Pathological Insights II: Bioresorable Scaffolds

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TCTAP

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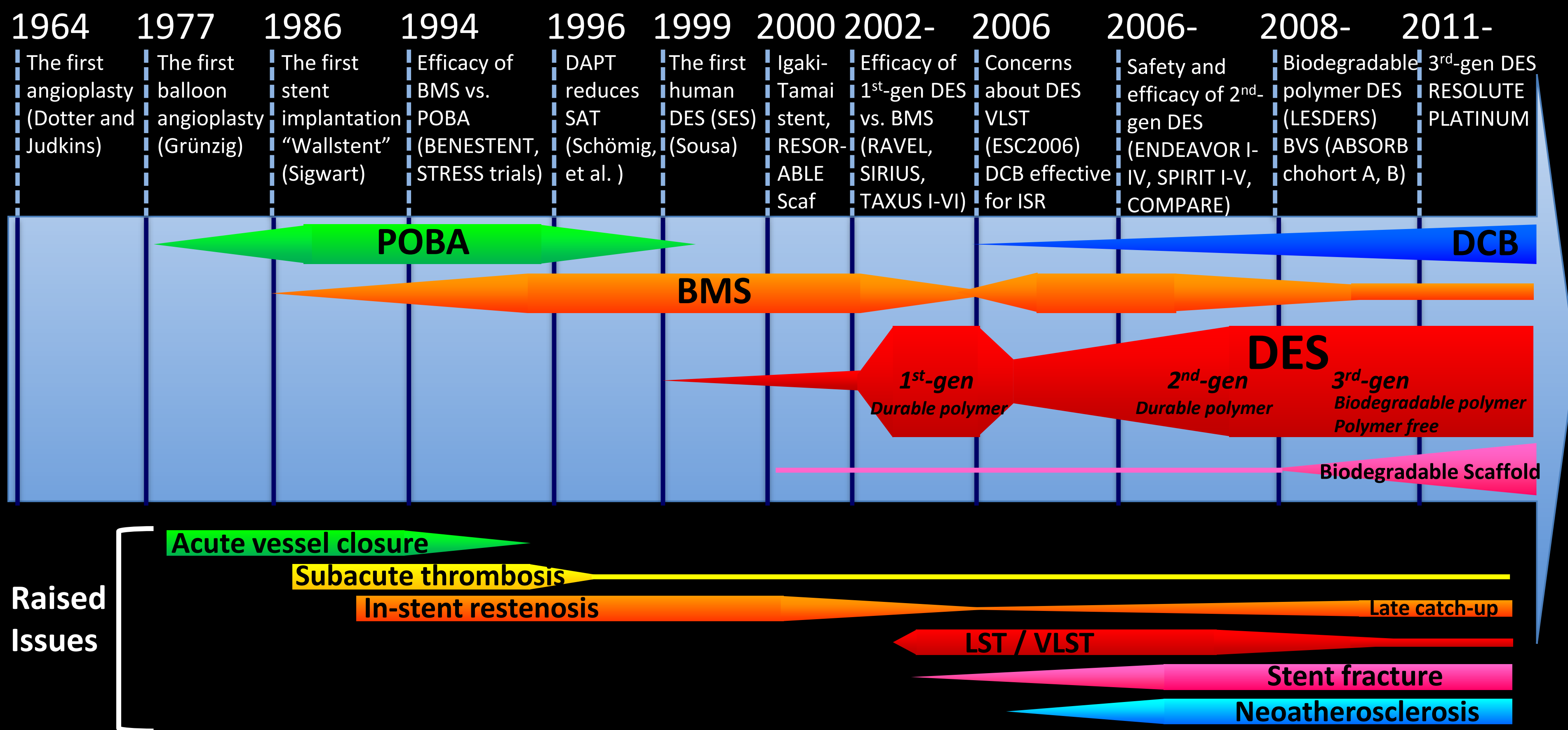
Conflict of Interest Declaration

- 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.

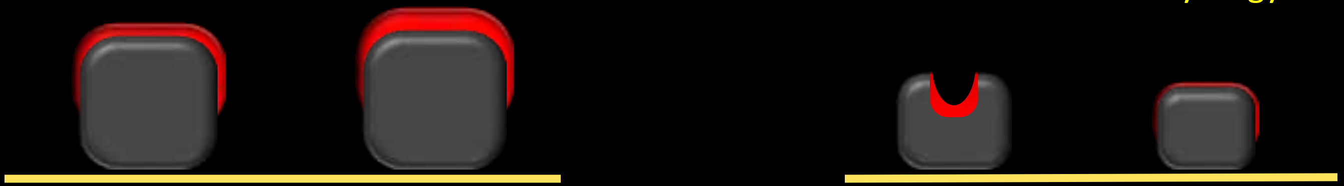
History of Percutaneous Coronary Intervention



	Balloon Angioplasty	BMS	DES
Success rate	70-85%	>95%	>95%
Restenosis	40-45%	20-30%	<10%
Early Thrombosis (≤30 days)	3-5%	1-2%	1-2%
Late Thrombosis (>30 days, ≤1y)	NA	<0.5%	1%
Very Late Thrombosis (>1y)	NA	≈0%	1-2%

Evolution of Metallic DES Technology

	First Gen			Second Gen		
Durable Polymer Stents	Cypher	TAXUS Express	TAXUS Liberte	Resolute Integrity	Xience Xpedition	Promus PREMIER
Strut Thickness	140 µm	132 µm	96 µm	89 µm	81 µm	81 µm
Coat Thickness	7µm / side	16µm/side	14µm/side	6µm / side	8µm / side	8µm / side



Bioabsorbable Polymer Stents	Biomatrix	Nobori	Firehawk	Synergy
Strut Thickness	120 µm	125 µm	86µm	74µm
Coat Thickness	10 µm	20 µm	10 µm	4 µm

Despite Improvements in technology, DES are permanent metallic implants

- -chronic reaction to polymer and/or metallic stent itself
- -Reduced Coronary Vasomotion
- -Loss of compensatory dilation in response to luminal narrowing
- -preclusion of bypass conduit attached to the stented portion

there is an intuitive attraction to knowing an implant is non permanent, perhaps assisting the body with healing itself and then disappearing

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

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

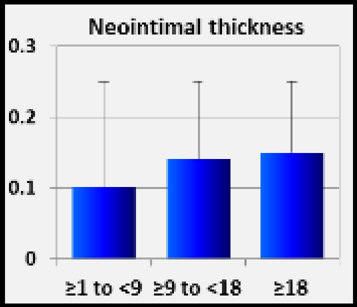
Late Stent Thrombosis / Restenosis

2nd-generation DES

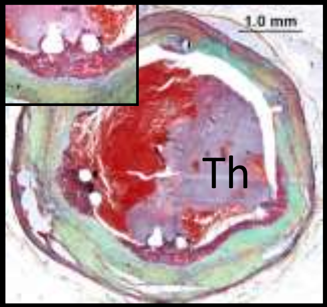
- Thinner struts
- More biocompatible polymer (Durable)
- Reduced drug dose

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

Clinical Late Catch-up

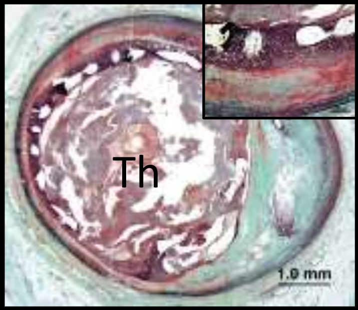


Late catch-up

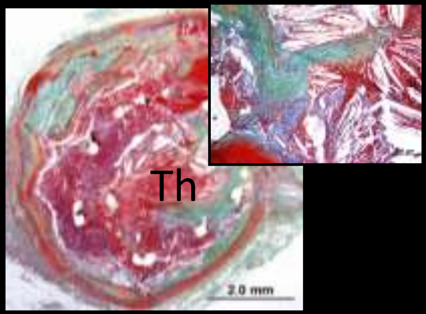


Uncovered struts

Hypersensitivity reaction



Malapposition from excessive fibrin deposition



Neoatherosclerosis

Evolution of DES Technology

Durable Polymer Stents

	First Gen: Cypher	First Gen: TAXUS Express	First Gen: TAXUS Liberte	Second Gen: Resolute Integrity	Second Gen: Xience Xpedition	Second Gen: Promus PREMIER
Strut Thickness	140 µm	132 µm	96 µm	89 µm	81 µm	81 µm
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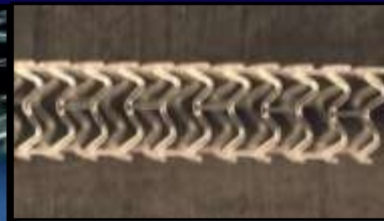
Bioabsorbable Polymer Stents

	First Gen: Biomatrix	First Gen: Nobori	Second Gen: Firehawk	Second Gen: Synergy
Strut Thickness	120 µm	125 µm	86µm	74µm
Coat Thickness	10 µm	20 µm	10 µm	4 µm

Fully Bioresorbable Stents

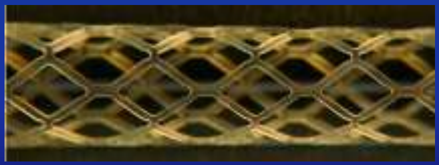
	First Gen: BVS	First Gen: ELIXIR DESolve	Second Gen: ART (bare bioresorbable scaffold)
Strut Thickness	150 µm	150 µm	170 µm
Coat Thickness	3 µm / side	<3 µm / side	NA

Completely Bioabsorbable Scaffolds

				
Igaki-Tamai	**Biotronik**	**Abbott Vascular**	**Bioabsorbable Therapeutics, Inc.**	**REVA Medical**
PLLA	Magnesium alloy	PLLA	PAE salicylic acid /	Poly (DTE carbonate)
NA	*NA*	Everolimus	Sirolimus	Paclitaxel
•Zigzag design •Heated balloon deployment	•High collapse pressure •Low elastic recoil	•80% drug release@30days	•Anti-inflammatory effect	•Radio-opaque •Ratchet lock design

PLA = poly-*L*-lactide, PAE = poly (anhydride ester), DTE = desaminotyrosyl-tyrpsine ethyl ester

Arterial Remodeling Technologies



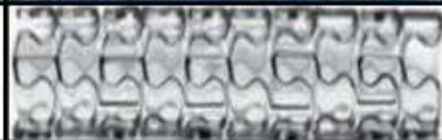
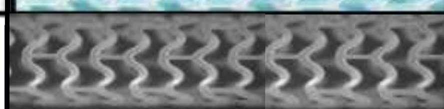
PLDA
No drug

ELIXIR: DESolve Bioabsorable Coronary Scaffold

PLLA resorbes in 2 years,
Myolimus Eluting

Virmani R: PCR Focus group 2013
Modified from Ramcharitar S, & Serruys PW; Am J Cardiovasc Drugs 2008: 8(5):305-314

Completely Bioabsorbable Scaffolds from Different Companies

Igaki-Tamai (Kyoto Medical)		DESolve (Elixir Medical)	
AMS 1.0 (Biotronik)		BTI (Xenogenics Corp.)	
AMS 3.0 (Dreams 1st generation)		IDEAL (BTI 2nd generation)	
AMS 4.0 (Dreams 2nd generation)		ART (Arterial Remodeling Technology) Investigational	
ReZolve (REVA 2nd generation)		ART18Z (ART 2nd generation)	
Fantom (REVA 3rd generation)		Amaranth (Amaranth Medical)	
BVS 1.0 (Abbott Vascular)		Xinsorb (Huaan Biotechnology)	
Absorb BVS (BVS 1.1)		Stanza (480 Biomedical)	
BRS (Microport)		MeRes (Meril Life Sciences)	

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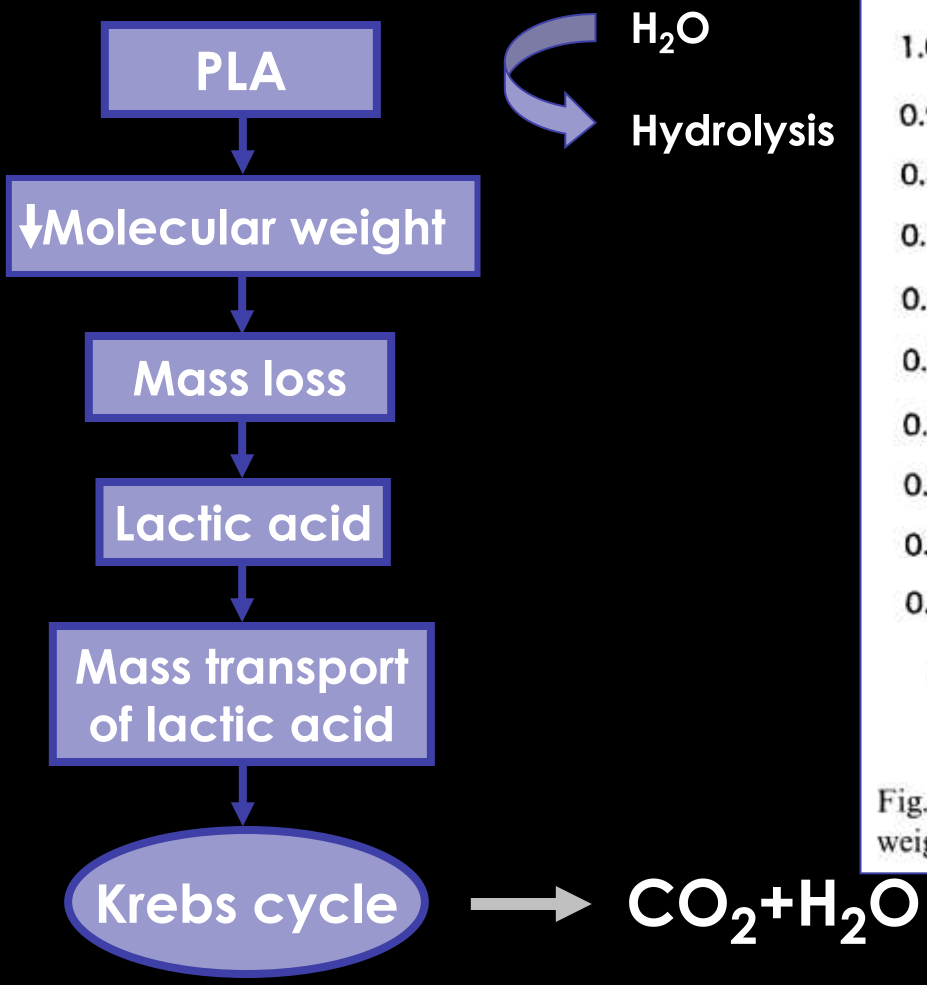
PLA Metabolic Pathway



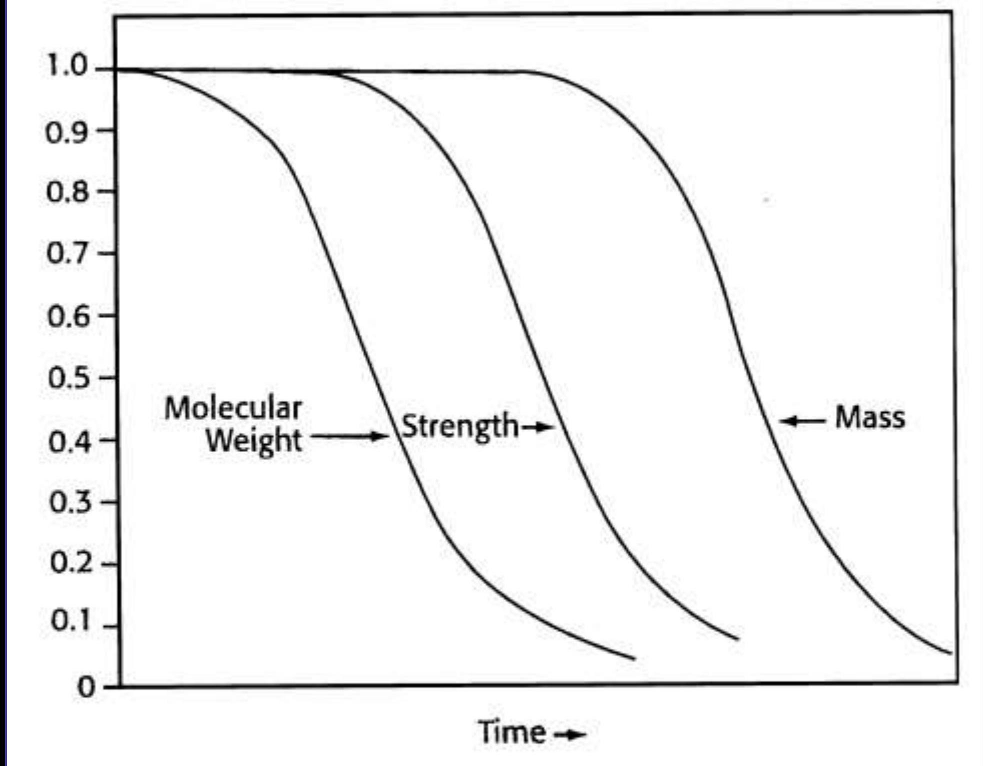
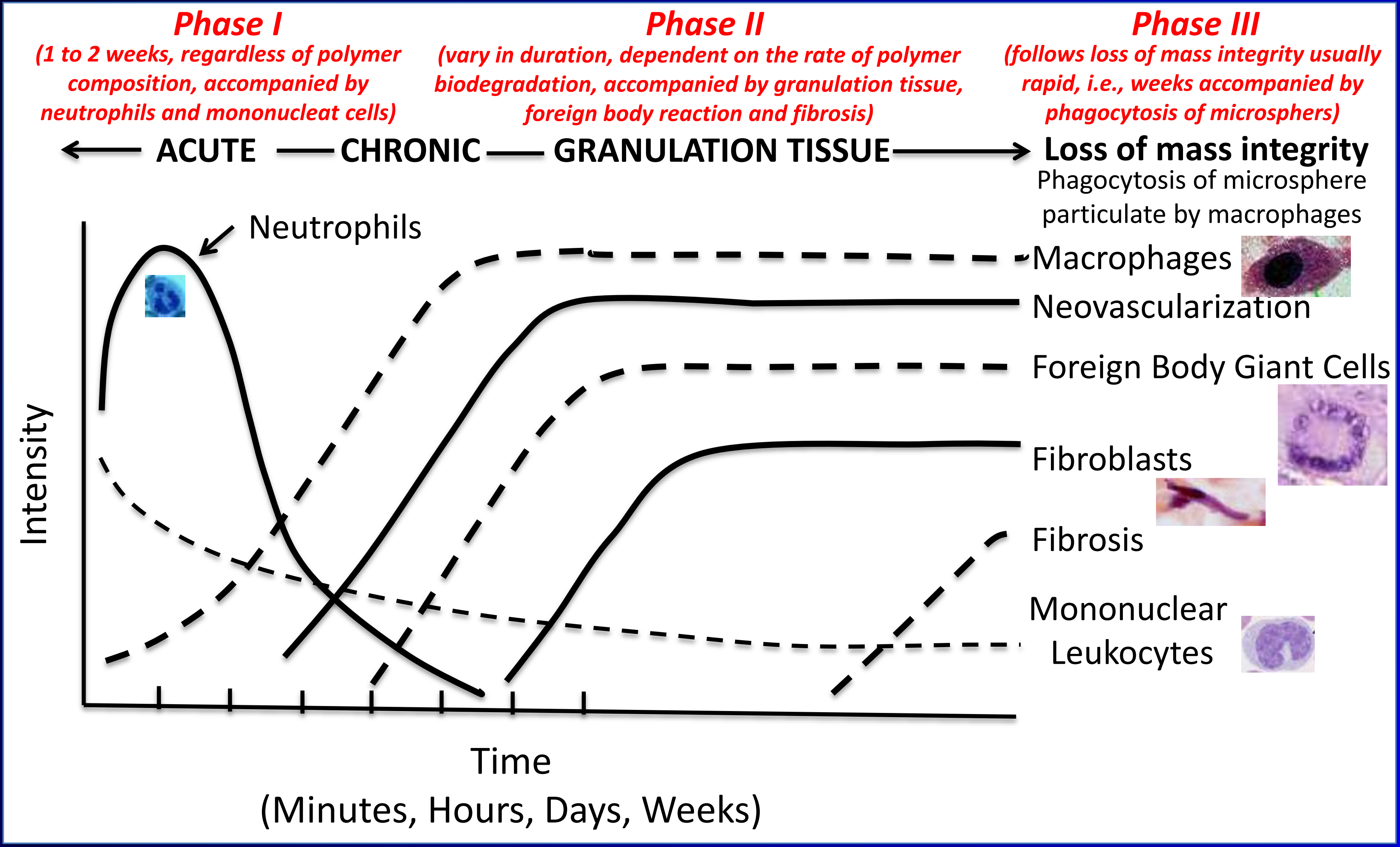


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

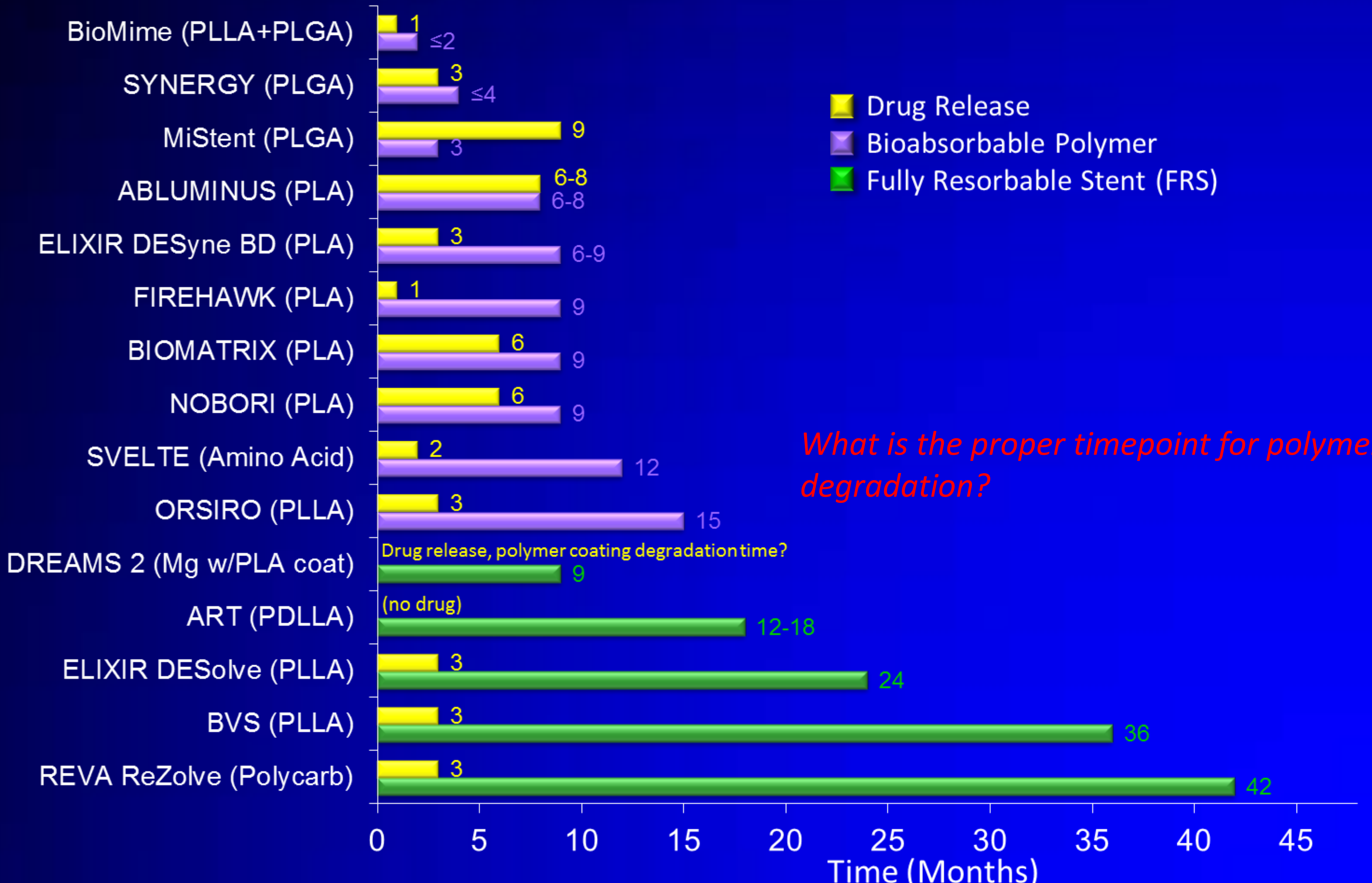
The temporal variation in the acute and chronic inflammatory responses, granulation tissue development, and foreign body reaction to implanted biodegradable microspheres



Anderson JM, Shive MS. Advanced Drug Delivery Reviews 1997;28:5-24.

Time Course For Polymer Bioabsorption

Not all bioabsorbable technologies are the same



Pre-clinical assessment for bioresorbable scaffolds (BRS)

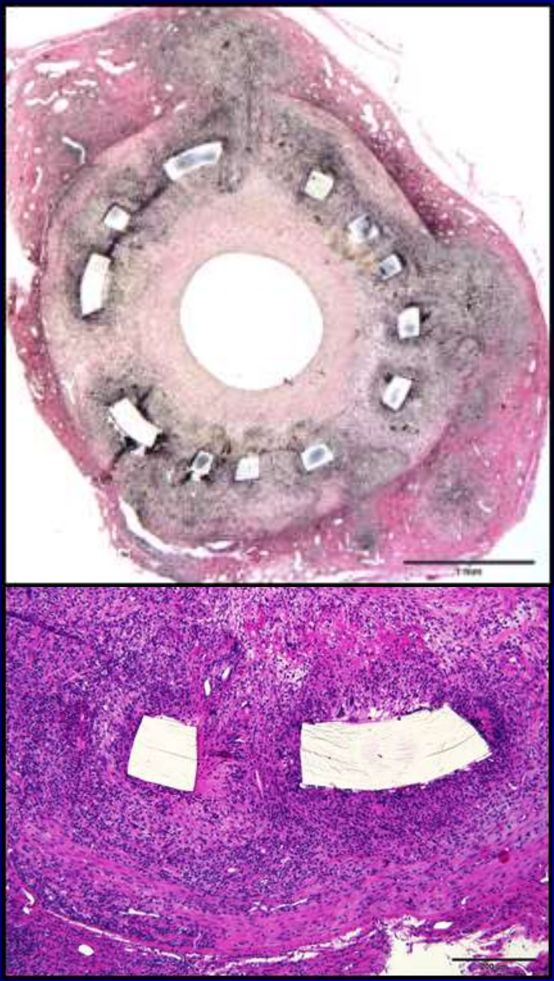
- Radiography
- Light microscopy (LM)
  - Histologic assessment
    - (Neointima, inflammation, Fibrin, etc)
  - Histomorphometric Assessment
  - Immunohistochemical staining
- Scanning electron microscopy (SEM)
- Transmission electron microscopy (TEM)
- Pharmacokinetic study (PK)
- Biochemical analysis
- Imaging study: Intravascular imaging (OCT), micro-CT, etc.

Assessment for degradation of bioresorbable scaffolds (BRS)

- *Measurement time points may need to be modified to better capture critical safety parameters*
  - ✓ Early time point: prior to degradation (when BRS is still intact, 4-5 time points within this period)
  - ✓ During degradation (yearly assessment)
  - ✓ Late time point: after complete resorption
- *Emphasis on late time point*
  - ✓ The last time point needs to establish that the vessel is healed and has reached a steady state.
  - ✓ This may not be until after degradation is complete.
  - ✓ Assess whether absence of rigid scaffold leads to adverse arterial remodeling & edge effects and for histology shrinkage is a problem especially once degradation begins
  - ✓ Evaluate potential toxicity of degradation products (seen as inflammation)
- *Ultimately, latest time point will also depend on evidence of acceptable healing and stability*

Inflammatory reaction following implantation of BRS B in porcine arteries

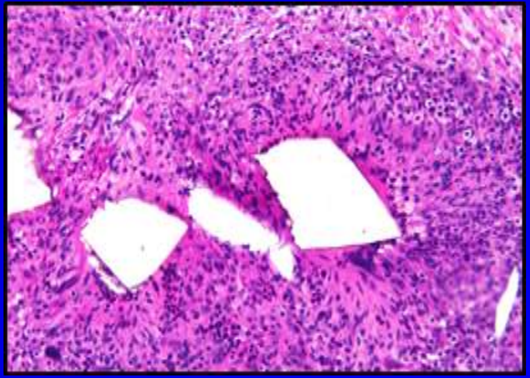
28 days



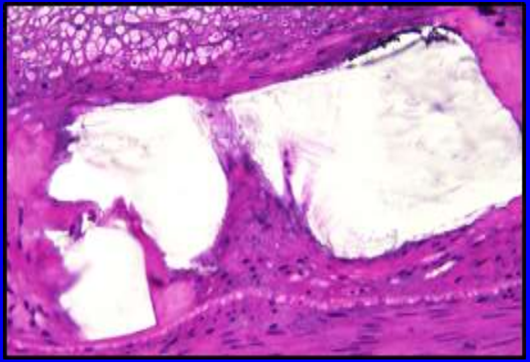
90 days

Discontinuities of bioresorbable scaffold strut

28 days

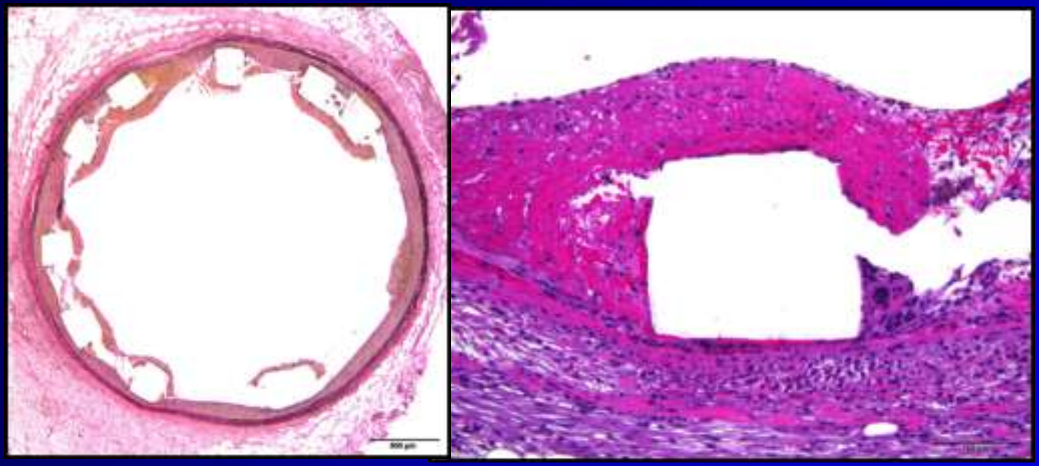


90 days

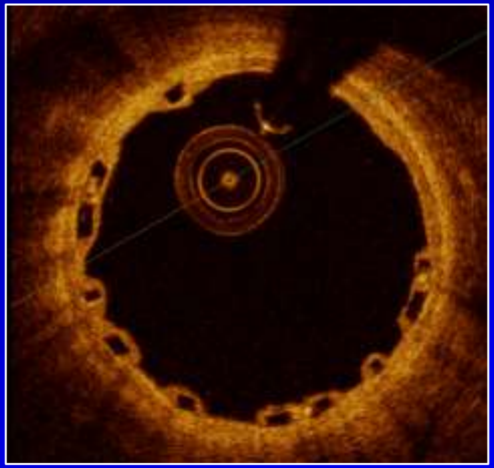


Pathological/OCT assessment following implantation of BRS D in healthy porcine arteries at 7 days

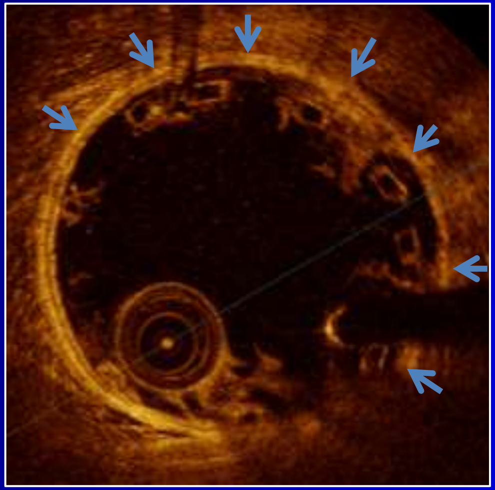
Histology



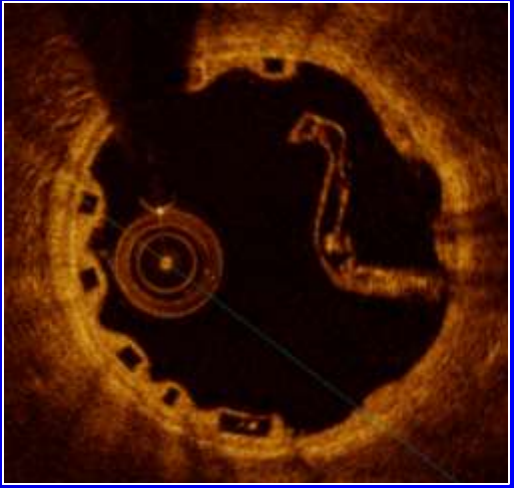
OCT



Scaffold Malapposition

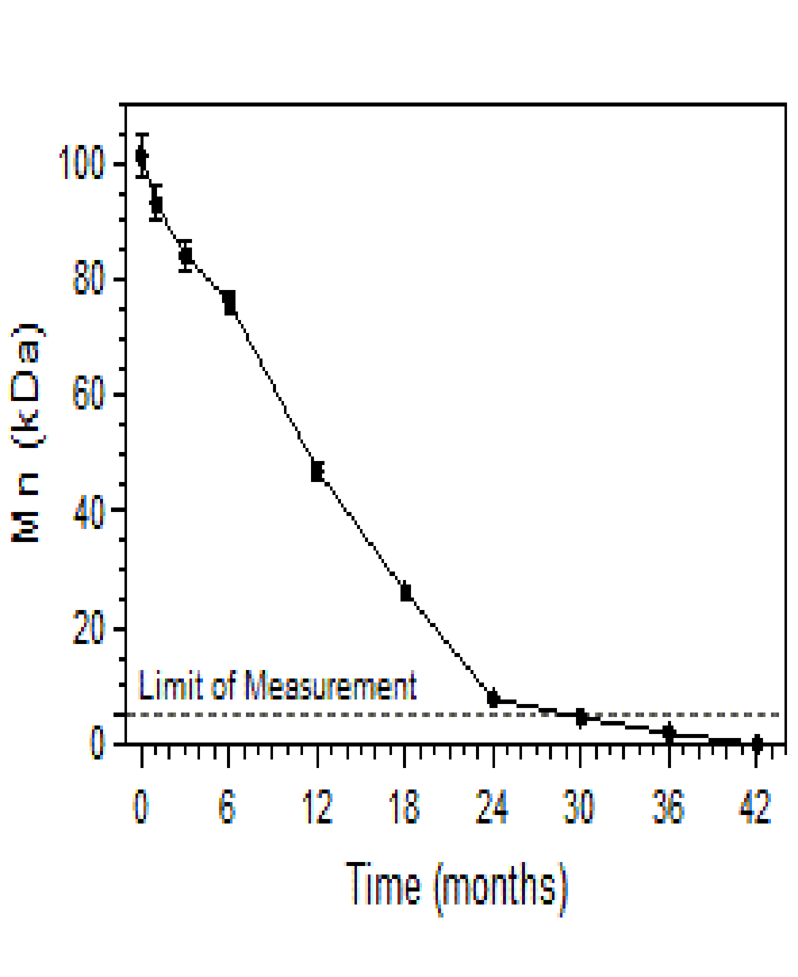


Scaffold Fracture

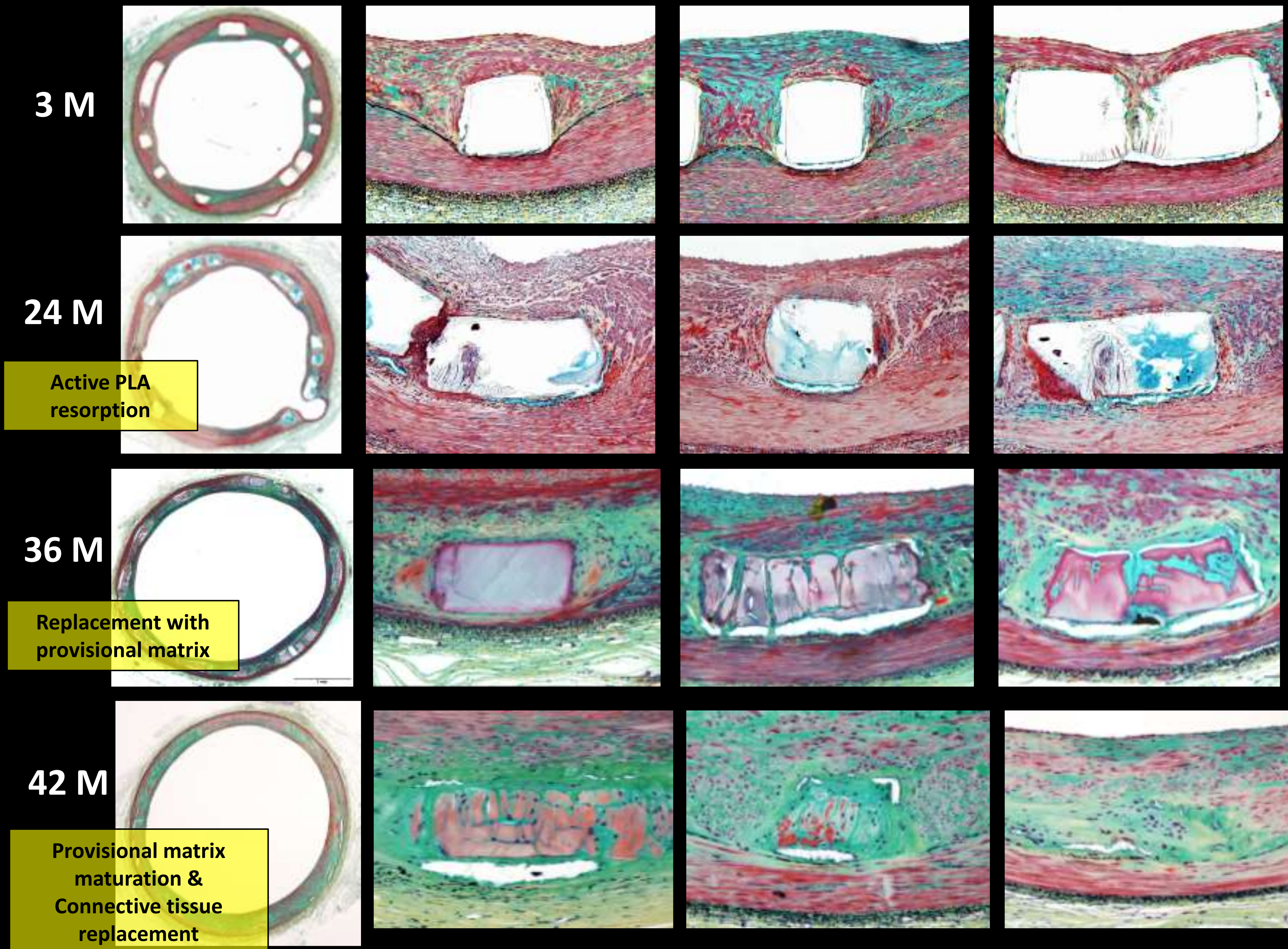


Degradation of PLA Stent and Histological Response in Swine Coronary Model

In vitro degradation predicts in vivo degradation

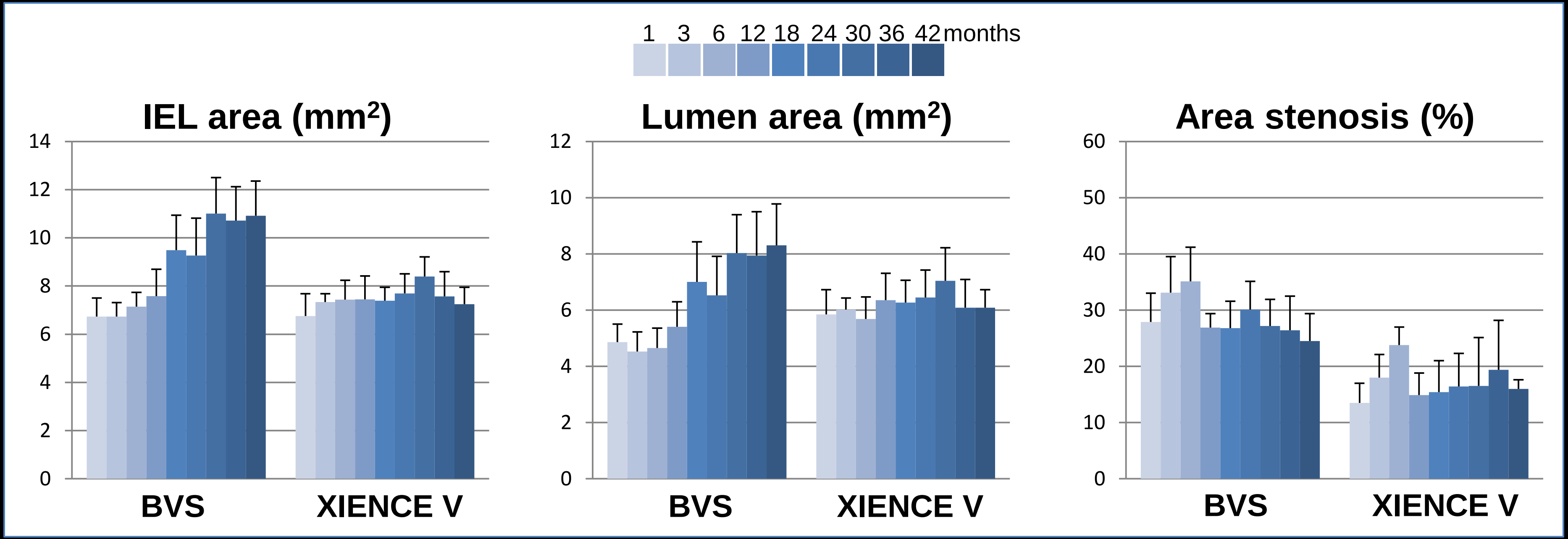


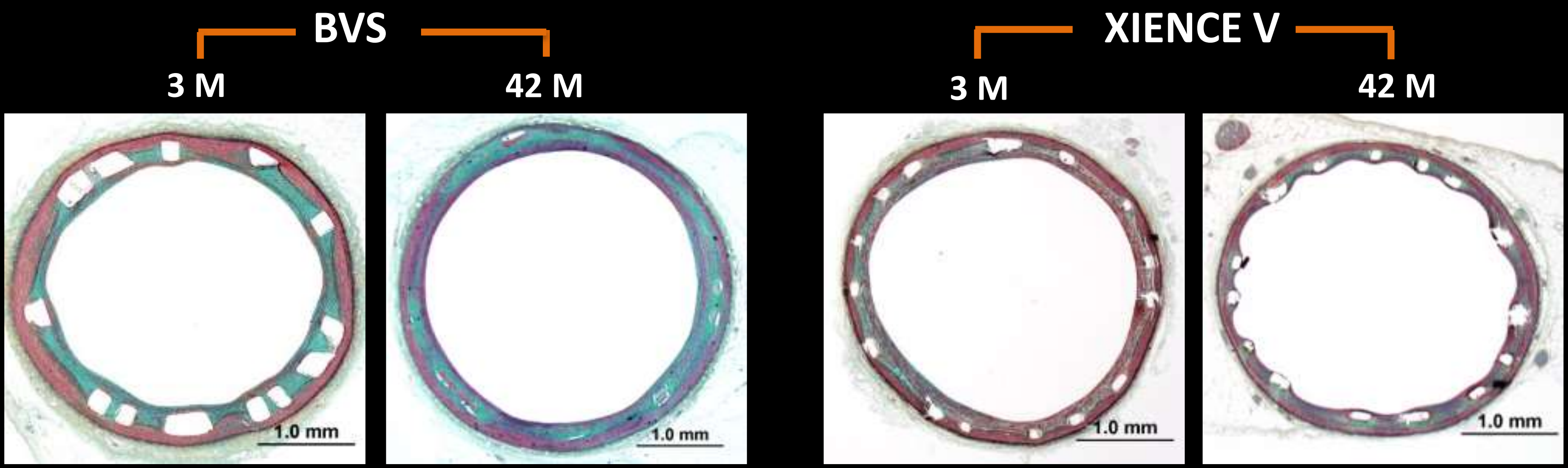
Degradation of BVS (Cohort B) in Porcine Coronary Arteries



Otsuka F, et al. Circ Cardiovasc Interv 2014;7:330-42

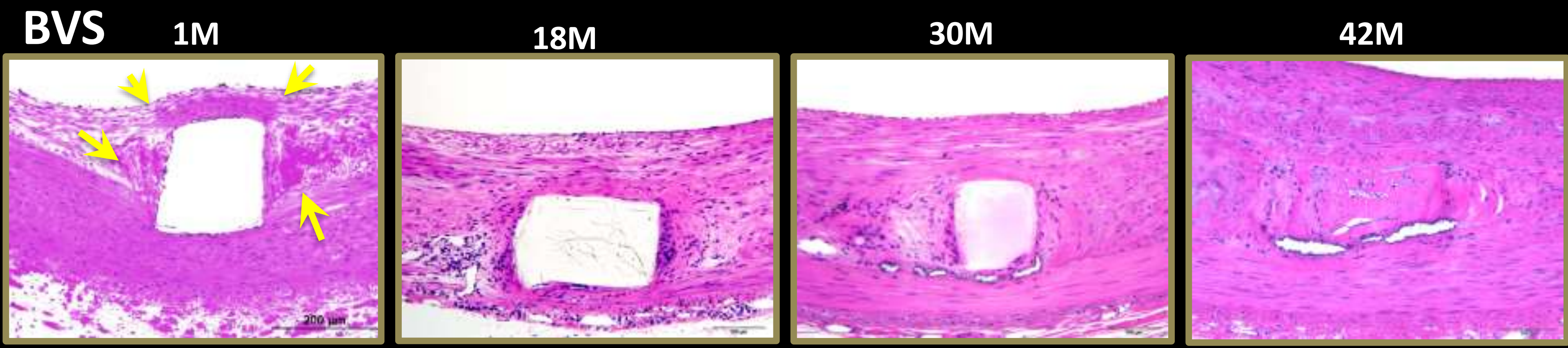
Morphometric Analysis of BVS and XIENCE V in Porcine Coronary Model – Cohort B

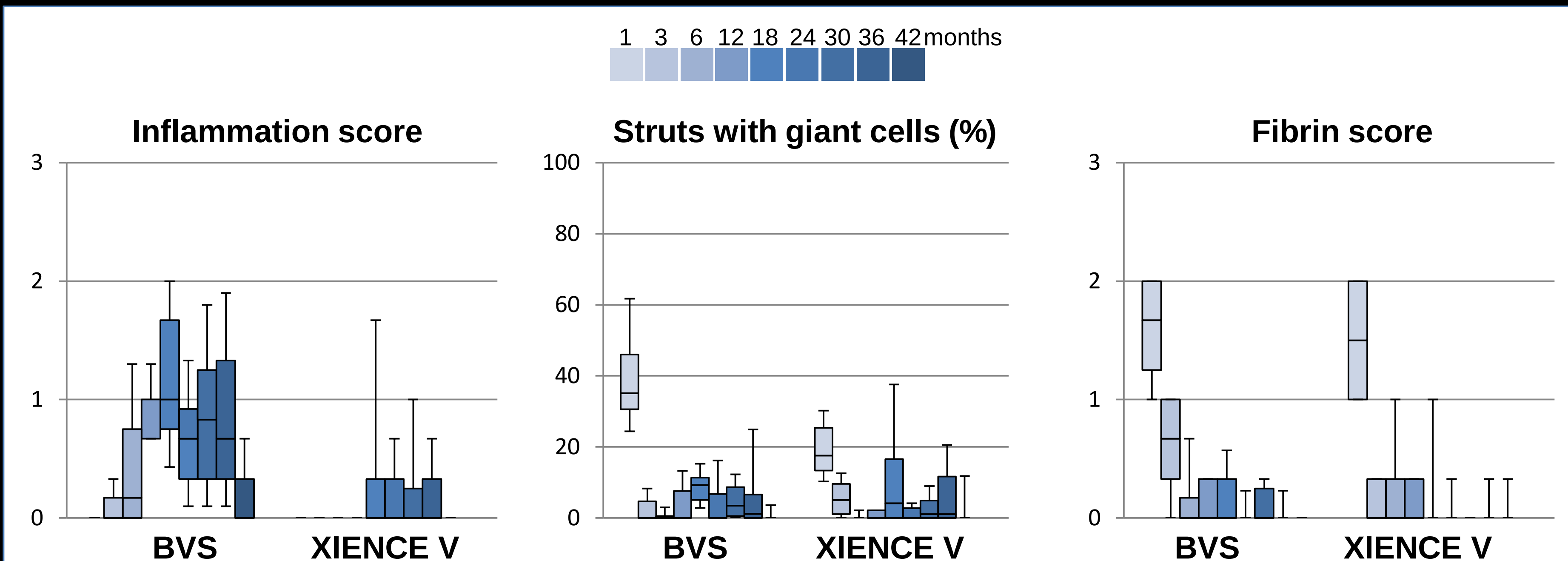




Otsuka F, et al. Circ Cardiovasc Interv 2014;7:330-42

Inflammatory Reaction to BVS and Xience V – Cohort B



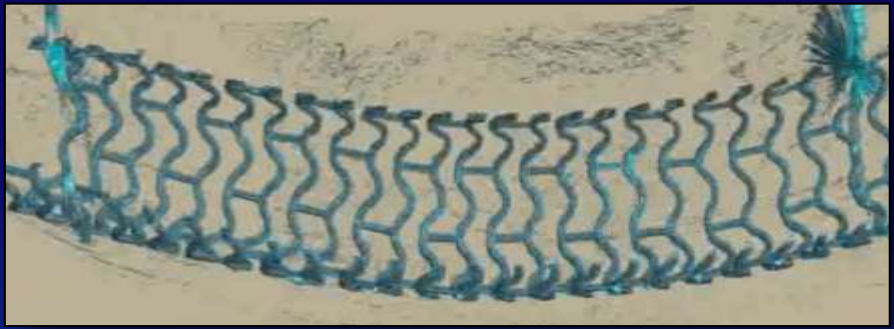


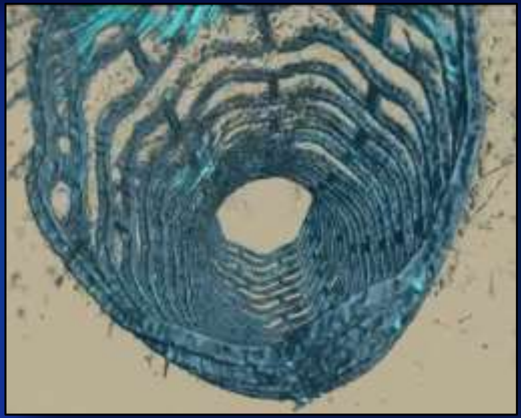
Severe granulomas were observed in 3/102 stents (3%) of BVS, and 4/67stents (6%) of Xience V, which were excluded from analysis.

Otsuka F, et al. Circ Cardiovasc Interv 2014;7:330-42

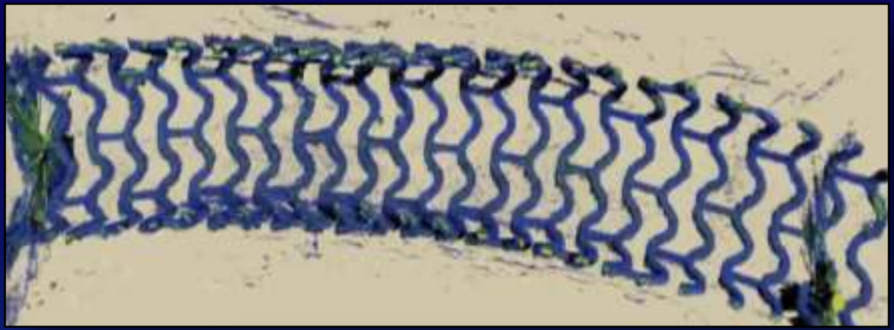
Micro-CT: Detect Strut Fractures and Signs of Dismantling at 28 and 180 Days in BRS A

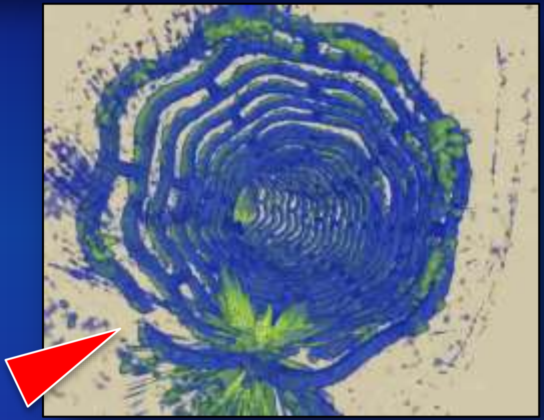
28 Days





180 Days

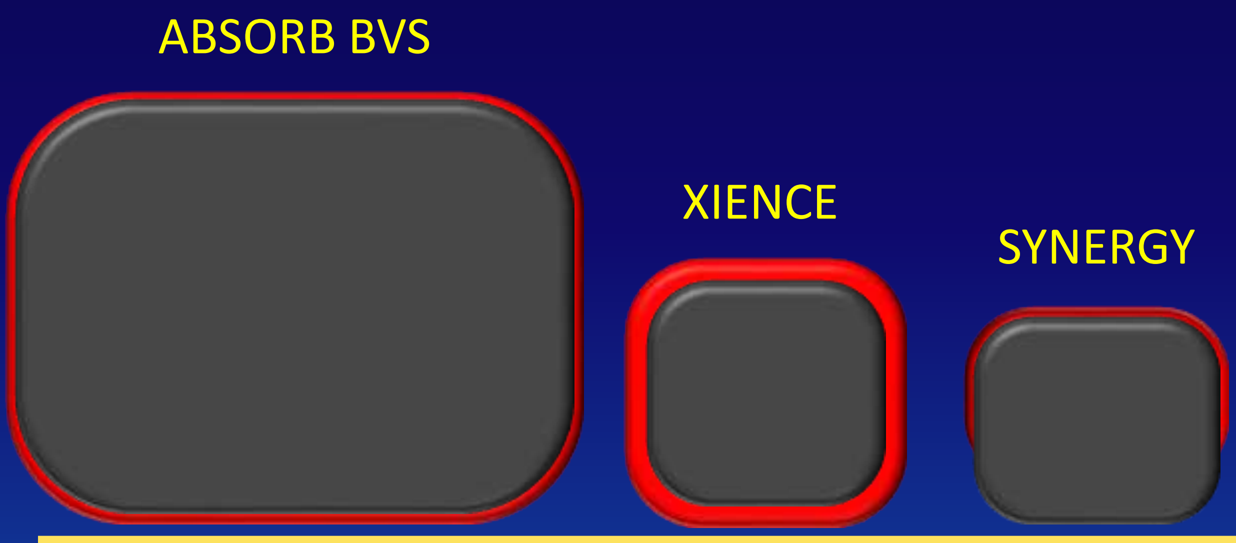




Beginning dismantling of stent struts at 180 days

What is the Stent of Choice for Today's Complex PCI?

Current BRS have significantly greater strut thickness and cross sectional area than metallic stents



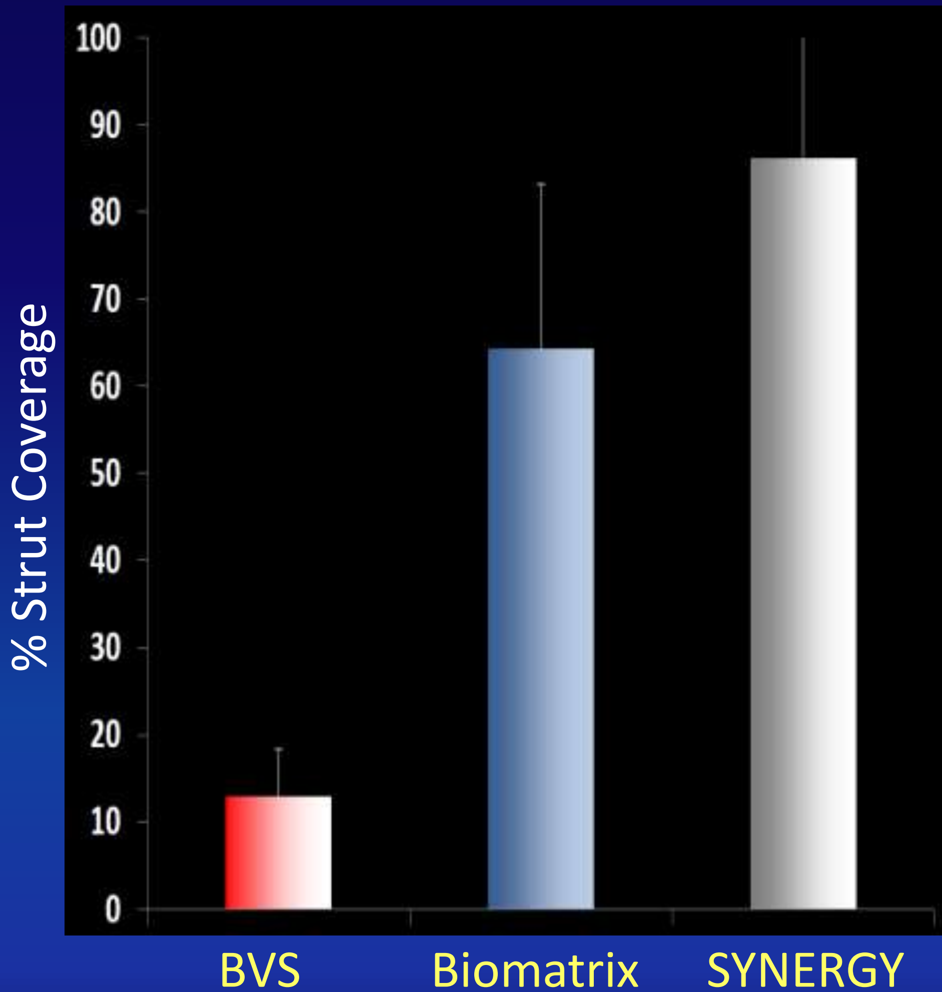
Strut Thickness: 150 µm	81µm	74µm
Coat Thickness: 3 µm/side	8 µm/side	3-4 µm

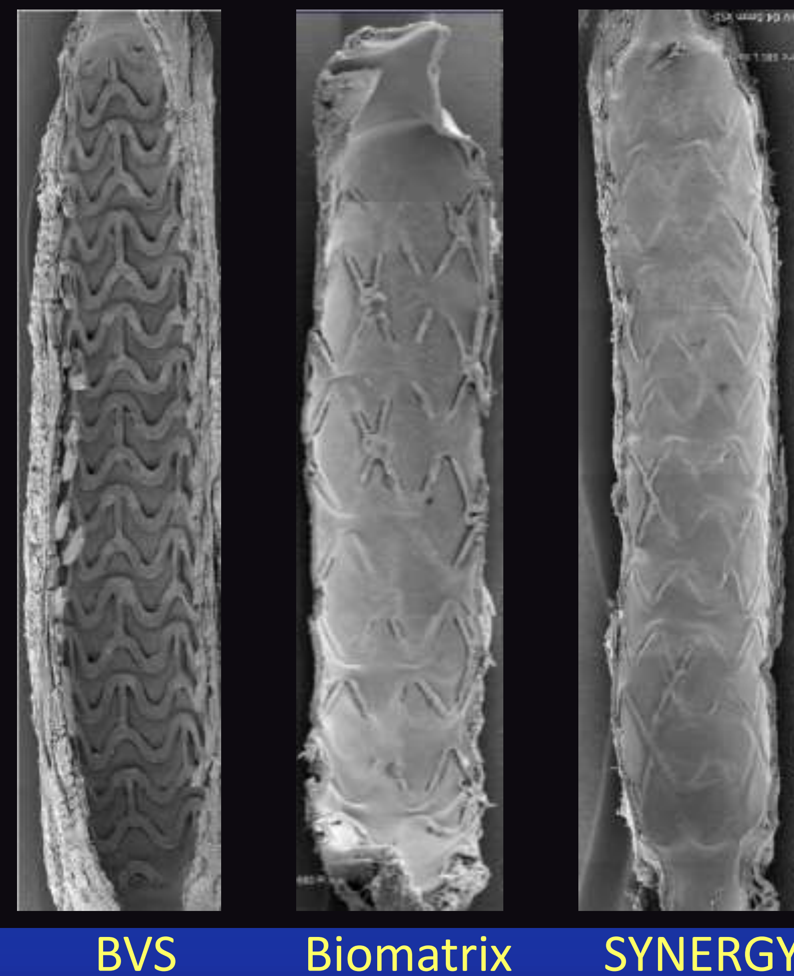
Greater strut thickness / cross sectional area hinders acute performance and may result in less optimal healing, increased risk of peri-procedural MI, and ST

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

Device Thrombosis to 1 Year

	Absorb (N=1322)	Xience (N=686)	p-value
Device Thrombosis (def/prob)	1.54%	0.74%	0.13
- Early (0 to 30 days)	1.06%	0.73%	0.46
- Late (> 30 to 1 year)	0.46%	0.00%	0.10
- Definite* (1 year)	1.38%	0.74%	0.21
- Probable (1 year)	0.15%	0.00%	0.55

*One "definite ST" in the Absorb arm by ITT was in a pt that was treated with Xience

Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials

Salvatore Cassese*, Robert A Byrne*, Gjin Ndrepepa, Sebastian Kufner, Jens Wiebe, Janika Repp, Heribert Schunkert, Massimiliano Fusaro, Takeshi Kimura, Adnan Kastrati

Lancet. 2016.

A Target lesion revascularisation

	BVS Events	BVS Total	EES Events	EES Total	Weight (%)	Fixed-effects odds ratio (95% CI)
ABSORB China	7	238	7	237	13·2	1·00 (0·34–2·88)
ABSORB II	4	335	3	166	5·9	0·64 (0·13–3·12)
ABSORB III	42	1313	19	677	51·6	1·14 (0·67–1·95)
ABSORB Japan	7	265	5	133	10·1	0·68 (0·20–2·31)
EVERBIO II	8	78	11	80	16·3	0·72 (0·28–1·87)
TROFI II	2	95	1	96	2·9	1·98 (0·20–19·29)
Overall	**70**	**2324**	**46**	**1389**	**100**	**0·97 (0·66–1·43)**

Heterogeneity: χ^2=1·69, df=5; p=0·89; I^2=0%
Test for overall effect: Z=0·16; p=0·87
Random-effects odds ratio 0·97 (95% CI 0·66–1·43)

B Definite or probable stent thrombosis

	BVS Events	BVS Total	EES Events	EES Total	Weight (%)	Fixed-effects odds ratio (95% CI)
ABSORB China	1	238	0	232	3·1	7·21 (0·14–363·23)
ABSORB II	3	335	0	166	8·2	4·49 (0·04–49·92)
ABSORB III	20	1301	5	675	69·1	1·89 (0·82–4·34)
ABSORB Japan	4	262	2	133	16·5	1·02 (0·18–5·58)
EVERBIO II	0	78	0	80		Not estimable
TROFI II	1	95	0	96	3·1	7·47 (0·15–376·35)
Overall	**29**	**2309**	**7**	**1382**	**100**	**1·99 (1·00–3·98)**

Heterogeneity: χ^2=1·90, df=4; p=0·75; I^2=0%
Test for overall effect: Z=1·96; p=0·05
Random-effects odds ratio 1·99 (95% CI 1·00–3·98)

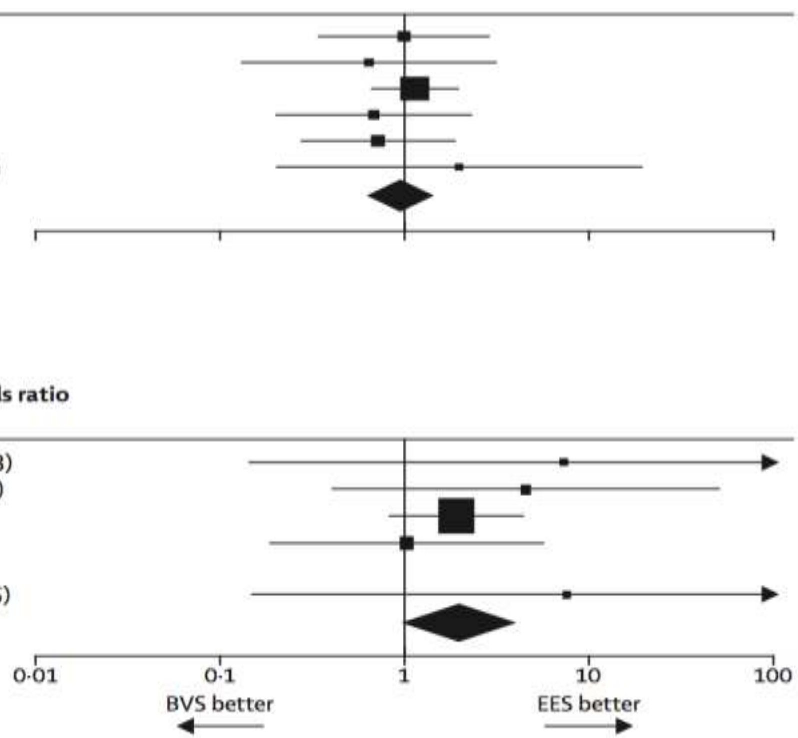
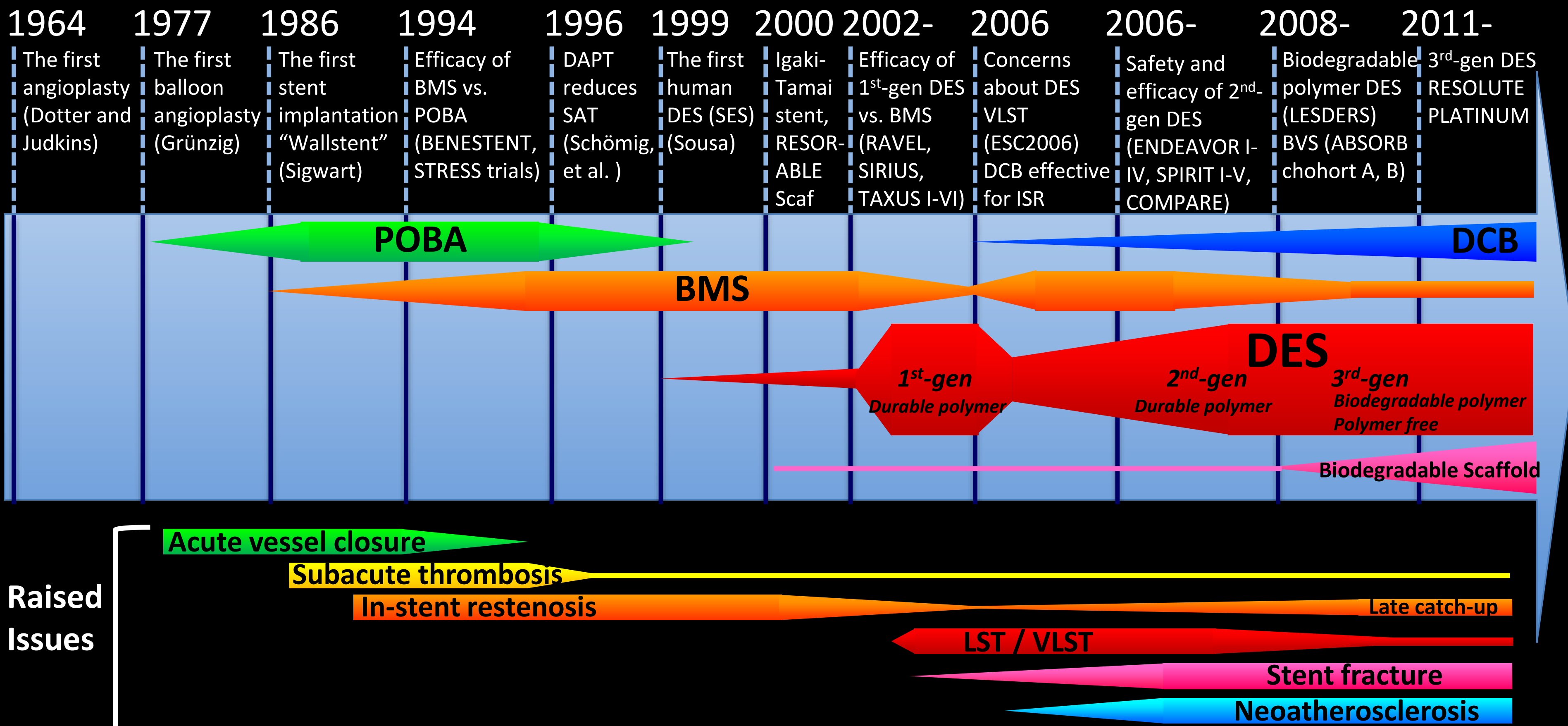


Figure 2: **Risk estimates of primary outcomes for BVS versus EES**
Forest plots show results for target lesion revascularisation (A) and definite or probable stent thrombosis (B). BVS=bioresorbable vascular scaffold. df=degrees of freedom. EES=everolimus-eluting stent.

History of Percutaneous Coronary Intervention



	Balloon Angioplasty	BMS	DES	BRS
Success rate	70-85%	>95%	>95%	>95%
Restenosis	40-45%	20-30%	<10%	<10%
Early Thrombosis (≤30 days)	3-5%	1-2%	1-2%	1-2%
Late Thrombosis (>30 days, ≤1y)	NA	<0.5%	1%	>2%
Very Late Thrombosis (>1y)	NA	≈0%	1-2%	?

Summary

- Bioresorbable vascular scaffolds (BVS) take a long time to degrade (at least 3 years) but show a unique ability to allow for lumen enlargement in a porcine coronary model, thus distinguishing this device from metallic stents.
- Major issues were identified by histopathological evaluation of BRS on a preclinical level:
  - Bioresorption of polymeric BRS is associated with increased inflammatory reaction.
  - Acute Thrombogenicity is greater in current BRS compared to contemporary DES.
  - Re-endothelialization of stent struts is delayed with current bioresorbable EES technology when compared to contemporary metallic EES.
- Large scale randomized clinical trials suggest reasonable restenotic efficacy in BRS with increased risk of ST. It remains to be seen whether long term data versus metallic DES show a definite benefit
- Absorb may be a reasonable option in patients with larger vessels able to tolerate long-term DAPT
- BRS platforms with thinner struts and improved healing characteristics are currently in development and likely will improve outcomes
- BRS remains a revolutionary technology which will change the future of the way PCI is performed

CVPath

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Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Liang Guo, PhD
Harry Davis, PhD
Renu Virmani, MD

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