	SD-CAD	<i>Non-occlusive</i>	Severe
58 M	UAP (E-SIRUS)	LCx	18 months	AMI rupture	<i>Occlusive</i>	Severe

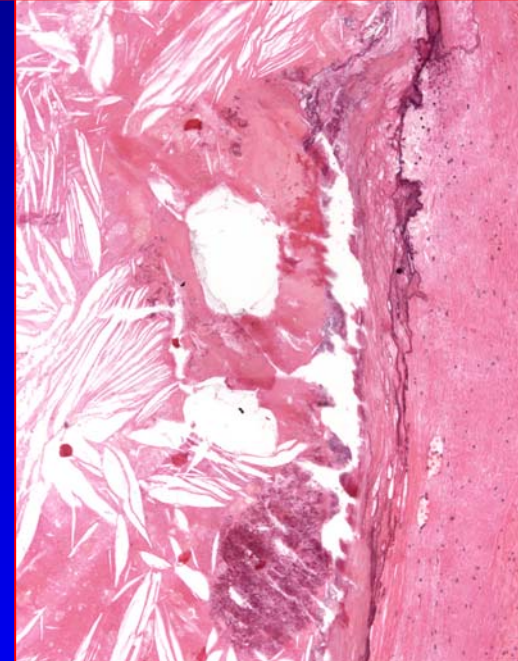
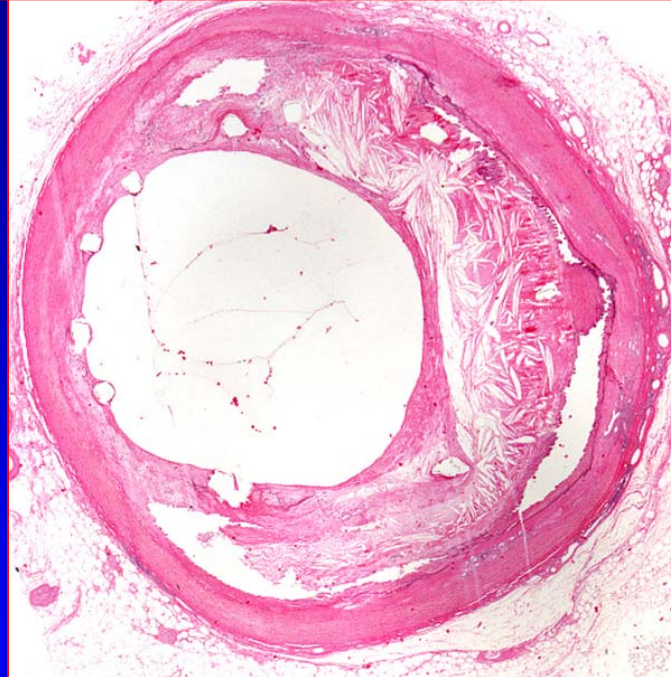
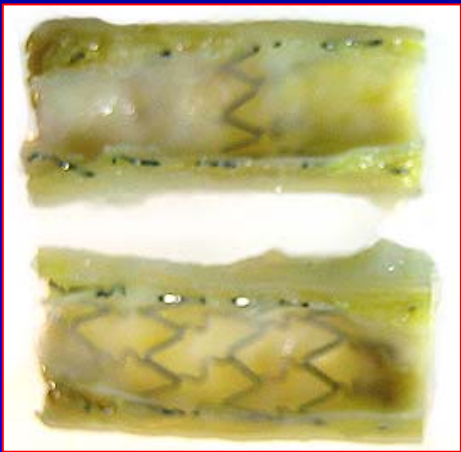
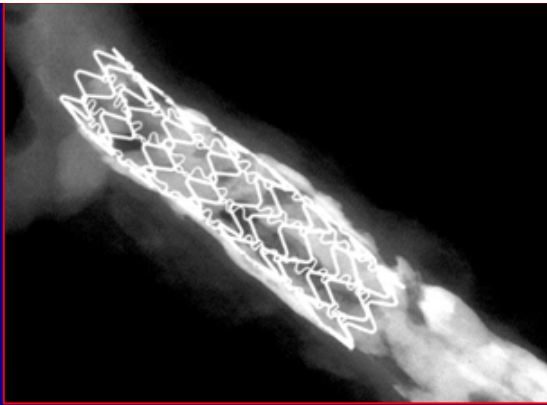
## *Cypher: Minimal Neointima and mild inflammation late after Stenting*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
71 F	Asymptomatic (RAVEL)	LAD	16 months	Stroke	Small thrombus side branch	Occasional giant cells
61 M	Asymptomatic AS+MS (FIM)	RCA	4 years	Plaq rupture, Stroke	None	Minimal

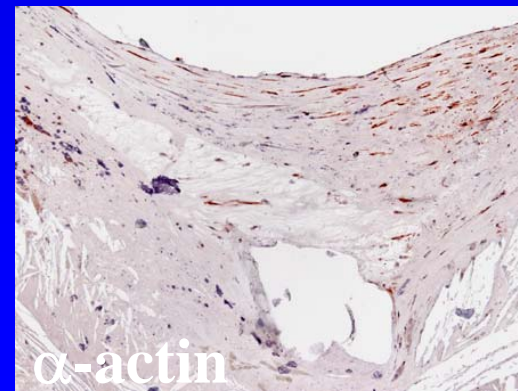
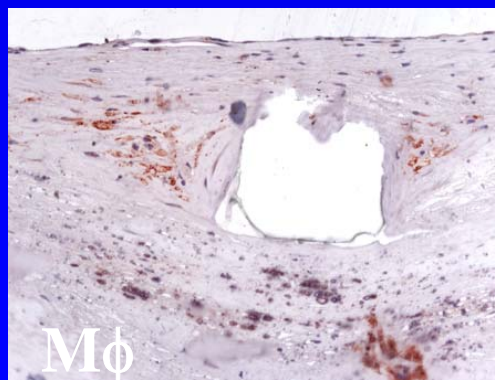
## *Cypher with Restenosis no inflammation*

Patient Age/Sex	Indication	CA	Interval implant to †	Cause of death	Thrombus	Inflammation
75 M	MI	LCX+ RCA	4 months	<b>Restenosis</b> diffuse + AMI	Non-occlusive	Minimal

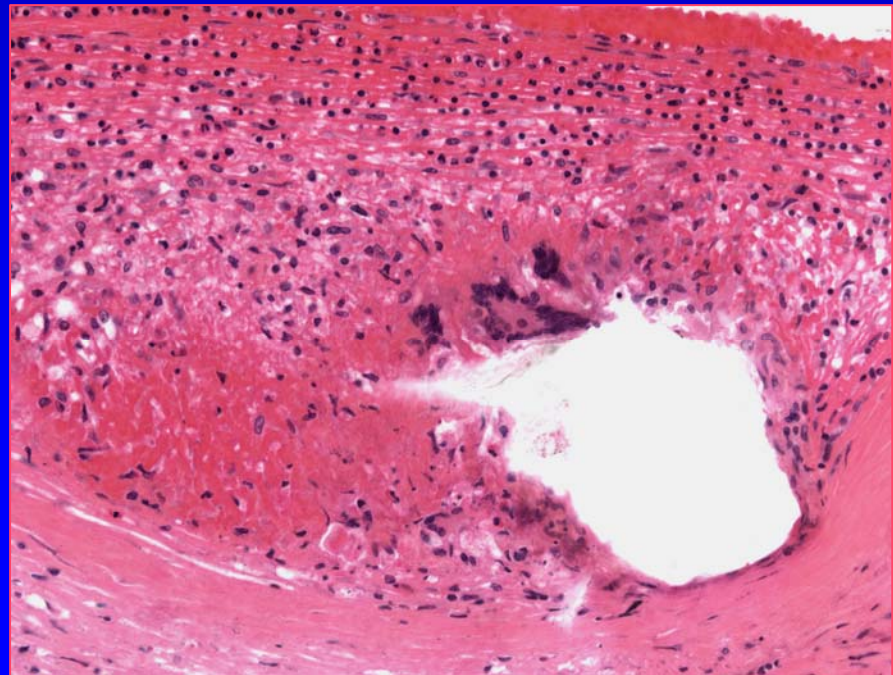
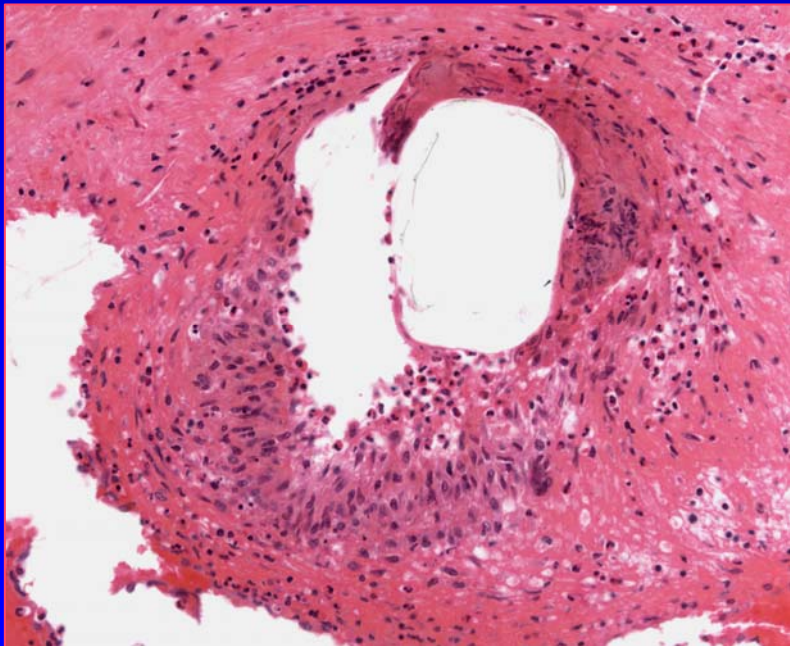
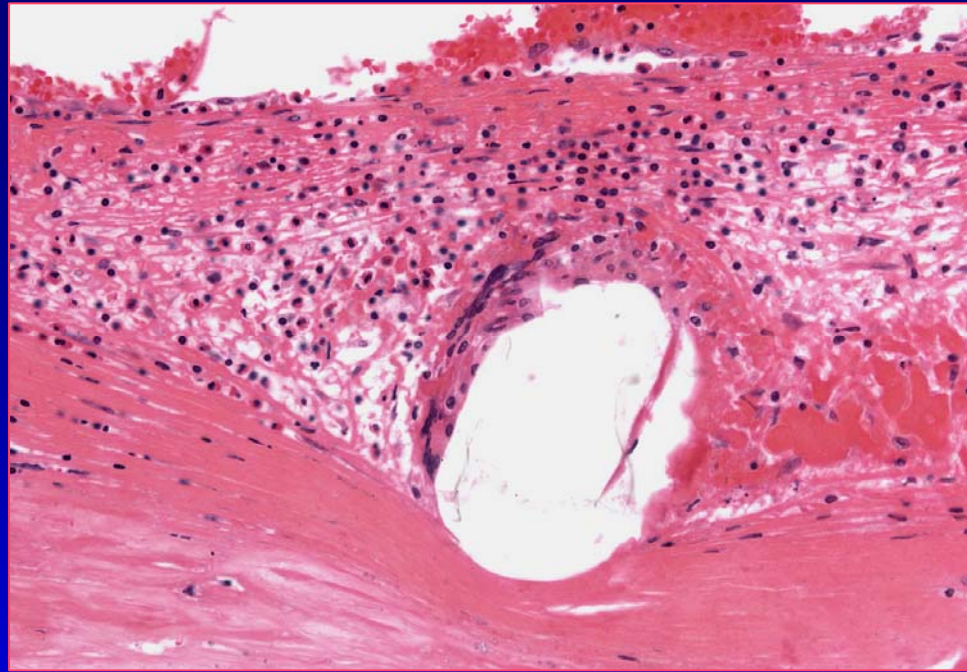
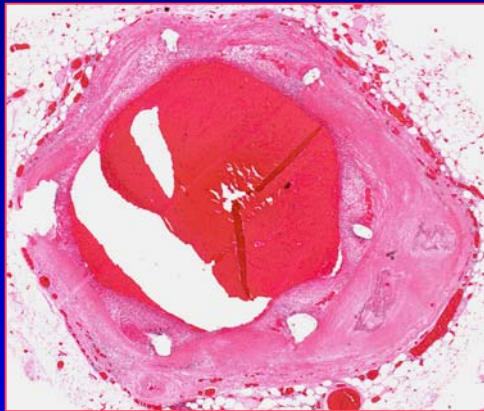
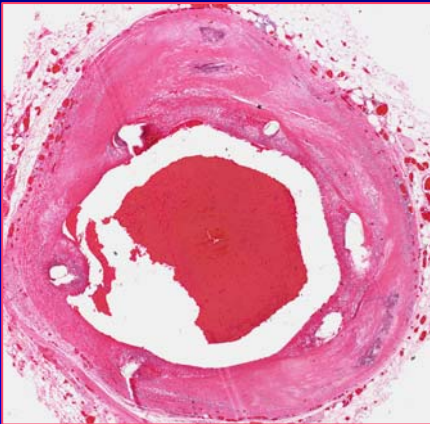
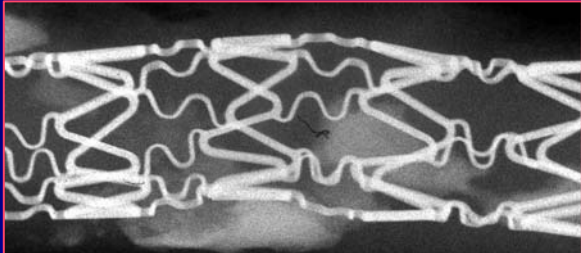




First in Man  
CYPHER Stent  
(Fast Release)  
4-Years Post-  
Deployment

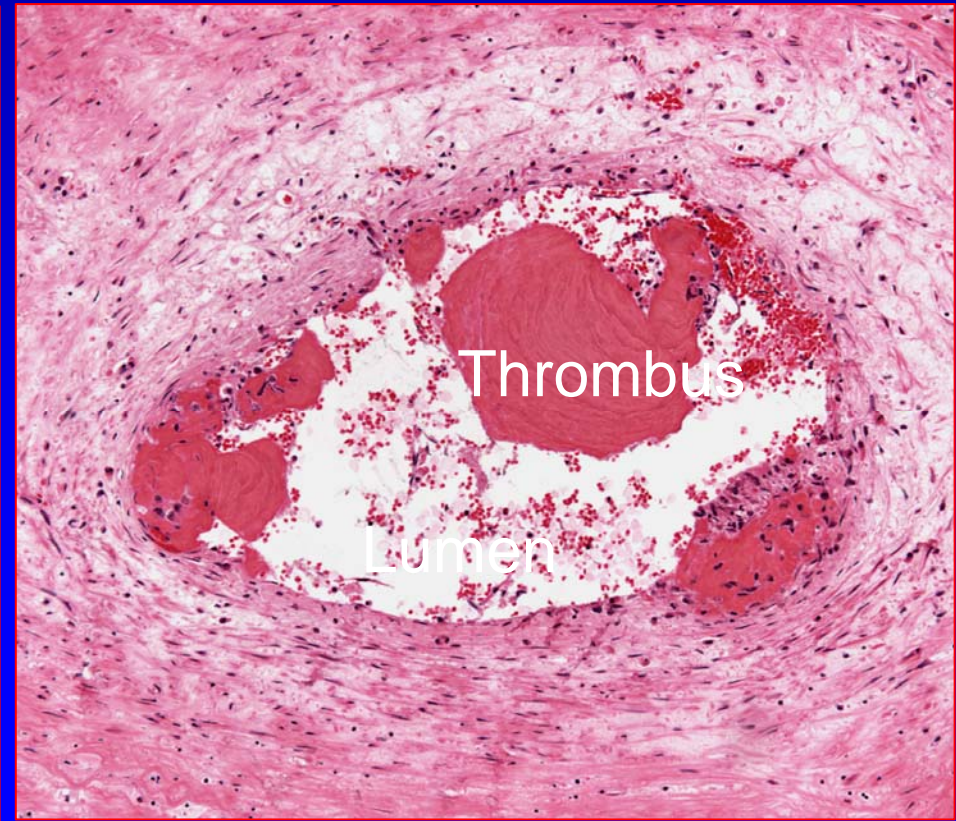
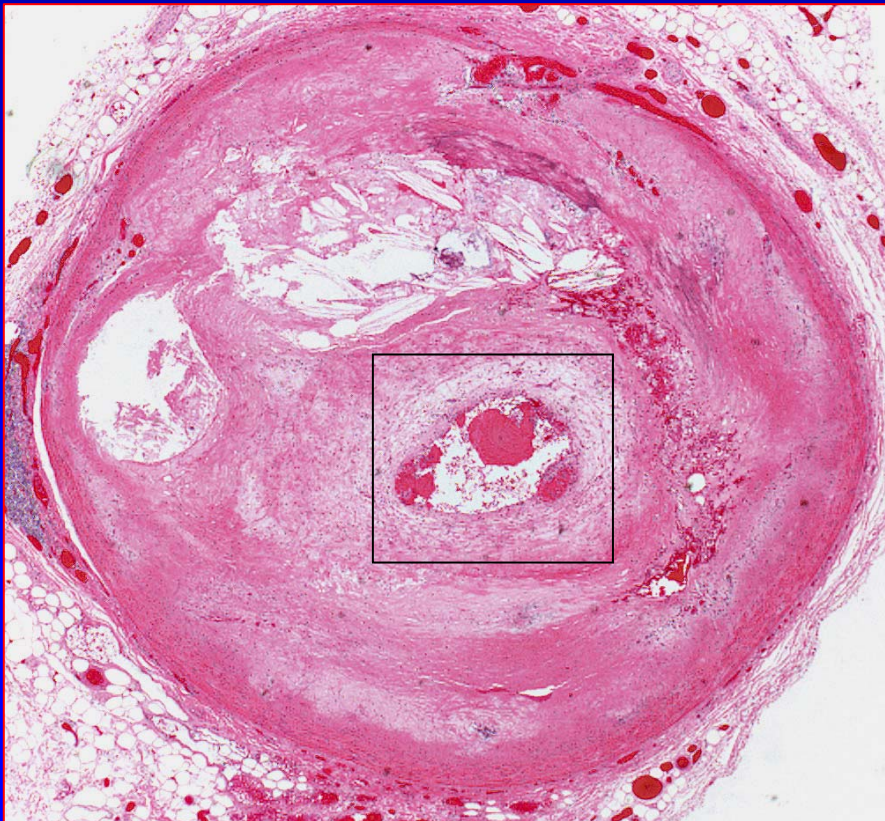


**CYPHER in LCX/PD - 4 months**



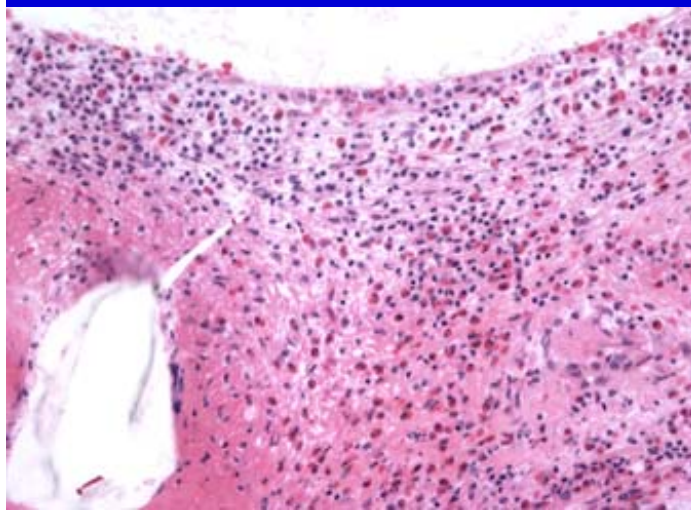
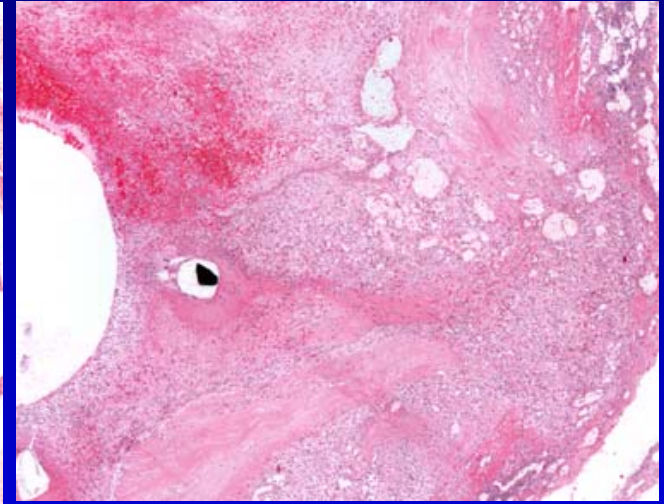
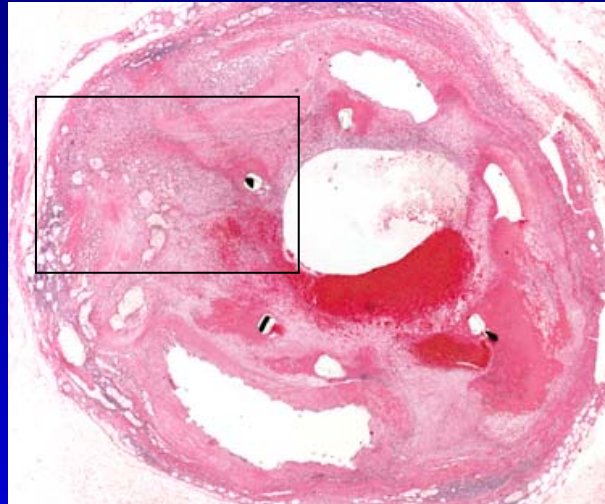
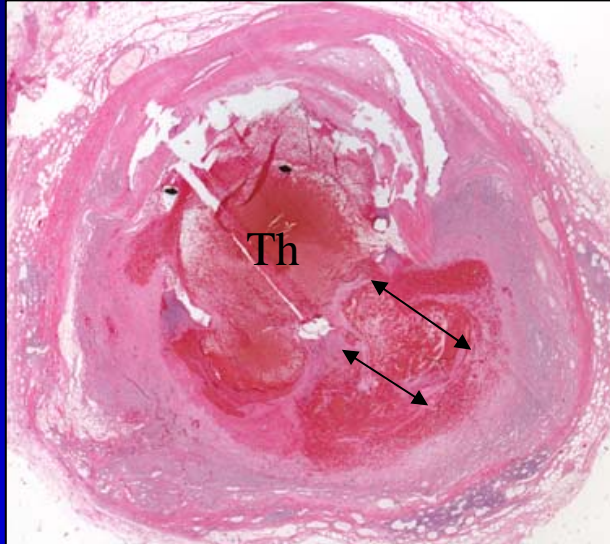
# ***CYPHER stent in place for 4 months***

**PDA just proximal to CYPHER stent -  
restenosis and thrombosis**

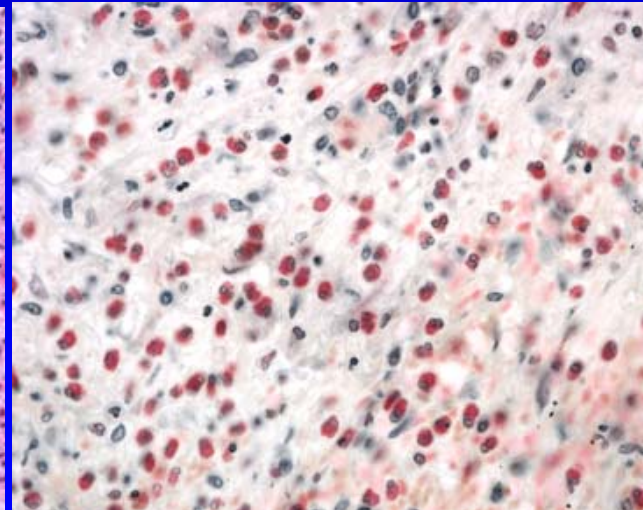


# Distal Stent (CA Aneurysm)

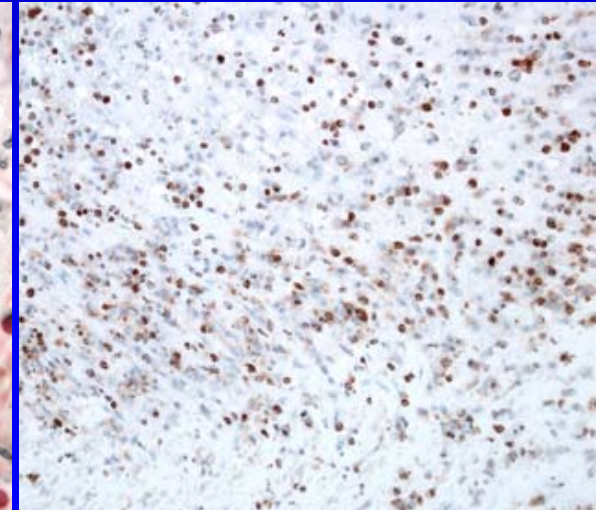
58-years old man two Cypher stents in place for 18 months



Chronic Inflammation

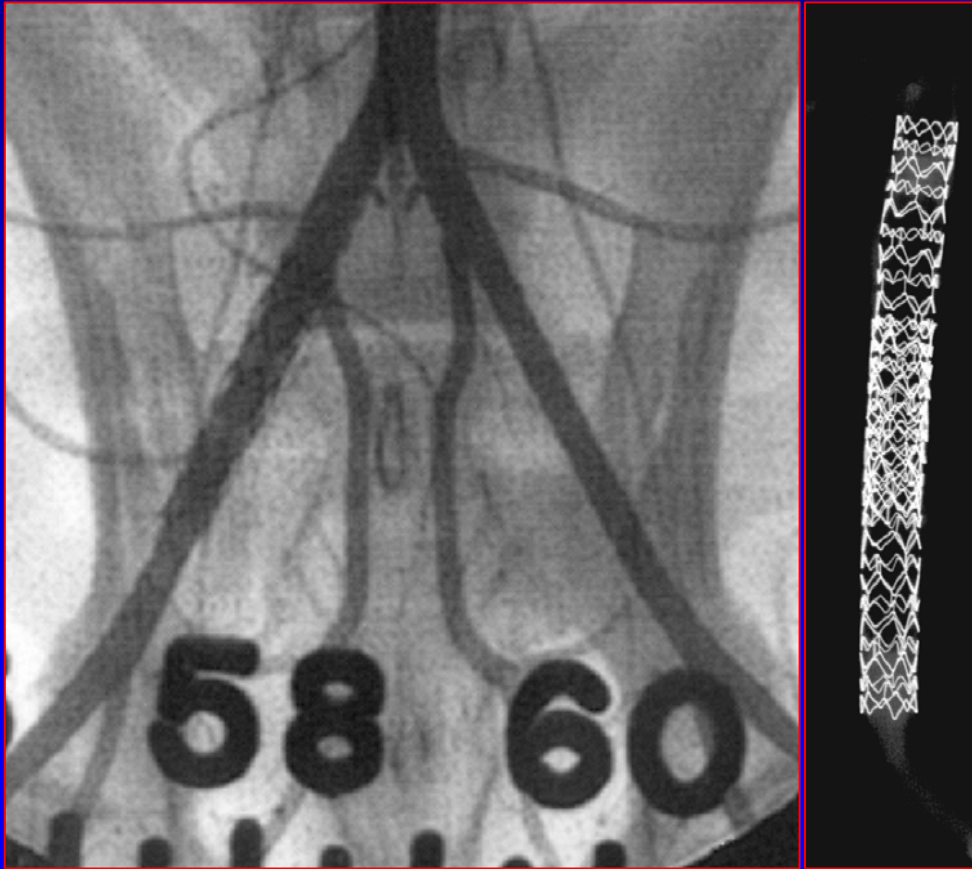


Eosinophils  
(Luna stain)



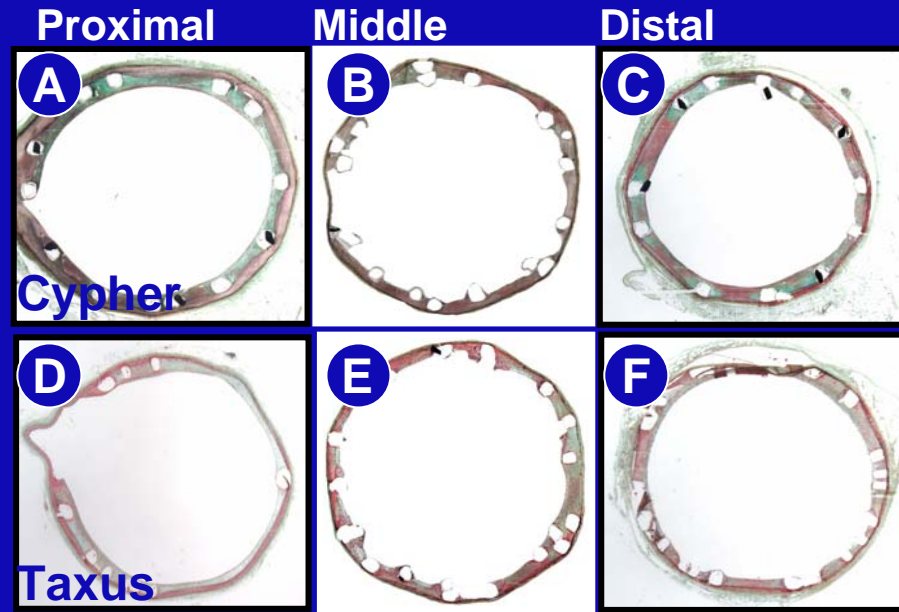
T-Lymphocytes (UCHL)  
*Virmani R, et al. Circulation 2004*

# Impact of Overlapping Drug Eluting CYPHER and TAXUS Stents on Vessel Wall Morphology in Rabbits

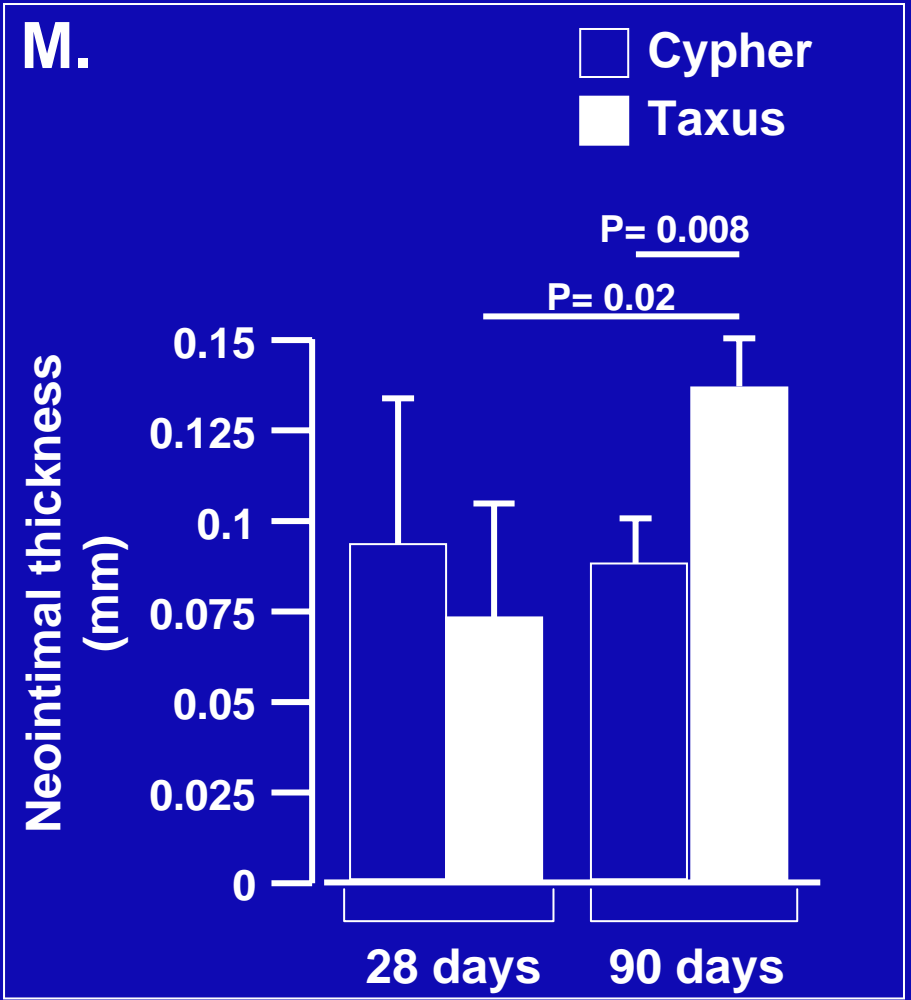
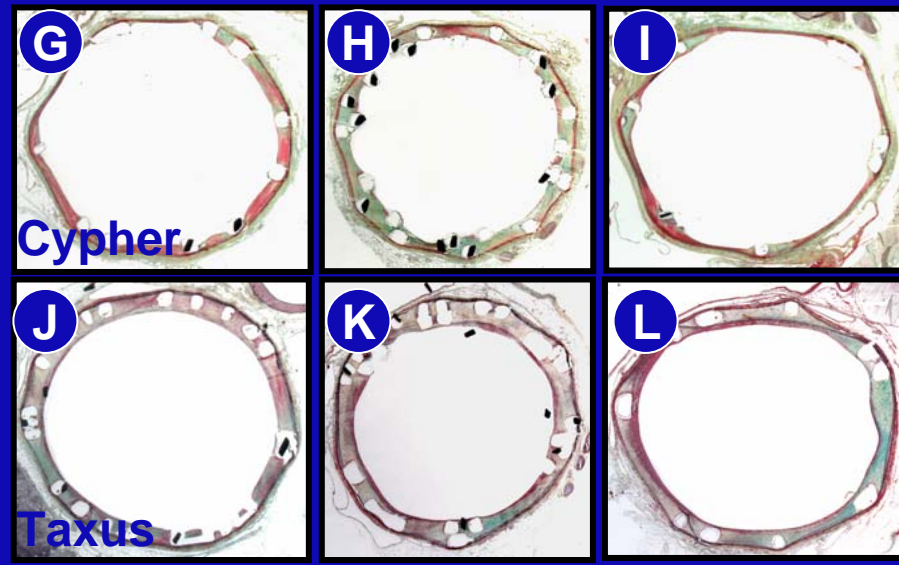


- 3.0 x18mm Cypher or 3.0 x 20mm Taxus stents were implanted in New Zealand White rabbit iliac arteries following balloon injury and compared to BMS.
- Animals were sacrificed at 28 or 90 days.
- Stented arteries were processed for light microscopy after plastic embedding. SEM performed in limited cases

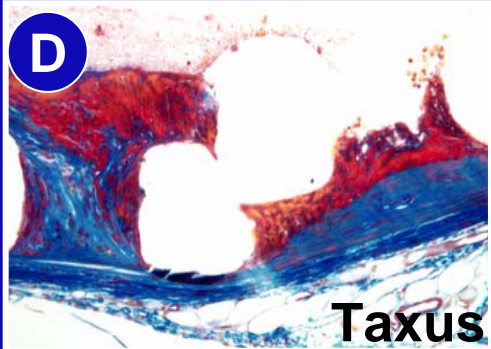
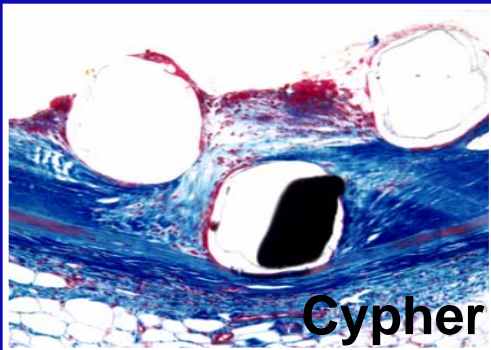
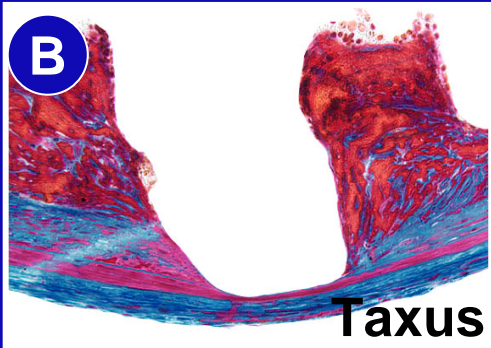
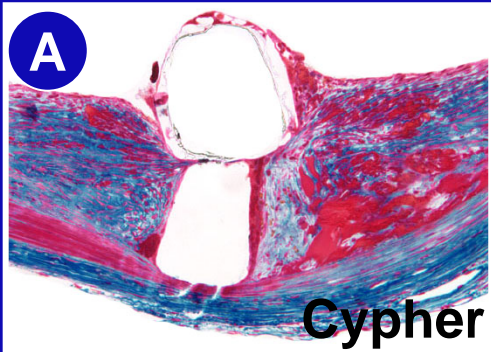
# Overlapping Drug-Eluting Stents (28-days)



## (90-days)

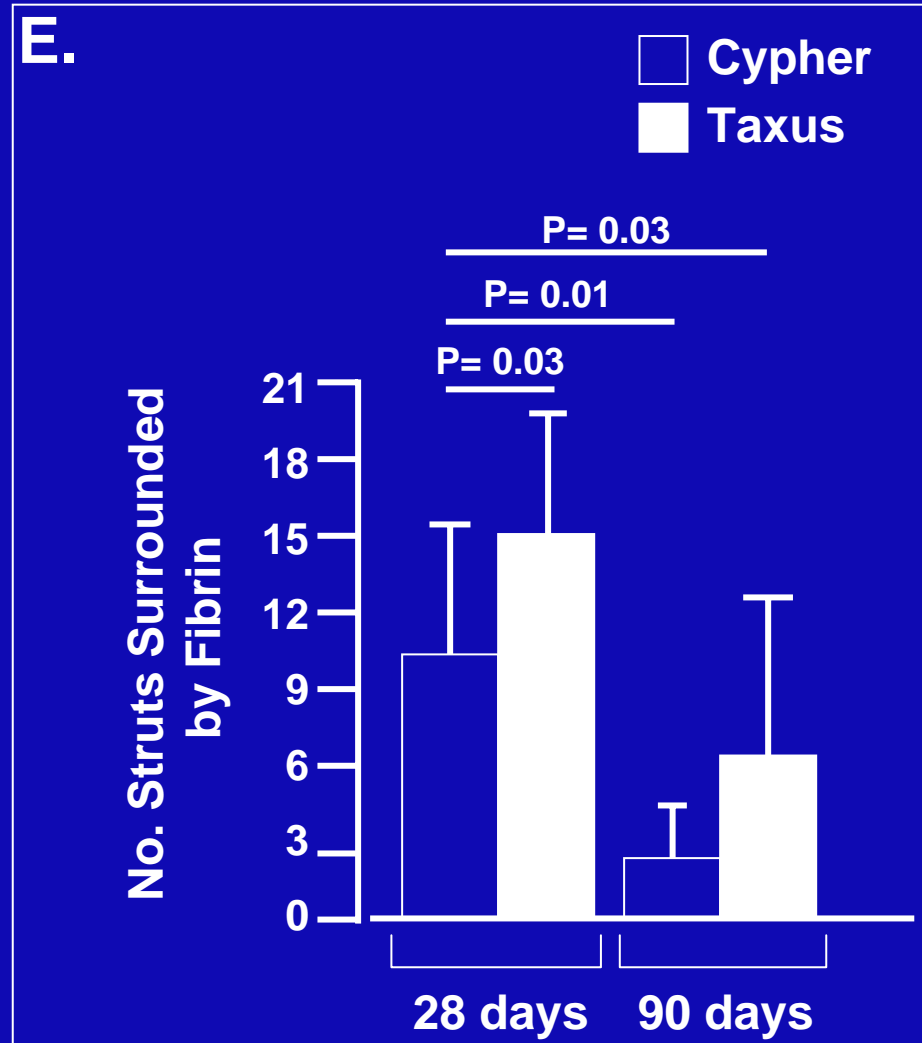


# Overlapped Cypher vs. Taxus: Comparison of peri-strut fibrin deposition

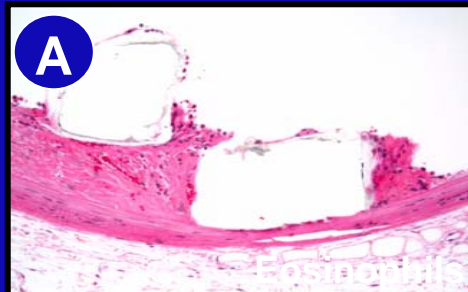


28 days

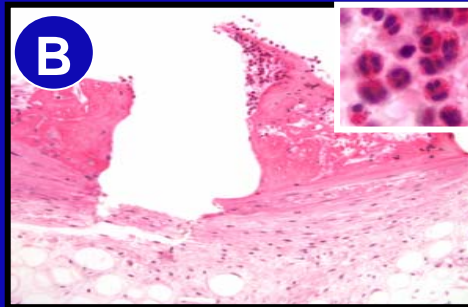
90 days



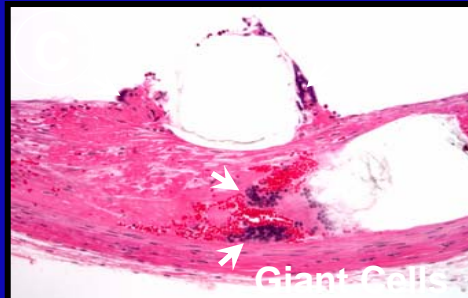
# Overlapped Cypher vs. Taxus: Comparison of inflammatory cells



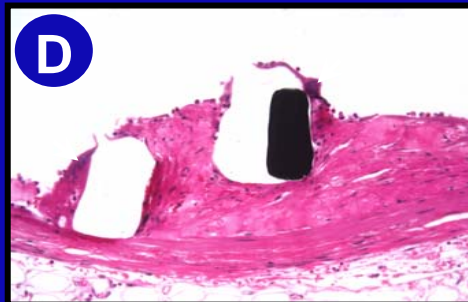
**Cypher**



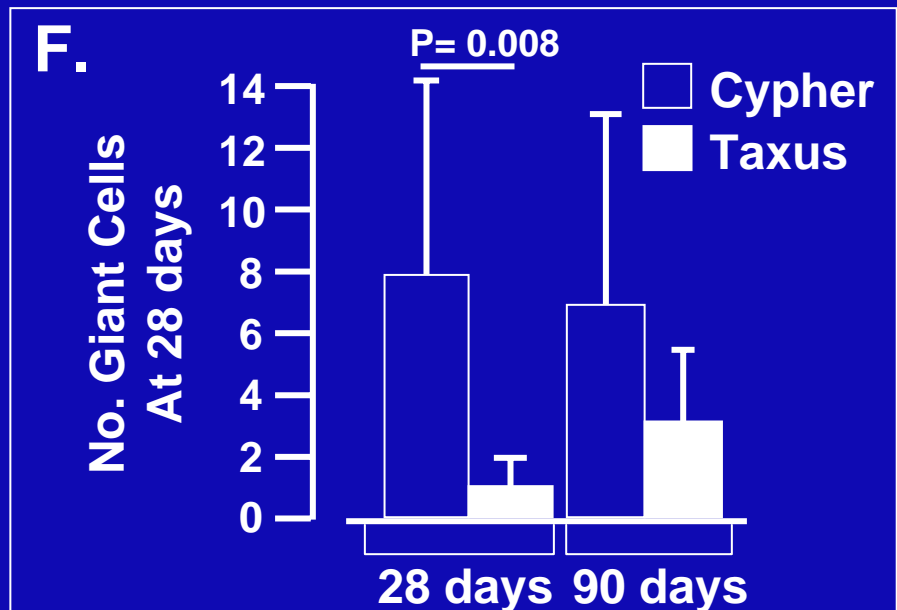
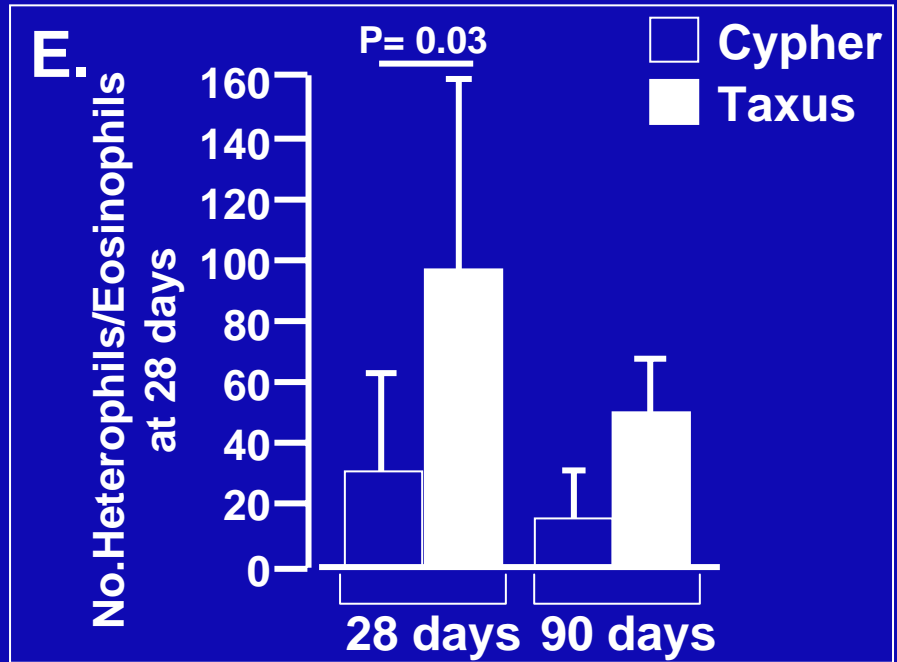
**Taxus**



**Cypher**

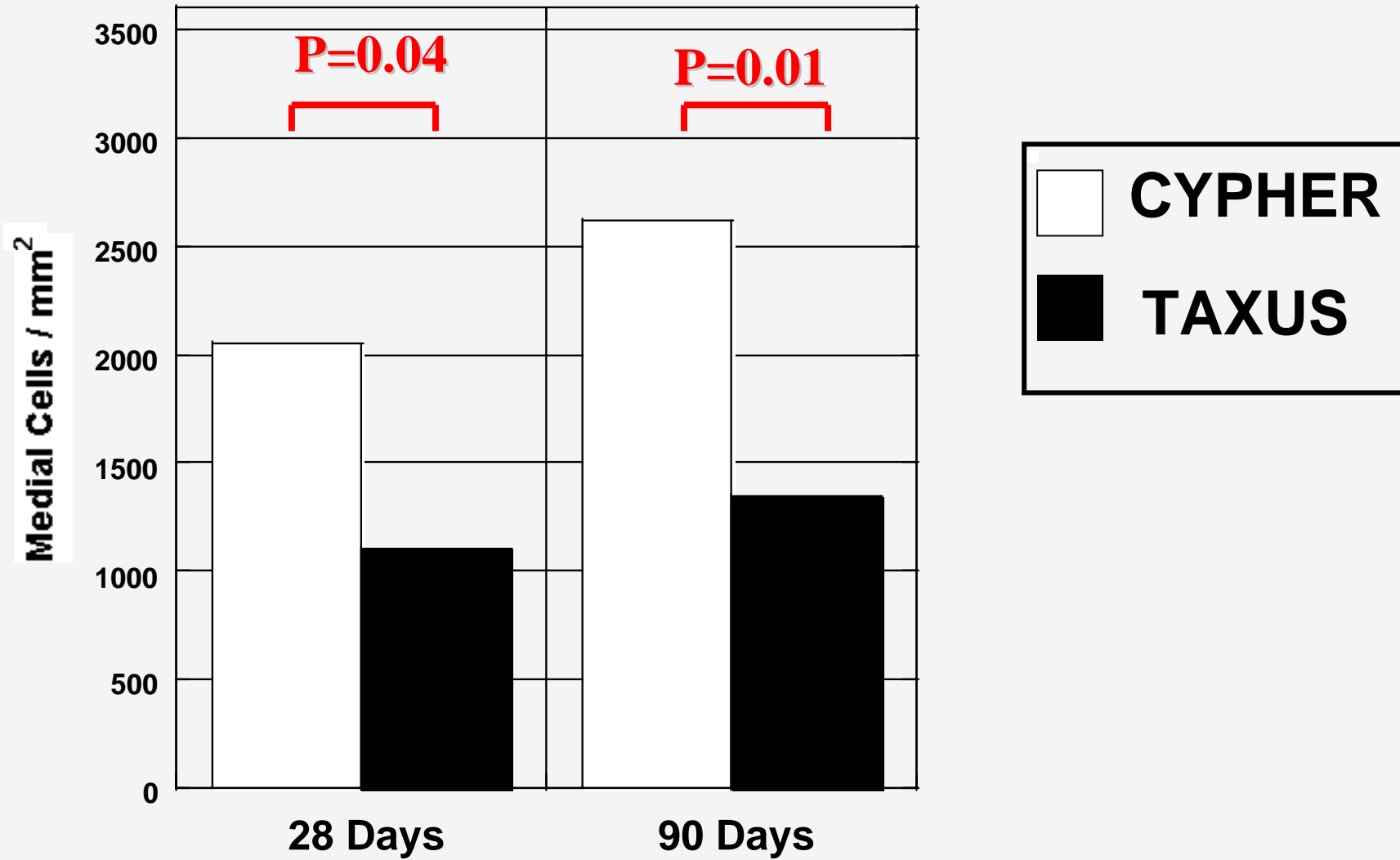


**Taxus**

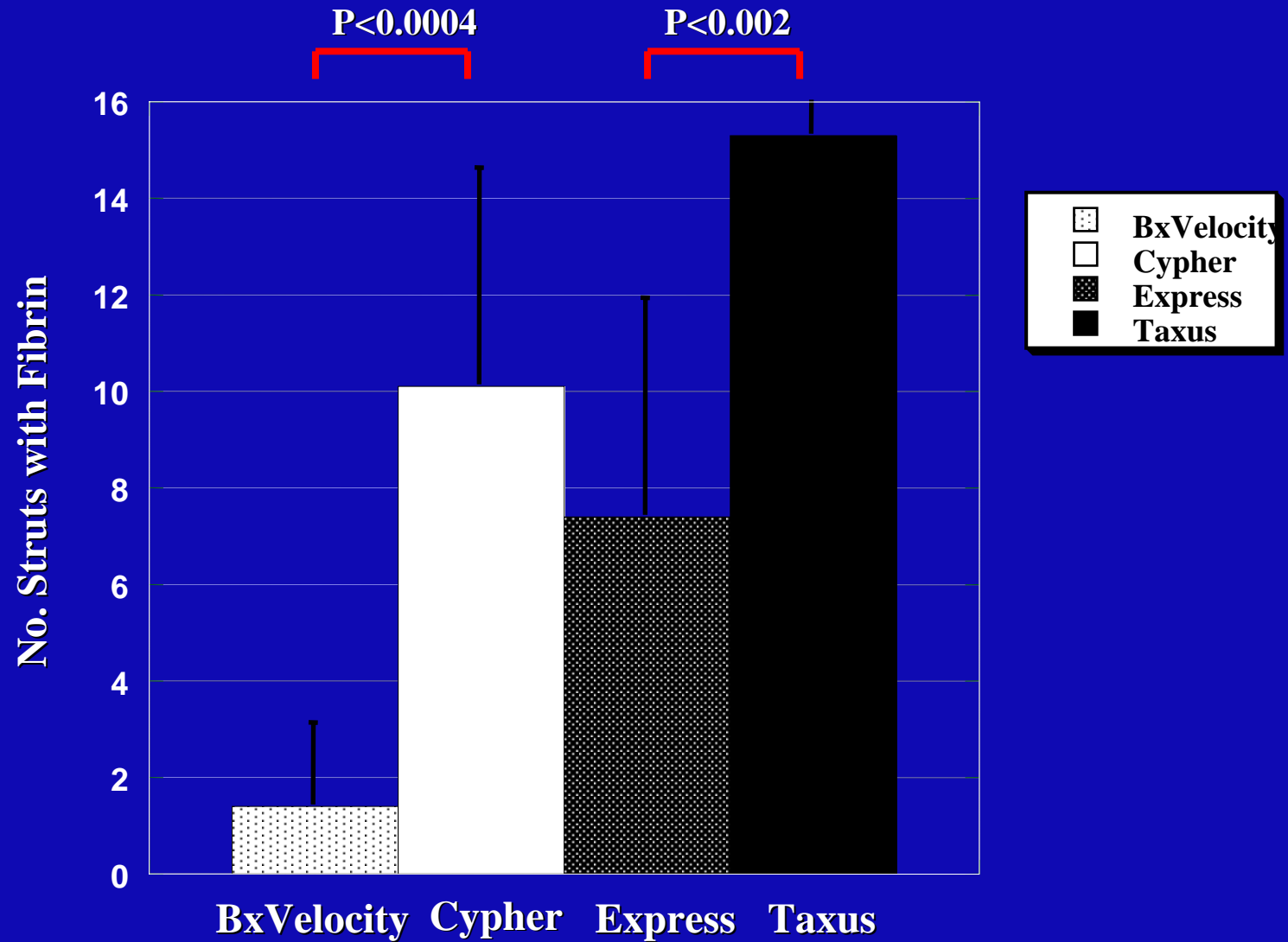




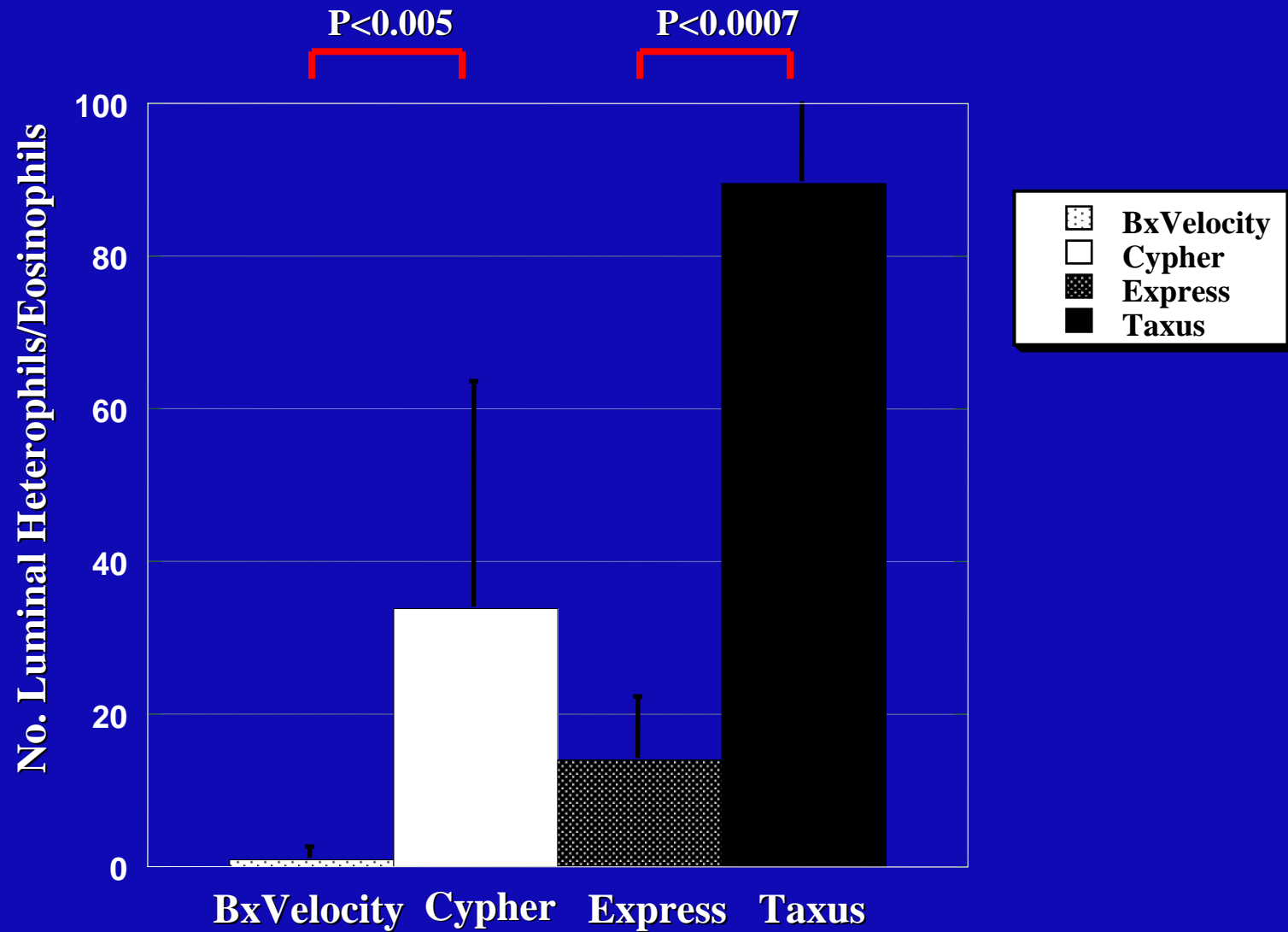
# Overlapped 28 and 90 Day Medial Cell Density



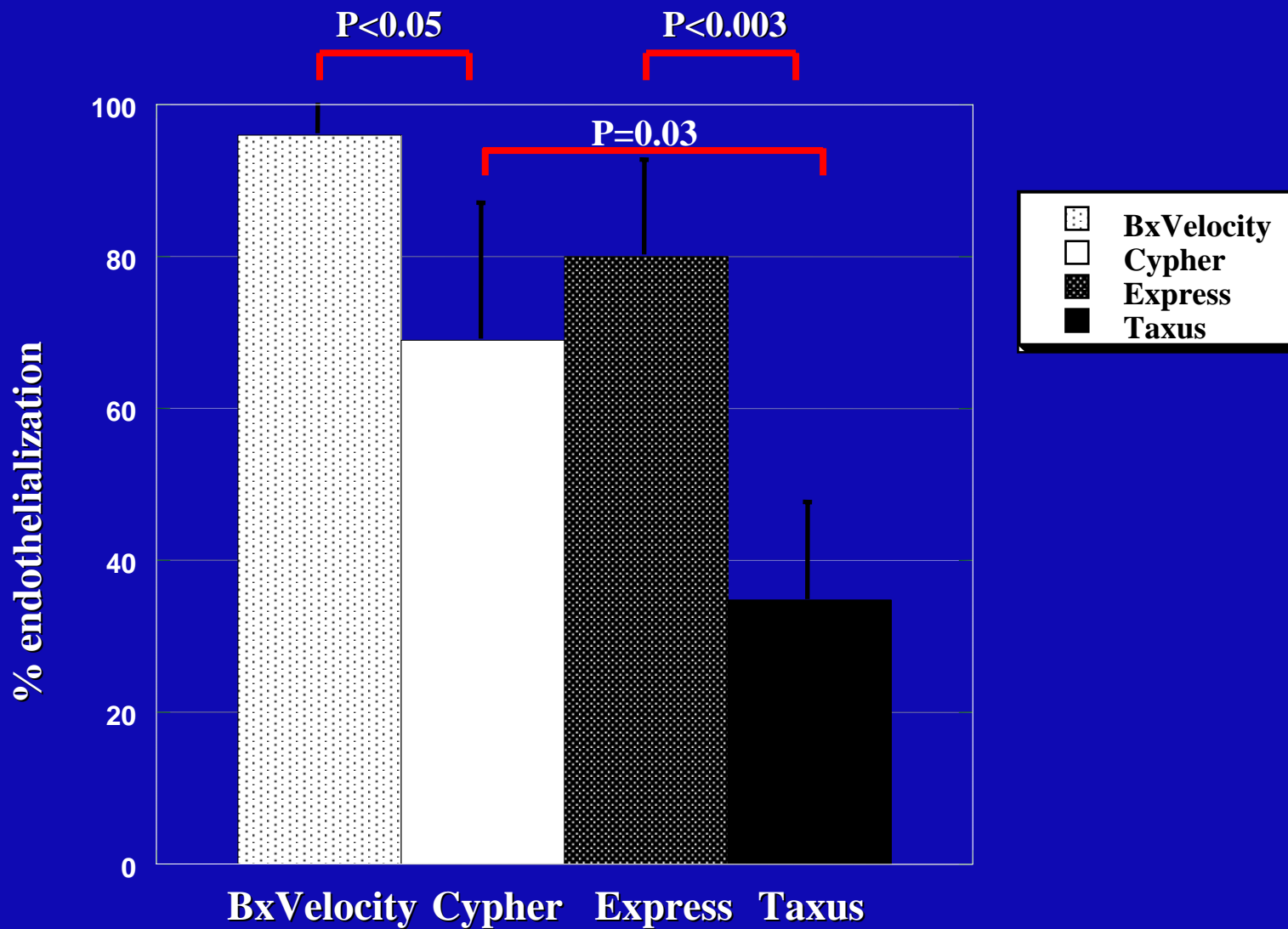
# Comparison of Strut associated Fibrin in Overlapped BMS vs DES at 28d



# Comparison of Luminal Heterophils/Eosinophils in Overlapped BMS vs DES at 28d



# Comparison of % Endothelialization by SEM in Overlapped BMS vs DES at 28d

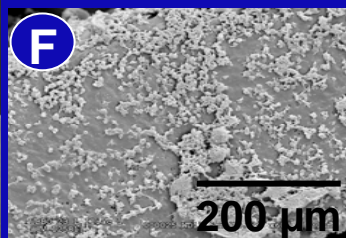
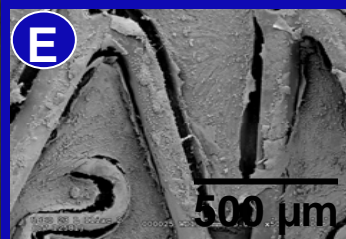
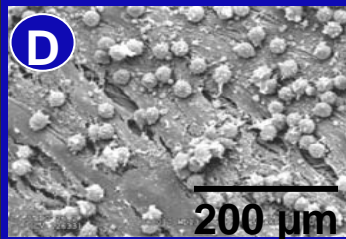
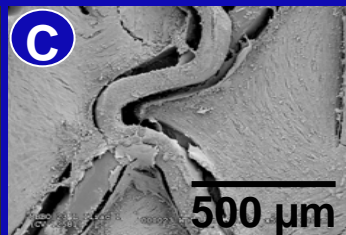


# SEM at 28d

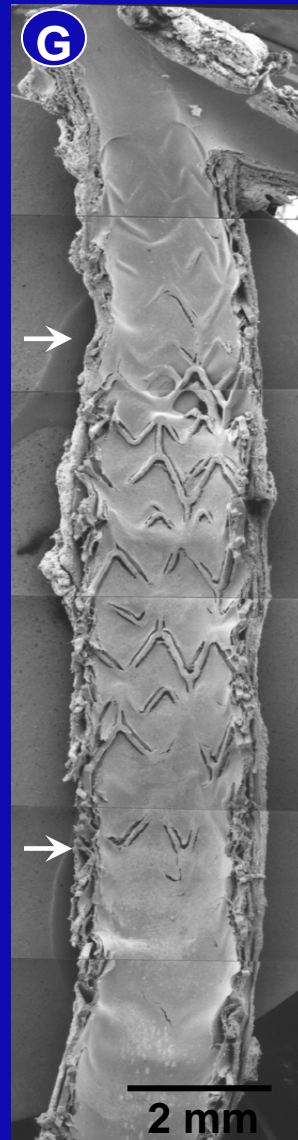
## BxVelocity



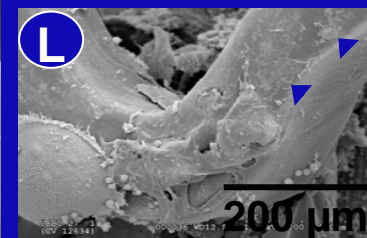
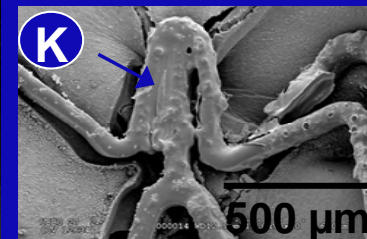
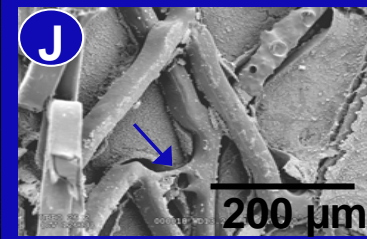
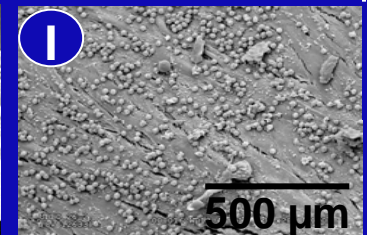
## Cypher



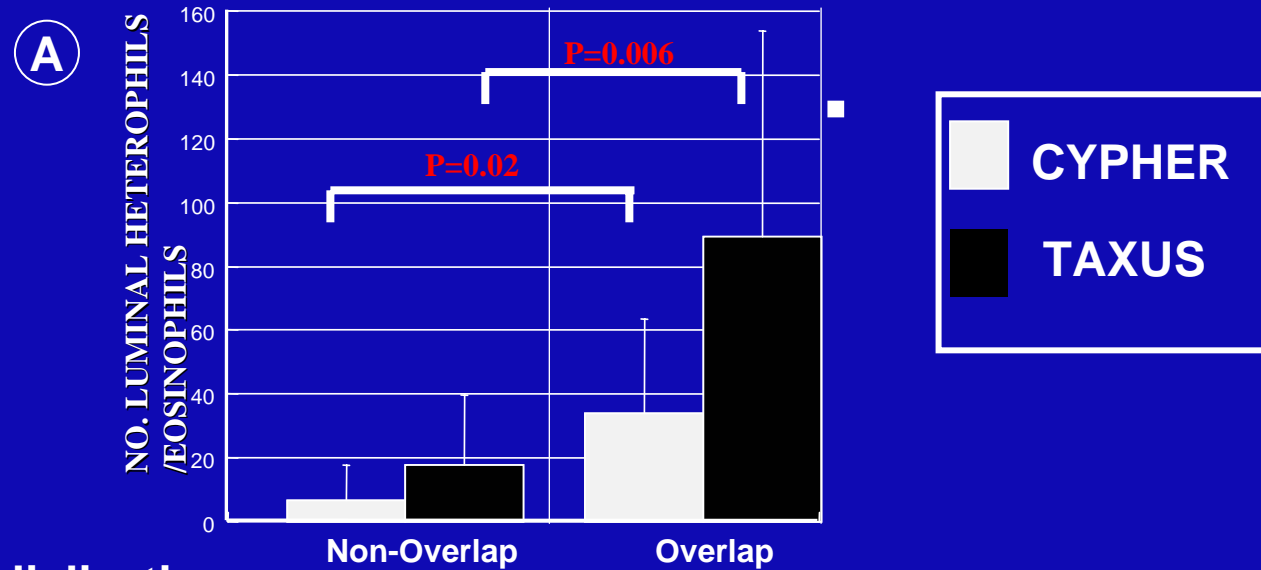
## Express



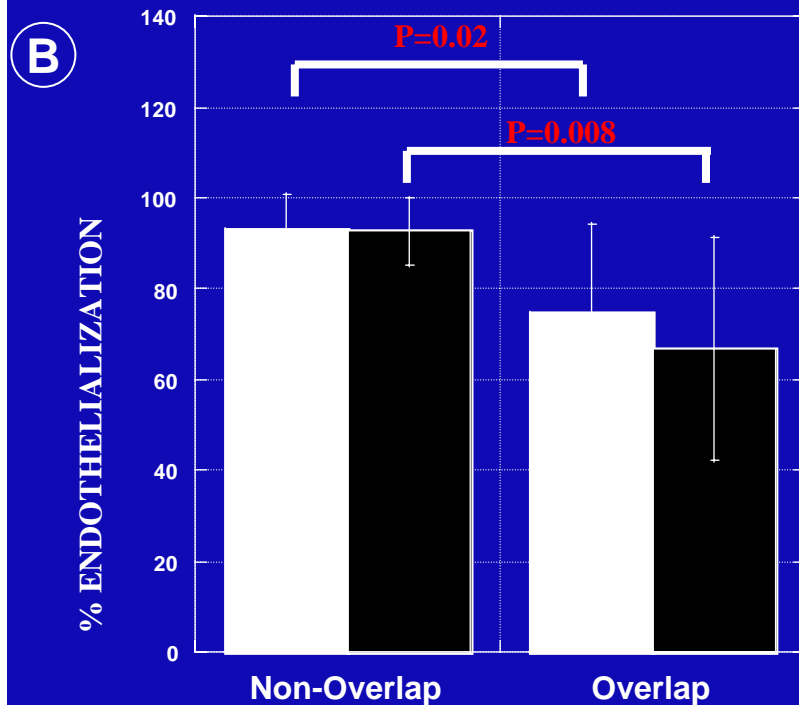
## Taxus



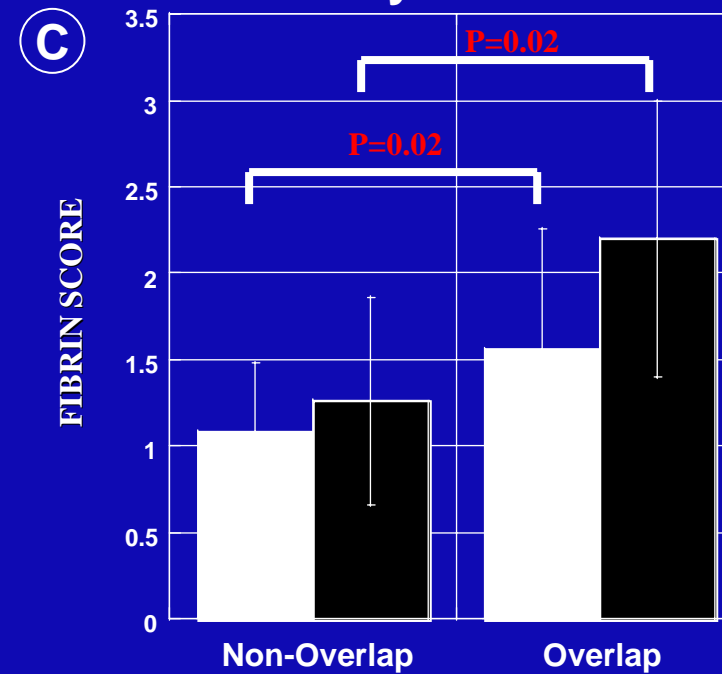
## 28 Day Heterophils/Eosinophils



## 28 Day Endothelialization



## 28 day fibrin score



# Are Current DES Stents Safe?

## Conclusions:

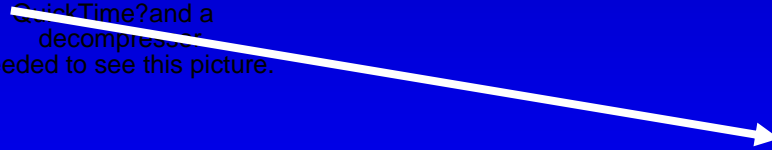
- Cypher and Taxus both inhibit neointimal formation, short term at overlapping sites; CYPHER more than TAXUS in the rabbit model shows persistence of neointimal inhibition long-term, inducing less inflammation and fibrin deposition than TAXUS.
- Human autopsy studies indicate delayed healing (persistence of fibrin) with poor endothelization, delayed total occlusions, excessive inflammation with occasional aneurysm formation and hypersensitivity reaction.
- Long-term studies in complex coronary artery disease are not going to be favorable and may even harm patients either due to drug toxicity (Taxus stent) or polymer induced inflammation (Taxus and Cypher) in select patients

**Good bare metal stent are safer than current generation of DES and do not require continued anti-platelet therapy for a long-time especially in the elderly patients needing surgical intervention.**

# The Clinical Consequences of Long Term Incomplete Healing?

58 yrs old male, one year after implantation of Cypher stent in proximal LAD

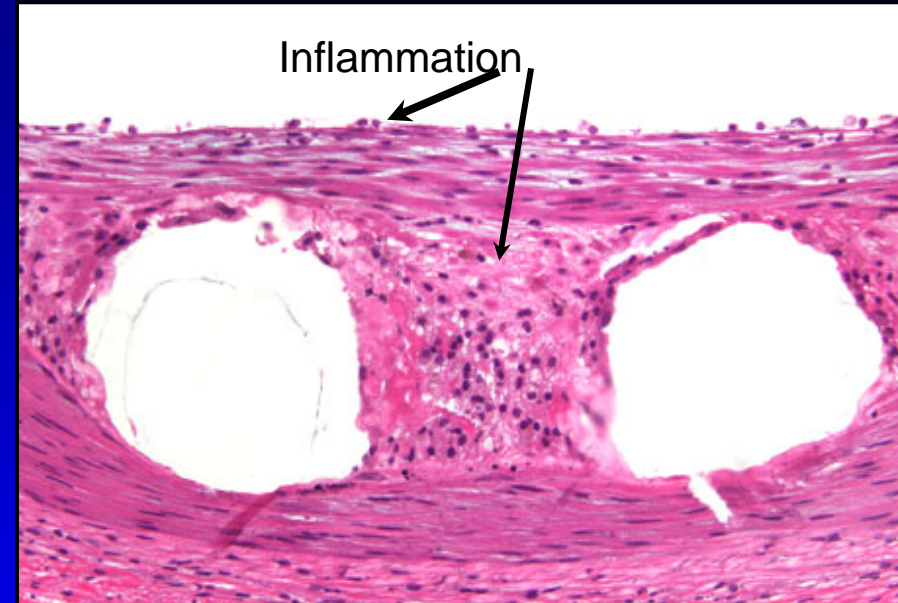
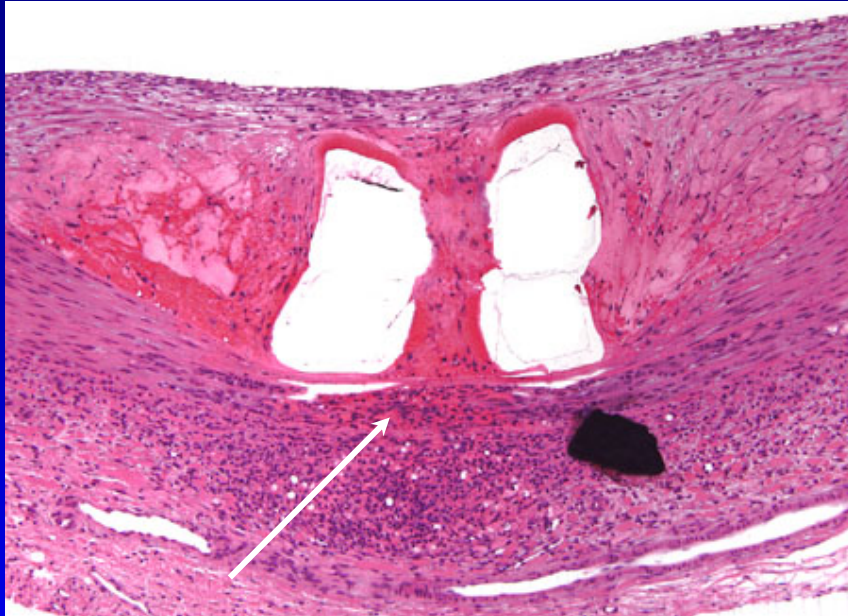
QuickTime?and a decompressor are needed to see this picture.



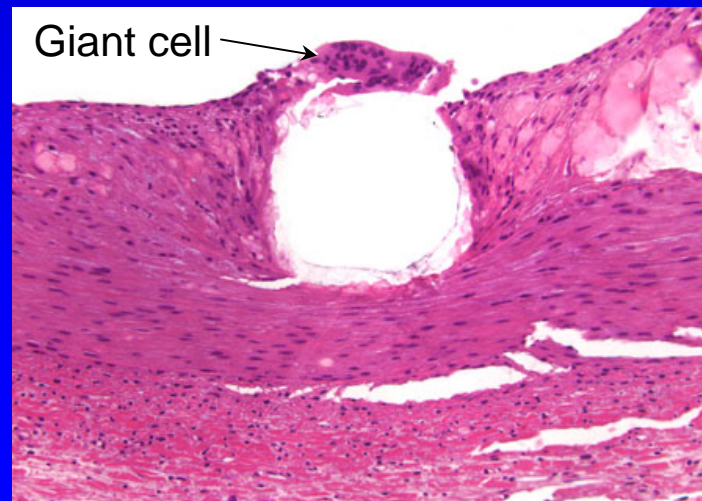
QuickTime?and a decompressor are needed to see this picture.



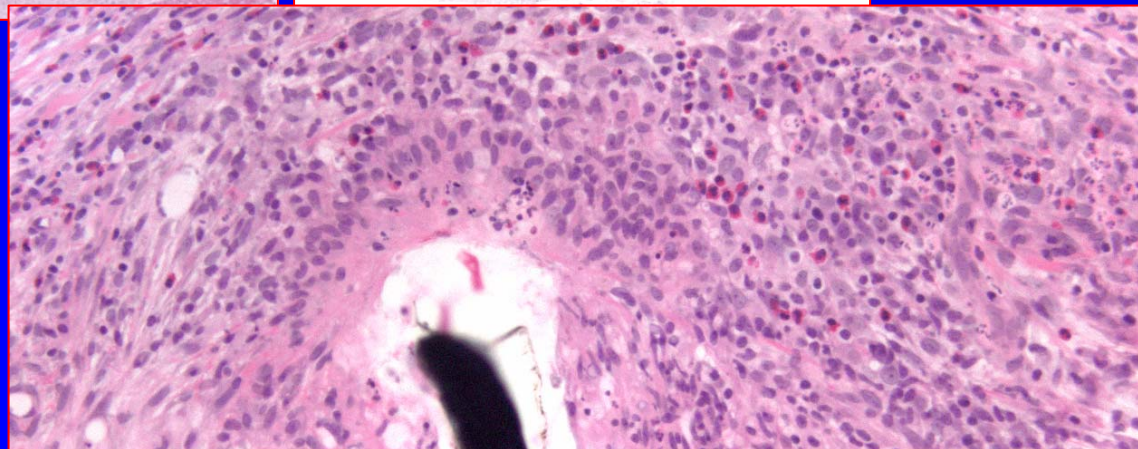
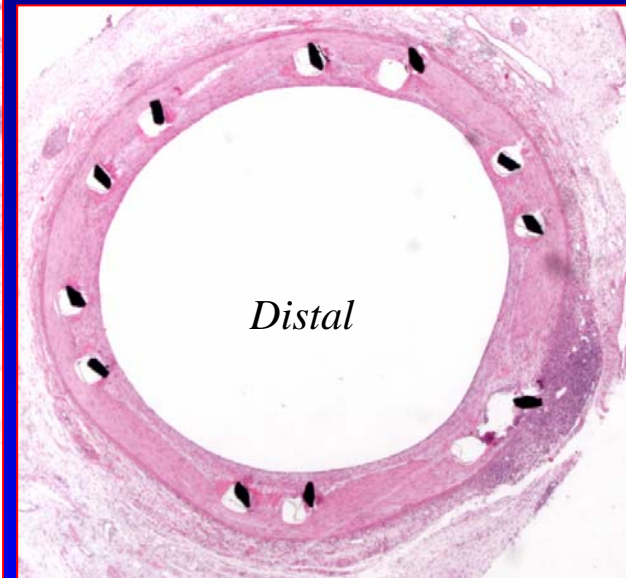
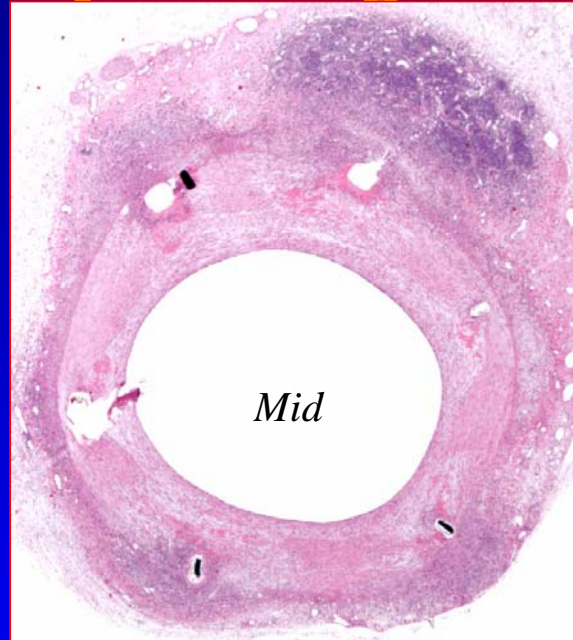
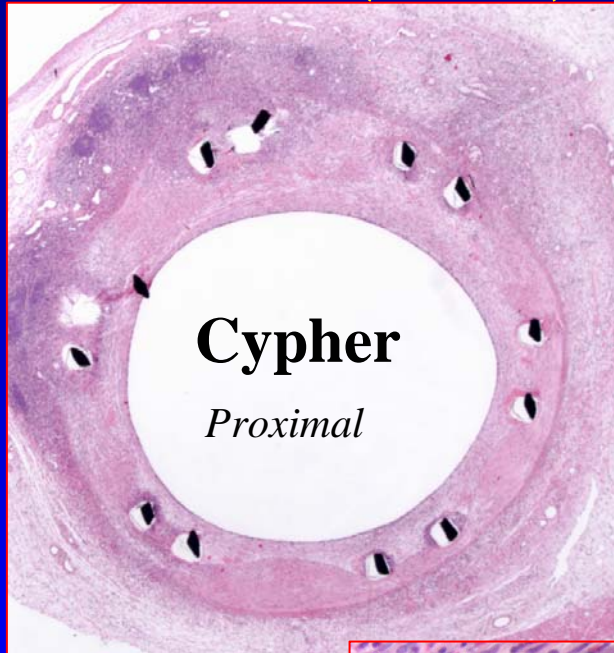
# TAXUS stent induces Inflammation at 28-days in the Coronary Arteries of Pigs



Hemorrhage, medial necrosis, and inflammation (medial and adventitial) in overlapping stents



Cypher DES stents when deployed as a single -  
show a Granulomatous reaction at 28(12.5%)  
and 90 (28%) days in Pig Coronary Arteries



# Taxus Stent: Acute & Chronic Inflammation - at 3 days: 40 yrs F, 1 vessel disease

