Why Contemporary Durable Polymer DES Are Not Good Enough; Insights From Pathology

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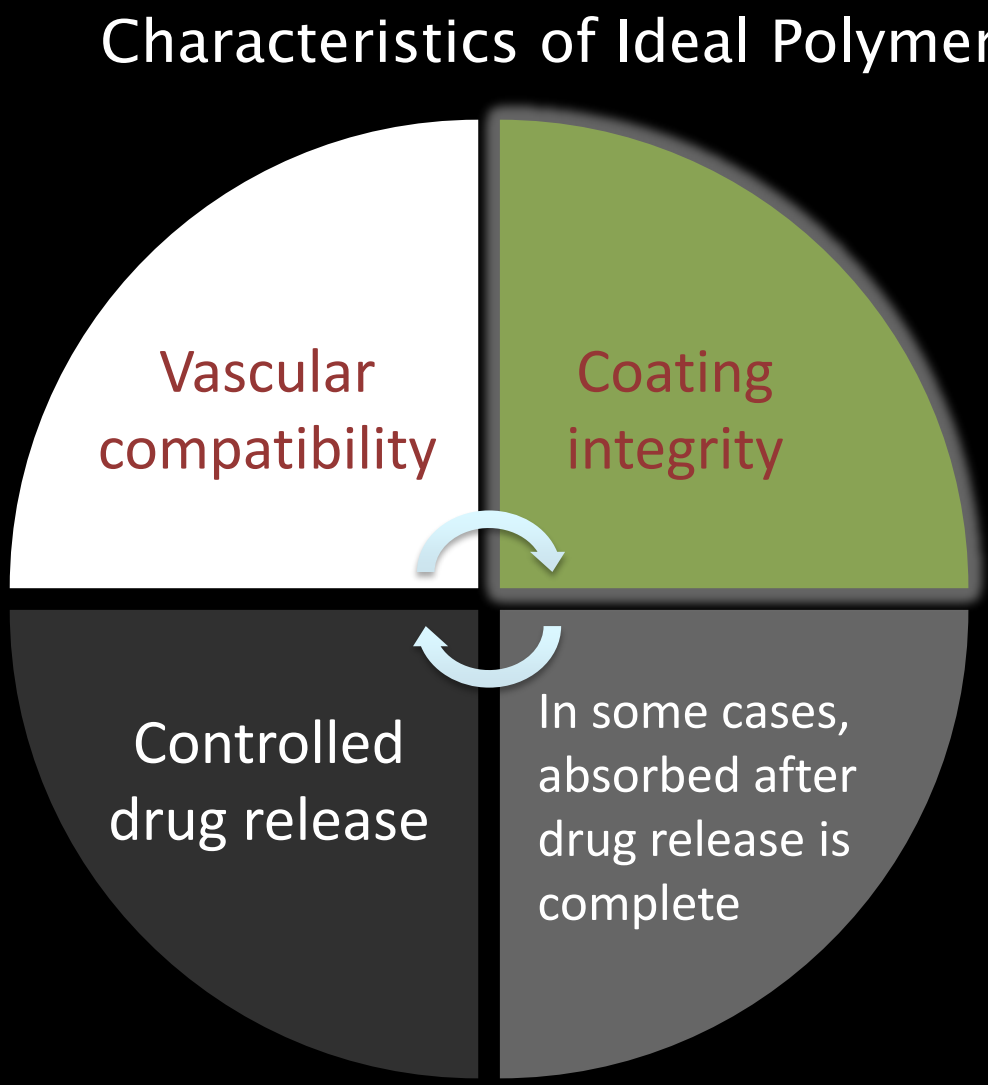
Conflict of Interest Declaration

- 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.

DES polymer coatings protect the drug and control the drug release – how are polymers optimized for healing?



Polymers: The good, the bad, the ugly

- Good
  - Allow for controlled drug release which is essential for inhibiting intimal formation
  - Some have already been FDA approved for other uses allowing for use in stents
- Bad
  - Biocompatability is never perfect
  - Integrity is an issue
  - Chronic inflammation –never goes away
- Ugly
  - Overwhelming hypersensitivity can occur leading to delayed healing and thrombosis

Problems Encountered with Permanent Polymer 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

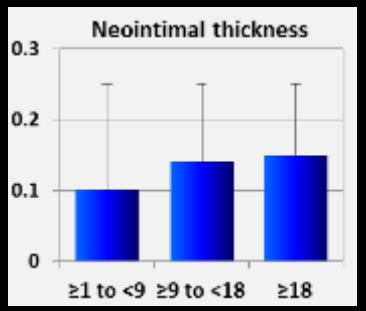
- Thinner struts
- More biocompatible polymer (Durable)
- Reduced drug dose

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

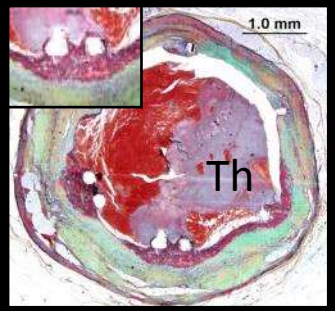
Late Stent Thrombosis / Restenosis

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

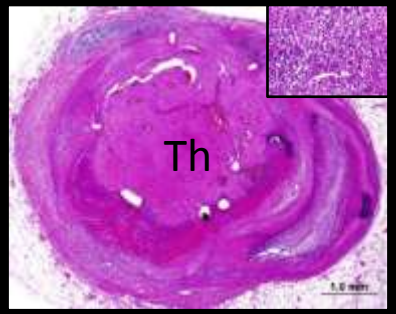
Clinical Late Catch-up



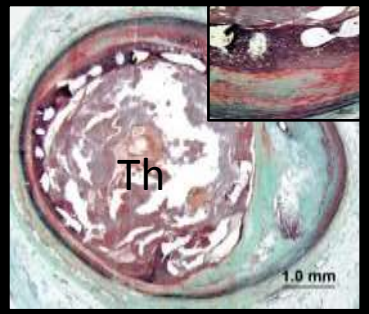
Late catch-up



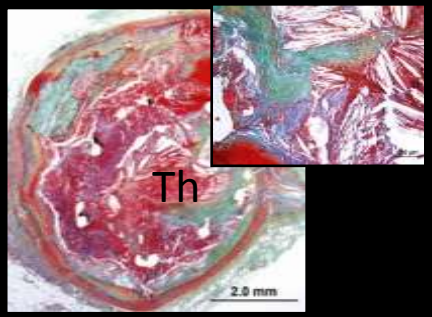
Uncovered struts



Hypersensitivity reaction



Malapposition from excessive fibrin deposition

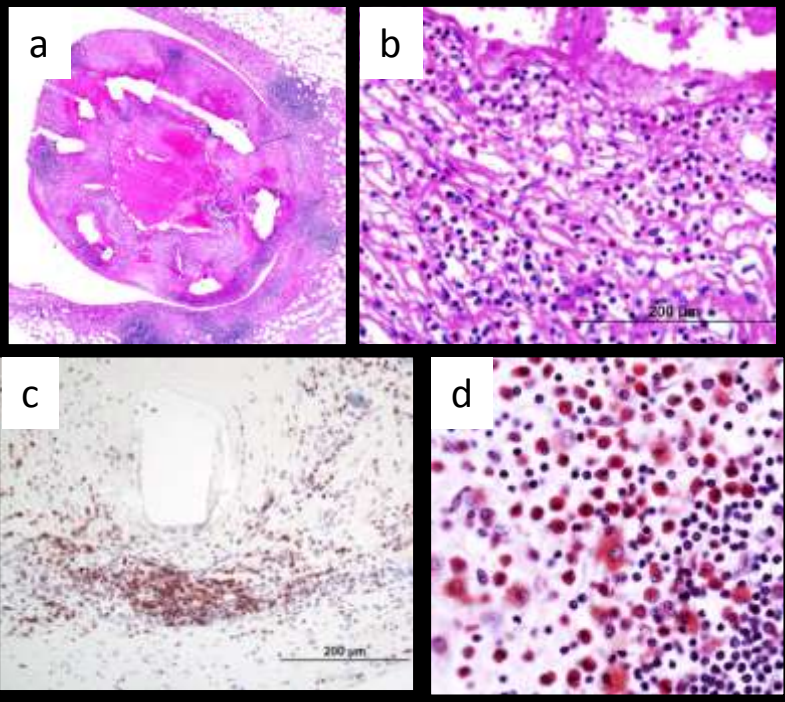


Neoatherosclerosis

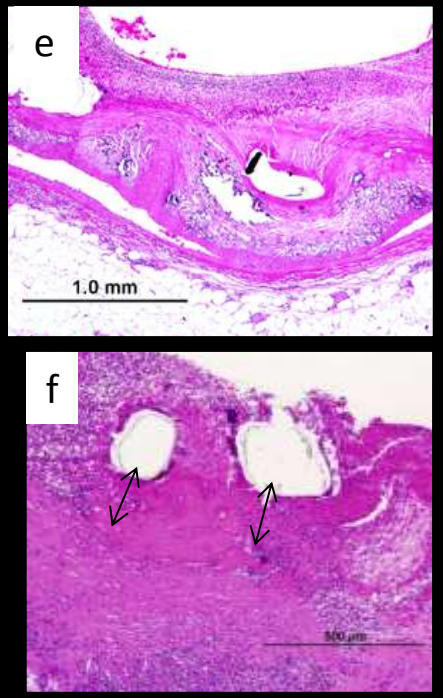
First-generation DES with localized Hypersensitivity and Malapposition

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)



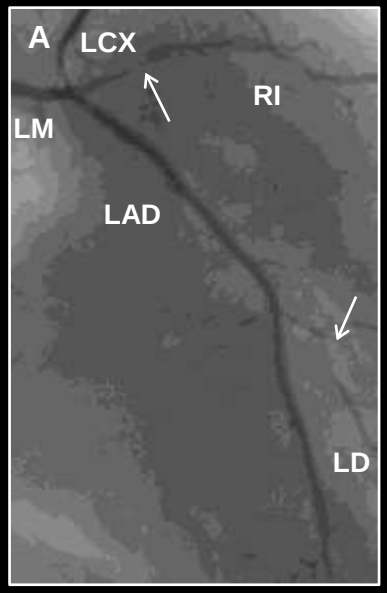
RCA: SES (17months)

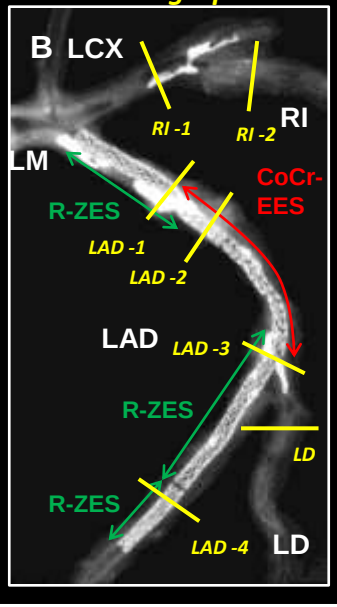


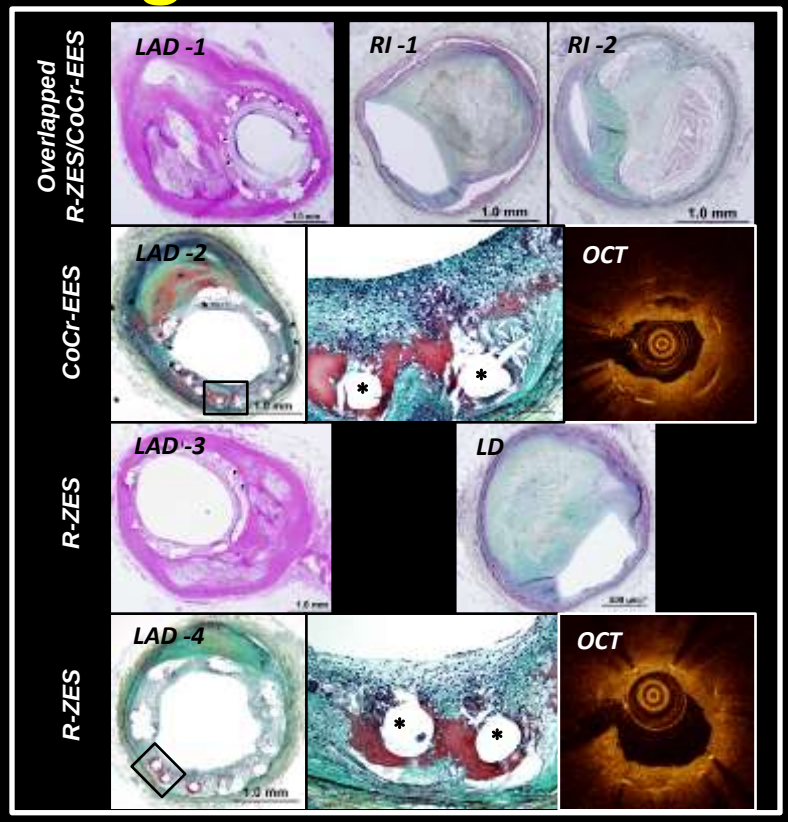
Nakazawa G. et al. J Am Coll Cardiol 2011;57:390-398

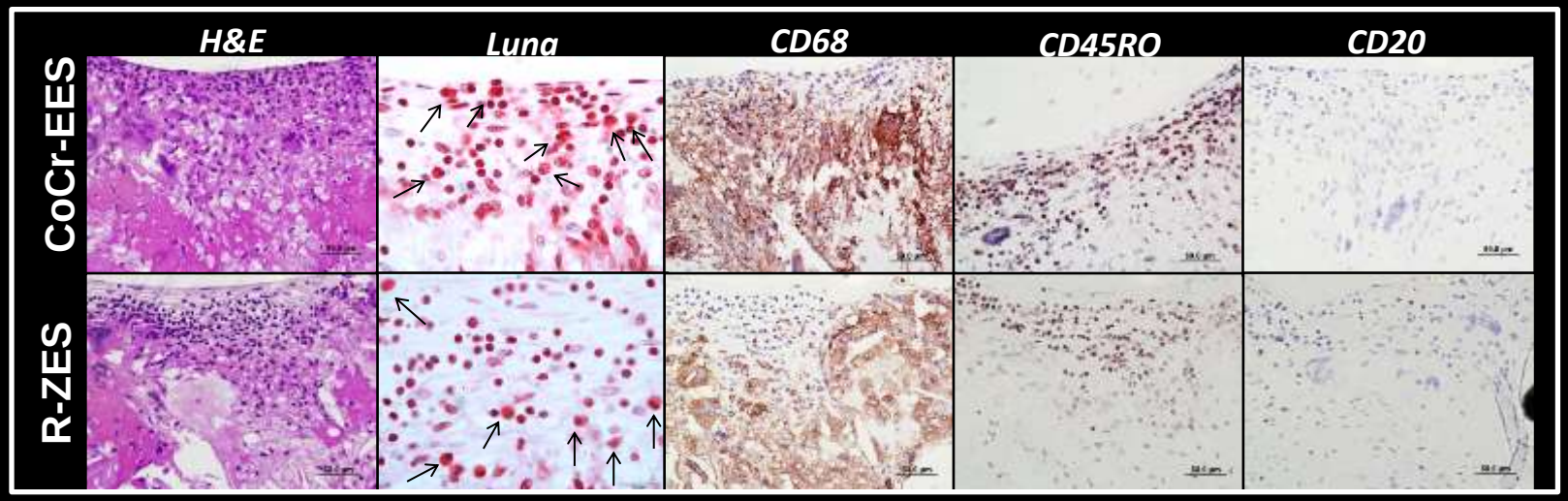
Hypersensitivity Reaction in 2nd generation DES

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.



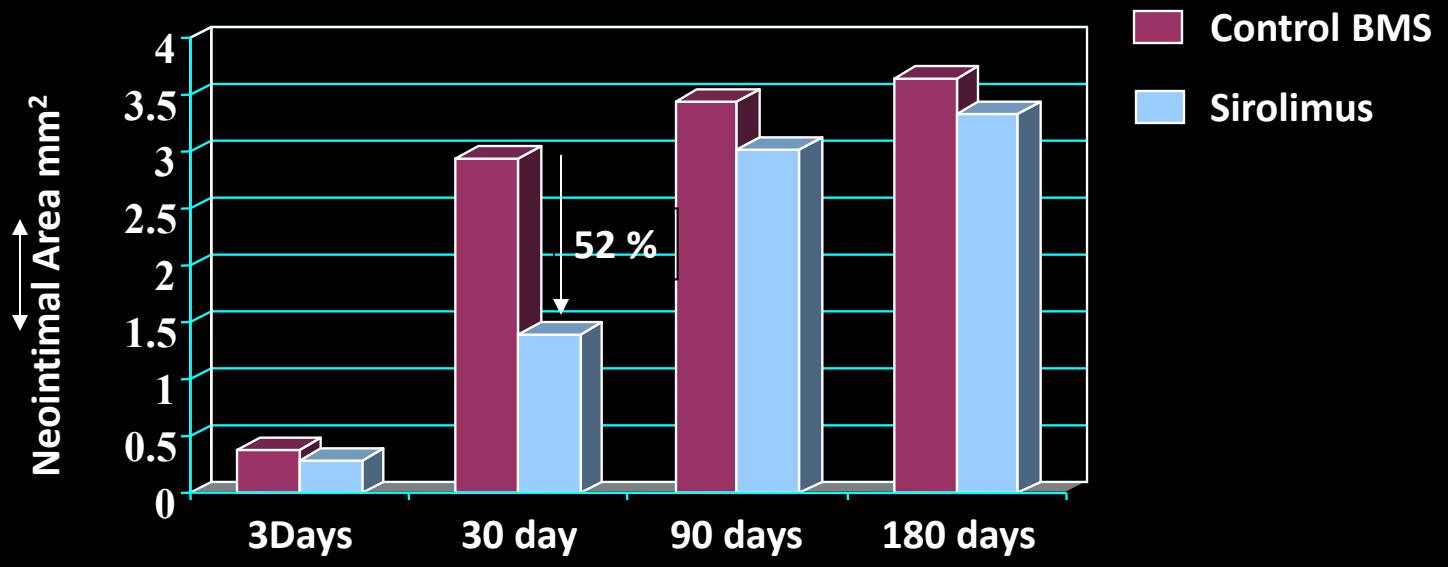


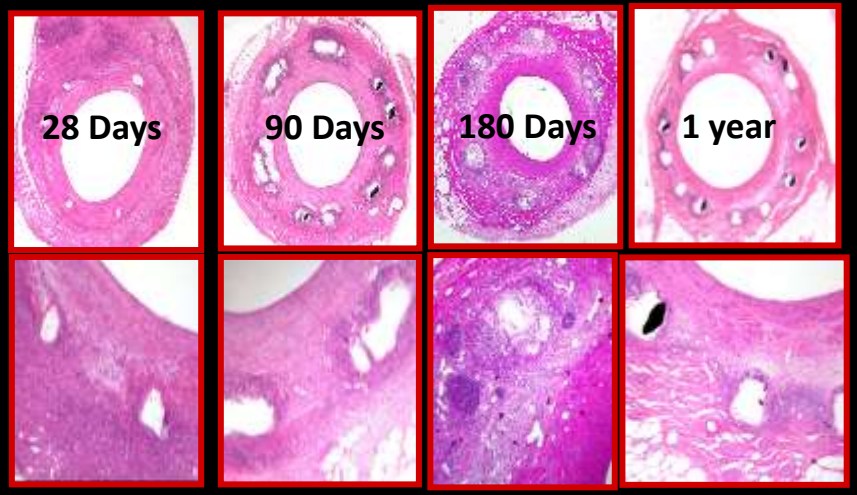




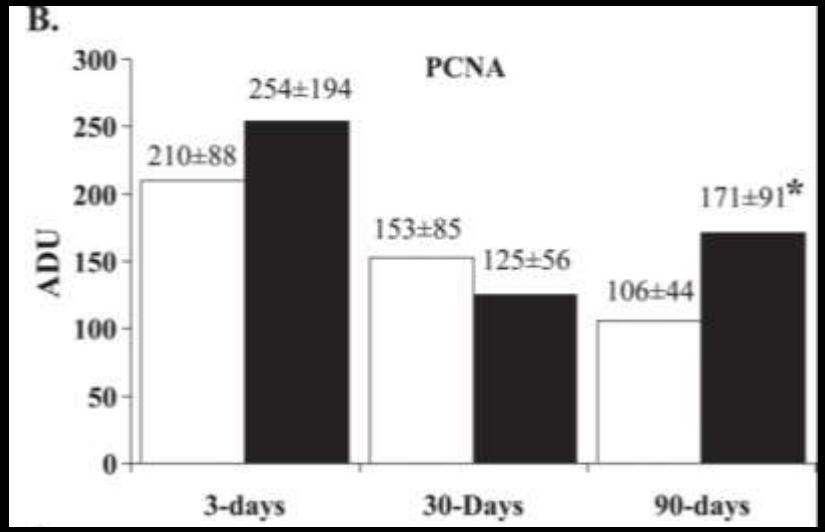
Circulation 2015

Permanent Polymers, Inflammation and Late Catch Up





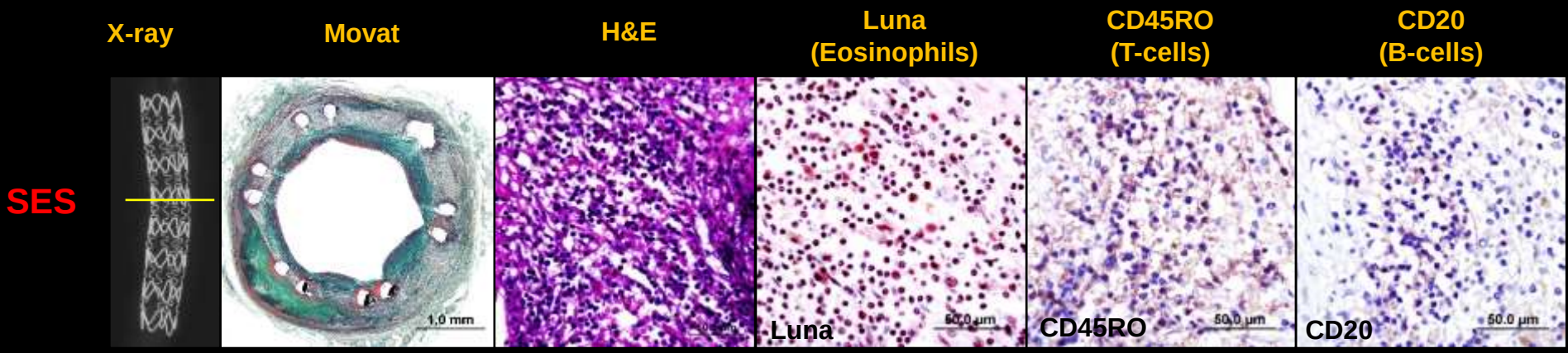
Increasing inflammation

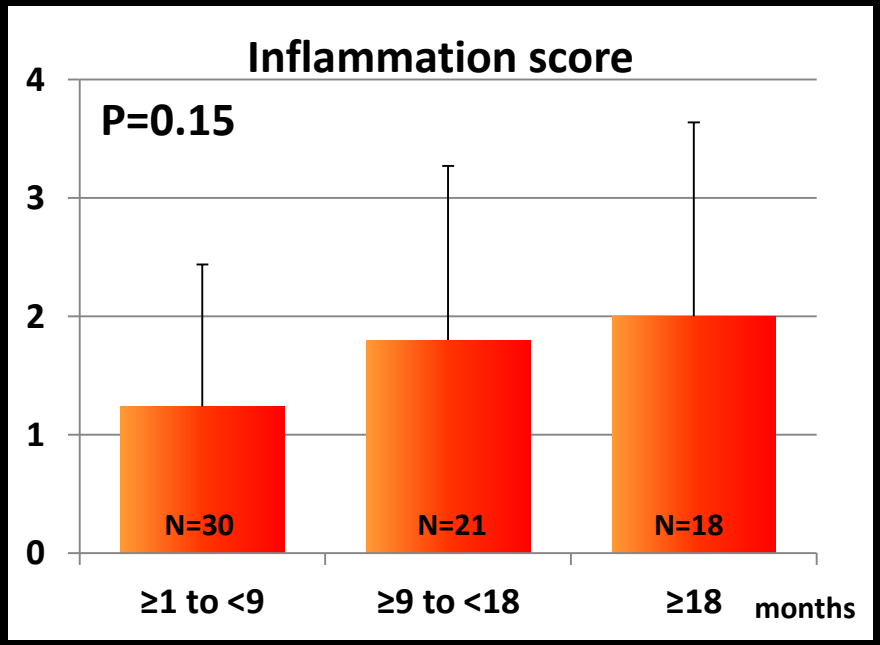


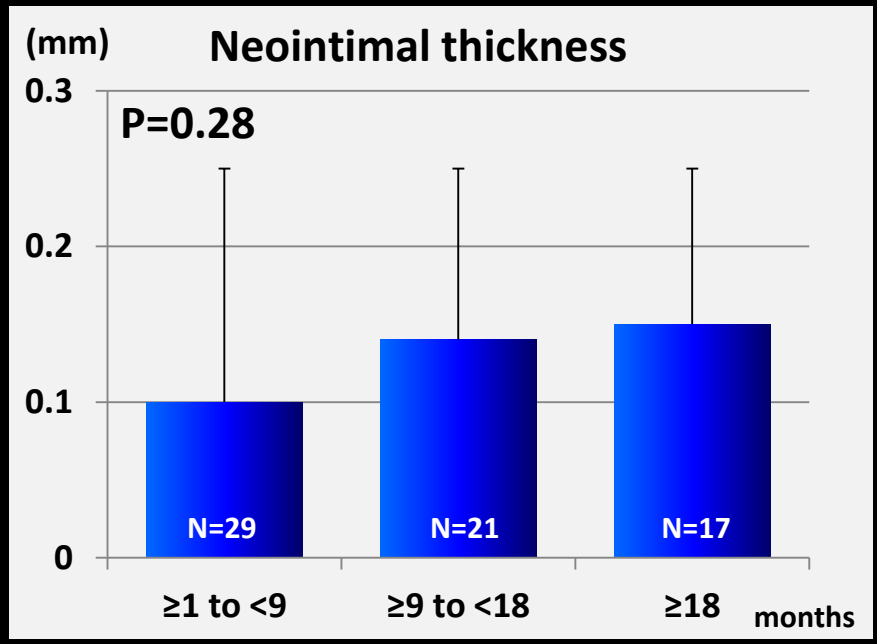
Carter AJ. Cardiovascular Research. 2004

Vascular Response following Implantation of Sirolimus-eluting stents (Cypher) 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.

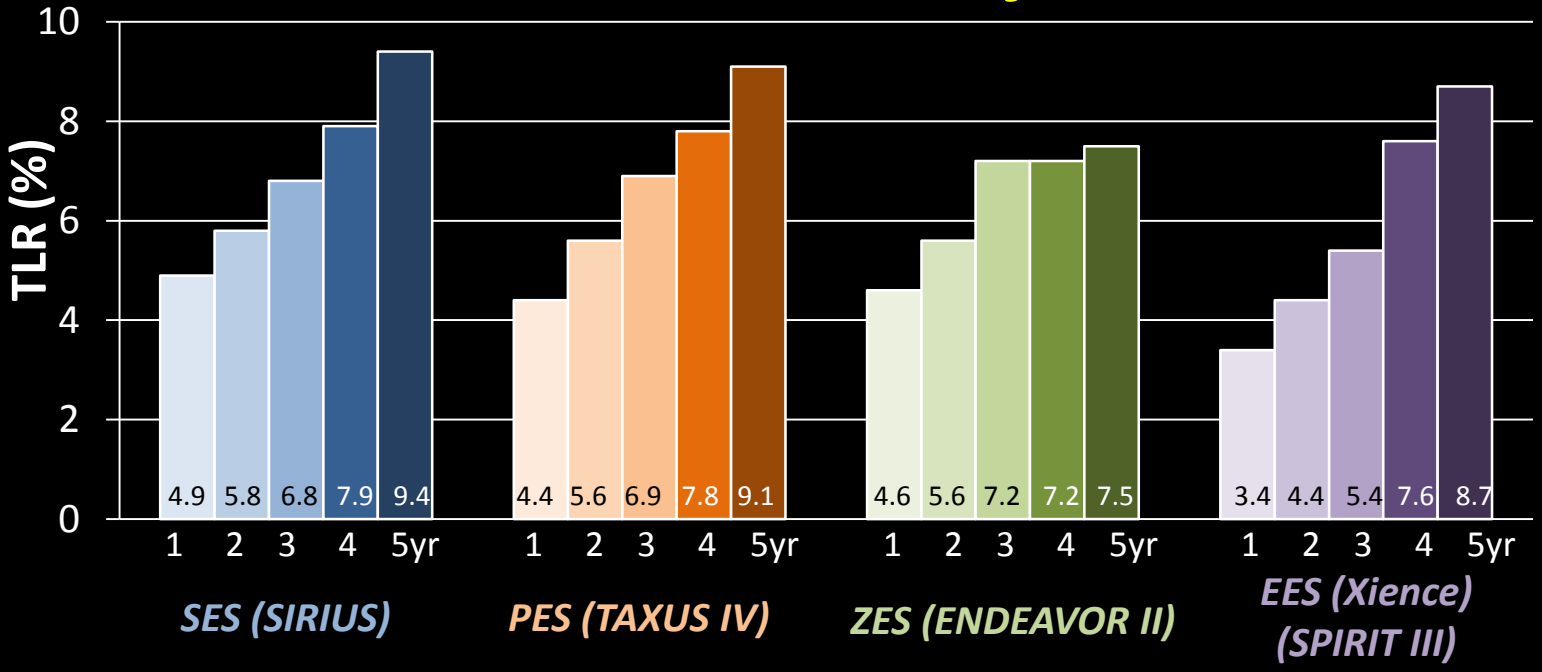




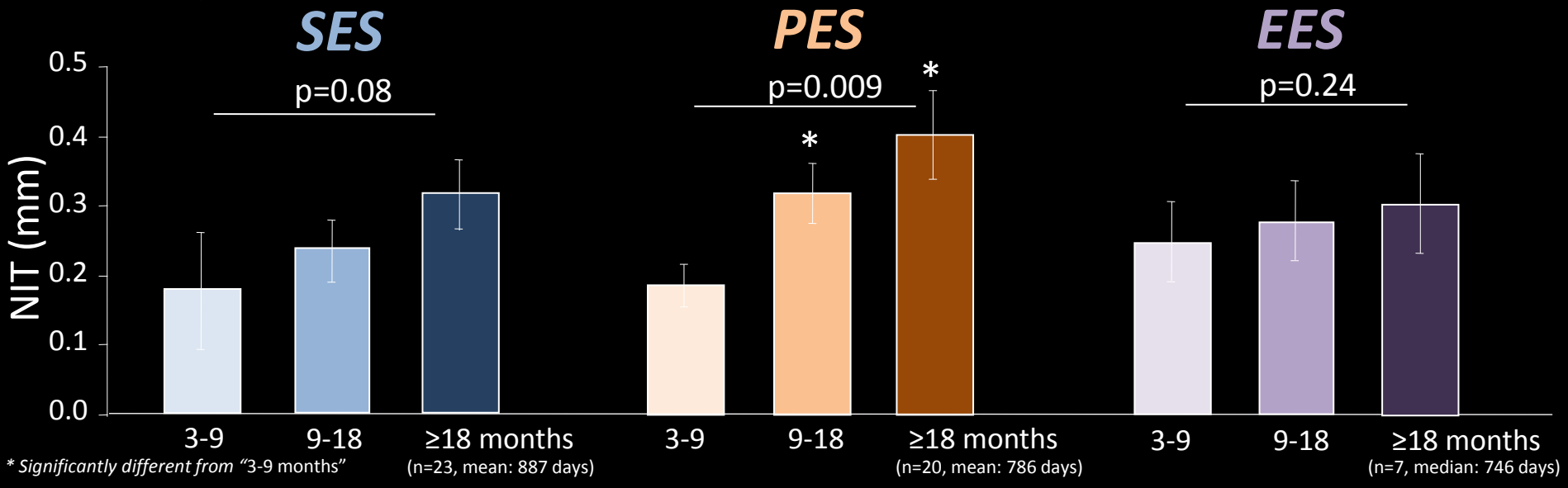


Figures; Otsuka F, et al. Circulation. 2014;129:211-223.

Long-term TLR in major clinical trials



Change in maximum neointimal thickness in human DES autopsy



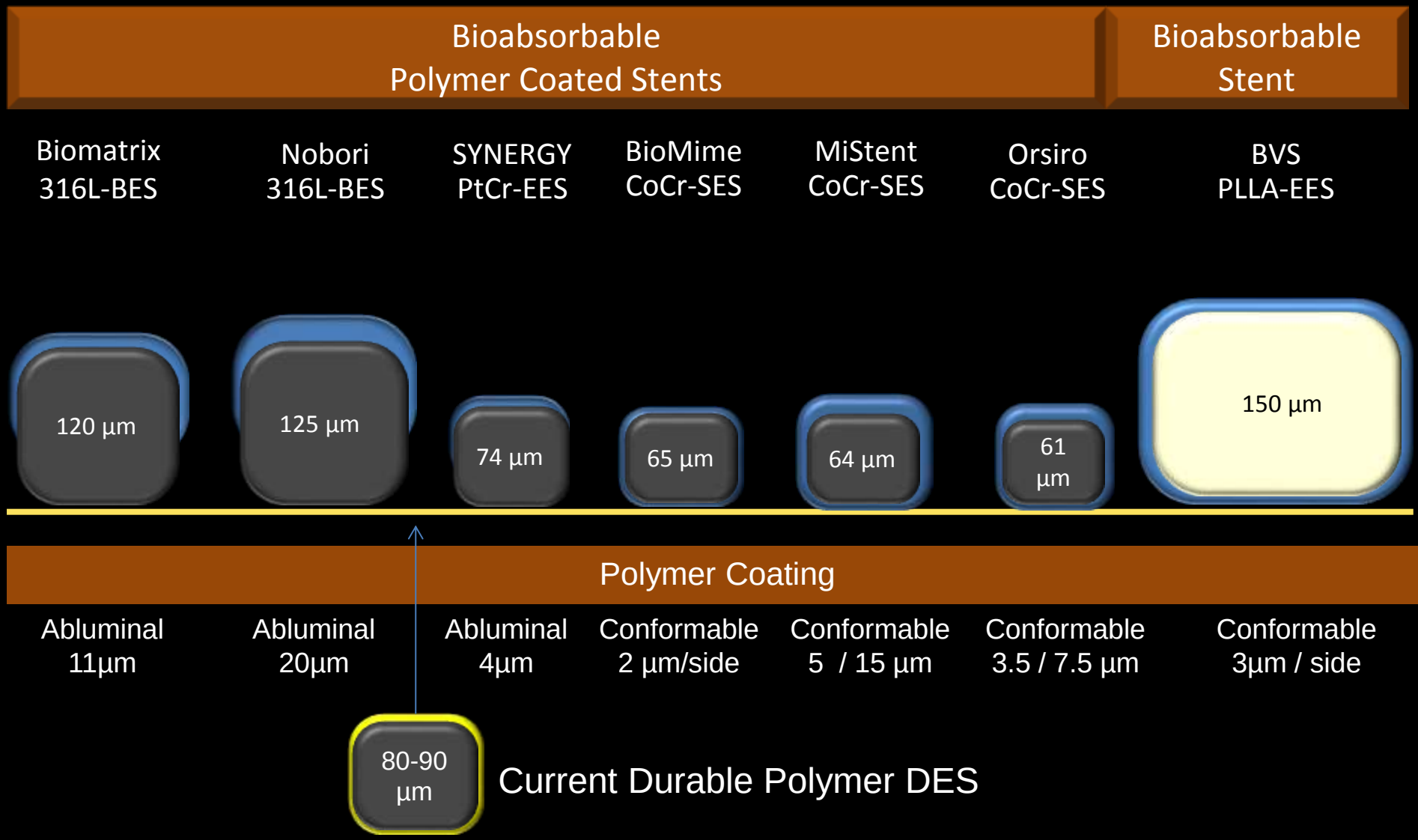
Contemporary DES Platforms

Strut and Coating Thickness In Perspective

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute	Biomatrix	Nobori	SYNERGY	BioMime	MiStent	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”	64µm 0.0025”	61µm 0.0024”
Polymer	PVDF	BioLINX	PLA	PLA	PLGA	PLLA + PLGA	PLGA	PLLA Probio*
Distribution / thickness	Conformal 7-8µm / side	Conformal 6µm / side	Abluminal 10µm	Abluminal 20µm	Abluminal 4µm	Conformal 2µ / 2µ	Conformal 5µm / 15µm	Conformal 3.5µm / 7.5µm

*silicon carbide

Bioabsorbable DES Platforms
Strut and Coating Thickness In Perspective

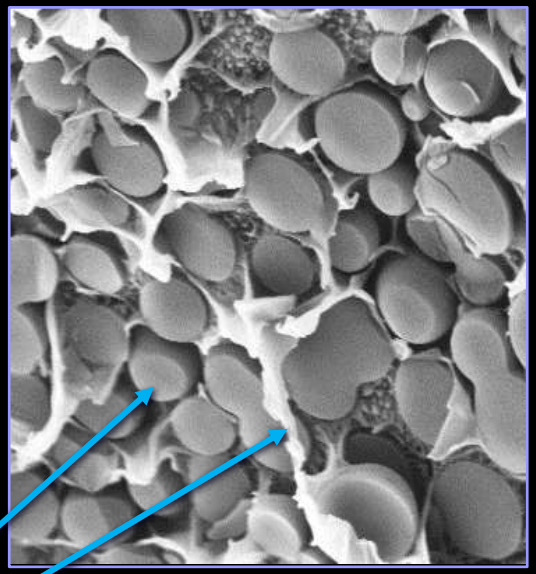


The SYNERGY™ stent is an investigational device and not for sale in the US. CE Mark Approved 2012. Information for the SYNERGY Stent is for use in countries with applicable product registrations

SYNERGY Stent Technology Design Goals

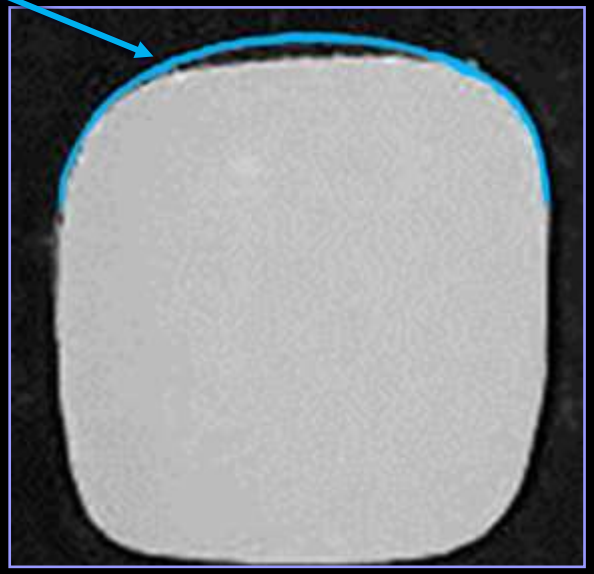
Everolimus Drug
PLGA Polymer

Drug & Polymer Coating



SEM of coating (x5000)

Abluminal (4µm)



Luminal

Platform
Platinum chromium
- 74 µm (0.0029in)

Polymer Coating
PLGA
- Abluminal
- 4 µm thick
- 85:15 ratio

Drug
Everolimus
- 100 µg/cm^2

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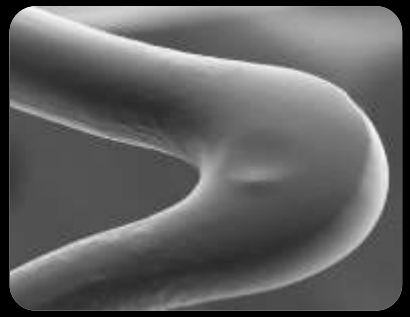
SYNERGY Stent

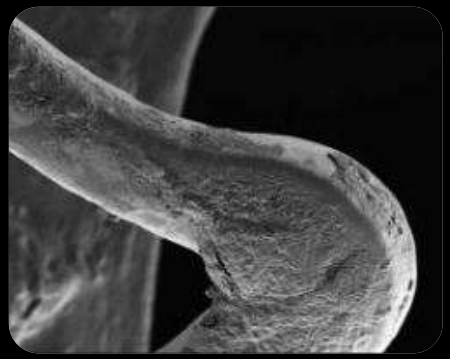
Visual Assessment of Coating Post Implantation in Swine

0 Days
(not implanted)



28 Days

60 Days



90 Days

FESEM @ 200x magnification

Presented by Yen-Lane Chen, PhD at EuroPCR 2012.

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PLA Metabolic Pathway

PLA

↓Molecular weight

Mass loss

Lactic acid

Mass transport of lactic acid

Krebs cycle → CO_2+H_2O

H_2O

Hydrolysis

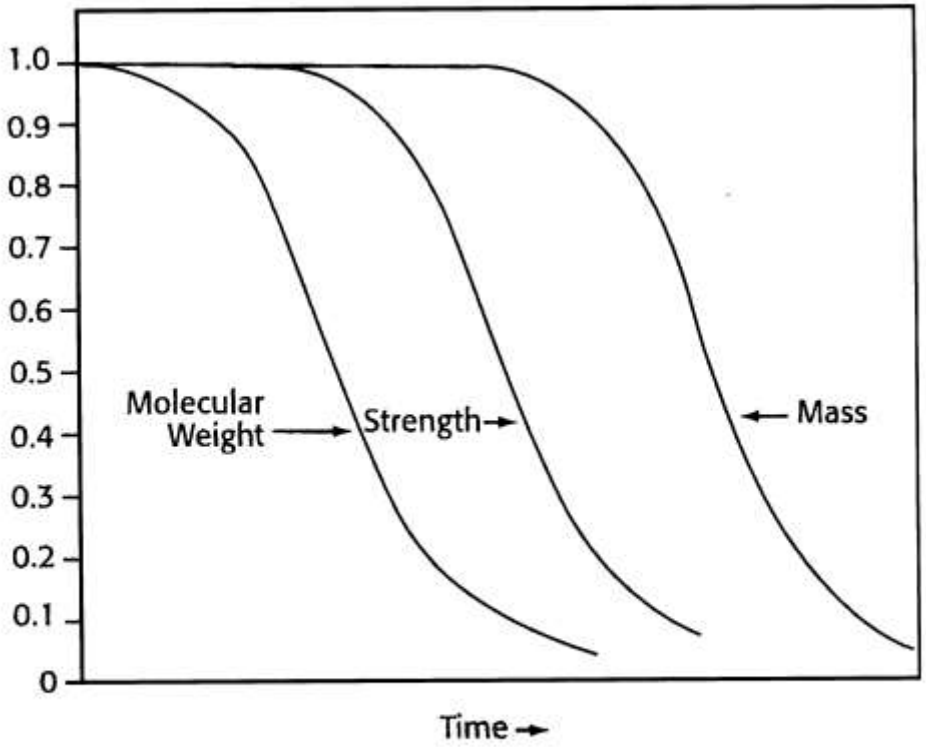
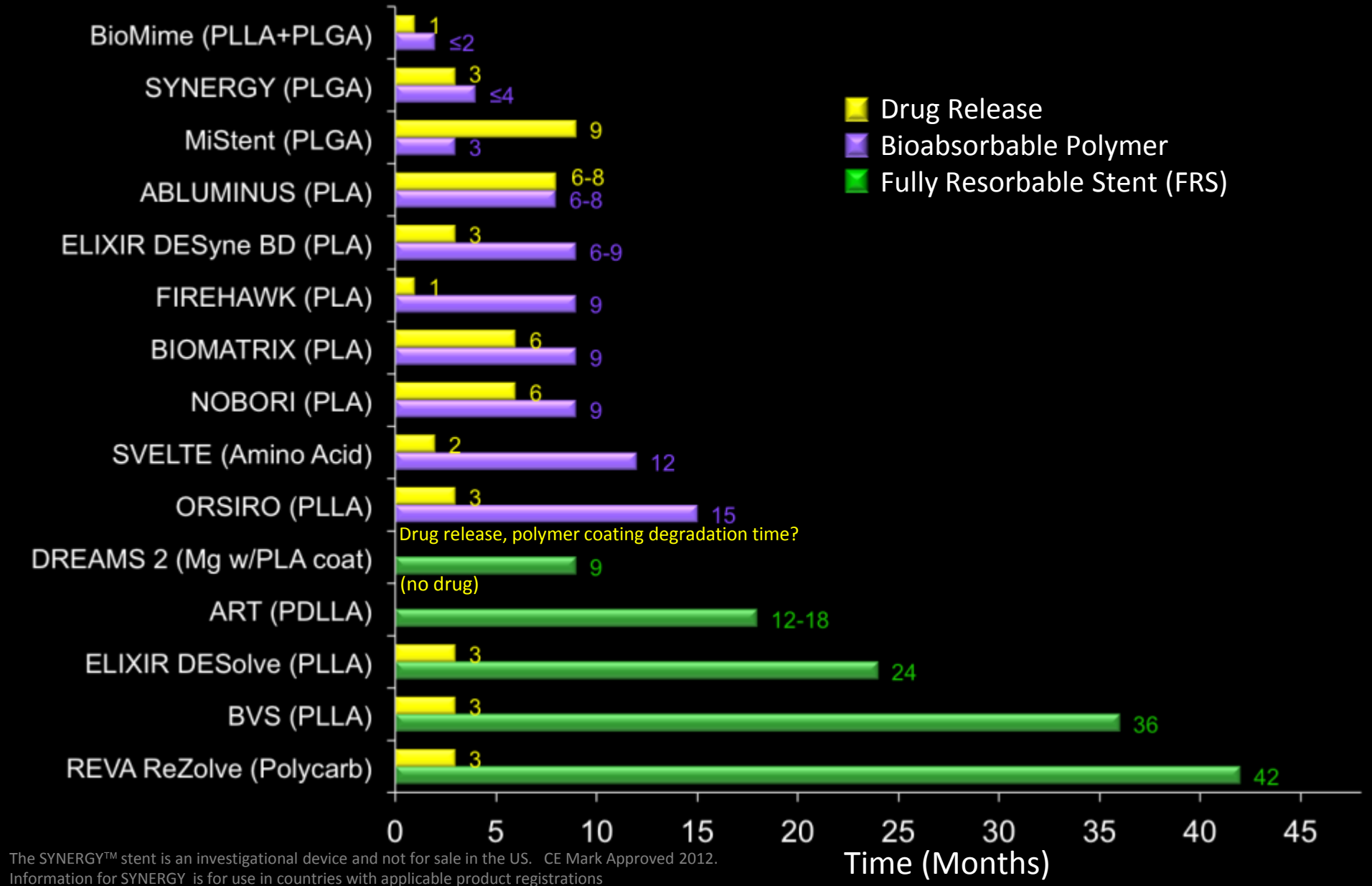


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

Time Course For Polymer Bioabsorption

Not all bioabsorbable technologies are the same



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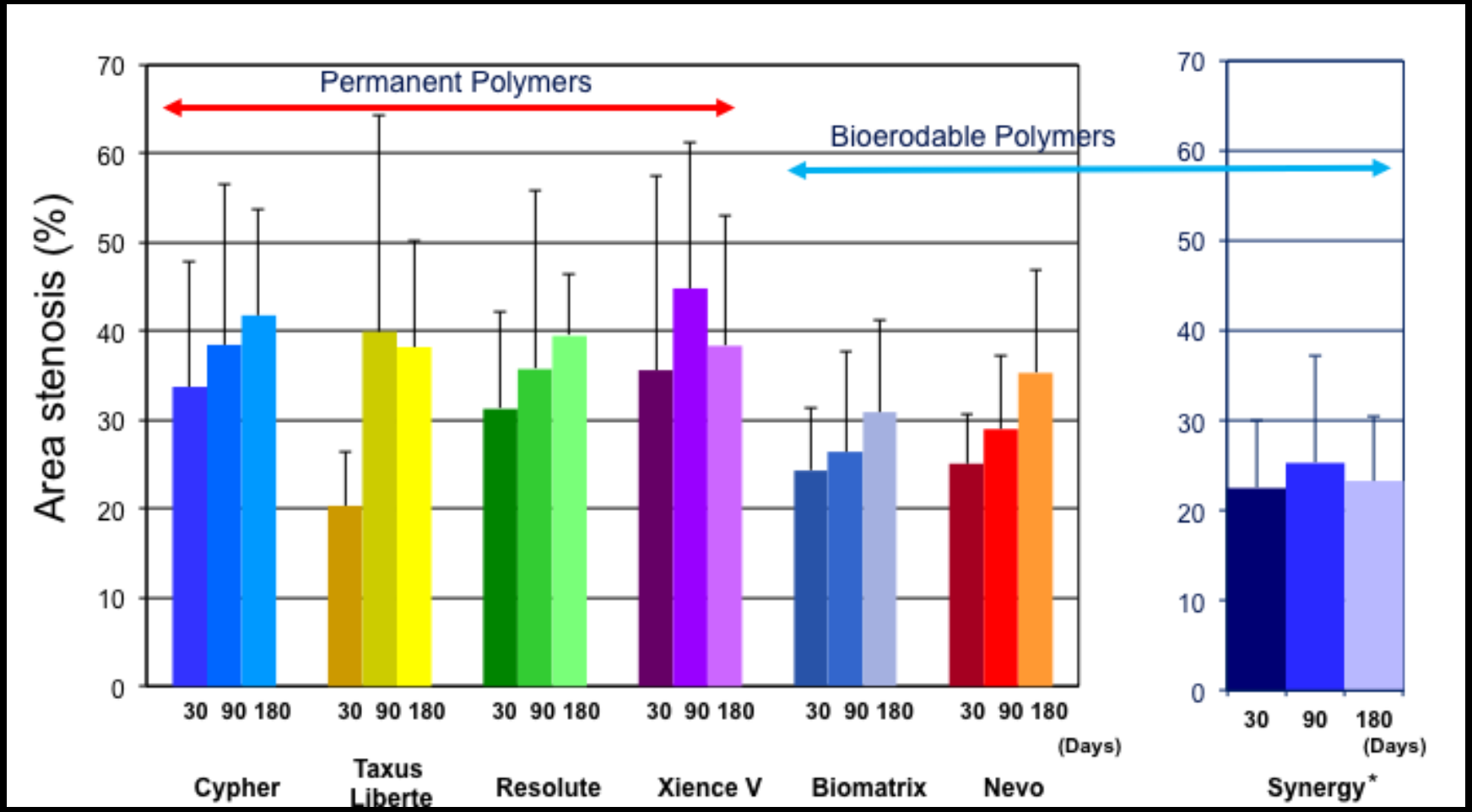
Permanent Versus Bioabsorable Polymer Stents: Pig Coronary Arteries



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

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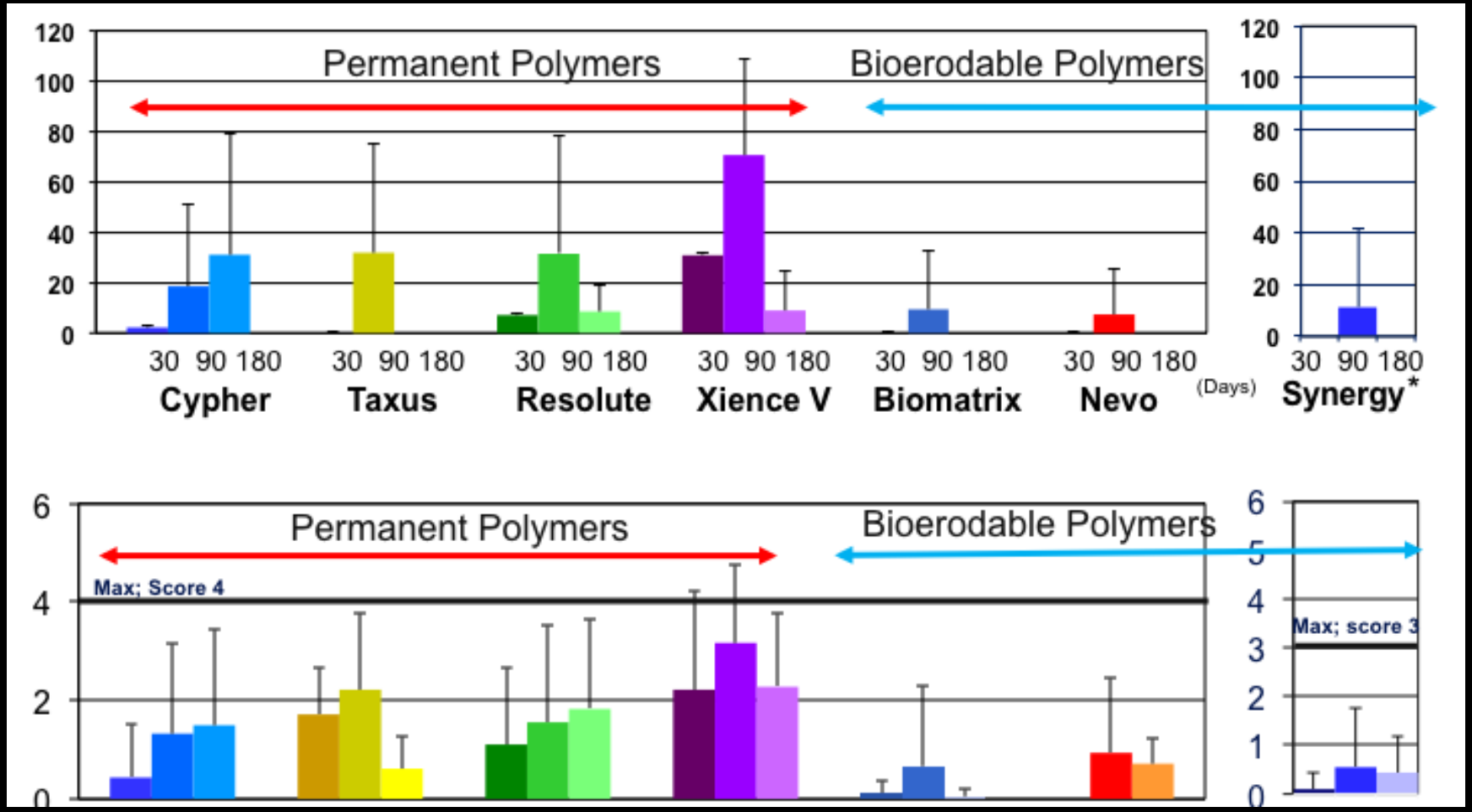

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Revascularization and Stent Thrombosis at 12 months

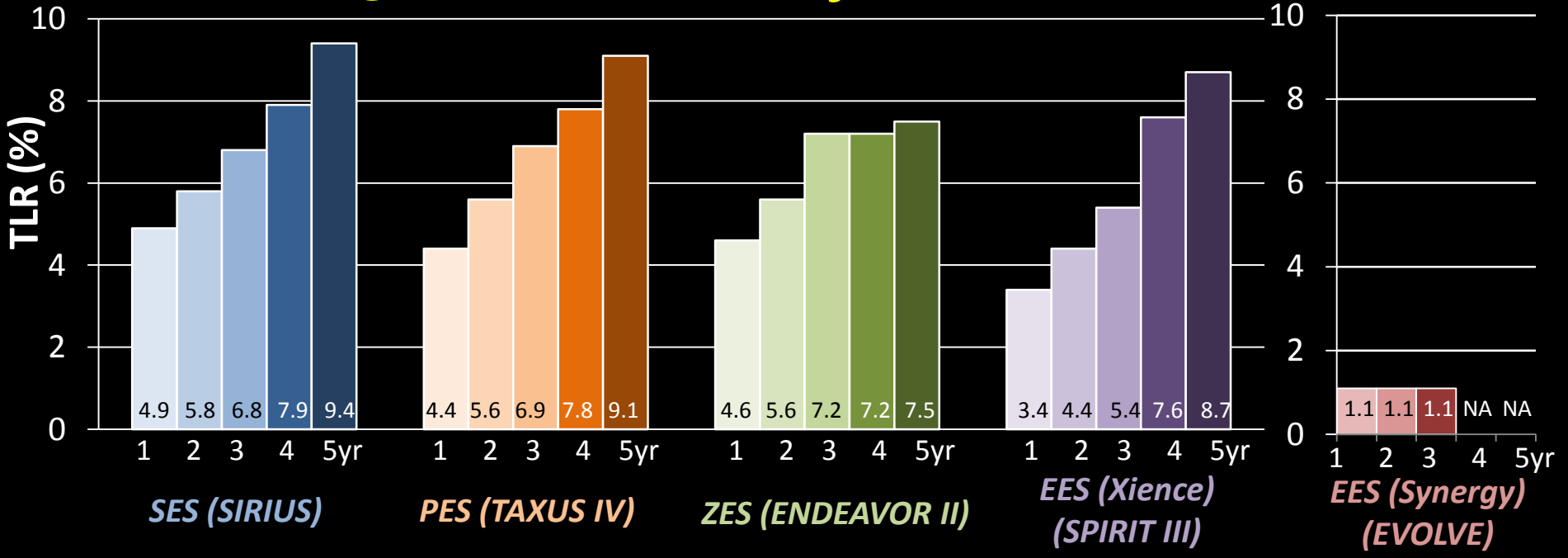
ITT Population

	PROMUS Element Plus n=838	SYNERGY 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

Keriakis et al AHA EVOLVEII 2014

How to show an advantage?

Long-term TLR in major clinical trials



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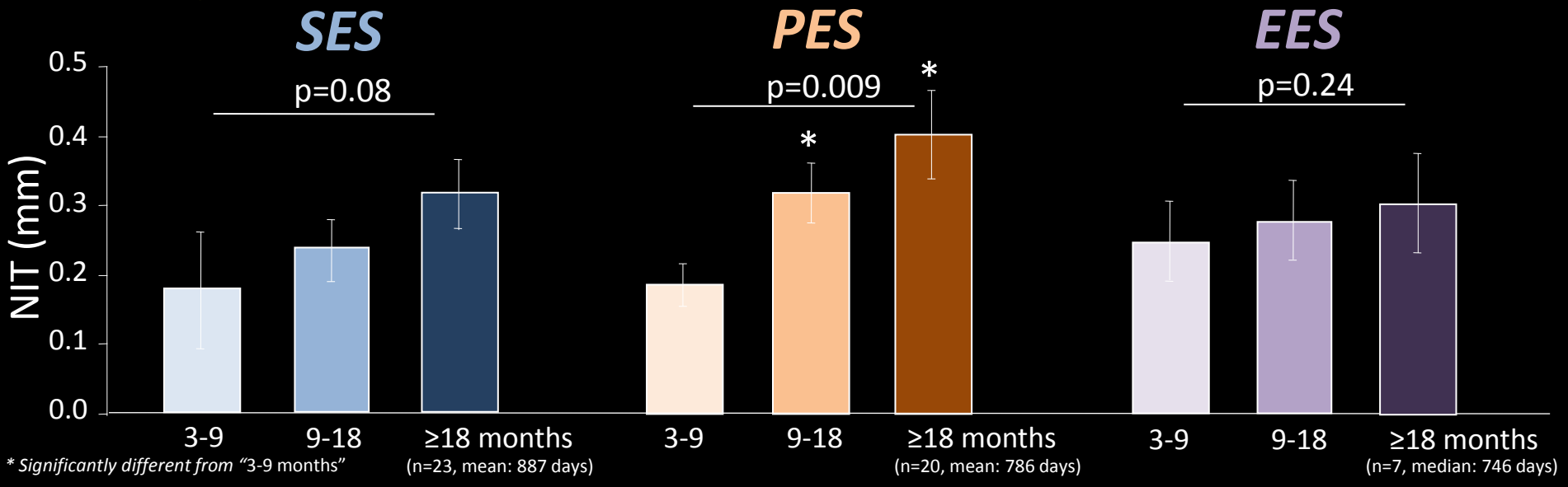

Conclusions:

- Preclinical animal studies have clearly shown that the amount of inflammation and neointimal thickening is greater with durable polymers as compared to bioabsorbable polymers.
- However, not all polymers are created equal. It depends on the type and amount of polymer load, degradation rate in relation to drug release.
- The less the polymer the less the inflammation and therefore less neointimal thickening.
- This concept should be able to be shown in clinical trials of bioabsorable polymer metallic DES