

Insights from Pathology Studies DCBs and DESs

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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.

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Speaker's Bureau

Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

Consultant/Advisory Boards

Amgen; Abbott Vascular; Boston Scientific; Celonova; Cook Medical; Lutonix Bard; Sinomed.

Evolution of DES Technology

1st Generation

Durable Polymer Stents

Cypher



TAXUS Express



TAXUS
Liberte



Strut Thickness

140 μm

132 μm

96 μm

Coat Thickness

7 μm / side

16 μm /side

14 μm /side

2nd Generation

Resolute
Integrity



Xience
Alpine



Promus
PREMIER



89 μm

81 μm

81 μm

6 μm / side

8 μm / side

8 μm / side

Bioabsorbable Polymer Stents

Biomatrix



Nobori



MiStent



Orsiro



Synergy



Ultimaster



Strut Thickness

120 μm

125 μm

64 μm

60 μm

74 μm

80 μm

Coat Thickness

10 μm

20 μm

5 μm luminal
15 μm Abluminal

4-7 μm / side

4 μm

14 μm

1st Generation Future Technologies

BIOFREEDOM



Drug Filled Stent



Fully
Bioresorbable
Stents

BVS



ELIXIR DESolve



DREAMS II



Polymer Free Stents

Strut Thickness

112

86

150 μm

150 μm

150 μm

Coat Thickness

NA

NA

3 μm / side

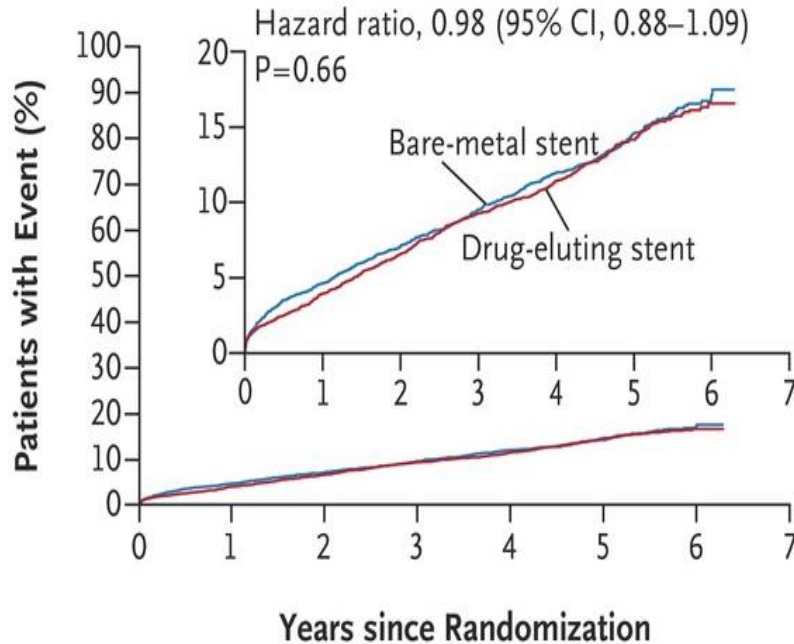
<3 μm / side

8 μm / side

2nd Gen DES could not improve the clinical outcome

Primary Outcome

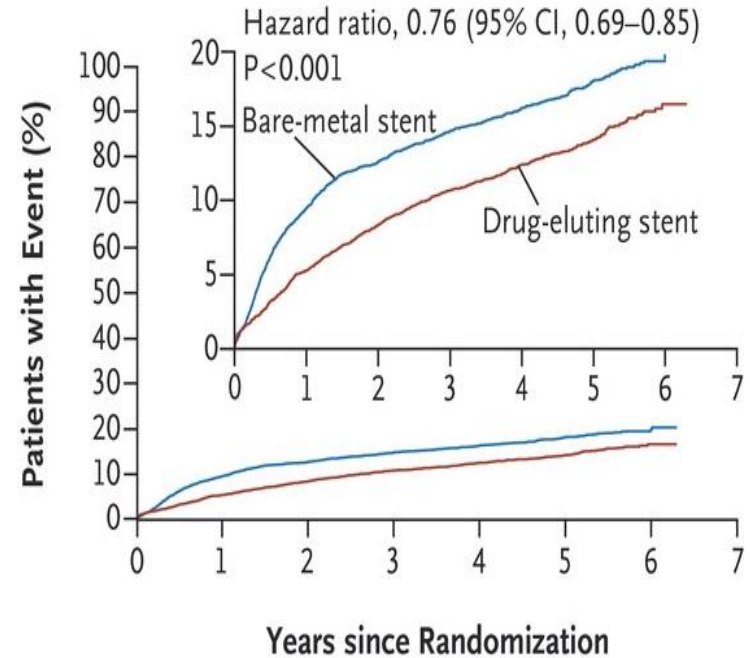
(All cause death and nonfatal MI)



No. at Risk

Drug-eluting stent	4504	4325	4206	4083	3814	2028	240
Bare-metal stent	4509	4300	4190	4076	3791	2019	224

Revascularization (PCI or CABG)



No. at Risk

Drug-eluting stent	4504	4192	4012	3853	3559	1887	200
Bare-metal stent	4509	4034	3856	3719	3426	1798	212

DES

2nd gen: EES 6141 (82.3%), R-ZES 832 (11.1%)

1st gen: E-ZES 56 (0.8%), SES 211 (2.8%), PES 175 (2.3%)

Problems Encountered with Drug-Eluting Stents

Thick strut DES with durable polymer

- Thick struts
- Uneven polymer distribution with poor integrity, and thick coating of durable polymers
- High drug dose

Thin strut DES with durable polymer

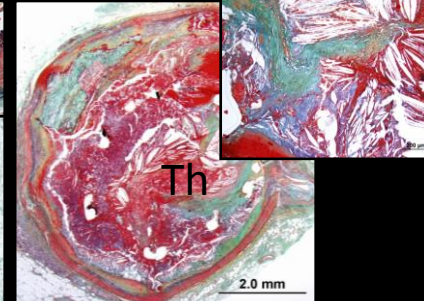
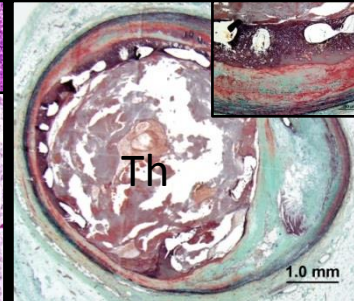
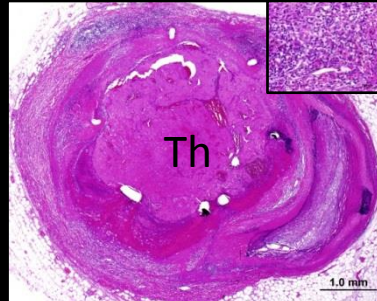
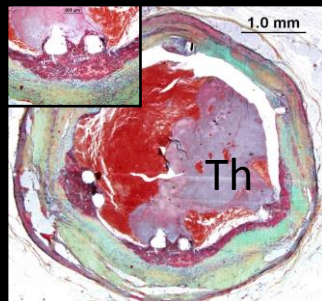
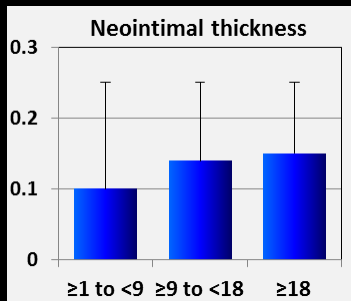
- Thinner struts
- More biocompatible polymer (Durable)
- Reduced drug dose

- ✓ Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition from fibrin deposition
- ✓ Stent fracture
- ✓ Neointimal hyperplasia

- ✓ Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition from fibrin deposition
- ✓ Stent fracture
- ✓ Neointimal hyperplasia

Late Stent Thrombosis / Restenosis

Clinical Late Catch-up



Late catch-up

Uncovered struts

Hypersensitivity reaction

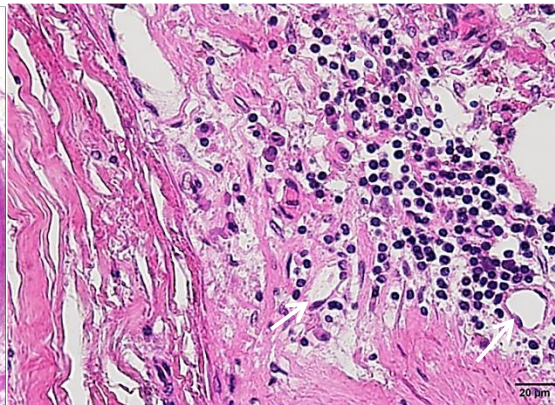
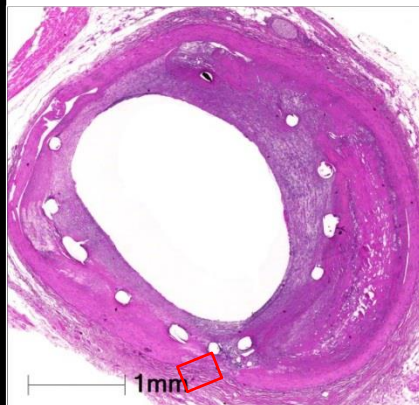
Malapposition from excessive fibrin deposition

Neointimal hyperplasia

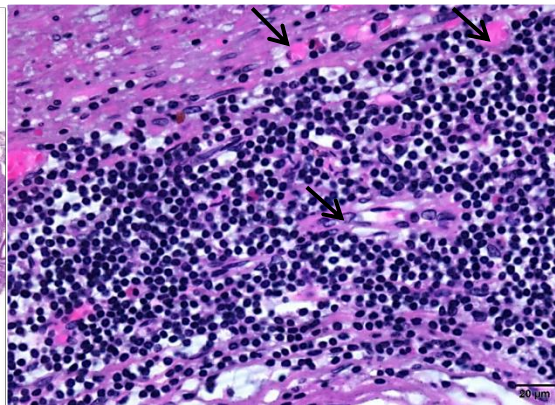
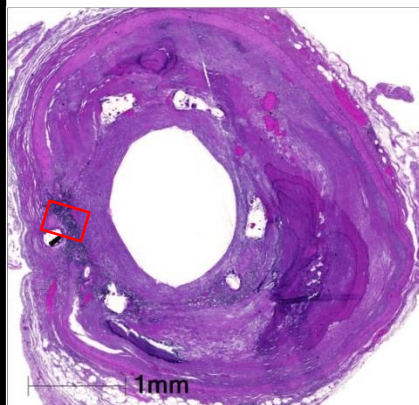
**Are long-term (1-5 years) results
different in 1st, vs. 2nd, vs. BMS
different in pathologic studies?**

Inflammation in long-term after stent implantation

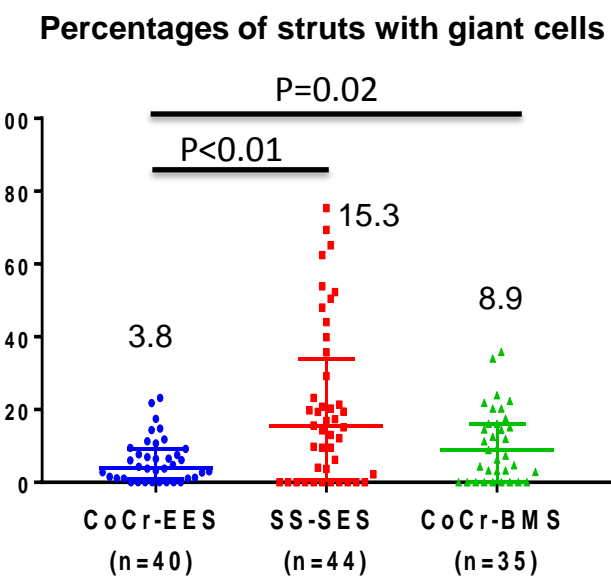
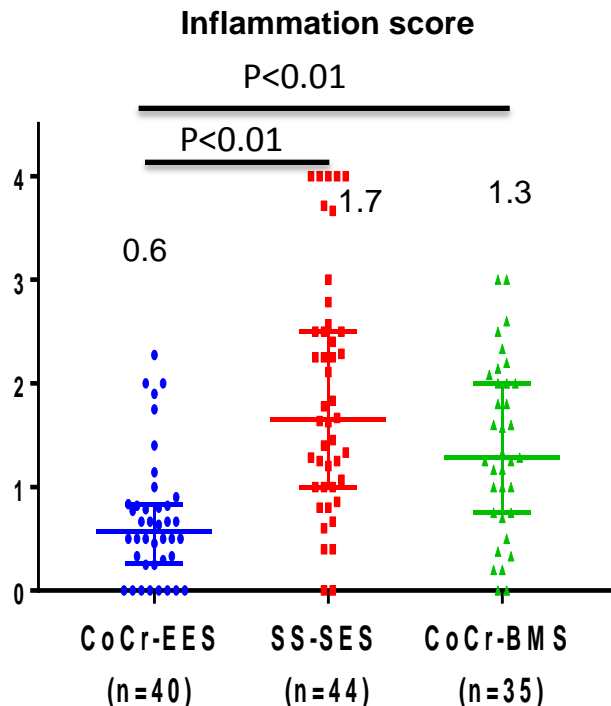
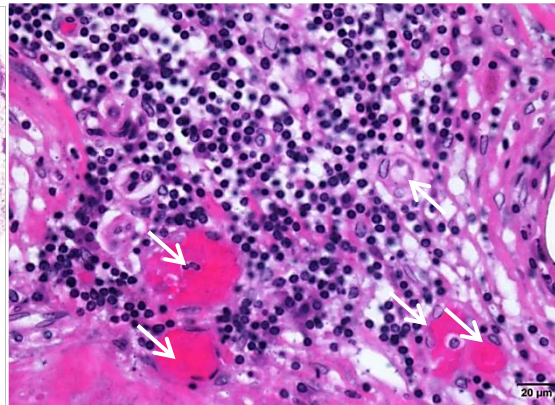
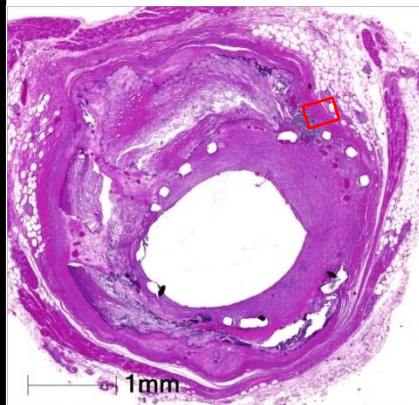
CoCr-EES
1.5 years



SS-SES
1 year

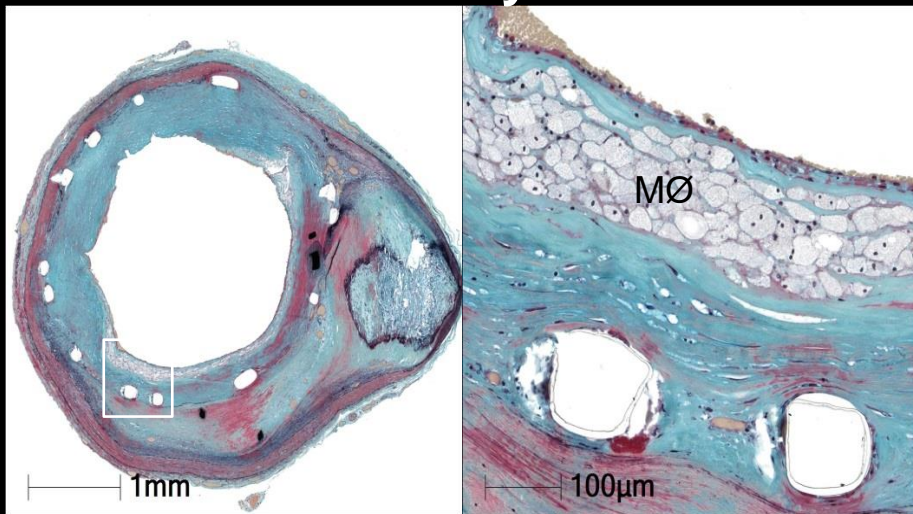


CoCr-BMS
2 years

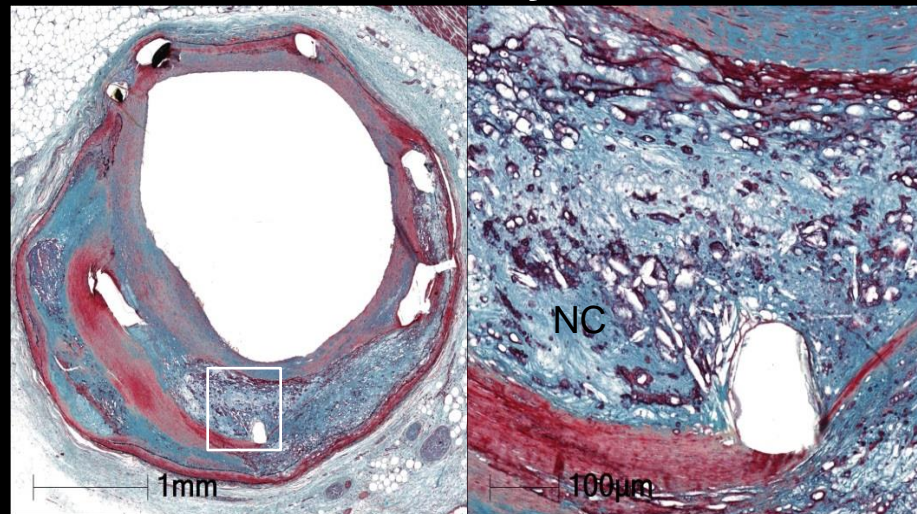


Neoatherosclerosis in Long-Term

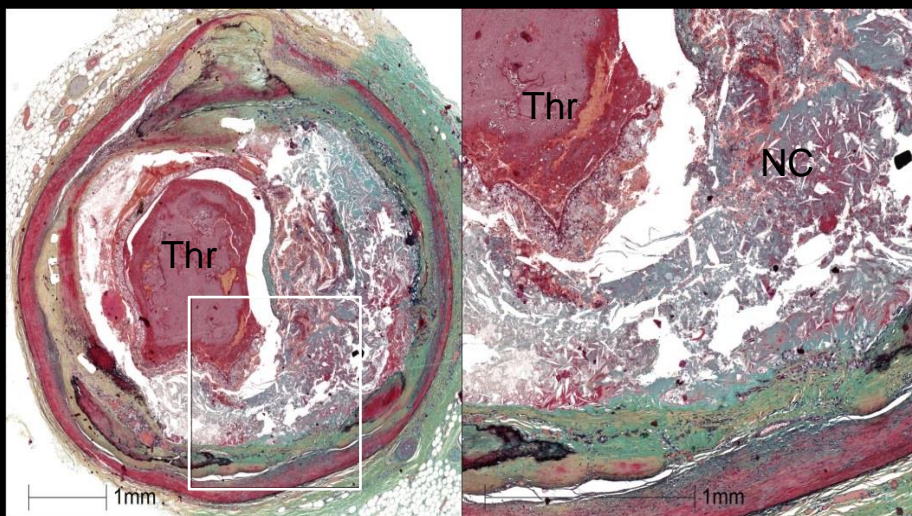
CoCr-EES 5 years



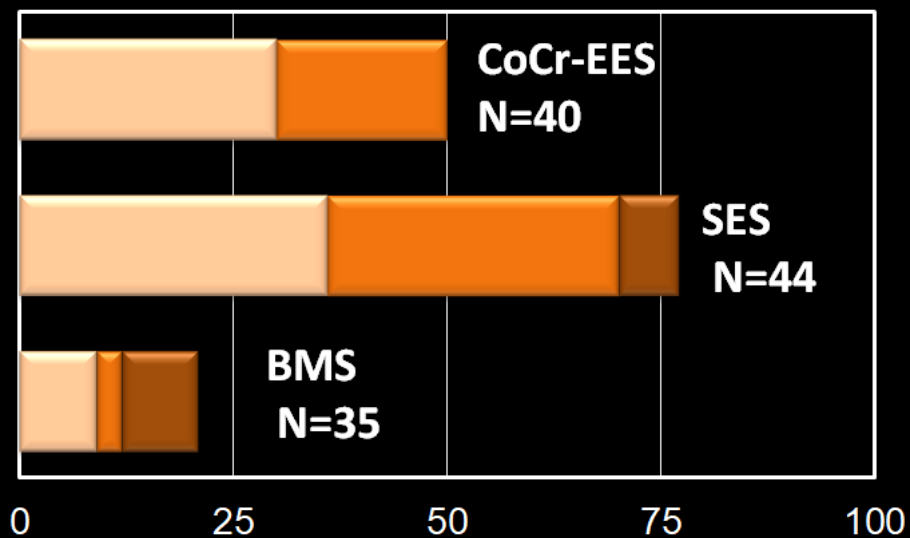
SS-SES 5 years



BMS 5 years



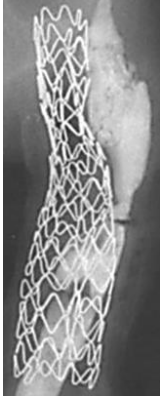
Prevalence and type of neoatherosclerosis



**How Do DES Perform
in
severe calcified lesions?**

Impact of Calcification on strut coverage after current generation DES

Severe calcification



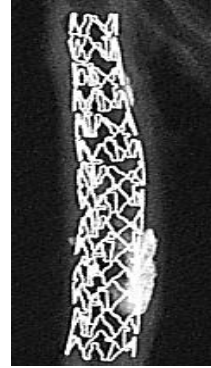
Severely calcified (SC) stented segment
69 patients/ 88 lesions

Uncovered

No calcification



Mild calcification



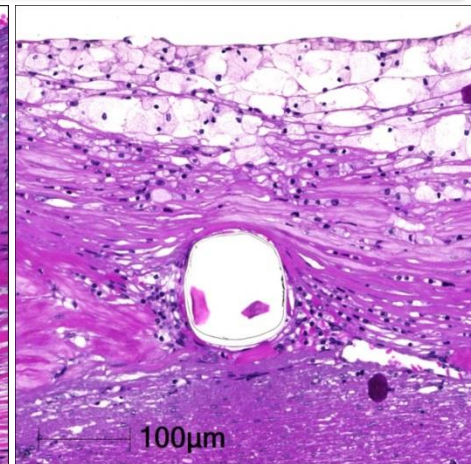
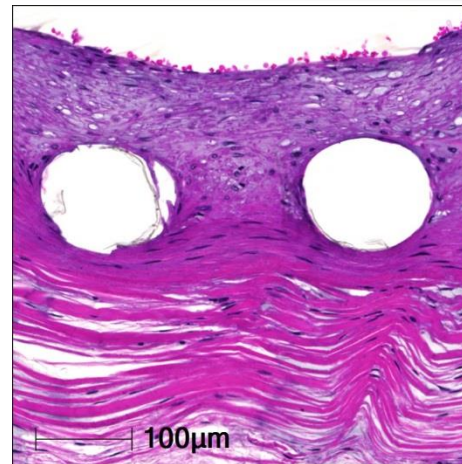
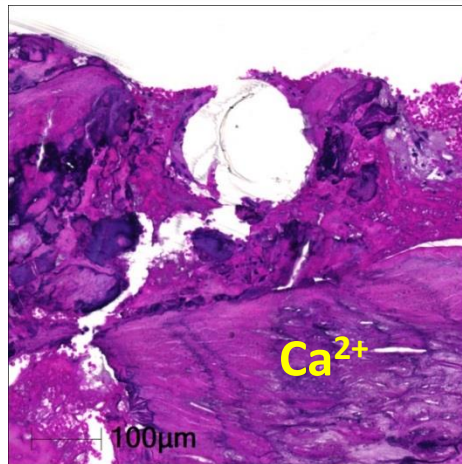
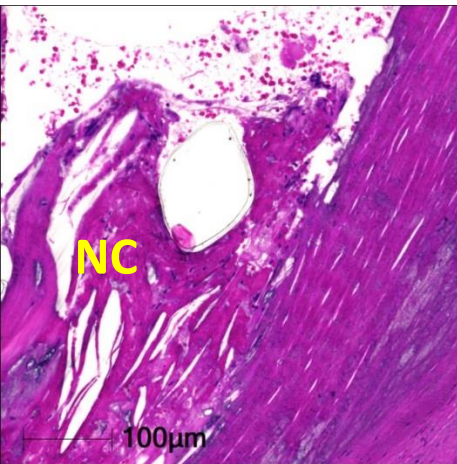
Moderate calcification



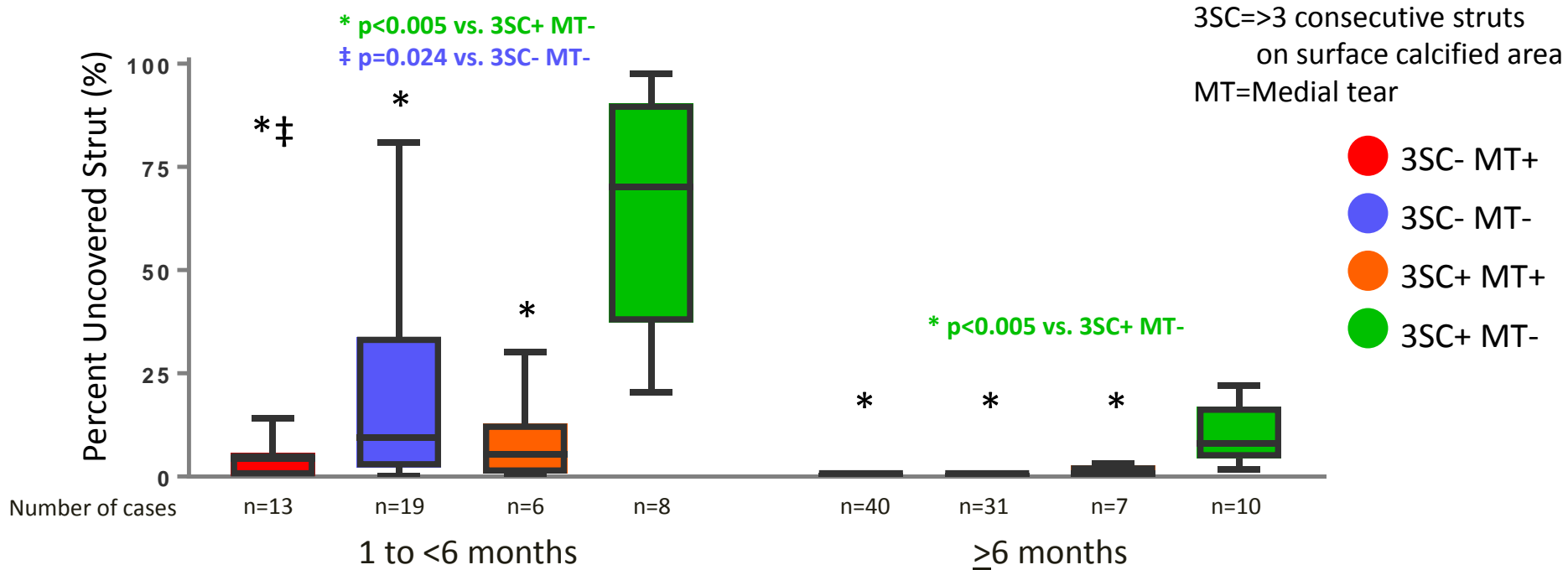
Non-severely calcified (NC) stented segment

35 patients/ 46 lesions

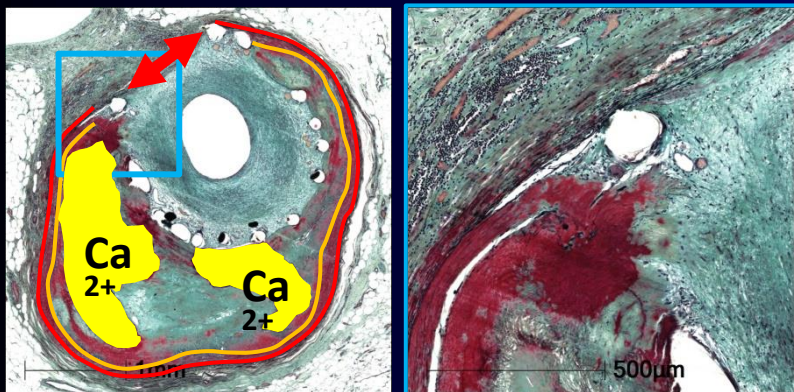
Covered



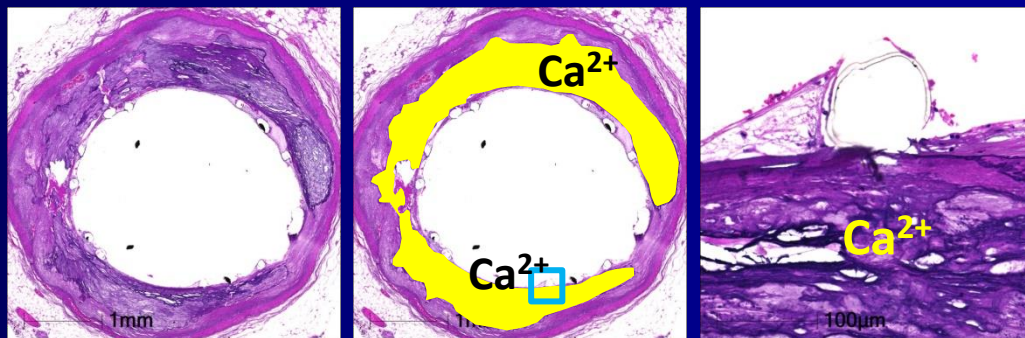
Impact of surface calcification and medial tear on uncovered struts



Severe medial tear



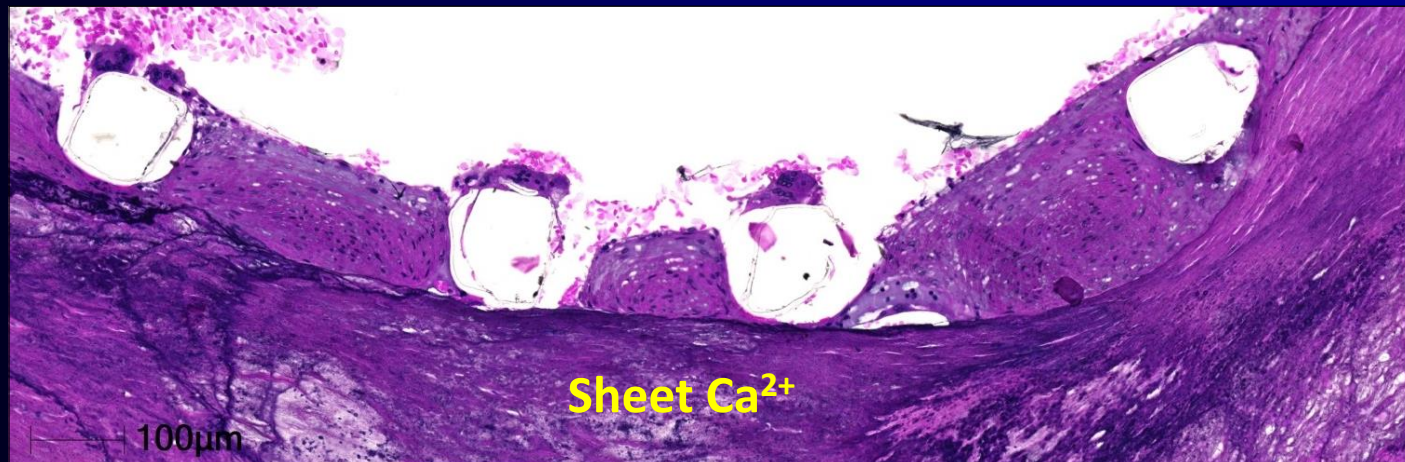
Surface calcified area



Surface calcification is a predictor for uncovered struts

Multivariate Analysis of Predictors for Delayed Strut Coverage in Newer-Generation DES

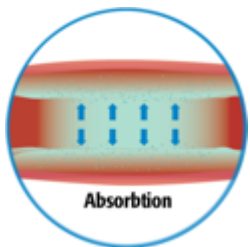
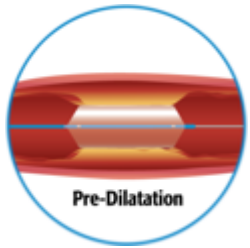
	OR	Lower 95% CI	Upper 95% CI	p value
Duration of implantation <6 months	7.7	5.18	11.50	<.0001
≥3 consecutive struts on surface calcified area	6.5	3.55	12.04	<.0001
Strut malapposition	5.0	3.34	7.57	<.0001
Lack of severe medial tear	2.5	1.53	4.34	0.0005



Limitation of DES

- Vessel caging
 - lack of adaptive remodeling
- Permanent metallic implant
 - Foreign body reaction
- Unsuitable lesions;
 - Long segment disease, small vessels, calcification
- Future treatment
 - Preclusion of bypass to stented segments

DRUG COATED BALLOON OVERCOMES UNMET CLINICAL NEED

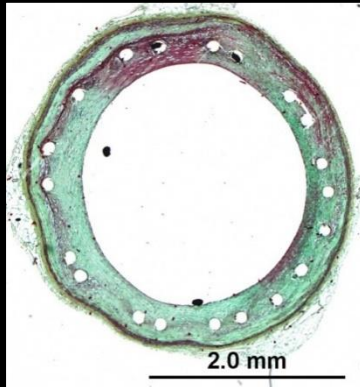


- Novel angioplasty balloon coated with an anti-restenotic drug
- Overcoming **unmet clinical need**:
 - Homogenous delivery of anti-restenotic drug **reduces amount of restenosis**
 - Due to absence of any stent **no stent fracture, vessel injury**
 - Allows original anatomy to remain intact **positive remodeling**
 - “Leaving nothing behind” **allowing fast ‘normalization’** of vascular function
 - True normalization of vasomotor function,
 - Restoration of physiological responses to stress
 - NO long-term consequences related to inflammation, accelerated atherosclerosis and thrombosis
 - No need for long term DAPT

DIFFERENCES: DES VS. DCB

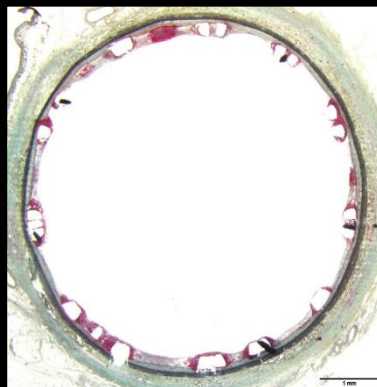
Parameters	DES	DCB
Drug concentration on the device	Low 5-10 $\mu\text{g}/\text{mm}$	Very High 2-3 $\mu\text{g}/\text{mm}^2$ (\approx 20-30 $\mu\text{g}/\text{mm}$)
Drug transfer at the time of deployment	Slow	Rapid, all at once
Reservoir of drug	Polymer or no polymer	No (excipient is needed)
Drug retention in tissues	Available for a long time	Need the drug in crystalline form (Ptx) and should be easily transferable to adjacent cells. Must binds to cell membranes
Diffusion	Good	Excellent
Distribution	Uniform circumferential	Uneven and usually 1 or 2 quadrants
Distal emboli	None	Depends on coating integrity

BMS

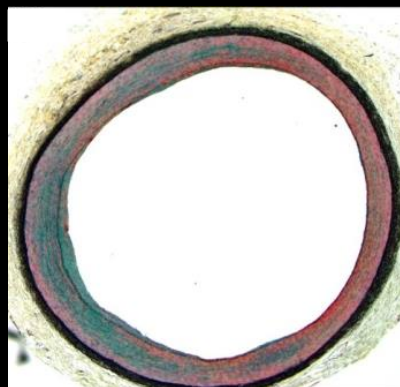


28 days

DES

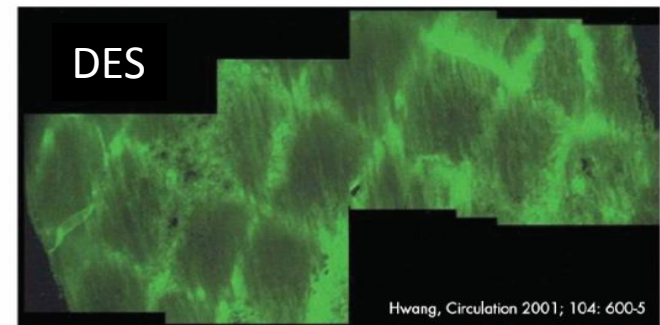


DCB

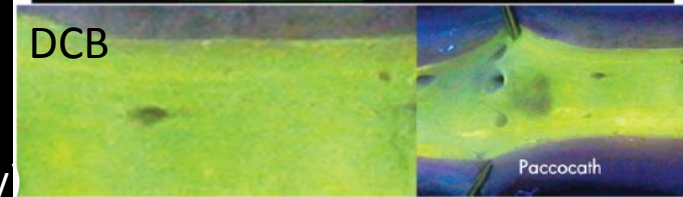


14 days (Porcine iliac artery)

DES



DCB

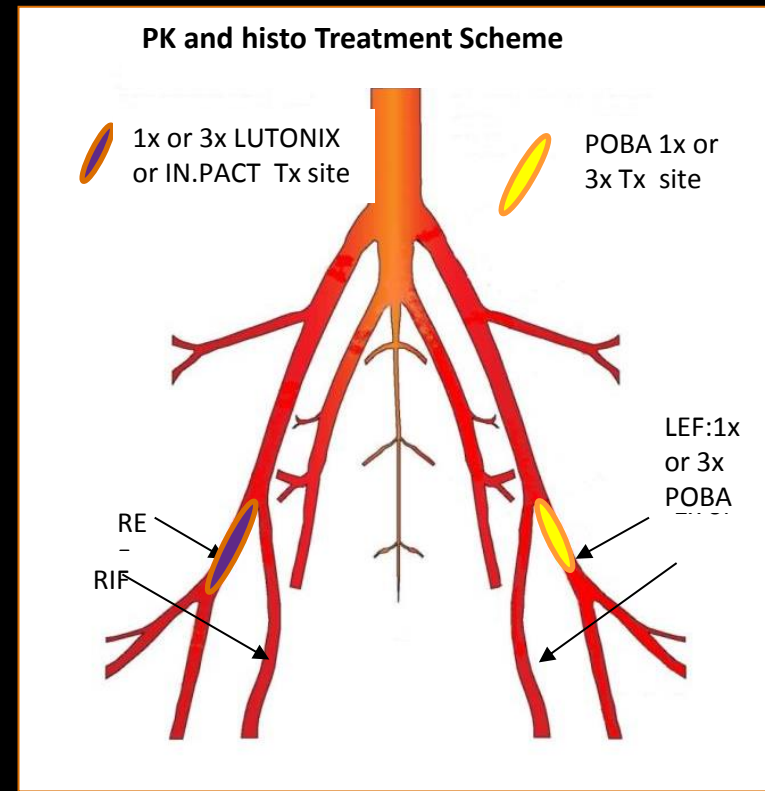
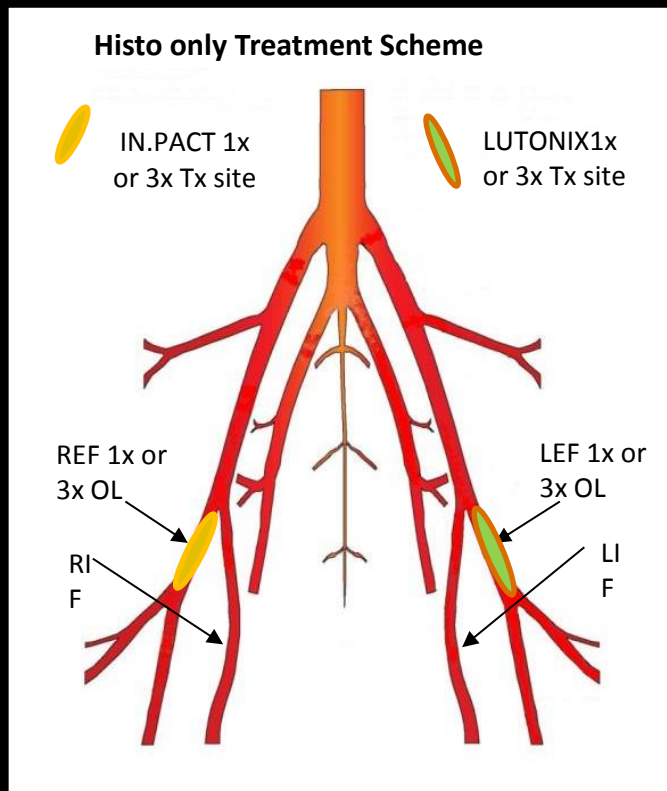


Elements of an Effective DCB Formulation

- Must deliver large quantities of the drug within seconds
- Distribute within the media in the first few days
- Therapeutic drug levels must be maintained for more than 4 weeks
- Must allow rapid healing as compared to DES
- No need for long-term anti-platelet therapy
- Biologic effects must be observed by histology at 28-days
- **Effective drug delivery to target tissue while avoiding non-target effect (i.e. minimize emboli)**

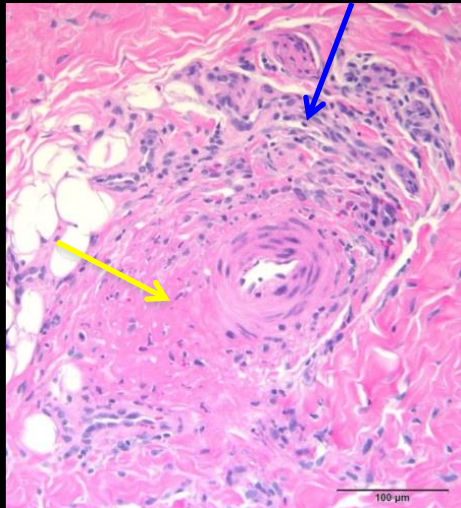
Pre-clinical Comparative Study

- Swine SFA were randomly treated by **LUTONIX**, **IN.PACT** or **POBA**, 1x and 3x dose.
- Evaluated downstream organs at 28 and 90 days
 - Distal drug concentration
 - Histology ;Distal embolization, Vascular changes

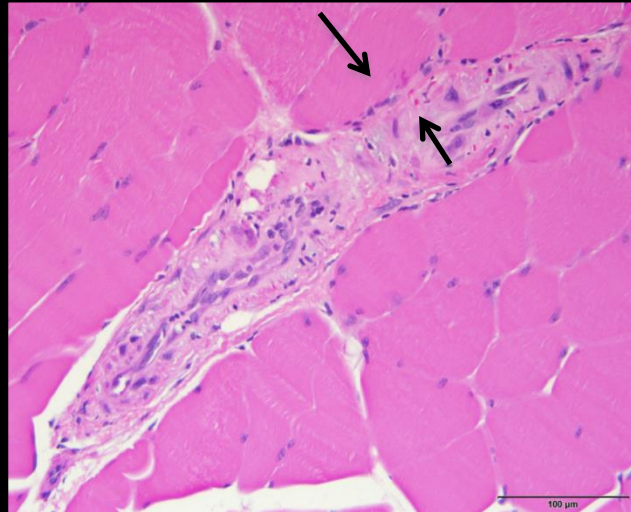


Downstream Findings in Porcine Skeletal Muscle (28-Day)

**Lutonix (1x)
Vascular Change**



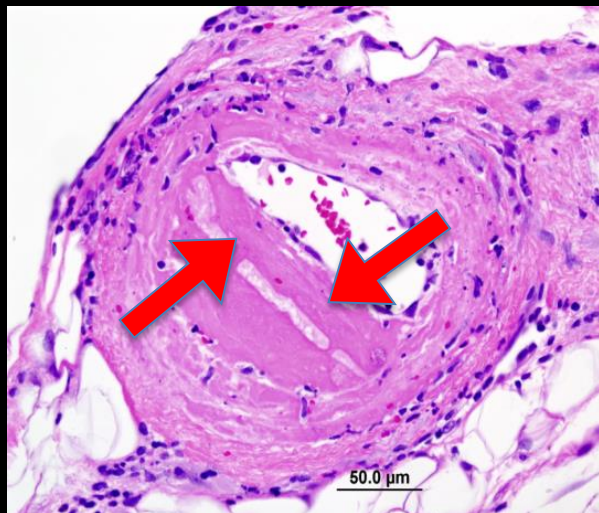
IN.PACT (1x) Vascular Change



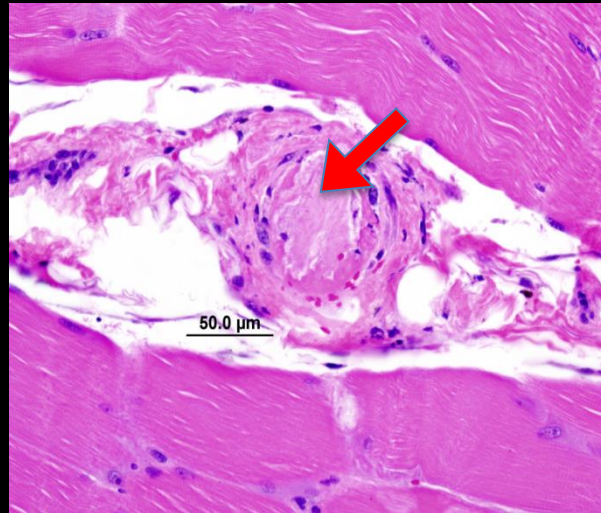
High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

IN.PACT (1x) Crystalline Material



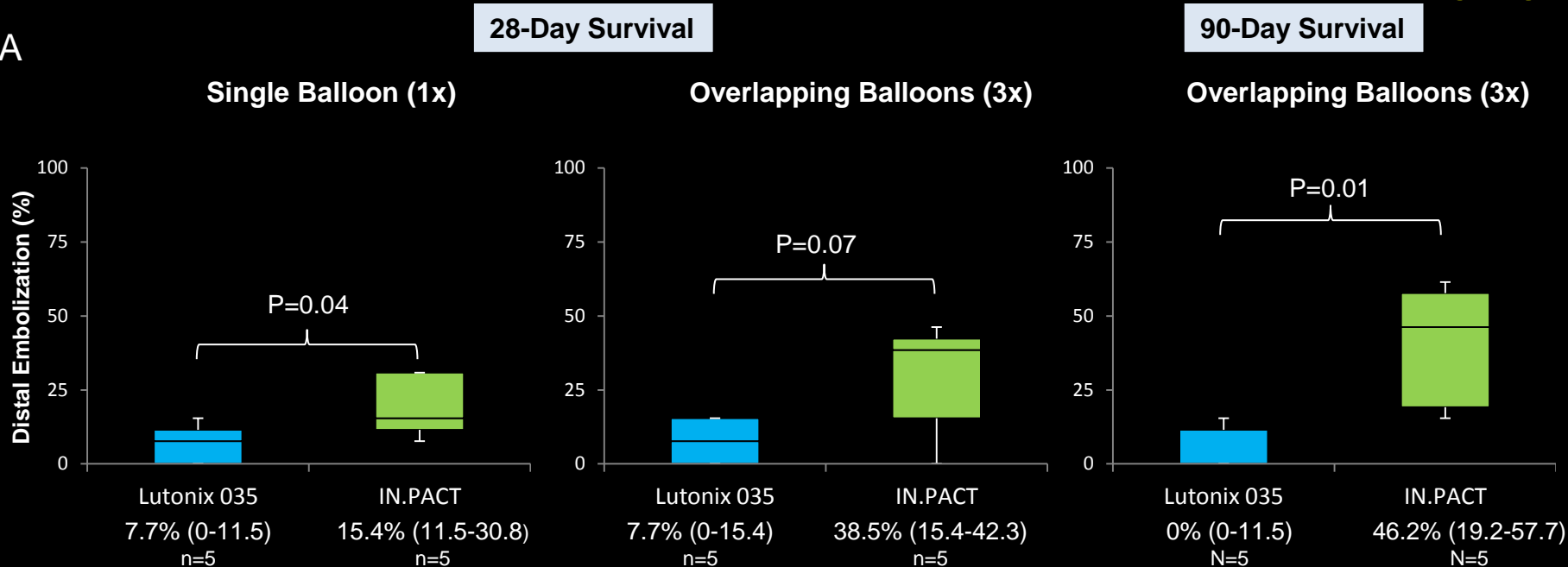
IN.PACT (3x) Crystalline Material



High (40x) power images of crystalline material (red arrows) at 28d

Downstream Incidence of Distal Embolization (%)

A



B

	Survival Treatment & Arteries	Lutonix 035	IN.PACT	P-value
Number of micro-vessels with paclitaxel-associated findings	28-day (1x, n=5)	1 (0-2)	4 (2-12)	0.03
	28-day (3x, n=5)	1 (0-12)	26 (11-34)	0.07
	90-day (3x, n=4)	0 (0-3)	11 (5-15)	0.02

C

	Survival Treatment & Arteries	Lutonix 035		IN.PACT		P-value	
		Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
Paclitaxel concentration in downstream tissues (ng/g)	28-day (1x, n=5)	1.3 (0.6-2.3)	1.5 (1.1-65.8)	60.8 (32.6-118.1)	189.0 (134.0-700.0)	0.009	0.02
	28-day (3x, n=5)	3.7 (1.3-10.9)	31.5 (5.9-54.1)	170.9 (19.7-221.5)	871.0 (567.5-1315.0)	0.08	0.009
	90-day (3x, n=4)	0.6 (0.5-6.4)	2.7 (0.0-25.5)	16.1 (12.8-319.2)	158.0 (6.3-1178.0)	0.009	0.05

Current DCB Controversy

SYSTEMATIC REVIEW AND META-ANALYSIS



Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

- A systematic review and meta-analysis published in Dec 2018.
- Paclitaxel DCB/DES vs POBA/BMS for femoropopliteal artery disease
- All cause patient death rate at
 - 1 year, 28 RCTs, n= 4432; 2.3% vs 2.3% (RR 1.08; 95% CI. 0.72-1.61)
 - 2 year, 12 RCTs, n=2316; 7.2% vs 3.8% (RR 1.68; 95% CI. 1.15-2.47)
 - 5 year, 3 RCTs, n=863; 14.7% vs 8.1% (RR 1.93; 95% CI. 1.27-2.93)

**Paclitaxel devices showed
higher risk of mortality at 2 years and 5 years**

Current DCB Controversy

U.S. FDA issued “Letter to healthcare Providers”

ISSUE: January 17, 2019

UP DATE: March 15, 2019

Recommendations

1. **Monitoring of patients** who have been treated with paclitaxel devices
2. For most patients, **alternative treatment options** to paclitaxel devices should generally be used until additional analysis of the safety signal has been performed
3. For **some individual patients** (i.e., high risk for restenosis) , clinicians may determine that the benefits of using a **paclitaxel devices may outweigh** the risks.
4. Ensure patients receive **optimal medical therapy** for PAD and other cardiovascular risk factors



The screenshot shows the FDA website interface. At the top, it says "U.S. Department of Health and Human Services" and "U.S. FOOD & DRUG ADMINISTRATION". There is a search bar and navigation links for "A to Z Index", "Follow FDA", and "En Español". Below the navigation bar, there are tabs for "Home", "Food", "Drugs", "Medical Devices", "Radiation-Emitting Products", "Vaccines, Blood & Biologics", "Animal & Veterinary", "Cosmetics", and "Tobacco Products". The "Medical Devices" tab is selected. The main content area displays the title "Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers" and a breadcrumb trail: "Home > Medical Devices > Medical Device Safety > Letters to Health Care Providers".

U.S. Food & Drug Administration (2019),

“Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents potentially Associated with Increased Mortality – Letter to Health Care Providers”,

Summary

- First generation DESs had problems with delayed arterial healing characterized by uncovered struts and higher inflammation, and hypersensitivity reaction.
- Second generation DESs have markedly improved, with significantly less thrombosis, inflammation, and uncovered struts.
- Even long-term results (>1 year) with permanent polymers are better than BMS and SES in terms of inflammation and target lesion failure.
- In long term study by histology (1 to 5 years), 2nd generation DES (EES) showed similar neoatherosclerosis with less advanced plaques observed in EES than SES.
- DCB might overcome clinical unmet of DES, however, further discussion are needed on the safety of paclitaxel devices.

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CVPath Institute

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Russ Jones

Ed Acampado, DVM

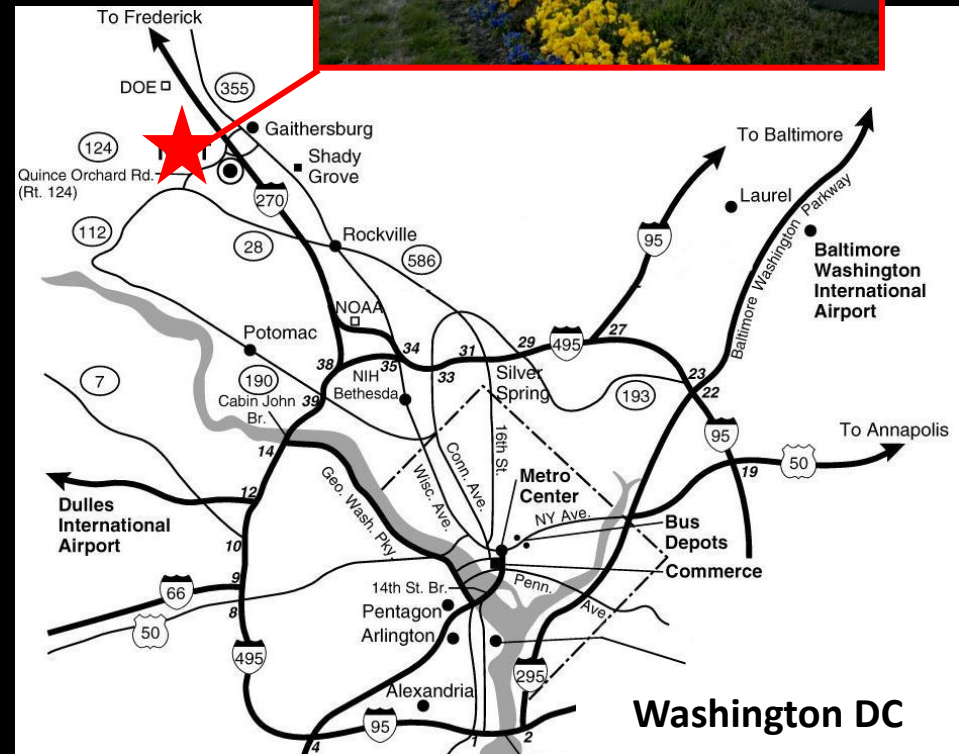
Abebe Atiso, HT

Jinky Beyer

Lila Adams, HT

Frank D Kolodgie, PhD

Renu Virmani, MD



Reactions



LINC; January 22-25, 2019, Germany.

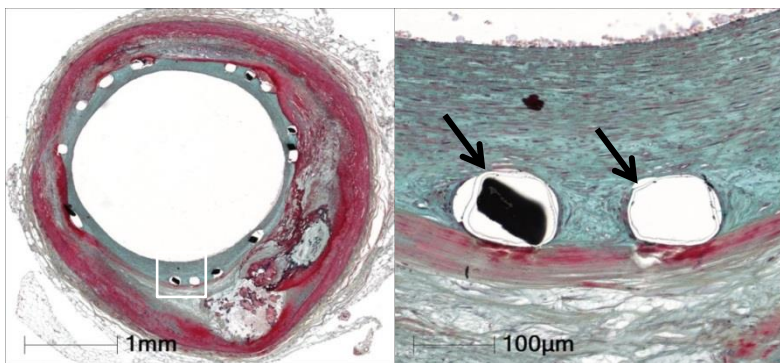
Makers with FDA approved paclitaxel devices reported a comparison of mortality between DCB/DES and POBA/BMS

- Medtronic Paclitaxel DCB/DES vs POBA/BMS, p value
 - IN.PACT Admiral™; **9.3% vs 11.2%**, p=0.399 (5 years, n=1980)
- BARD
 - Lutonix®; **14.2% vs 10.6%**, p=0.198 (5 years, n=1189)
- PHILIPS
 - Stellarex™; **7.9% vs 9.9%**, p=0.78 (3 years, n=2521)
- Cook Medical
 - Zilver® PTX®; **18.7% vs 17.6%**, p=0.53 (5 years, n=479)
- Boston Scientific
 - Eluvia™; **2.10% vs 4.0%**, p=0.23 (1 year, n=465) * *Lancet. 2018 Oct 27;392(10157):1541-1551.*

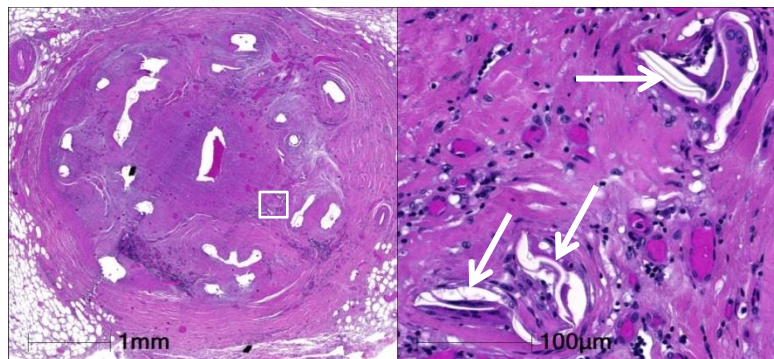
**There was no difference in mortality
between paclitaxel devices and non-paclitaxel devices.**

Polymer Delamination in Long-Term

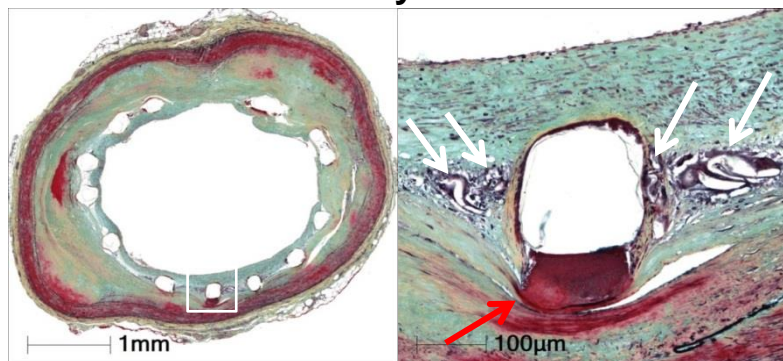
CoCr-EES 4 years



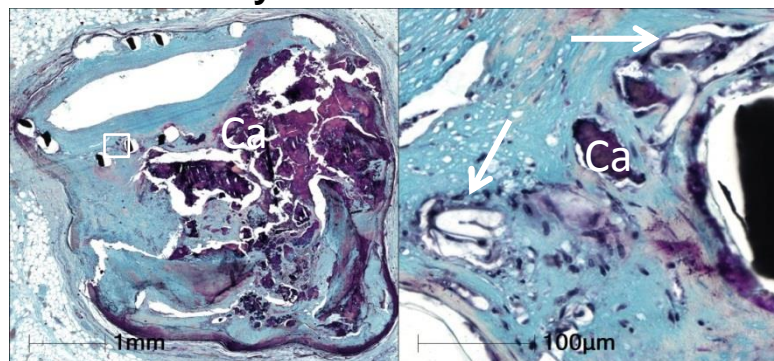
CoCr-EES 5 years



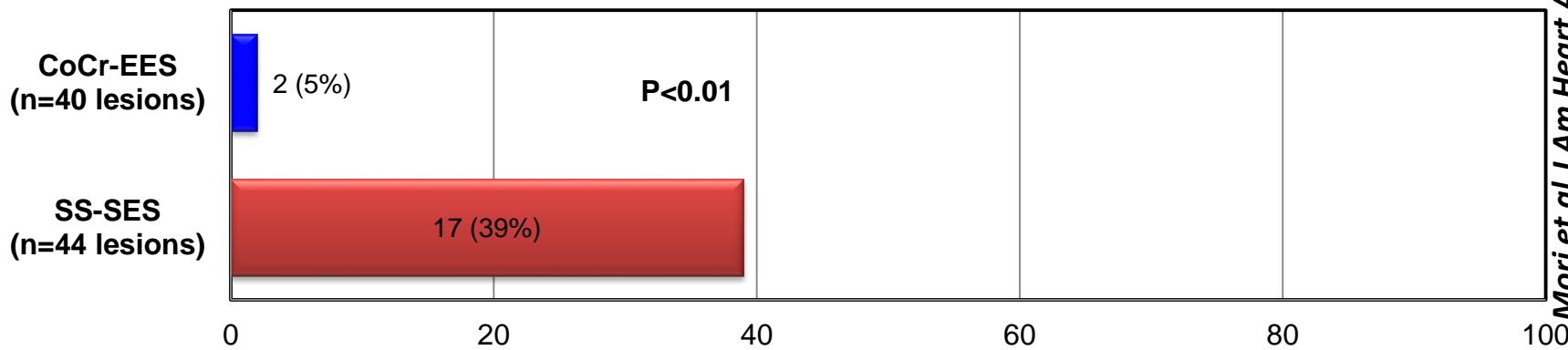
SS-SES 2 years



SS-SES 2.6 years



Prevalence of Polymer Delamination (%)



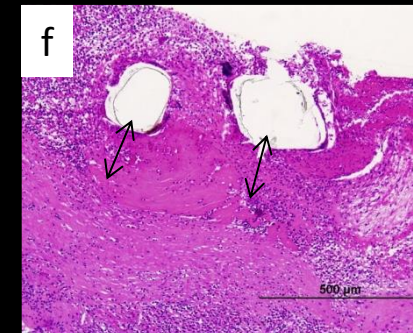
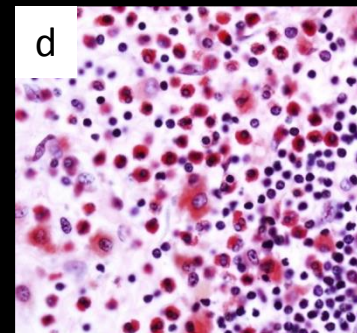
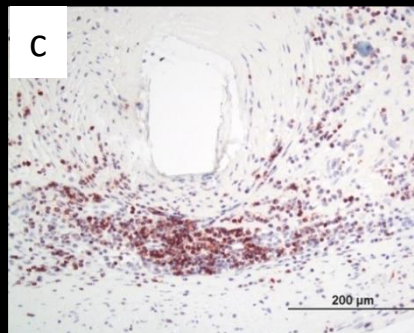
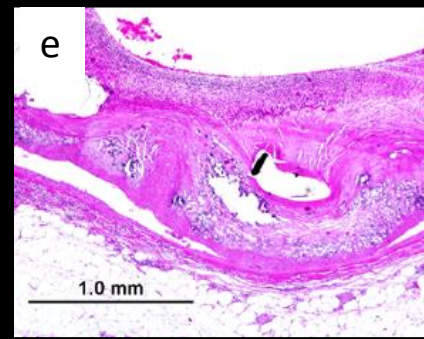
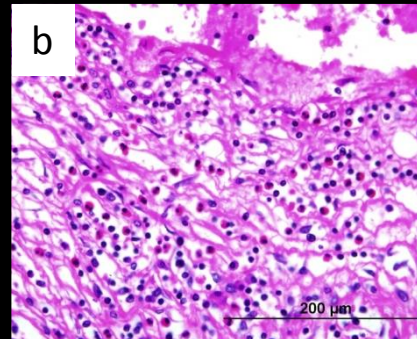
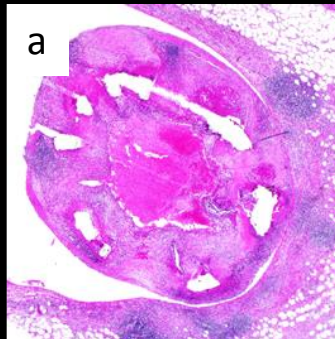
**Pathological studies
in 1st vs. 2nd Generation DES**

First-generation DES with localized Hypersensitivity and Malapposition

Patient #	Age (yrs)/ Sex	Lesion	Stent Type	Total Stented Segment (mm)	Duration of Implants (Months)	Indication for Implants	Clinical Presentation	Malapposition	Malapposed Distance (μm)
SES with localized hypersensitivity reaction									
1	61/M	RCA	SES	18	4	SAP	Sudden death	No	—
2*	40/F	LAD	SES	27	17	AMI	Sudden death	Yes	650
		RCA	SES	25	17	AMI		Yes	320
3	49/M	LCX	SES \times 2	27	18	UAP	AMI	Yes	1,620
4	46/M	LAD	SES	23	31	SAP	AMI	Yes	930
		RCA	SES \times 2	30	31	AMI		Yes	1,200
5	62/F	LAD	SES \times 3	41	36	SAP	Repeat occlusion	NA†	—

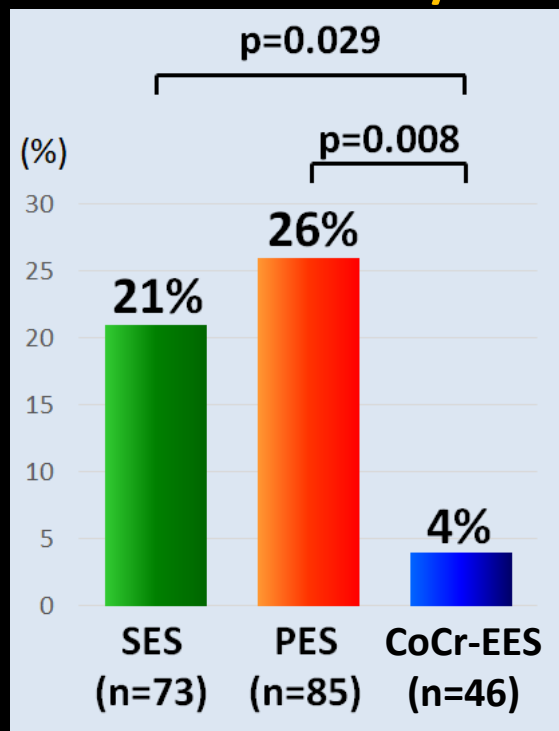
LAD: SES (17months)

RCA: SES (17months)



Pathology of 2nd-gen CoCr-EES vs. 1st-gen SES/PES

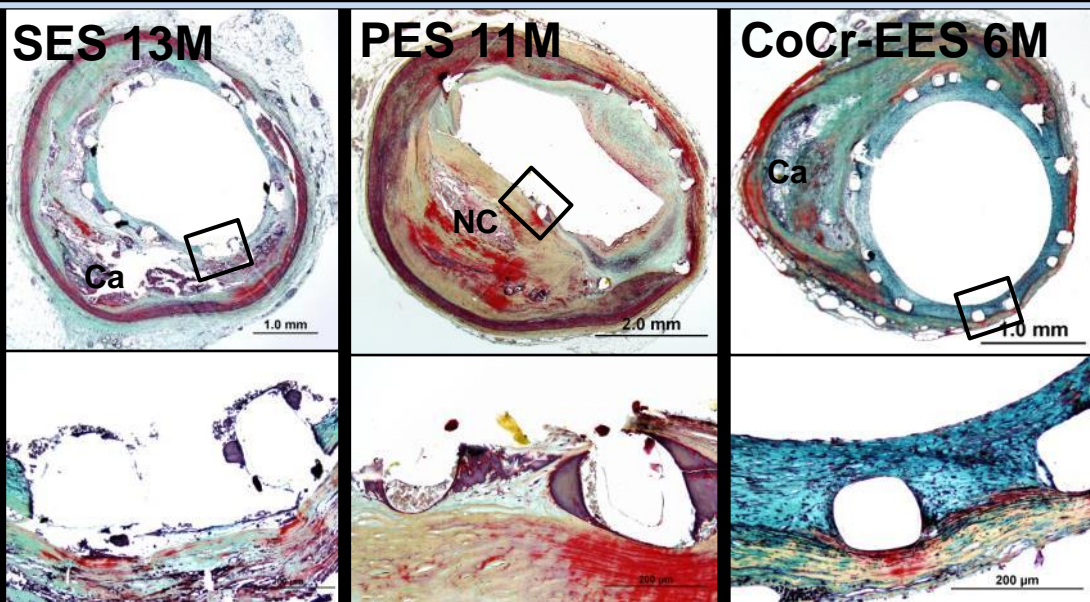
Prevalence of LST/VLST



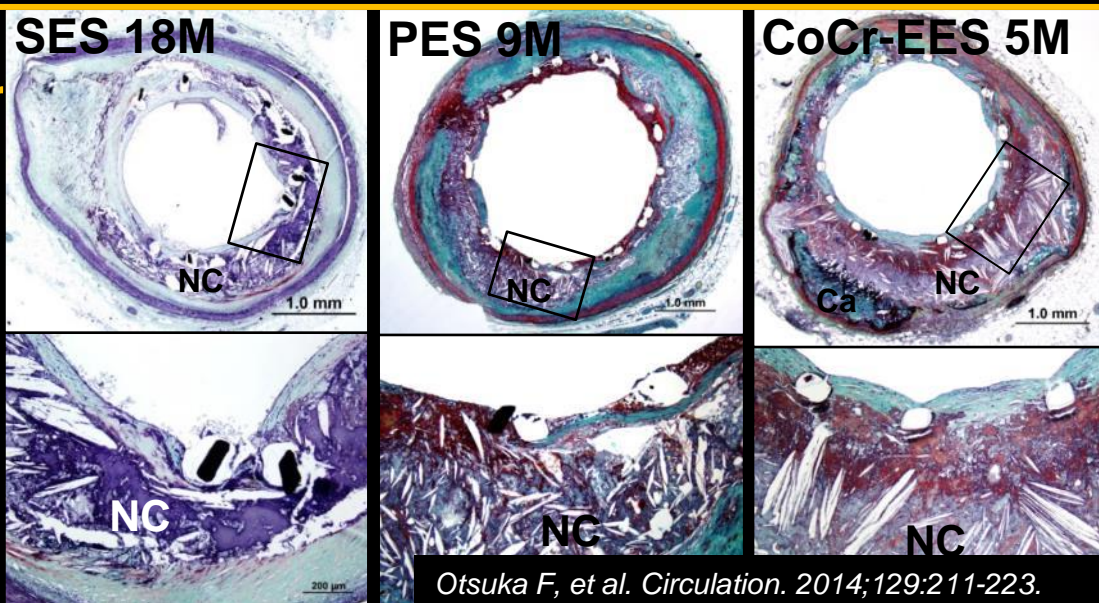
Cypher: 15/73 (21%)
Taxus: 22/85 (26%)
XIENCE V: 2/46 (4%)

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

DES for Stable CAD



DES for ACS



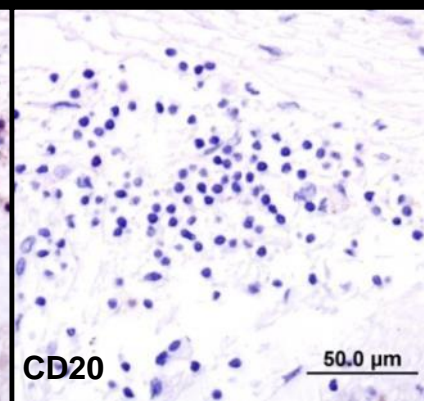
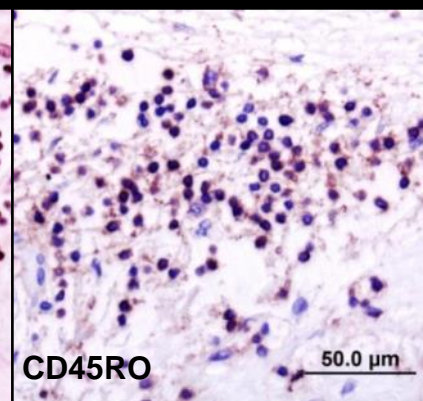
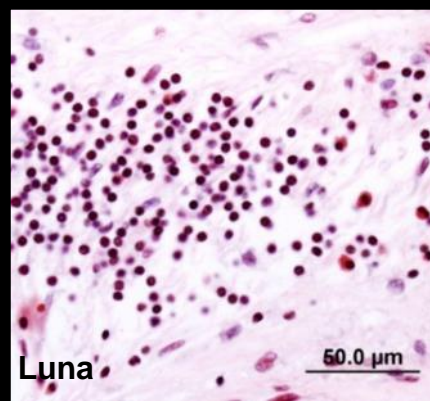
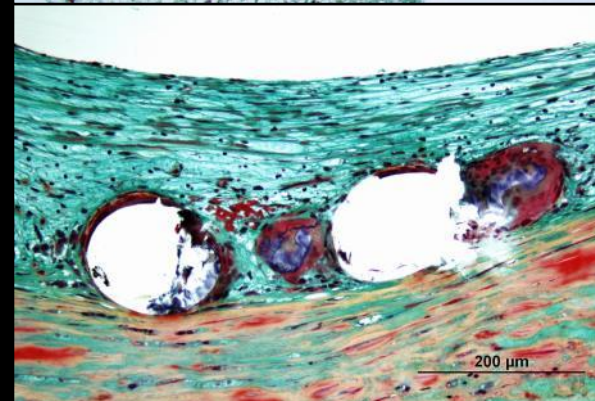
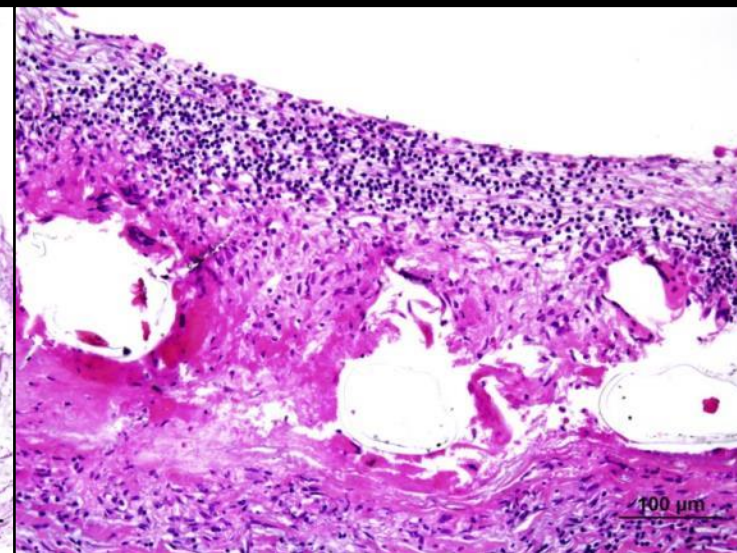
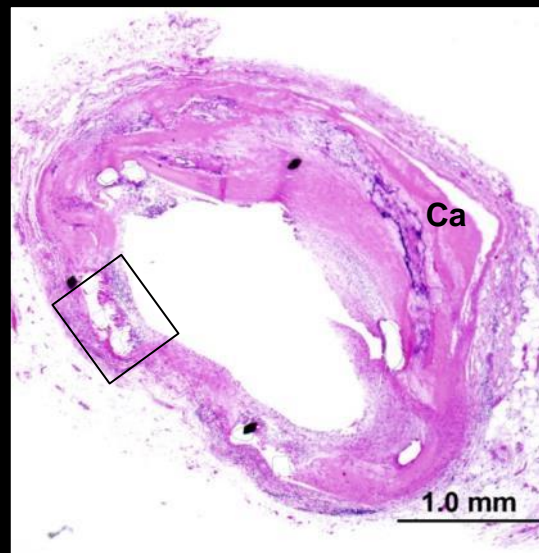
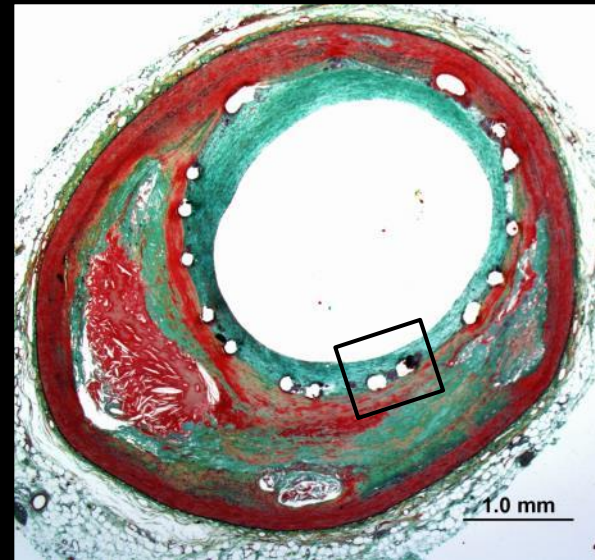
Otsuka F, et al. *Circulation*. 2014;129:211-223.

Duration of implant:
 >30 days, ≤3 years

Inflammation in the 2nd-generation DES

61M, E-ZES (3 months)

51M, CoCr-EES 4 months

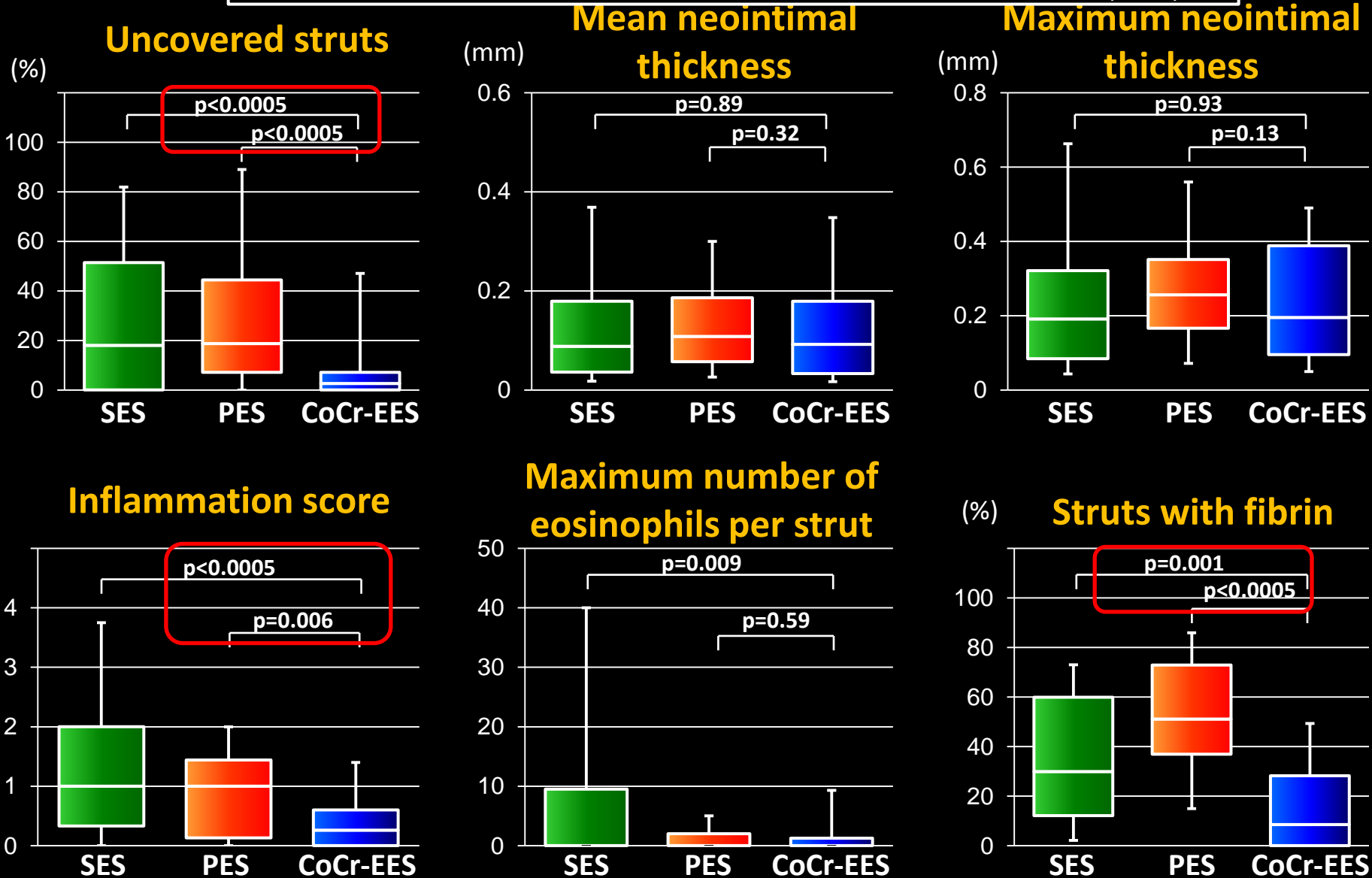


Chronic inflammation consisting with giant cells secondary to polymer delamination in ZES

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

Morphometric Analysis: CoCr-EES vs. SES/PES

SES (n=72) PES (n=78) CoCr-EES (n=41) Duration of implant: >30 days, ≤3 years

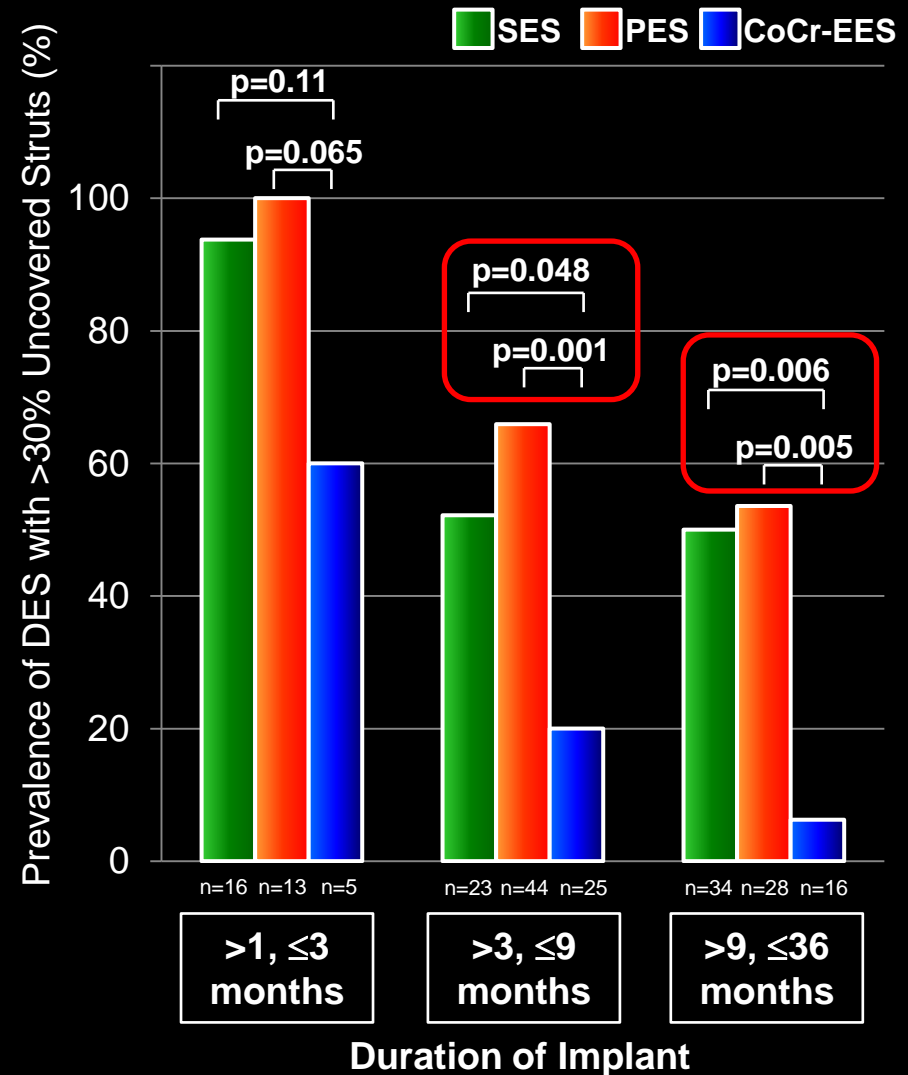
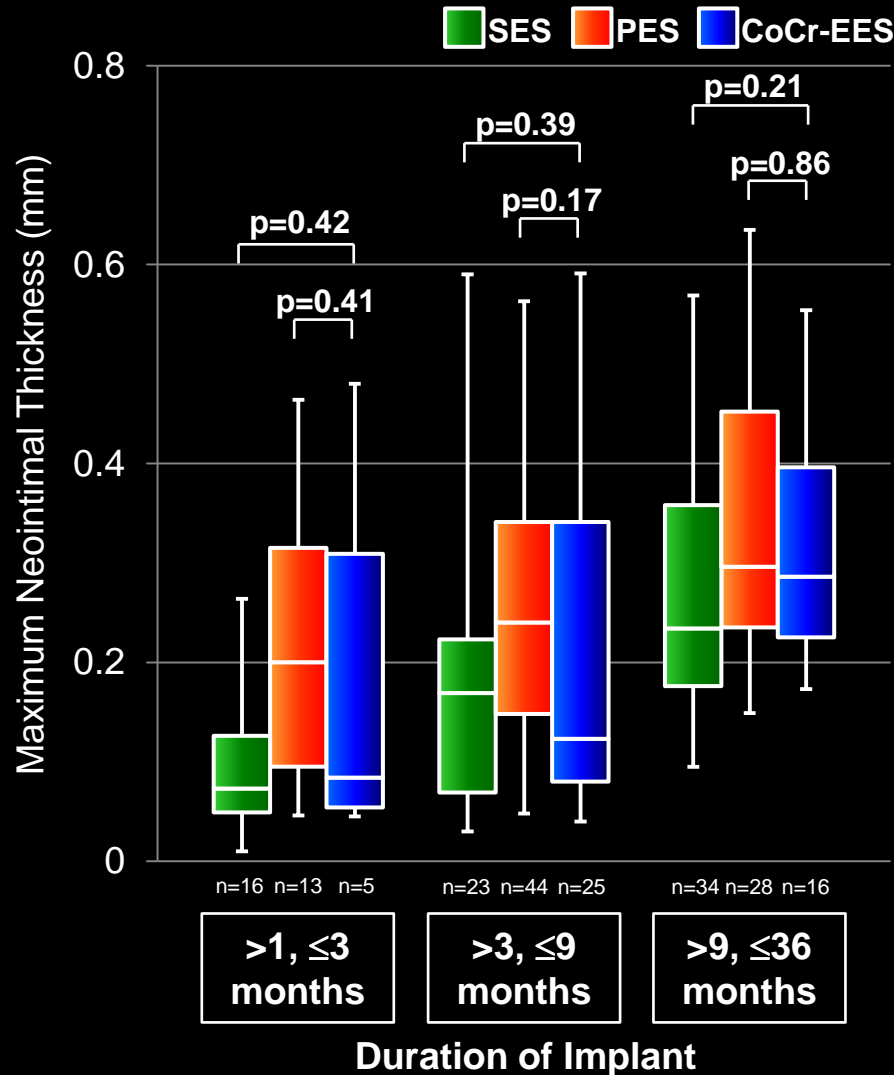


All statistical analyses were corrected for duration of implant.
Modified from Otsuka F, et al. Circulation. 2014;129:211-223.

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

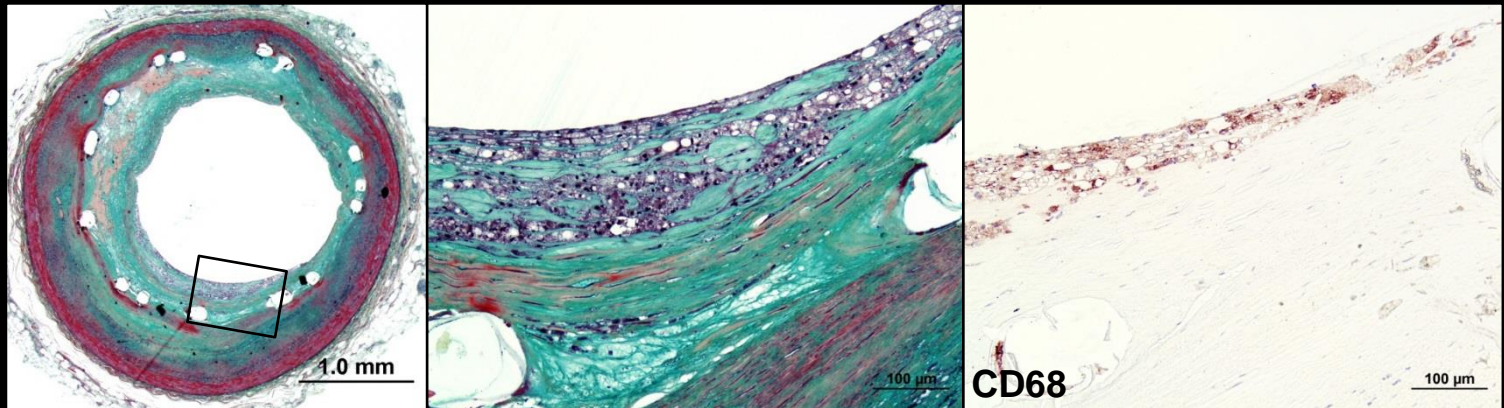
Maximum Neointimal Thickness (mm)

Prevalence of >30% Uncovered Struts

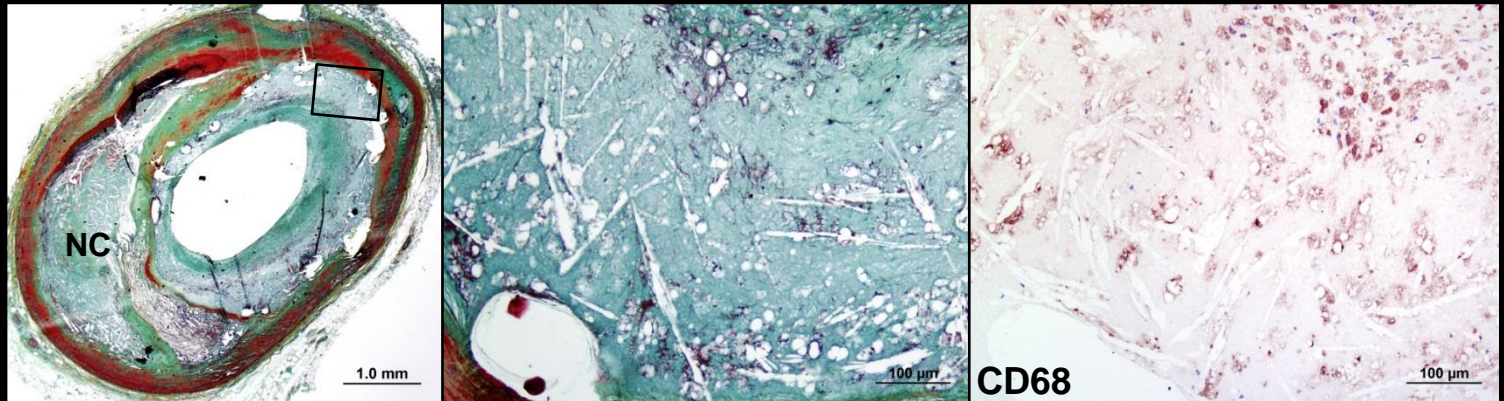


Neoatherosclerosis in CoCr-EES

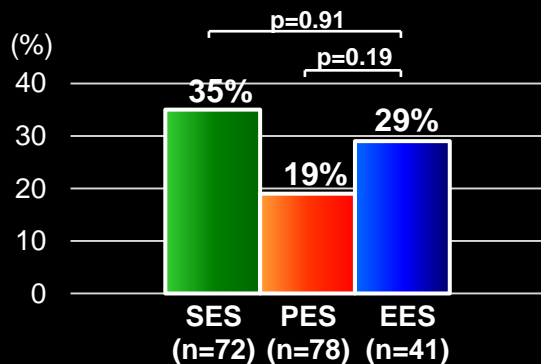
CoCr-EES
24M



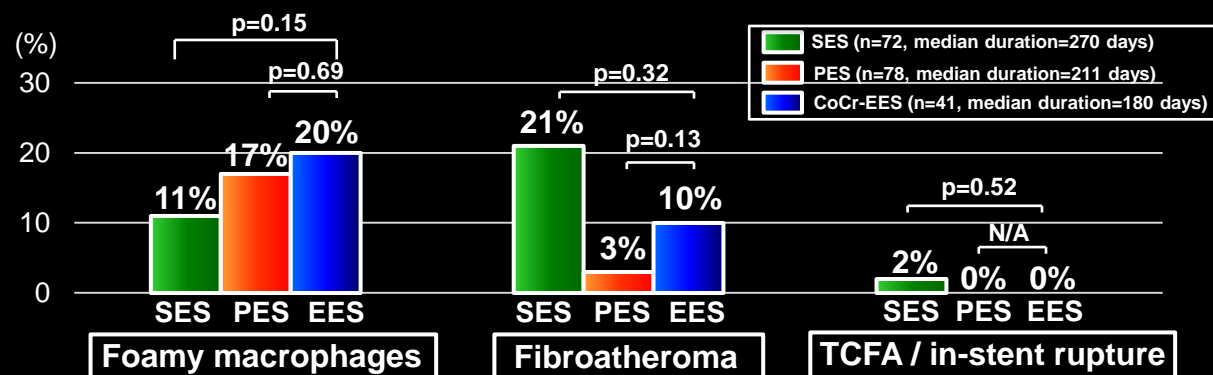
CoCr-EES
36M



Overall prevalence of NeoAth

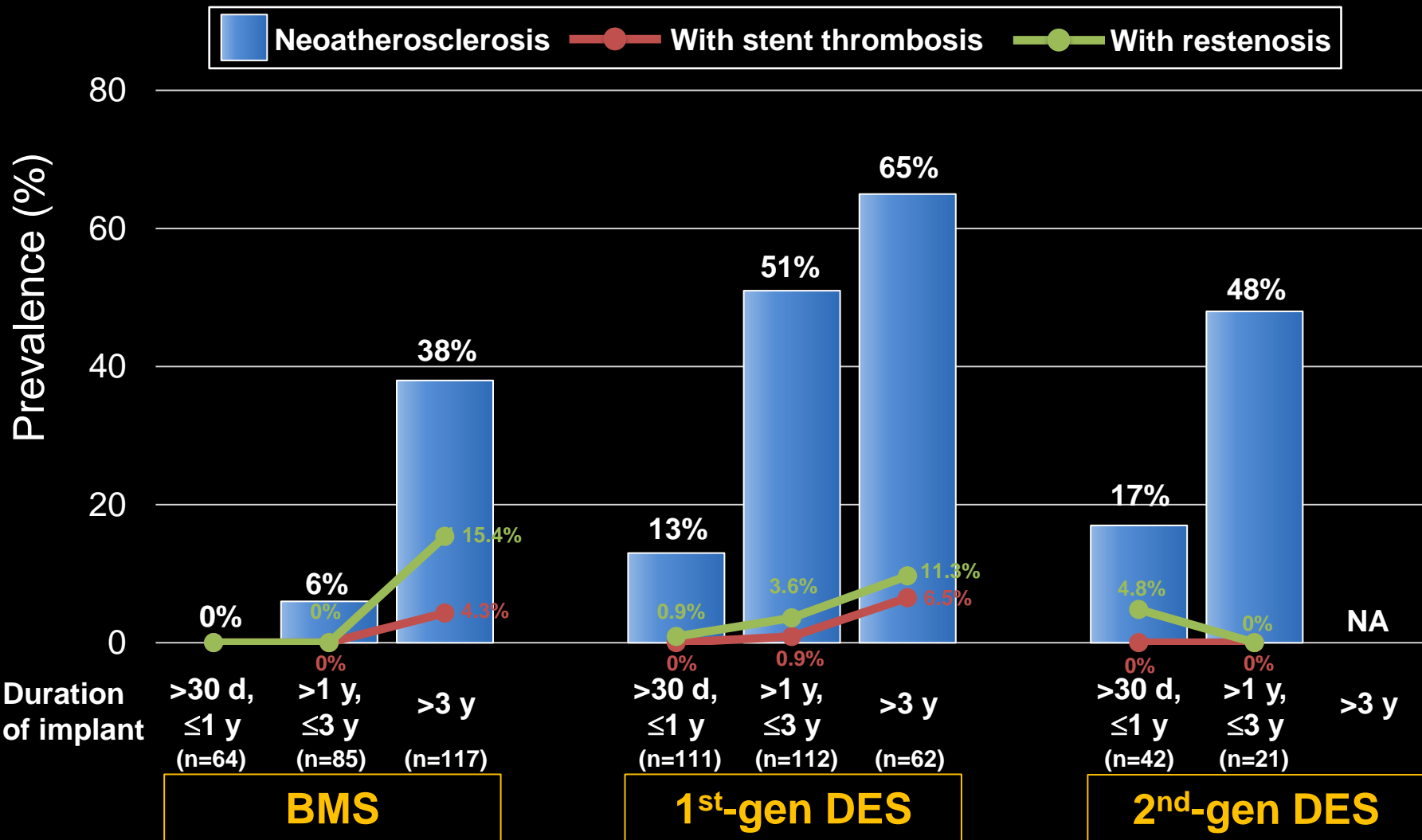


Prevalence of Various Features of Neoatherosclerosis



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

Prevalence of Neoatherosclerosis, Stent Thrombosis with Neoatherosclerosis, and Restenosis with Neoatherosclerosis Stratified by Duration of Implant in BMS, 1st- and 2nd-gen DES



A total of 614 stented coronary lesions (BMS=266, 1st-generation DES=285 [143 SES and 142 PES], and 2nd-generation DES=63 [7 E-ZES, 3 R-ZES, and 53 EES]) from 384 autopsy cases were pathologically examined (mean duration of implant = 913±989 days).