Should We Expect "Late Catch-up" (Late Restenosis) after DES Treatment ---- Is the Genie out of the Bottle? You have Simply Postponed the Inevitable

Angioplasty Summit 2004

30th April, 2004

Santorini

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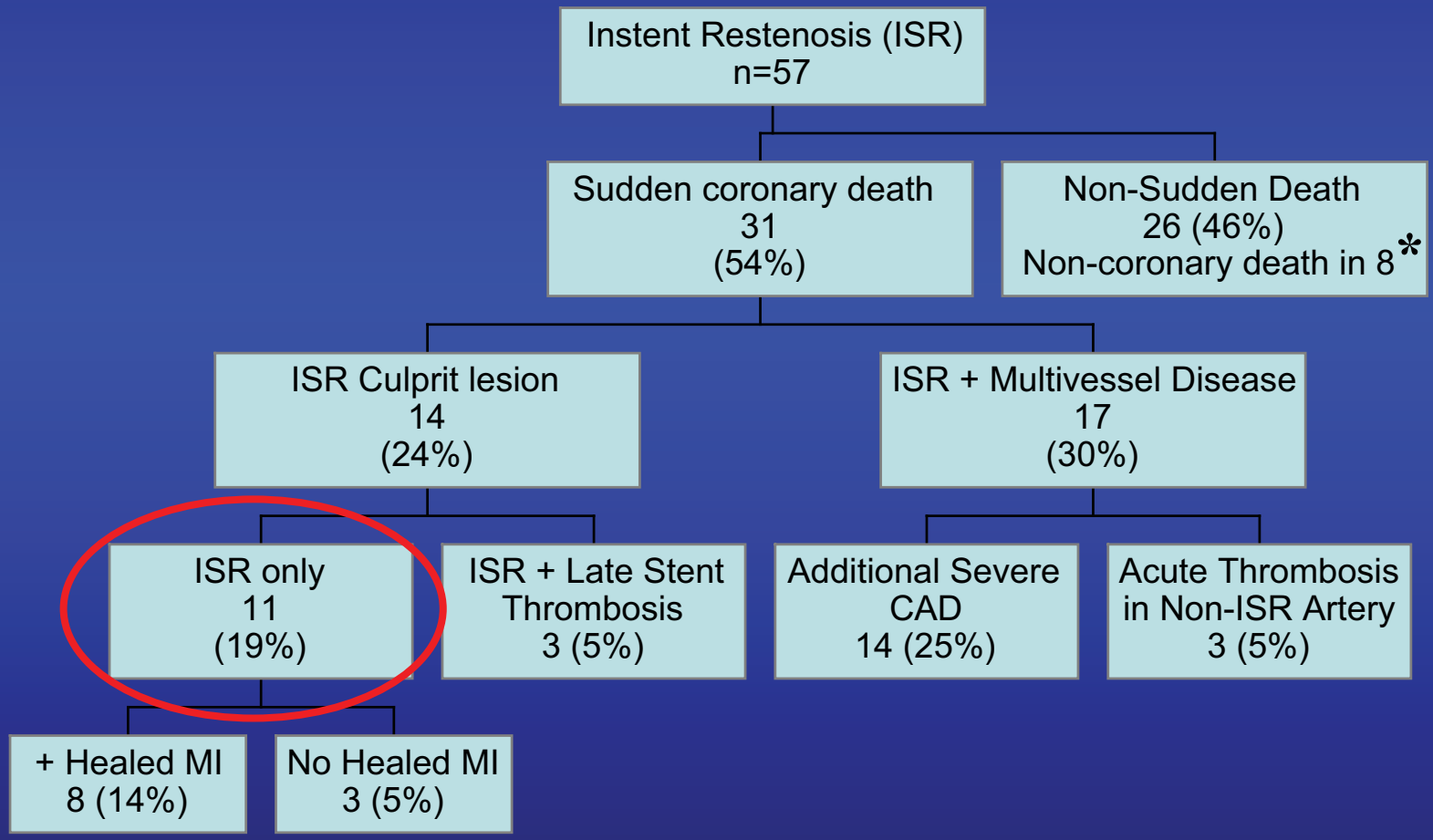
Washington, DC

What is the problem and why we need Drug-Eluting Stents

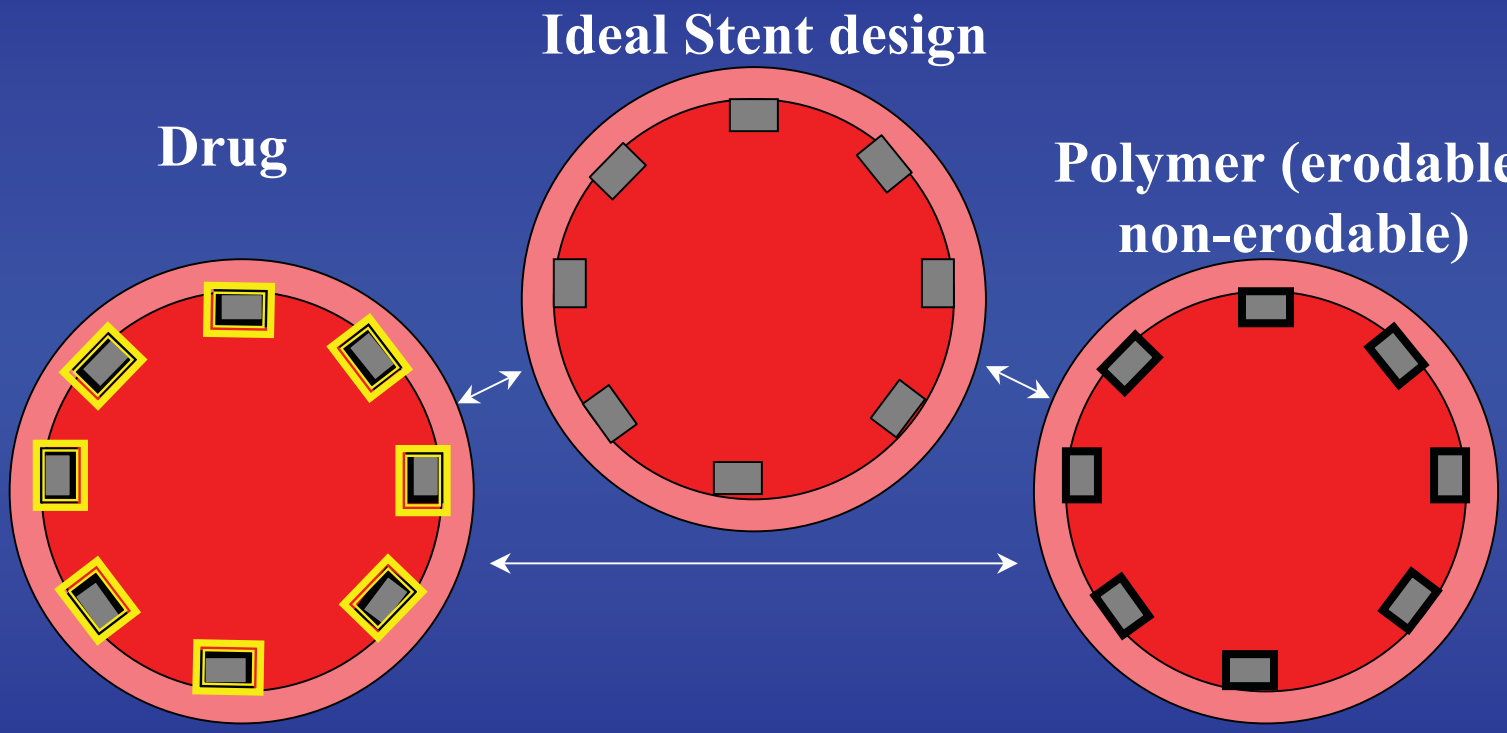
- Incidence of in-stent restenosis by angiography - as high as 30 to 40%
- Incidence of clinical symptomatic restenosis is close to 10 to 15%
- Of the 81 patients who died >3 months following stenting, 57 (70%) patients had ISR, and of these 25 patients (40%) died from severe coronary disease elsewhere (with or without thrombus 17 patients) and from non-cardiac death (8 patients).

In-Stent Restenosis and Sudden Coronary Death



* Post PCI for Instent Restenosis in 5, Post CABG in 5, additional CAD in 5, acute thrombus in 3

Drug-Eluting Stents Comprise a Three-Component System



Drug (lipophylic), binds
to tissues better than to blood,
Cytostatic, and allows endothelialization
while suppressing smooth muscle cell
proliferation and migration

Polymer that does
not induce inflammation
but allows rapid release followed by slow
release of drug over a long period

Polymer Based Drug Delivery

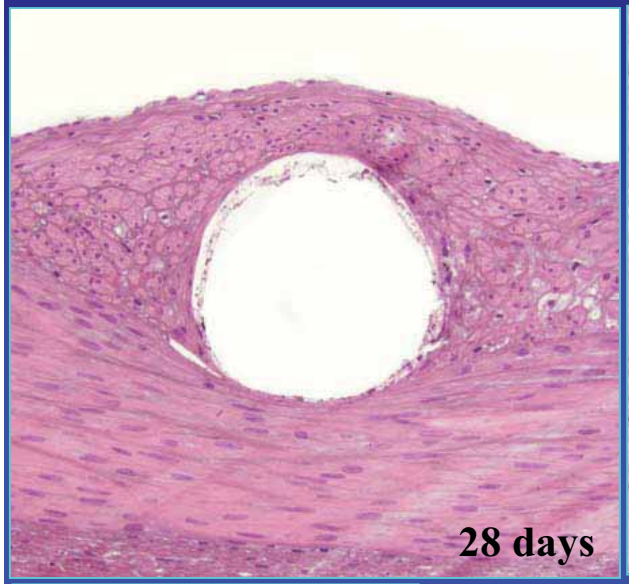
❖ Biodegradable

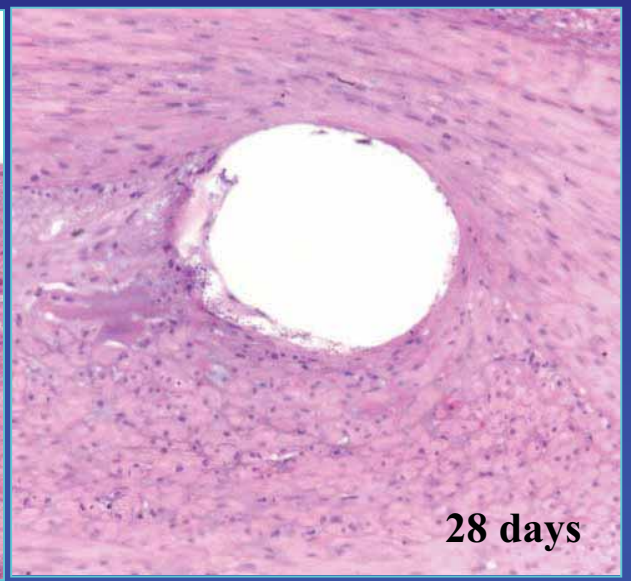
- *Polyglycolic acid/polylactic acid copolymer
- Polycaprolactone
- *Polyhydro-butyrate/-valerate copolymer
- Polyorthoester
- Polyethyleneoxide/polybutylene terephthalate copolymer
- *Copolymeric polylactide

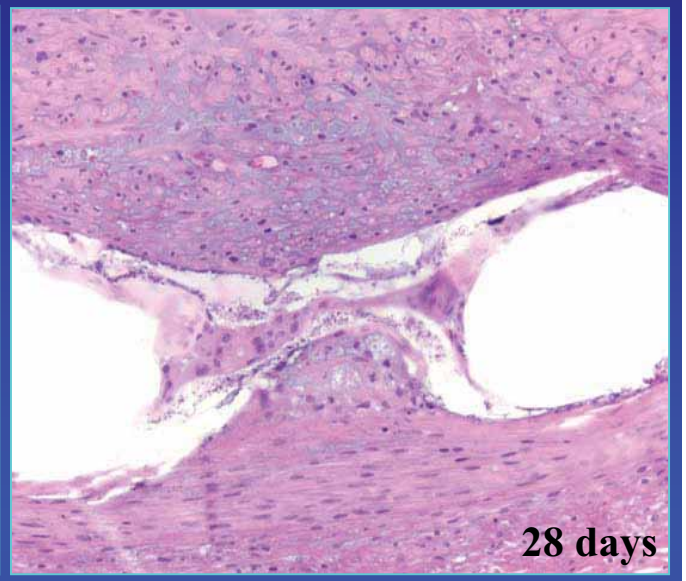
❖ Nonbiodegradable

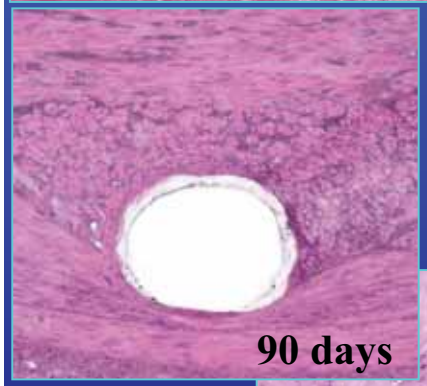
- Polyurethane
- Poly(dimethyl)-siloxane
- Polyethyene terephthalate
- Polyethylene-vinyl acetate copolymer (PEVA)
- Ethylene vinyl alcohol (EVAL)
- Ethylene vinyl acetate (EVA)
- Poly Butyl Methacrylate (PBMA)
- Phosphorylcholine (PC)

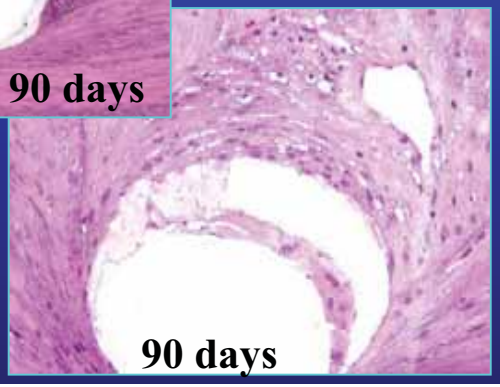
Non-Bioerodable Polymer

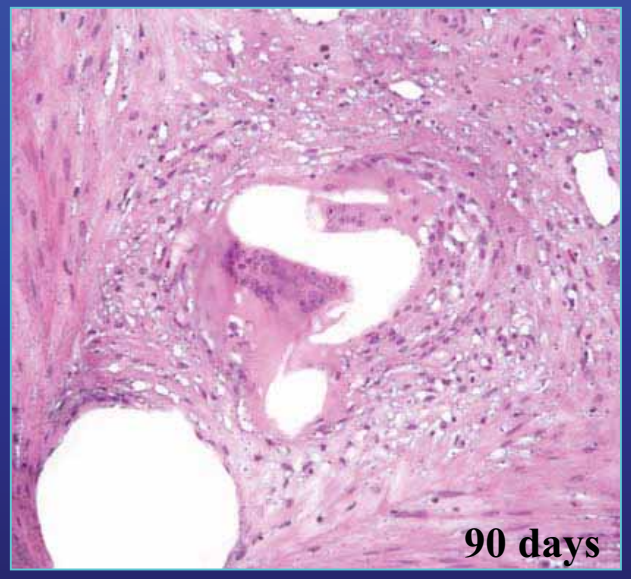


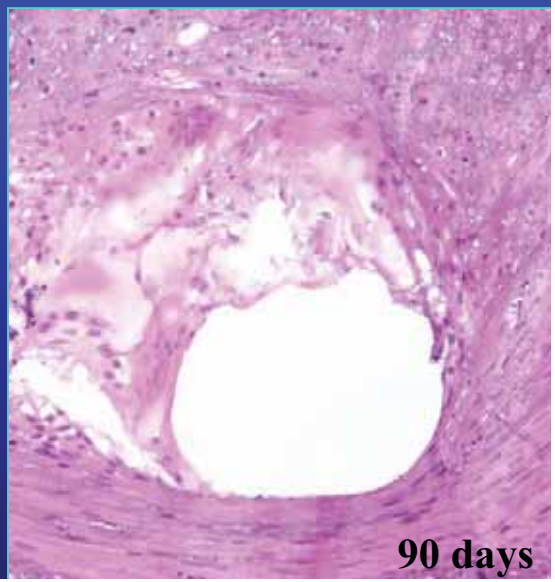




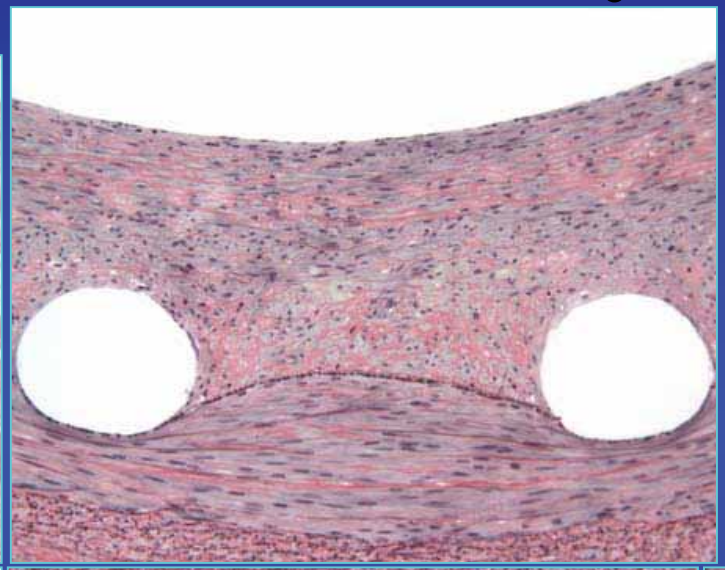


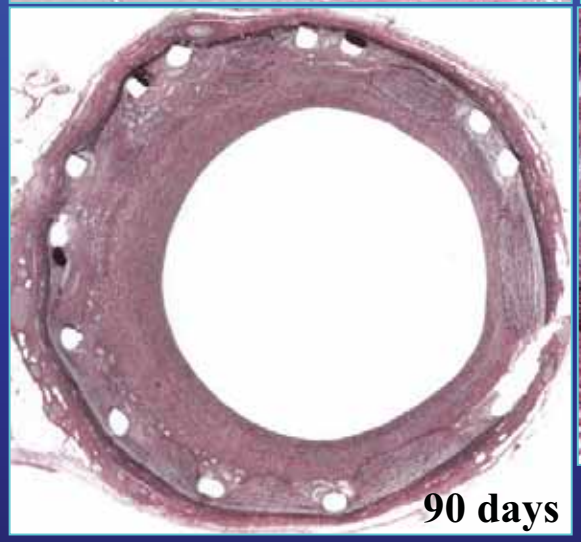


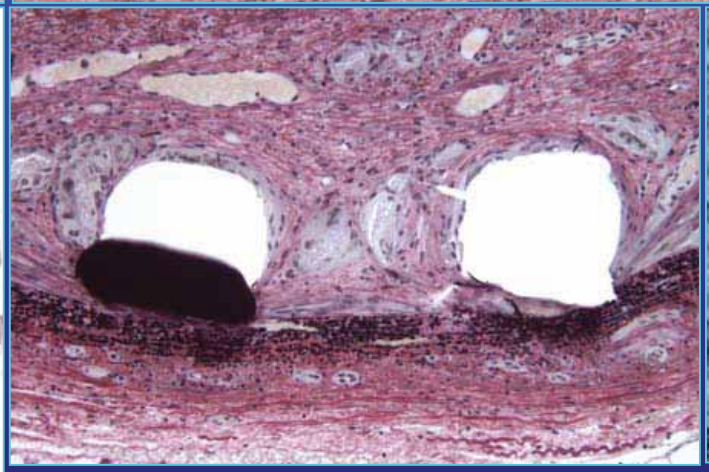


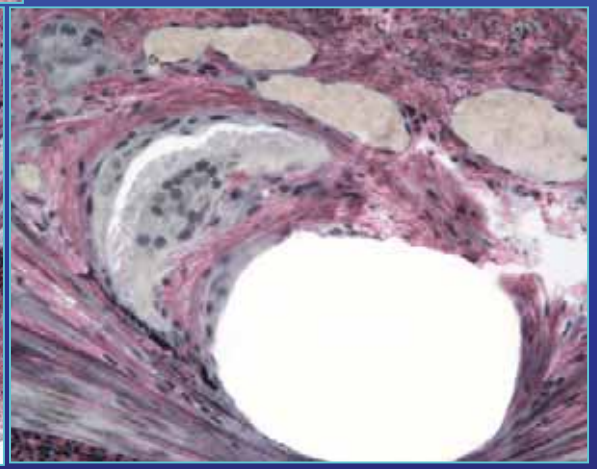


Bioerodable Polymer

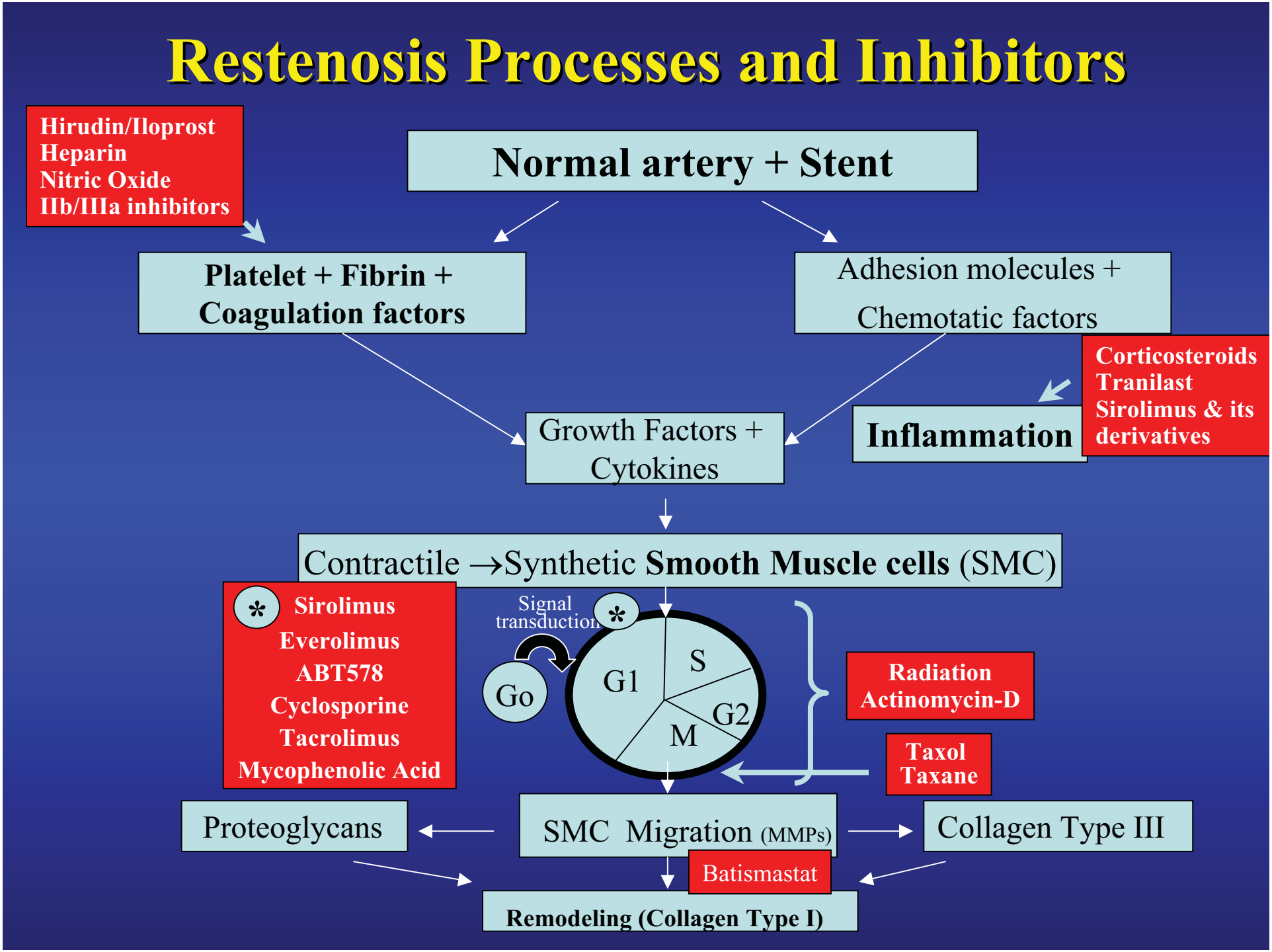








Restenosis Processes and Inhibitors



Morphologic Changes Observed with Various Drugs Used on Stents in Preclinicl Studies Performed in Animals

Sirolimus

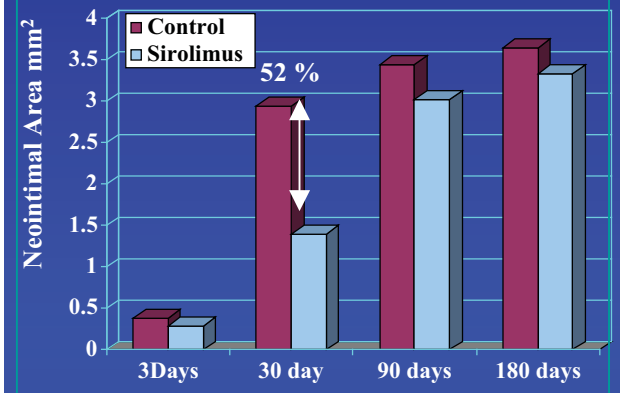
Paclitaxel

Actinomycin-D

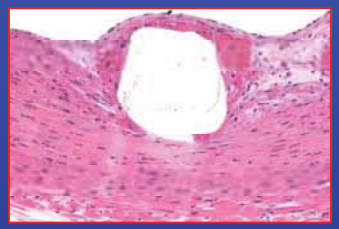
Lessons From Preclinical Studies of DES

Impaired Arterial Healing

Efficacy at 28 days but
no beneficial effect at 90 and 180 days



SIROLIMUS - PIG STUDY



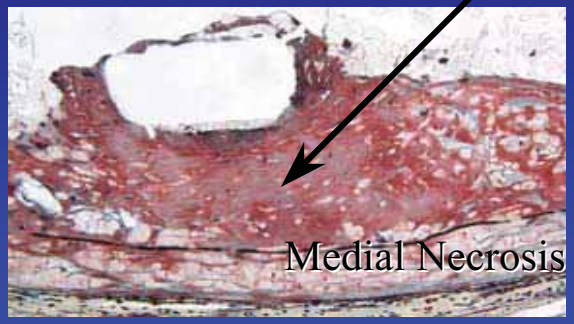
Cypher

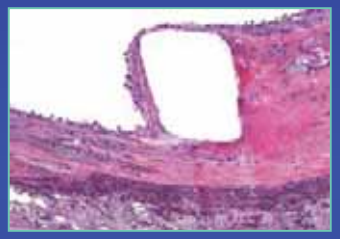
Bx Velocity

Neointimal Decrease - 28 days

Undesirable Effects of DES

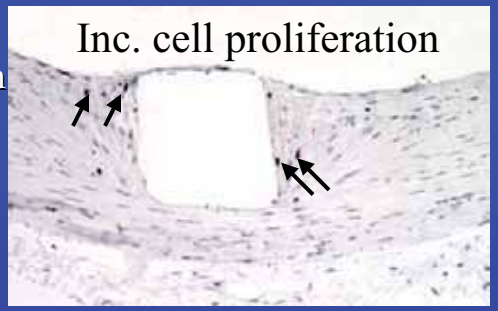
Stent Malapposition

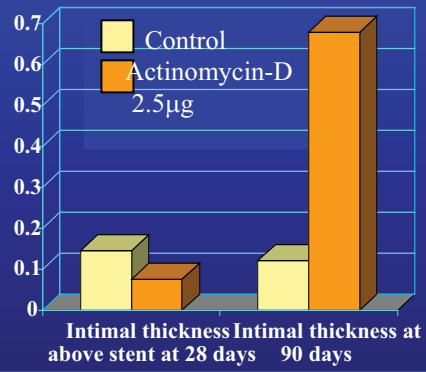




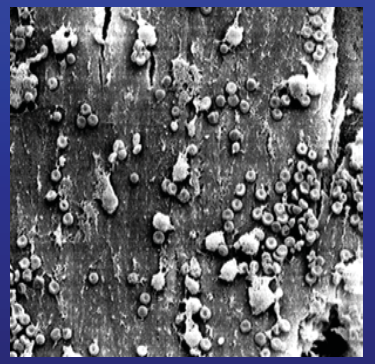
Paclitaxel
Induced
Inflammation
28 days

Hypersensitivity





Incomplete Endothelialization



Pathology of Drug Eluting Stents in Humans

A rare glimpse!!

Human Atherectomy specimens Examined from patients who had received QuaDS-QP2 (7-Hexanoyltaxol)-Eluting Stent or TAXUS Stent

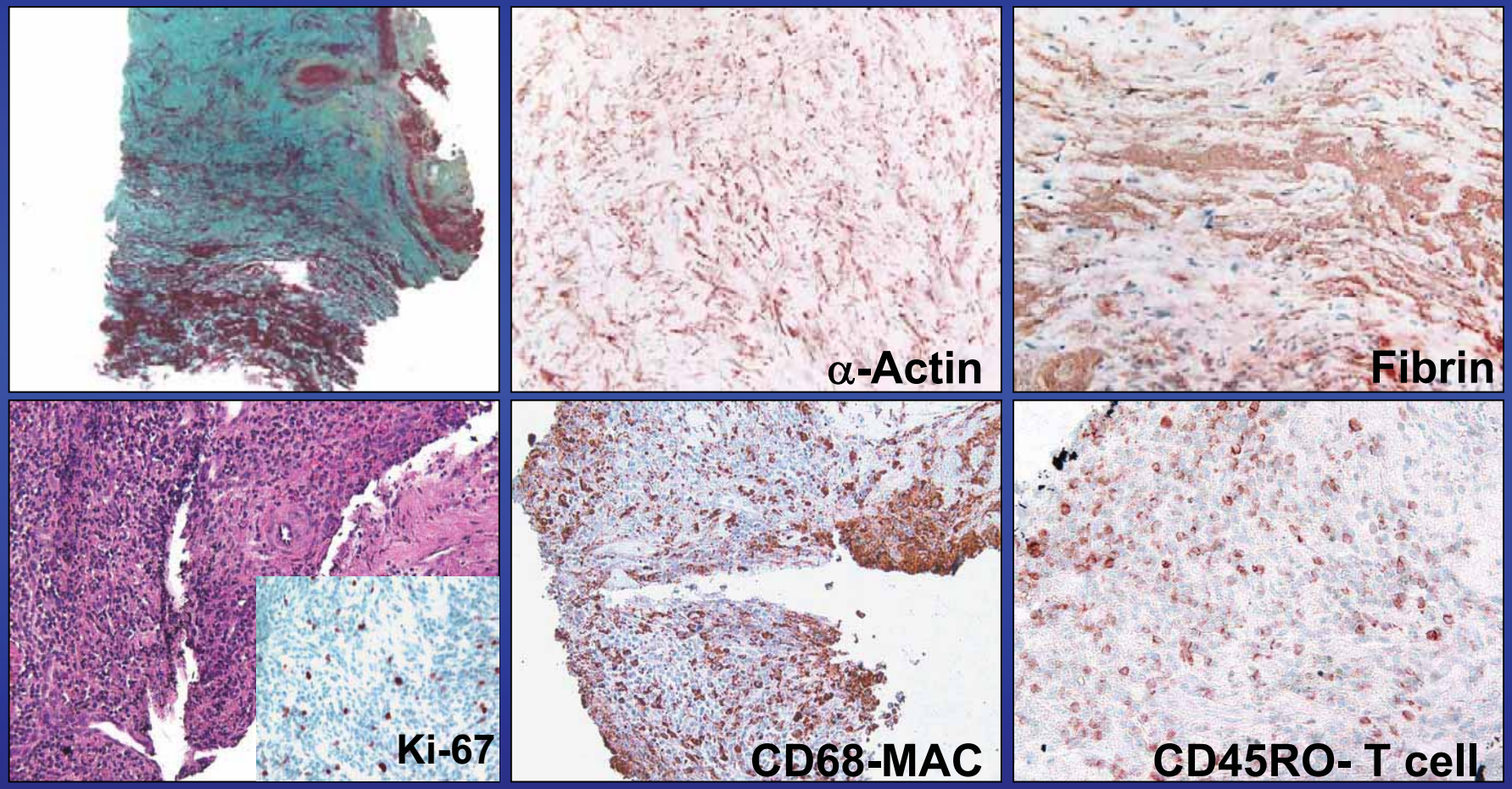
QuaDS-QP2 (7-Hexanoyltaxol) Stent

- Registry of 15 patients with ISR
- 6 months: 3 TLR's, angiographic restenosis 13.3%
- 12 months: Angiographic restenosis in 61.5% (late, late lumen loss)
- In-stent DCA specimens reviewed in 5 pts.
  - 11.2 ± 1.0 months post-stenting
- Mechanisms
  - Toxicity of high drug dose
  - Reaction to plastic sleeve

Liistro et al. Circulation 2002; 105: 1883
Virmani et al. Circulation 2002; 106

Atherectomy From Patient Treated with QuaDS-QP2 for Recurrent In-Stent Restenosis

Patient 2



"Taxane" a paclitaxel derivative 2400 μg for 13 mm stent length

Virmani et al. Circulation 2002

Morphometric Assessment of Atherectomy Specimens From Patients Treated with QuaDS-QP2 for Recurrent In-Stent Restenosis at 11 months

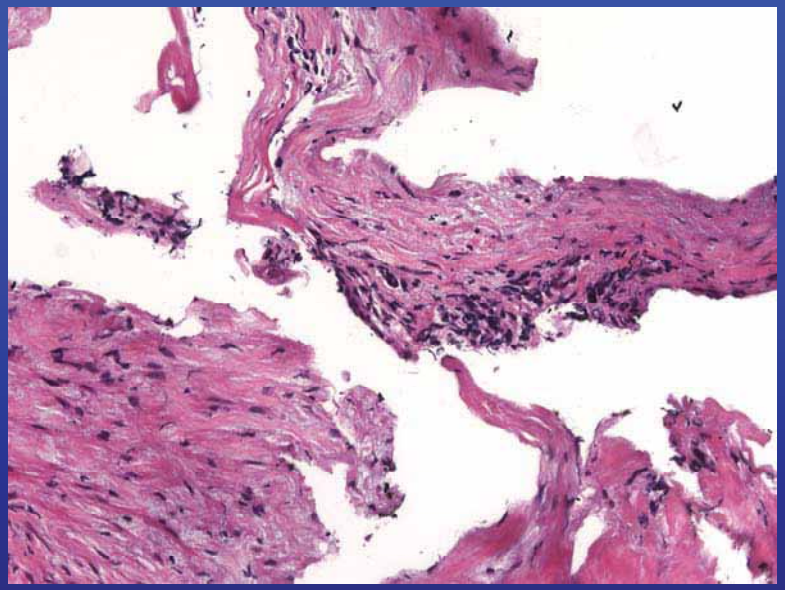
Patient No.	Age/Sex	MLD At 12 months	Restenotic Lesion area (mm^2)	α-Actin (%)	Fibrin (%)	CD68 (%)	CD45RO (mm^2)	*Ki-67 (%)
1	50/F	0.0	4.94	5.45	16.85	4.01	134.13	0.85
2	49/M	1.19	7.13	3.90	10.26	0.63	2.10	0.48
3	67/M	1.59	2.23	3.59	14.46	0.61	0.90	0.41
4	65/M	0.52	3.74	4.60	3.83	0	4.81	0.61
Total	–	–	4.51±2.07	4.38±0.82	11.35±1.82	1.31±1.82	35.48±65	0.59±0.19

*Proliferative index in the restenotic area without inflammation. In the two cases with marked inflammation (patients 1 and 2), the proliferative index was 5.2 and 4.7 respectively. [α-Actin= smooth muscle cells, CD68= macrophages, CD45RO= T cells.]

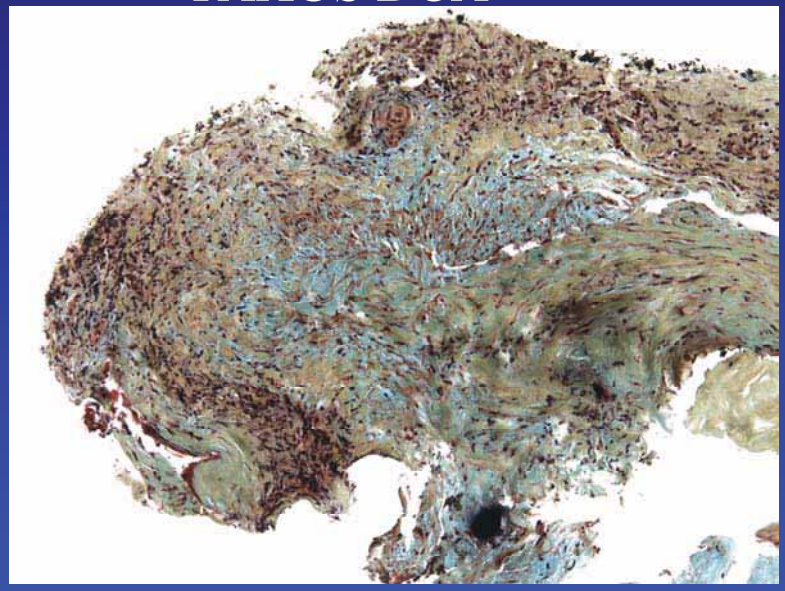
Virmani et al. Circulation 2002

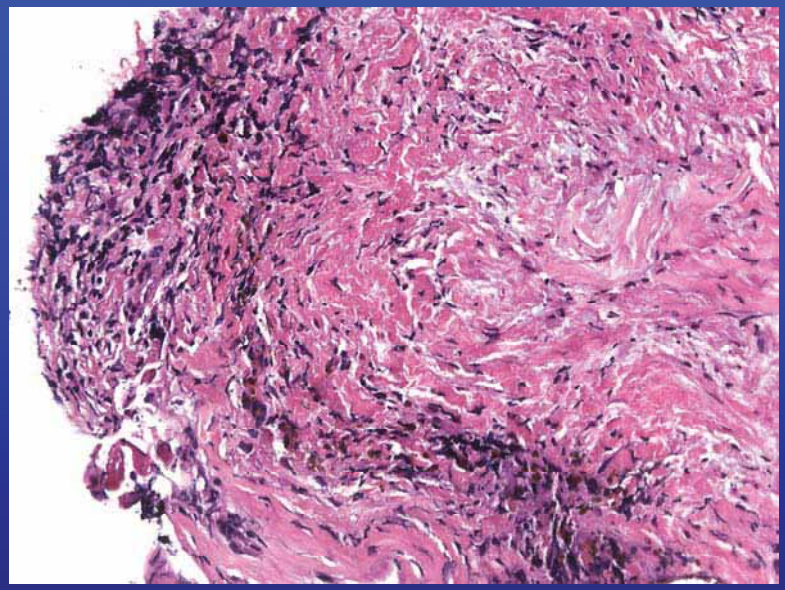
60-year -old man 6 mo post stent deployment

BMS DCA



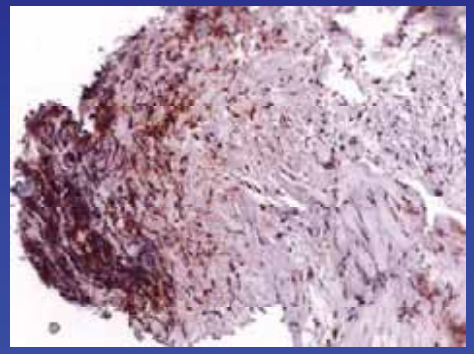
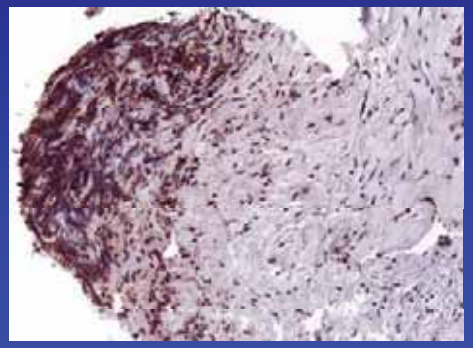
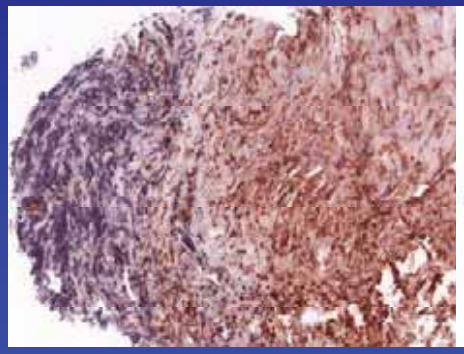
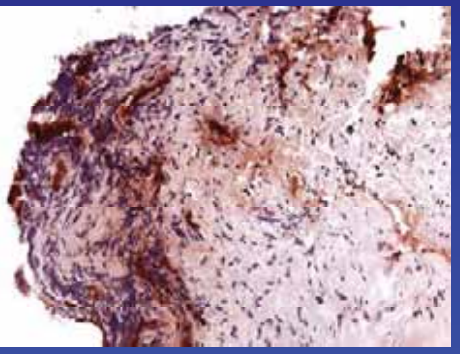
TAXUS DCA



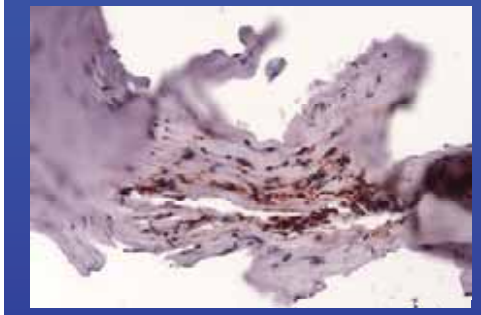
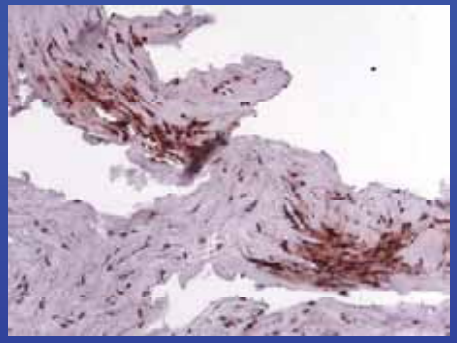
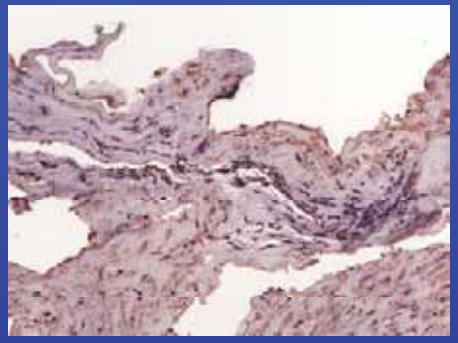
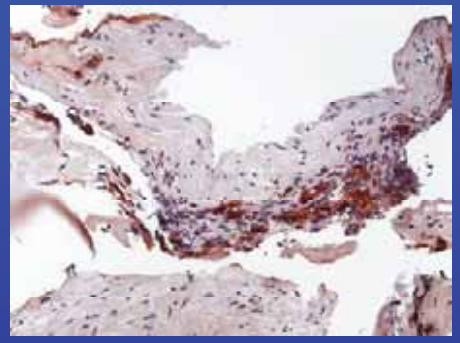


Increased chronic inflammation
& hemosiderin

TAXUS DCA

KP-1 (Mac) | T-cell | Actin | Factor VIII

BMS DCA

Is there a problem with Boston Scientific's TAXUS? (NY Times 23rd April, 2004)

- 27 to 30 patients had adverse events involving the Taxus stent caused by an inability to separate the balloon from the expanded Stent.
- Of these 5 patients had to undergo surgical removal of the device with coronary endarterectomy and bypass surgery.

- A French report from 2 catheterization laboratories (Lyon and Brest) that performed bench tests claim:
  - ✓ Paclitaxel coating is sticky and non uniform leading to mechanical difficulties after stent implantation.
  - ✓ Paclitaxel local concentration may vary within the stent
  - ✓ Manufacturers quality control is questioned

Lynne Peterson, April 2004, Trend's in Medicine

Patient underwent endarterectomy after a TAXUS stent placement that resulted in a dissection, an Express stent was placed however, the dissection extended and a second Express was placed. While withdrawing the balloon it got stuck at the TAXUS stent and had to be removed surgically.

ACTION STUDY
Actinomycin-D Eluting Stent

- 2.5 and 10 μg/stent
- Increased in-stent and stent edge neointimal growth
- Increased TLR
- Increased MACE
- Trial halted

Patrick W. Serruys, JACC, In Press

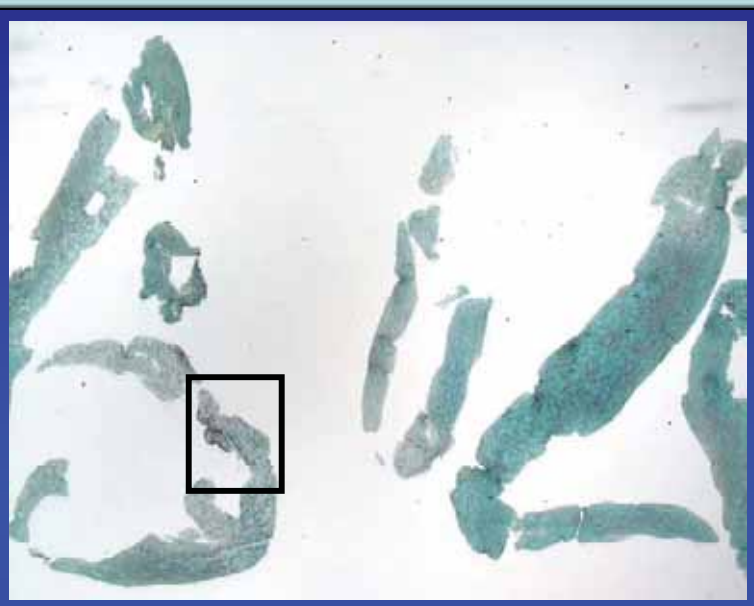
Table 1. Morphologic analysis of lesion components and cell proliferation in human atherectomy specimens from actinomycin D-eluting stents

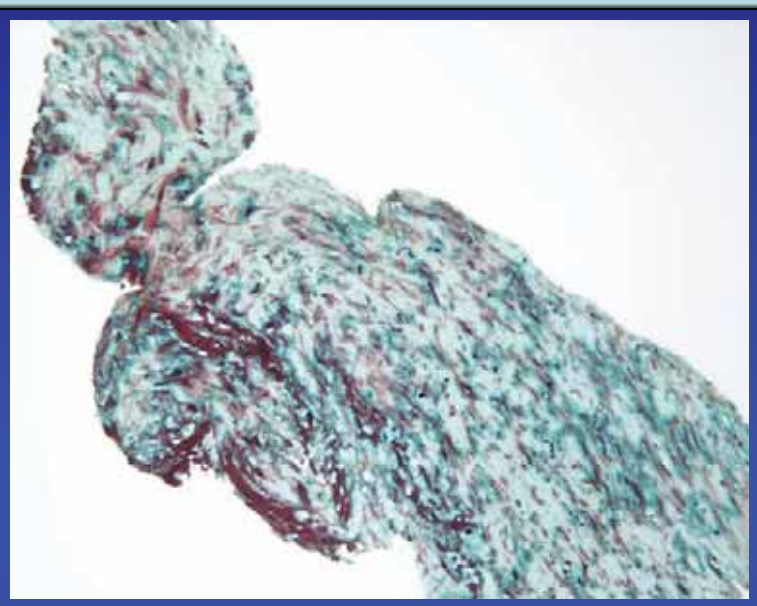
Restenosis	Age (years)	Area (mm^2)	SMCs (%)	MΦs (%)	T-cells (mm2)	Fibrin (%)	Ki-67 (%)
Pt. 1	58	13.28	12.6	0.08	0.08	5.9	0.13
Pt. 2	63	10.90	18.3	0.10	0.10	1.0	0.43
Pt. 3	78	2.80	3.8	0.17	0	26.0	0.81
Pt. 4	-	11.69	1.4	0	0	0.1	0.38
Total		9.67±4.69	9.0±7.8	0.09±0.07	7.8±9.7	8.2±12.1	0.44±0.28

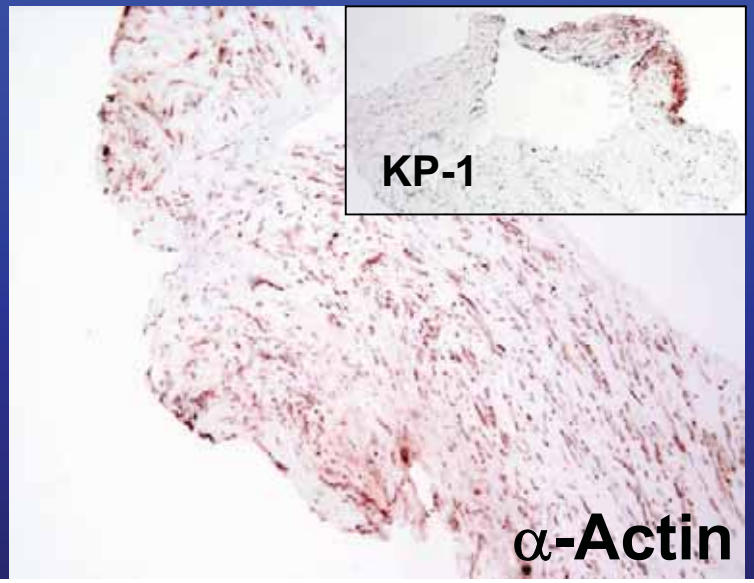
* Two patients received actinomycin-D dose 2.5 µg/cm^2, one 10 µg/cm^2 and one unknown. At trial mandated 6-months follow-up severe stenosis was found in all 4 patients and underwent DCA.

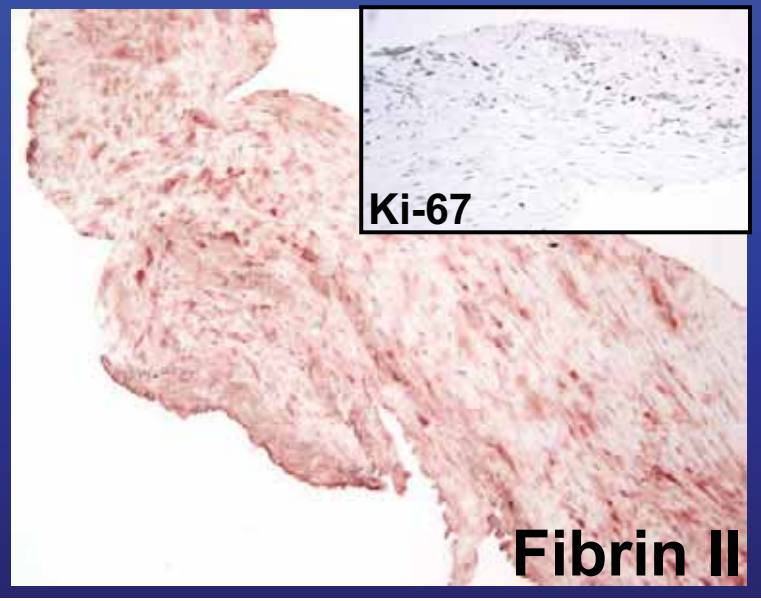
John Ormiston 2004

Atherectomy From a Patient with In-stent Restenosis in an Actinomycin D Eluting Stent









AFIP Experience at Autopsy Following Cypher Stent Placement

Patient age/Sex	Indication	CA	Interval stent to †	Cause of death	Thrombus at stent site	Inflammation
37 F	MI (non-Q)	LAD/LOM &LCx	7 days	AMI	Occlusive	Minimal
51 M	AP with in-stent restenosis	LCx & distal RCA	10 days	SD -CAD	Minimal	Occasional
65 M	Recent AMI	LAD prox	38 days	Stroke, stent thrombosis	Occlusive	Absent
61 M	AMI	LCx/ PD	4 months	SD-CAD	Non-occlusive	Severe
71 F	Asymptomatic	LAD	16 months	Stroke -AMI	Small thrombus side branch	Occasional giant cells
58 M	UAP (E-SIRUS)	LCx	18 months	AMI thrombus	Occlusive	Severe
61 M	Asymptomatic, (FIM)	RCA	4 year (AS+MS, 1year †)	Plaque rupture-stroke	None	Minimal

October 29, 2003 FDA Advises Physicians of Adverse Events Associated with Cordis CYPHER™ Stents

- CYPHER™ stent approved in April 2003 for patients undergoing PCI, since its approval 450,000 units have been distributed worldwide (>260,000 US and >180,000 Outside US). To date FDA has received 290 reports (>260 US and >25 Outside US) involving subacute (occurring between 24 hours and 30 days post procedure) thrombosis (SAT) associated with CYPHER™ stent. More than 60 reports of SATs were associated with patient death. Also, more than 50 reports, including some deaths, that Cordis considers possible hypersensitivity reactions.
- "We have received numerous reports of adverse events for CYPHER™ stent through MDR system, which is subject to significant under reporting."

FDA Talk Paper, 2003

- .

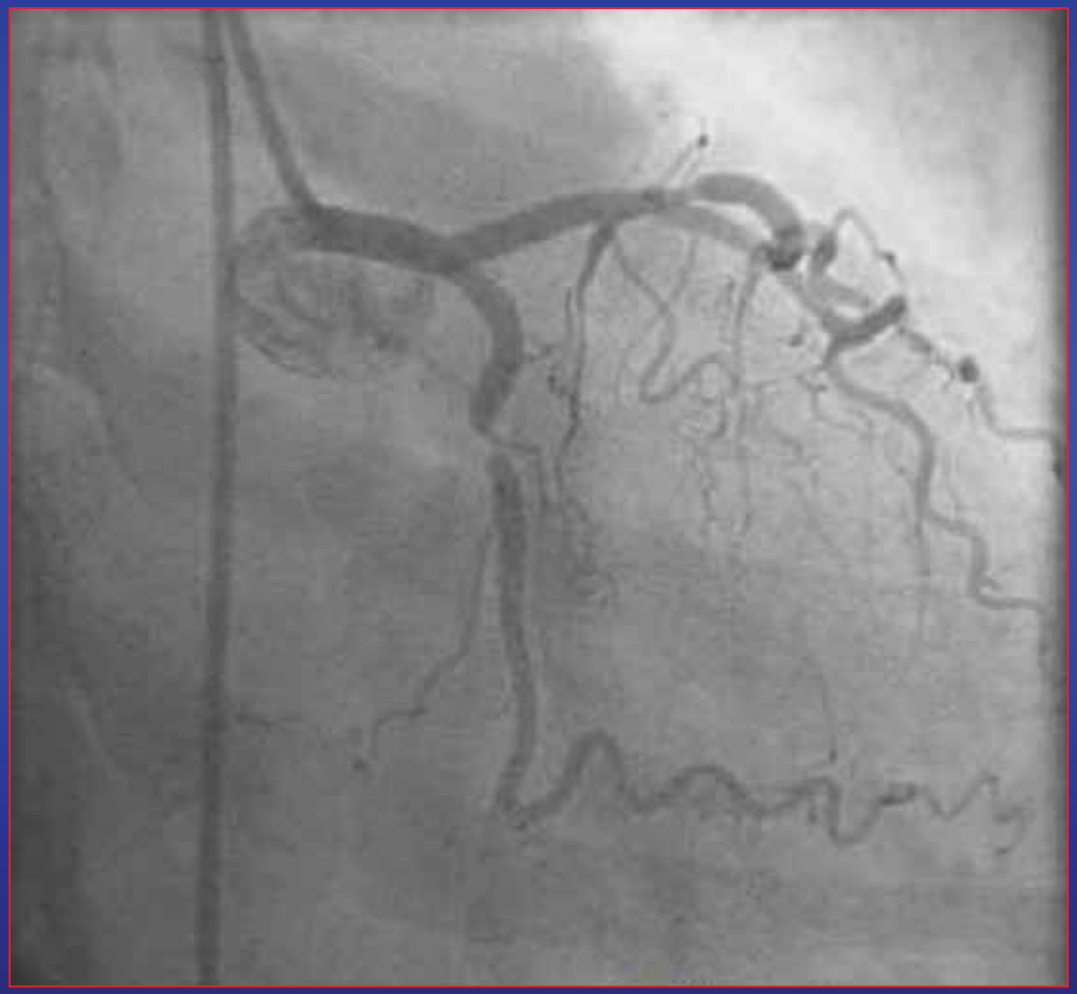
37-year old white woman with CAD, hyperlipidemia (total cholesterol 252, HDL 27, triglycerides 442 mg/dl) and cigarette smoker; developed chest pain and had a non-Q wave myocardial infarction 10 days antemortem. Cardiac catheterization: Severe LAD and LCX disease and occluded RCA

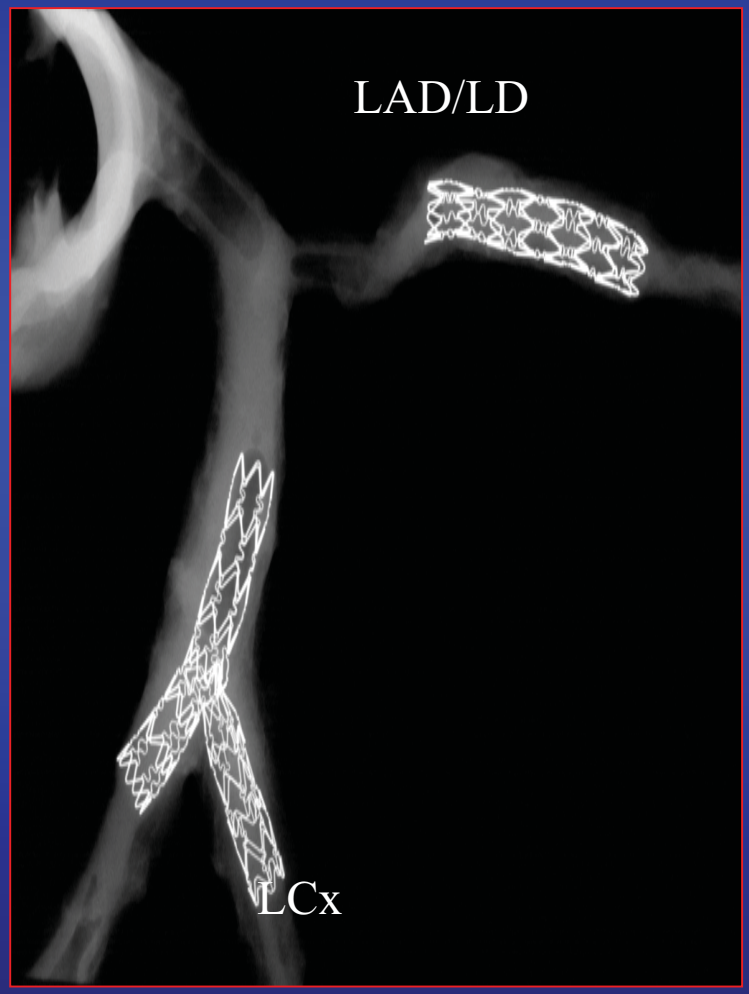
Multivessel stenting performed:

- Two ZETA stents placed in mid-RCA 8 days antemortem
- CYPHER stent placed in mid-LCX 7 days antemortem
- CYPHER stent placed in mid-LAD + bifurcation stenting of LD (PC-coated BiodivYsio) 7 days antemortem

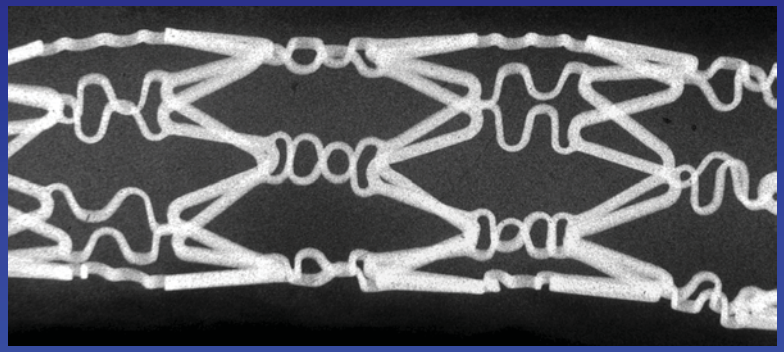
Presented to ER on day of expiration with chest pain and ECG evidence of acute anterior MI followed by cardiac arrest.

Cypher™ Stent in Left Circumflex and Left Anterior Descending Coronary Arteries and BiodivYsio Stent in Left Diagonal

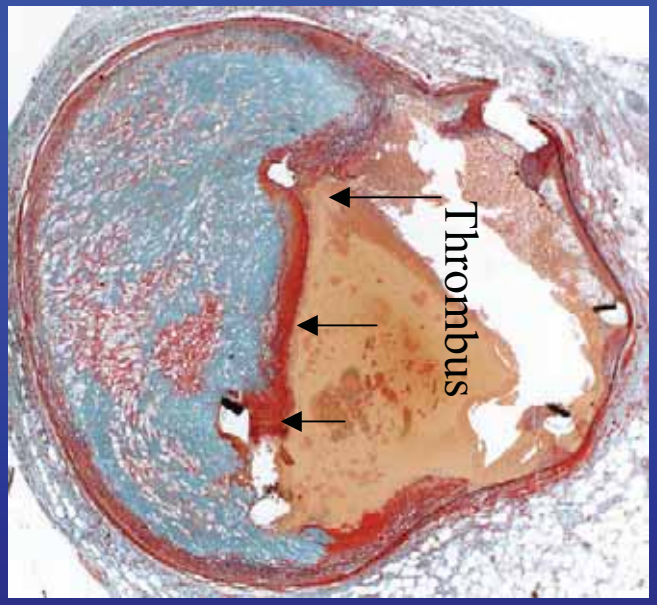




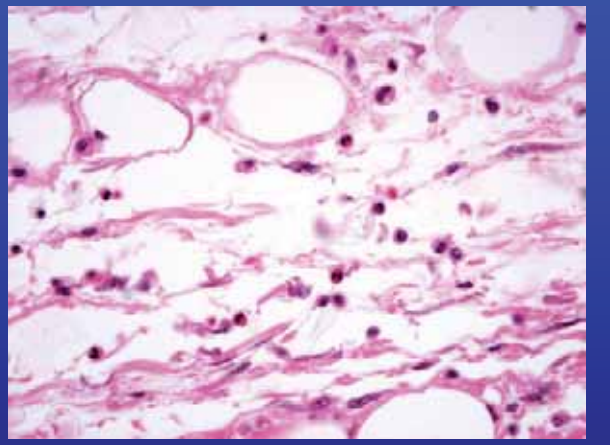
Clinical: AMI & Cardiac arrest 7 days post-CYPHER



Pathology:
Patent CYPHER Stent
in Mid-LCX



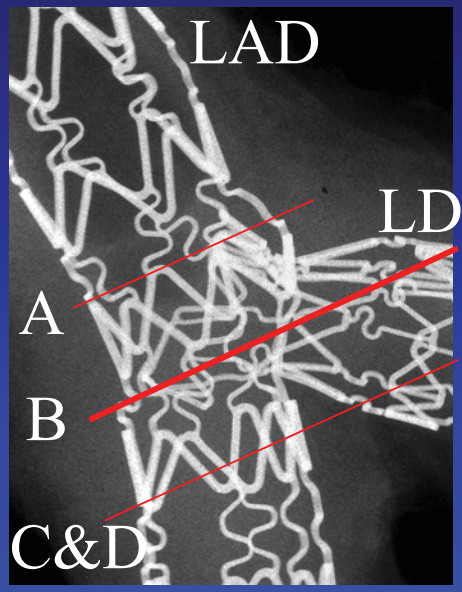
Platelet thrombus +
acute inflammation

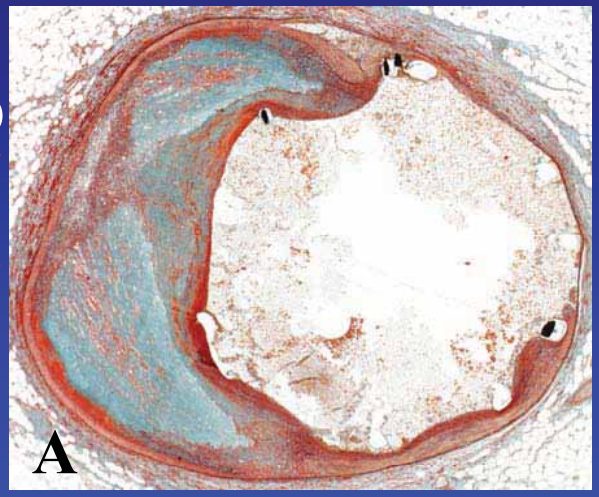


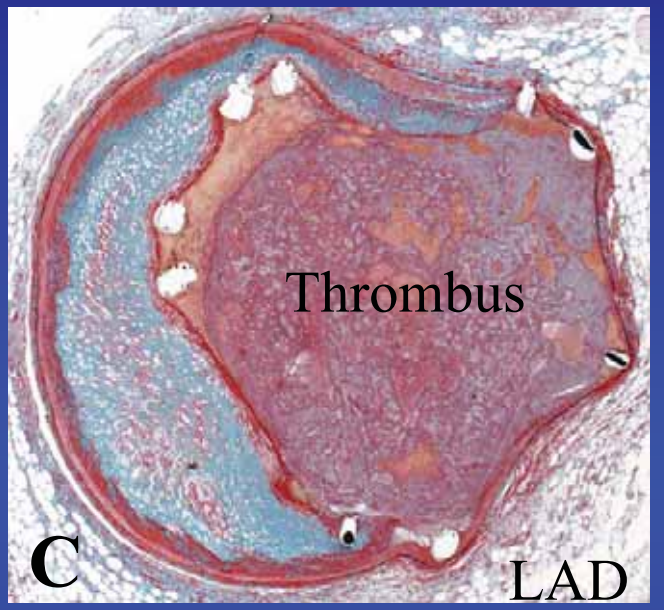
Adventitia

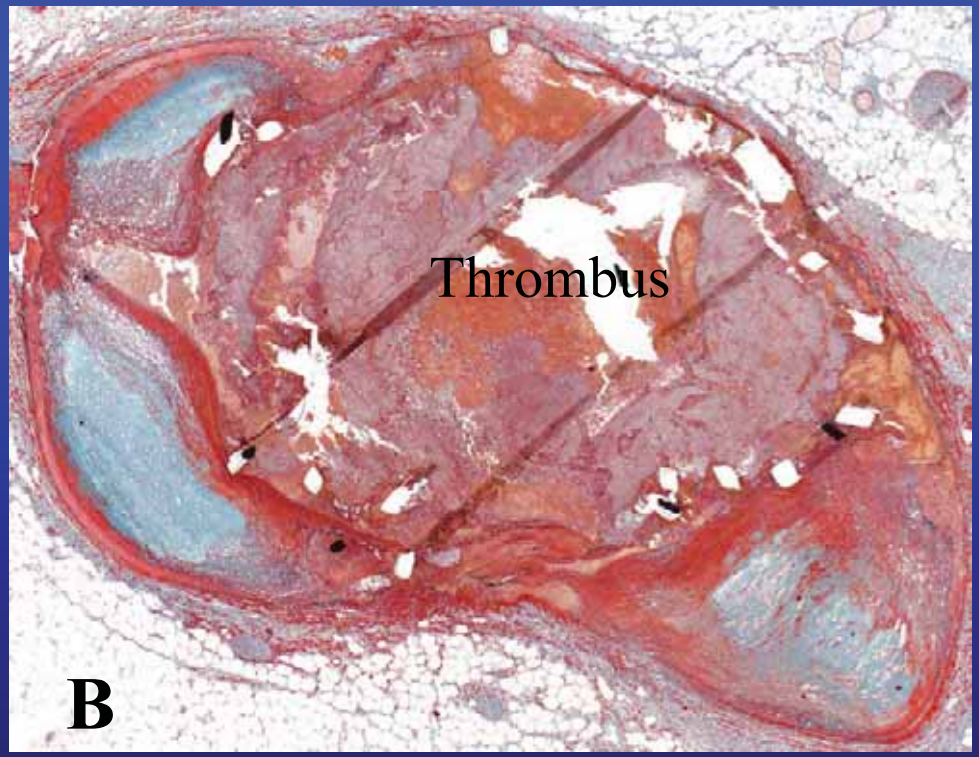
A. Farb, R. Virmani, AFIP, Washington, DC

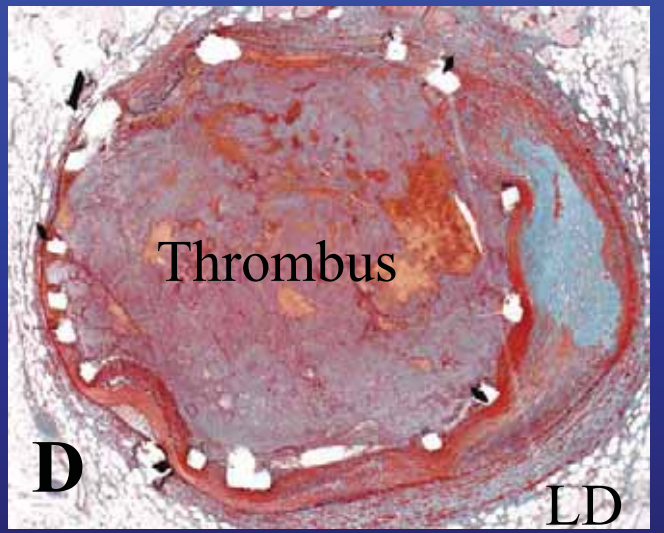
Subacute Stent Thrombosis - 7 days







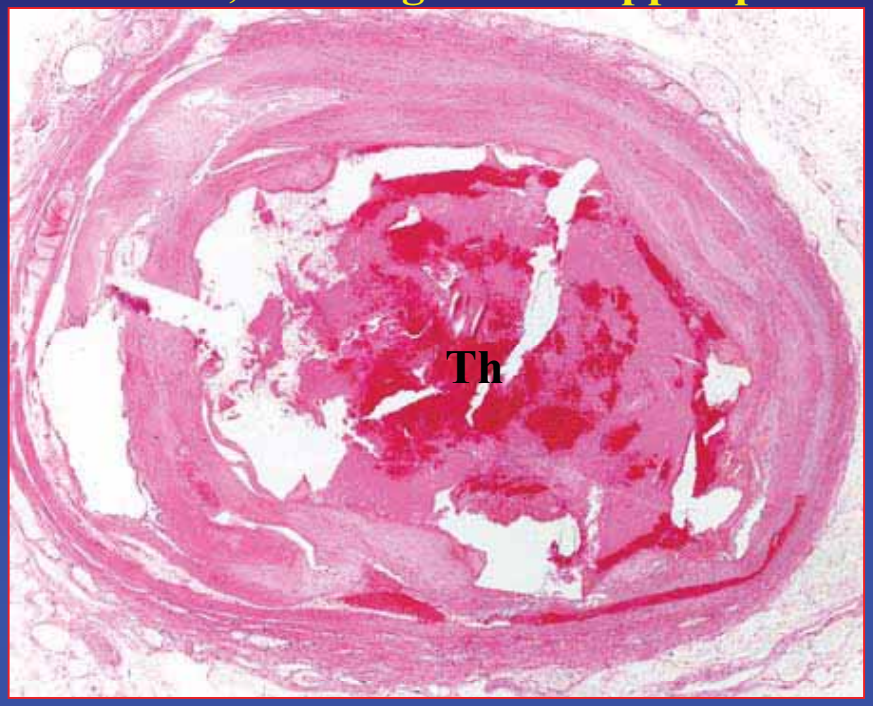


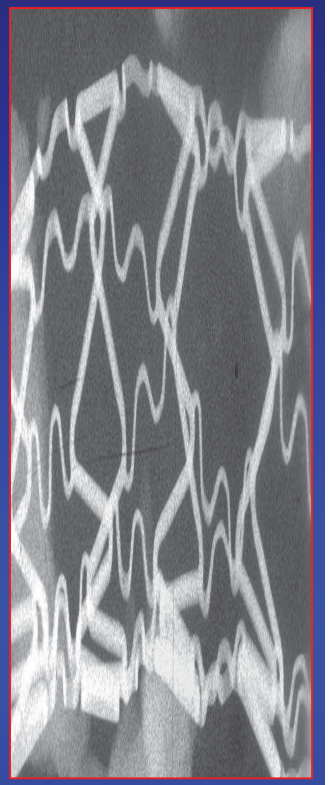


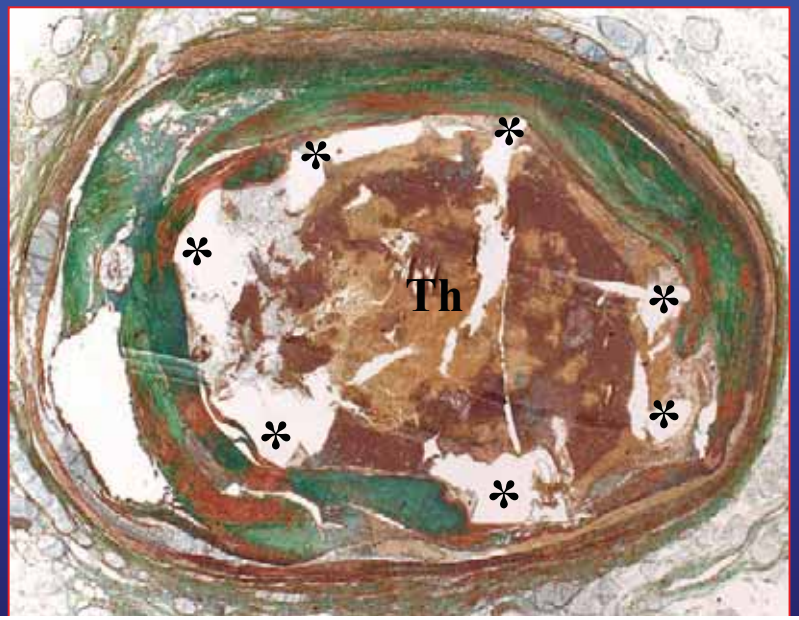
Causes of subacute thrombosis - CYPHER ?

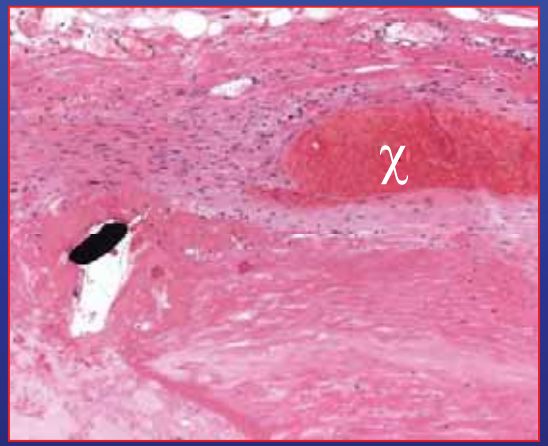
- ✓ Polymer peeling off the stent during deployment
- ✓ Under expansion of the stent
- ✓ Small stent used in a larger vessel-cracking of polymer
- ✓ Drug?
- ◆ **Inappropriate location chosen for stent - bifurcation, crush technique**

65-year old male with CYPHER stent placed post AMI; 33 days later presented with stroke, anticoagulants stopped patient died 38 days post stenting.









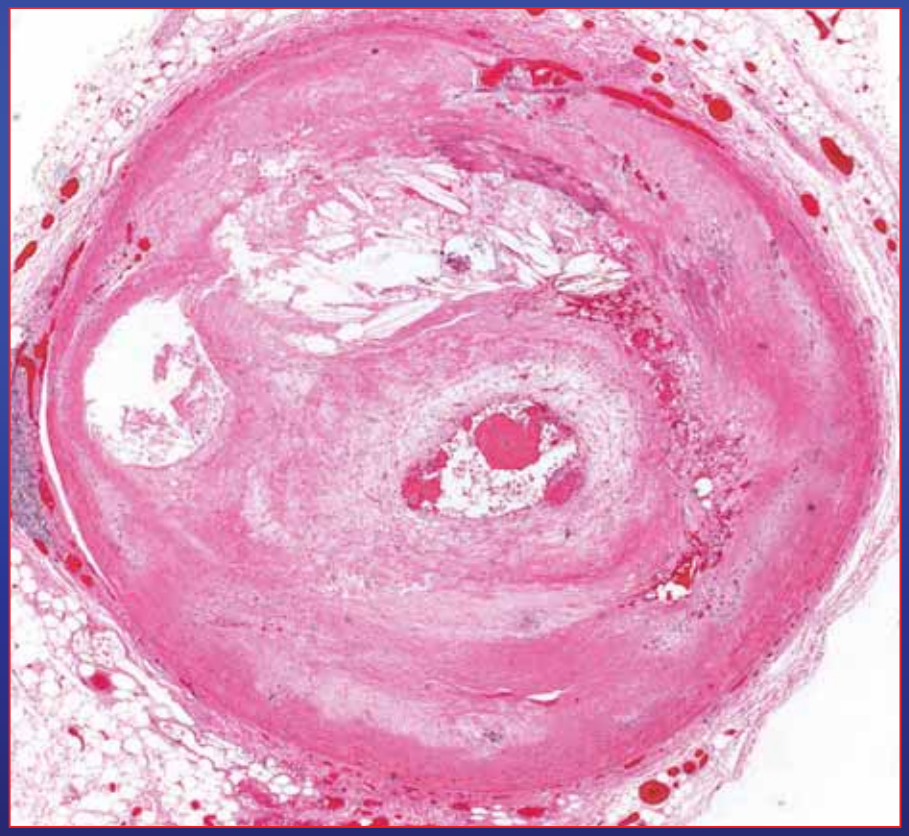
χ Medial dissection

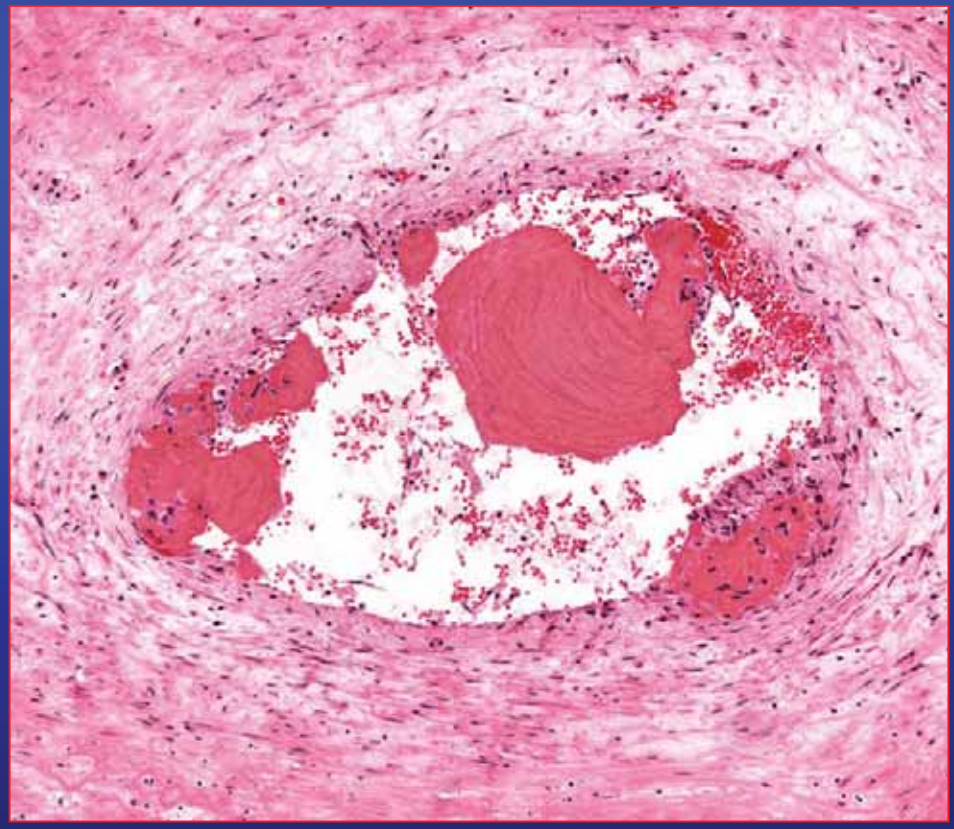
* Stent strut

Absence of healing

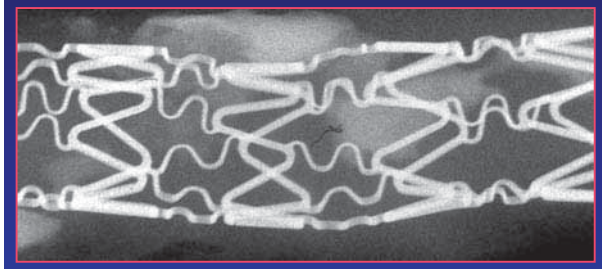
61 year-old male with hypertension and hyperlipidemia presented with acute coronary syndrome 4 months before death. Catheterization: 99% stenosis of PDA, CYPHER stent placed 2.5x18 mm.
1 month before death catheterization repeated for positive stress test - No restenosis.
Sudden death after complaining of dyspnea and diaphoresis

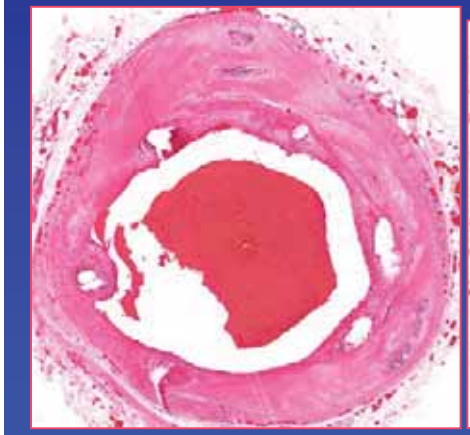
PDA just proximal to CYPHER stent

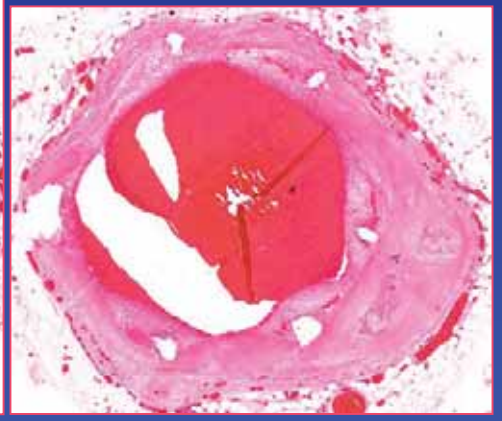


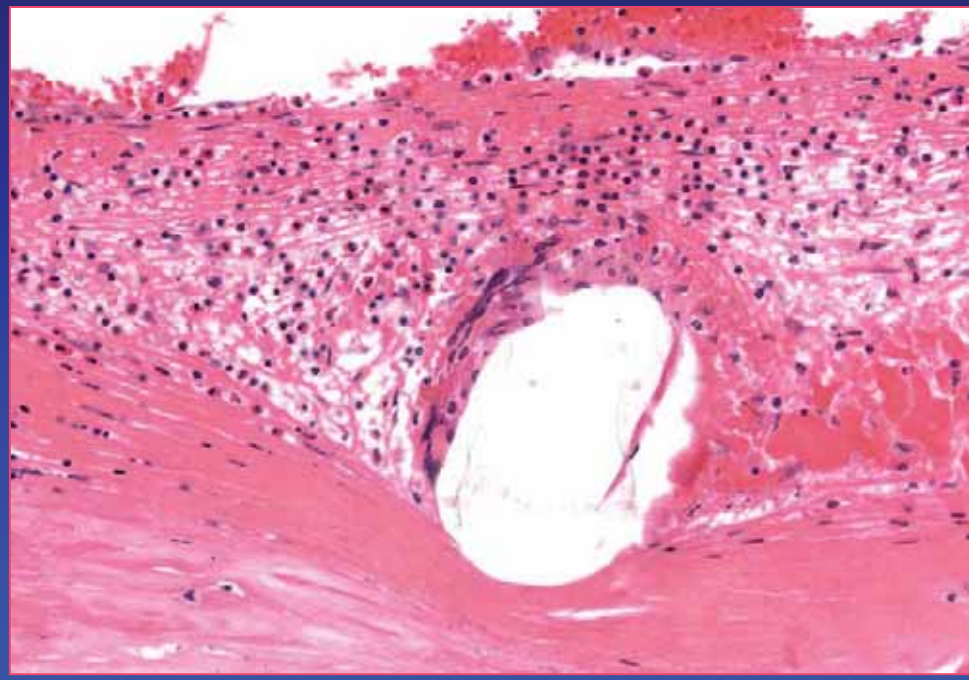


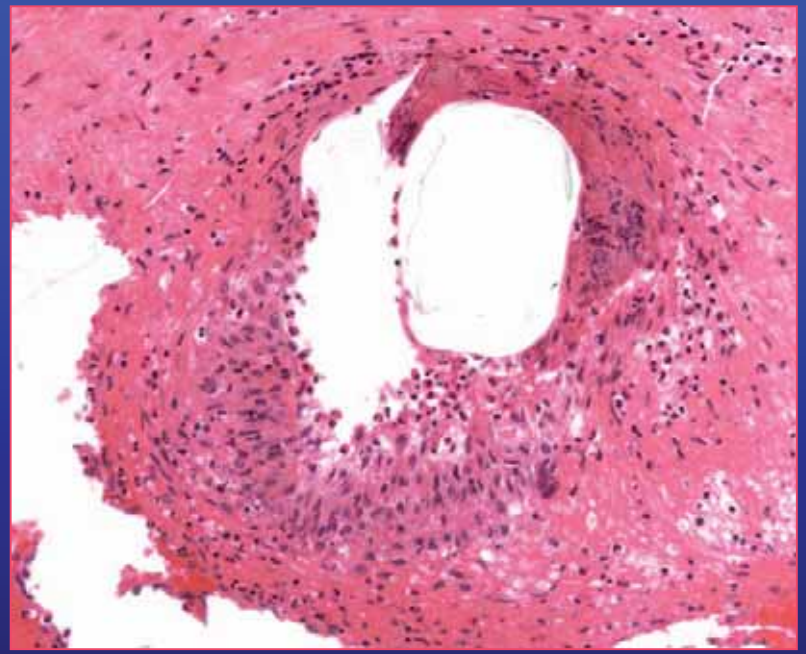
CYPHER stent - 4 months duration

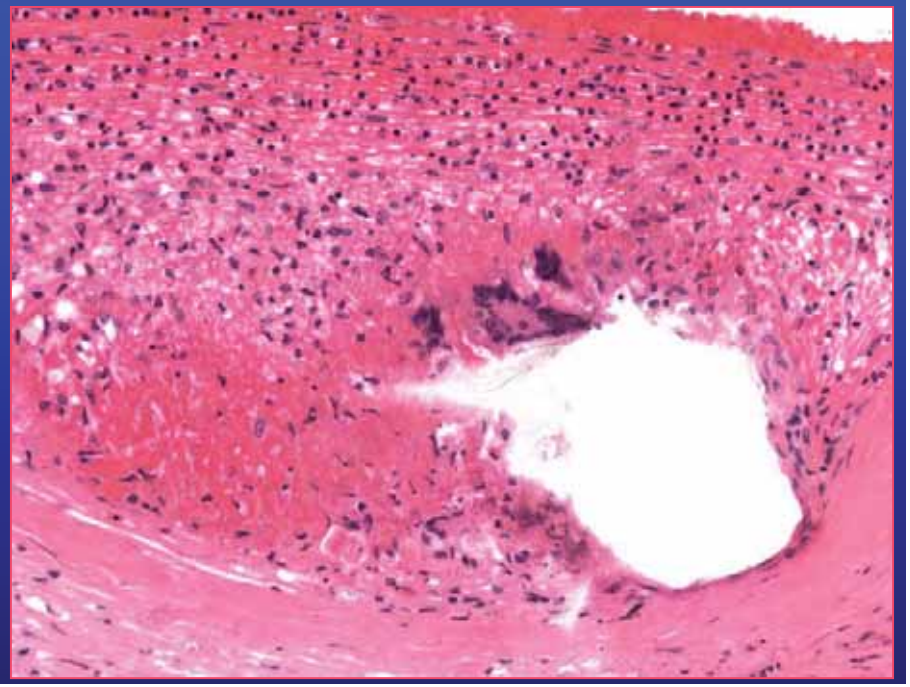






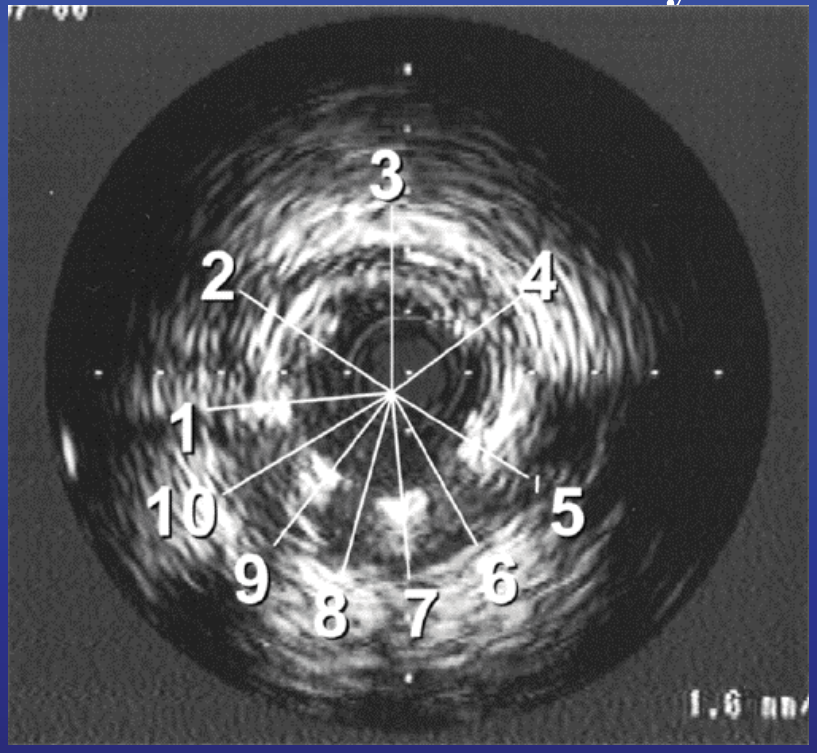


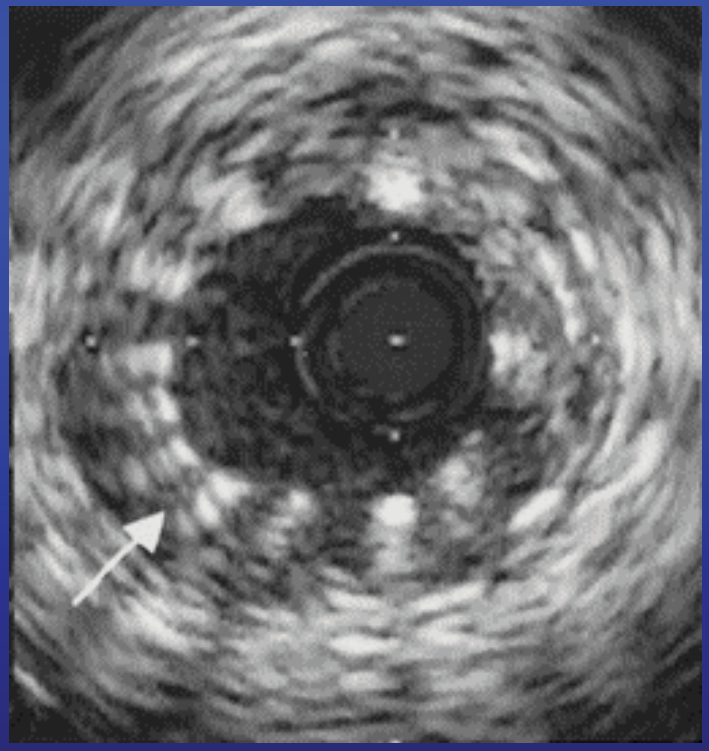




IVUS observations in CYPHER

- **Incomplete Apposition of Stent**
  - **RAVEL - DES stents = 10/48 (21%)**
  - **Uncoated Bx Velocity Stents = 2/47 (4%)**
  - **SIRIUS - DES stents = 7%**
  - **Uncoated Bx Velocity = 0%**





Serruys PW, et al. Circulation 2002;106: 798

A 58-year old man was first seen on 12/20/01 with UAP. He was a smoker, non-diabetic, non-hypertensive. Coronary angiography showed:

-95% narrowing with >20mm long lesion in prox and mid LCX

-70% mid LAD , and non-critical lesion in prox RCA

- 2 CYPHER™ stents (3.0x18 and 2.5x18 mm) stents implanted following PTCA (2.5 at 12-14 ATM), with overlap. IVUS showed stent well apposed to the wall without mal-apposition.

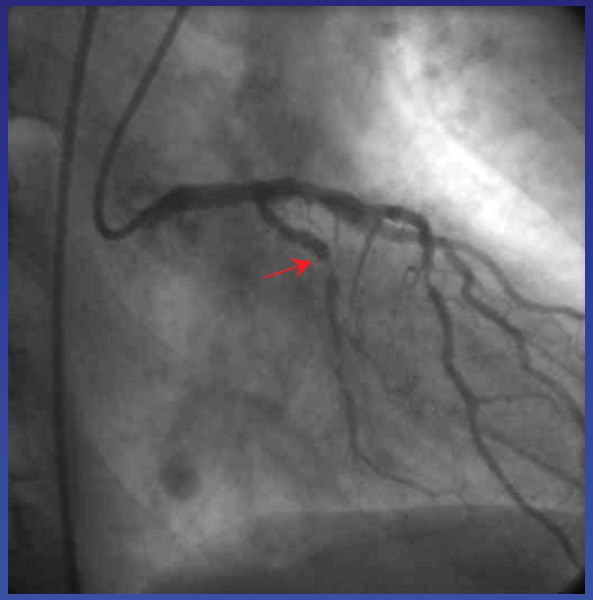
1/10/02 skin rash- trunk, ankle, and wrist with itching and irritation - interpreted as secondary to ticlopidine and patient switched to clopidogrel. Rash resolved.

- 8 months post-stenting protocol driven angiography and IVUS, no in-stent stenosis nor neointimal formation

6/9/03 patient experienced epigastric CP of >20 min duration with a syncopal episode, recovered. Developed recurrent intermittent CP admitted to CCU on 6/13/03, DX recent non-Q wave MI.

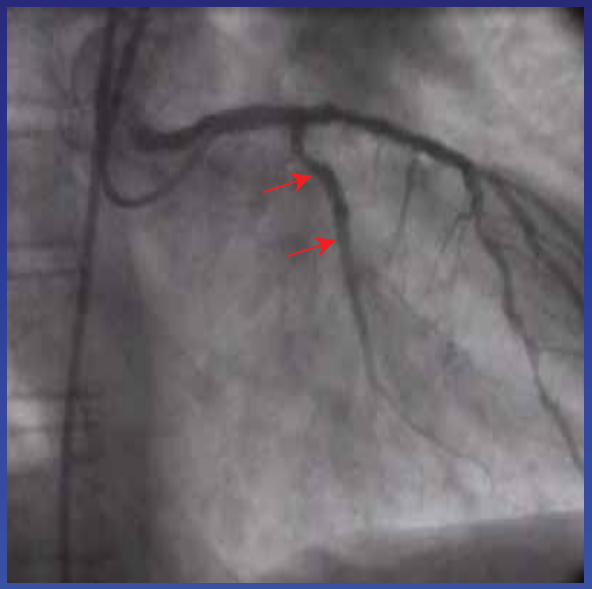
- 6/16/03 angiography, LCX total occlusion (TIMI 1), could not be crossed, LAD 85%, RCA 90%. While attempting to cross RCA patient arrested and could not be resuscitated.

58-WM enrolled in E-SIRUS for UA (Dec 2001) presented 18 month later with CP for 4 d



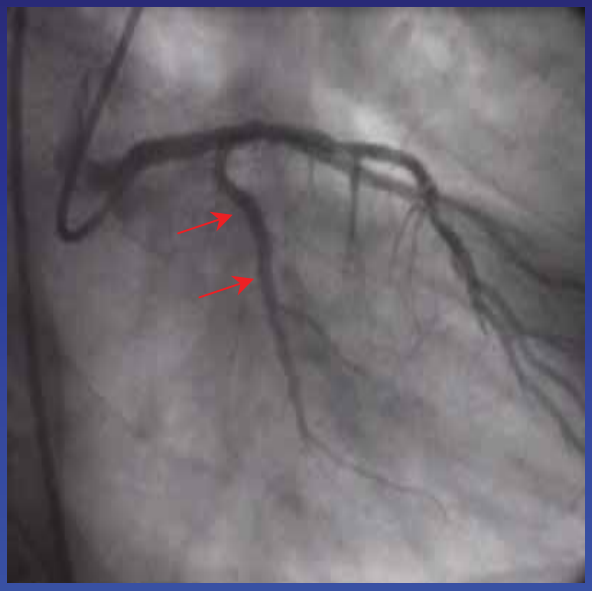
Pre procedure

Long LCx lesion (70% stenosis)

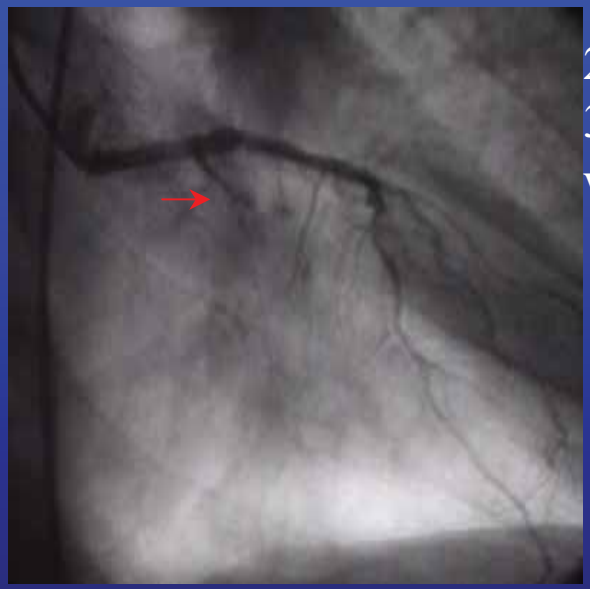


Post-Implant

2 CYPHER stents placed in LCx 3x18 mm and 2.5x18 mm, without much overlap



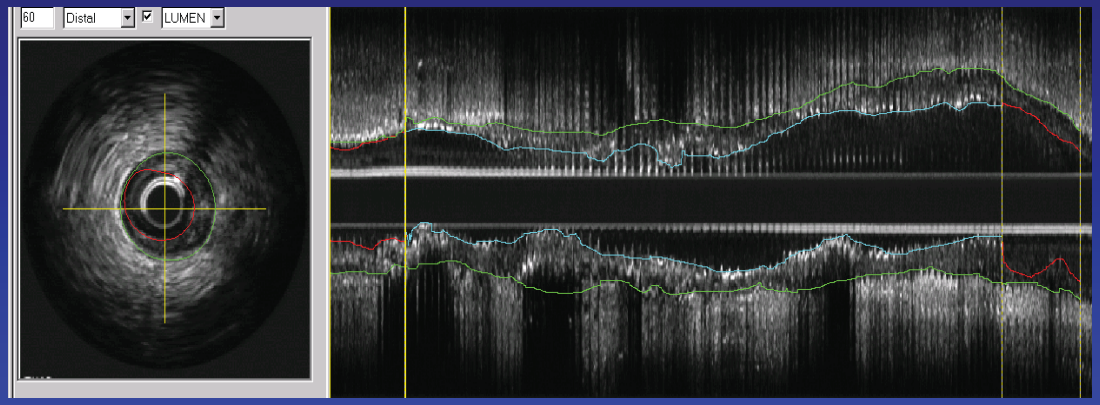
8 months post SRLstent

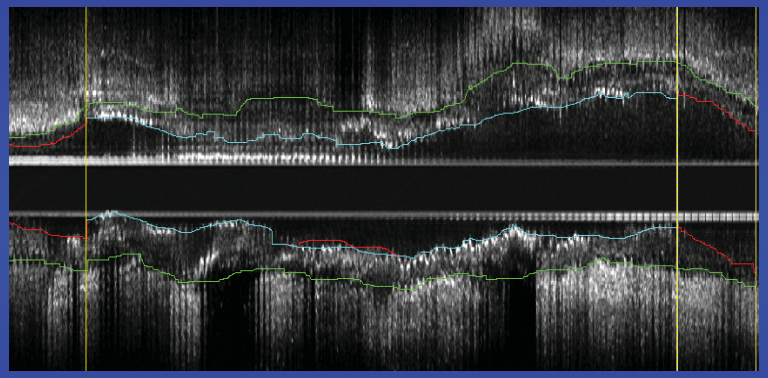


18 months post SRL stent

Giulio Guagliumi, MD

ICUS Analysis, Cardialysis Rotterdam

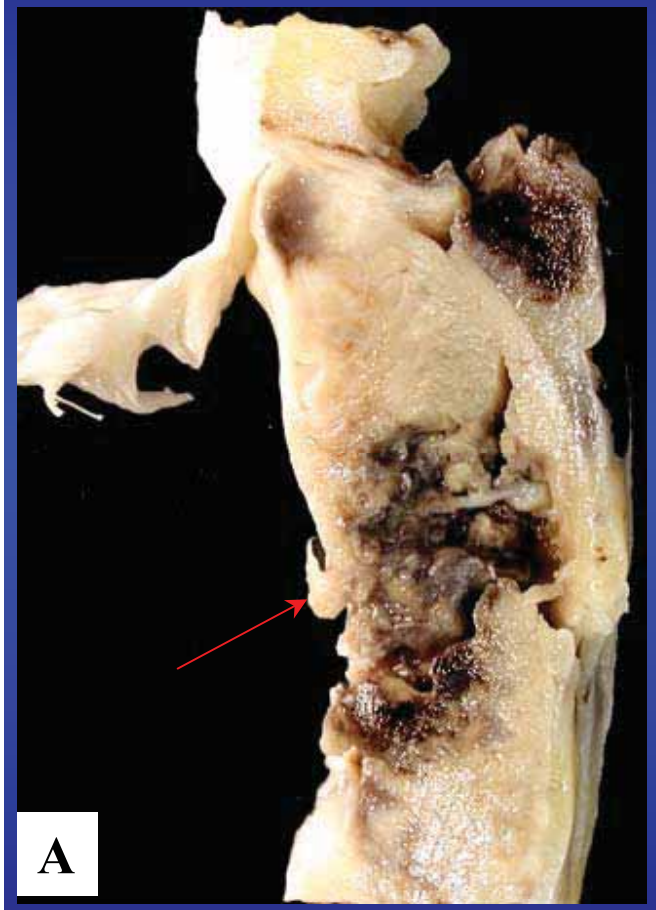




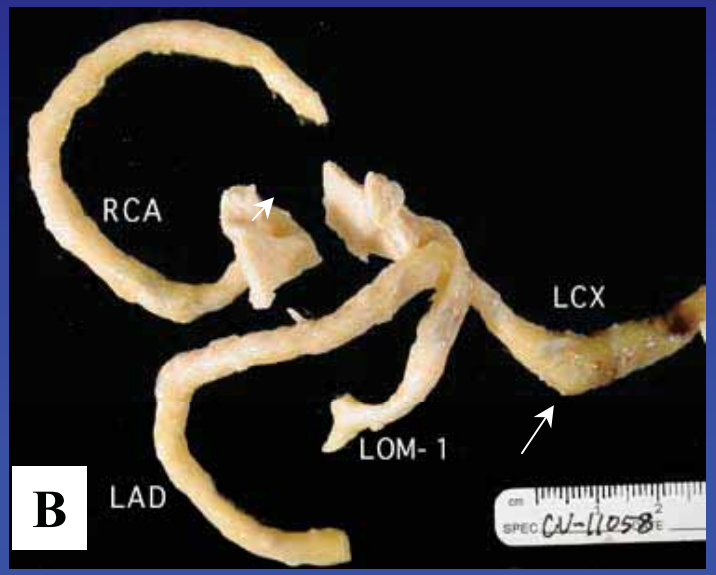
	Baseline	8 Months
Vessel Volume mm^3	407	462
Stent Volume mm^3	187	194
Plaque behind stent mm^3	221	269
Neointimal Volume mm^3	0	0.7
% Stent Volume Obstruction mm^3	-	

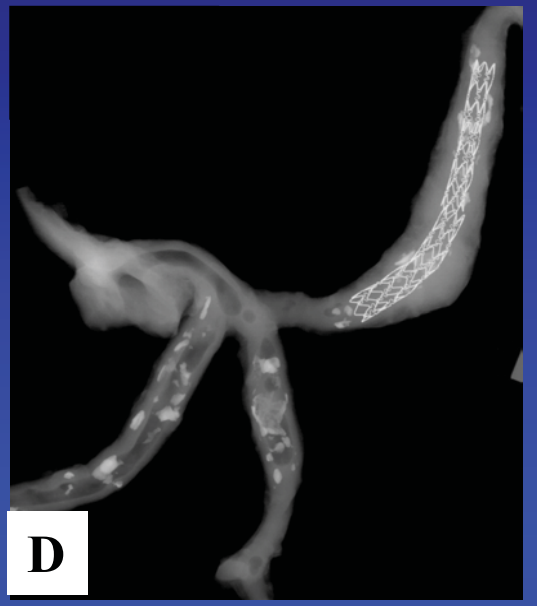
1

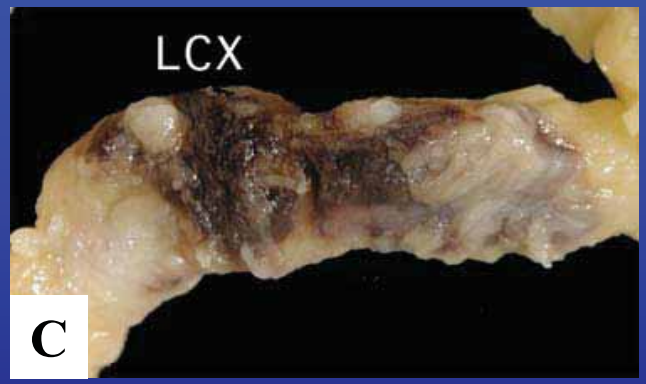
Gross Findings in the Heart

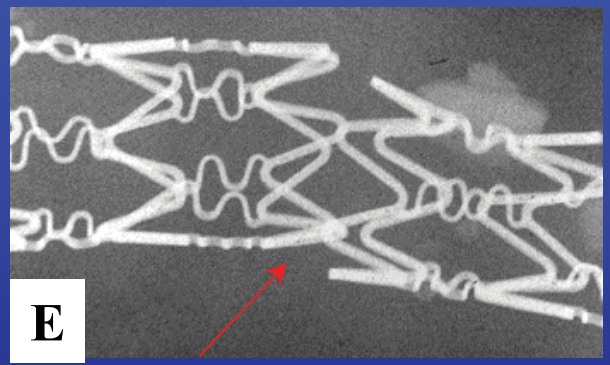


Cardiac rupture seconary to AMI



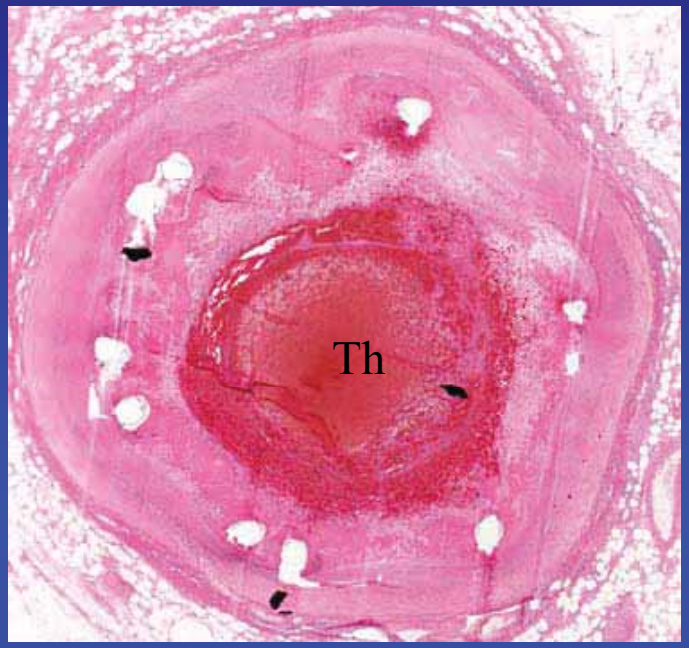


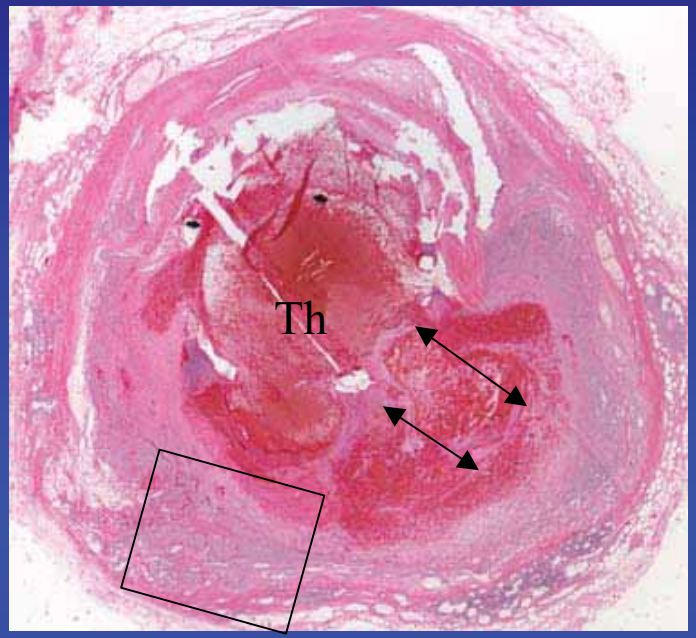


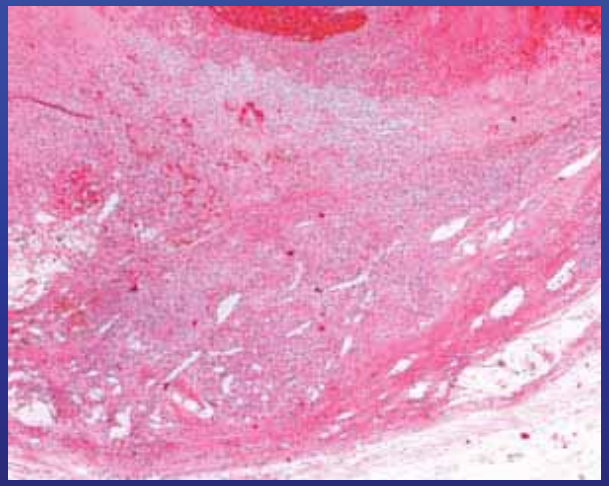


No overlap

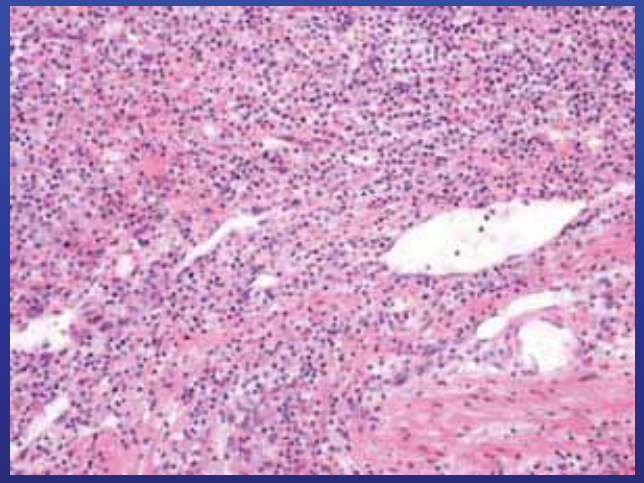
Proximal Stent



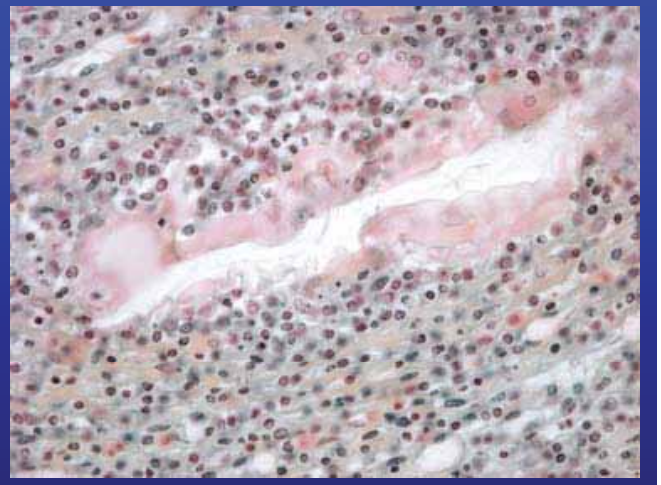




Medial destruction

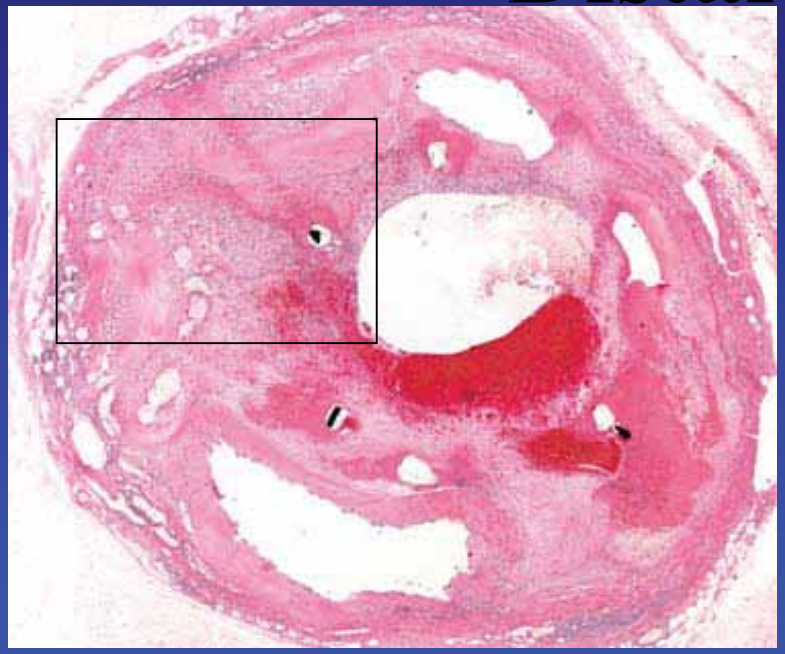


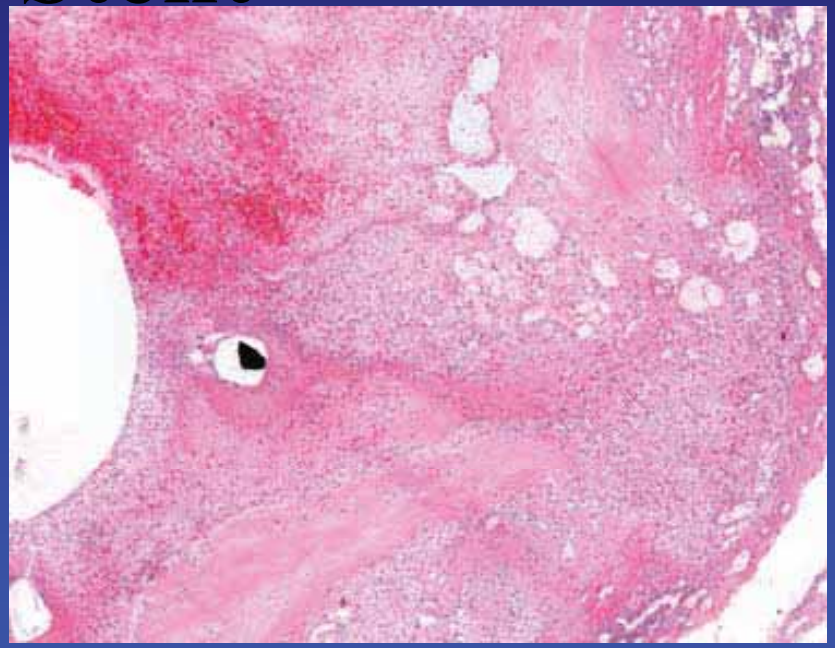
Inflammation

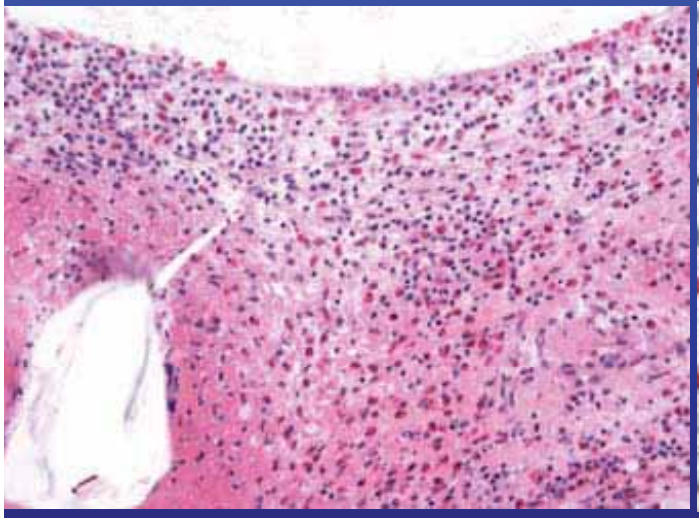


Foreign body giant cell reaction

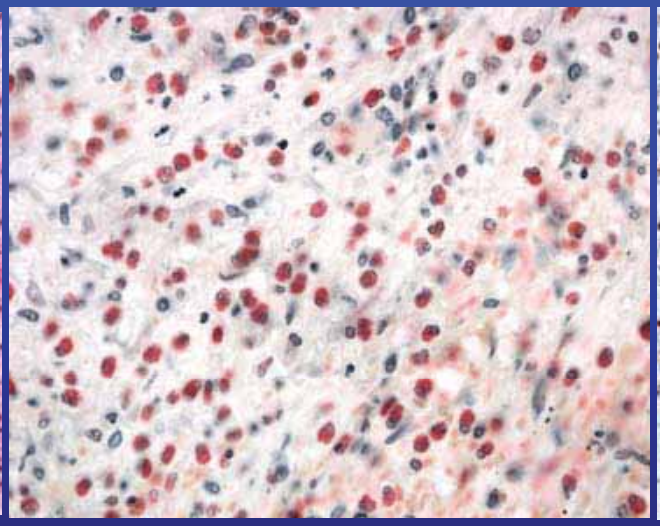
Distal Stent



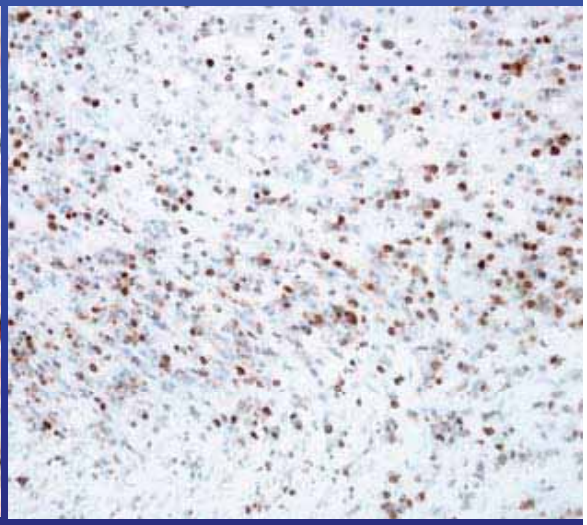




Chronic Inflammation



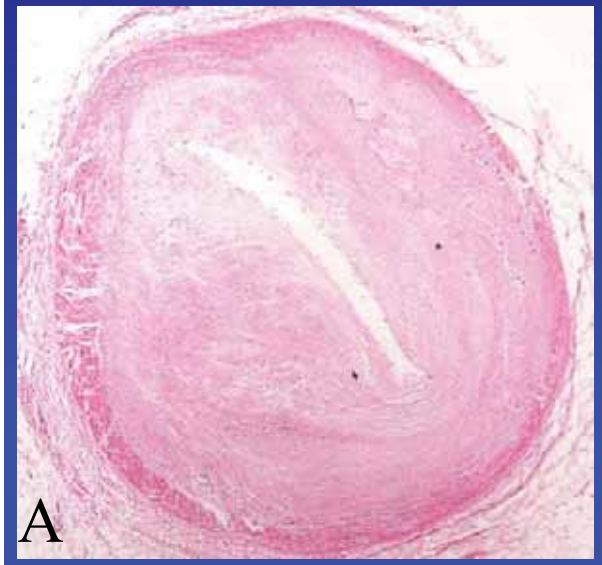
Eosinophils
(Luna stain)



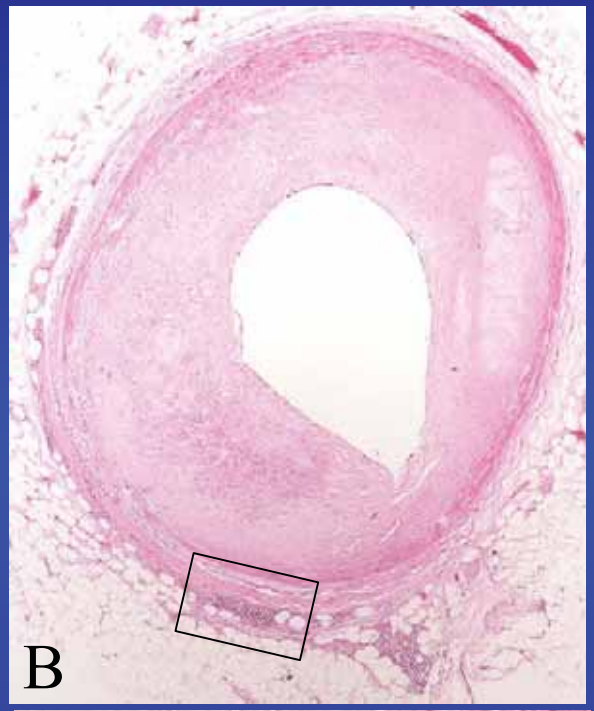
T-Lymphocytes (UCHL)

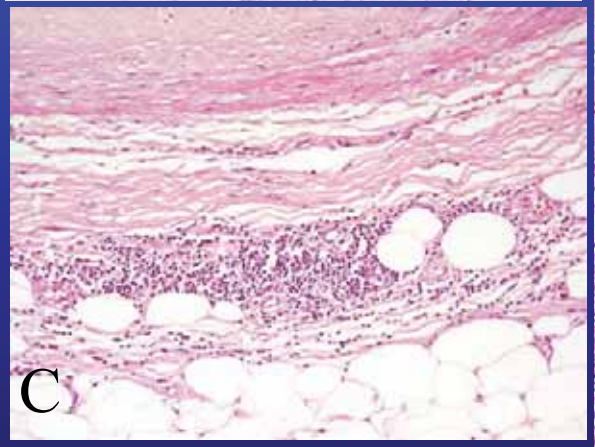
Selected Non-Stented Native Coronary Artery with Sever Stenosis

Distal LCx

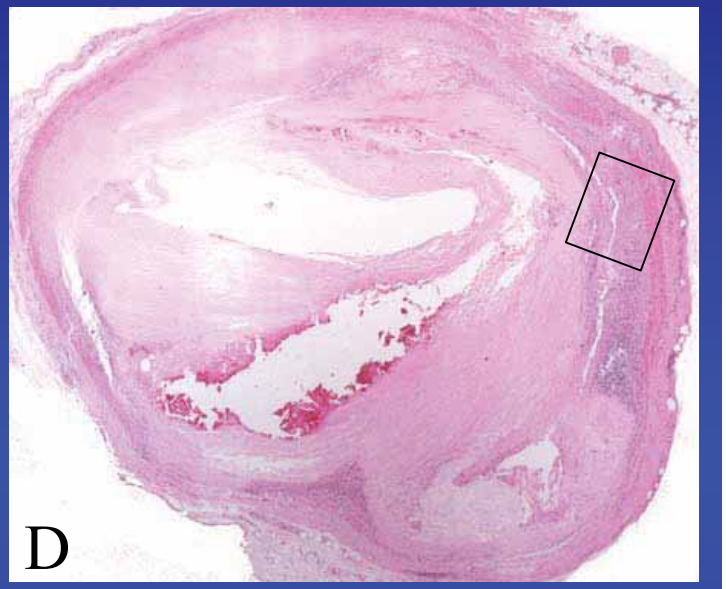


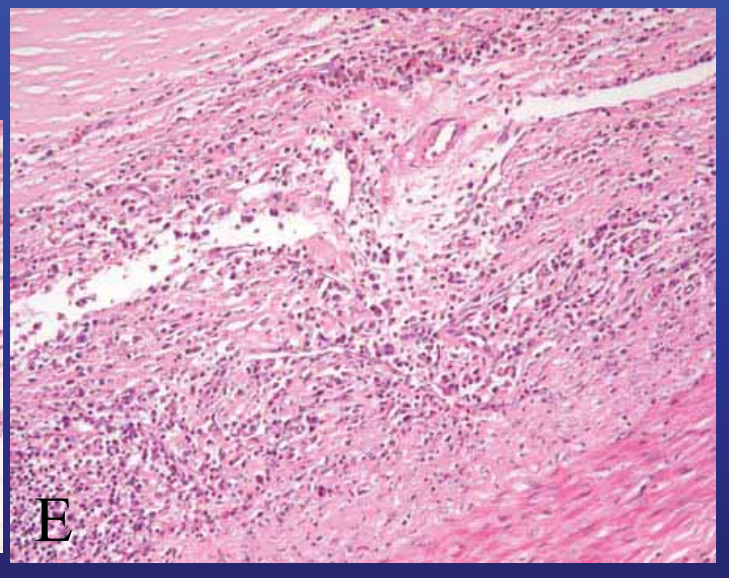
Mid LAD





Proximal RCA





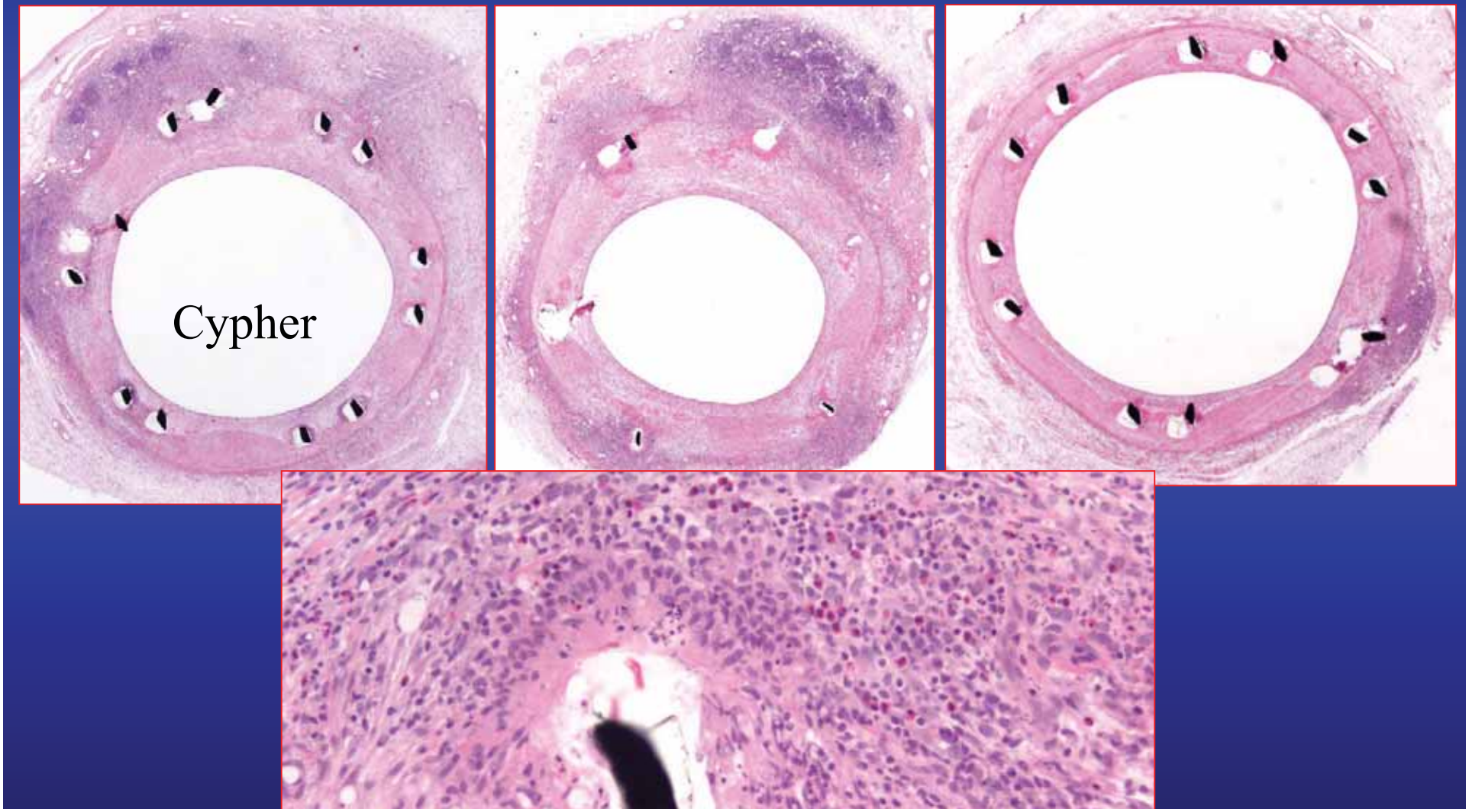
All native arteries showed inflammation typical of atherosclerosis.
None of the non-stented coronary arteries showed an eosinophilic inflammatory reaction.

Causes of Adventitial, Medial and Intimal Inflammation (↑eosinophils) limited to the area of the Stent:

- Hypersensitivity reaction to drug?
- √ Hypersensitivity reaction to polymer?
- Part of atherosclerosis
- Infection

Adverse side effects to Sirolimus mostly limited to: bone-marrow suppression, hypercholesterolemia and triglyceridemia. Other reported side-effects include hypocalemia, hyperglycemia, diarrhea, and abnormal liver function tests. Hypersensitivity has been reported in one patient following Sirolimus.

Granulomatous reaction seen in 12.5 and 35% of CYPHER Stents Implanted for 28 and 90 days in Pig Coronary Arteries



Stent Mal-apposition and Plaque Expansion is Related to Hypersensitivity to Cypher™ Stent (polymer) in Selected Patients?

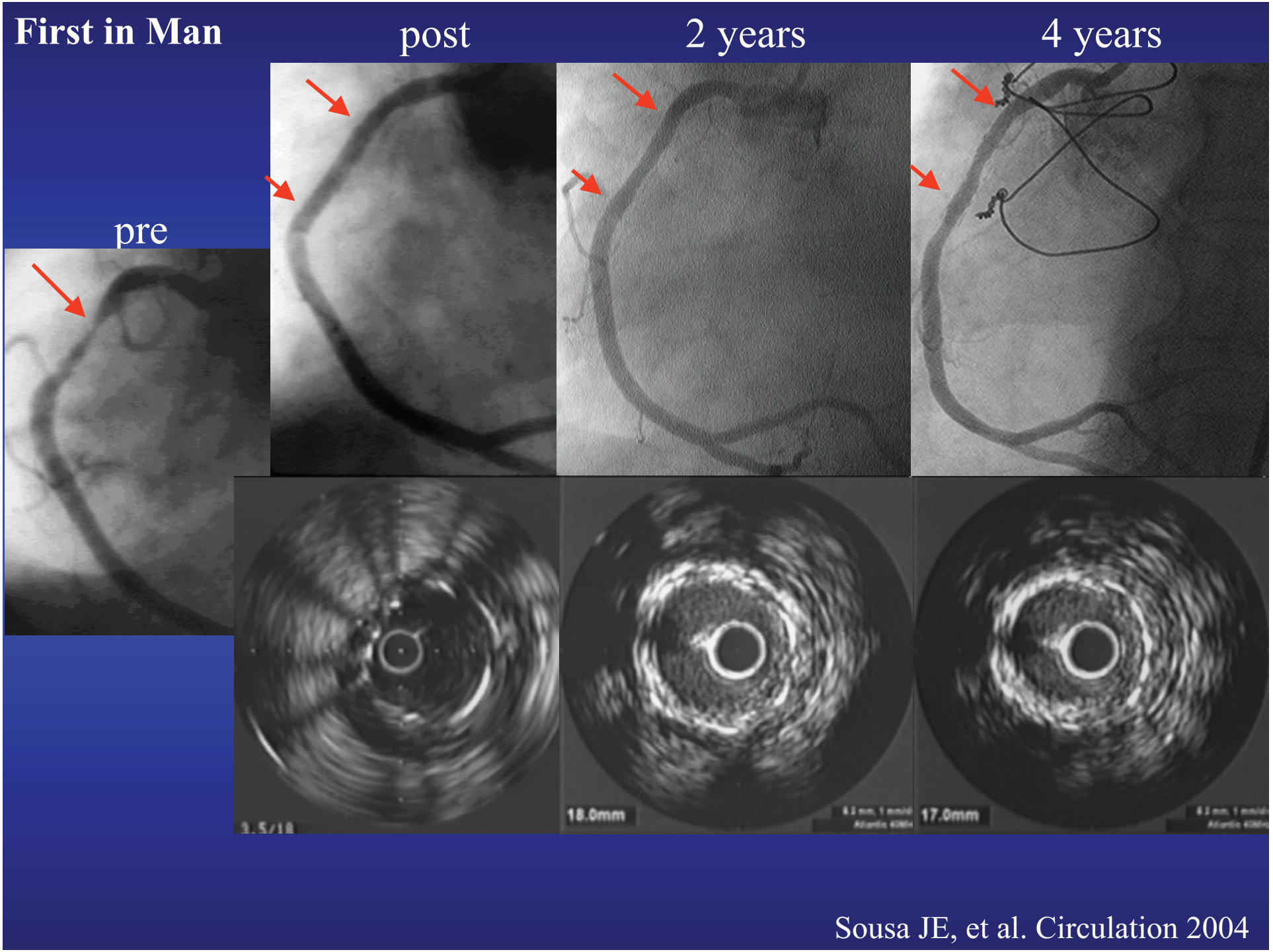
- CYPHER™ polymer is non-erodable consisting of co-polymer poly-n-methacrylate (PBMA) and polyethylene-vinyl acetate (PEVA). PBMA a component of bone cement when implanted subcutaneously results in a macrophage and giant cell reaction accompanied by tissue damage and fibrosis. PEVA in rabbit elicits an intense inflammation in 25% of animals subjected to subcutaneous or intramuscular implants.

Clinical History Case 7

- 61-yrs old man received SRL-Eluting Stent (Fast Release) in RCA 4 years prior to death
- Angio and IVUS at 4 months, 1 year, and 2 years showed minimal neointimal growth in mid-stent
- AVR and MVR 1 year prior to death
- Presented with cardiac arrest & suffered severe cerebral damage
- Angio showed widely patent stent and no change in neointimal growth
- Developed brain death and expired

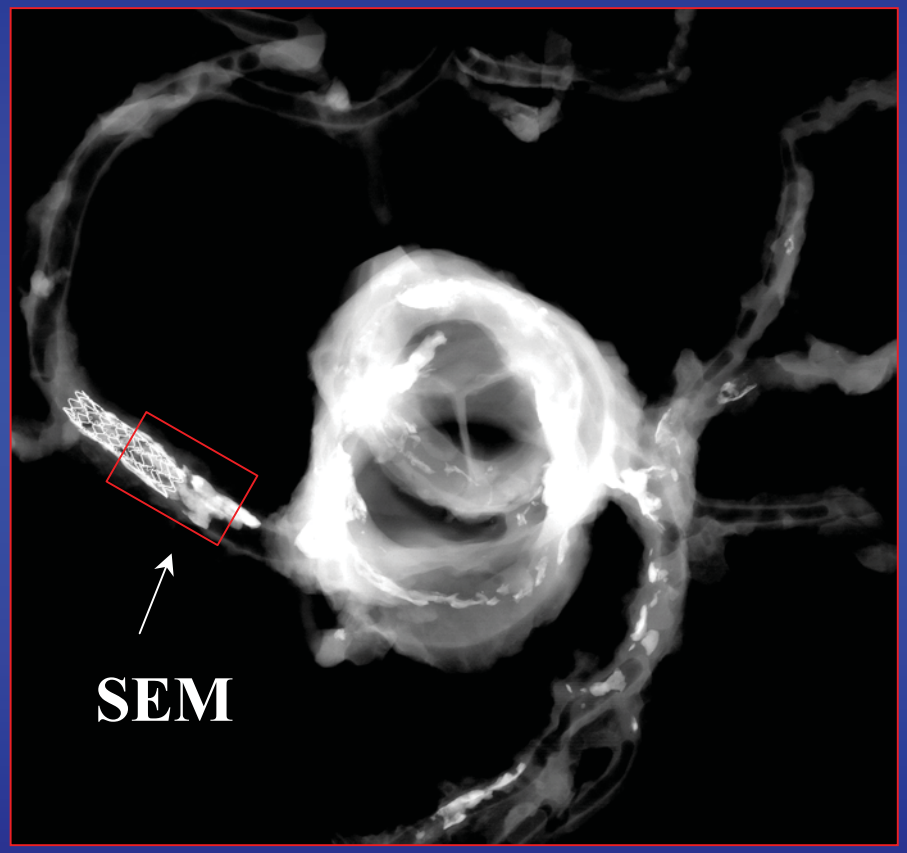
Sousa JE, et al. Circulation 2004

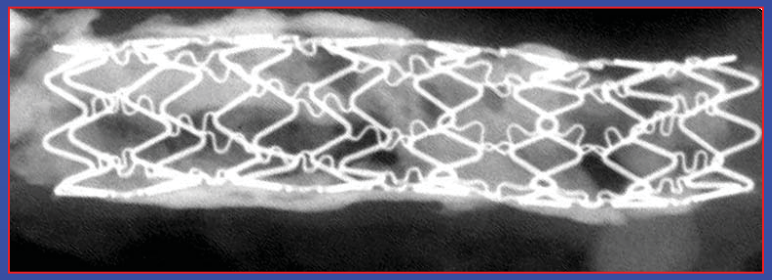
First in Man



Sousa JE, et al. Circulation 2004

RCA FIM SRL-Eluting Stent (Fast Release)
4-Years Post-Deployment



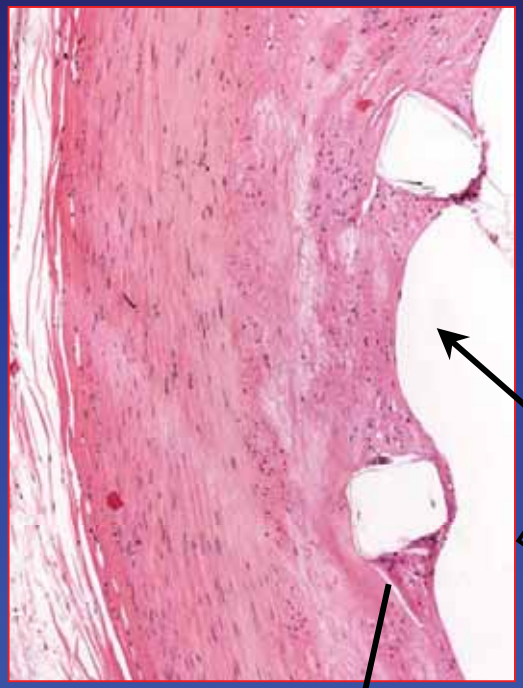


Post-Mortem Radiographs

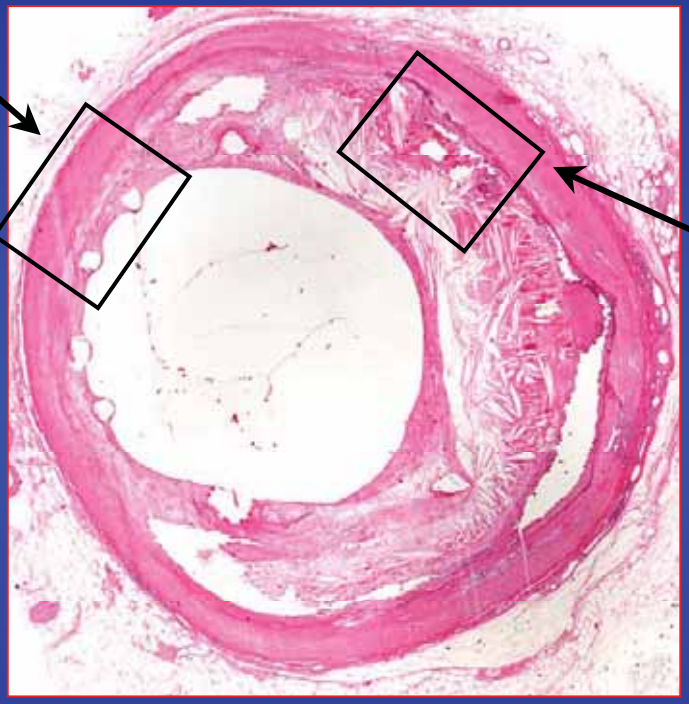
Sousa JE, et al. Circulation 2004

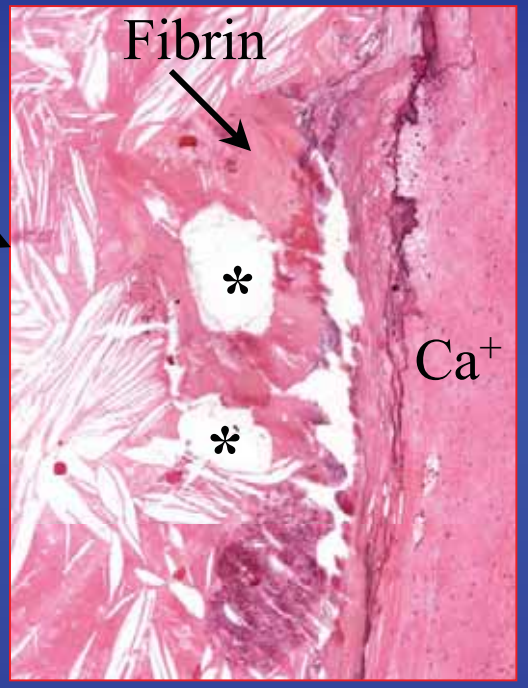
RCA FIM SRL-Eluting Stent (Fast Release) 4-Years Post-Deployment

*Struts in necrotic core

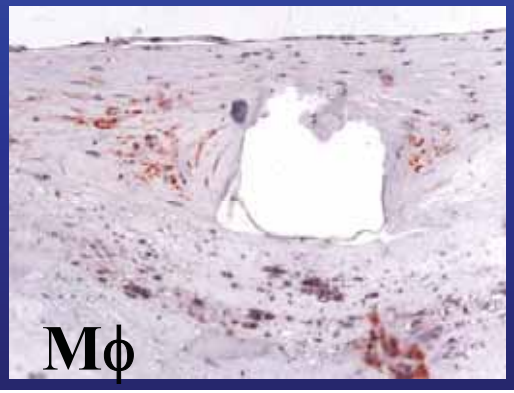


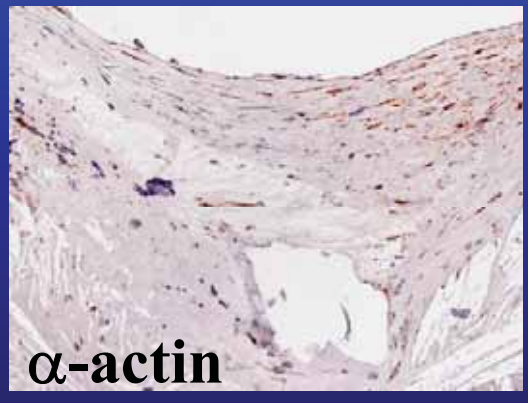
Thin healed neointima

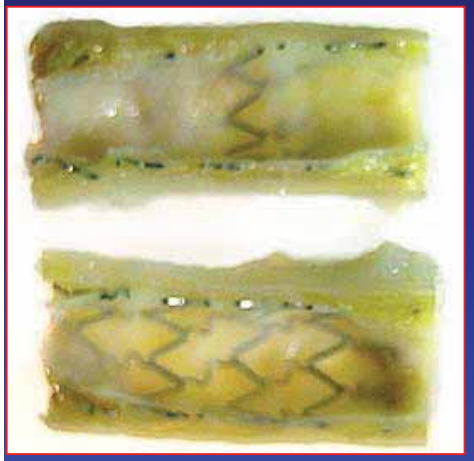


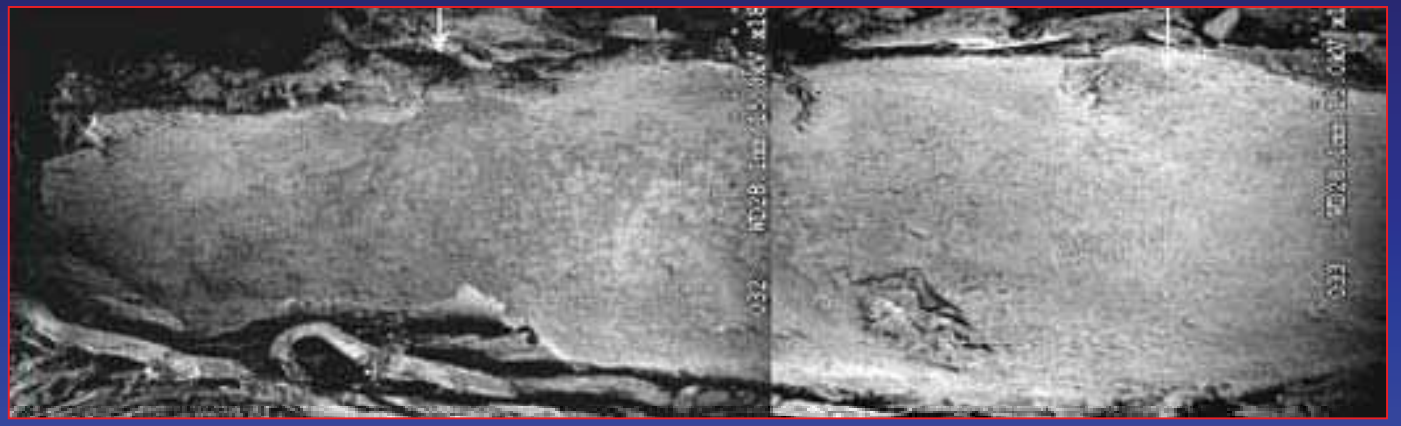


Strut + Polymer (polarized light)

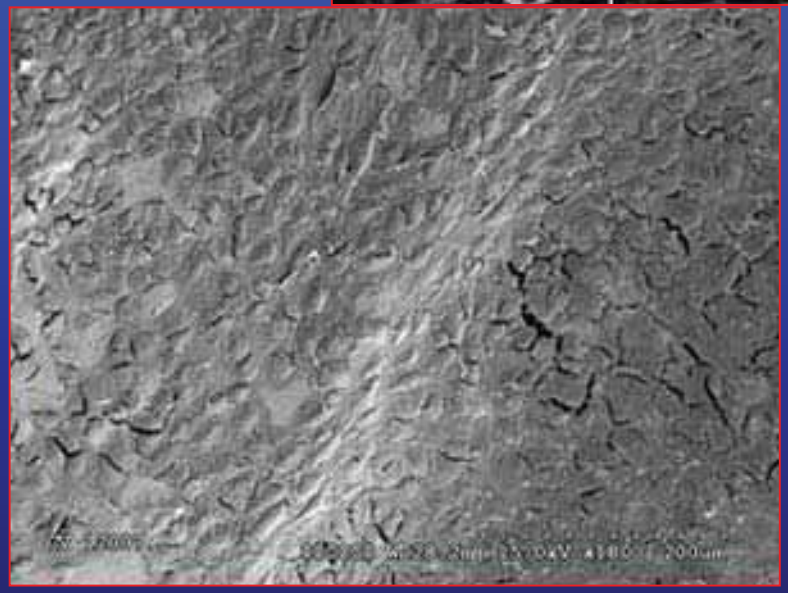


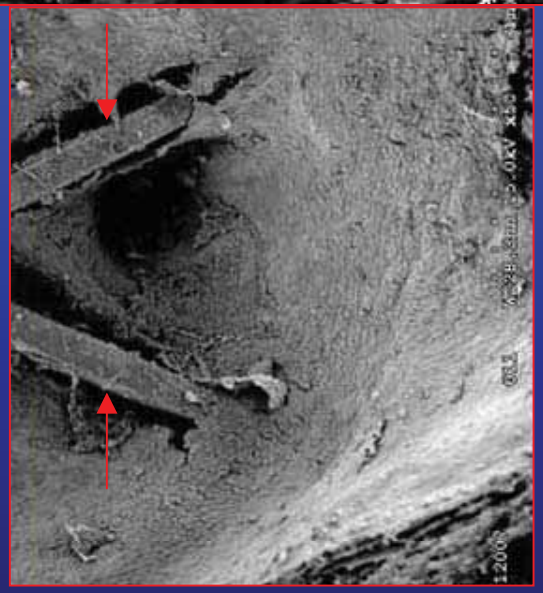






>95%Endothelialized

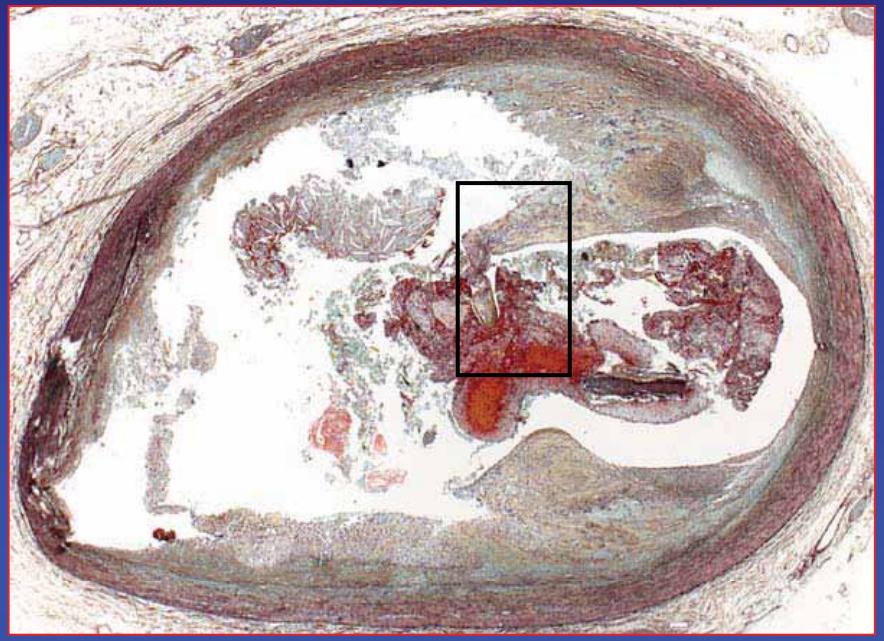


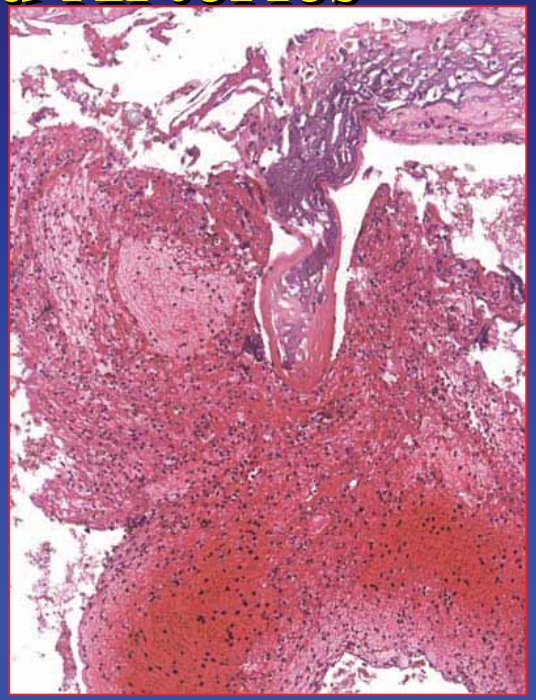


Uncovered strut at branch ostium

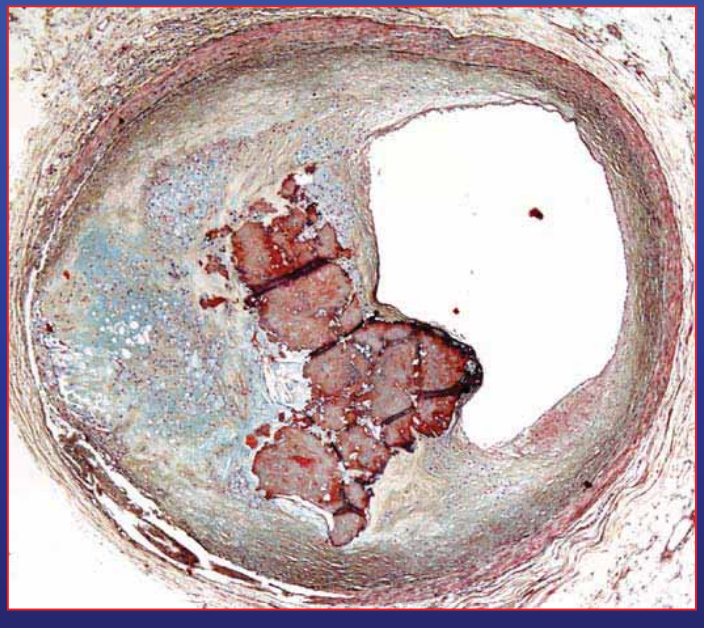
Sousa JE, et al.
Circulation 2004

Non-Stented Arteries



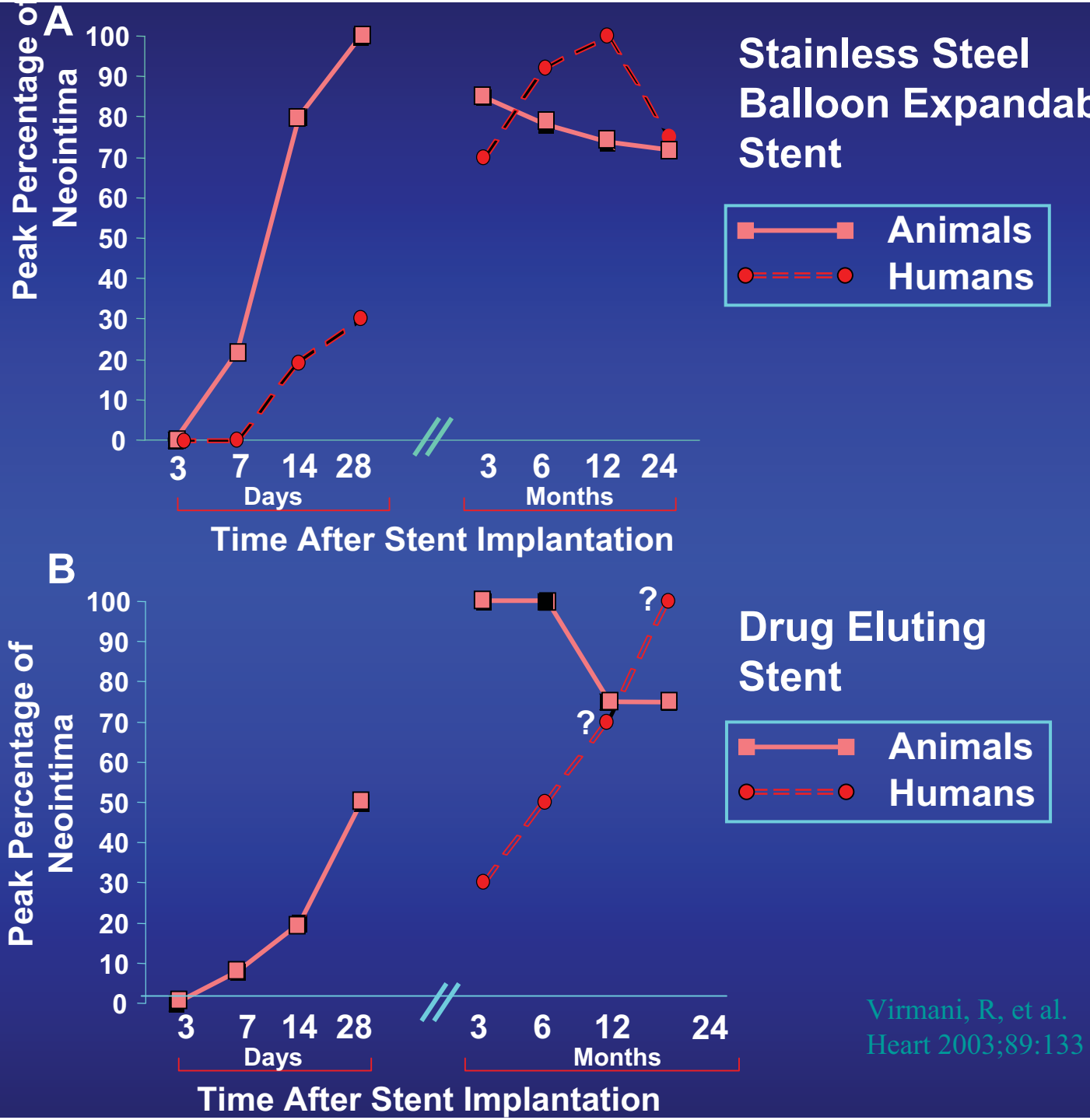


Proximal
LAD
Plaque
Rupture



PDA
Nodular
Calcification

Arterial Healing Following Stainless Steel and Drug Eluting Stent Placement in Animals and Humans



Virmani, R, et al.
Heart 2003;89:133

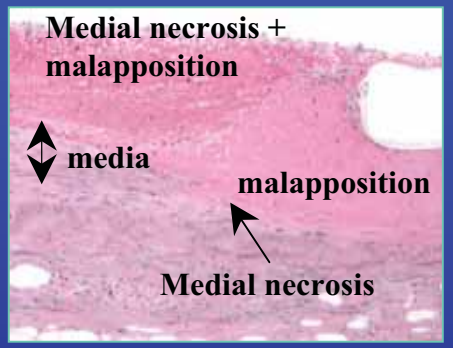
Drug Eluting Stents

Conclusion:

- DES reduce neointima upto 12-24 months - but will the effect be permanent!!!!
- Drug-Eluting Stents only Delay the Inevitable - late clinical results done carefully will fail to show long-term benefit
- May Even in Sensitive Patients Cause Harm by:
  - Thrombosis (early and late)?
  - Inflammation induced by the polymer or through toxic effect of drug resulting in positive remodeling and stent malapposition!!
- Safest, to design better stents and in combination with oral therapy will reduce restenosis until better polymer/drug combination are available!!!

Morphologic Predictors of Poor Outcome in Drug Eluting Stents

Poor endotheilaization



- Persistent poor endothelialization
- Excessive thrombus
- Medial necrosis ± stent malapposition
- Excessive inflammation
- Hypersensitivity reaction

"Science is always wrong. It never solves a problem without creating ten more."

George Bernard Shaw (1856-1950), Irish dramatist and critic

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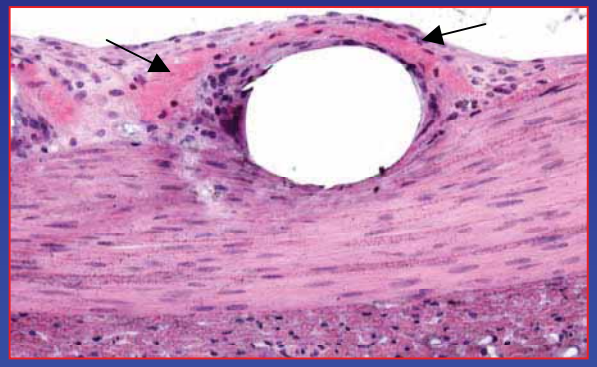
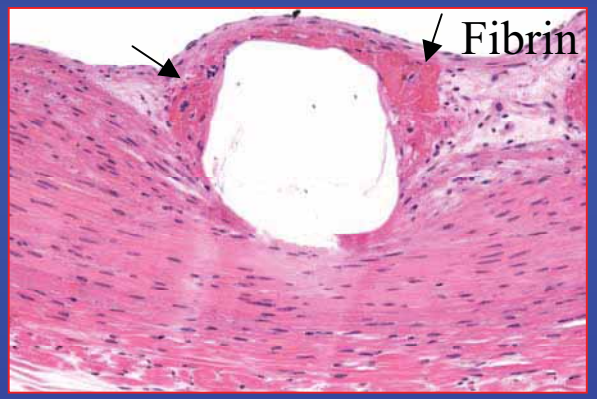
- Lila Adams
- Rosalind Mathew
- Leslie Keefer

Comparison of 7 days Bare SS Stent Implant to 28 days Sirolimus-Eluting Stent and Bare SS Stent

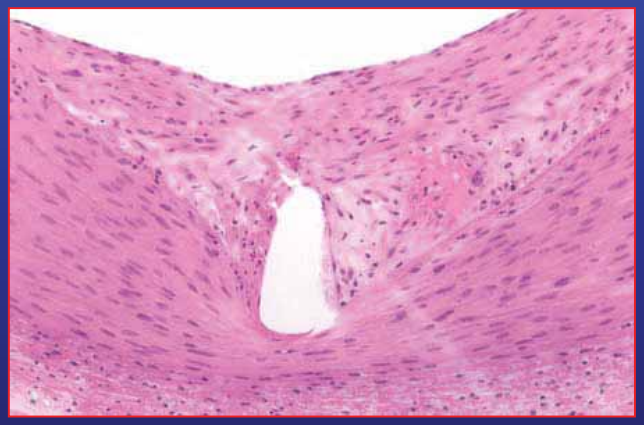


Bare Stainless Steel (SS) stent at 7 days

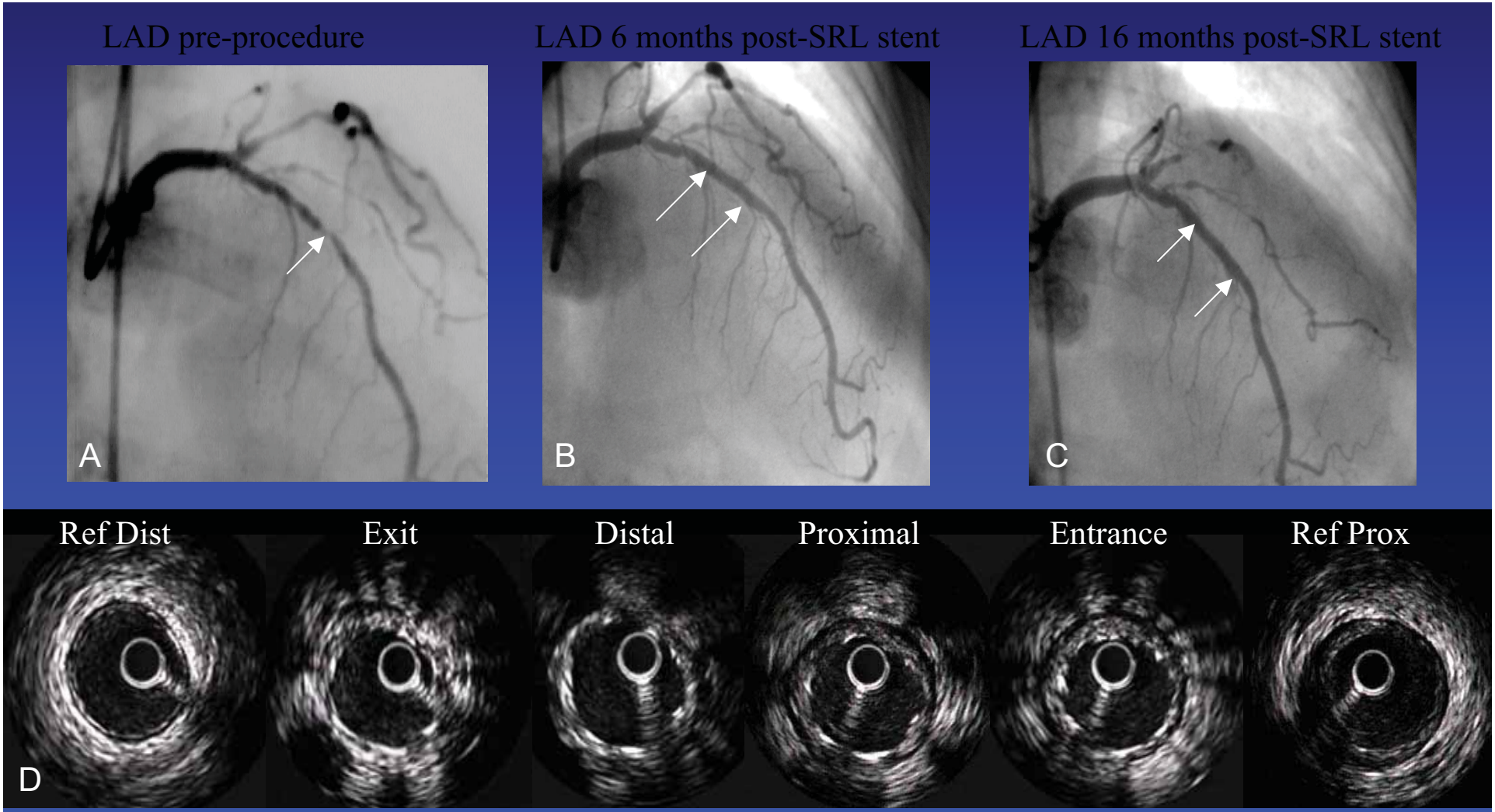


Sirolimus-eluting stent at 28 days

PIG NORMAL CORONARY ARTERIES



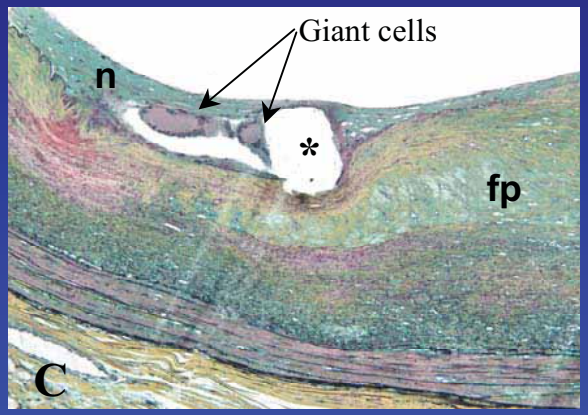
Bare SS stent at 28 days

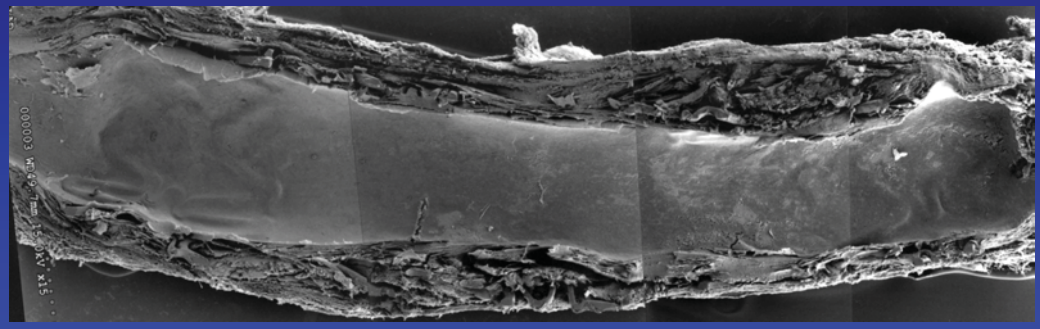


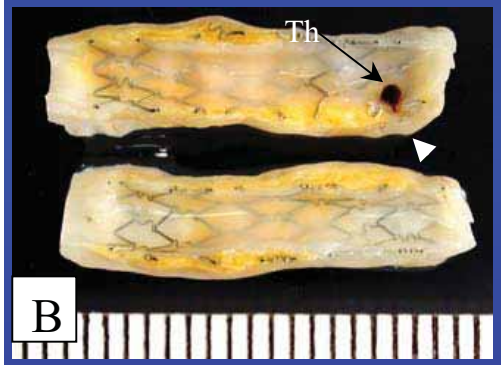
Sirolimus-Eluting Stent Implanted in Human Coronary Artery for 16 Months: Pathologic Findings

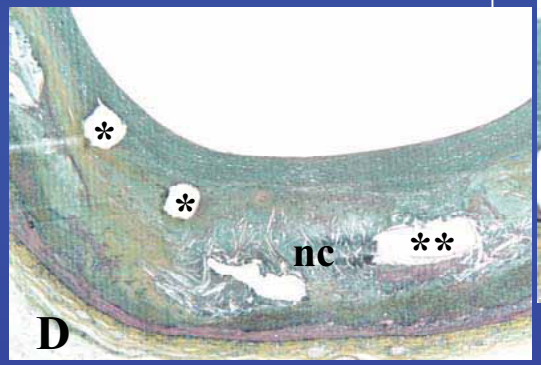
Giulio Guagliumi, Andrew Farb, Giuseppe Musumeci
Orazio Valsecchi, Maurizio Tespili, Teresio Motta,
Renu Virmani, M.D.

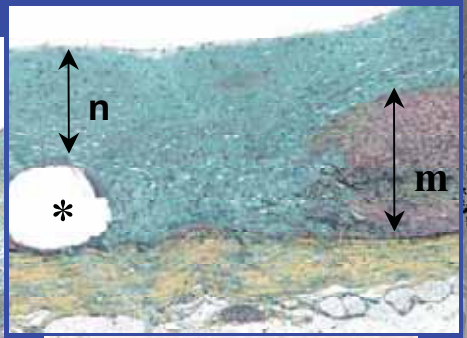
Sirolimus-Eluting Stent Implanted in Human Coronary Artery for 16 Months: Pathologic Findings

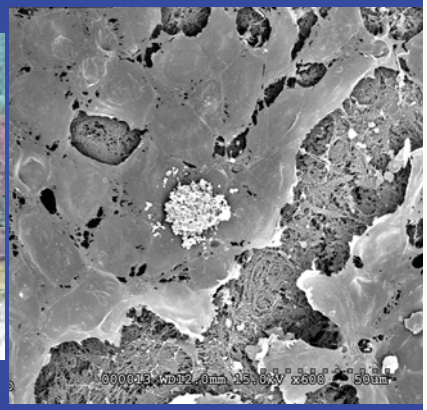


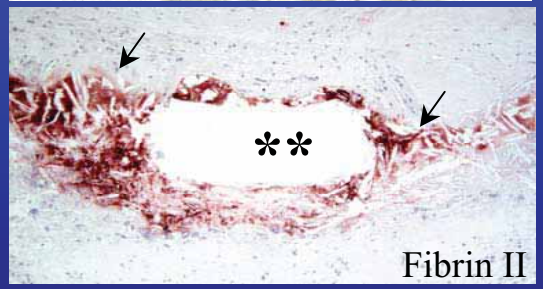












- Well-healed neointima
- Very small thrombus at side branch

- Fibrin w/strut embedded in core
- Minimal inflammation

- >80% surface endothelialization
- Loose intercellular junctions
- Rare minute platelet aggregates