Ultimaster-From the Pathological Point of View

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Conflict of Interest Declaration

- Institution 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, Spectronics, CSI, Lutonix Bard, Surmodics, Microport, Meril Life Sciences.

Evolution of DES Technology

First Gen

Durable Polymer Stents

	Cypher	TAXUS Express	TAXUS Liberte
Strut Thickness	140 µm	132 µm	96 µm
Coat Thickness	7µm / side	16µm/side	14µm/side

Bioabsorbable Polymer Stents

	Biomatrix	Nobori
Strut Thickness	120 µm	125 µm
Coat Thickness	10 µm	20 µm

Fully Bioresorbable Stents

	BVS	ELIXIR DESolve	DREAMS II
Strut Thickness	150 µm	150 µm	150 µm
Coat Thickness	3 µm / side	<3 µm / side	8 µm / side

Second Gen

Durable Polymer Stents

	Resolute Integrity	Xience Xpedition	Promus PREMIER
Strut Thickness	89 µm	81 µm	81 µm
Coat Thickness	6µm / side	8µm / side	8µm / side

Bioabsorbable Polymer Stents

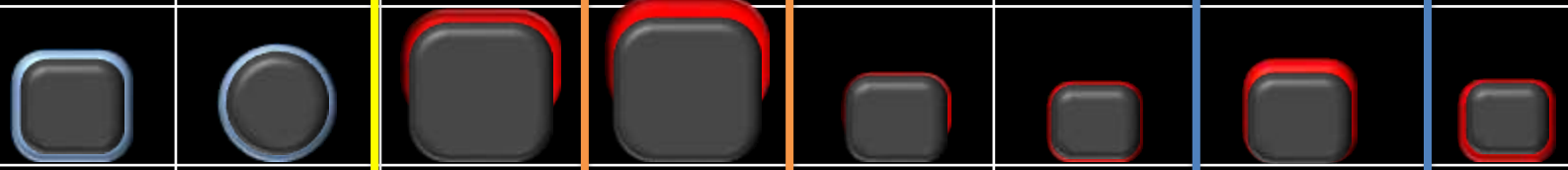
	Firehawk	Synergy	Ultimaster
Strut Thickness	86µm	74µm	80µm
Coat Thickness	10 µm	4 µm	14 µm

First Generation Future Technologies

Polymer Free Stents

	BIOFREEDOM	Drug Filled Stent
Strut Thickness	112	86
Coat Thickness	NA	NA

Contemporary DES Platforms
Strut and Coating Thickness In Perspective

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute	Biomatrix	Nobori	SYNERGY	BioMime	Ultimaster	Orsiro
	Promus PtCr-EES	CoNi-ZES	316L-BES	316L-BES	PtCr-EES	CoCr-SES	CoCr-SES	CoCr-SES
								
Strut thickness	81µm 0.0032”	89µm 0.0035”	120µm 0.0046”	125µm 0.0047”	74µm 0.0029”	65µm 0.0026”	80µm 0.0030”	61µm 0.0024”
Polymer	PVDF	BioLINX	PLA	PLA	PLGA	PLLA + PLGA	PDLLA+PCL	PLLA Probio*
Distribution / thickness	Conformal 7-8µm / side	Conformal 6µm / side	Abluminal 10µm	Abluminal 20µm	Abluminal 4µm	Conformal 2µ / 2µ	Abluminal 15µm	Conformal 3.5µm / 7.5µm

Various Biodegradable Polymers and Degradation Speed

Material	Degradation Period
50/50 Poly-DL-lactide-co-glycolide (DLPLG)	1-2 month
Poly (DL-lactide/glycolide) copolymer (PLGA)	2-3 months
Polyglycolic acid (PGA)	2-3 months
Poly DL-lactide-co-caprolactone copolymer (PDLLA+PCL)	3-4 months
85/15 Poly-DL-lactide-co-glycolide (DLPLG)	5-6 month
Poly(hydroxybutyrate/hydroxyvalerate)copolymer (PHBV)	6 months
Polylactic acid (PLA)	9 months
Polyorthoester (POE)	10 months (60%)
Poly-L-lactic acid (PLLA)	12-18 months
Polycaprolactone (PCL)	36 months

PLA Metabolic Pathway

PLA

↓Molecular weight

Mass loss

Lactic acid

Mass transport of lactic acid

Krebs cycle → CO_2+H_2O

H_2O

Hydrolysis

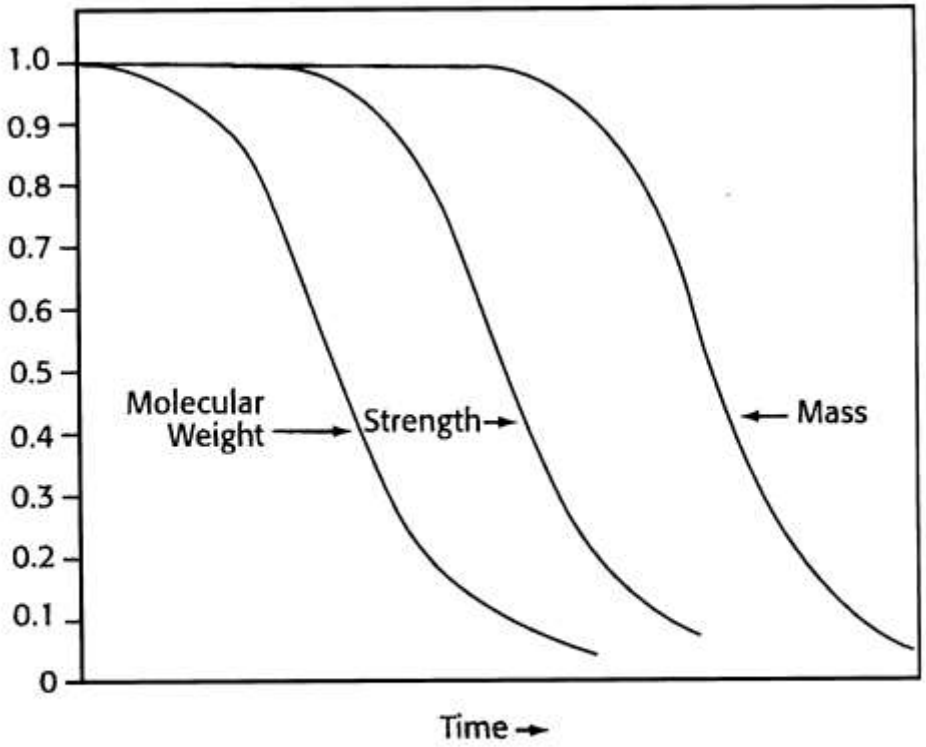
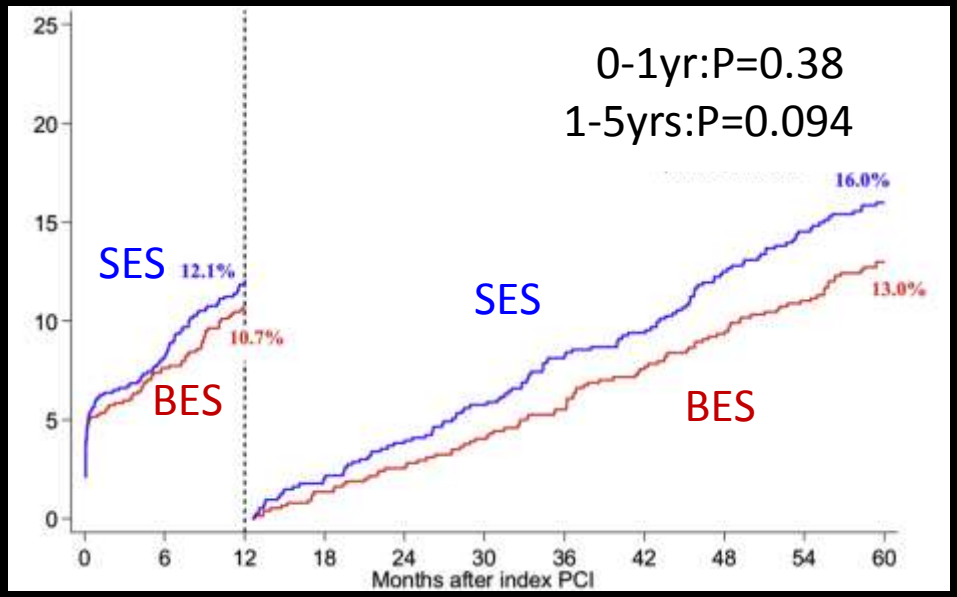


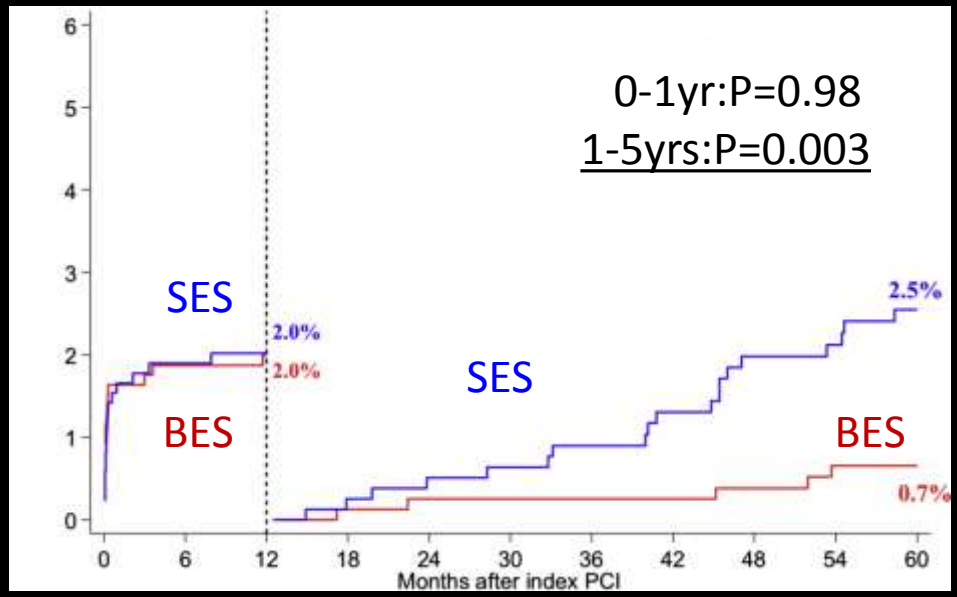
Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

Five-year outcome following revascularization with biodegradable polymer BES and durable polymer SES in all comer (LEADERS-TRIAL)

Cardiac Death, MI, TVR

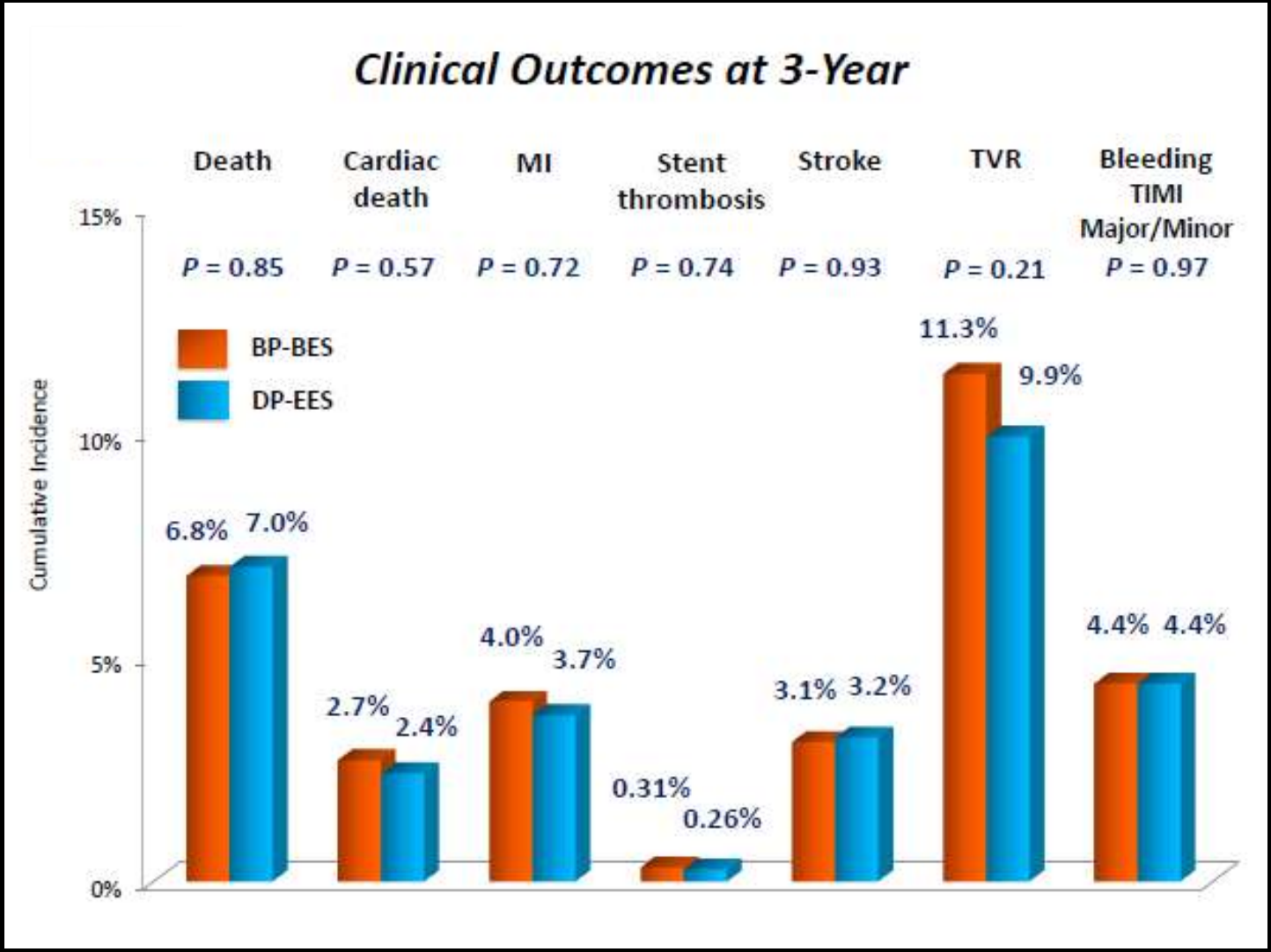


Definite stent thrombosis



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

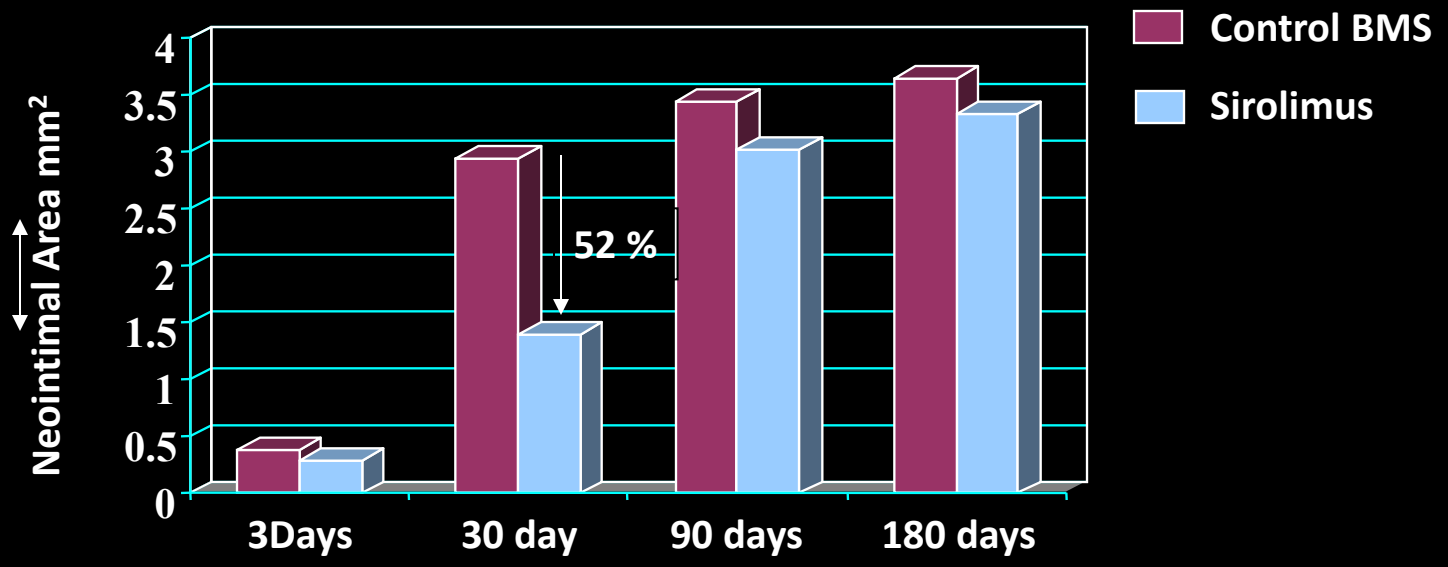
3 year outcome from NEXT trial
Biodegredable polymer BES (Nobori, n=1617) vs. Durable polymer EES (Xience, n=1618)

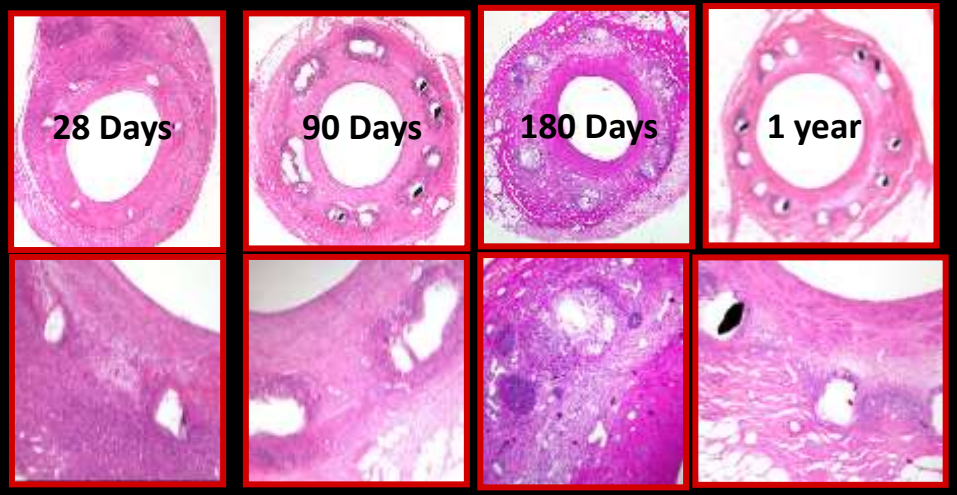


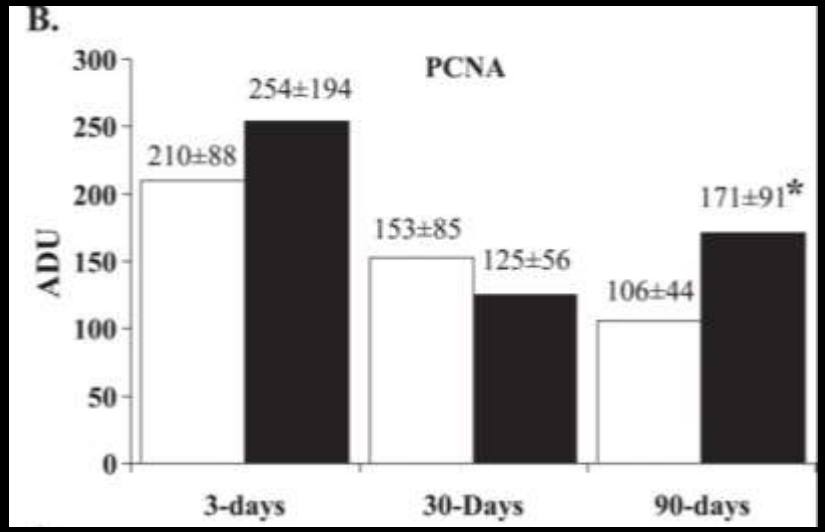
Natsuaki et al, EuroPCR2015

Why Contemporary Durable Polymers Are Not Good Enough.

Permanent Polymers, Inflammation and Late Catch Up



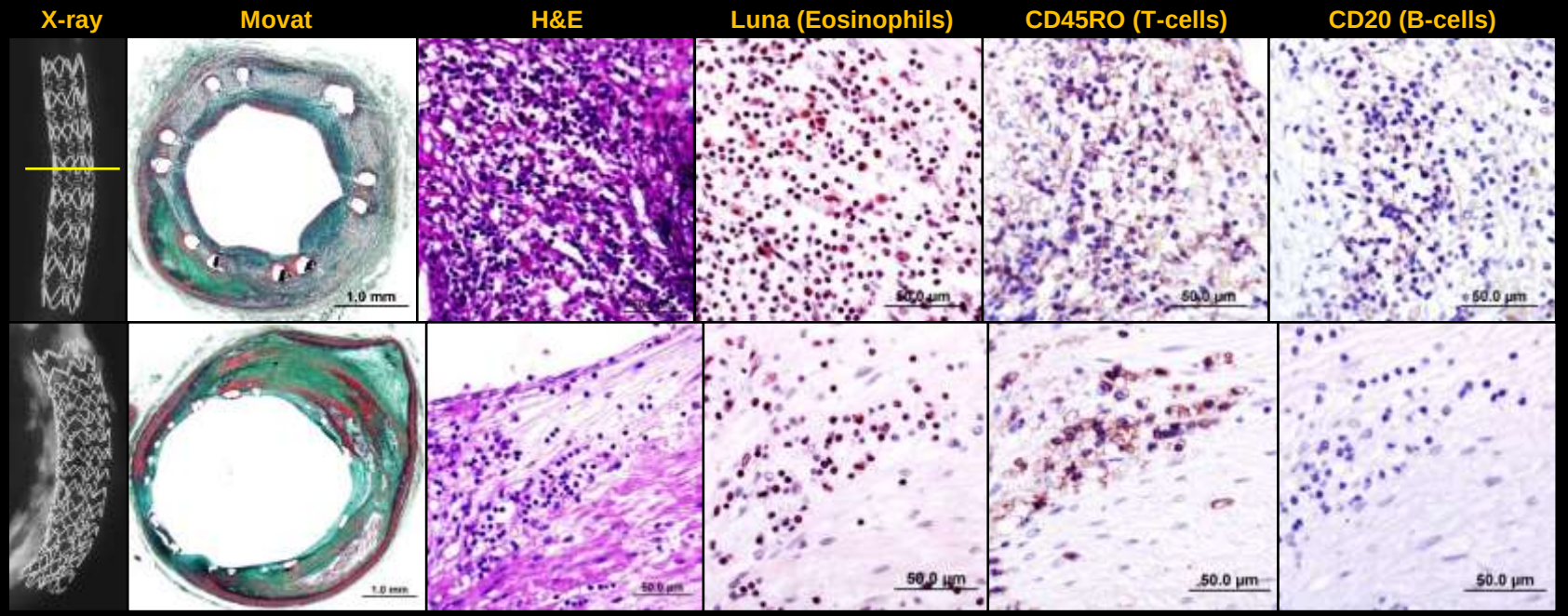


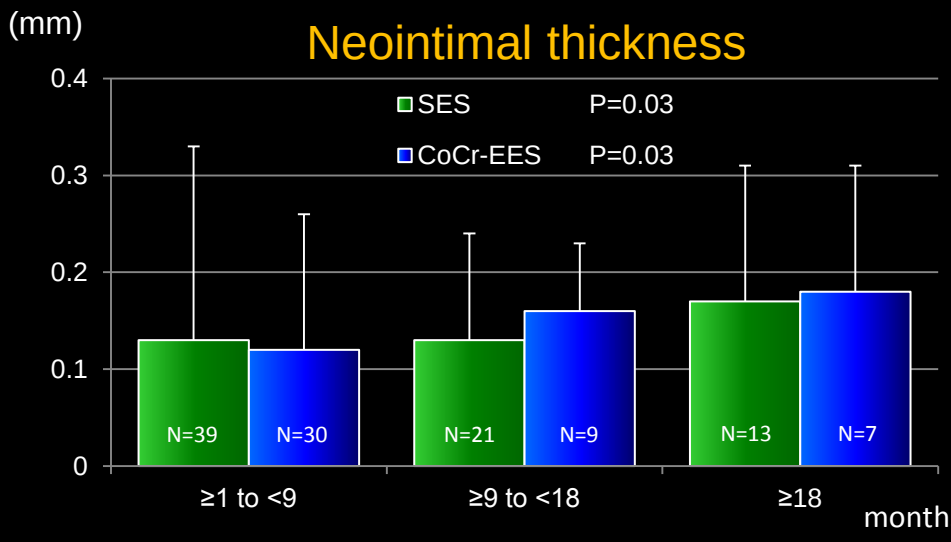


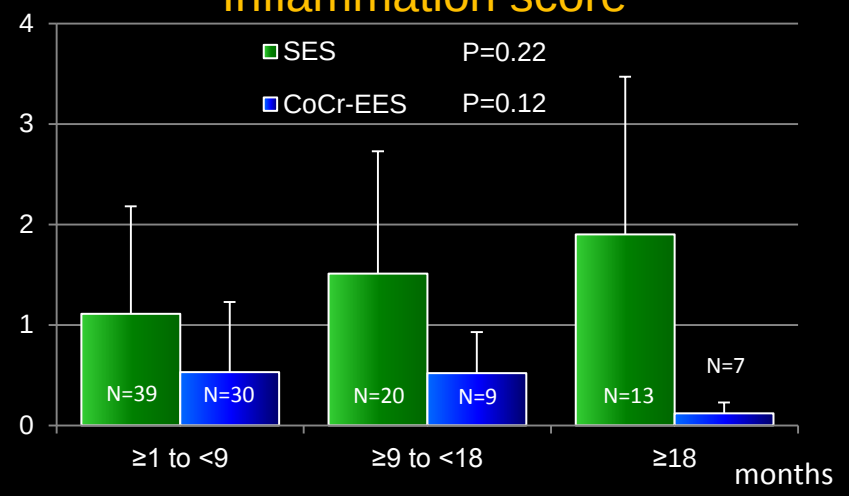
Carter AJ. Cardiovascular Research. 2004

Vascular Response following Implantation of Drug-eluting stents in Human

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.



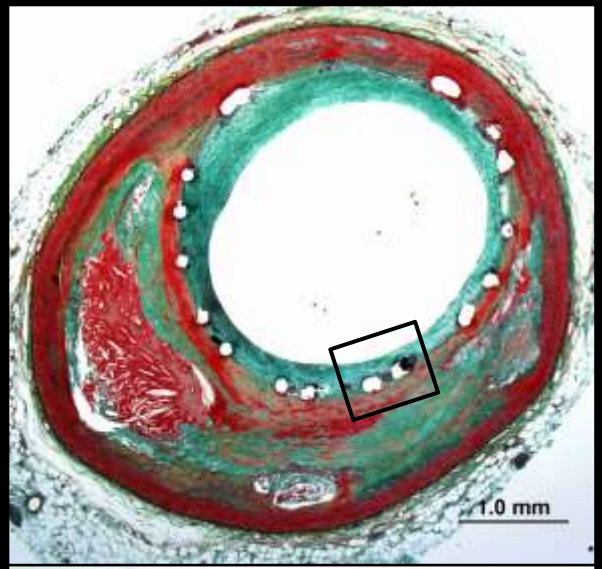


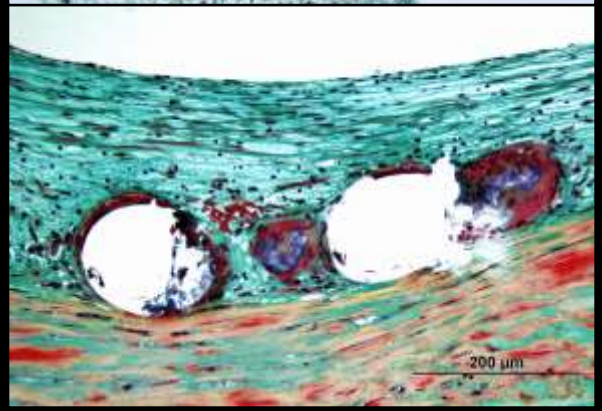


Modified with Otsuka F, et al. Circulation. 2014;129:211-223.

Inflammation in the 2nd-generation DES

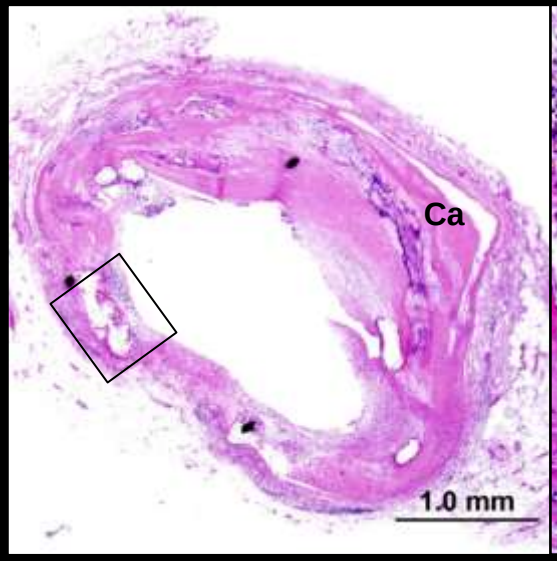
61M, E-ZES (3 months)

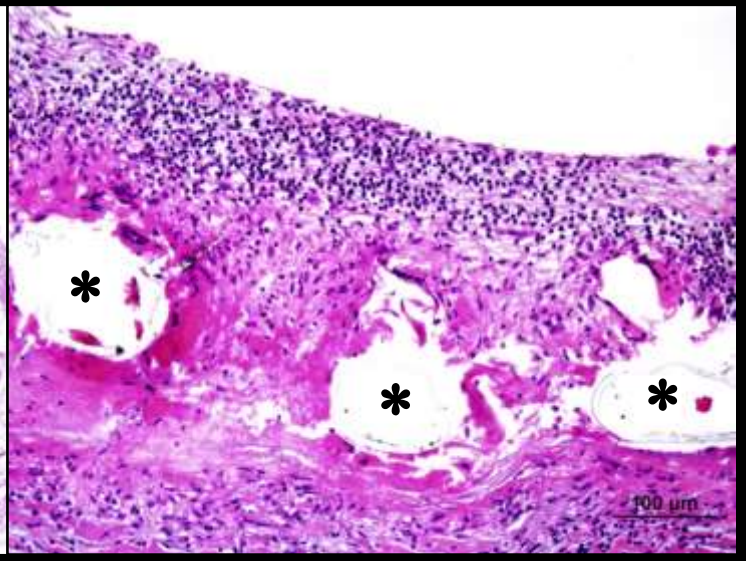


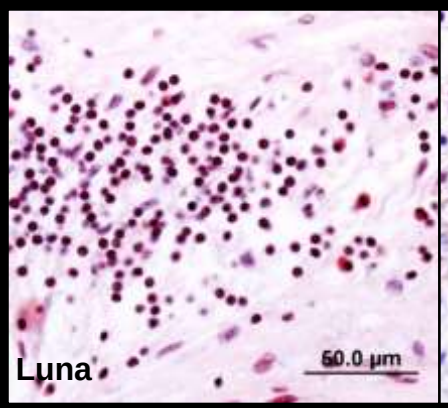


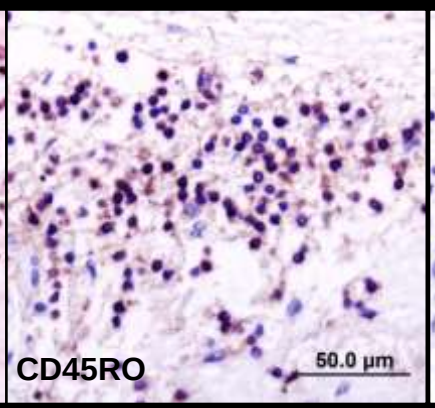
Chronic inflammation consisting with giant cells secondary to polymer delamination in ZES

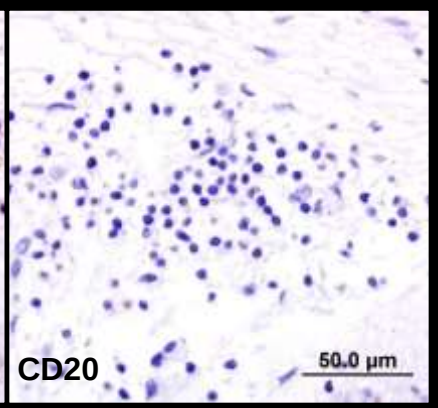
51M, CoCr-EES 4 months





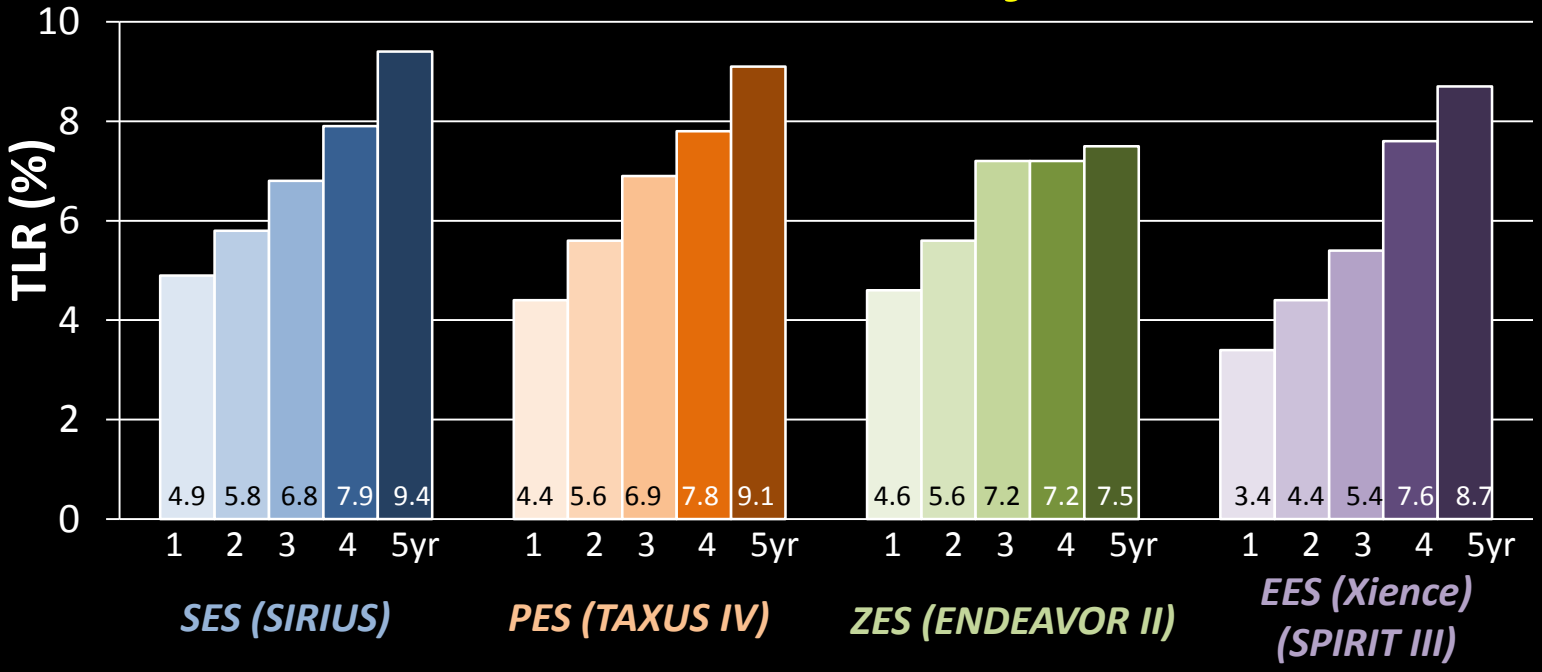




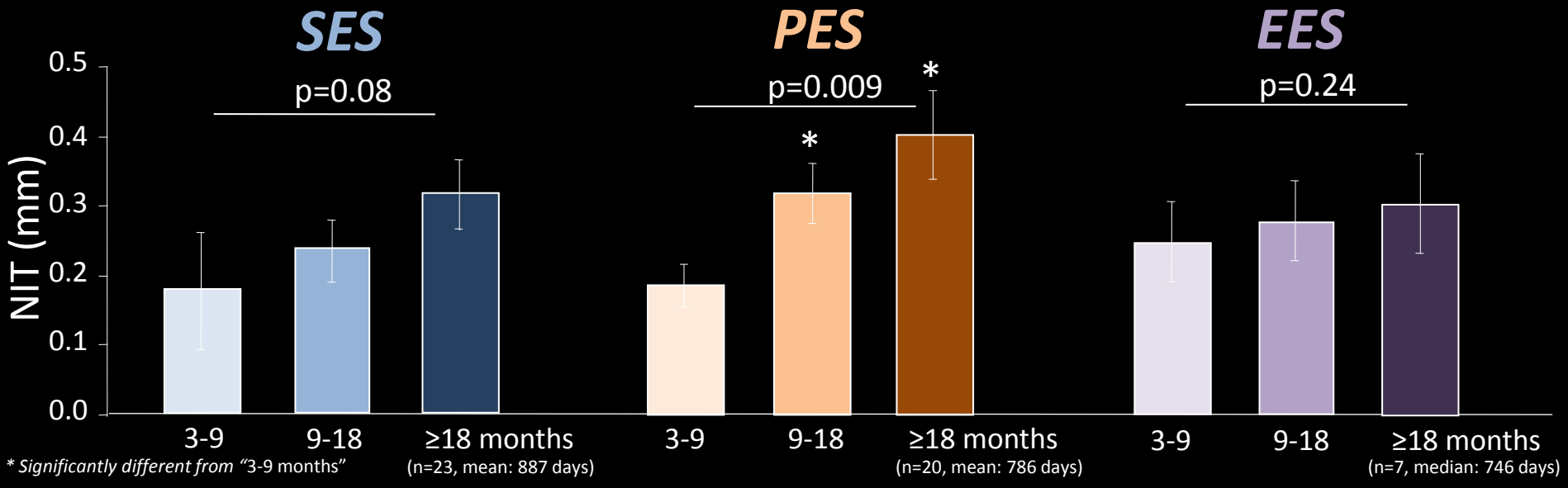


Otsuka F, et al. Circulation. 2014;129:211-223.

Long-term TLR in major clinical trials



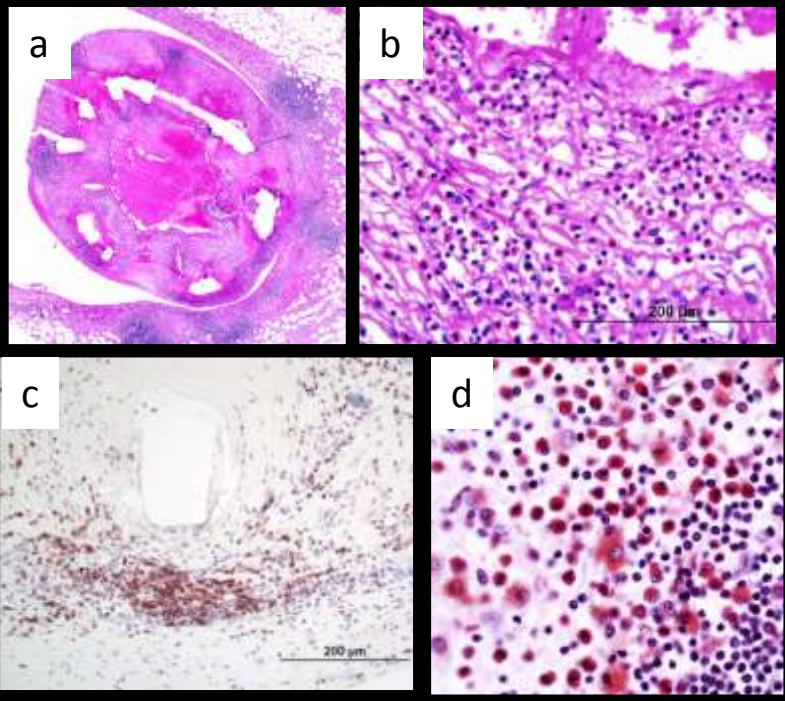
Change in maximum neointimal thickness in human DES autopsy



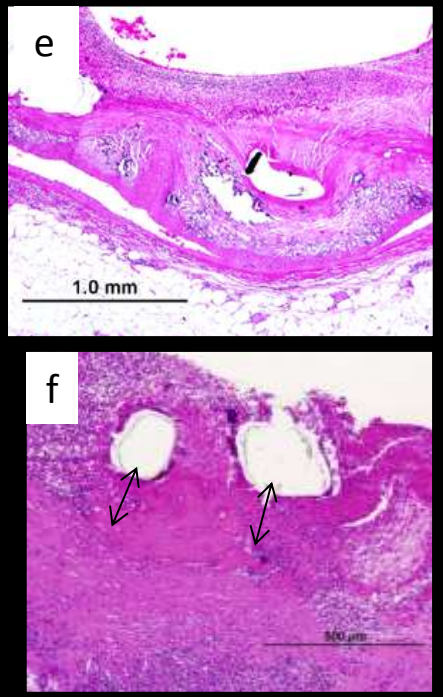
First-generation DES with localized Hypersensitivity and Malapposition

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 × 2	27	18	UAP	AMI	Yes	1,620
4	46/M	LAD	SES	23	31	SAP	AMI	Yes	930
		RCA	SES × 2	30	31	AMI		Yes	1,200
5	62/F	LAD	SES × 3	41	36	SAP	Repeat occlusion	NA†	—

LAD: SES (17months)



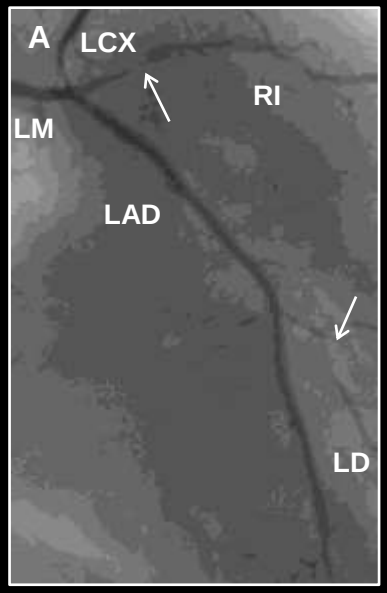
RCA: SES (17months)

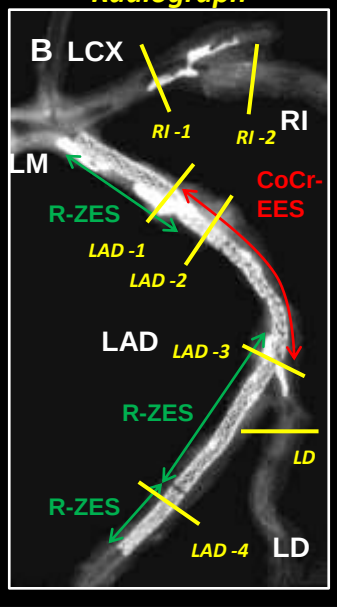


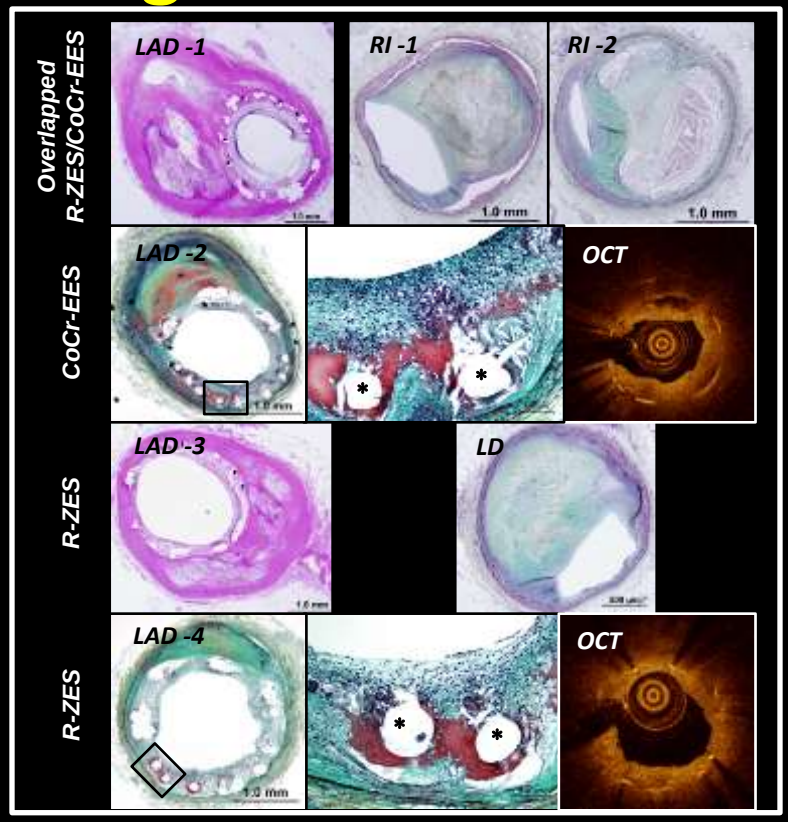
Nakazawa G. et al. J Am Coll Cardiol 2011;57:390-398

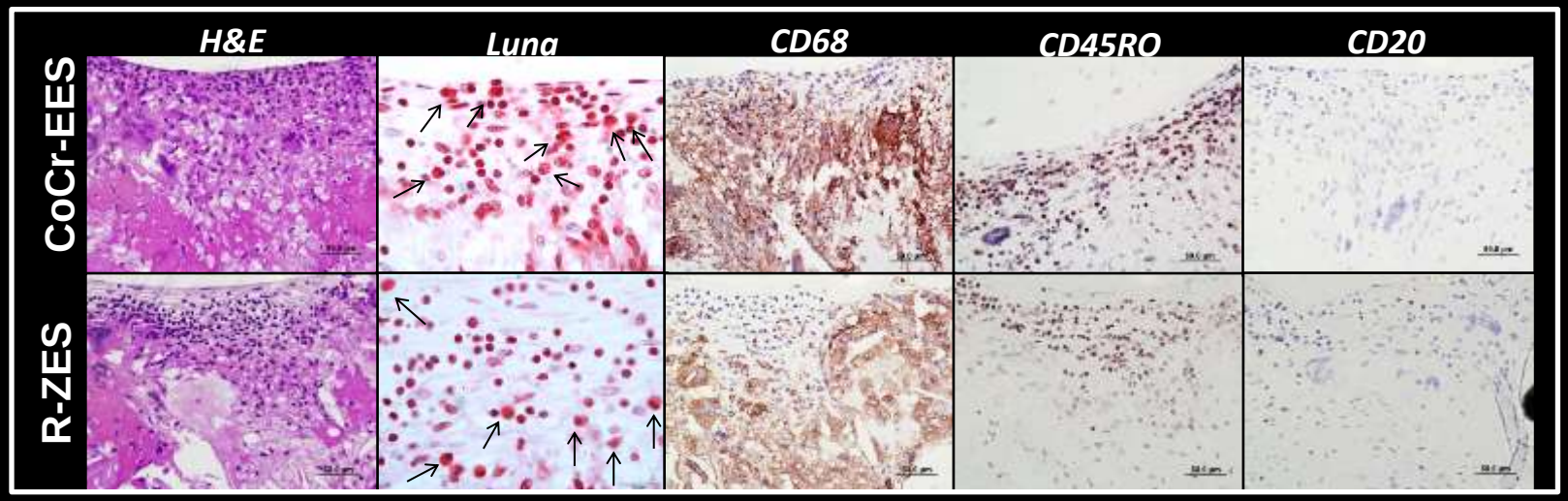
Hypersensitivity Reaction in 2nd generation DES

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.









Otsuka F, et al. Circulation. 2015;131:322-324.

Problems Encountered with Drug-Eluting Stents

1st-generation DES

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

2nd-generation DES

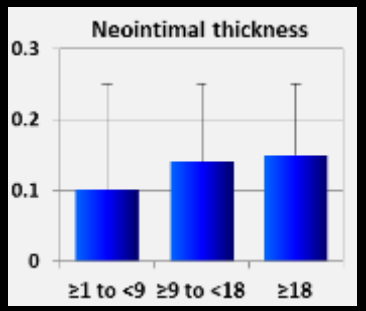
- Thinner struts
- More biocompatible polymer (Durable)
- Reduced drug dose

- ✓ Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition from fibrin deposition
- ✓ Stent fracture
- ✓ Neoatherosclerosis

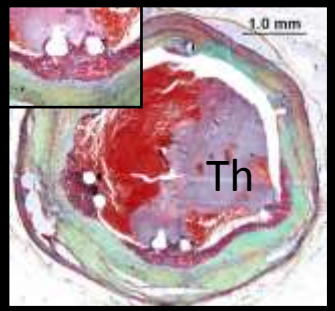
Late Stent Thrombosis / Restenosis

- Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition from fibrin deposition
- ✓ Stent fracture
- ✓ Neoatherosclerosis

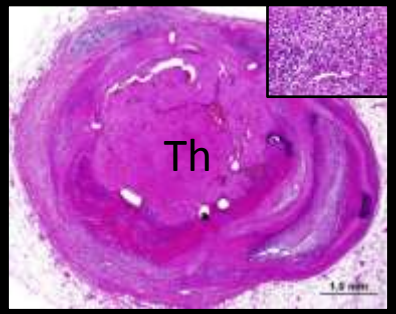
Clinical Late Catch-up



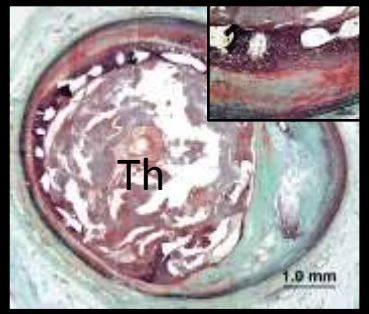
Late catch-up



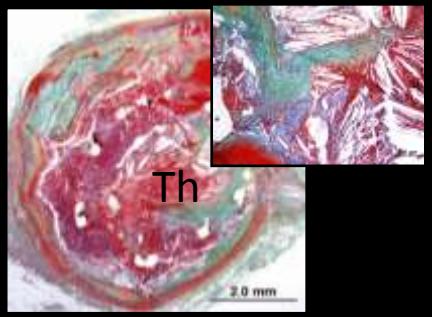
Uncovered struts



Hypersensitivity reaction



Malapposition from excessive fibrin deposition

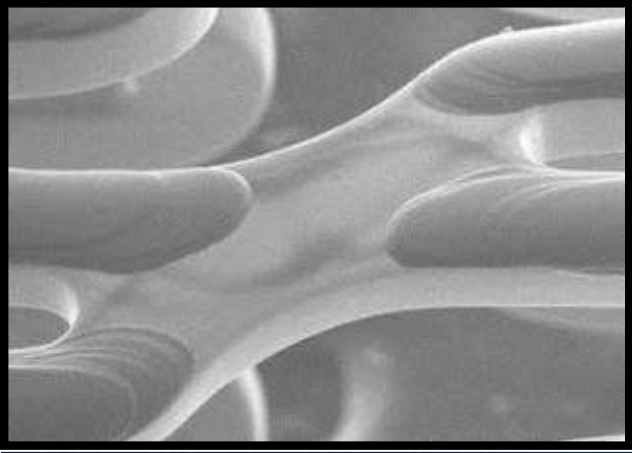


Neoatherosclerosis

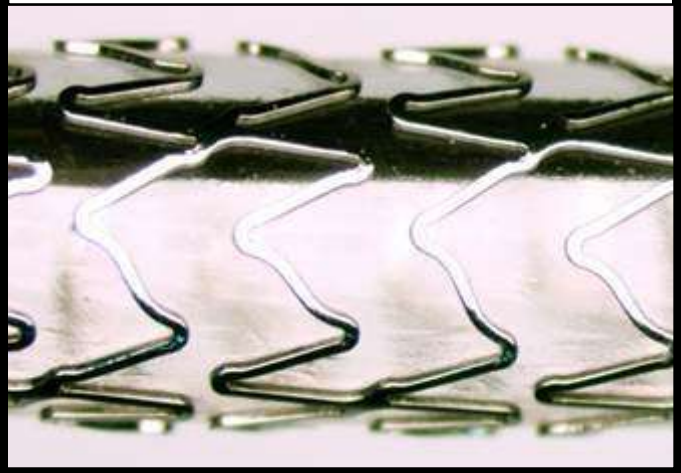
Do Any of the Current Bioabsorable Polymers Make the Grade?

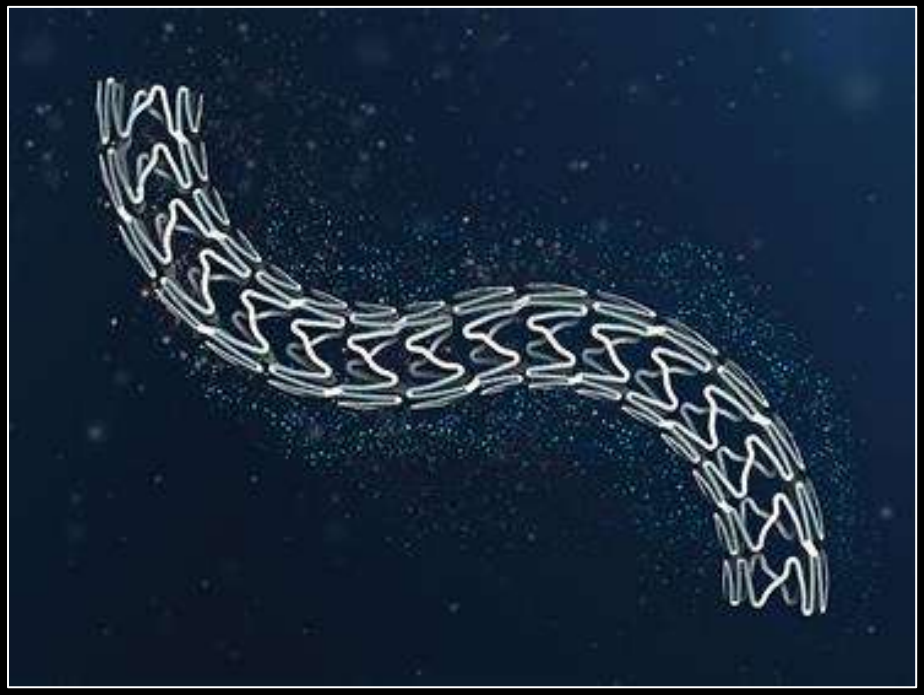
Ultimaster

Terumo original gradient & abluminal coating with biodegradable polymer



Material	CoCr（L605）
Thickness	80μm
# of links	2

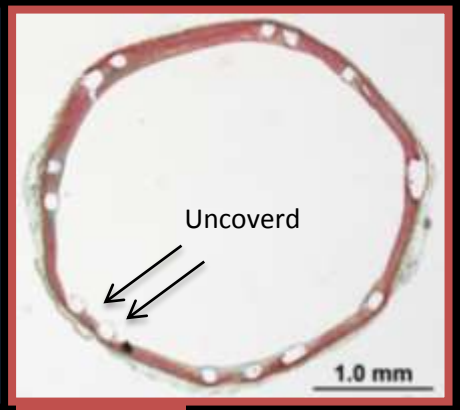




Ultimaster vs Xience

28 days

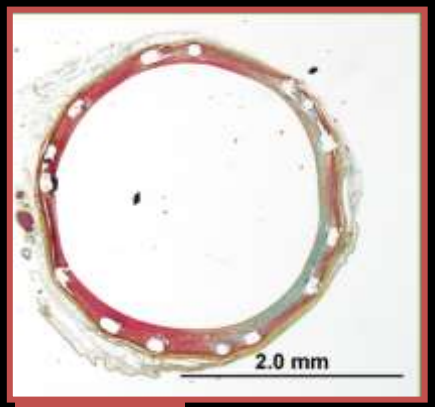
Ultimaster



Xience

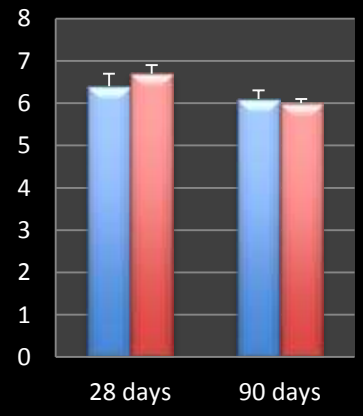
90 days

Ultimaster

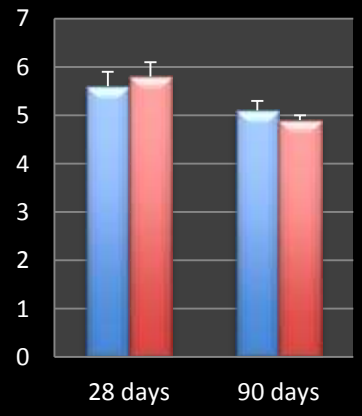


Xience

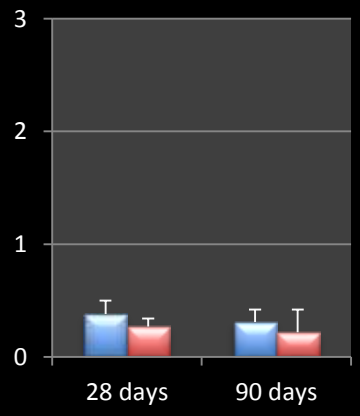
IEL area(mm2)



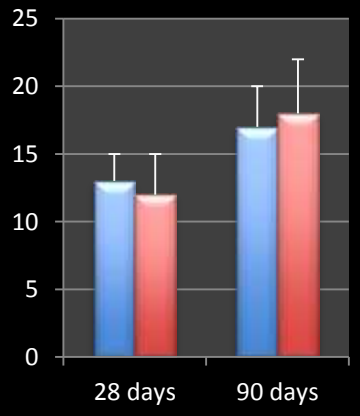
Lumen area(mm2)



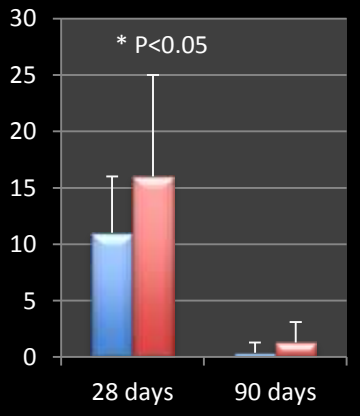
Injury score



Area stenosis(%)

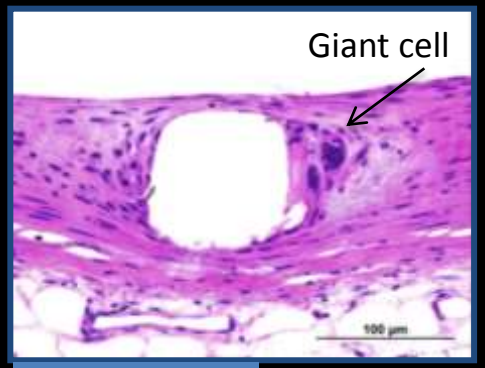


Uncover struts(%)

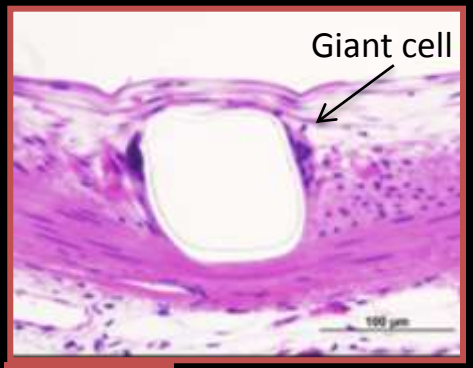


Ultimaster vs Xience

28 days

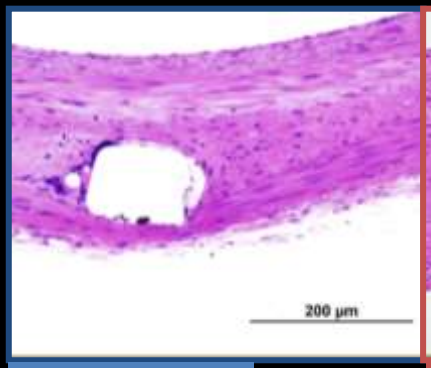


Ultimaster

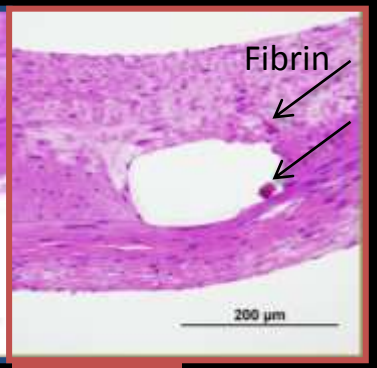


Xience

90 days

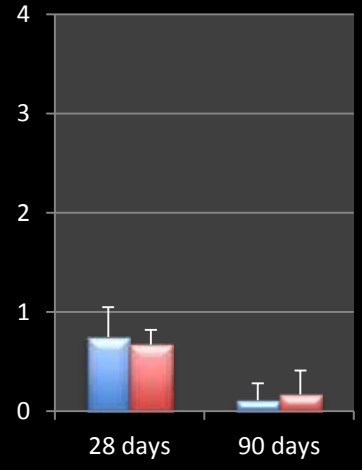


Ultimaster

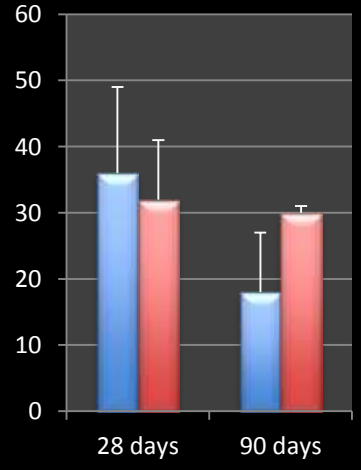


Xience

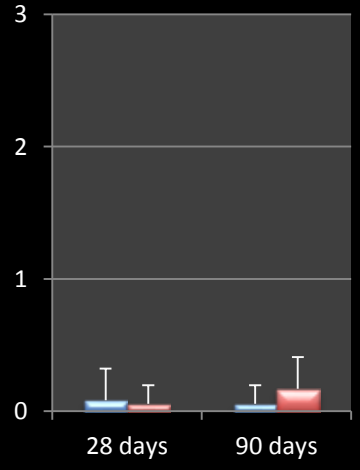
Inf score



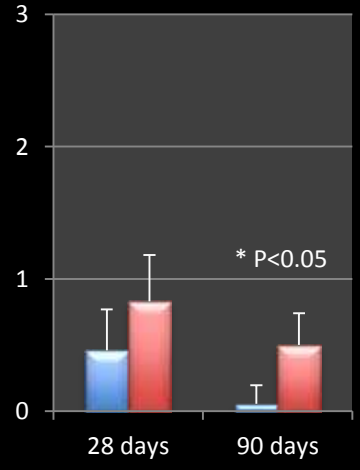
Giant cells(%)



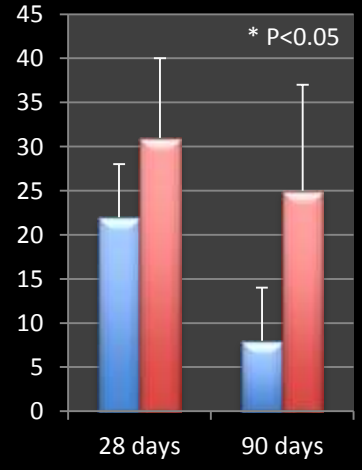
Adv inf Score



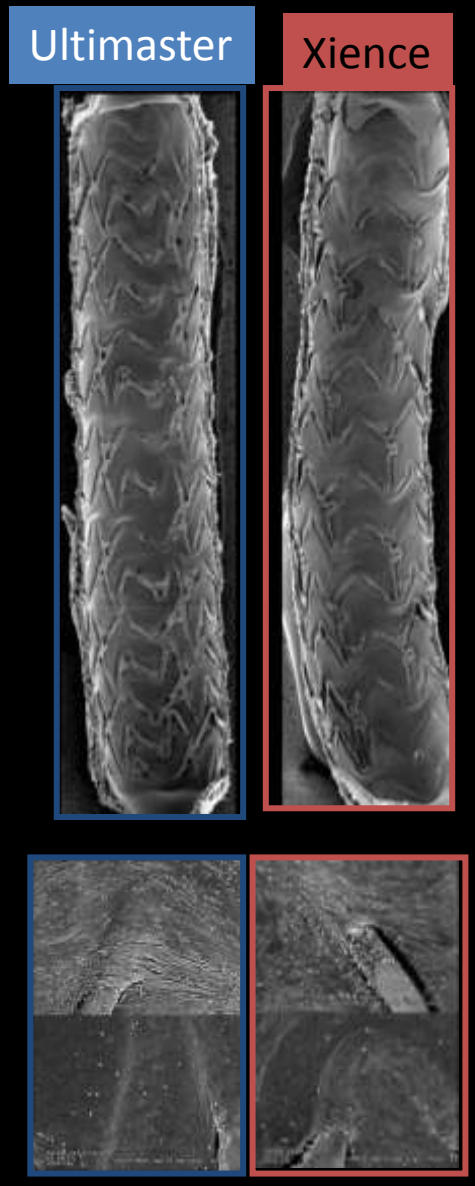
Fibrin score

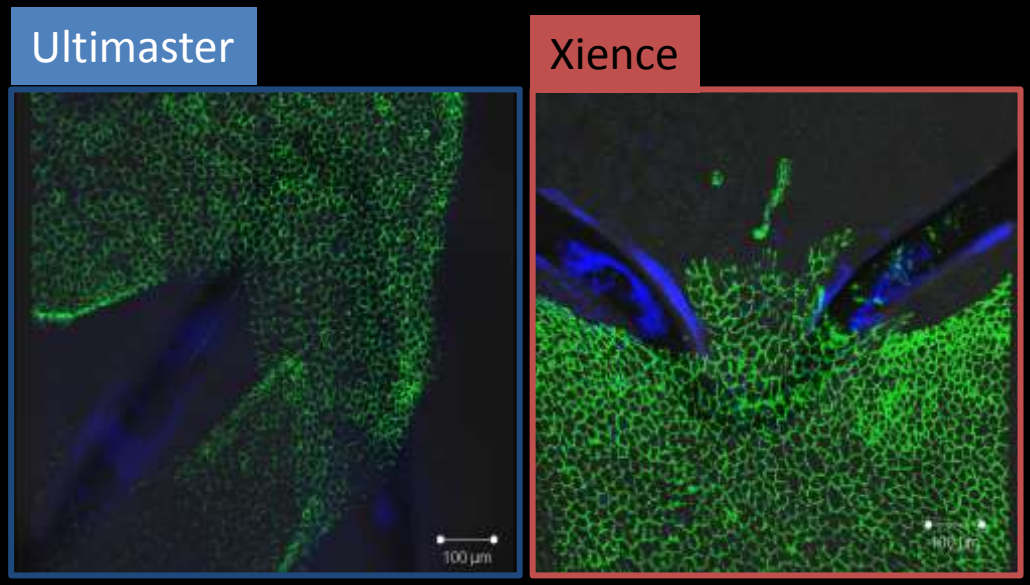


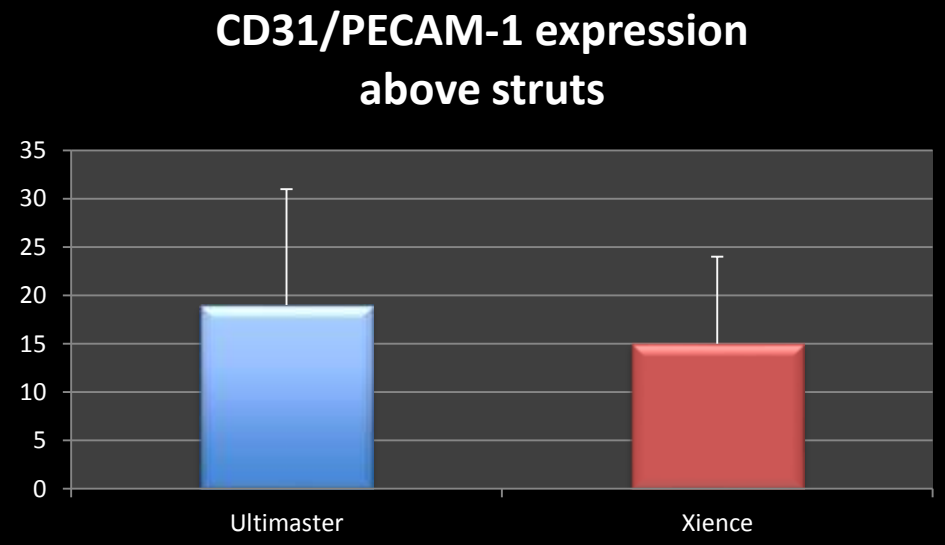
Fibrin(%)



Ultimaster vs Xience at 14days



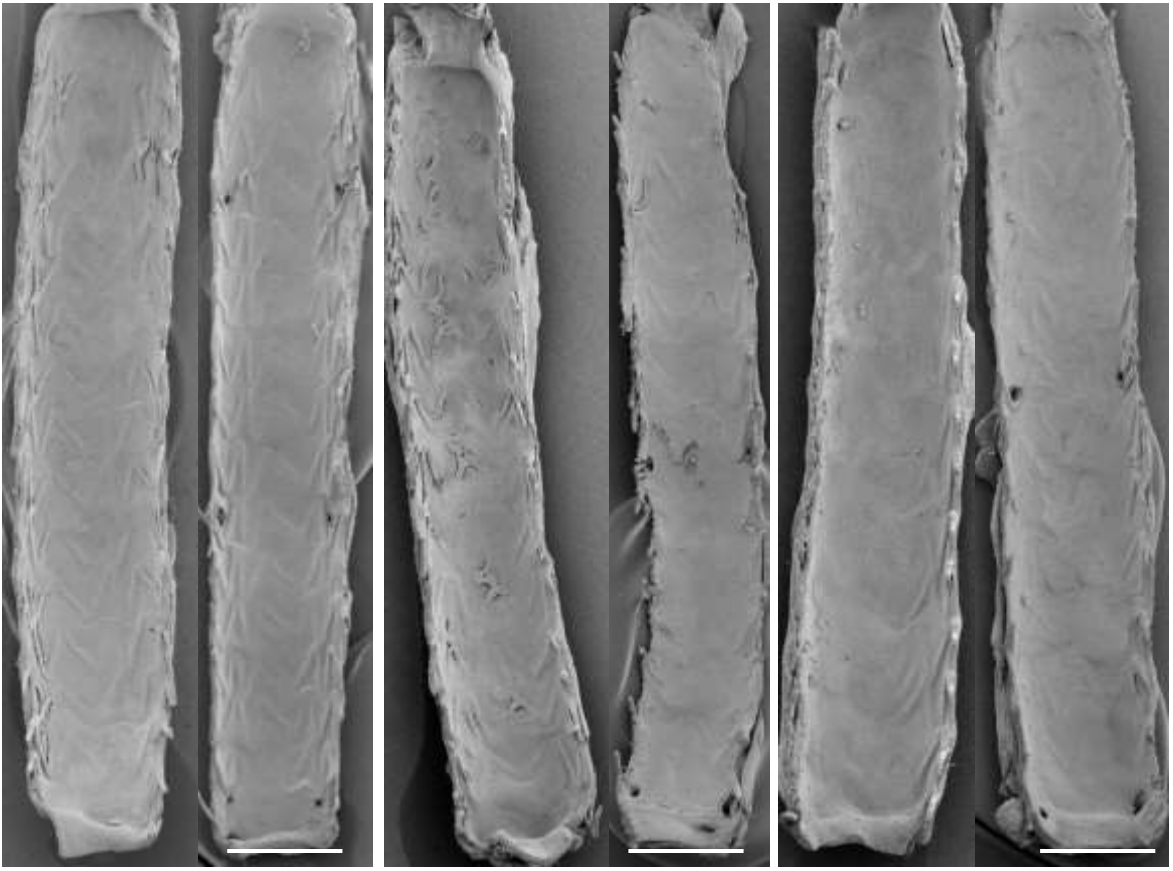




Strut coverage by SEM

Ultimaster® **Xience®** **Kaname®**

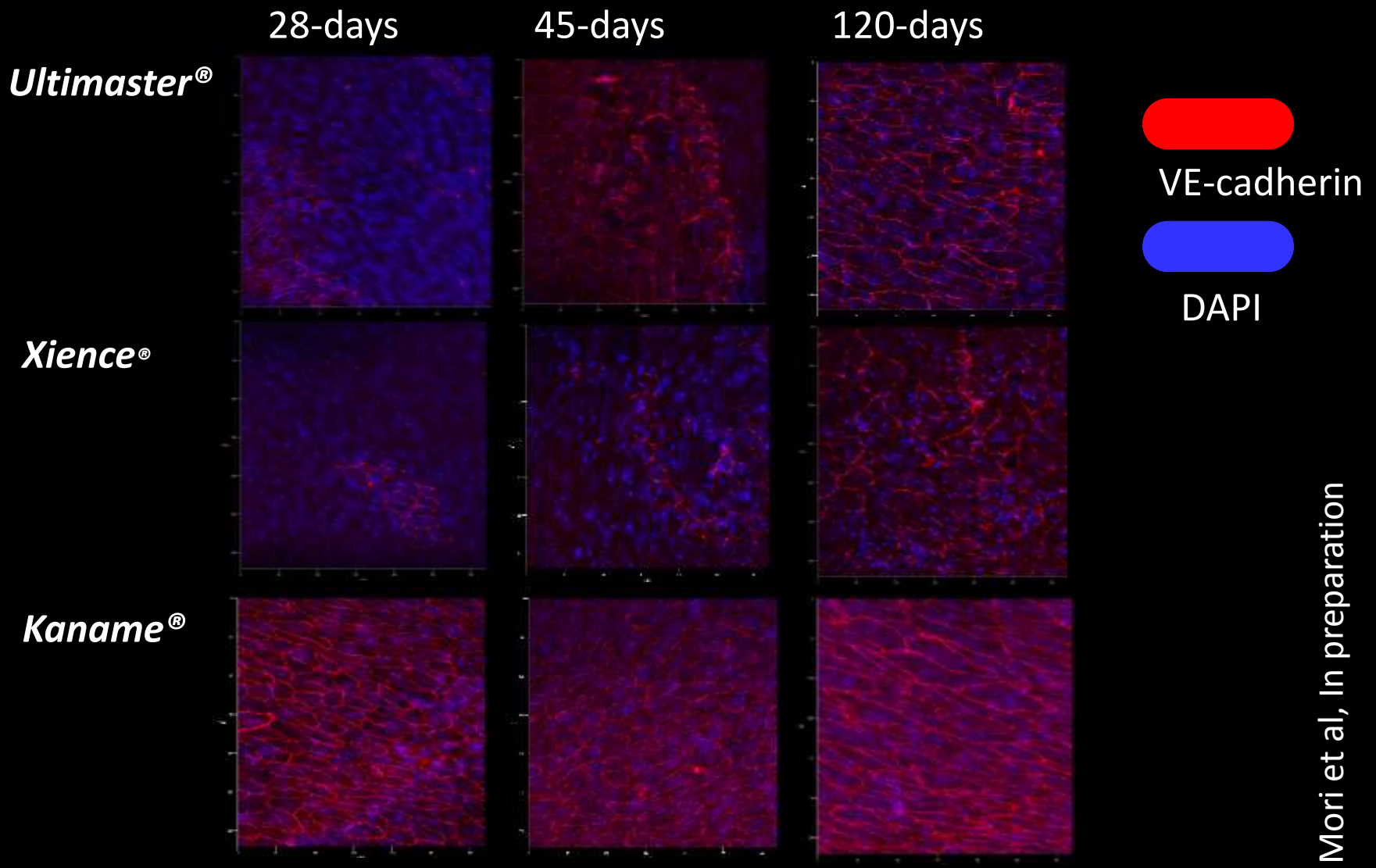
28-days 45-days 28-days 45-days 28-days 45-days



	28-day	45-day
Ultimaster®	82.3 (74.4-85.7)%	97.1 (95.5-98.7)%
Xience®	67.2 (47.7-78.1)%	86.9 (82.4-98.9)%
Kaname®	100 (100-100)%	100 (99.8-100)%
P-value (between different stent type)	U vs X , P=0.36 **U vs K , P=0.02** **X vs K , P=0.02**	U vs X , P=0.22 **U vs K , P=0.03** **X vs K , P=0.006**

Data: Median value(interquartile data)

Endothelial Maturity
VE-cadherin expression



Mori et al, In preparation

VE-cadherin positive area(% of ROI)

28-day

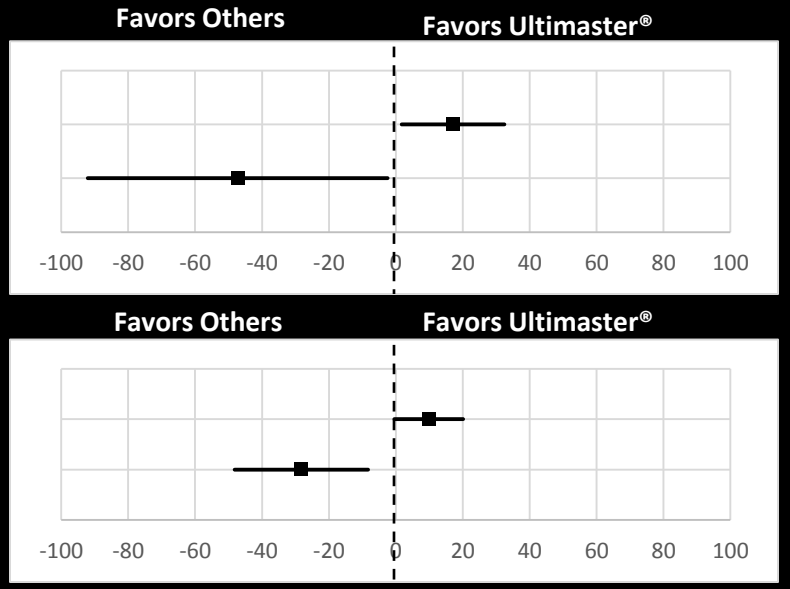
Ultimaster® vs.	Mean Difference(95% CI)	P value
Ultimaster® -Xience®	17.1(1.7 to 32.4)	**0.03**
Ultimaster® -Kaname®	-47.3(-92.1 to -2.5)	**0.04**

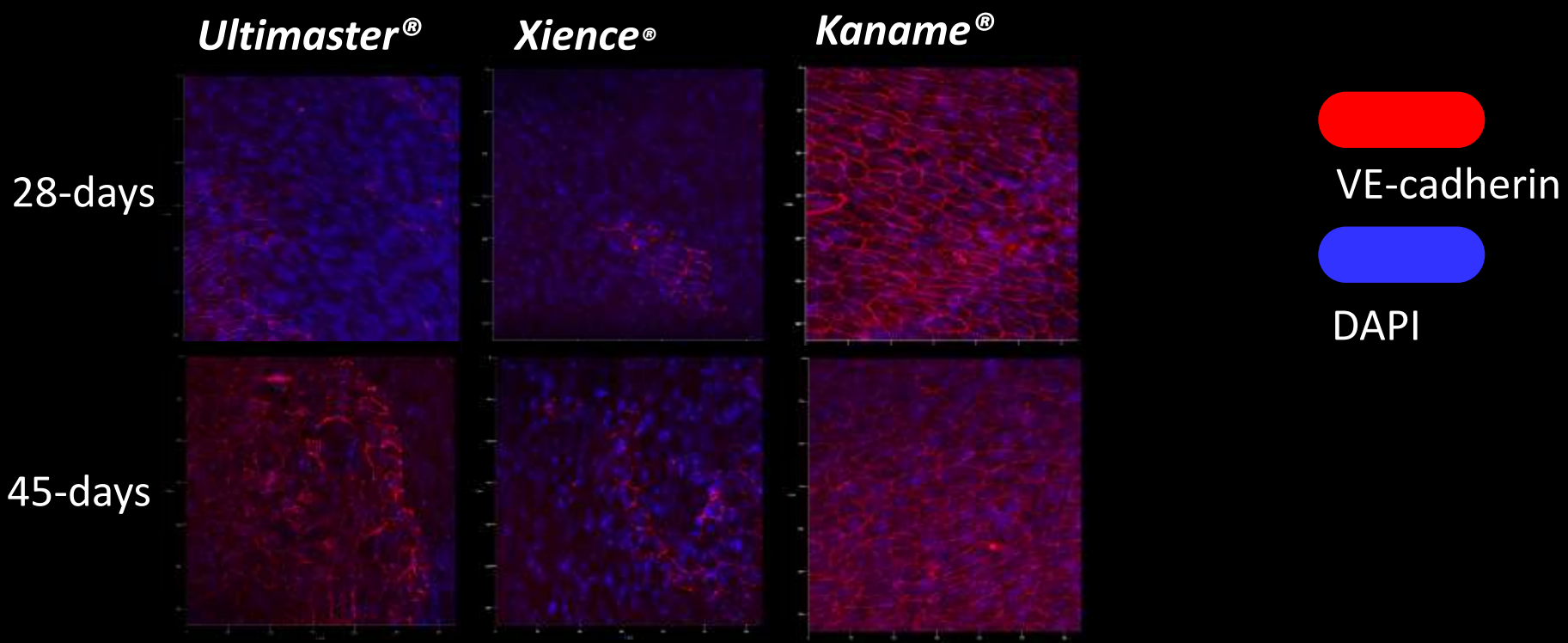
Estimated mean: Ultimater 31.6%, Xience14.6%, Kaname78.9%

45-day

Ultimaster® vs.	Mean Difference(95% CI)	P value
Ultimaster® -Xience®	10.0(-0.5 to 20.6)	0.06
Ultimaster® -Kaname®	-28.3(-18.2 to -8.3)	0.06

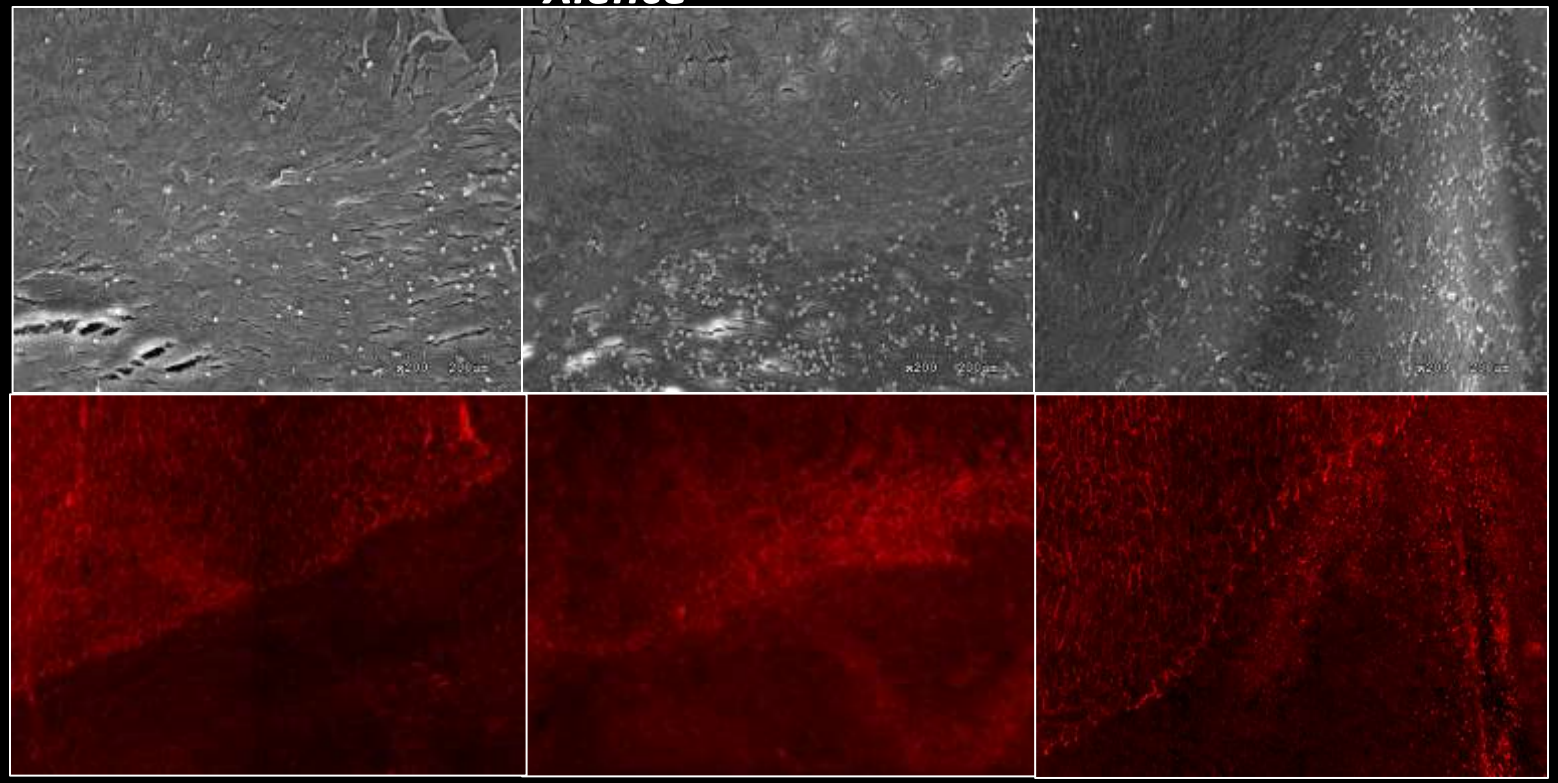
Estimated mean: Ultimater 47.7%, Xience37.7%, Kaname76.0%





White Blood Cell Adherence

Ultimaster® *Xience®* *Kaname®*



VE-cadherin

Stent Type	28-day	45-day
Ultimaster® (number/mm²)	156(48-508)	181(90-366)
Xience® (number/mm²)	193(59-635)	731(348-1537)
Kaname® (number/mm²)	385(118-1250)	132(63-277)
P-value (between different stent type)	K vs U, P=0.25 K vs X, P=0.33 U vs X, P=0.72	K vs U, P=0.53 K vs X, P=0.04 U vs X, P=0.053

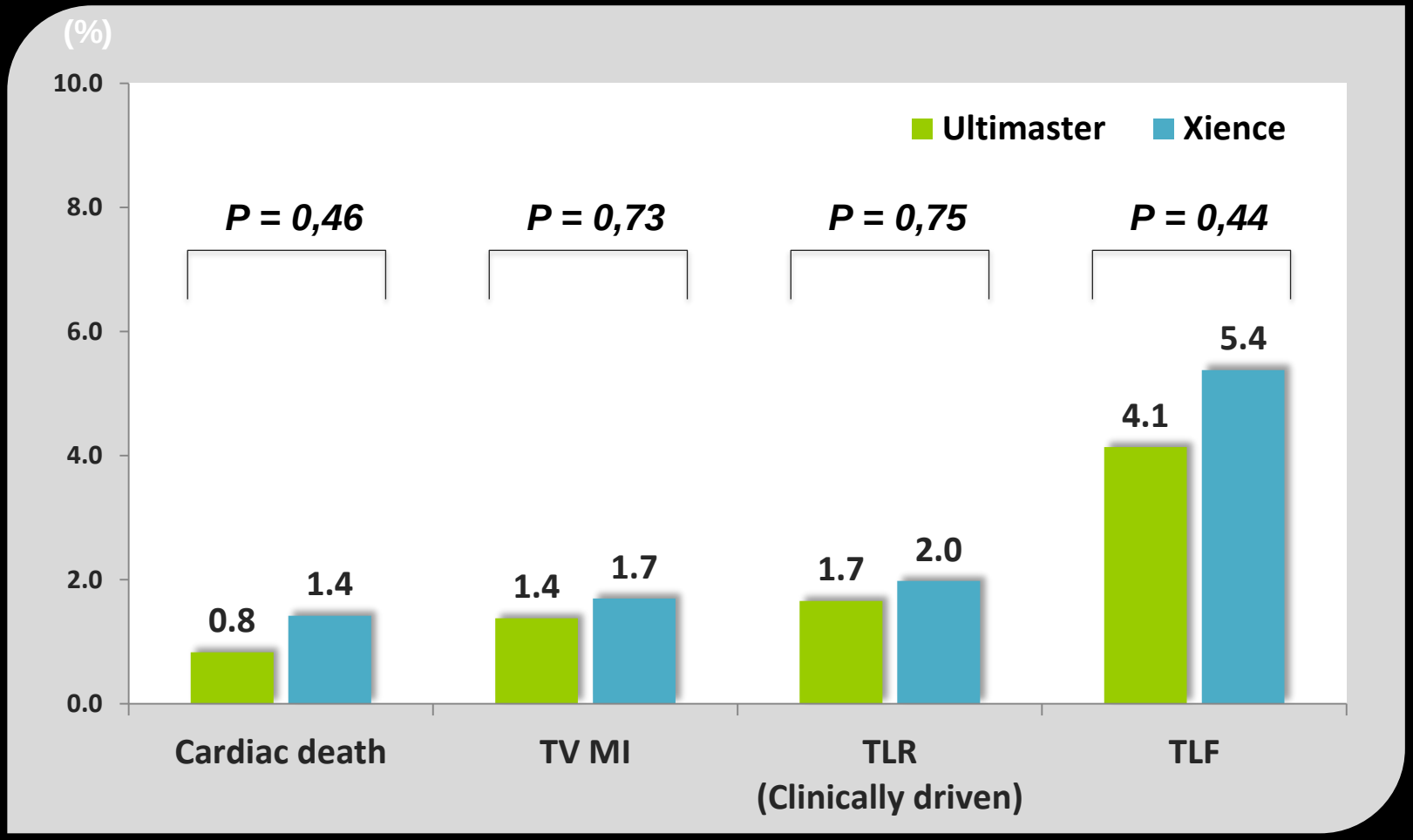
U:Ultimaster®, X:Xience®, K:Kaname®, 28:28-day, 45:45-day, 120:120-day,
Data are shown as estimated mean value with 95% confidence interval

CENTURY II

Cohort JR

Target Lesion Failure

Clinical Outcome @ 9 months



W. Wijns et al, EuroPCR2015

9 months = 284 days

TLF = composite of cardiac death, target vessel MI and clinically driven TLR

Conclusions

- Permanent polymers are associated with chronic inflammation and late catch up
- Preclinical rabbit studies show significantly less uncovered struts at 28-days and less fibrin at 90- days in Ultimaster than Xience by light microscopy.
- By confocal and SEM the endothelial coverage in rabbit iliac arteries was greater with higher maturation (i.e. more VE cadherin expression) in Ultimater than Xience.
- Not all polymers are created equal. The quantity and quality and the rate of degradation of the biodegradable polymers determines the extent of inflammation, which regulates neointimal thickening.
- Clinical studies suggest either non-inferior or superiority of bioabsorable polymer as compared to durable polymer stents

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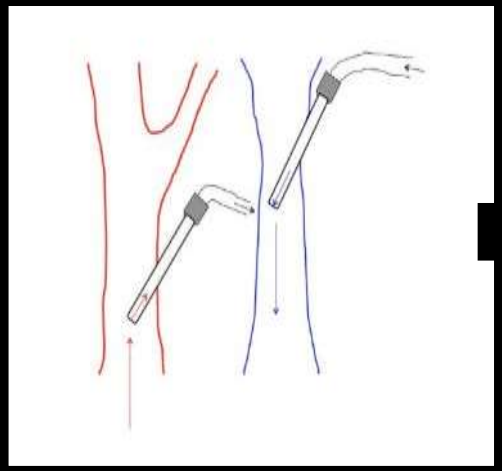
Liang Guo, PhD
Harry Davis, PhD
Renu Virmani, MD

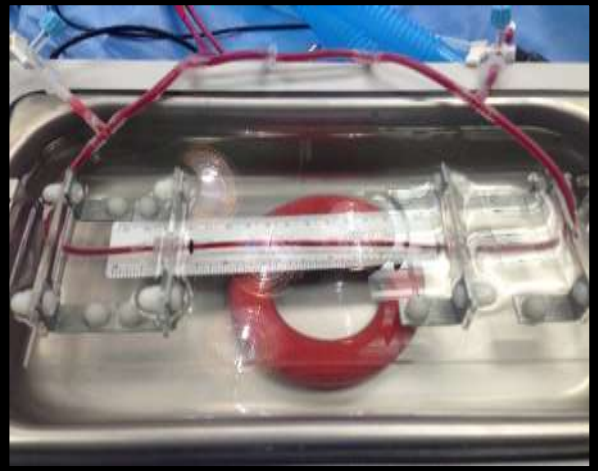
Washington DC

My email: afinn@cvpath.org

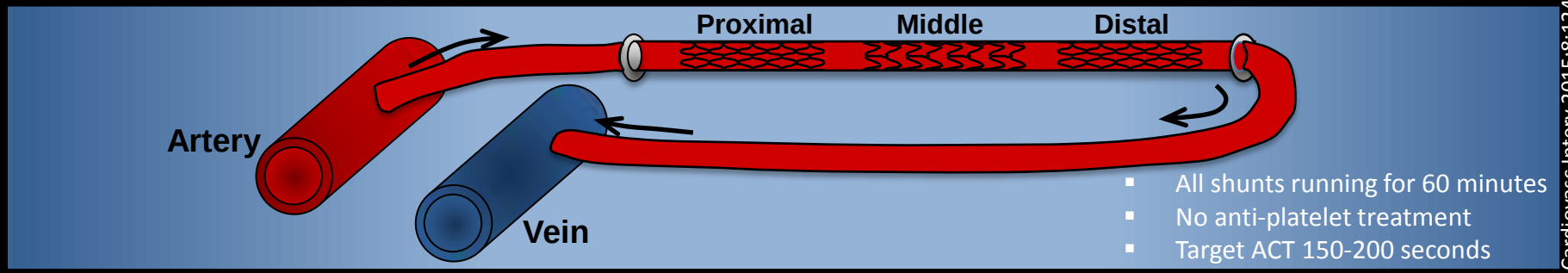
1. Porcine AV shunt: carotid-jugular using customized sheath

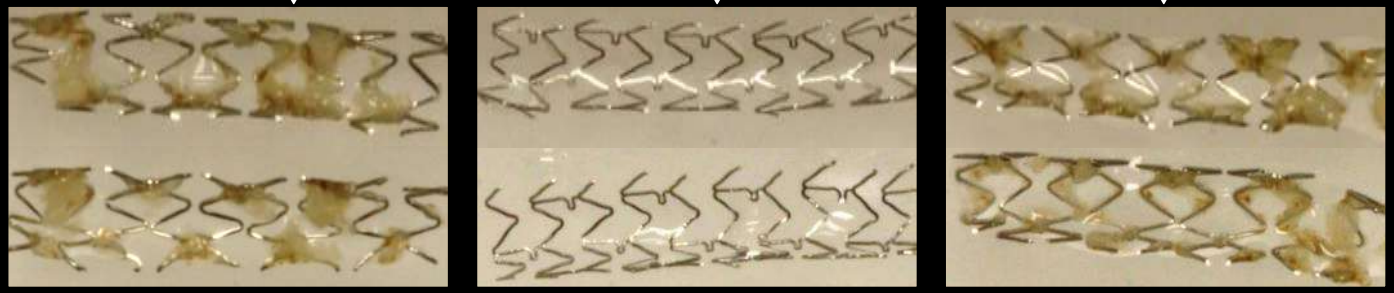


2. Arterialized flow using Sylgard tube



3. Thrombus formation after 1 hour



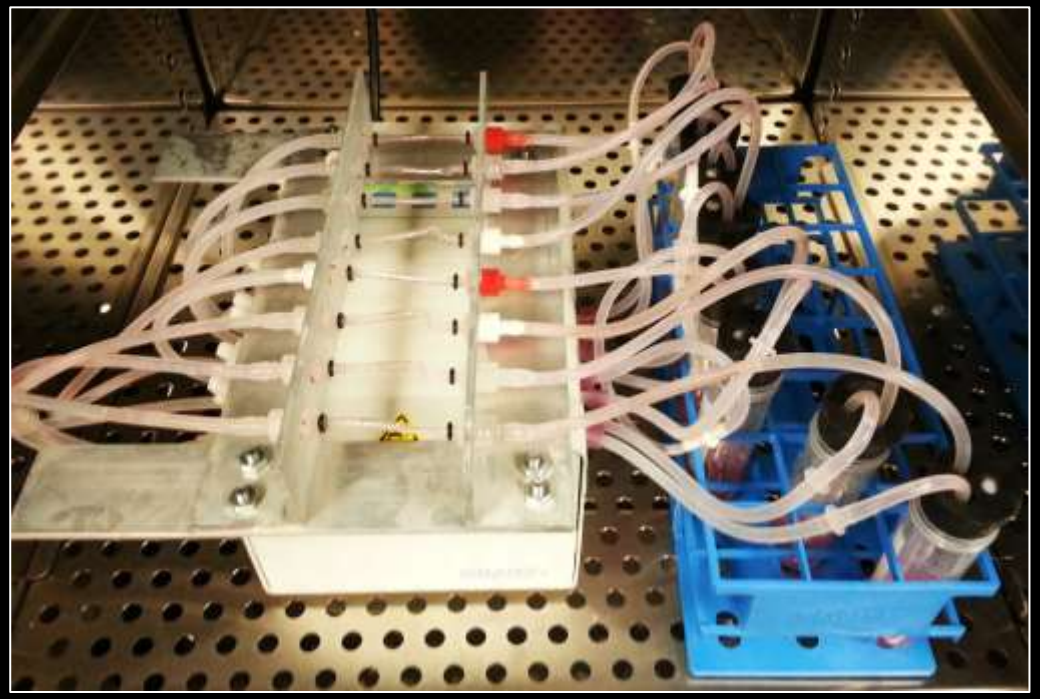


Immunofluorescent staining for platelet (CD61/42b) and assessed by CM

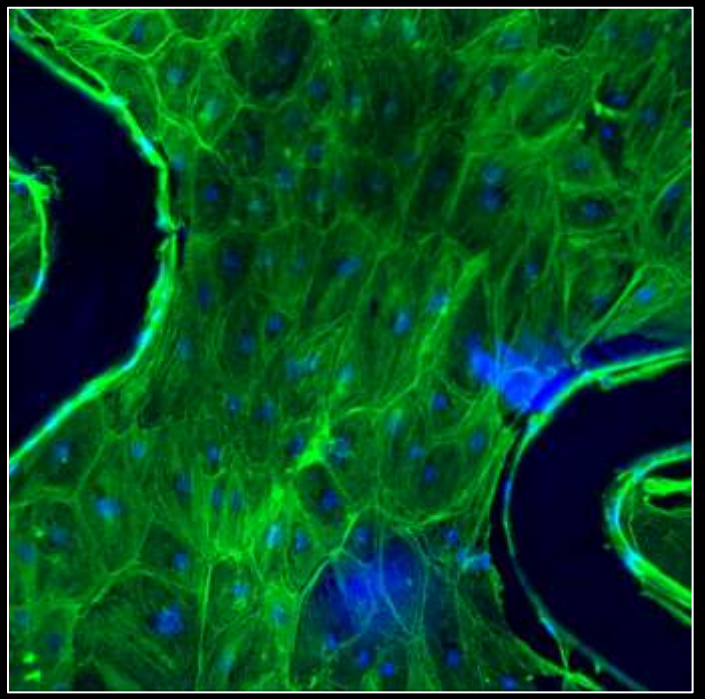
SEM

Otsuka F, et al JACC Cardiovasc Interv 2015;8:1248

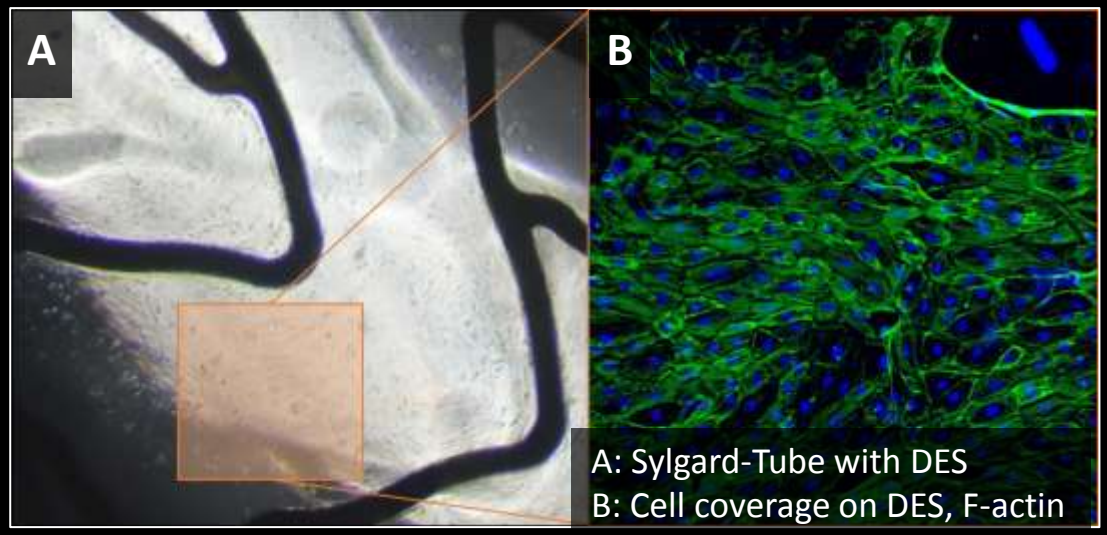
In vitro cell culture of Porcine endothelial cells, grown in Sylgard Elastomer Tubes with Xience and Synergy stents under flow conditions for 4 days



↑ Setup for flow conditions in CO2 incubator.

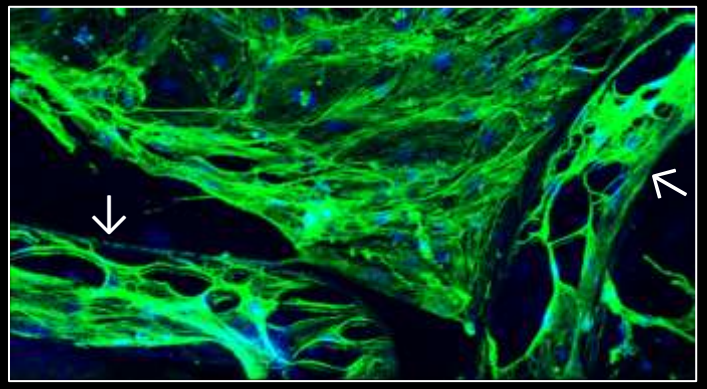


↑ DES after 4 d in static conditions.
(Green = Phalloidin, Blue = DAPI)



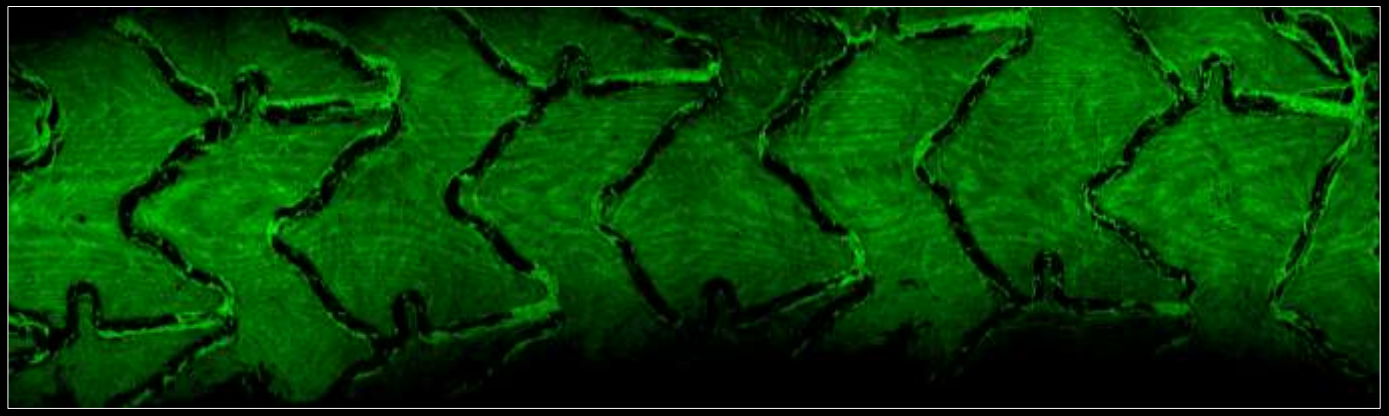
A: Sylgard-Tube with DES
B: Cell coverage on DES, F-actin

↓ Strut coverage in DES (4d static)



Abbott Vision

Abluminal side



Luminal side