

# 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 organization(s) listed below.

**Consultant:** 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

**Employment in industry:** No

**Honorarium:** 480 Biomedical, Abbott Vascular, Boston Scientific, Cordis J&J, Lutonix, Medtronic, Merck, Terumo Corporation, and W.L. Gore.

**Institutional grant/research support:** 480 Biomedical, Abbott Vascular, Atrium, BioSensors International, Biotronik, Boston Scientific, Cordis J&J, GSK, Kona, Medtronic, MicroPort Medical, CeloNova, OrbusNeich Medical, ReCore, SINO Medical Technology, Terumo Corporation, and W.L. Gore.

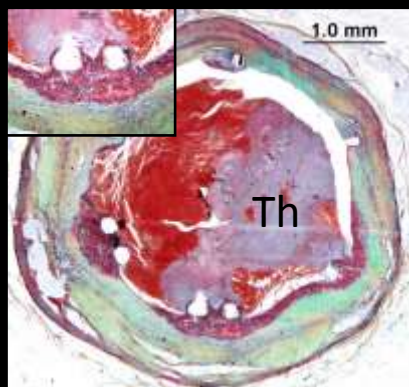
**Owner of a healthcare company:** No

**Stockholder of a healthcare company:** No

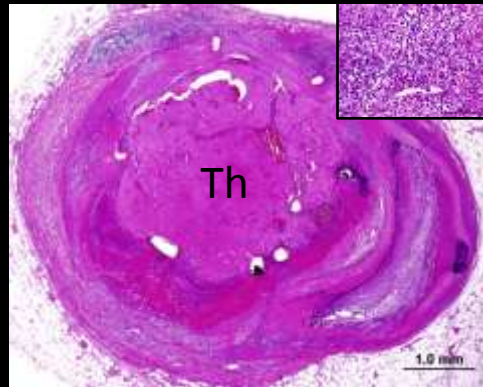
# Problems Encountered with 1<sup>st</sup>-Generation DES (Durable polymers)

- Thick struts
- Uneven polymer distribution with poor integrity, and thick coating (~15 microns) of durable polymers
- High drug dose

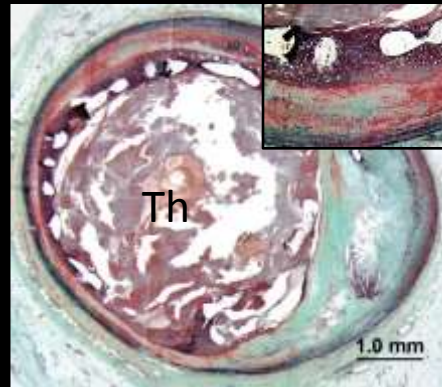
- ✓ Delayed arterial healing
- ✓ Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition
- ✓ Late stent thrombosis
- ✓ Stent Fracture
- ✓ Neoatherosclerosis



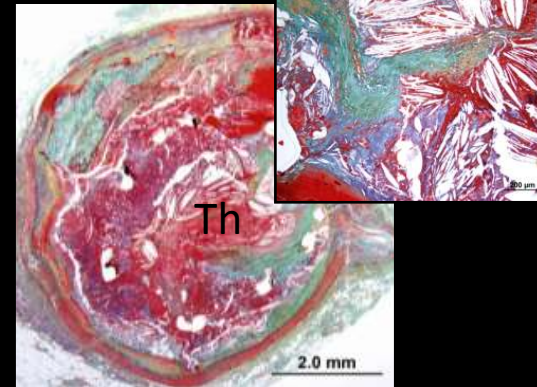
Uncovered struts



Hypersensitivity reaction



Malapposition from  
excessive fibrin deposition

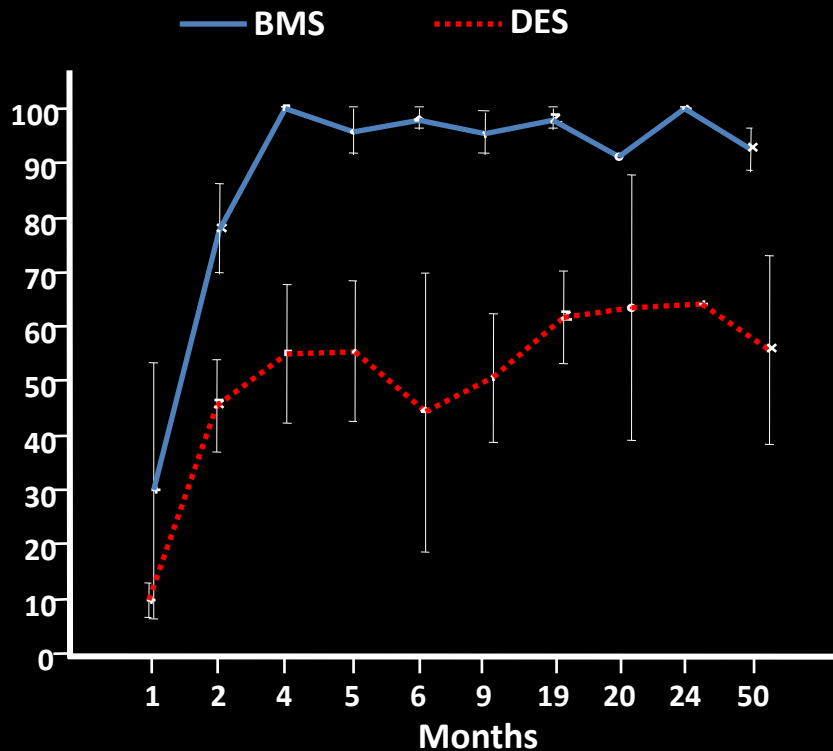


Neoatherosclerosis

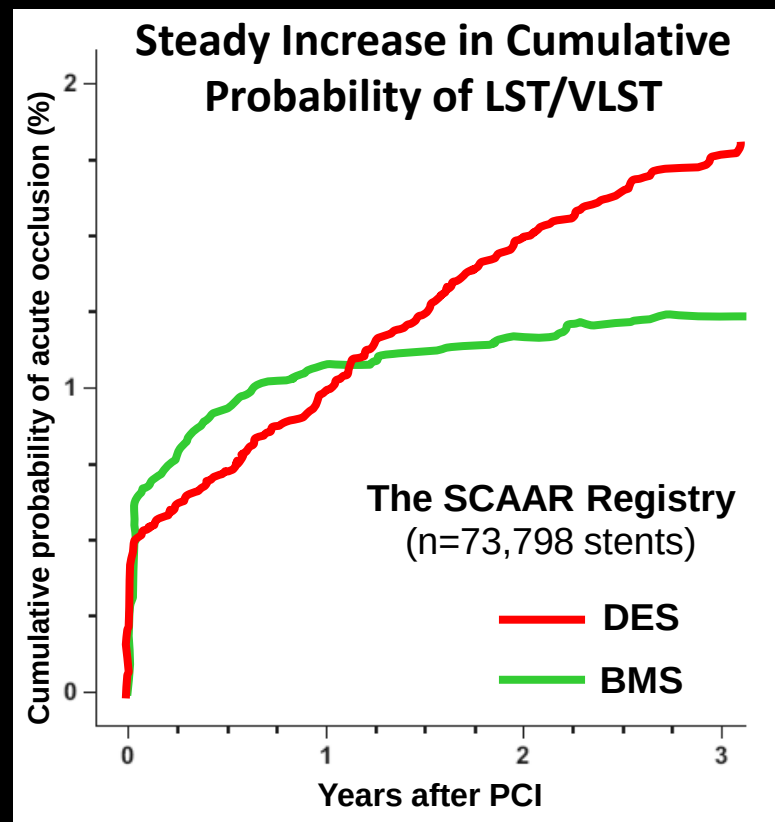
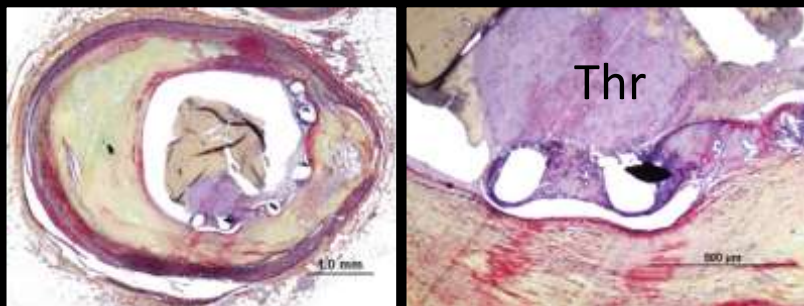
# Endothelialization and Stent Thrombosis (LST/VLST)

## Following 1<sup>st</sup>-generation DES vs BMS

### Mean % Endothelialization



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



Lagerqvist, et al. Circ Cardiovasc Intervent 2009

### Annual Rate of LST/VLST

- ✓ 0.4-0.6%/year up to 4 years (Bern/Rotterdam registries: SES and PES)
- ✓ 0.26%/year up to 5 years (j-Cypher: SES)

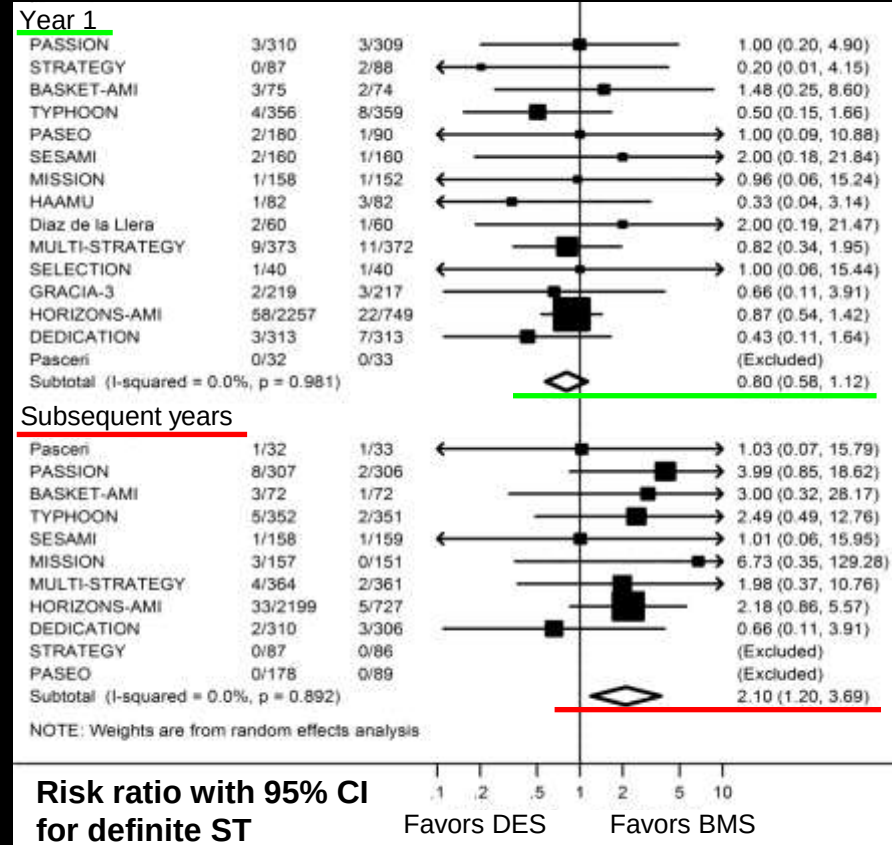
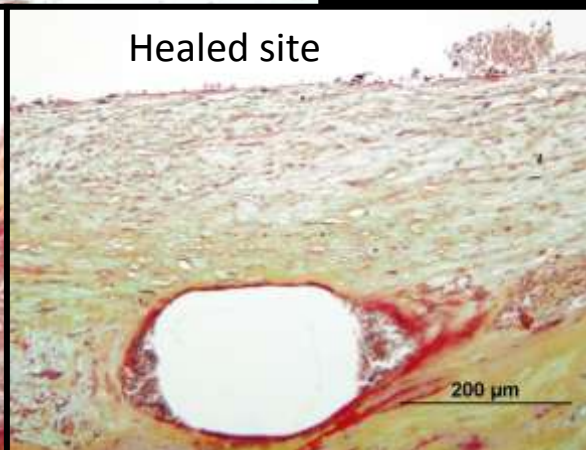
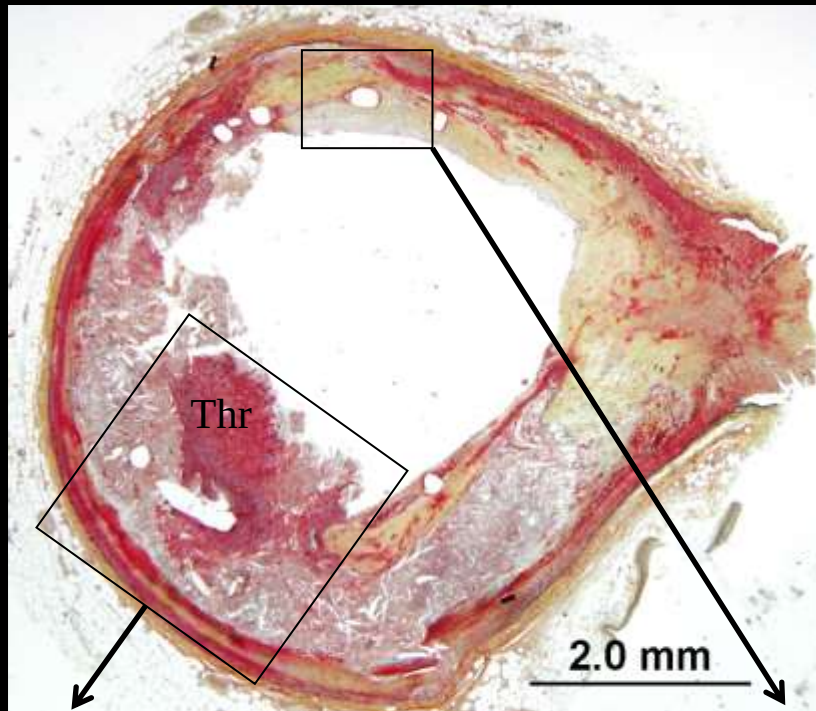
Wenaweser P, et al. J Am Coll Cardiol 2008;52:1134-40.

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



# LST following DES placement for ACS

65M, presenting ACS, PES was implanted in the LAD 9 months antemortem



A meta-analysis of 15 RCTs comparing 1<sup>st</sup>-generation DES with BMS in patients with STEMI. Kalesan B et al. Eur Heart J 2012;33:977-987.

However, the 2<sup>nd</sup>-gen CoCr-EES showed less stent thrombosis vs. BMS (ML VISION) in STEMI up to 2 years (EXAMINATION trial).

Sabate M, et al. Lancet 2012;380:1482-1490.

Sabate M. TCT 2012..

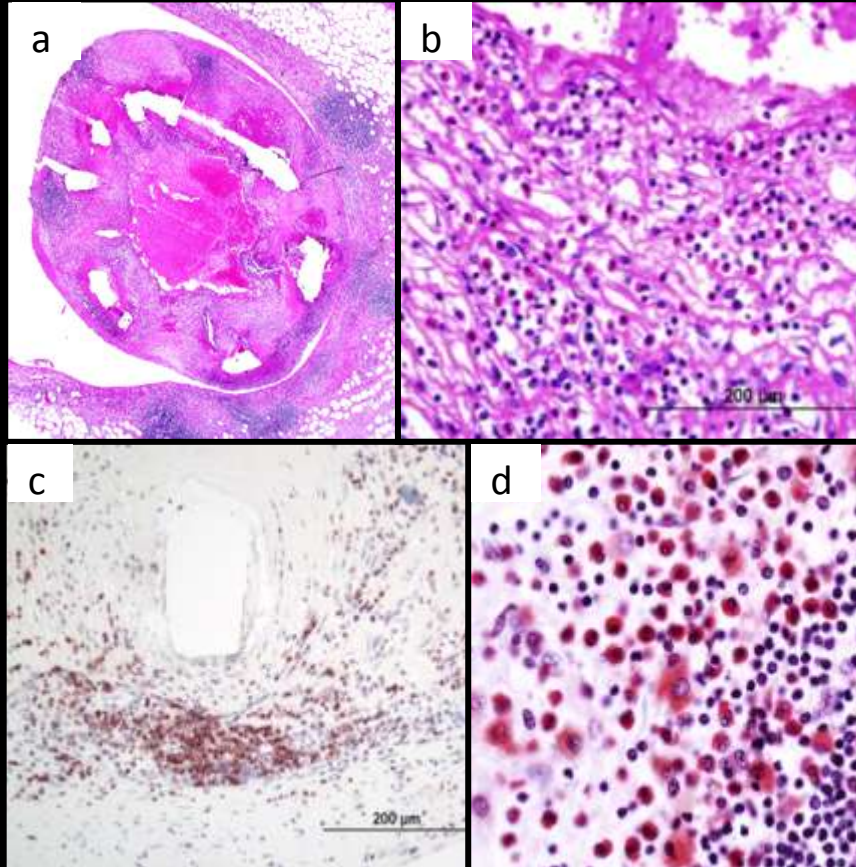


# Hypersensitivity Reaction to SES

40F with 2 SES in LAD and RCA, died suddenly 4 days after surgical removal of melanoma. DAPT was discontinued 5 days before surgery.

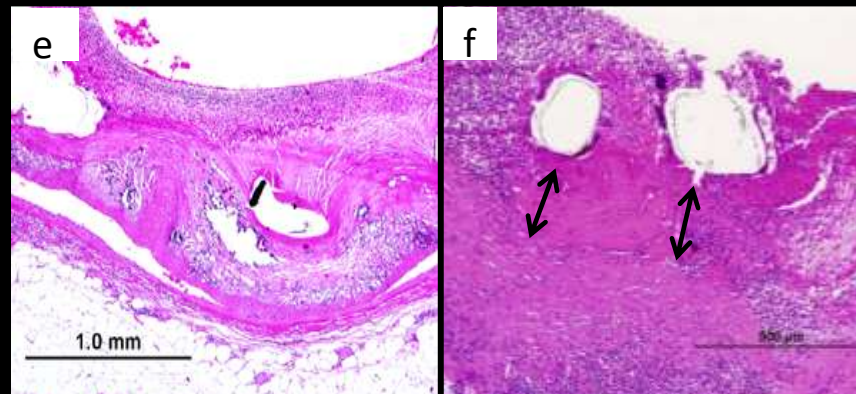
(a)-(d)

LAD: SES  
17months

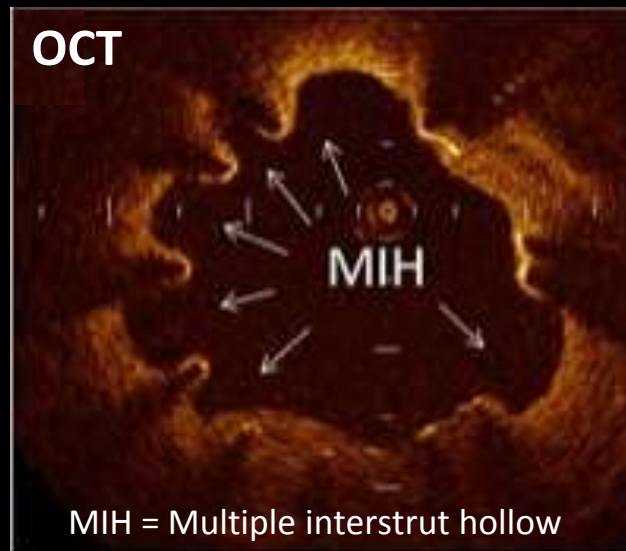
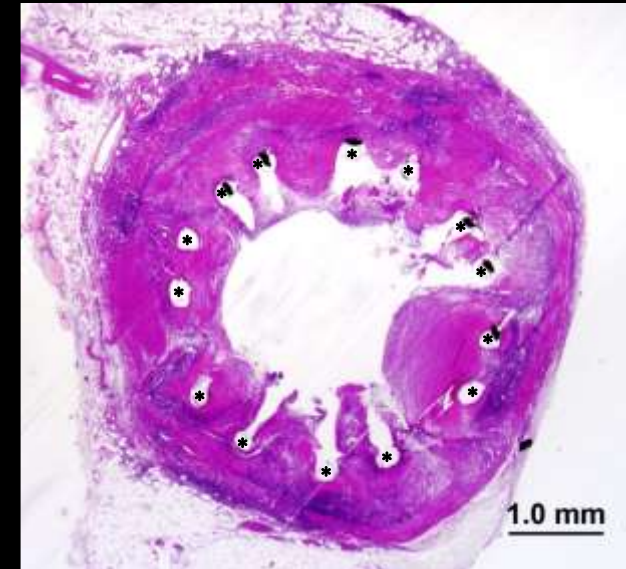


(e), (f)

RCA: SES  
17months



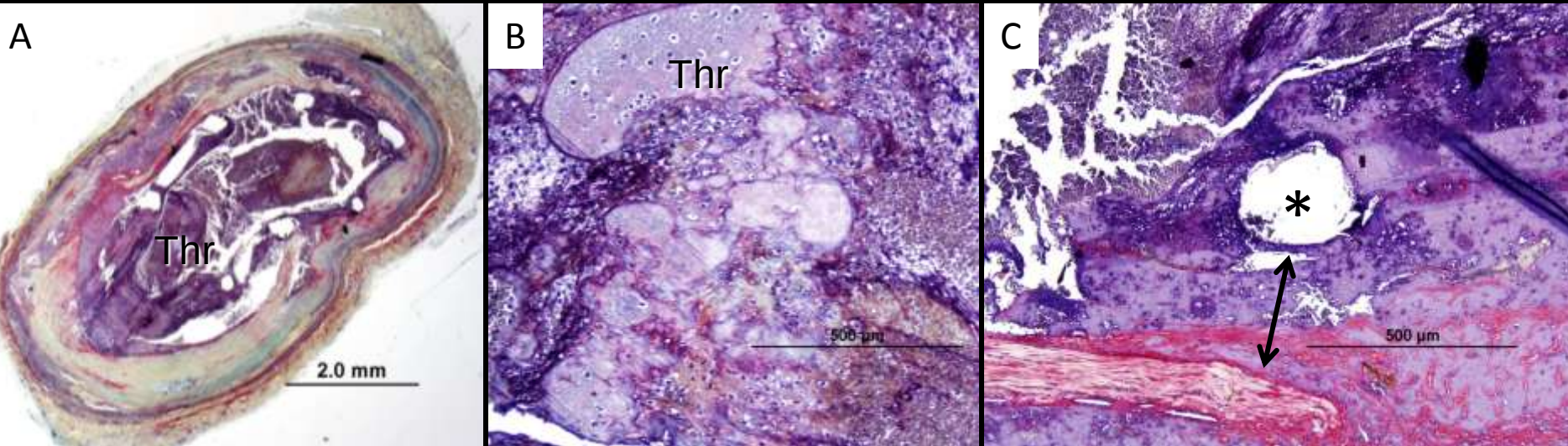
39F SES in LMCA for 5 yrs.  
The patient recently stopped taking medication due to lack of insurance.



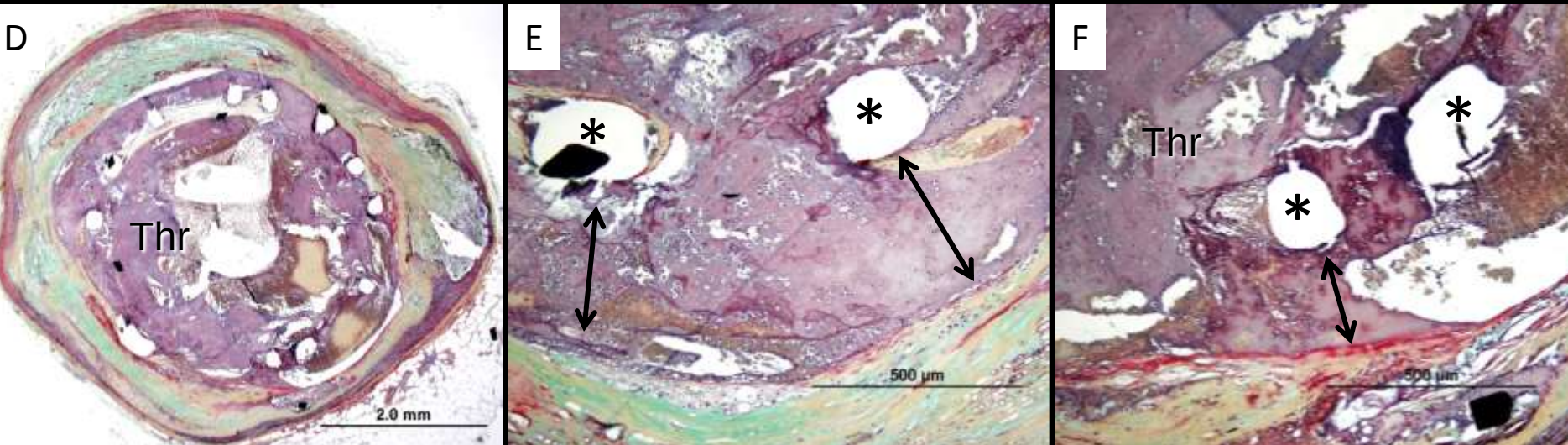


# Fibrin accumulation & Malapposition (Positive remodeling) in PES

PES (3 months)

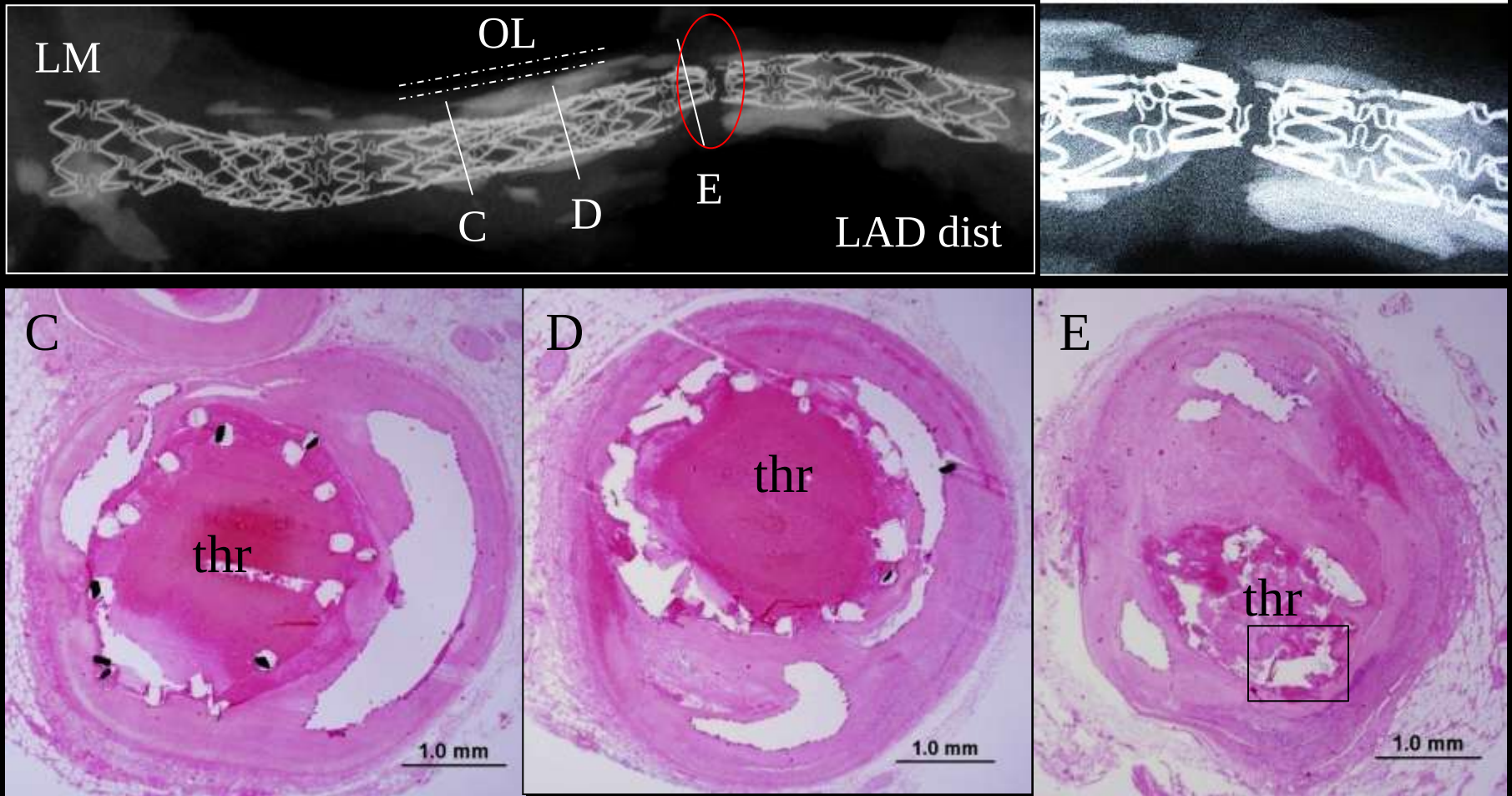


PES (40 months)



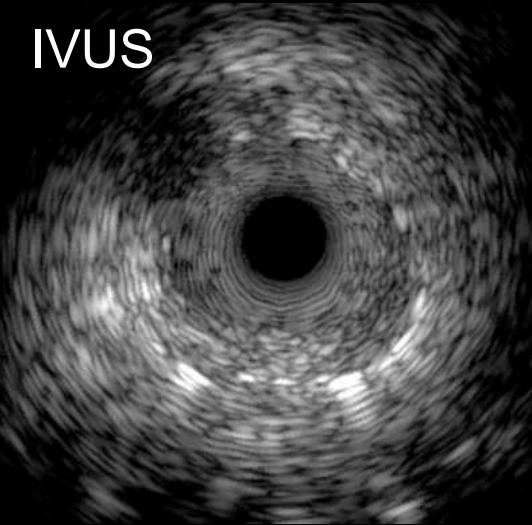


# Stent Fracture in SES

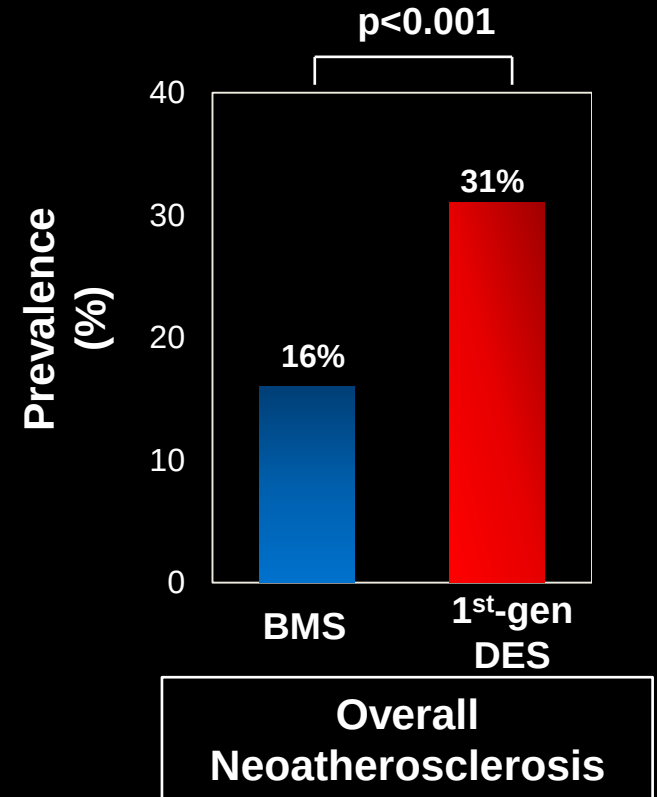
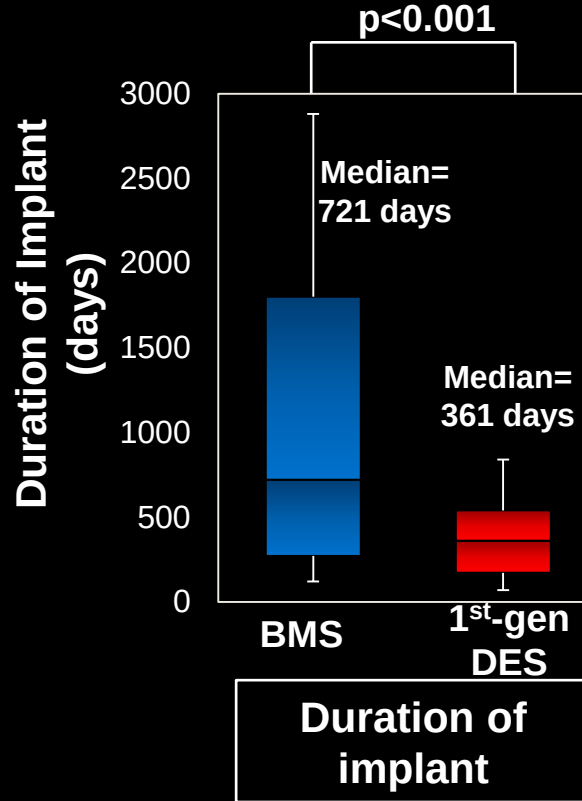
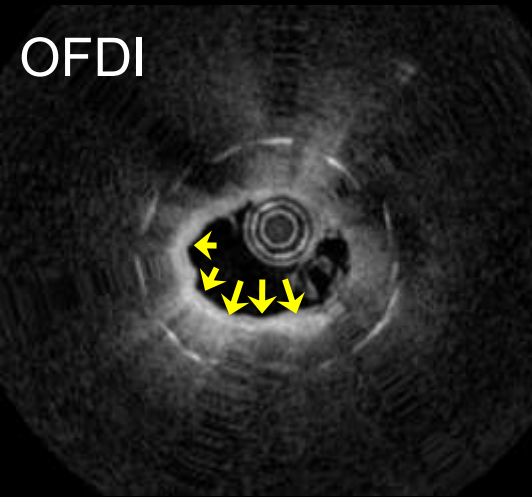


# Prevalence of Neoatherosclerosis

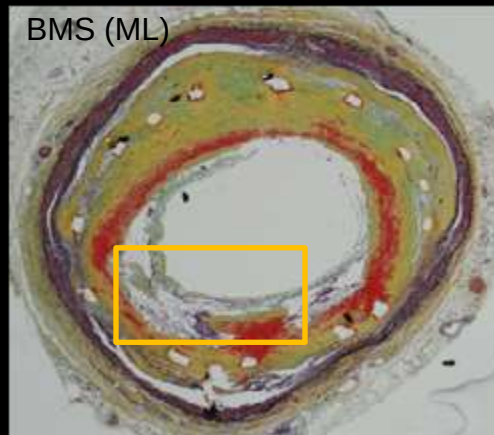
IVUS



OFDI



Nakazawa G, et al. JACC Imaging 2009 Nakano M, et al. JACC Imaging 2012



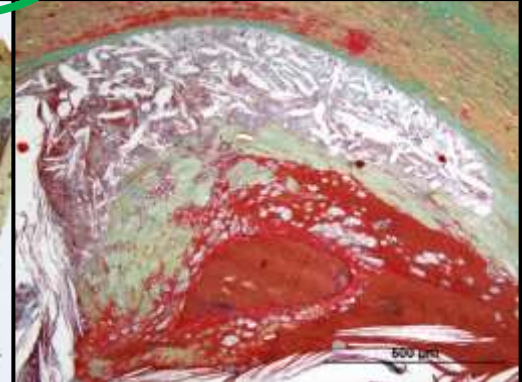
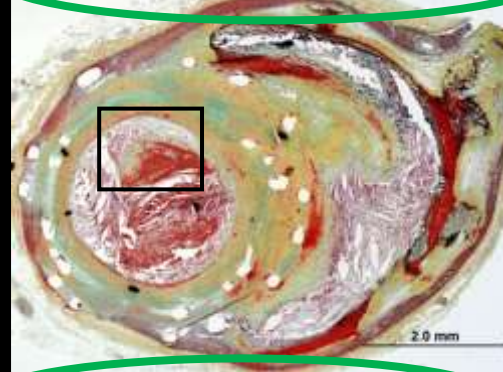


# In-stent Plaque Rupture (Neoatherosclerosis)

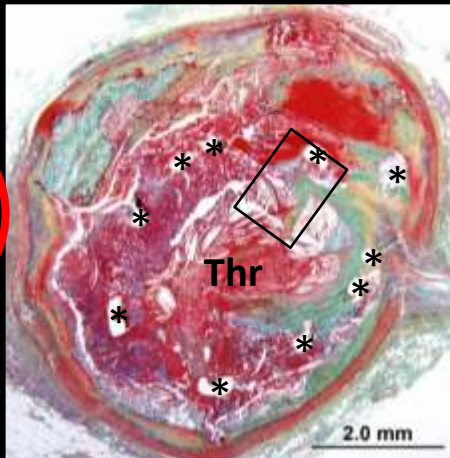
43M, BMS  
(Mini-Crown)  
84 months



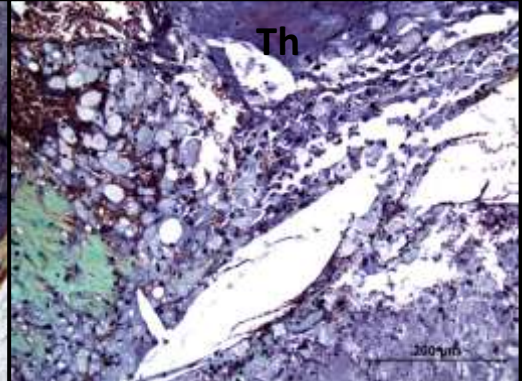
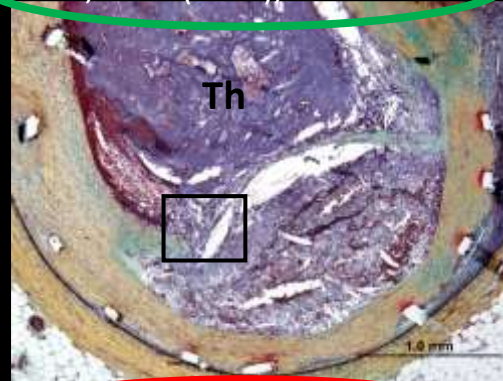
43M, BMS (ML Zeta), 61 months



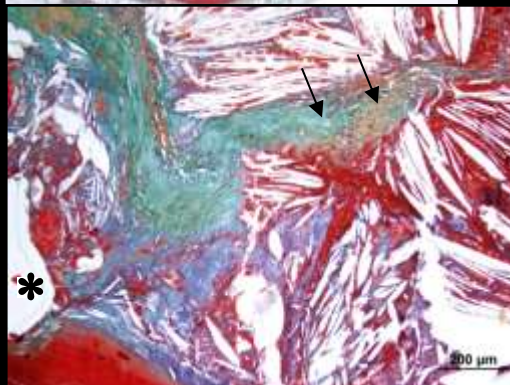
61M  
DES (SES) 37  
months



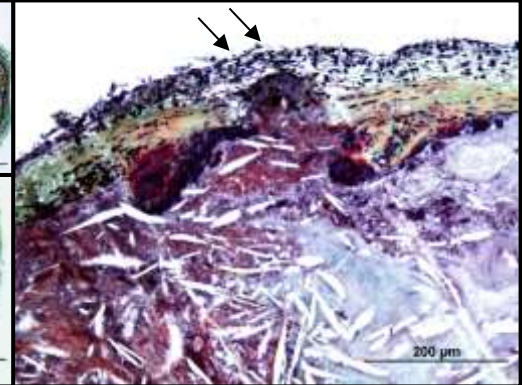
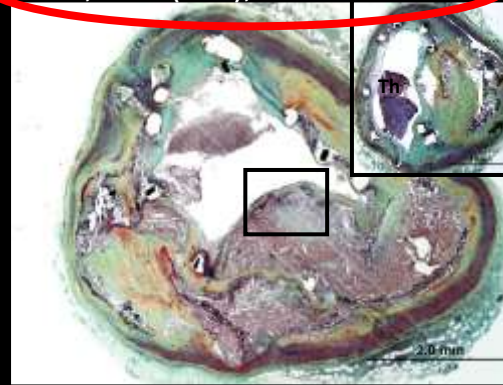
47M, BMS (GR II), 96 months



4 of 10 cases  
had severe  
restenosis



59M, DES (SES), 23 months



# What did stent technology change from 1<sup>st</sup> DES to 2<sup>nd</sup> DES?

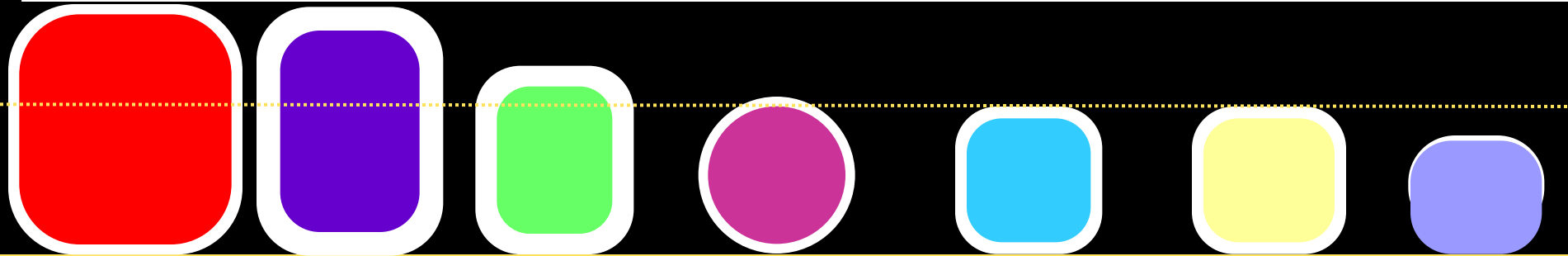
|         |
|---------|
| 1st DES |
| 2nd DES |

- Thick struts
  - Thinner struts
- Uneven polymer distribution with poor integrity, and thick coating (~15 microns) of durable polymers
  - Thinner and more biocompatible polymer (still durable)
- High drug dose
  - Reduced drug dose



# Thin Stent Strut Profiles on New Stent Platforms

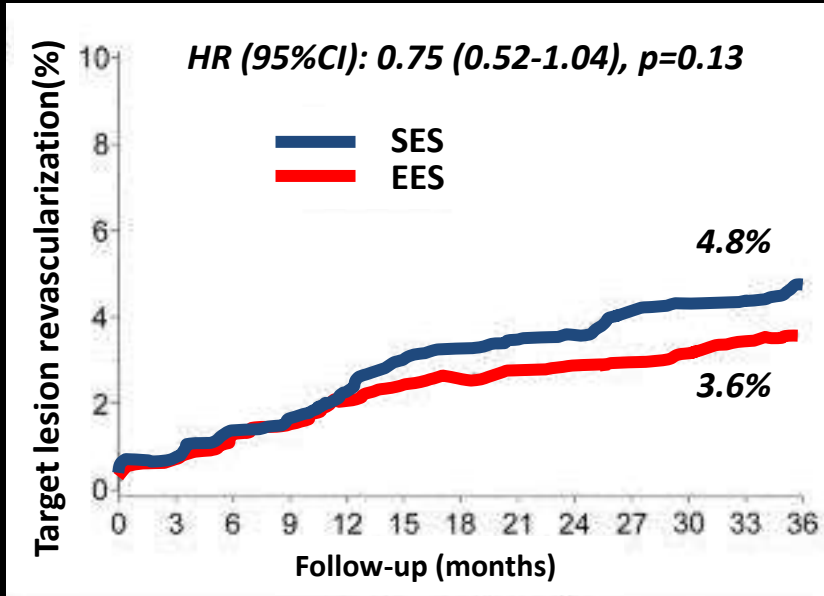
| 1 <sup>st</sup> Generation |                |                | 2 <sup>nd</sup> Generation |                            |                 | 3 <sup>rd</sup> Gen |
|----------------------------|----------------|----------------|----------------------------|----------------------------|-----------------|---------------------|
| Cypher™                    | TAXUS Express™ | TAXUS Liberte™ | Resolute Integrity™        | Xience V™<br>Xience Prime™ | PROMUS Element™ | SYNERGY™            |



| Drug Type              |                      |                      |                        |                              |                      |                       |
|------------------------|----------------------|----------------------|------------------------|------------------------------|----------------------|-----------------------|
| Sirolimus              | Paclitaxel           | Paclitaxel           | Zotarolimus            | Everolimus                   | Everolimus           | Everolimus            |
| Drug Concentration     |                      |                      |                        |                              |                      |                       |
| 1.4 µg/mm <sup>2</sup> | 1 µg/mm <sup>2</sup> | 1 µg/mm <sup>2</sup> | 1.6 µg/mm <sup>2</sup> | 1 µg/mm <sup>2</sup>         | 1 µg/mm <sup>2</sup> | ~1 µg/mm <sup>2</sup> |
| Avg. Coating Thickness |                      |                      |                        |                              |                      |                       |
| 7µm / side             | 16µm/side            | 14µm/side            | 6µm / side             | 8µm / side                   | 8µm / side           | 4µm                   |
| Strut Thickness        |                      |                      |                        |                              |                      |                       |
| 140 µm<br>(0.0055")    | 132 µm<br>(0.0052")  | 96 µm<br>(0.0038")   | 89 µm<br>(0.0035")     | 81 µm<br>(0.0032")           | 81 µm<br>(0.0032")   | 74 µm<br>(0.0029")    |
| BMS Platform           |                      |                      |                        |                              |                      |                       |
| Bx Velocity™           | Express™             | Liberte™             | Integrity™             | Vision™ and<br>Multi Link 8™ | Element™             | SYNERGY™              |
| Material               |                      |                      |                        |                              |                      |                       |
| Stainless Steel        | Stainless Steel      | Stainless Steel      | Cobalt Nickel          | Cobalt Chromium              | Platinum Chromium    | Platinum Chromium     |

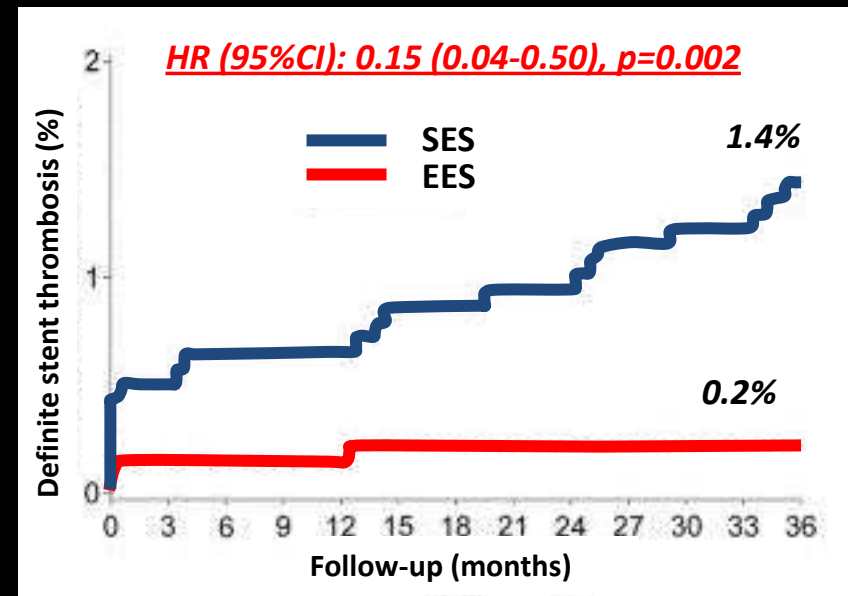
# Three-year outcomes after revascularization with EES and SES (SORT OUT IV Trial)

## Target lesion revascularization (TLR)



| Patients at risk | 0 month | 12 months | 24 months | 36 months |
|------------------|---------|-----------|-----------|-----------|
| EES              | 1390    | 1320      | 1280      | 1241      |
| SES              | 1384    | 1318      | 1270      | 1229      |

## Definite stent thrombosis

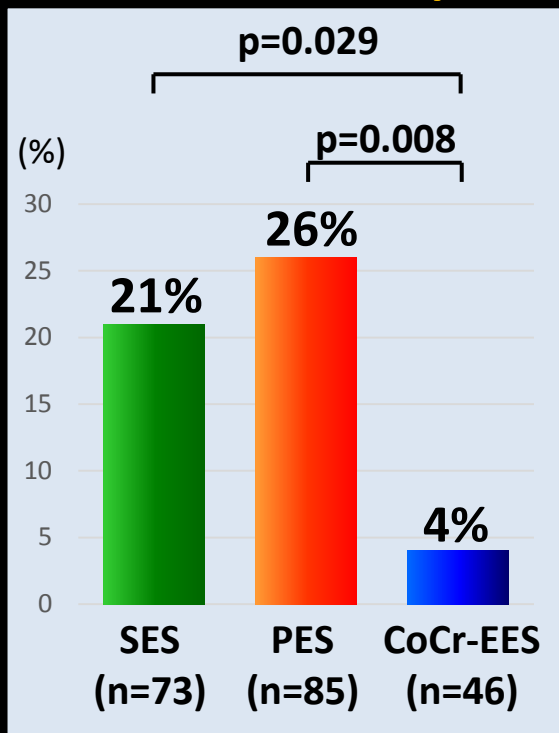


| Patients at risk | 0 month | 12 months | 24 months | 36 months |
|------------------|---------|-----------|-----------|-----------|
| EES              | 1390    | 1347      | 1316      | 1287      |
| SES              | 1384    | 1341      | 1305      | 1271      |



# Pathology of 2<sup>nd</sup>-gen CoCr-EES vs. 1<sup>st</sup>-gen SES/PES

## Prevalence of LST/VLST

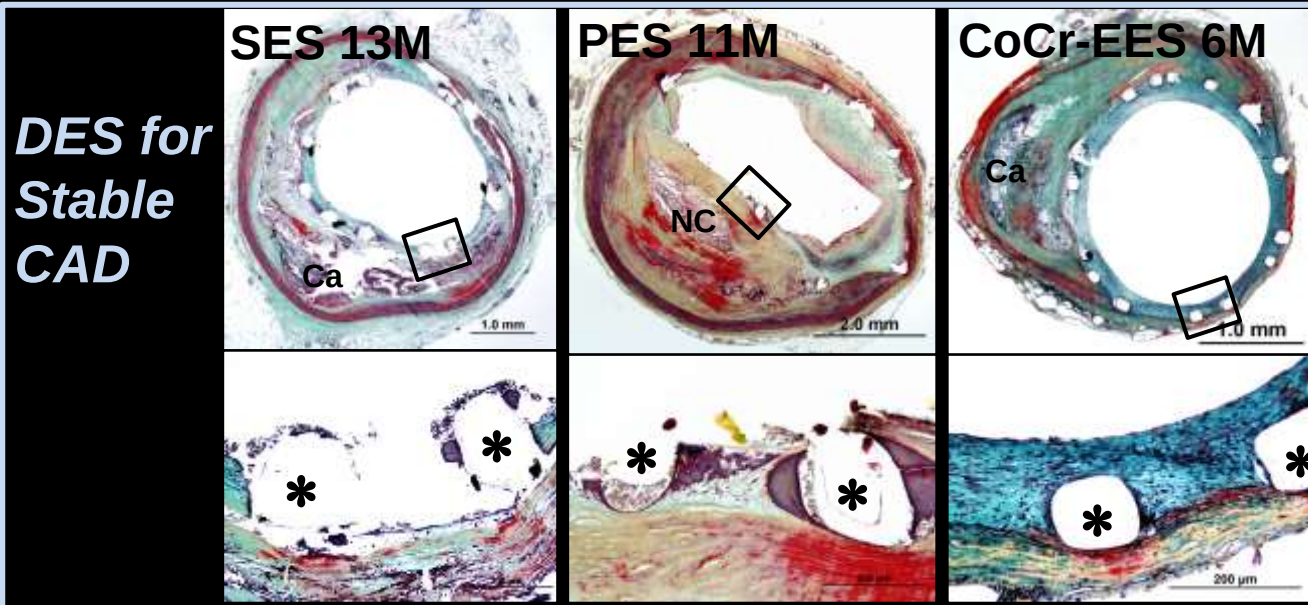


Cypher: 15/73 (21%)  
Taxus: 22/85 (26%)  
Xience V: 2/46 (4%)

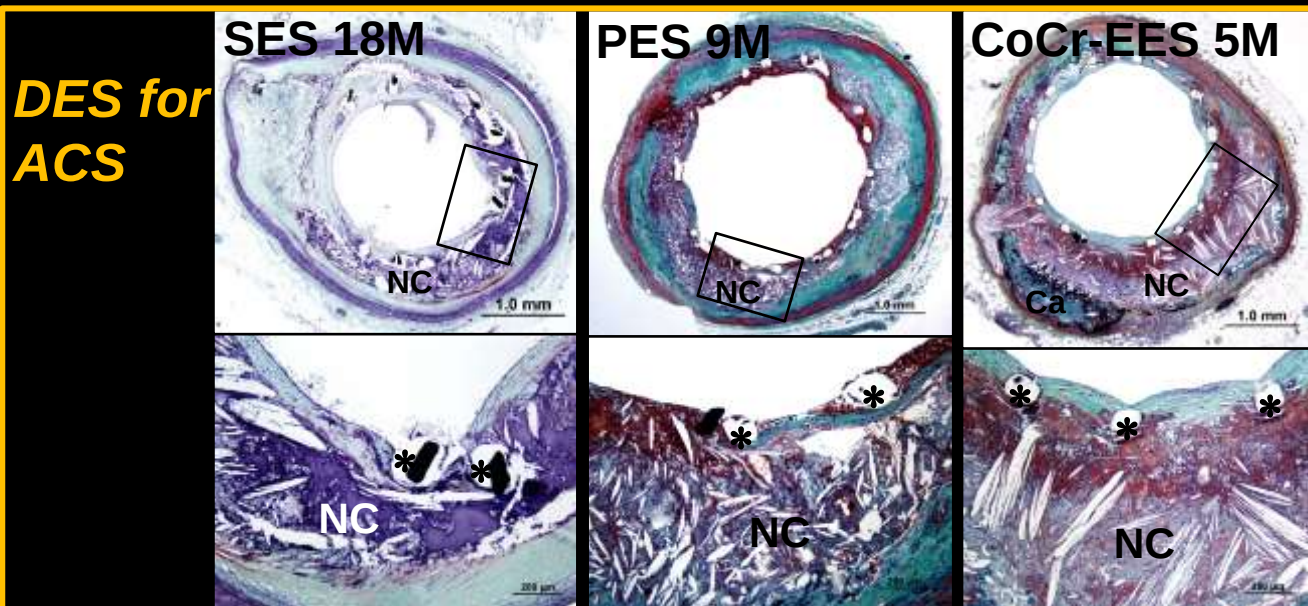
Endeavor: 0/6 (0%)  
Resolute: 0/1 (0%)

Duration of implant:  
>30 days, ≤3 years

## DES for Stable CAD



## DES for ACS



# Morphometric Analysis: CoCr-EES vs. SES/PES

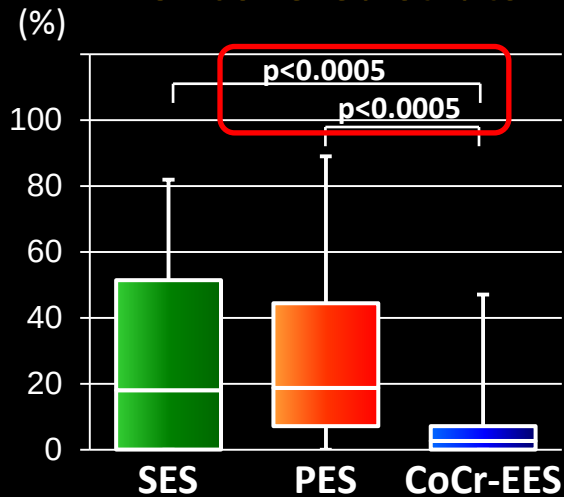
SES (n=72)

PES (n=78)

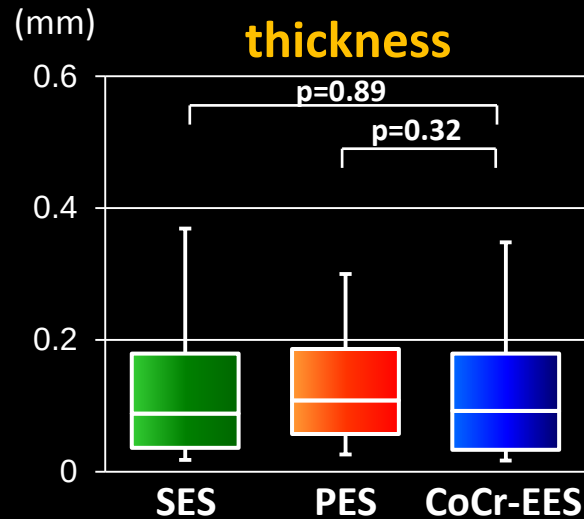
CoCr-EES (n=41)

Duration of implant:  
>30 days, ≤3 years

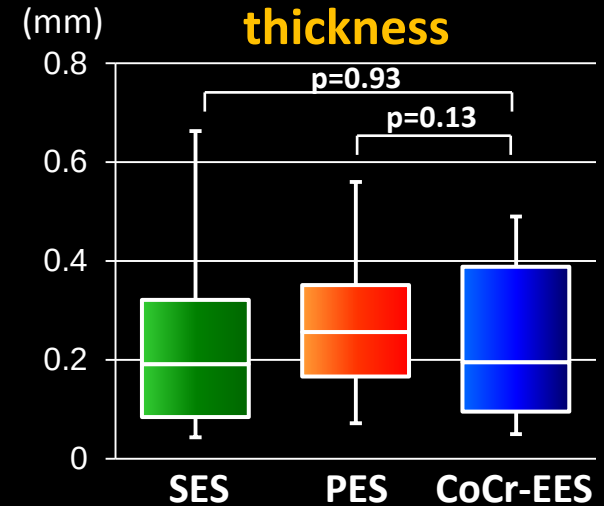
## Uncovered struts



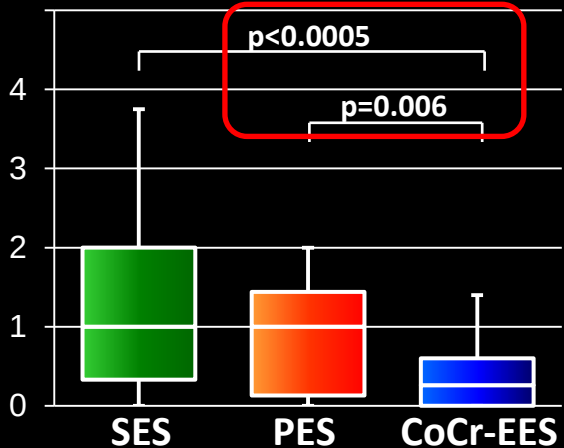
## Mean neointimal thickness



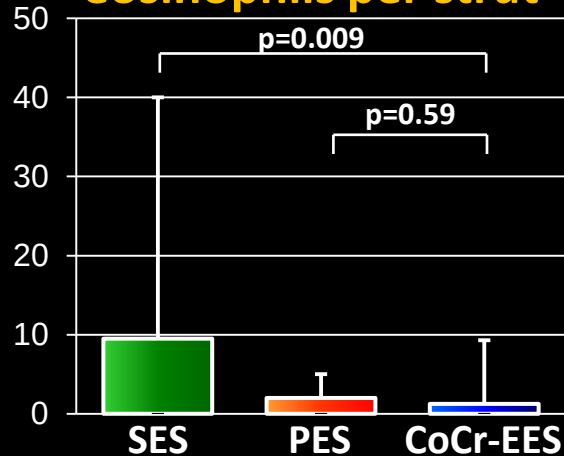
## Maximum neointimal thickness



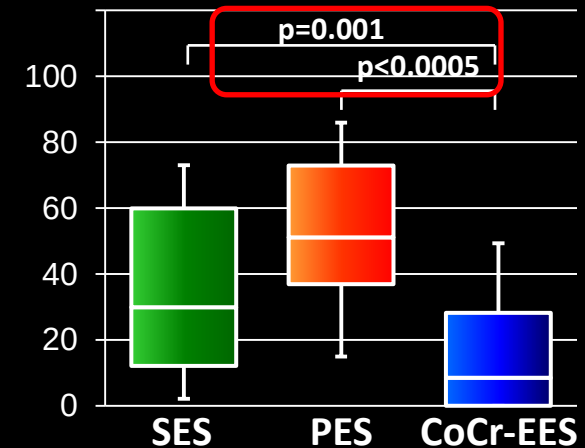
## Inflammation score



## Maximum number of eosinophils per strut



## Struts with fibrin



All statistical analyses were corrected for duration of implant.

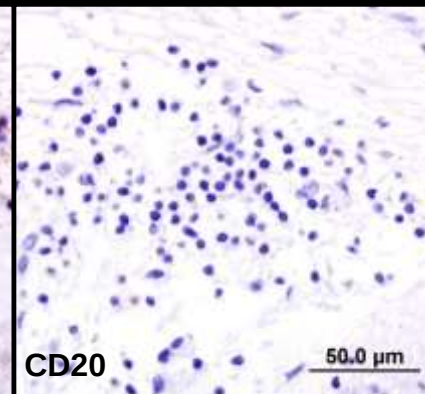
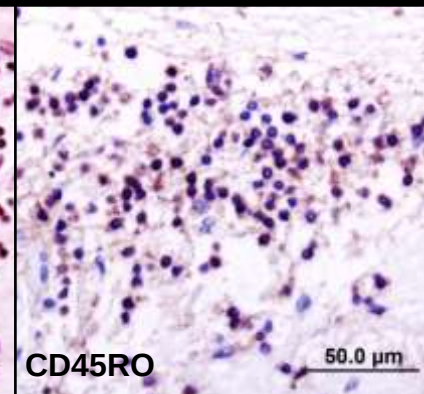
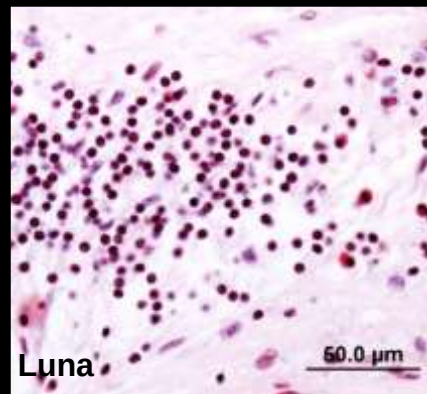
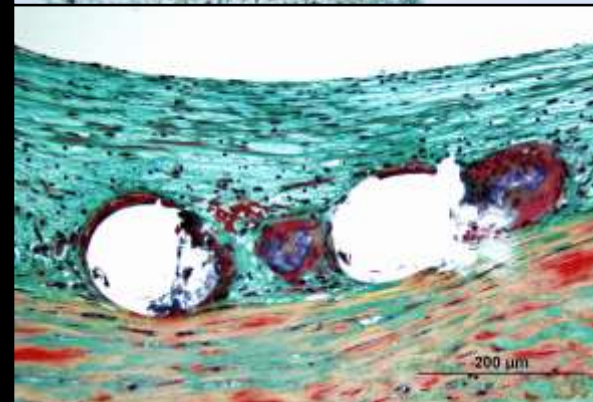
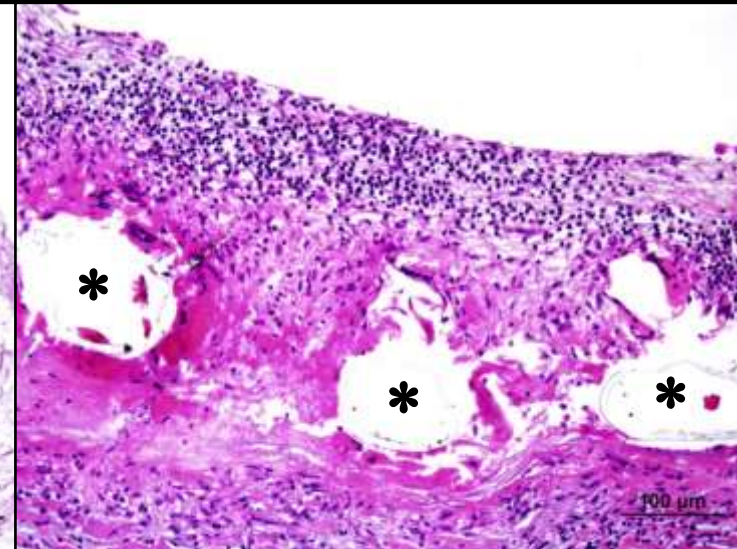
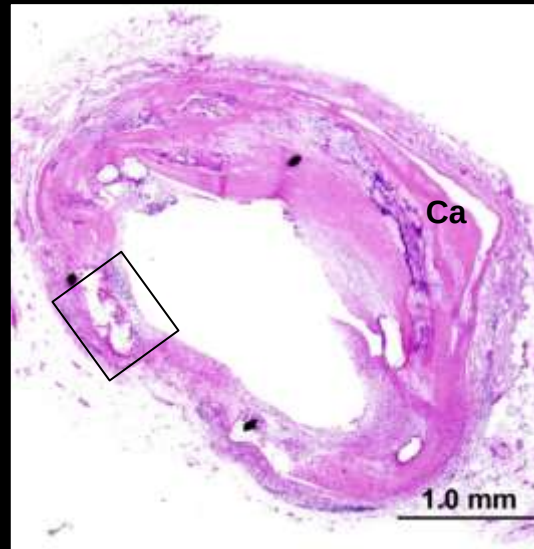
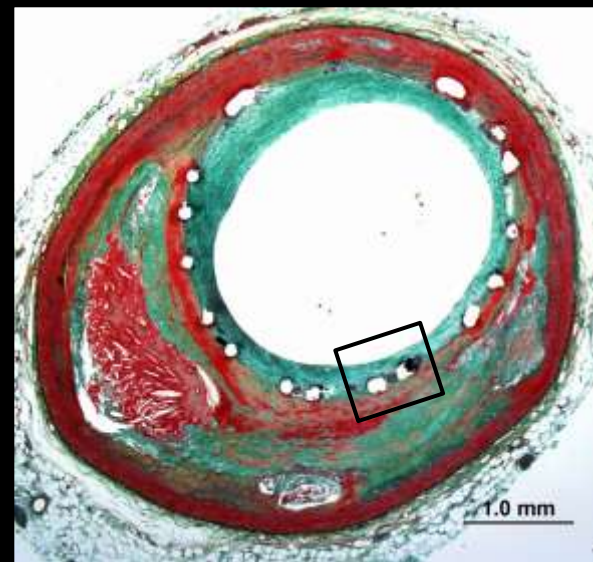
Modified from Otsuka F, et al. Circulation. 2014;129:211-223.



# Inflammation in the 2<sup>nd</sup>-generation DES

61M, E-ZES (3 months)

51M, CoCr-EES 4 months



Chronic inflammation consisting with giant cells secondary to polymer delamination in ZES

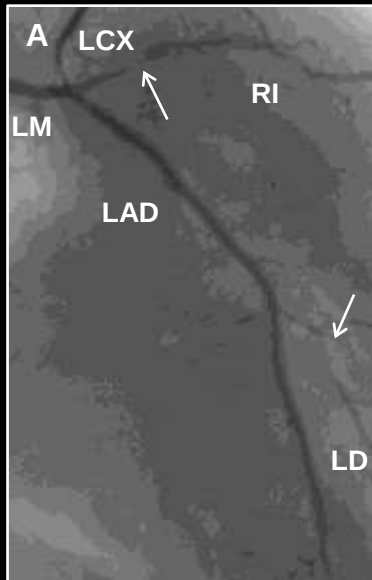
Otsuka F, et al. *Circulation*. 2014;129:211-223.



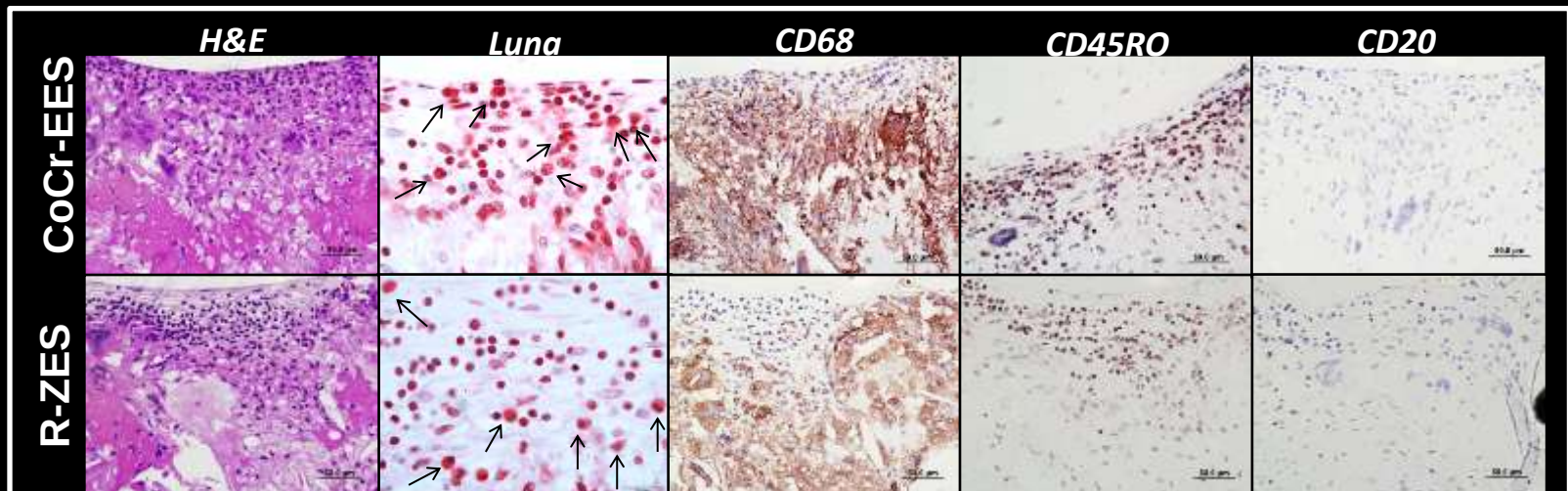
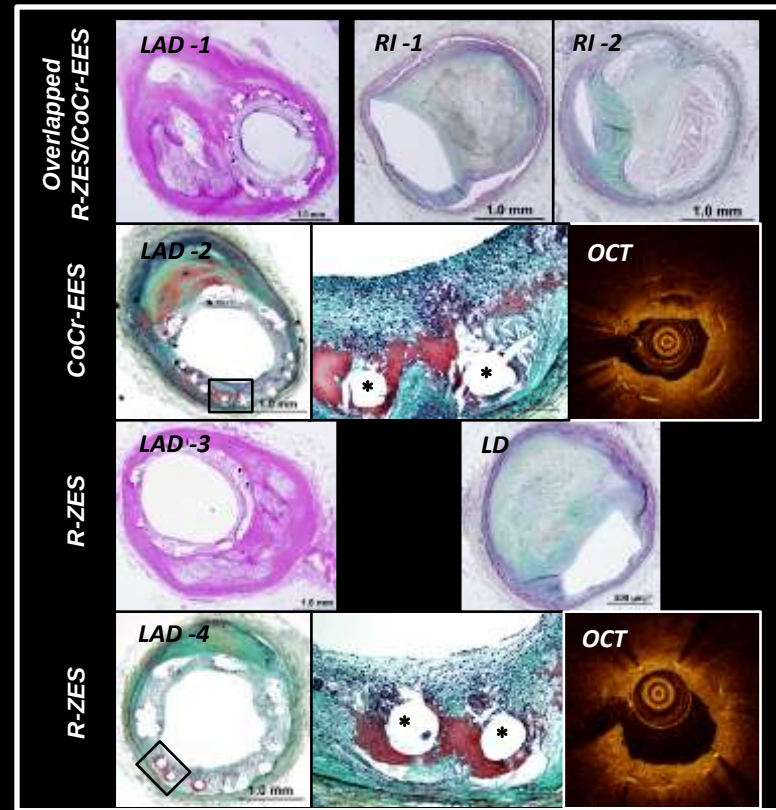
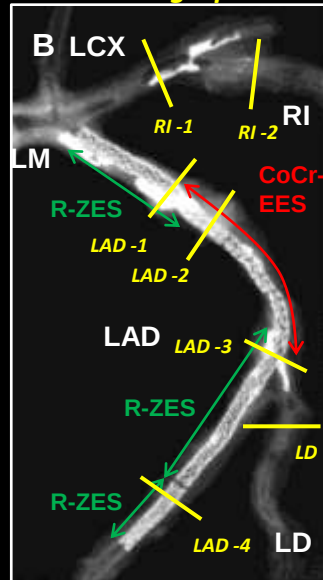
# Hypersensitivity Reaction in 2<sup>nd</sup> generation DES

A 55-year old male who presented with unstable angina secondary to diffuse disease in the LAD; four stents were implanted (3 Resolute zotarolimus-eluting stents (R-ZES) and a single cobalt-chromium everolimus-eluting stent (CoCr-EES)). At 238-days following implantation of the 4 stents the patient died suddenly.

**Coronary angiograph**



**Radiograph**

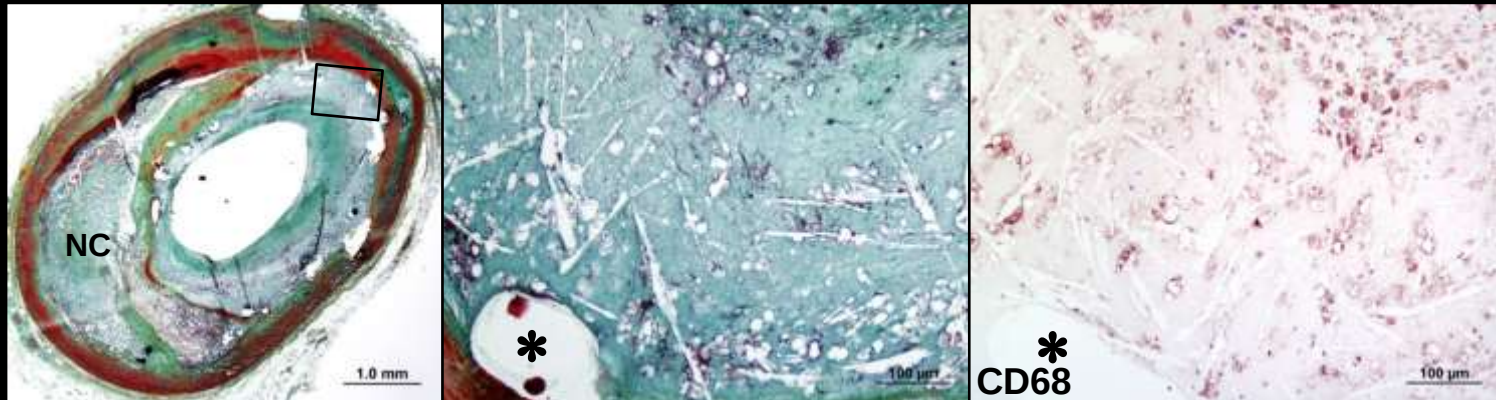


# Neoatherosclerosis in CoCr-EES

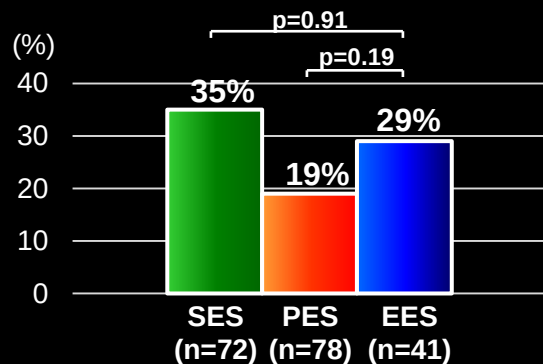
CoCr-EES  
24M



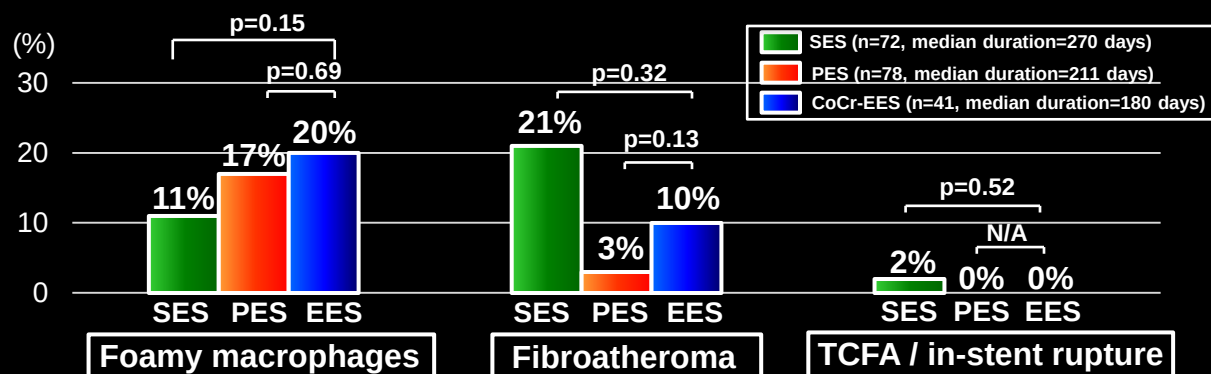
CoCr-EES  
36M



Overall prevalence of NeoAth



Prevalence of Various Features of Neoatherosclerosis

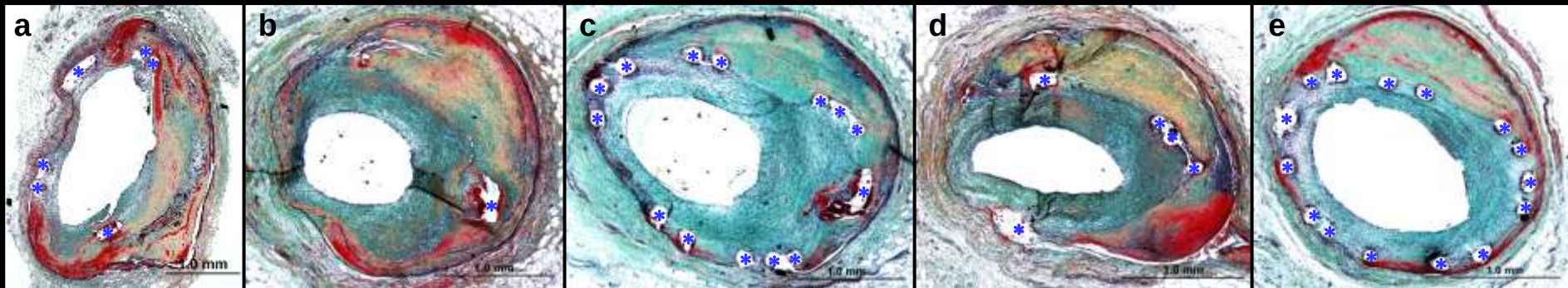
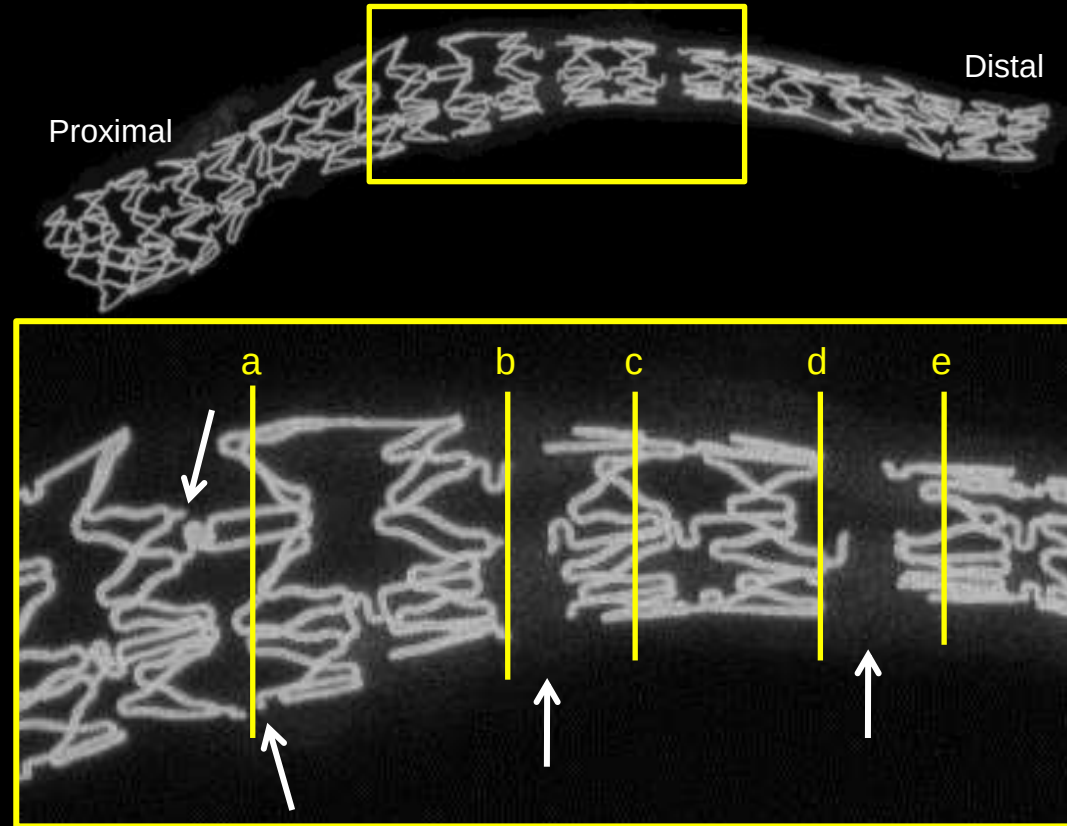
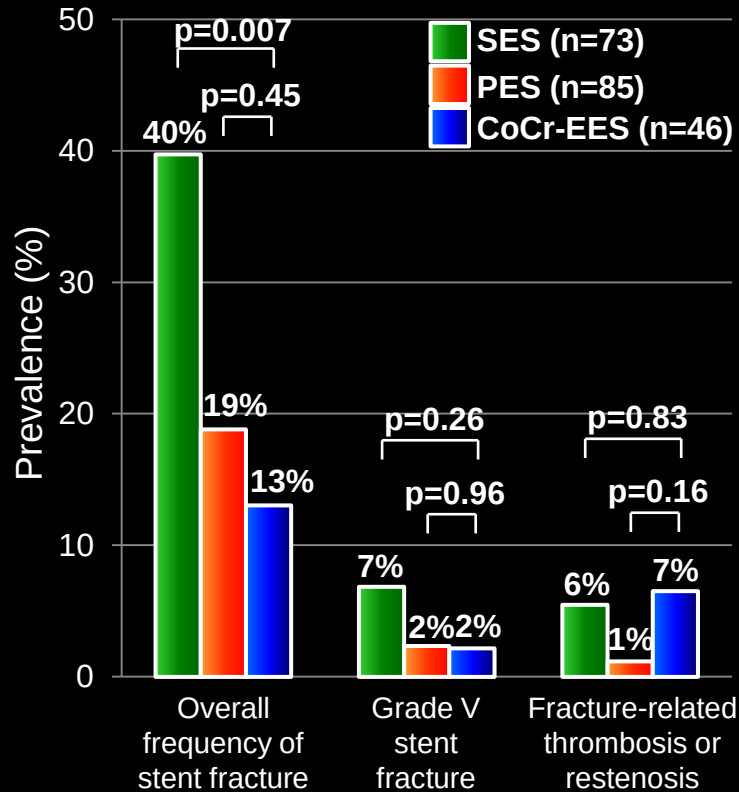


Duration of implant: >30 days, ≤3 years  
All statistical analyses were corrected for duration of implant.



# Stent Fracture in CoCr-EES

51M with CoCr-EES implanted in LOM for 4 months.

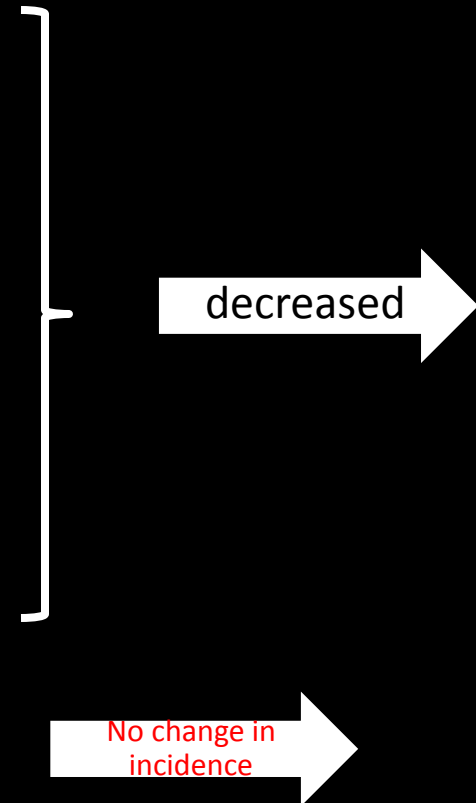


All statistical analyses were corrected for duration of implant.

Otsuka F, et al. *Circulation*. 2014;129:211-223.

# There is marked Improvement between 1<sup>st</sup> DES and 2<sup>nd</sup> DES.

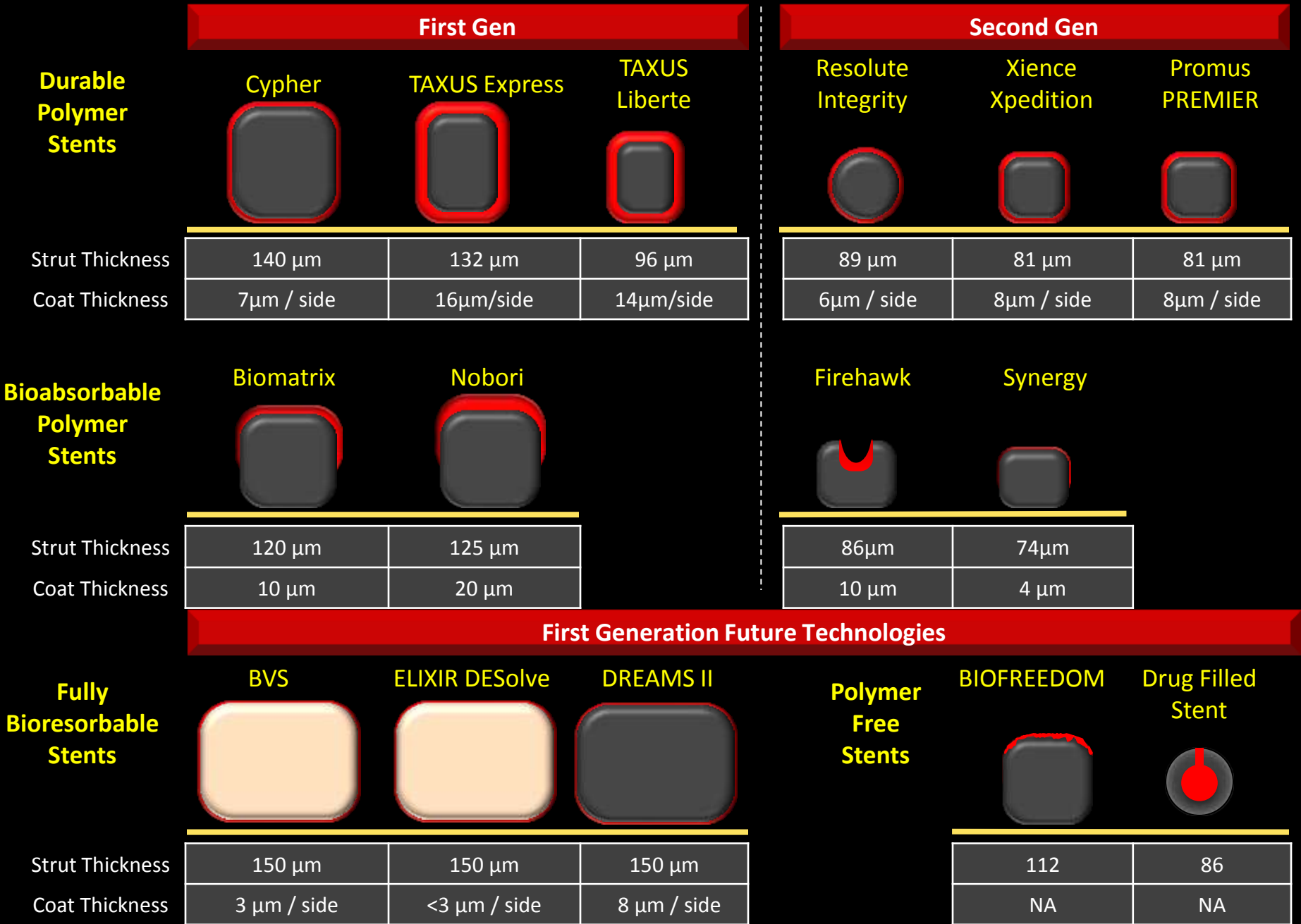
- ✓ Delayed arterial healing
- ✓ Uncovered struts
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- ✓ Hypersensitivity
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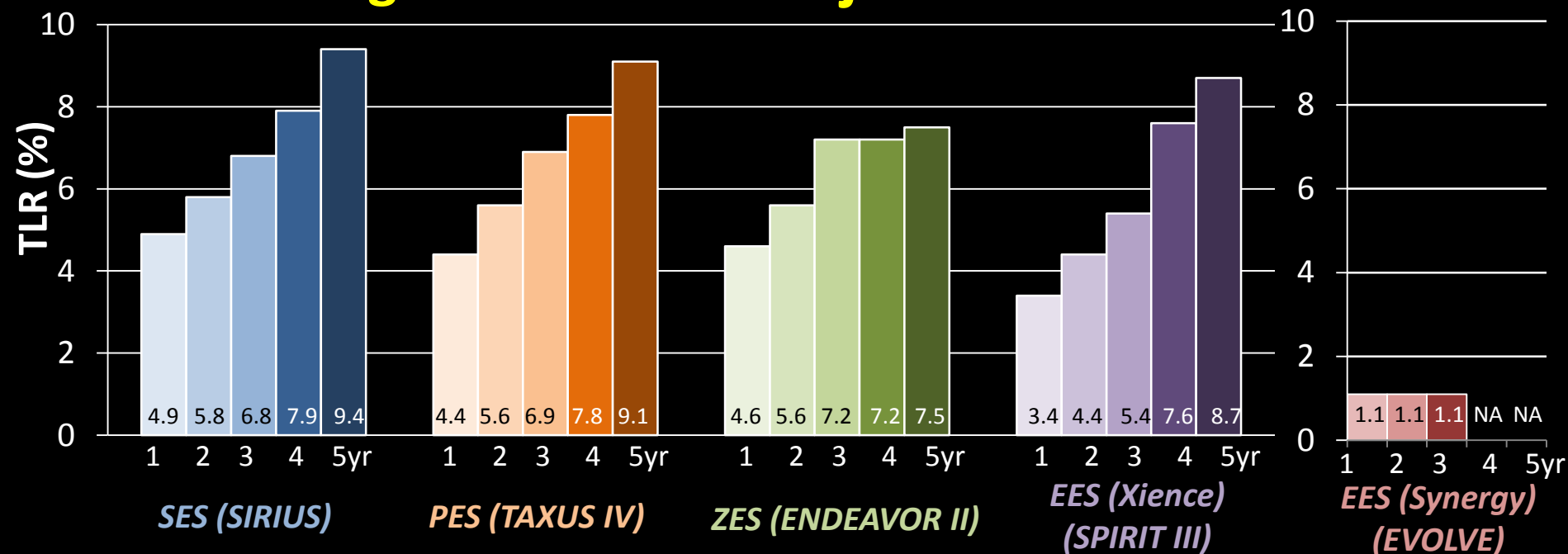
What do we expect from the  
next generation DES?

# Evolution of DES Technology

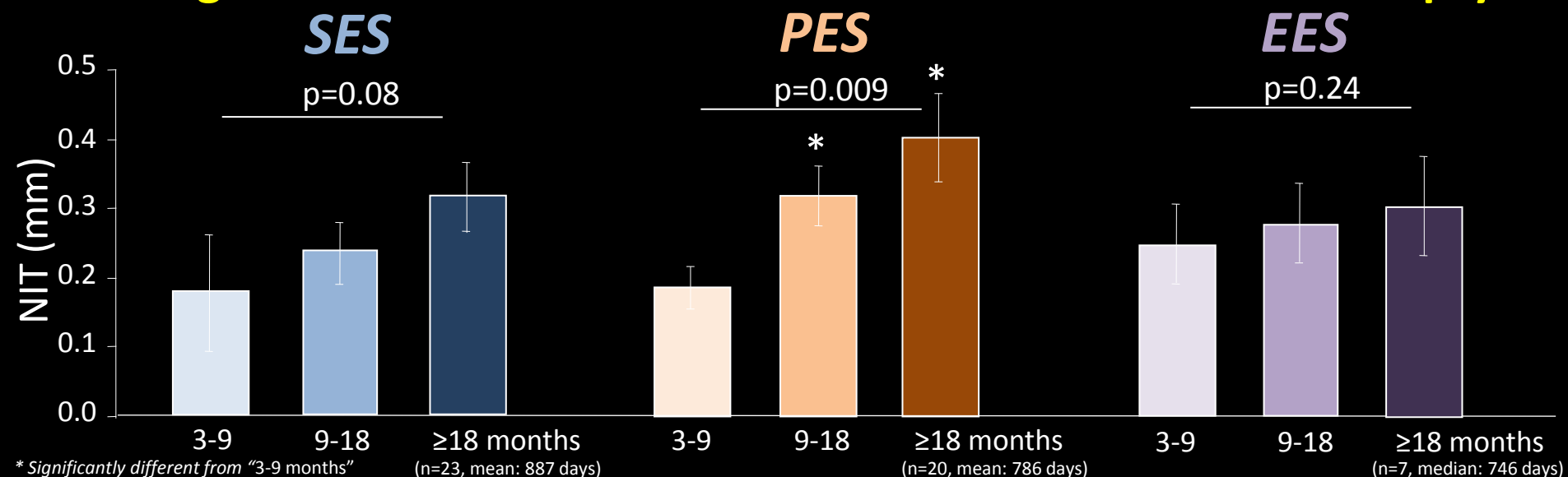




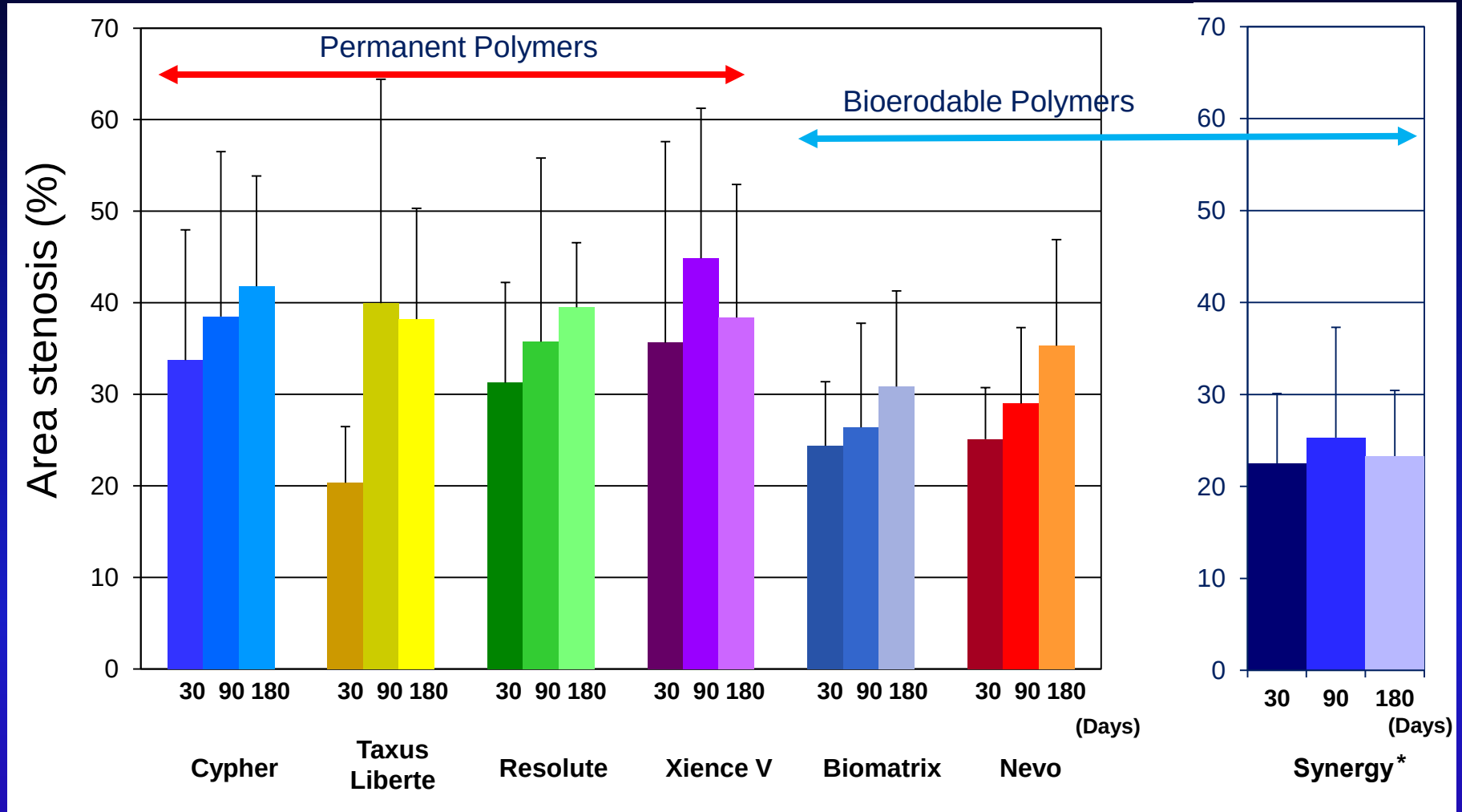
# Long-term TLR in major clinical trials



## Change in maximum neointimal thickness in human DES autopsy



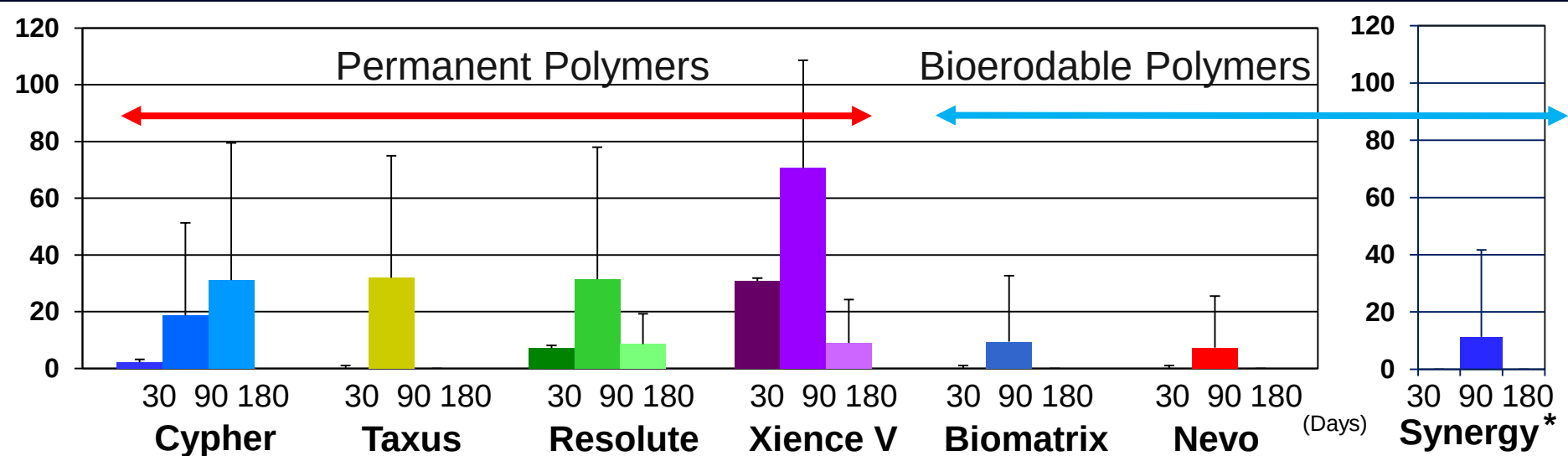
# All DES Not Created Equal: Pig Coronary Arteries



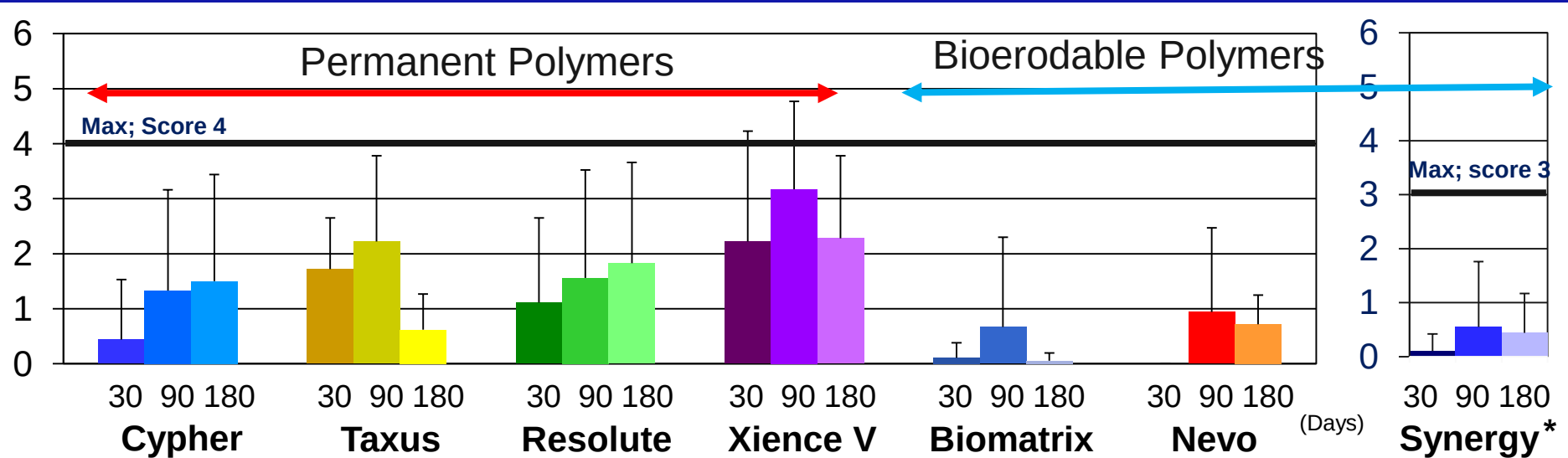
\* Wilson GJ, et al. EuroIntervention. 2012;8:250-7

# Granulomatous Reaction and Inflammation Following Comparator DES Implantation in Pig Coronary Arteries

## Struts with Granulomas (%)



## Inflammation Score





# Revascularization and Stent Thrombosis at 12 months

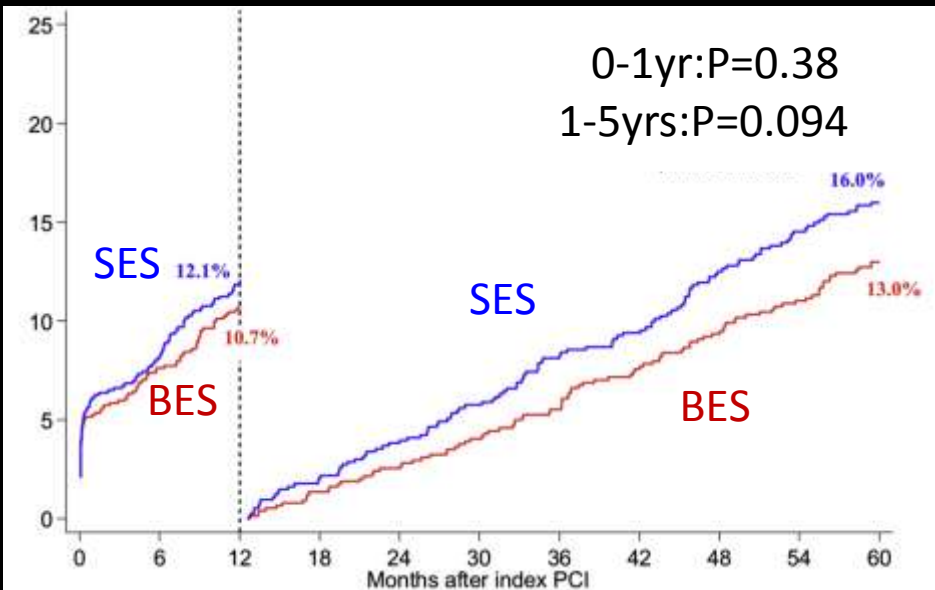


## ITT Population

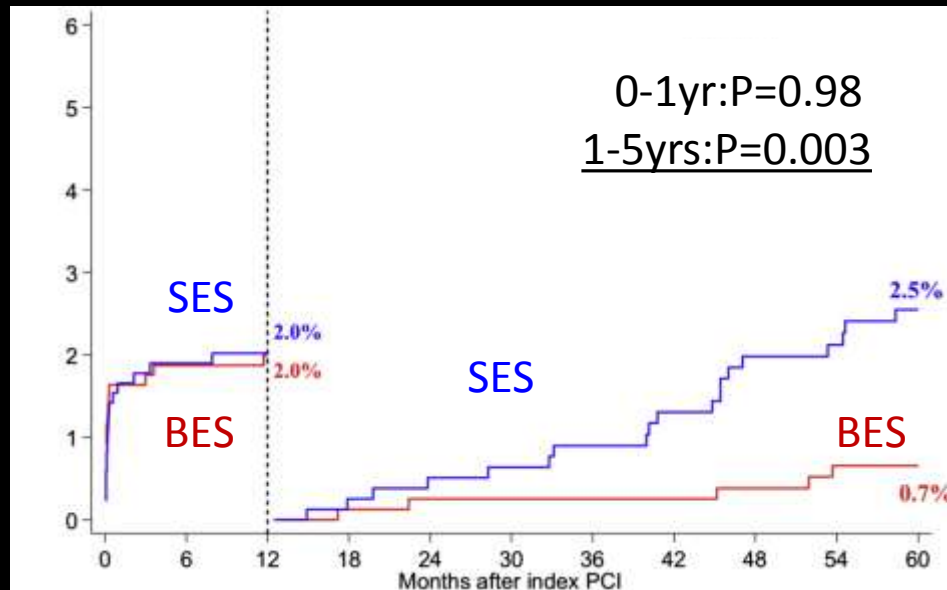
|                       | PROMUS Element Plus<br>n=838 | SYNERGY<br>n=846 | P value |
|-----------------------|------------------------------|------------------|---------|
| TVR                   | 3.6%                         | 3.8%             | 0.78    |
| TLR                   | 1.7%                         | 2.6%             | 0.21    |
| TLR, PCI              | 1.7%                         | 2.0%             | 0.64    |
| TLR, CABG             | 0.0%                         | 0.6%             | 0.06    |
| TVR non-TLR           | 2.2%                         | 1.8%             | 0.54    |
| ARC* Stent Thrombosis |                              |                  |         |
| Definite/Probable     | 0.6%                         | 0.4%             | 0.50    |
| Definite              | 0.2%                         | 0.2%             | >0.99   |
| Probable              | 0.4%                         | 0.1%             | 0.37    |
| Possible              | 0.1%                         | 0.2%             | >0.99   |

# Five-year outcome following revascularization with biodegradable polymer BES and durable polymer SES in all comers (LEADER-Trial)

## Cardiac Death, MI, TVR



## Definite stent thrombosis



*P. Serruys. J Am Coll Cardiol. 2013;6:777-89.*

# Summary

- Poor strut coverage is the primary pathologic substrate responsible for LST/VLST following first-gen DES, where stent struts penetrated into the necrotic core (AMI indication), hypersensitivity (SES) and malapposition (PES and SES) are associated with delayed healing.
- Second-generation DES have shown improvement in arterial healing by modifying the stent design, polymer and drug and concentration.
- Stent fracture and in-stent neoatherosclerosis have emerged as other important contributing factor for LST/VLST and restenosis, even in the second-generation DES. Rapid and more frequent development of neoatherosclerosis in DES vs. BMS might be attributed to incompetent re-generated endothelium.
- Biodegradable polymer DES may show a decrease in neoatherosclerosis and very late catch-up.



# Acknowledgments

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## CVPath Institute

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Abebe Atiso, HT

Jinky Beyer

Lila Adams, HT

Elena Ladich, MD

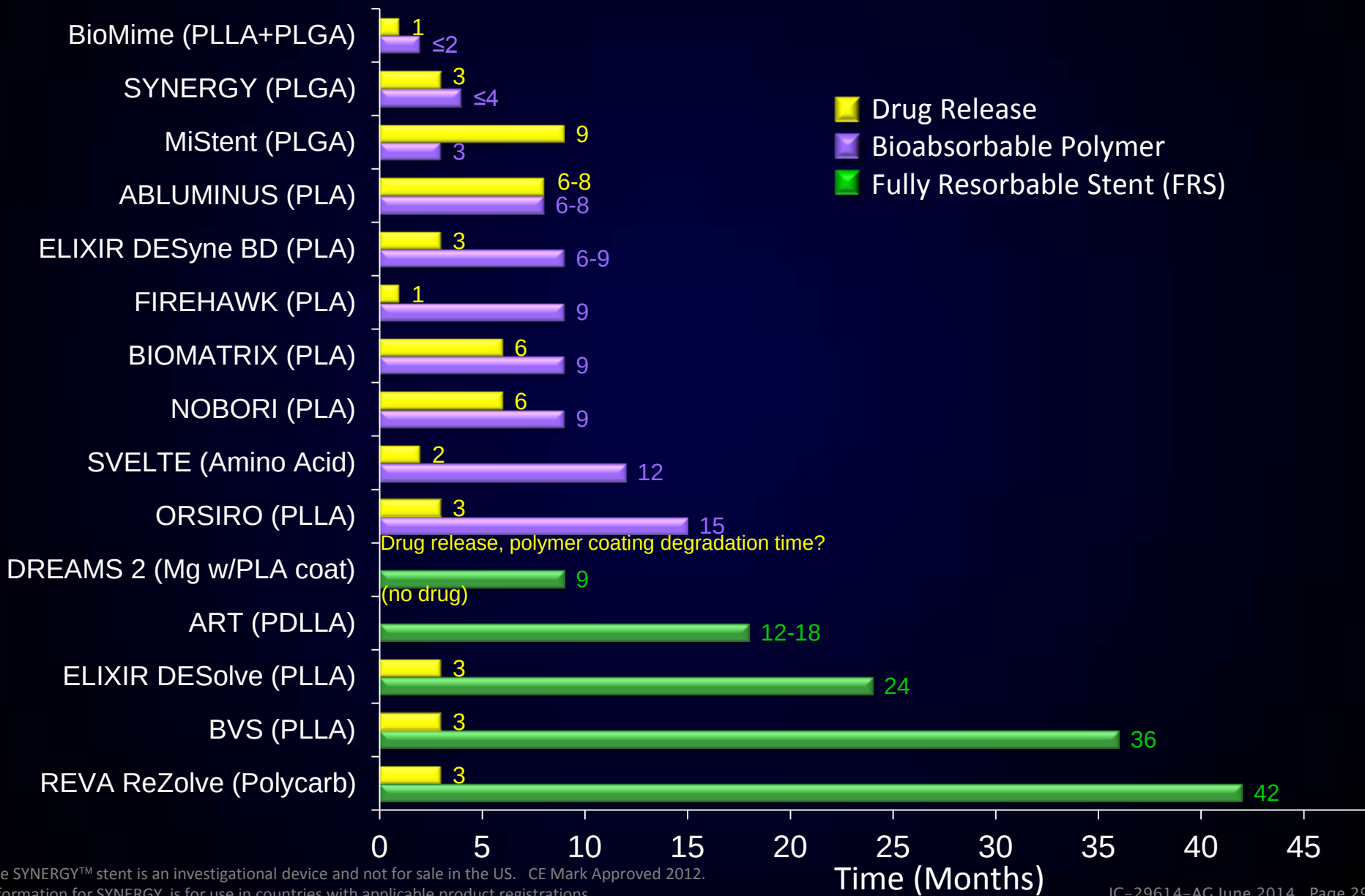
Frank D Kolodgie, PhD

**Michael Joner, MD. CEO**



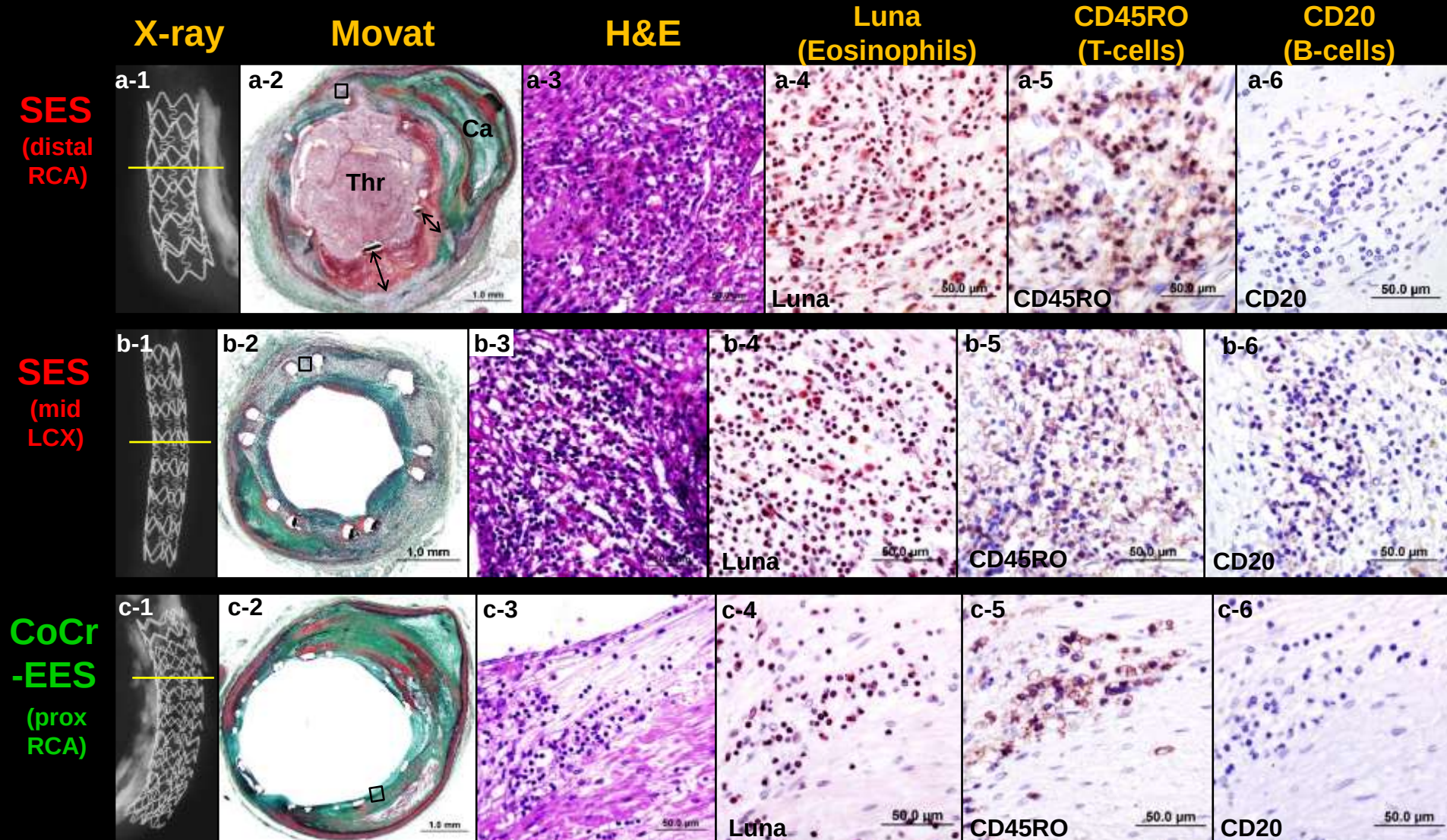
# Time Course For Polymer Bioabsorption

Not all bioabsorbable technologies are the same



# Hypersensitivity in SES vs. Focal Inflammation in CoCr-EES

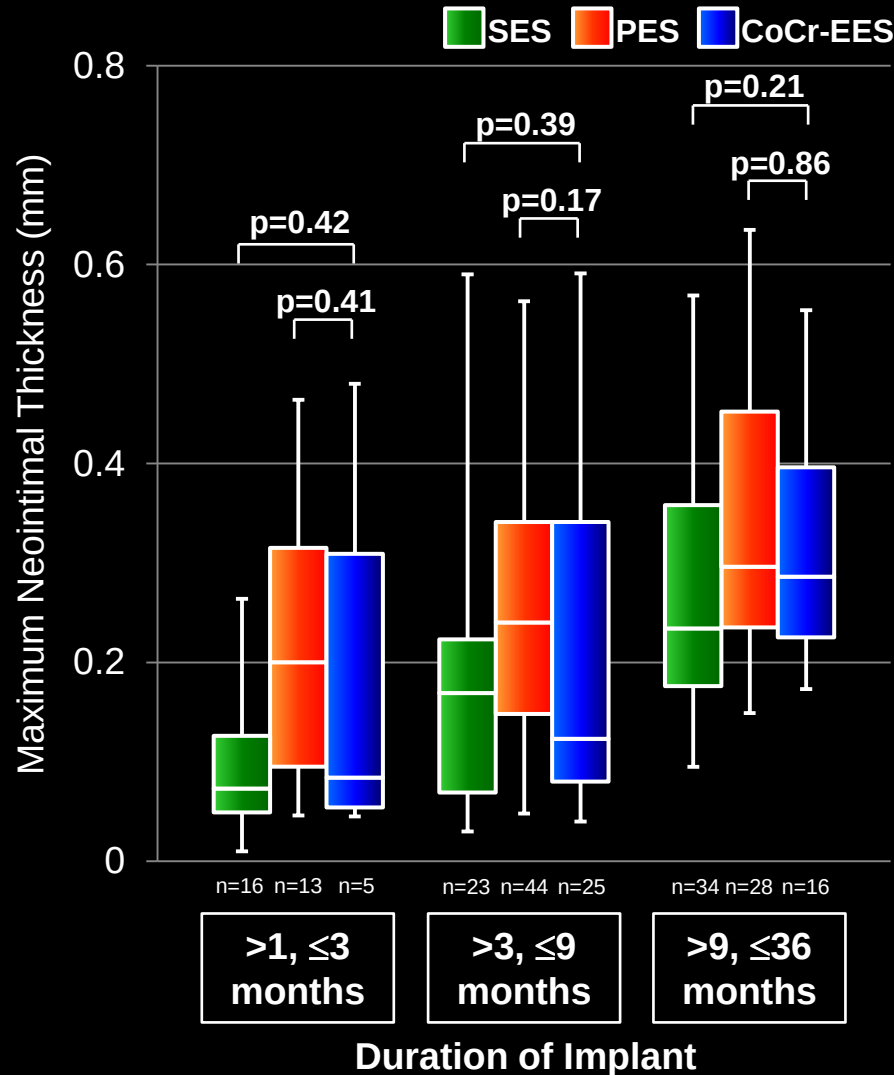
A 58-year-old man who had received 2 SES (for 3 years) and 1 CoCr-EES (for 7 months) died suddenly 1 day after nasal polyp surgery. DAPT was discontinued 5 days before the surgery.



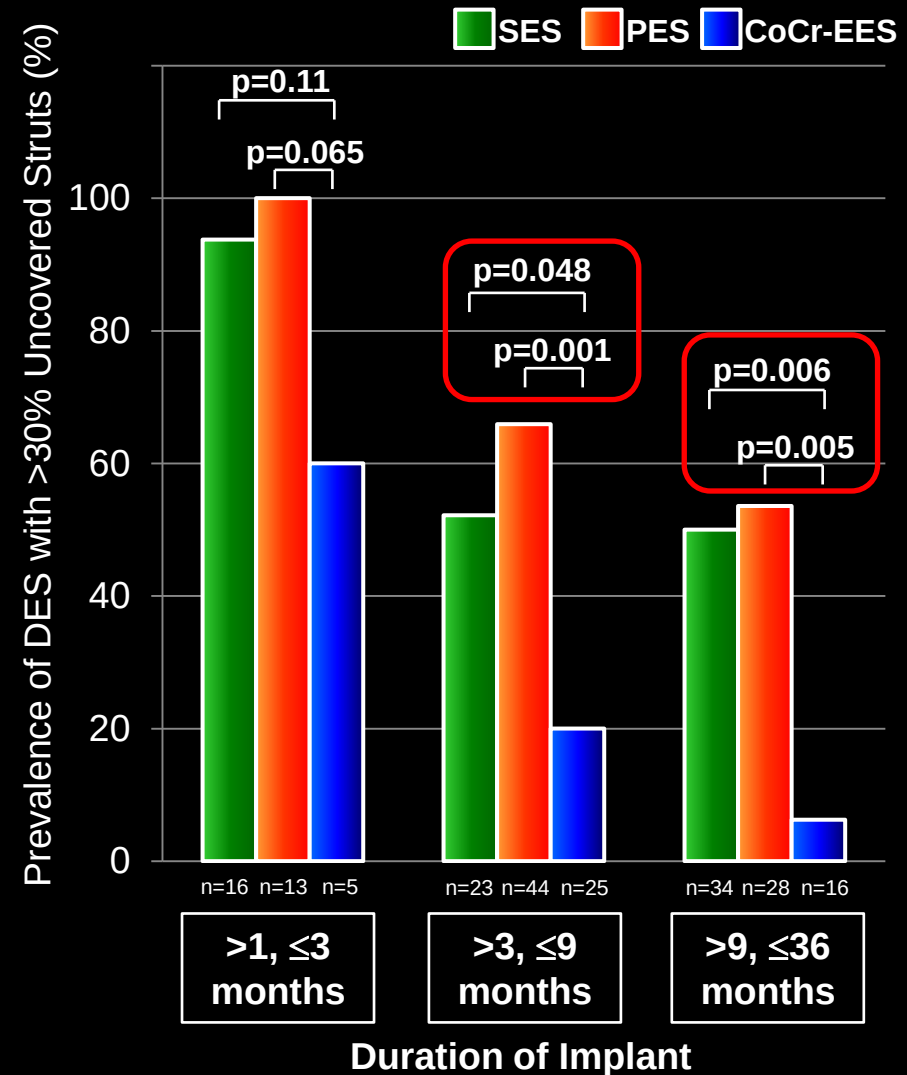


# Neointimal Thickness and Prevalence of Uncovered Struts Stratified by Duration of Implant in CoCr-EES vs. SES/PES

**Maximum Neointimal Thickness (mm)**

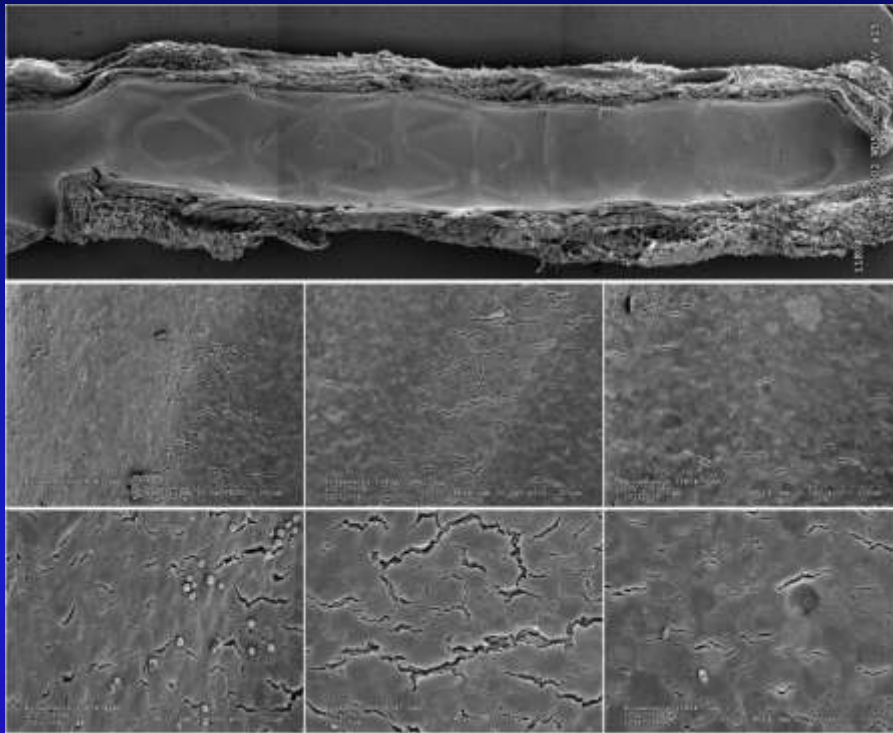


**Prevalence of >30% Uncovered Struts**

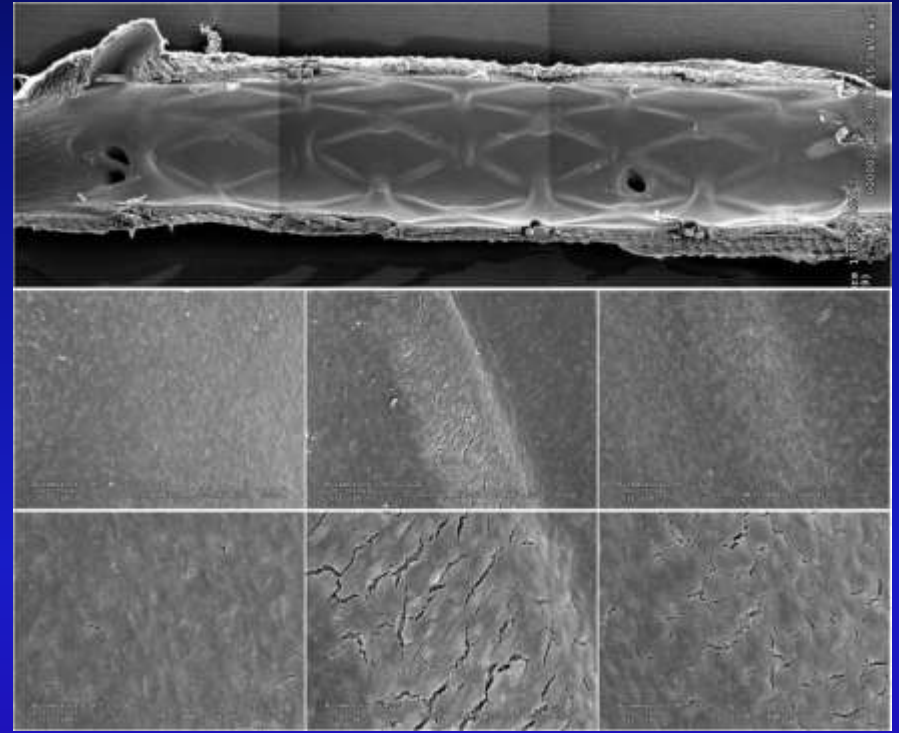


# Re-endothelialization at 28-Day in Porcine model

**Biolimus A9 coated  
BioFreedom Stent**



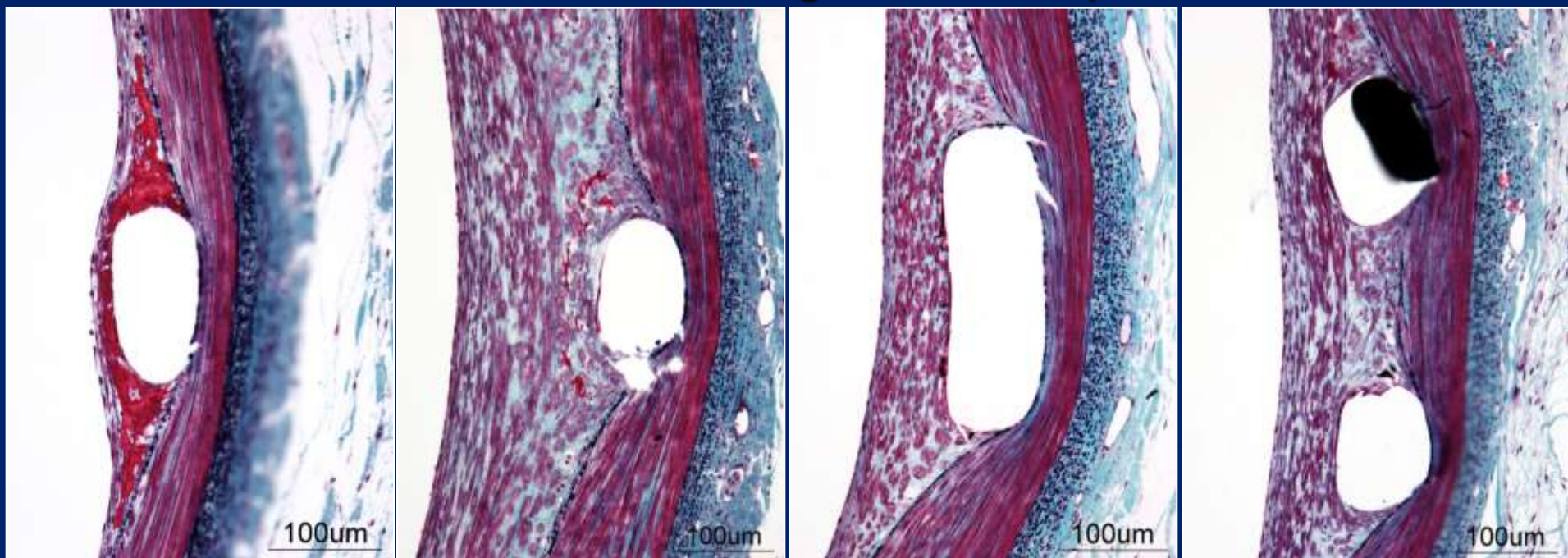
**Bare metal  
Control Stent**



Full endothelium recovery equivalent to BMS at 28-Days

# Para-strut Fibrin Deposition at 28 Days

More para-strut fibrin (red) with the drug-eluting stent SYNERGY than its Polymer only or bare metal controls on single stent implantation



*SYNERGY*

*1x Polymer  
SYNERGY*

*Bare Metal  
SYNERGY*

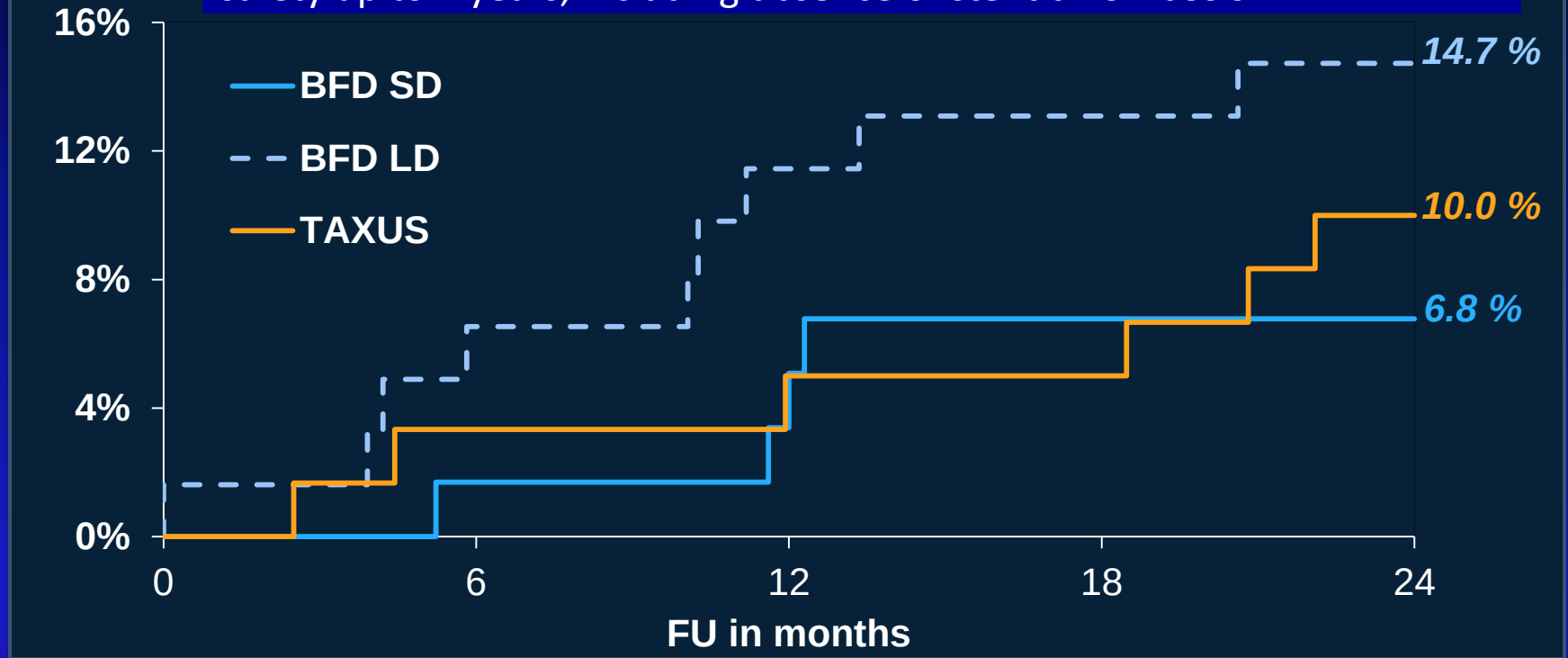
*Bare Metal  
OMEGA*



# BioFreedom Drug Coated Stent FIM: MACE

## All patients – 1<sup>st</sup> and 2<sup>nd</sup> Cohorts

- The BioFreedom™ Standard Dose (SD) demonstrated numerically lower rates of MACE and TLR up to 2 years vs. Taxus.
- Both BioFreedom SD and BioFreedom LD demonstrated sustained safety up to 2 years, including absence of stent thrombosis



### Number at Risk

|        |    |    |    |    |    |
|--------|----|----|----|----|----|
| BFD SD | 60 | 58 | 57 | 55 | 38 |
| BFD LD | 62 | 57 | 54 | 53 | 34 |
| TAXUS  | 60 | 58 | 57 | 57 | 37 |

*All P values are non-significant.*

*Tests were performed for BFD SD vs. TAXUS and BFD LD vs. TAXUS.*

*Grube E., oral presentation, TCT 2011*

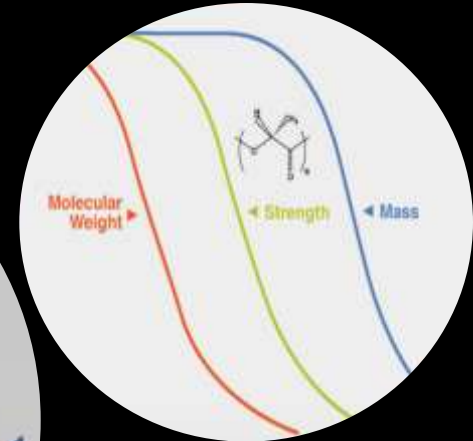
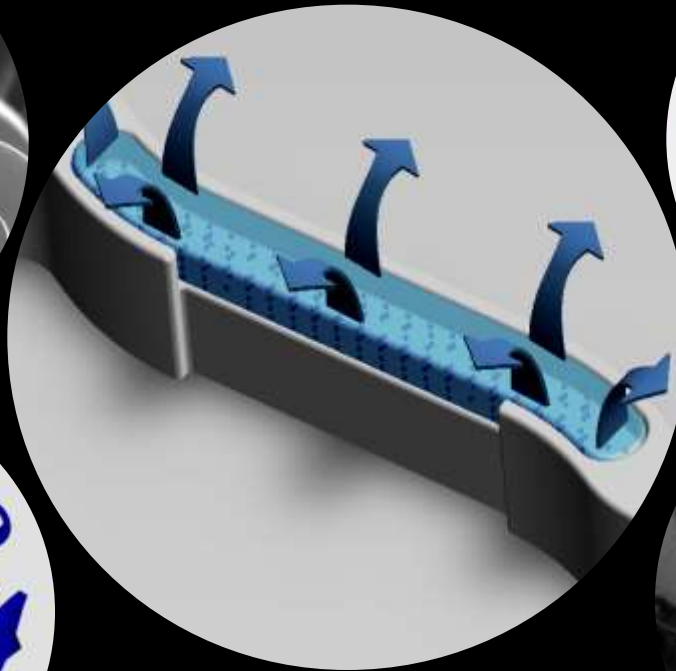
# FIREHAWK<sup>®</sup> Components

An Abluminal Groove-Filled Biodegradable Polymer Sirolimus-Eluting Stent

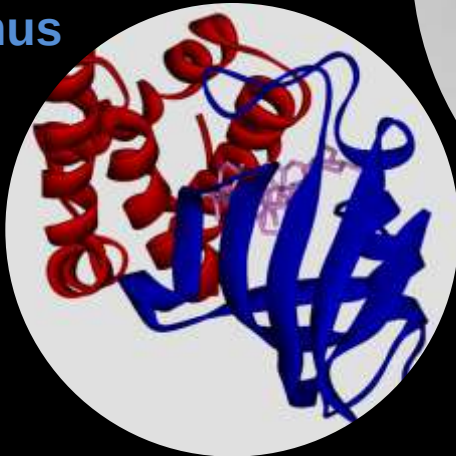
Co-Cr stent  
with grooves



D,L-PLA absorbed after 6-9 mo  
and recover to metallic surface



Sirolimus

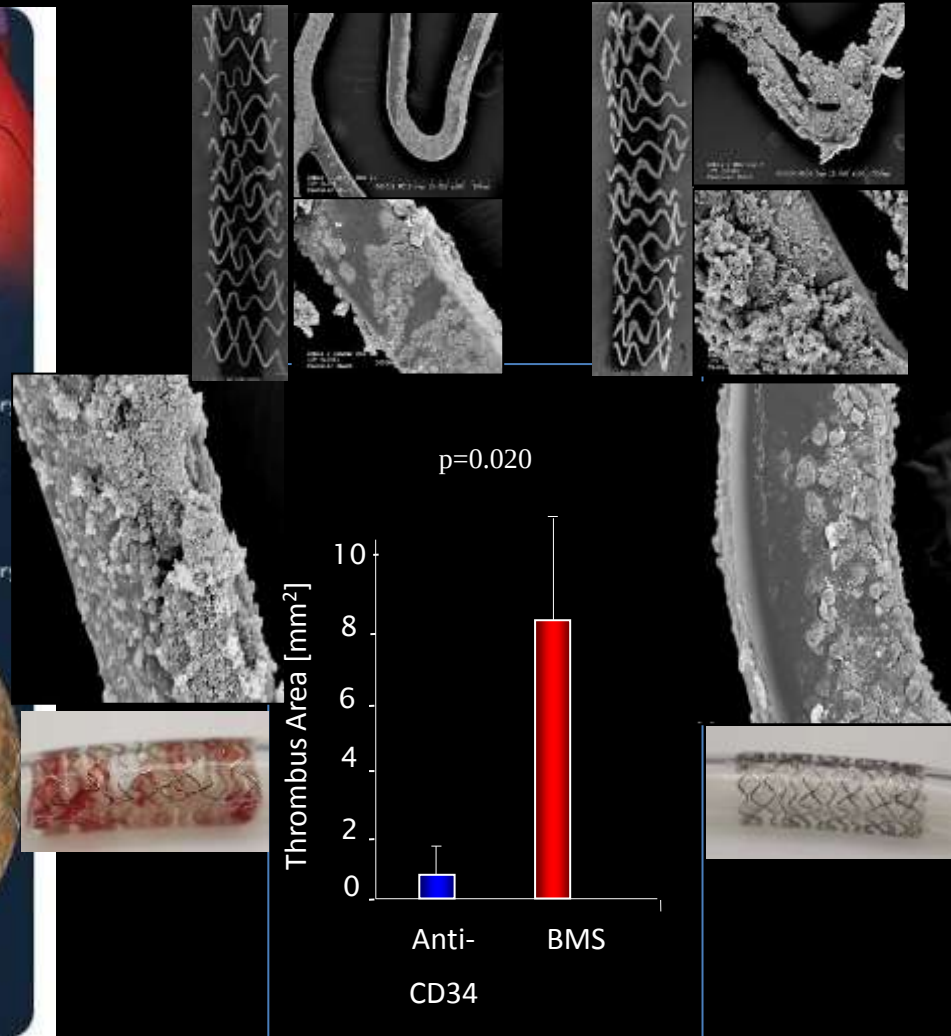
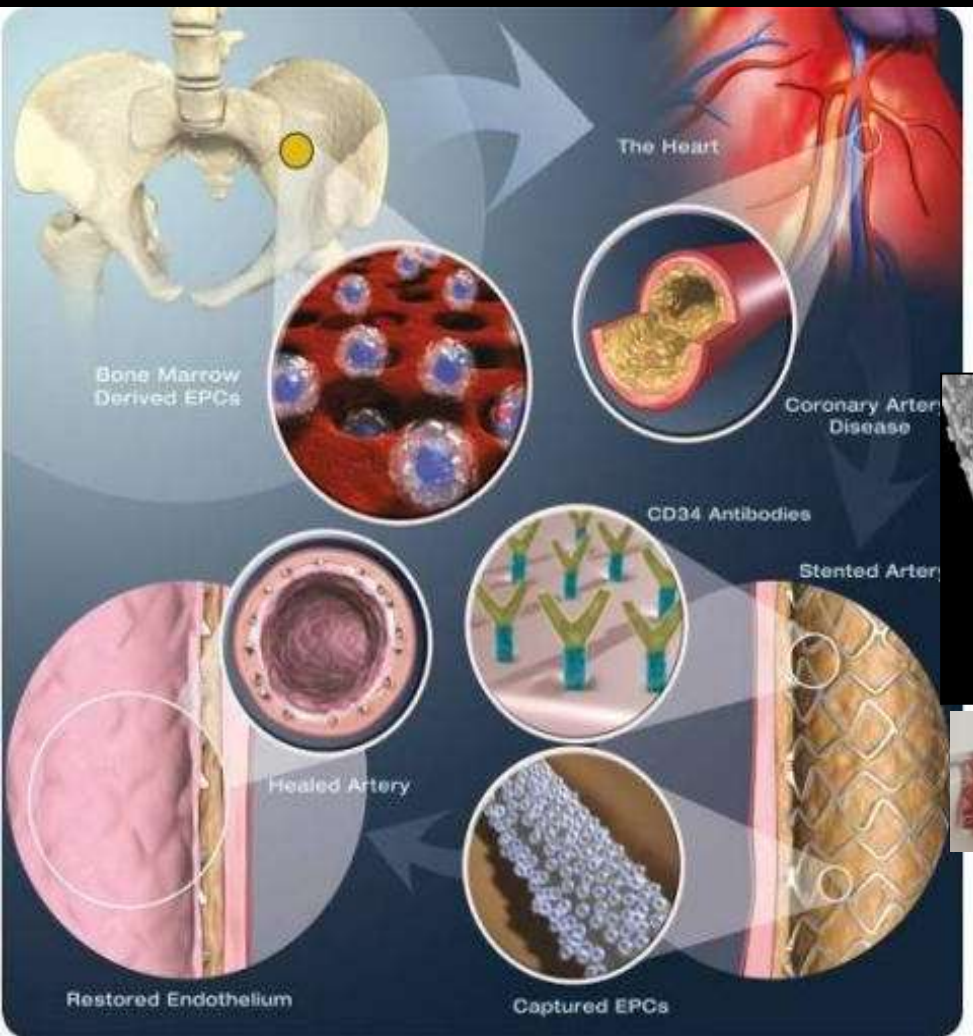


Printing technology



# COMBO stent Facilitated EPC Attachment and Endothelialization

Scanning Electron Microscopy (SEM)

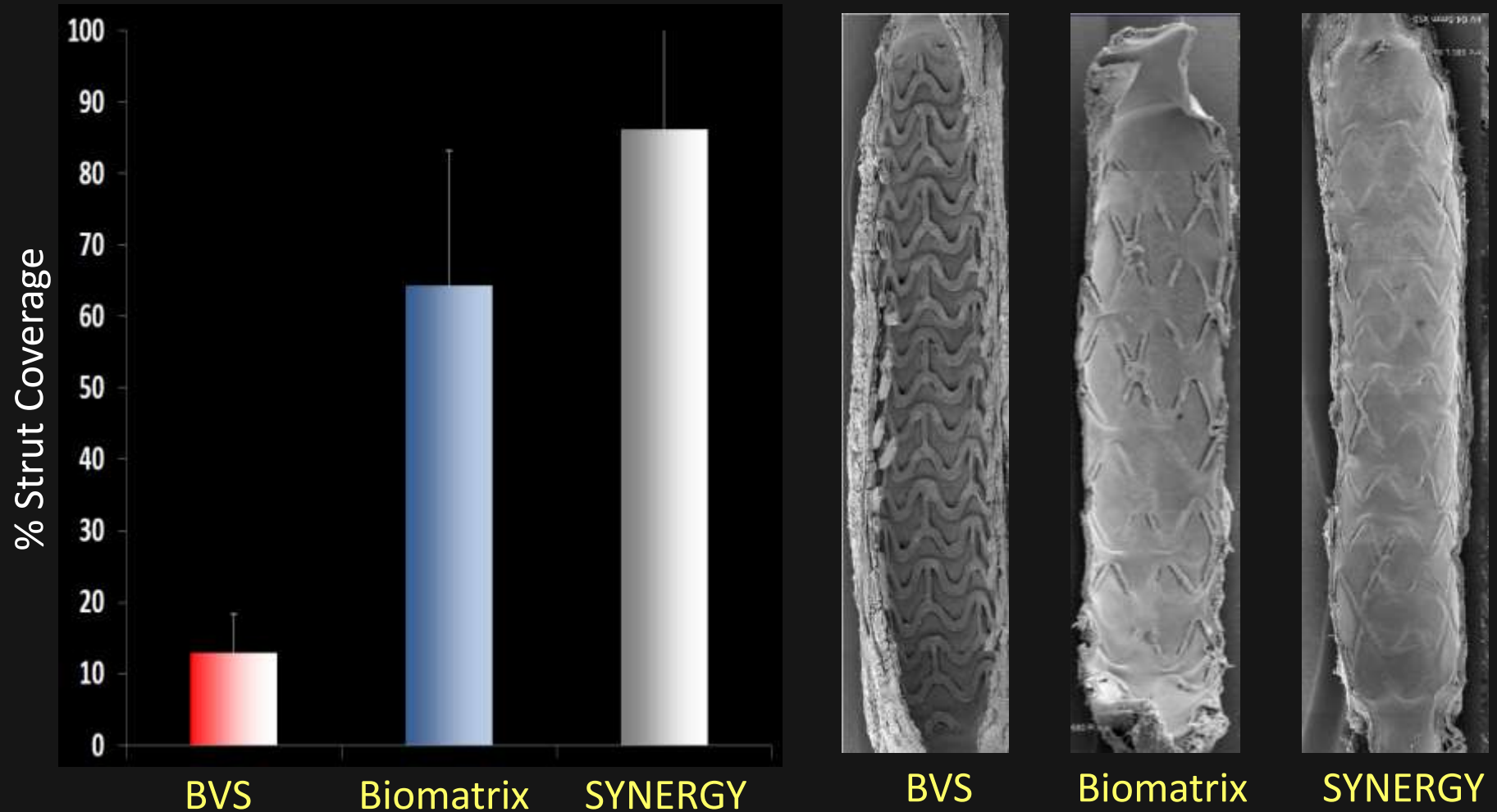




# Thick vs. Thin Strut DES

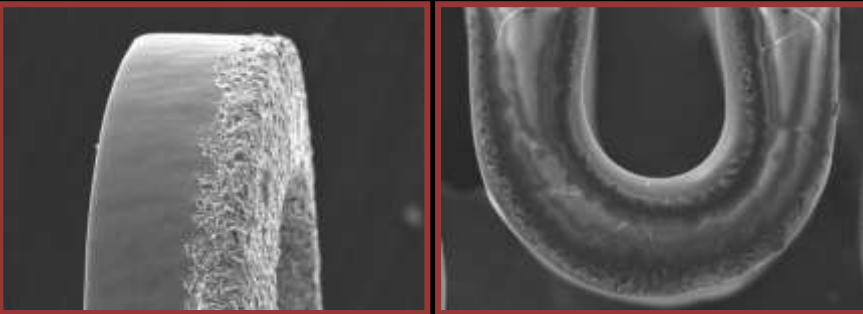
Healing and Endothelialization in SYNERGY, Biomatrix, and Absorb BVS

Endothelialization in Rabbit at 28 Days

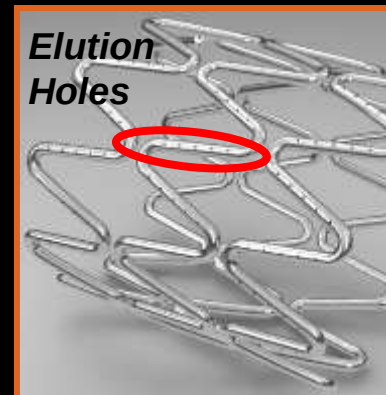


Preliminary data presented by Renu Virmani, MD at TCT AP 2014

# “Polymer-free” DES Design Types



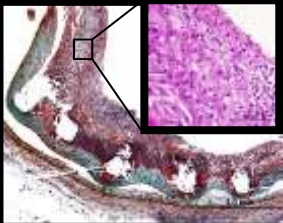
Pure Biolimus A9 impregnated in metal stent surface



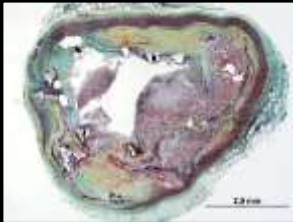
# TCFA and Rupture cases in DES

| Case | Age, Sex | Stent type | Duration of implant, months | Representative images |
|------|----------|------------|-----------------------------|-----------------------|
|------|----------|------------|-----------------------------|-----------------------|

## Thin-cap fibroatheroma

|   |      |           |           |                                                                                     |
|---|------|-----------|-----------|-------------------------------------------------------------------------------------|
| 1 | 40 F | DES (SES) | 17 months |    |
| 2 | 67 M | DES (SES) | 13 months |    |
| 3 | 49 M | DES (SES) | 36 months |   |
| 4 | 60 M | DES (PES) | 60 months |  |

## Rupture

|   |      |           |           |                                                                                       |
|---|------|-----------|-----------|---------------------------------------------------------------------------------------|
| 1 | 59 M | DES (SES) | 23 months |    |
| 2 | 61 M | DES (SES) | 36 months |    |
| 3 | 78 F | DES (SES) | 46 months |    |
| 4 | 43 M | DES (SES) | 72 months |   |
| 5 | 61 M | DES (PES) | 60 months |  |



# Bioabsorbable Polymer Stents

## SYNERGY



## Biomatrix Flex



## Nobori



## Combo



## Orsiro



## Platform

## Polymer

## Coating Design

**SYNERGY Element**  
**0.0032"**

**Bioabsorbable**  
**(PLGA)**

**Abluminal**

**Juno Stent (SS)**  
**0.0042"**

**Bioabsorbable**  
**(PLA)**

**Abluminal**

**S-Stent (SS)**  
**0.0042"**

**Bioabsorbable**  
**(PLA)**

**Abluminal**

**R-Stent (SS)**  
**0.0040"**

**Bioabsorbable**  
**SynBiosys**

**Abluminal**

**PRO-Kinetic Energy**  
**0.0024"**

**Bioabsorbable**  
**(PLLA)**

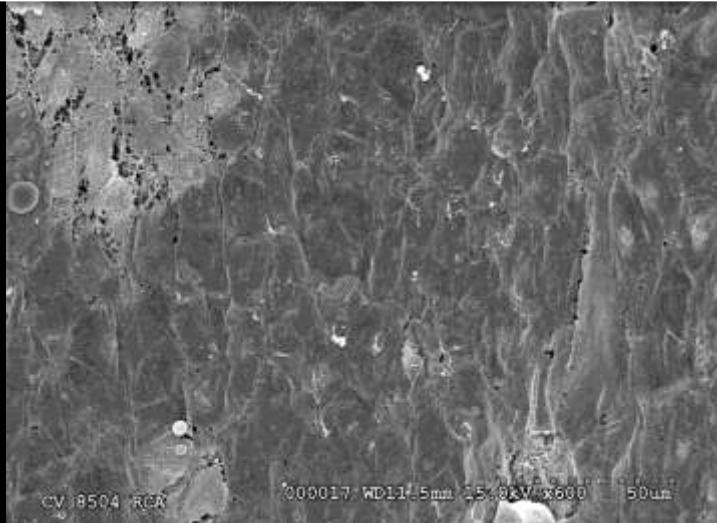
**Circumferential**

# Poorly Formed Cell Junctions

71-year-old woman who died of stroke

BMS

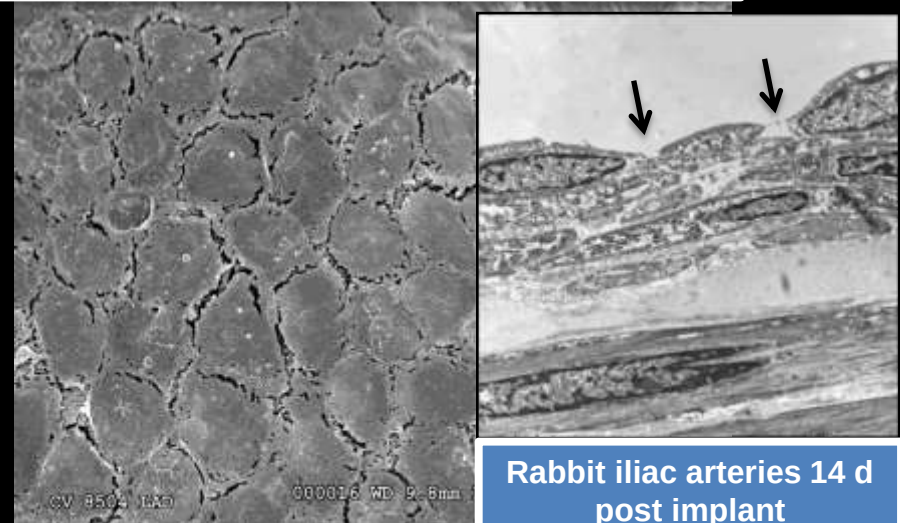
Implanted in RCA 2 y antemortem



Pavement-shaped endothelial cells with endothelial cell-to-cell contact, a small area exhibits poorly formed cell junctions

SES

Implanted in LAD 16 m antemortem



Poorly formed endothelial cell junctions

# Evaluation of Thrombus Formation on Contemporary Biodegradable and Permanent Polymer DES in Porcine Shunt Model

