Is BRS Free From Stent Thrombosis? Lessons From Pathologic Findings

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TCTAP
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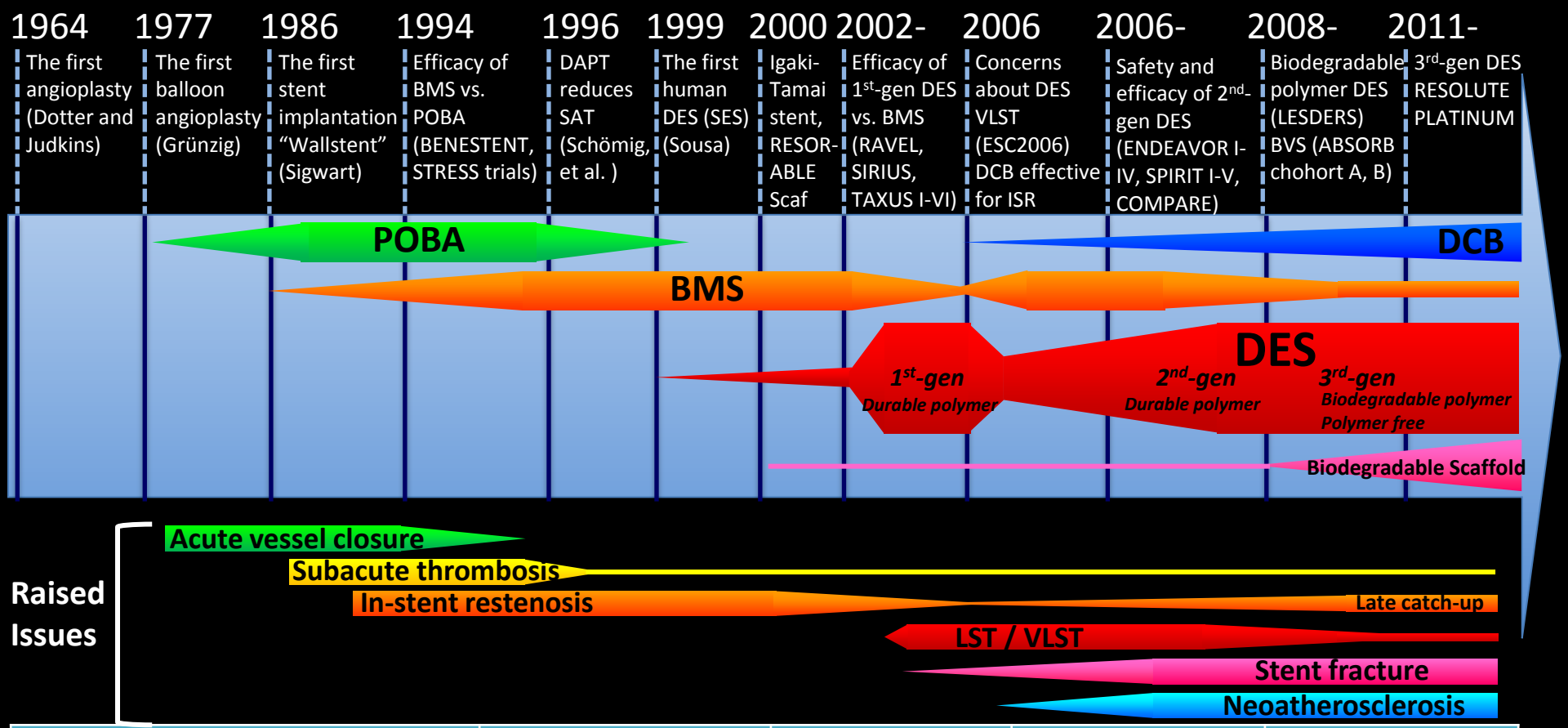
Conflict of Interest Declaration

- 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	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%	?

1st Generation DES: Expectation Versus Reality

- DES were created to prevent excessive neointimal thickening which was the primary cause of increase target lesion revascularization
  - milestone event in interventional cardiology

"… the sirolimus-eluting stent has achieved the delicate balance of preserved safety and improved efficacy…"

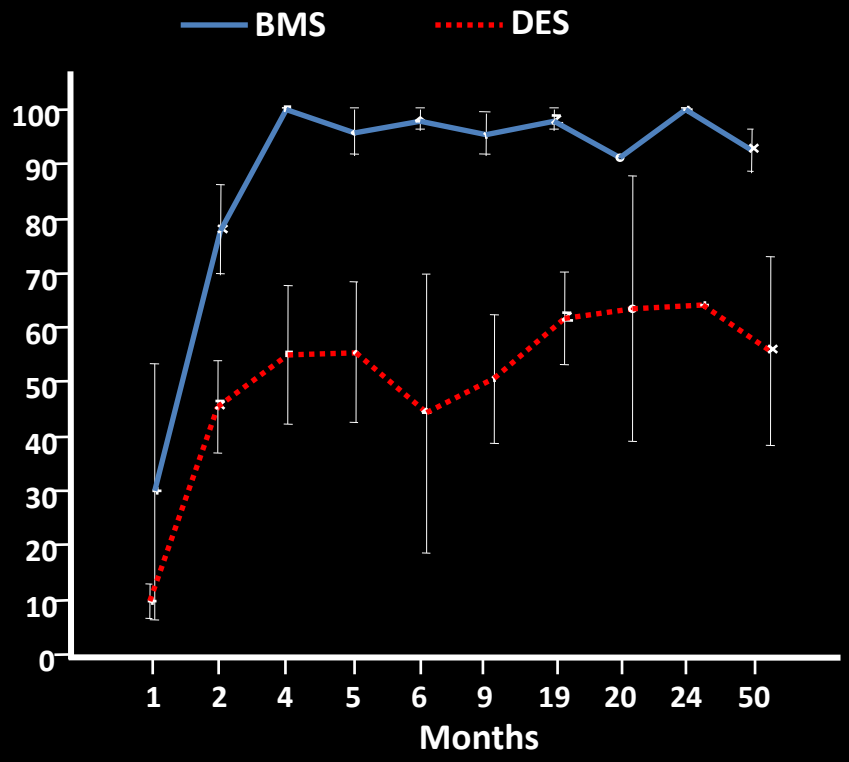
NEJM October 2, 2003 Volume 349, p. 1315-1323.

"Use of the paclitaxel-eluting stent was safe, with no excess risks apparent..."

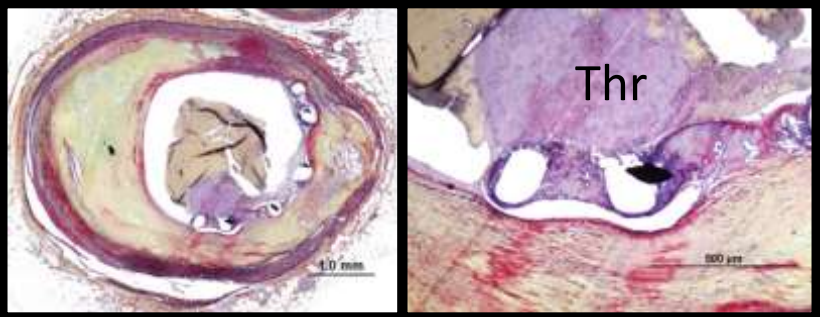
NEJM January 15, 2004 Volume 350, p. 221-231.

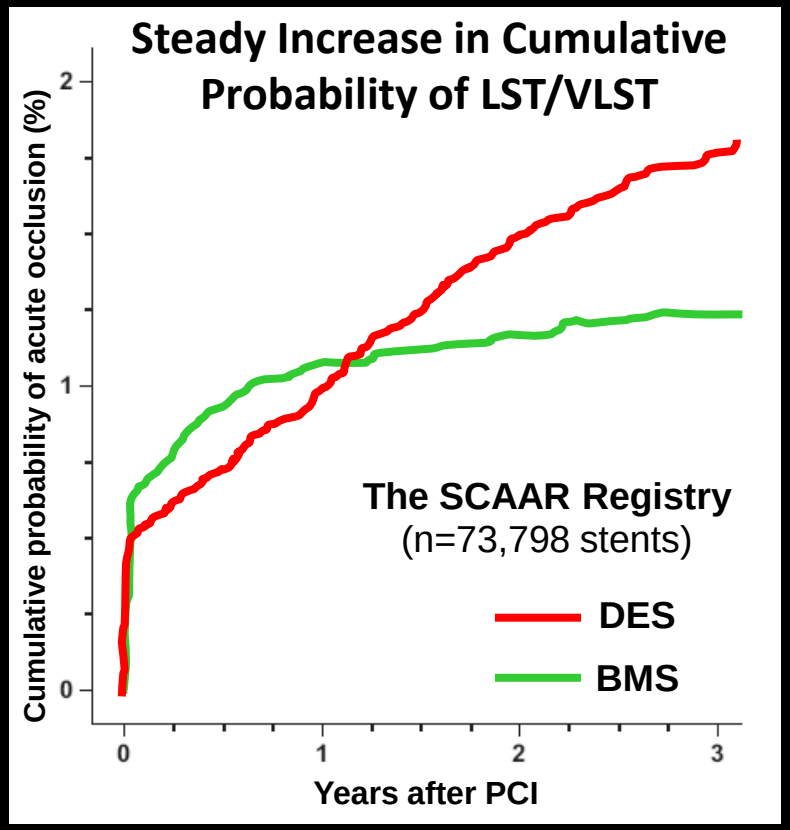
Endothelialization and Stent Thrombosis (LST/VLST) Following 1st-generation DES vs BMS

Mean % Endothelialization



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





Lagerqvist, et al. Circ Cardiovasc Intervent 2009

Annual Rate of LST/VLST

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

Wenaweser P, et al. J Am Coll Cardiol 2008;52:1134-40.
Kimura T, et al. Circulation 2012;125:584-591.

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

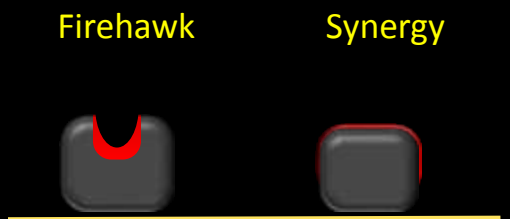
	Biomatrix	Nobori
Strut Thickness	120 µm	125 µm
Coat Thickness	10 µm	20 µm

Fully Bioresorbable Stents

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

Second Gen

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

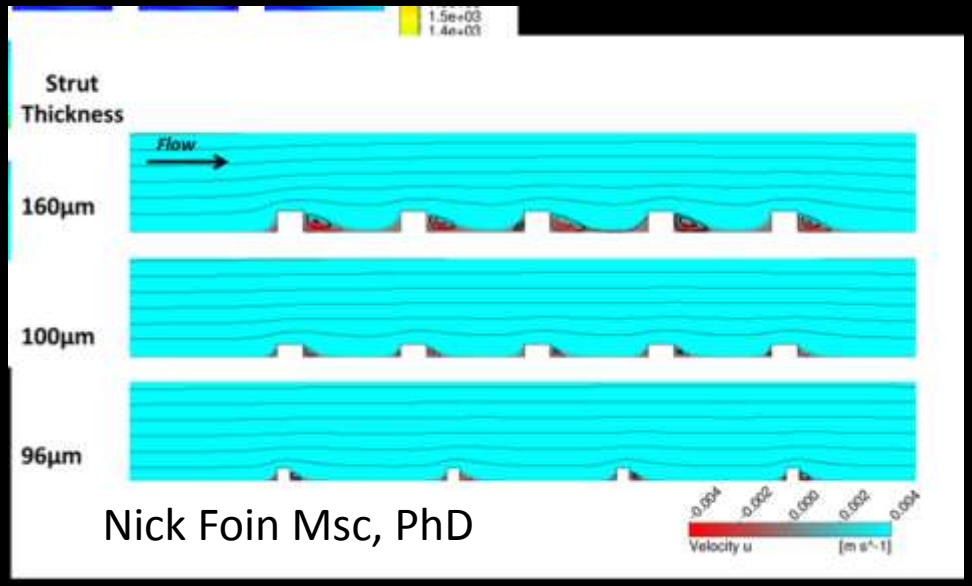


	Firehawk	Synergy
Strut Thickness	86µm	74µm
Coat Thickness	10 µm	4 µm

	ART (bare bioresorbable scaffold)
Strut Thickness	170 µm
Coat Thickness	NA

Where Are We with BRS?

- Mechanical properties of polymeric scaffolds are controlled by various parameters
- Currently larger strut width/thicknesses are required to achieve comparable mechanical properties to metallic platforms though next gen devices with 100uM thickness are in development
- When we evaluate BRS pathologically we need to keep in mind how these structural limitations affect vascular responses to BRS



Nick Foin Msc, PhD

Contemporary DES Platforms

Strut and Coating Thickness In Perspective

Durable Polymer Coated Stents		Bioabsorbable Polymer Coated Stents			Bioabsorbable Stent
Xience CoCr-EES Promus PtCr-EES	Resolute CoNi-ZES	Biomatrix 316L-BES	Nobori 316L-BES	SYNERGY PtCr-EES	BVS PLLA-EES

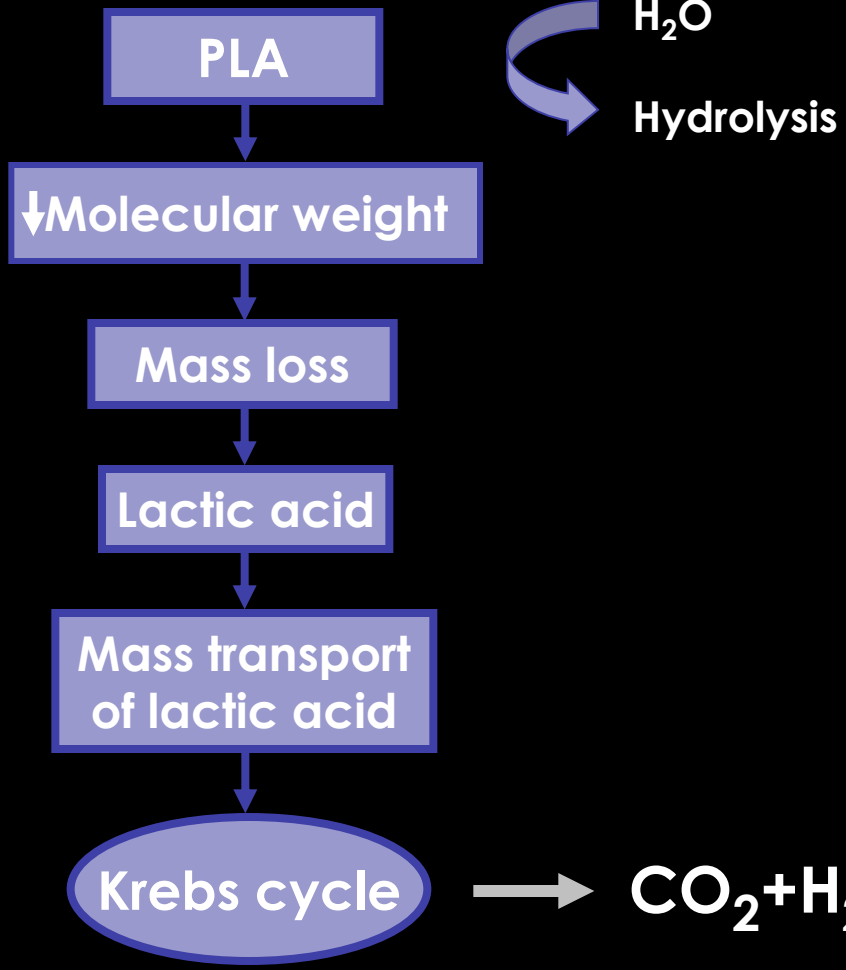
Strut Thickness

81µm	89µm	120µm	125µm	74µm	150µm

Polymer Coating

Conformable 7-8µm / side	Conformable 6µm / side	Abluminal 11µm	Abluminal 20µm	Abluminal 4µm	Conformable 3µm / side

PLA Metabolic Pathway



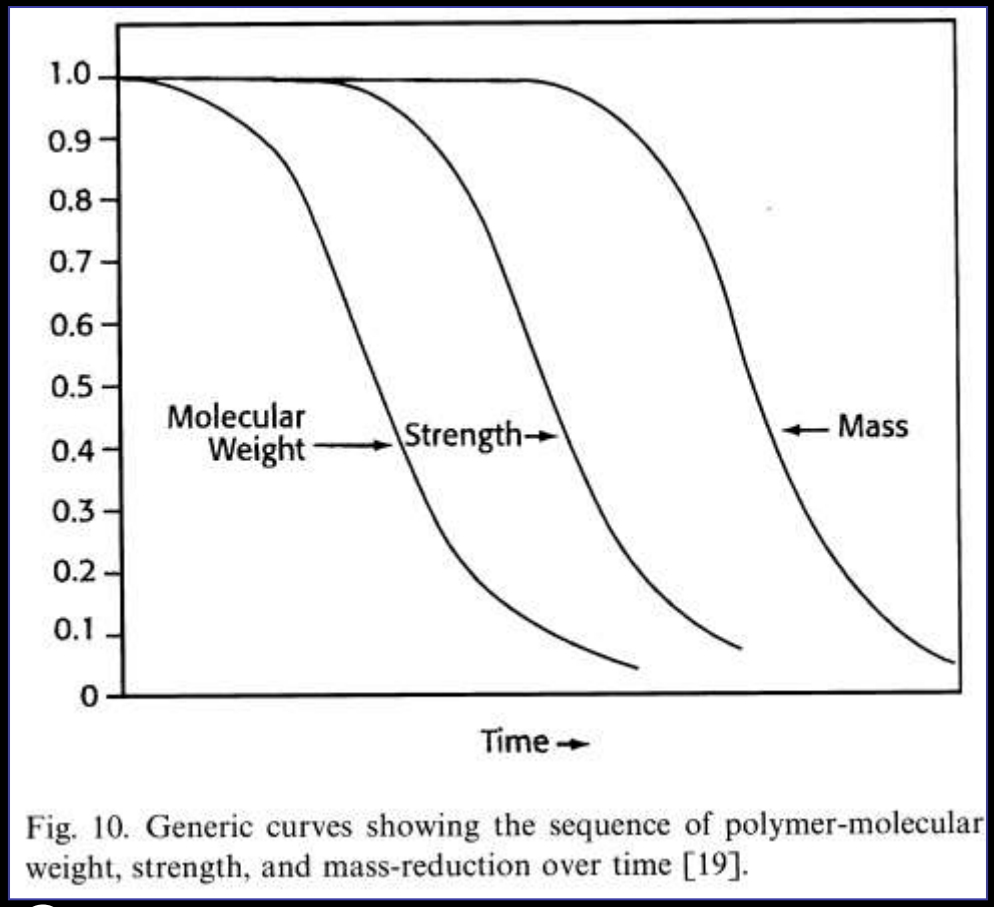
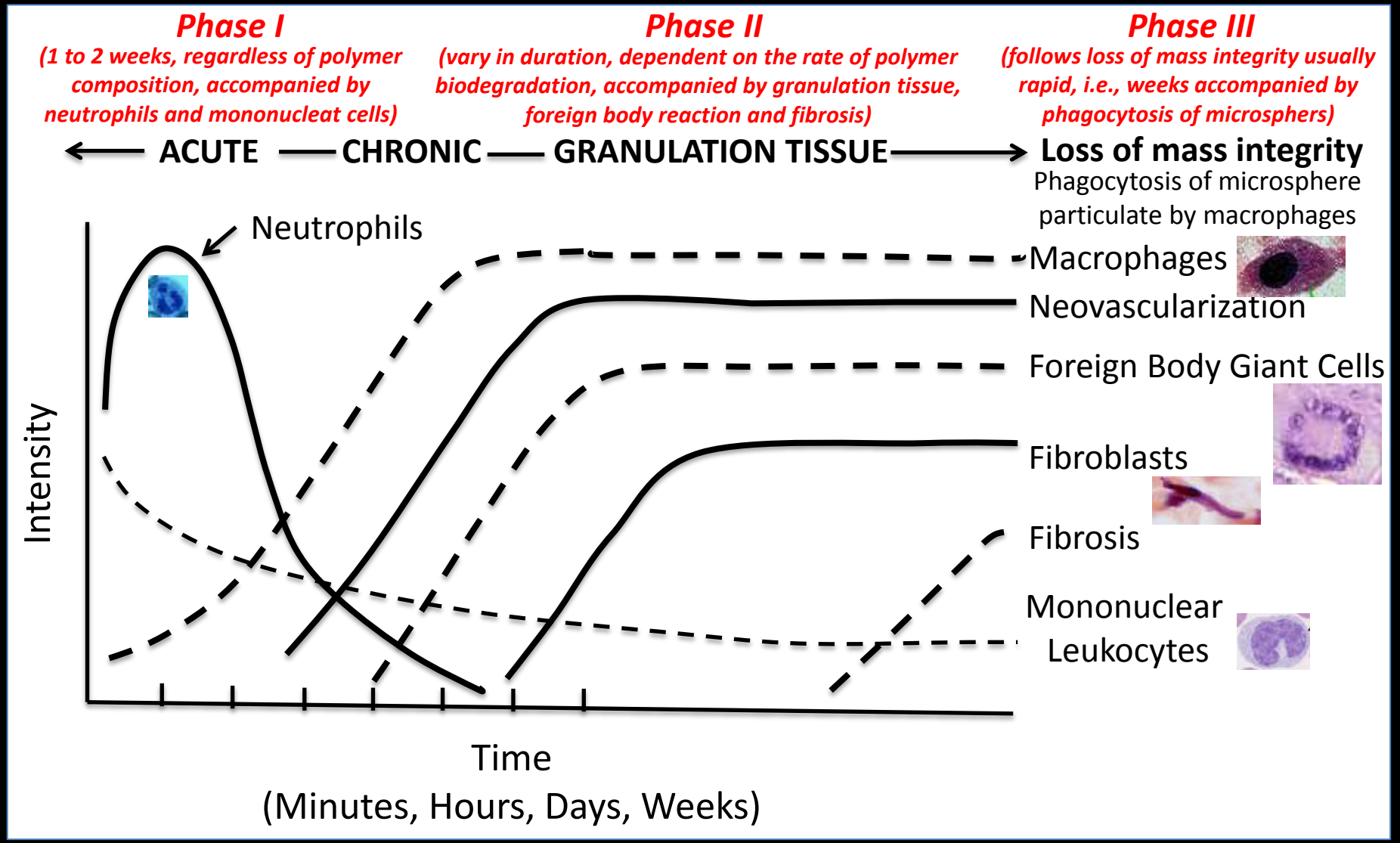


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

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.

Assessment for degradation of bioresorbable scaffolds (BRS)

- Histology (Immunohistochemical staining)
- Imaging study: Intravascular imaging (Optical coherence tomography; OCT), Computed Tomography (CT)
- Biochemical analysis

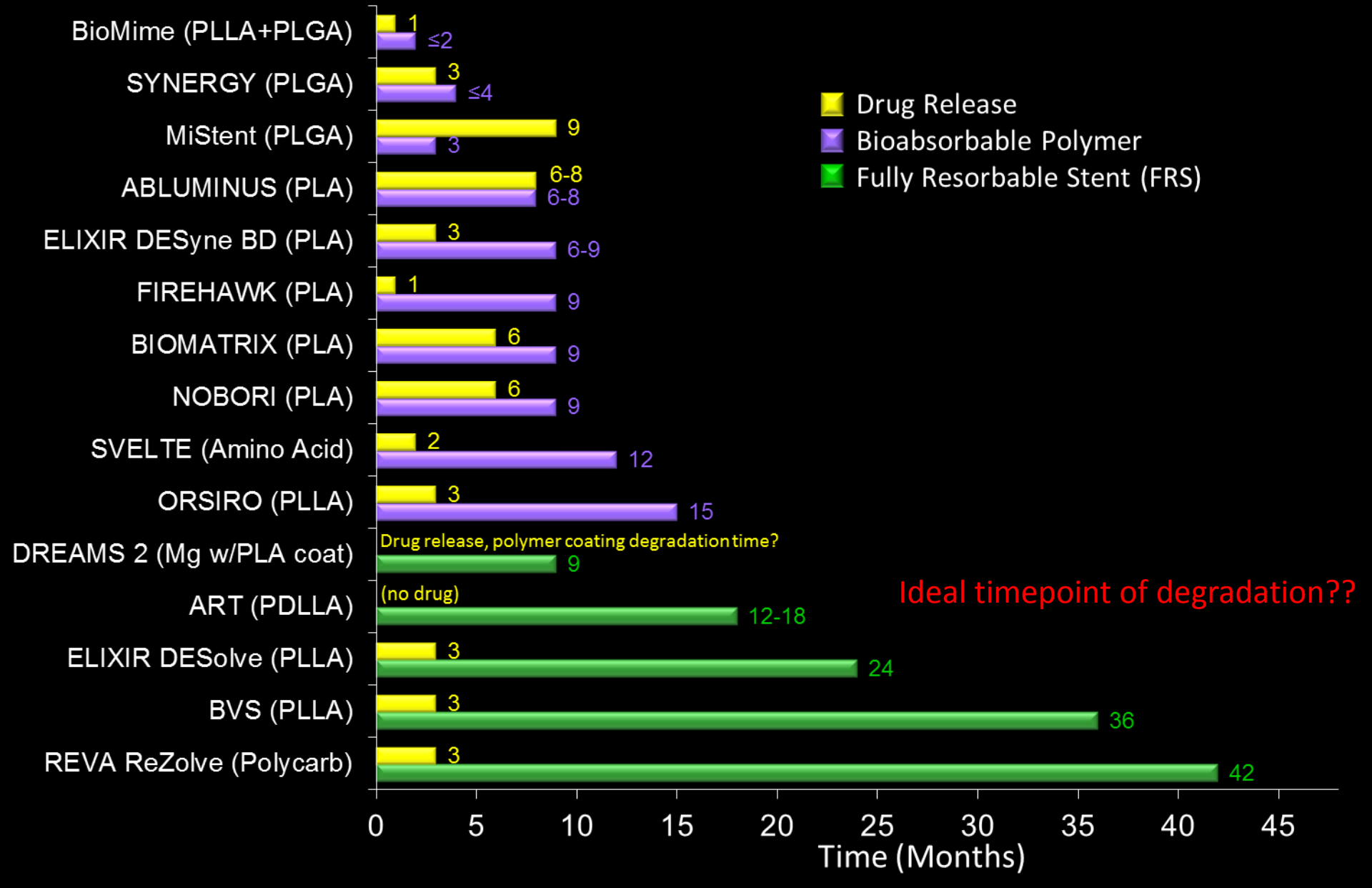
- *Measurement time points may need to be modified to better capture critical safety parameters*
  - ✓ Early time point: prior to degradation (when BRS is still intact, 4-5 time points within this period)
  - ✓ During degradation (yearly assessment)
  - ✓ Late time point: after complete resorption

- *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*

Time Course For Polymer Bioabsorption

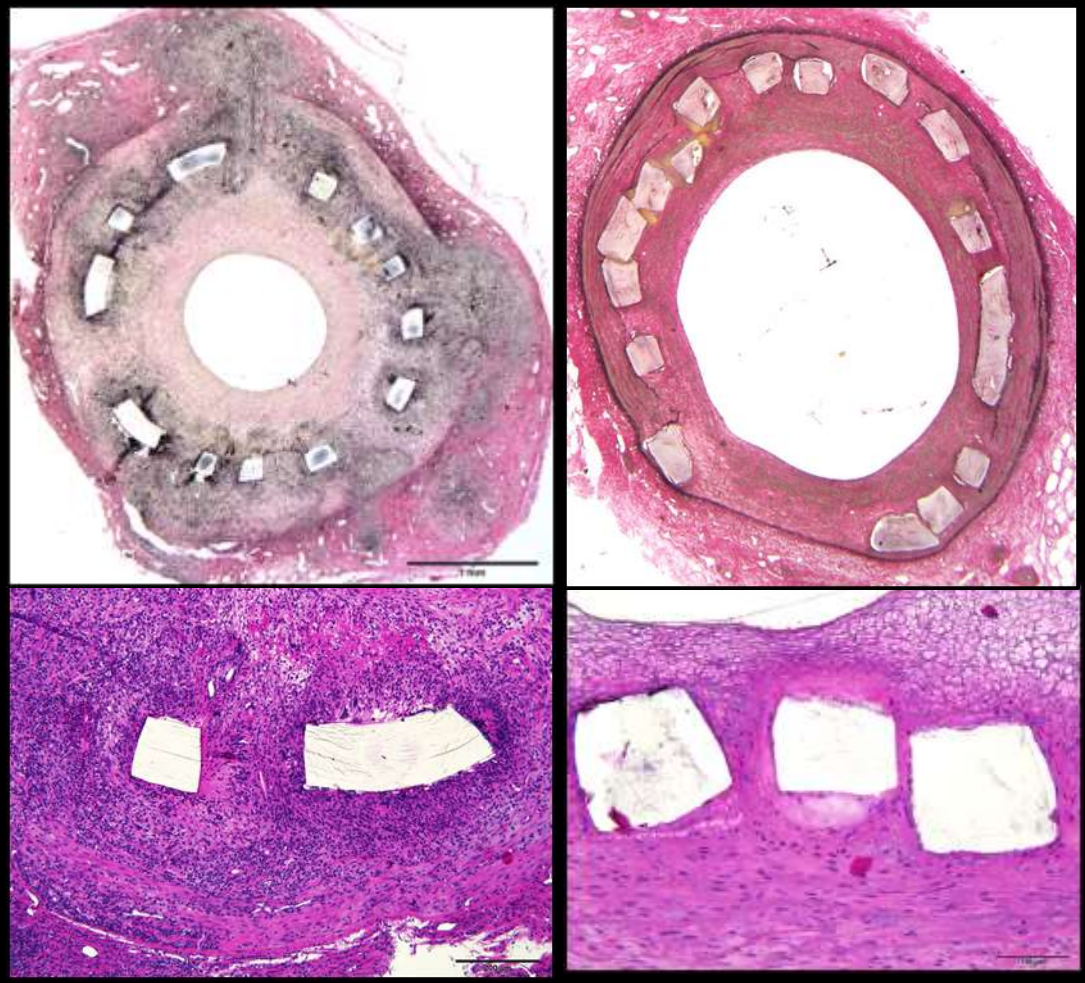
Not all bioabsorbable technologies are the same



Inflammatory reaction following implantation of BRS B in porcine arteries

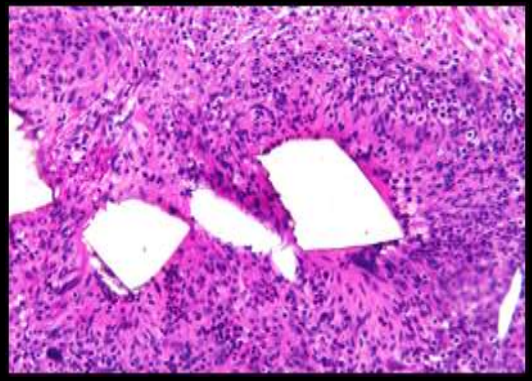
28 days

90 days

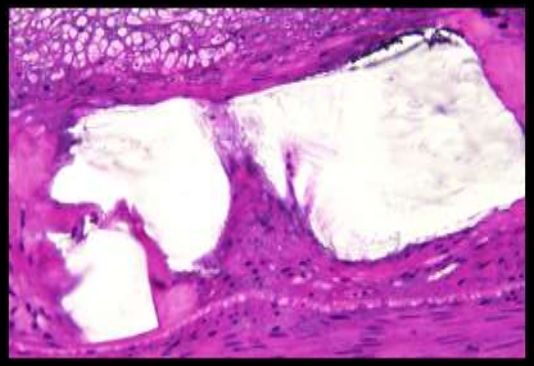


Discontinuities of bioresorbable scaffold strut

28 days

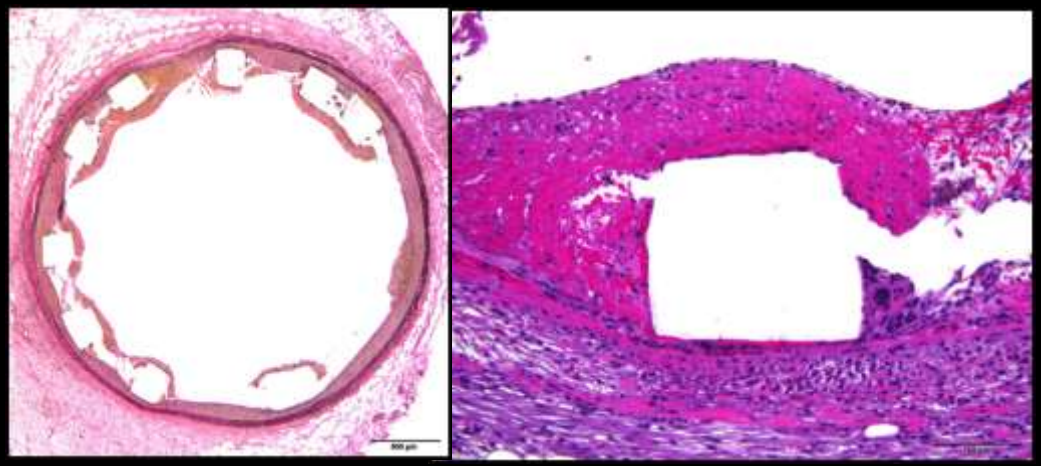


90 days

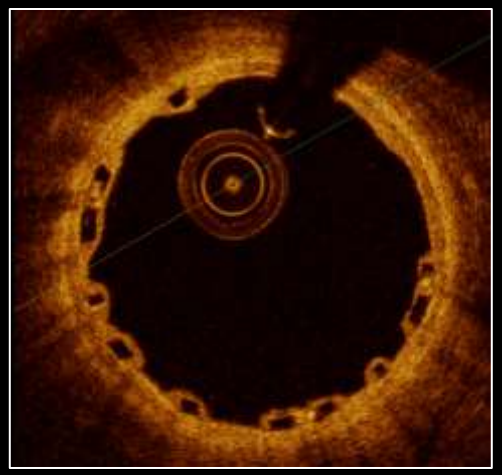


Pathological/OCT assessment following implantation of BRS D in healthy porcine arteries at 7 days

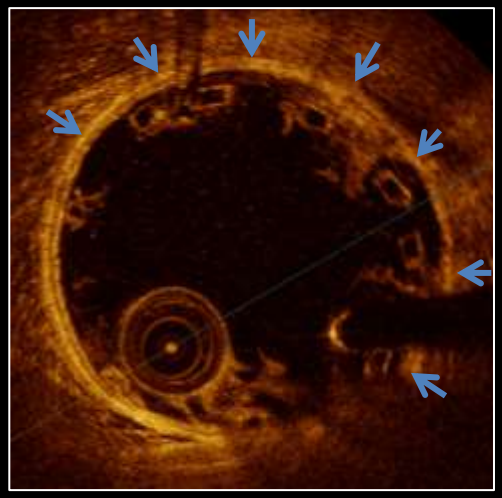
Histology



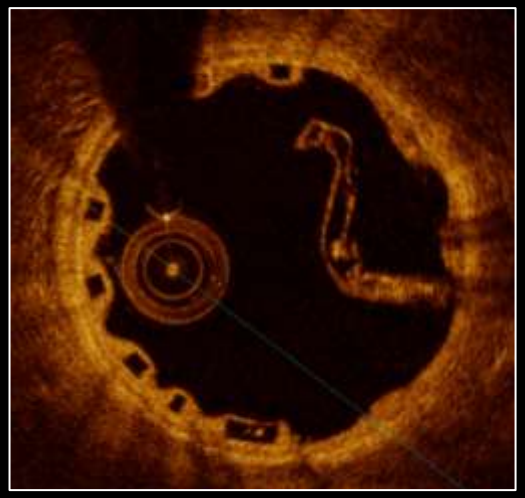
OCT



Scaffold Malapposition



Scaffold Fracture



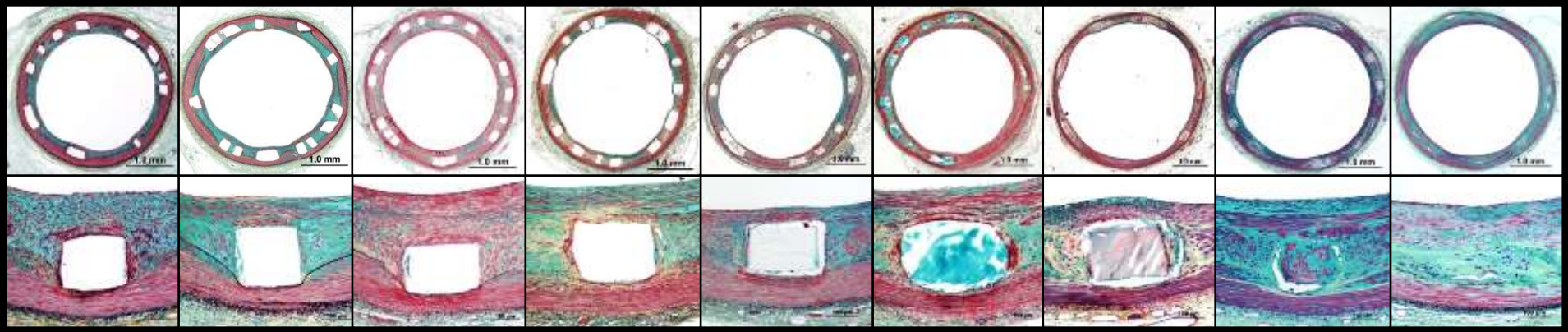
BVS (Cohort B) vs. XIENCE V in Porcine Coronary Arteries from 1- to 42-months

(Movat pentachrome)

36-42 months for complete reabsorption

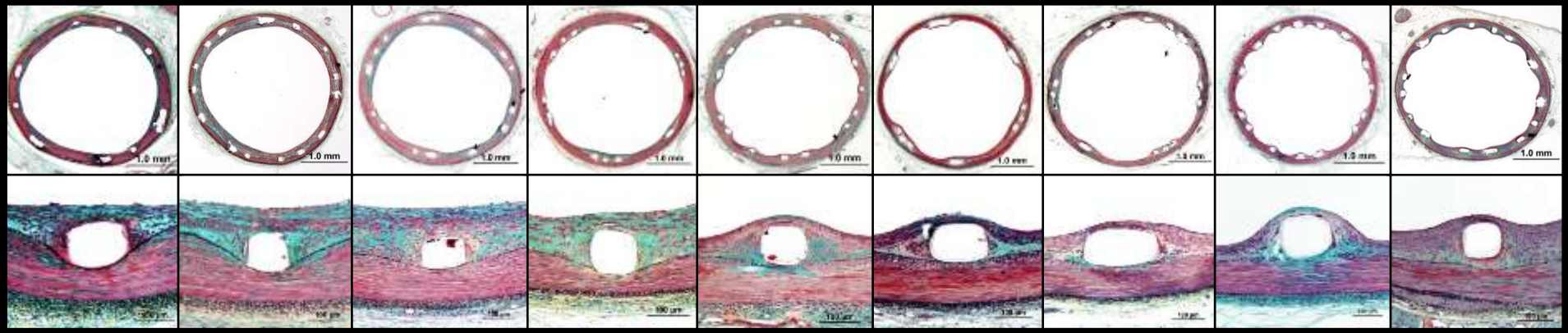
BVS

1 month | 3 months | 6 months | 12 months | 18 months | 24 months | 30 months | 36 months | 42 months



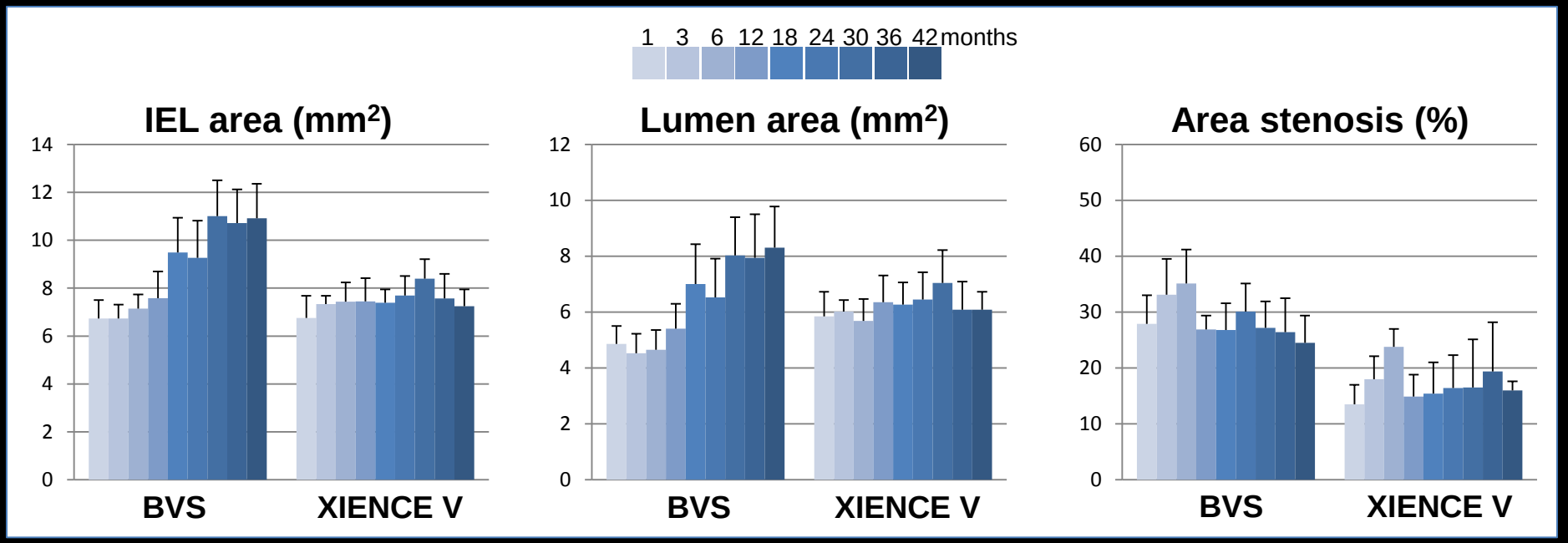
XIENCE V

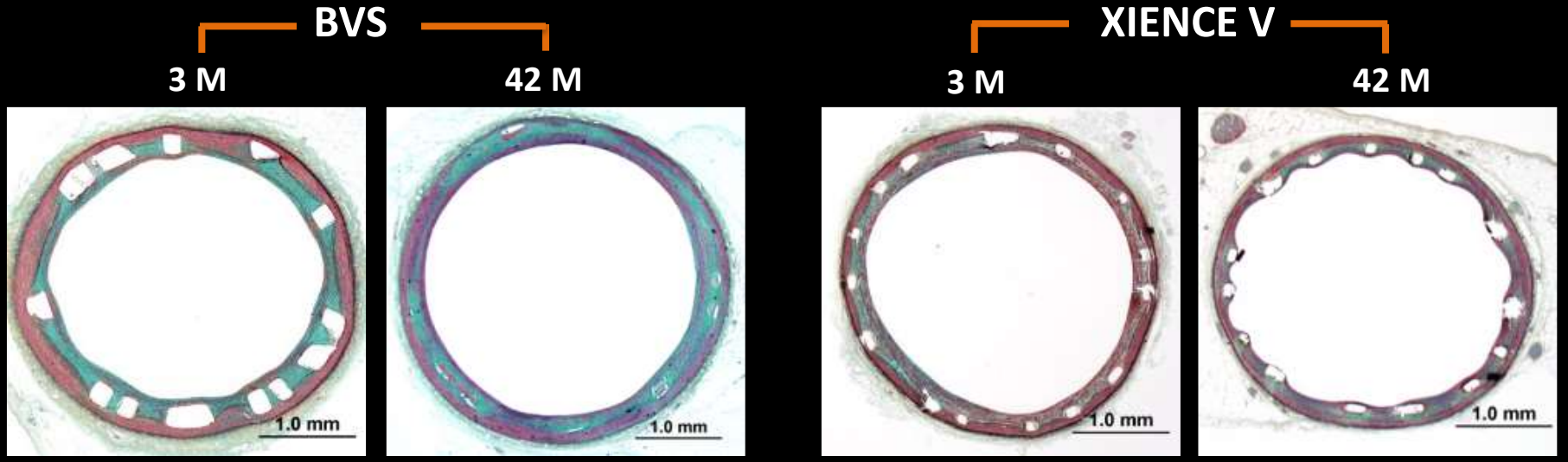
1 month | 3 months | 6 months | 12 months | 18 months | 24 months | 30 months | 36 months | 42 months



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

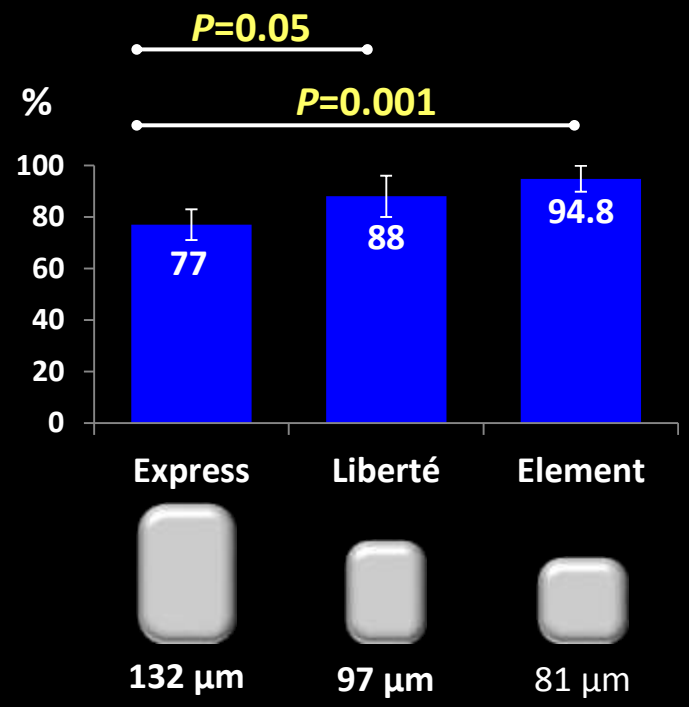
Impact of Strut Thickness on Healing

Delayed strut coverage and healing with thicker struts

Uncovered struts predictive of late stent thrombosis

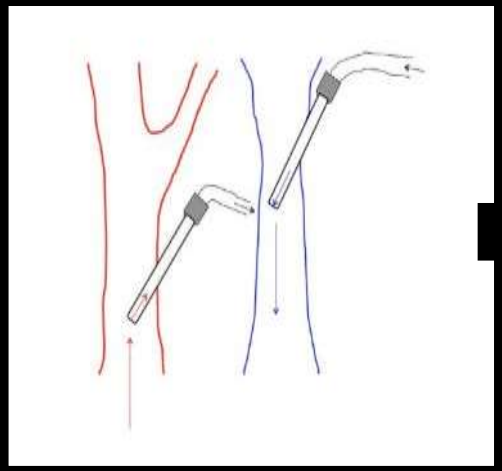
Finn A, Joner M et al, Circulation 2007;115:2435-2441

BMS Strut Coverage at 14 days in Rabbit

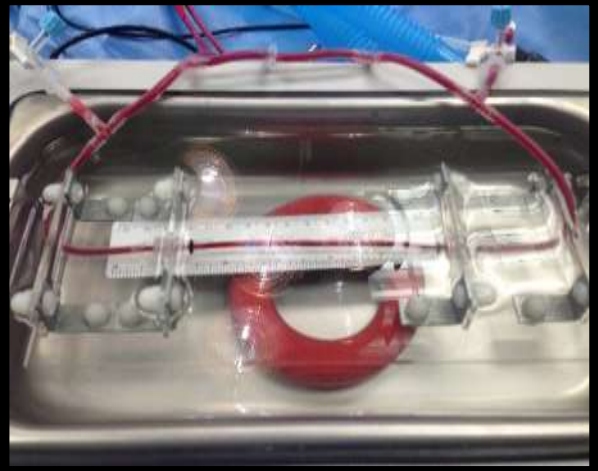


Soucy N, Feygin J et al, EuroIntervention. 2010 Nov;6(5):630-7

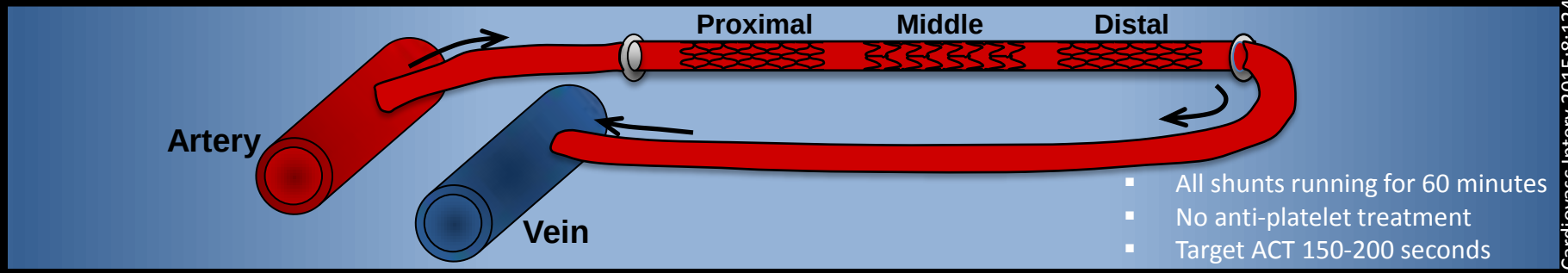
1. Porcine AV shunt: carotid-jugular using customized sheath

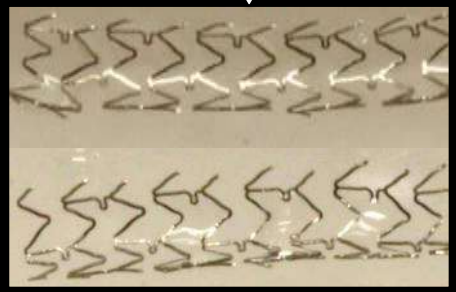


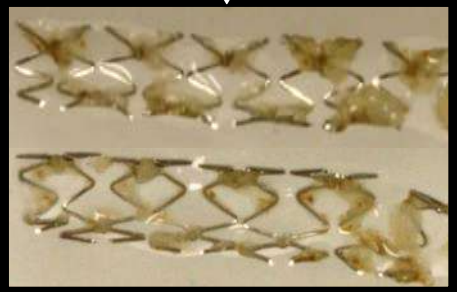
2. Arterialized flow using Sylgard tube



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

Platelet deposition by confocal microscopy of immunofluorescent staining (CD61/CD42b)

74 µm

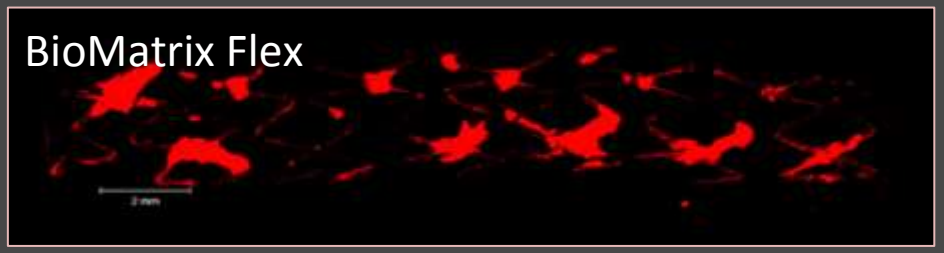
Synergy

150µm

Absorb BVS

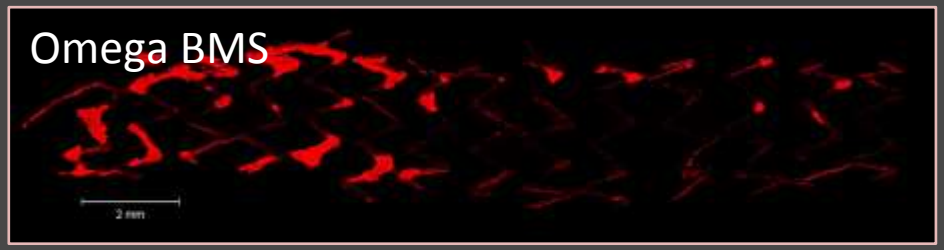
120 µm

BioMatrix Flex



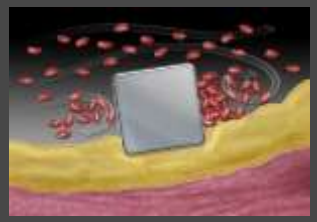
81 µm

Omega BMS

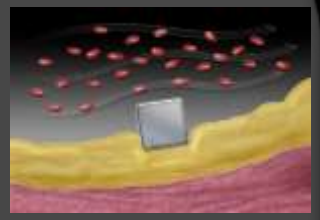


Platelet deposition was assessed by immunofluorescence staining for platelet marker CD61/CD42b as shown in red after 1 hour in ex-vivo pig AV shunt model

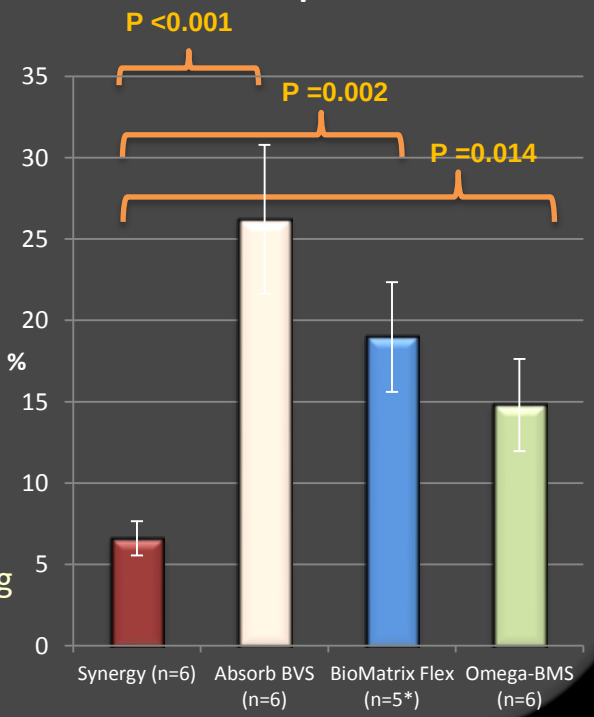
Thick Strut DES



Thin Strut DES



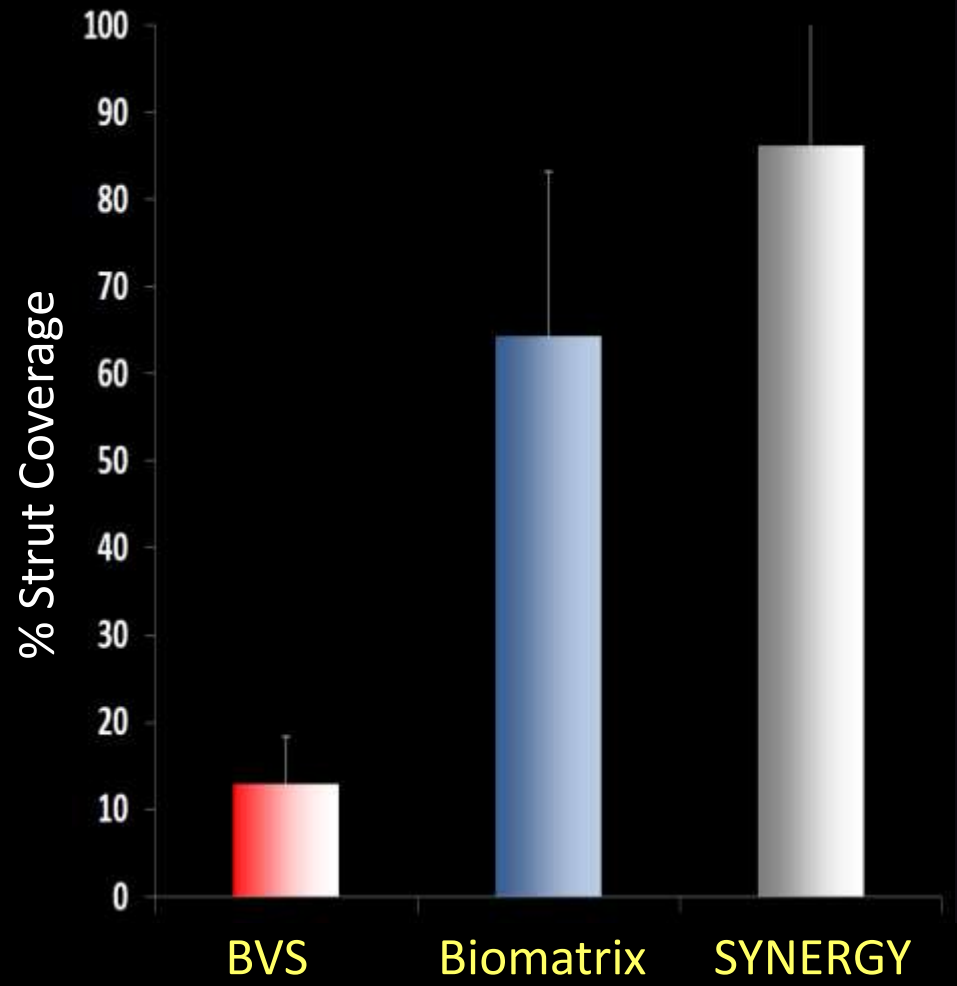
Mean positive area of adherent platelets

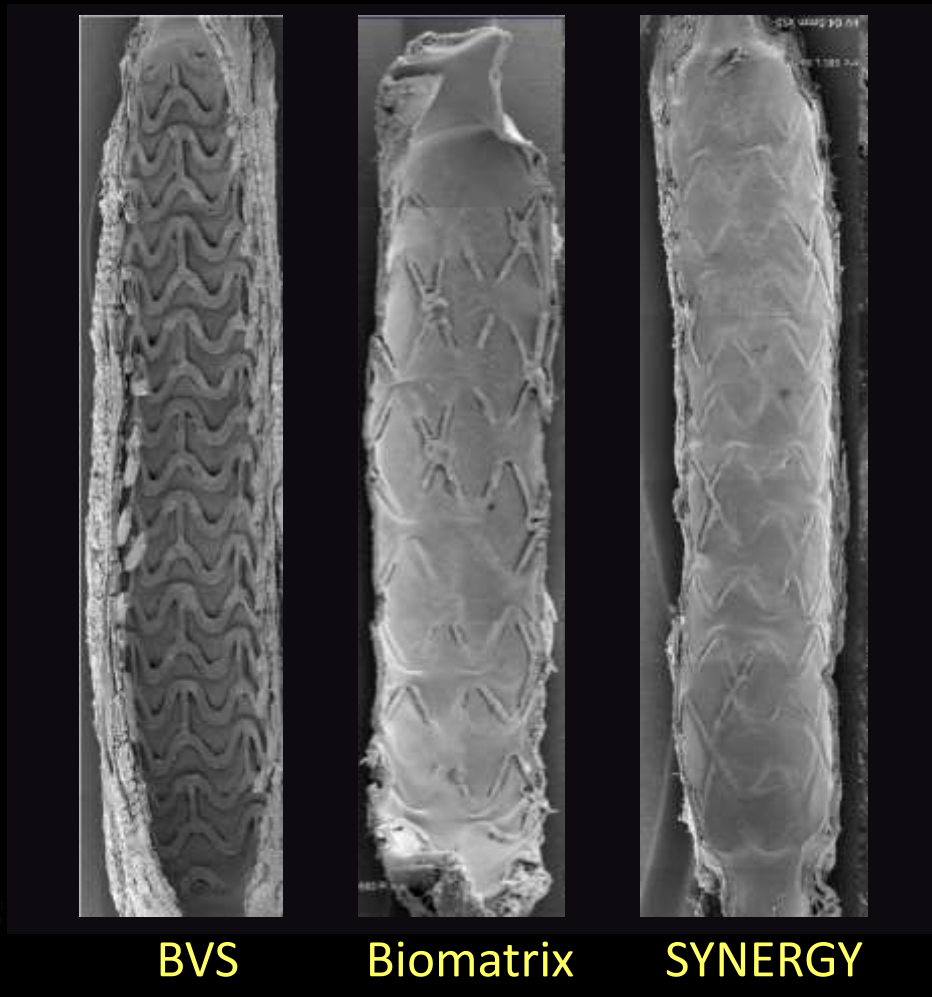


Thick vs. Thin Strut DES

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)

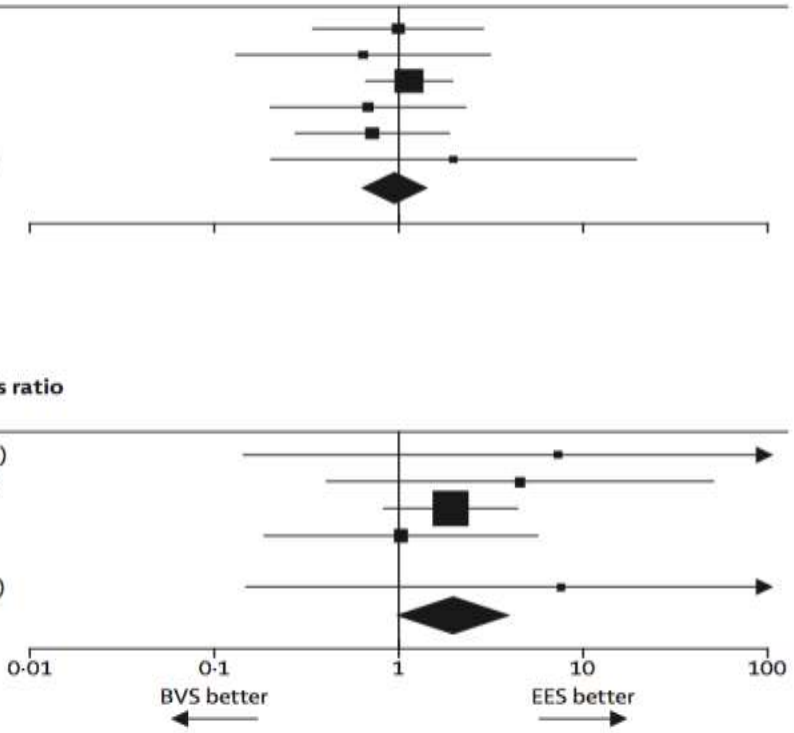
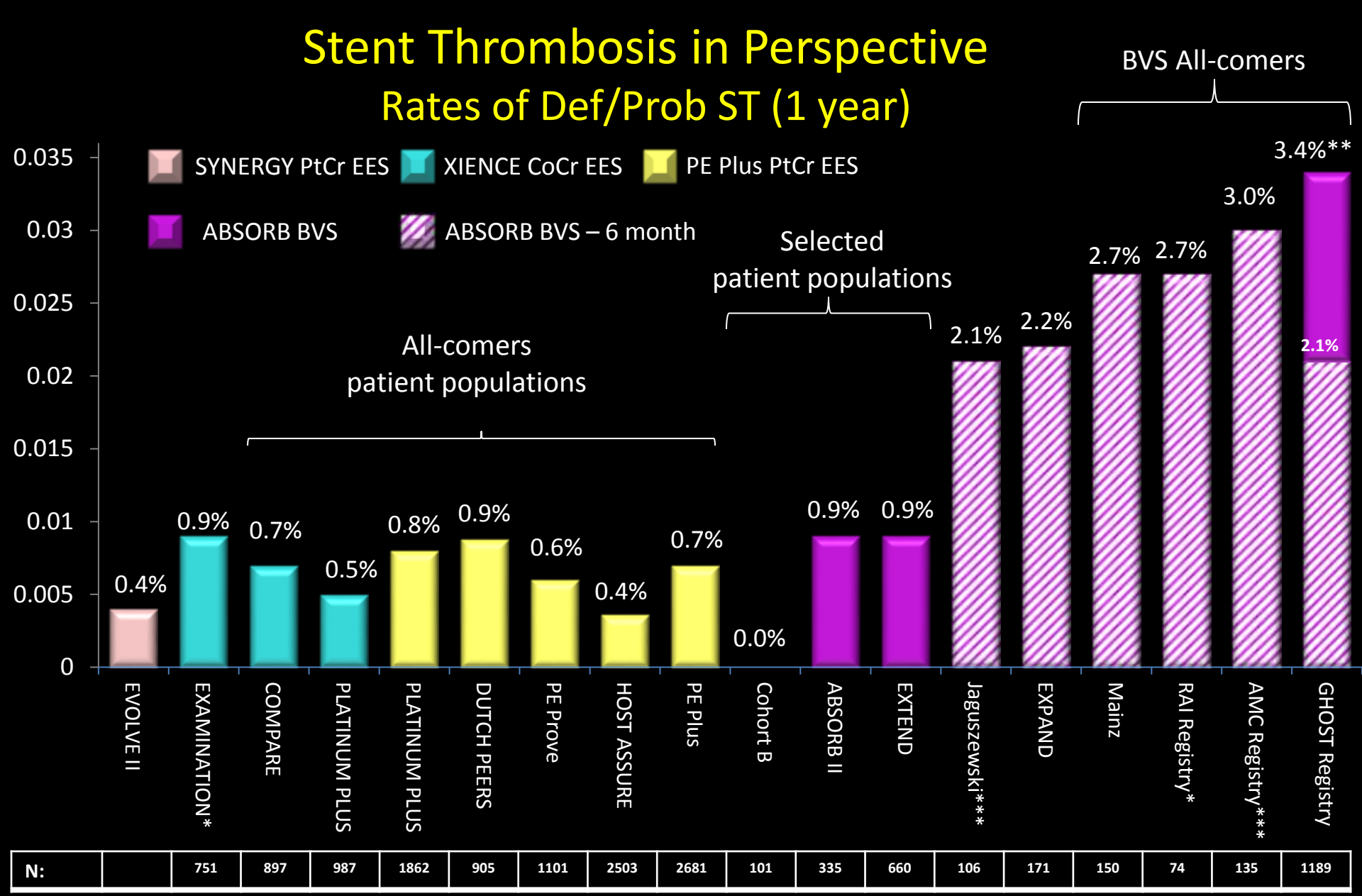


Figure 2: **Risk estimates of primary outcomes for BVS versus EES**
Forest plots show results for target lesion revascularisation (A) and definite or probable stent thrombosis (B). BVS=bioresorbable vascular scaffold. df=degrees of freedom. EES=everolimus-eluting stent.

Stent Thrombosis in Perspective

Rates of Def/Prob ST (1 year)



N:		751	897	987	1862	905	1101	2503	2681	101	335	660	106	171	150	74	135	1189

*STEMI Population, **Annualized Rate, ***Def ST Only

EVOLEV II: Keriakes AHA 2014. EXAMINATION: Sabate, et al. *Lancet* 2012. COMPARE: *Lancet* 2010 Jan 16;375(9710):201-9., RESOLUTE All-Comers: Serruys et al *N Engl J Med* 2010; 363:136-146., TWENTE: Clemens von Birgelen at TCT 2011. , DUTCH PEERS: Clemens von Birgelen at TCT 2013; PE Prove: Raul Moreno, MD PCR 2013. HOST Assure: Hyo-Soo Kim, MD, PhD ACC 2013; ABSORB Cohort B: Serruys, PW, ACC 2013; ABSORB EXTEND: Chevalier B. , EuroPCR 2013; Jaguszewski, et al. Clin Res Cardiol 2014. BVS EXPAND: Robert-jan van Guens. EuroPCR 2014. Mainz: Presented by Gori at ESC 2014. RAI: Ielasi, A. EuroPCR 2014. AMC Registry: Kraak, et al. *Eurointervention*2014. GHOST: Capodanno, et al. *EuroIntervention* 2014.; PLATINUM Plus, DUTCH PEERS, PE-PROVE and HOST ASSURE studied PROMUS Element stent (PtCr EES).

Results from different studies are not directly comparable. Information provided for educational purposes only.

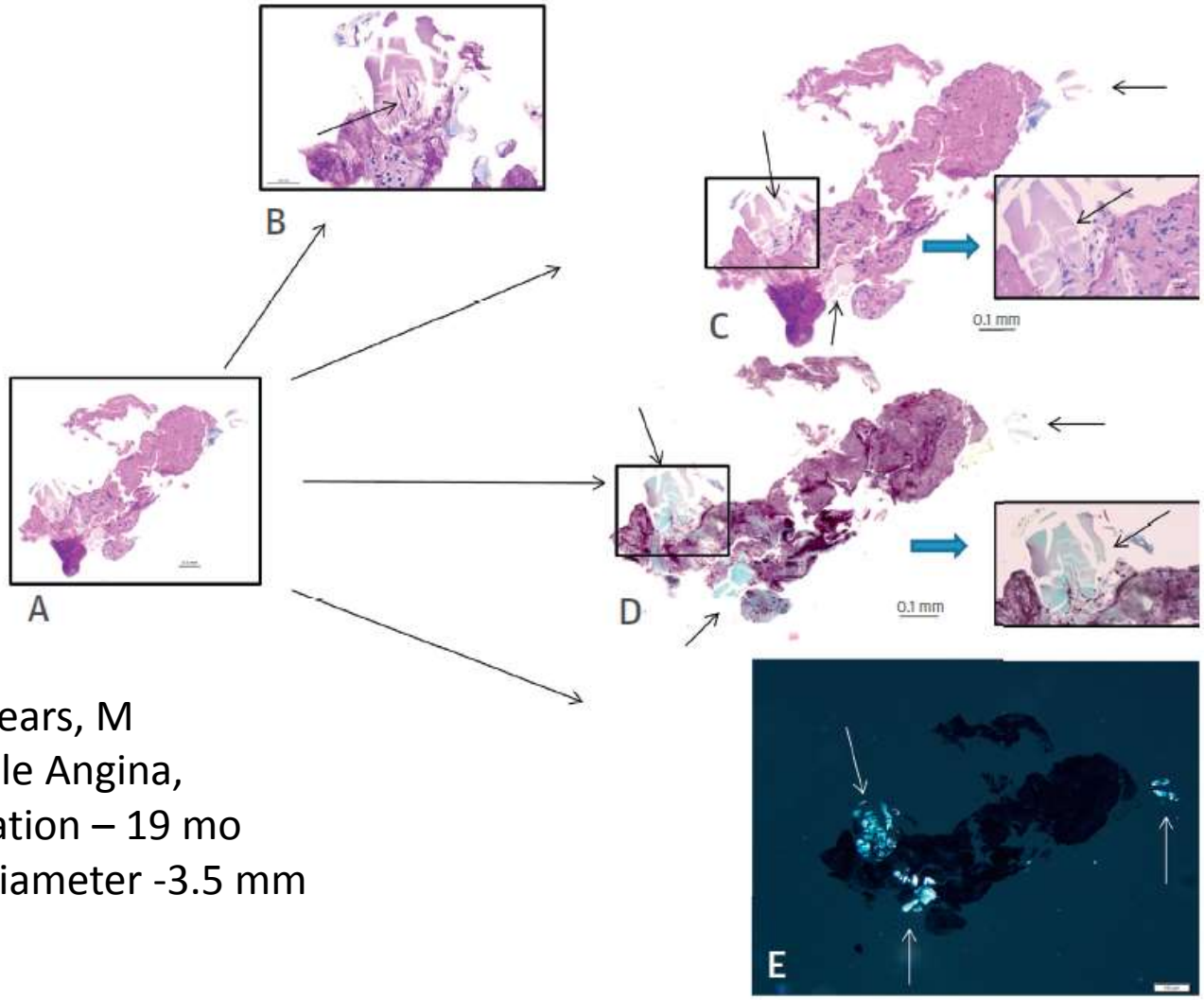
Case reports of late BRS failure

➢ Very Late Scaffold Thrombosis (VLST)

	Author	Age	Sex	Treatment	Duration	Symptom	DAPT
1	Karanasos A, et al.	57	Male	Absorb	24 months	Unstable angina	DAPT were discontinued 4 days prior to ST
2	Timmers L, et al.	39	Male	Absorb	18 months	Acute myocardial infarction	DAPT were discontinued after 12 months of implantation
3	Sato T, et al.	47	Male	Absorb	22 months	Atypical symptoms	Treated with antiplatelets and oral anticoagulation due to atrial fibrillation Antiplatelet therapy was discontinued after 6 months of implantation.
4	Kesavamoorthy B, et al.	42	Male	Absorb (3.0x28 mm)	15 months	Acute coronary syndrome	DAPT were discontinued 1 months prior to ST
5	Raber L et al.	68	Male	Absorb (3.0x18 mm)	44 month	Stable Angina	Aspirin monotherapy
6	Raber L et al.	53	Male	Absorb (3.0x18 mm)	19 months	Stable Angina	Aspirin monotherapy
7	Raber L et al.	55	Male	Absorb (2.5x28 mm)	21 months	NSTE-ACS	Aspirin & Prasugrel
8	Raber L et al.	55	Male	Absorb (3.5x12 mm)	19 month	Stable Angina	Aspirin & Prasugrel

➢ Malapposition / Aneurysm

	Author	Age	Sex	Treatment	Duration	Symptom
1	Cortese B, et al.	54	Male	Absorb (2.5x18 mm)	11 months	atypical effort angina
2	Cortese B, et al.	56	Female	Absorb (3.5 x12 mm)	2 months	None (scheduled PCI)
3	Nakatani S, et al.	83	Male	Absorb (3.0x18mm)	6 months	None (follow-up angiography)



55 years, M
Stable Angina,
Duration – 19 mo
Sc Diameter -3.5 mm

No post dilatation

Räber et al. JACC 2015 Oct 27;66(17):1901-14

When stained with hematoxylin and eosin, fibrin stains pink and platelets stain grayish at 10 and 20 magnification (A and C). Glycoproteins and proteoglycans within foreign material appear purple magenta with Periodic acid–Schiff stain at 20 magnification (B). Foreign material stains green when assessed in Movat pentachrome staining (D). Polarized light shows birefringence within foreign material at 10 magnification (E). Arrows point to foreign material within aspirated thrombus.

Bioresorbable Stents and Thrombosis

- Bioabsorable polymers definitely have an advantage over durable polymers –simply polymer disappears with time
- Animal studies with some biodegradable polymer stents have clearly shown larger lumens and less long term inflammation.
- Not all bioerodable polymers are created equal, it depends on the type and amount of polymer load, degradation rate in relation to drug release.
- But the limitations of polymers versus metal in terms of scaffolding are obvious and thus BRS have larger struts to accommodate for their relatively lower radial strength
- Fully absorbable polymeric scaffolds need to get thinner to really compete with DES
  - In multiple clinical trials and registries there is greater thrombosis and higher late loss
- However, this does not mean we should not use them. Correct patient selection in those with large vessels who are able to take extended duration DAPT they may be a better option