Biodegradable Stents: Future or Fancy…

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Why Degradable Stents?

- No late adverse events
  - Late thrombosis
  - Hypersensitivity reactions (chronic inflammation)
  - Stent fractures
- Does not restrict arterial remodeling
- Permits non-invasive imaging of artery
- Permits bypass surgery in future

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Materials Applied for Development of Biodegradable Stents

	Material	Stent	Status	
Polymers	PLA	Thermal balloon expandable, ring (Igaki-Tamai)	4-year clinical data	**Tamai et al. CCT 2004**
	PLA	Balloon expandable, tubular (Abbott Vascular, Inc.)	Phase I Clinical trial (Absorb)	**Stack RS. TCT 2005** **Ormiston J. TCT 2006**
	Tyrosine-polycarbonate	Balloon expandable, (REVA Medical)	Pre-clinical	**Kaluza G. TCT 2006**
	PAE-Salicylate	Balloon expandable, tubular	Pre-clinical	**Robinson KA. TCT 2006**
Metallic				
	Magnesium	Balloon expandable, tubular (Biotronik)	Phase I Clinical	**Heublein B et al. Heart 2003;89:651-656**
	Iron	Balloon expandable, tubular	Pre-clinical	**Peuster M et al. Heart 2001;86:563-569**

Bioresorbable Stents

Igaki-Tamai		PLA
BVS		PLA
REVA		Tyrosine-Policarbonate
BIT		PAE-Salicylate
Biotronik		Magnesium

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PLA Metabolic Pathway

PLA

H_2O

Hydrolysis

↓ Molecular Weight

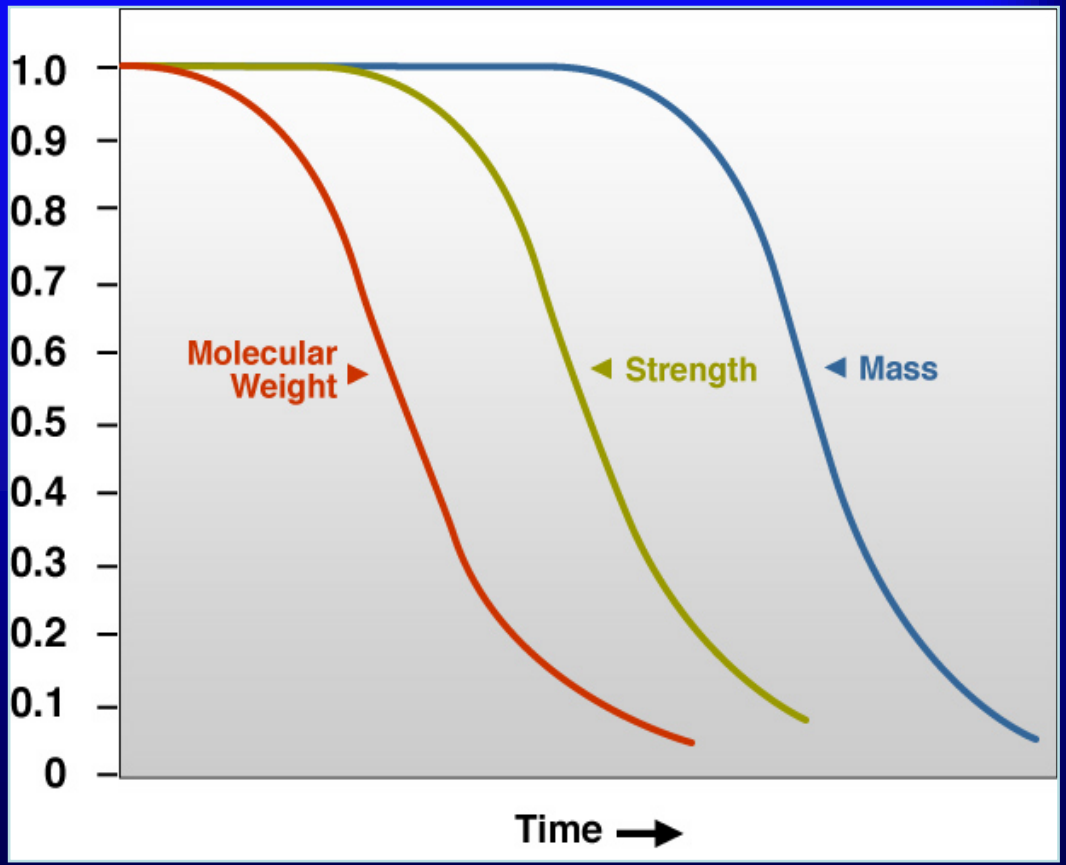
Lactic Acid

Mass Loss

Mass Transport

Krebs Cycle → $CO_2 + H_2O$

Generalized Degradation Curves[1]



[1]Pietrzak WS, et al. J. Craniofaxial Surg, 1997; 2: 92-96.
Middleton JC, Tipton AJ, Biomaterials, 21 (2000) 2335-2346.

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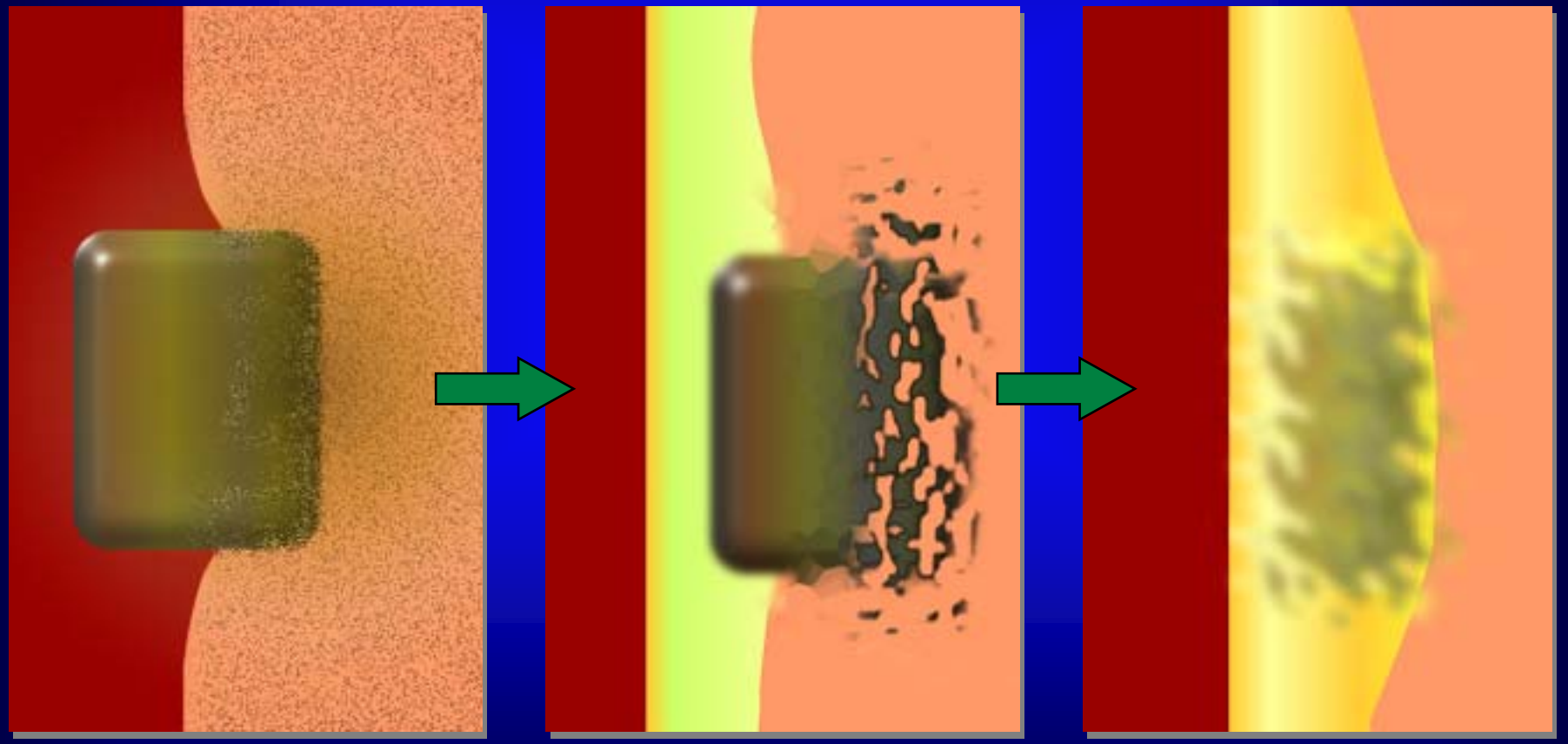
Biodegradable Stents: Time Course

Diffusion Bulk Erosion Isolation



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Bioabsorbable Stents

Bioabsorbable material	Degradation period
1. polyglycolic acid (PGA)*	2~3 months
2. poly-l-lactic acid(PLLA)*	12~18 months
3. Poly (d,l-lactide/glycolide) co-polymer (PGLA)	2~3 months
4. Polyorthoester (POE)	10 months
5. Mg Alloy	2-3 months
6. polycaprolactone(PCL)	36 months~

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Challenges with Bioabsorbable Stents

- Scaffolding and radial force
- Time of degradation
- Rate of degradation
- Biocompatability
- Recoil: early and late
- Biodegradable products
- Remaining polymer
- Elution of the drug from a biodegradable stents
- Radioopacity of the stents

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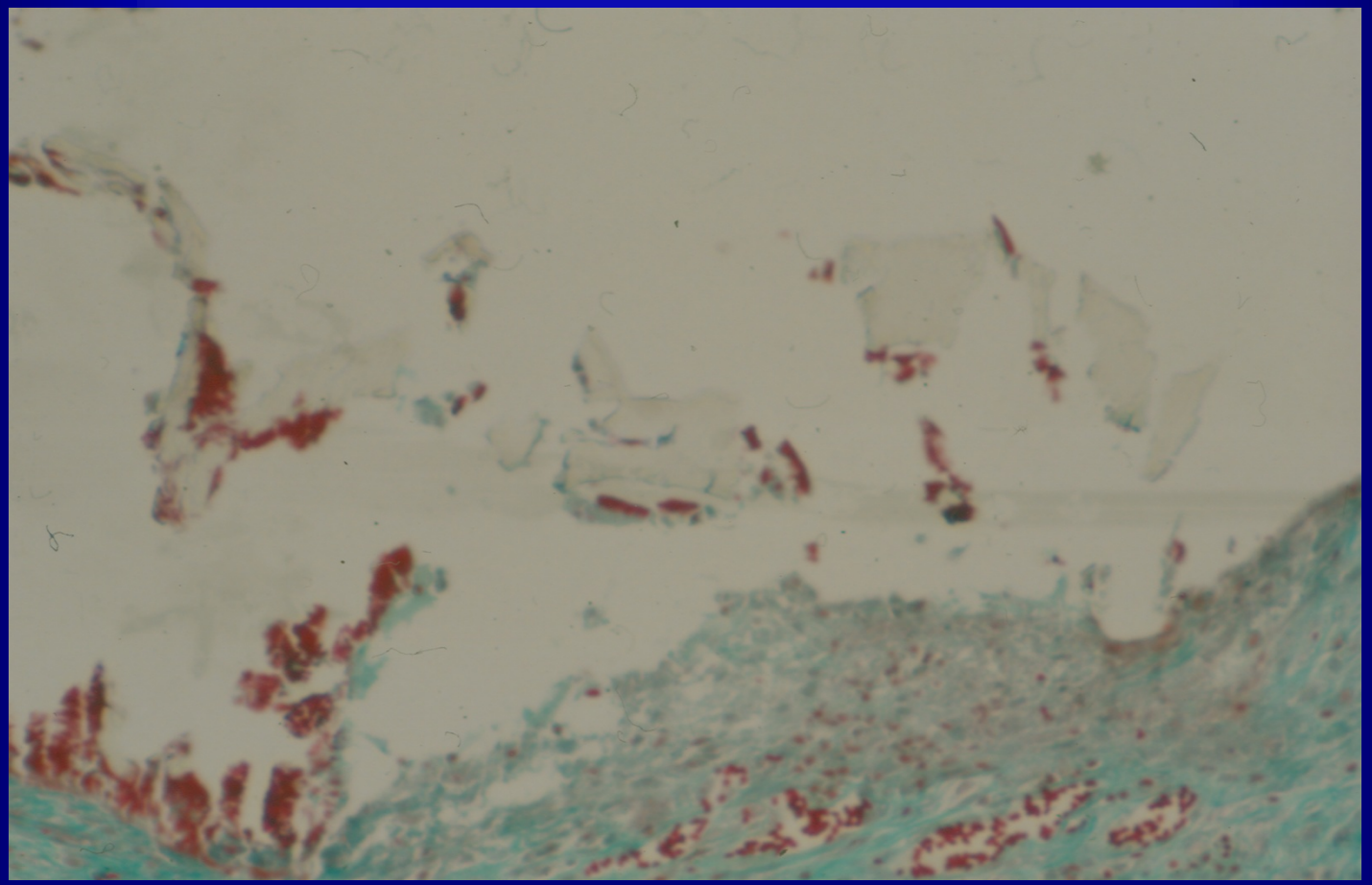
Biodegradation and Biocompatibility



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Igaki-Tamai PLLA Bioabsorbable Stent

- 63 lesions in 50 patients, 84 stents
- Non drug eluting stent
- Four year follow-up data demonstrated no unusual findings

Long Term (3-years)

Death	0
QMI	1/50* (2.0%)
CABG	0
Stent Thrombosis	1/50* (2.0%)

* = same patient

ABRR**	Repeat PCI
6 mo	12/60 (20%)
	6/50 (12%)
12 mo	9/53 (17%)
	7/50 (14%)
36 mo	8/50 (16%)

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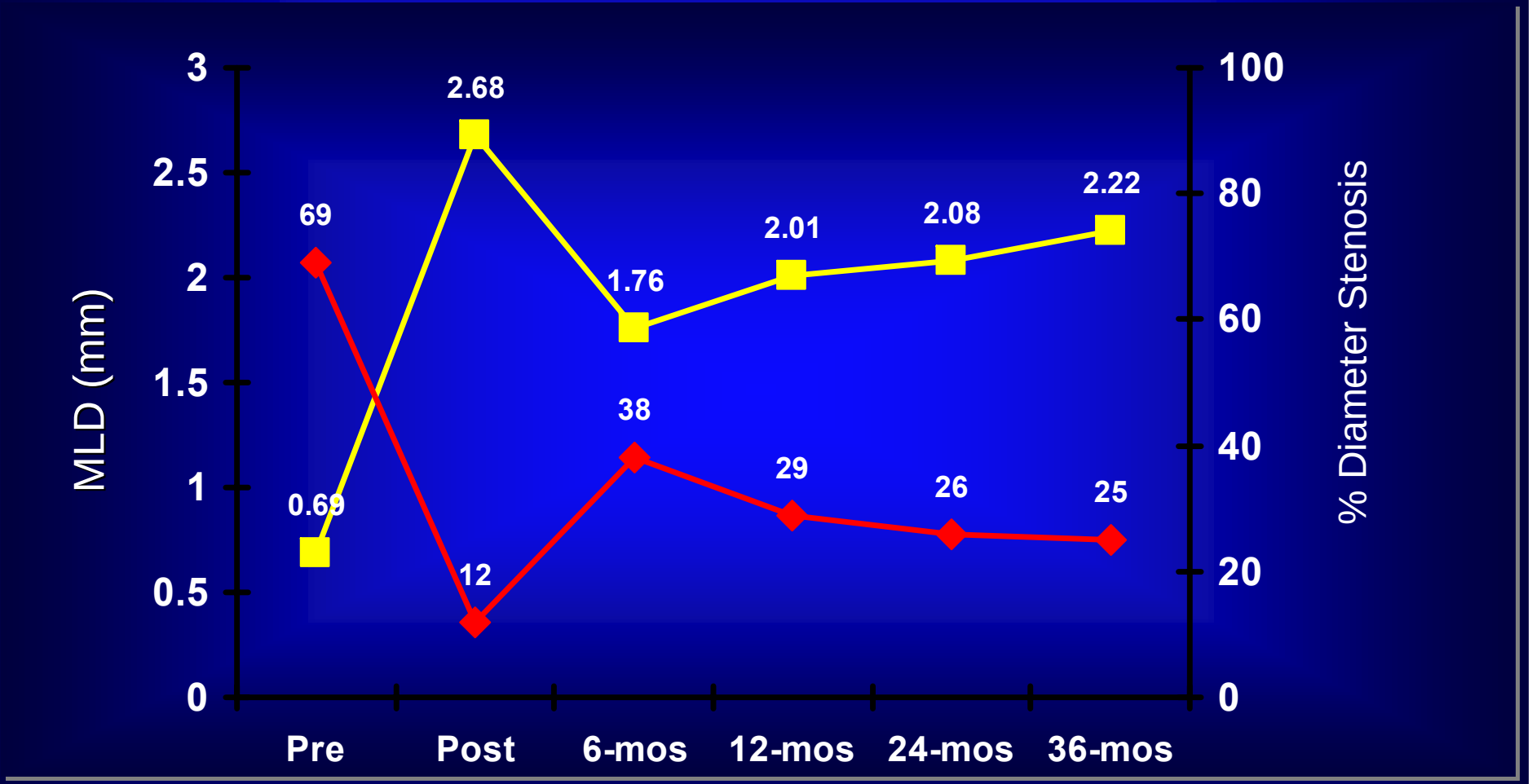
"Biodegradable Stents An update and work-in-progress" Presentation, Hideo Tamai CCT 2003
**ABRR (Angiographic Binary Restenosis Rate) per lesion.

Igaki-Tamai PLLA Bioabsorbable Stent: 3-year Angiographic Analysis



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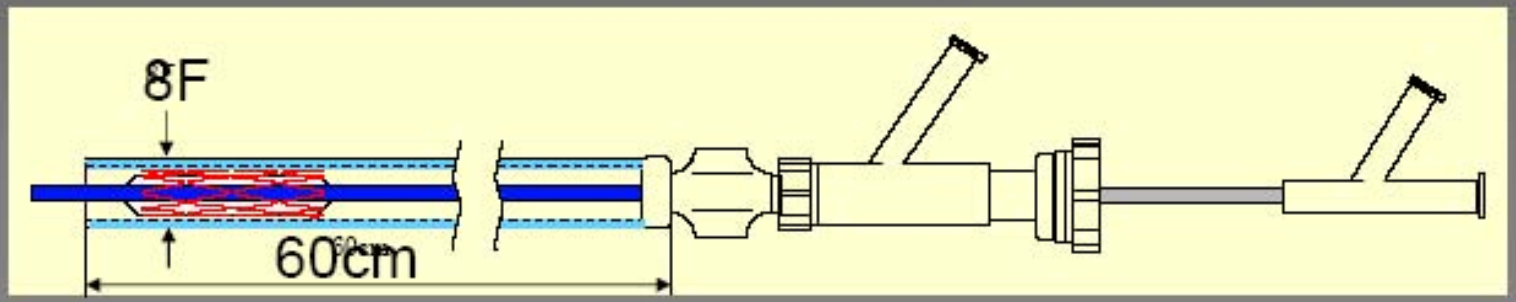
Tamai CCT 2004

Peripheral Stent Delivery System

Balloon-expandable system covered with a protective sheath



Protective sheat:	Outer diameter; 8F
System length:	60 cm and 120 cm
Balloon length:	4 cm (Stent lenth 36 mm)
Balloon size:	6.0, 7.0, 8.0 mm

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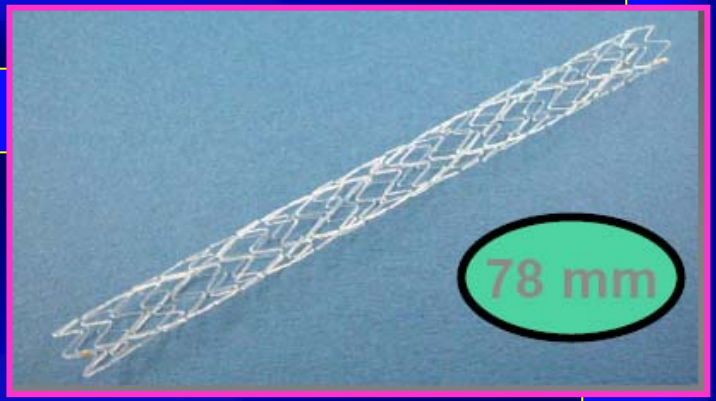
PERSEUS IGAKI-Tamai in SFA CE MARK NOV 2007



Study Results

- Primary success rate 100 %
- No serious adverse event

6-Month Angiographic Follow up

- No reocclusions or thrombosis
- 9 symptomatic restenoses (20%), all successfully retreated
- Asymptomatic angiographic restenosis (< 50%) in 3 cases (6.6 %)

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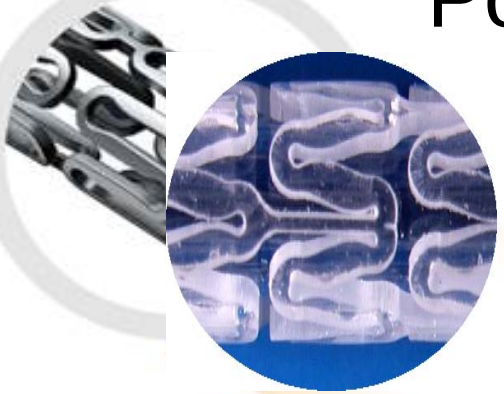
BVS Fully Bioabsorbable Drug Eluting Stent

Poly Lactic Acid (PLA)

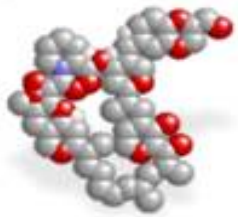


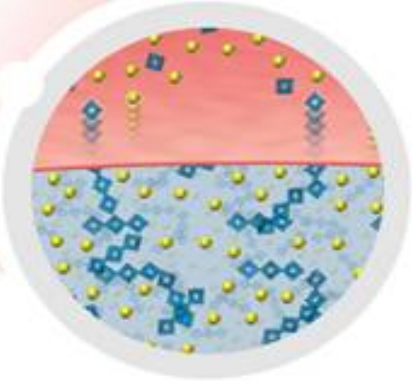
PLA safely used in numerous medical applications since the 1960s

ML VISION®
Balloon SDS

Everolimus

Champion™
Bioabsorbable
Polymeric Drug
Release

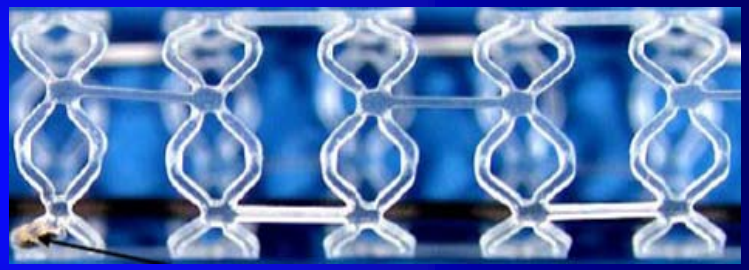




Material Characteristics of the BVS Bioabsorbable Polymeric DES

Everolimus/PLA Matrix Coating

- Thin coating layer
- 1:1 ratio of Everolimus/PLA matrix
- Controlled drug release



PLA Stent

- Laser cut, tubular
- Processed for increased radial strength

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ABSORB TRIAL
FIM Trial of A Fully Bioabsorbable Drug-eluting Coronary Stent

Assess t he Safety and Performance of the BVS Everolimus-Eluting Coronary Stent System in the Treatment of Patients with Single, De Novo, Native Coronary Artery Disease.

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ABSORB Study Design

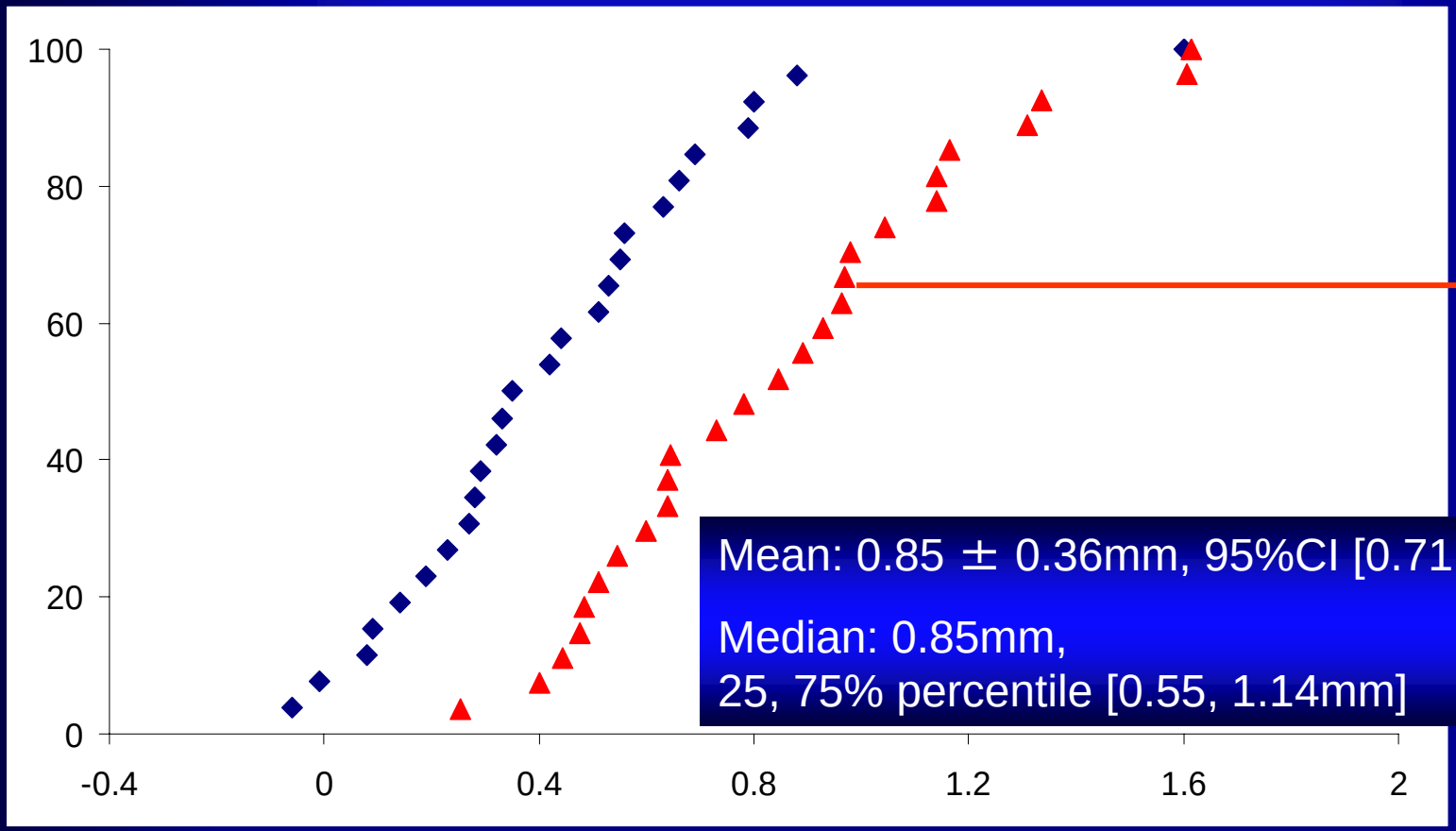
Single, *de-novo* lesion → **3.0 mm n = 30** → **BVS Stent**

- Sponsor: Abbott Vascular
- Primary Investigators:
  - J Ormiston MD
  - PW Serruys MD, PhD
- DSMB: J Tijssen PhD, T Lefèvre MD, P Urban MD
- CEC: C Hanet MD, D McClean MD, V Umans MD
- Angiographic and IVUS Corelab: Cardialysis (Rotterdam, NL)

- Prospective, open label, FIM
- 3.0 x 12mm stents (3.0 x 18mm* stents available after enrolment start and used in 2 pts)
- 6 sites EU, NZ

Rotterdam, NL, Patrick Serruys (16)
Krakow, PL, Dariusz Dudek (6)
Auckland, NZ, John Ormiston (5)
Arhus, DN, Leif Thuesen (3)
Aalst, BE, Bernard de Bruyne
St Denis, F, Bernard Chevalier

ABSORB
Late Loss (26 pts)



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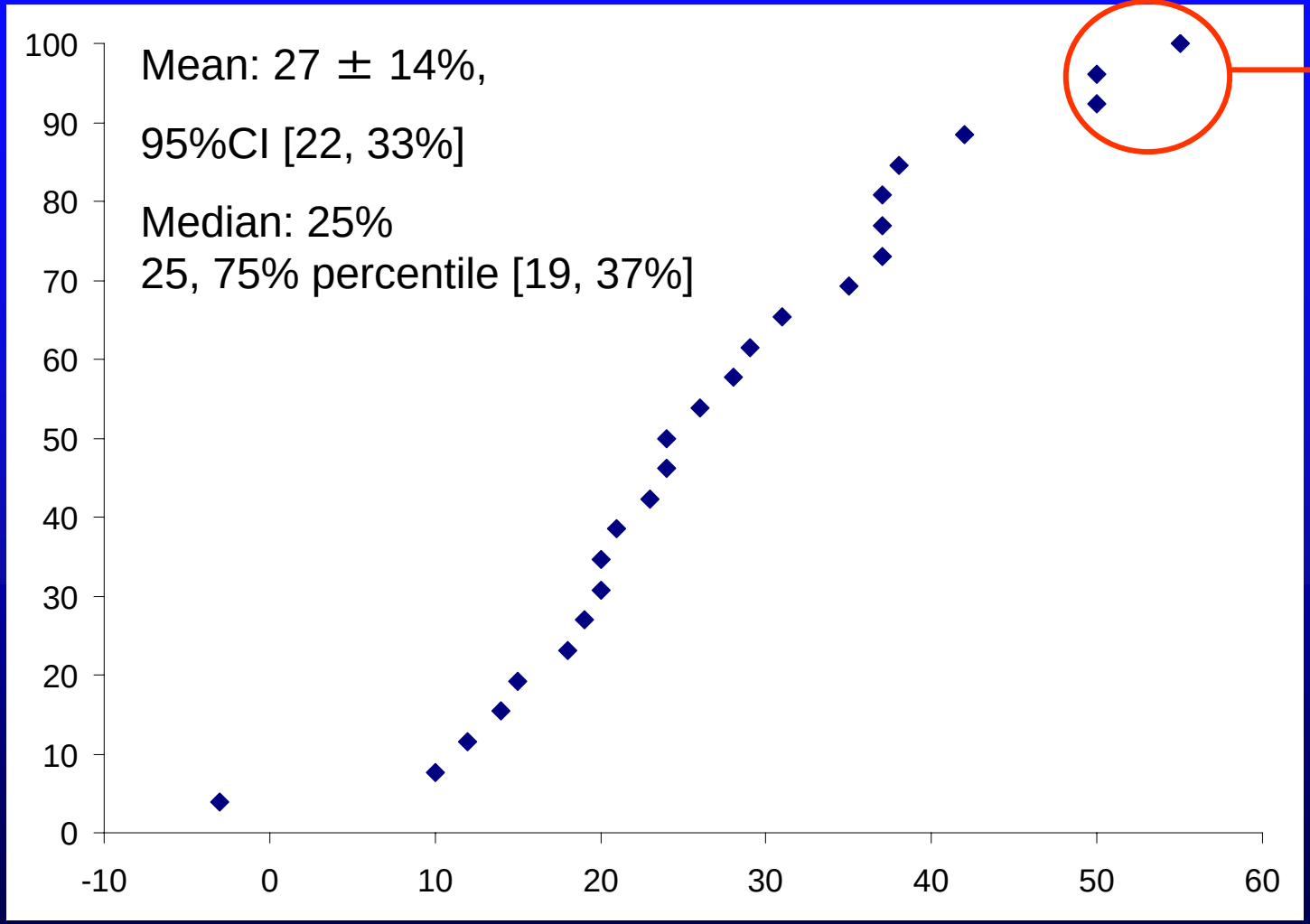
Diameter stenosis at follow-up (26pts)



Binary restenosis: 11.5 % (3/26)

No TLR

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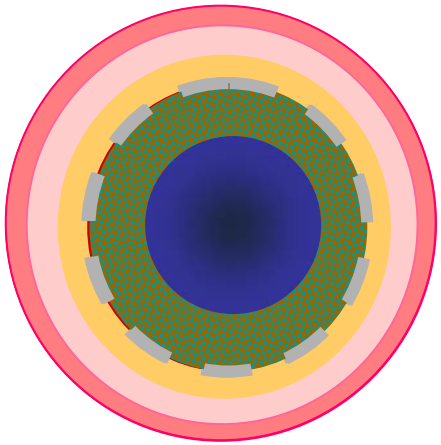
ABSORB:IVUS results (24 pts)

	Post-PCI	Follow-up	% Difference	p-value
Vessel area (mm^2)	13.55	13.49	-0.4	NS
EEM-Stent Area (mm^2)	7.47	8.08	+8.2	0.003
Stent area (mm^2)	6.08	5.37	-11.7	<0.001
Neointimal hyperplasia area (mm^2)	0	0.30	NA	NA
Lumen area (mm^2)	6.08	5.07	-16.6	<0.001
Stent area obstruction (%)	0	5.55	NA	NA

What is Contributing to Late Loss?

SPIRIT-First
ML Vision Stent



Late Loss = 0.87mm*

Δ Vessel Area (mm^2) = -0.29 ***(-1.9%)***

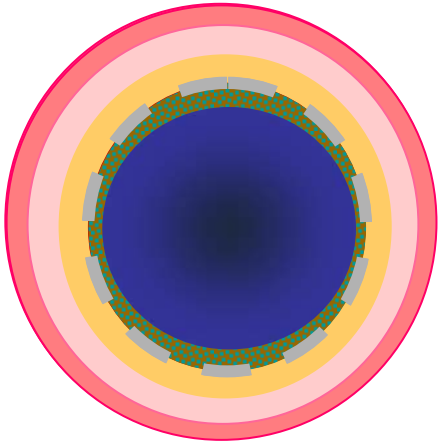
Δ Stent Area (mm^2) = -0.14 ***(-2.0%)***

Δ Lumen Area (mm^2) = -2.12 ***(-29.4%)***

NIH Area (mm^2) = 1.98

% VO = 28.1%

SPIRIT-First
Xience V Stent



Late Loss = 0.10mm**

Δ Vessel Area (mm^2) = 0.19 ***(+1.2%)***

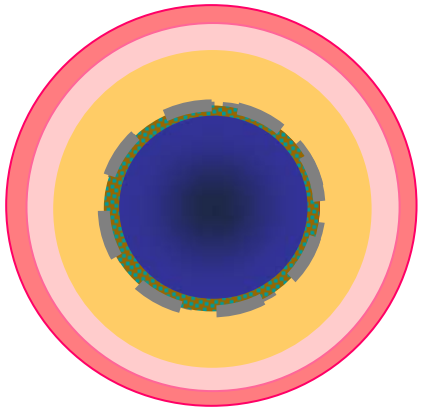
Δ Stent Area (mm^2) = -0.02 ***(-0.3%)***

Δ Lumen Area (mm^2) = -0.51 ***(-7.2%)***

NIH Area (mm^2) = 0.50

% VO = 8.0%

ABSORB
BVS Stent



Late Loss = 0.44mm

Δ Vessel Area (mm^2) = -0.06 ***(-0.4%)***

Δ Stent Area (mm^2) = -0.71 ***(-11.7%)***

Δ Lumen Area (mm^2) = -1.01 ***(-16.6%)***

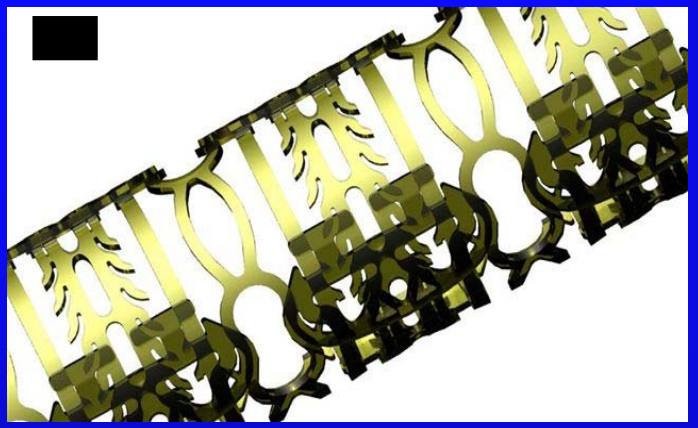
NIH Area (mm^2) = 0.30

% VO = 5.5%

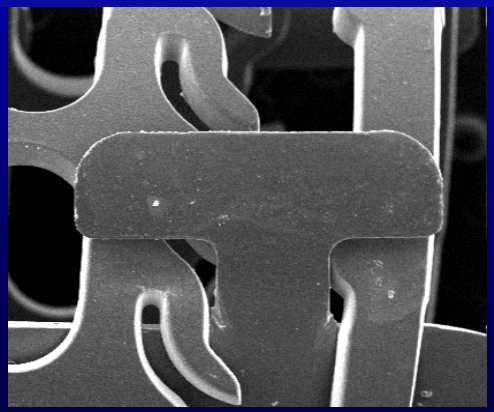
*Serruys PW, et al., Eurointervention 2005; 1: 58-65. 94.

REVA
Slide & Lock Design

- Steel-like performance in a polymer stent
- Low recoil (<1%)
- High radial strength
- Flexible and conformable



Deploys (expands) in artery with sliding, locking parts rather than material deformation



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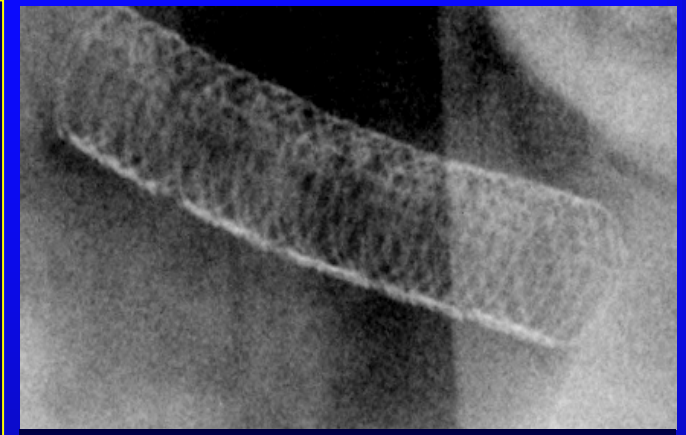
REVA
Bioresorbable Polymer Material

- Developed for stent performance
- Tunable resorption rate
- Benign breakdown products
- X-ray visibility
- MRI/CT compatibility



Tyrosine-derived
Polycarbonate Stent

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RESORB Clinical Trial

The REVA Endovascular Study of a Bioresorbable Coronary Stent

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RESORB Trial
Endpoints and Follow-Up

- Endpoints
  - Primary – 30 day MACE
  - Secondary – 6 month QCA & IVUS derived parameters (restenosis)
- Clinical Follow-up
  - Discharge, 2 weeks, 1, 6, 12*, 24*, 36, 48 and 60 months
  - * Subset of patients returning for long term angiographic follow-up
- FIM initiated and currently on Hold

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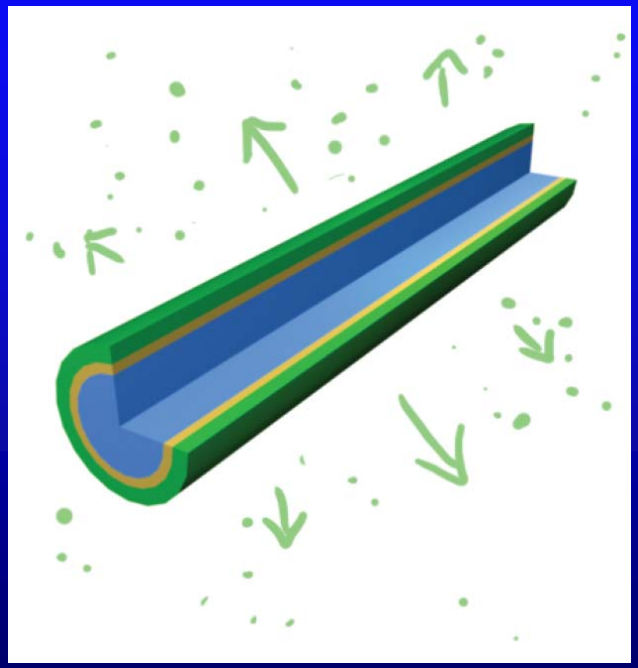
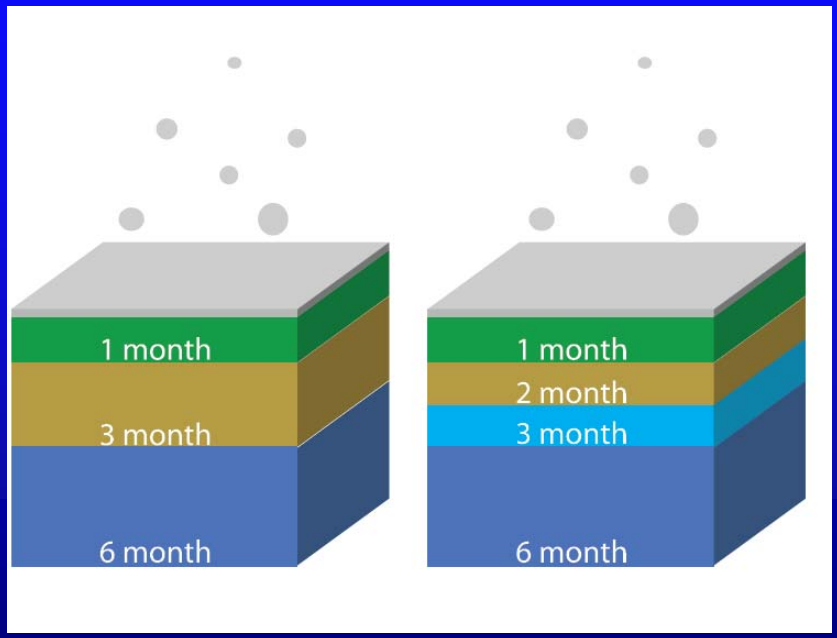
Multi-Layer, Combination Drug Delivery





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Stent Design

- Balloon expandable
- No foreshortening
- Suitable for primary stenting
- Radiopaque
- Good scaffolding and mechanical properties
- Excellent side branch access
- Full range of diameters and lengths
- No special storage required

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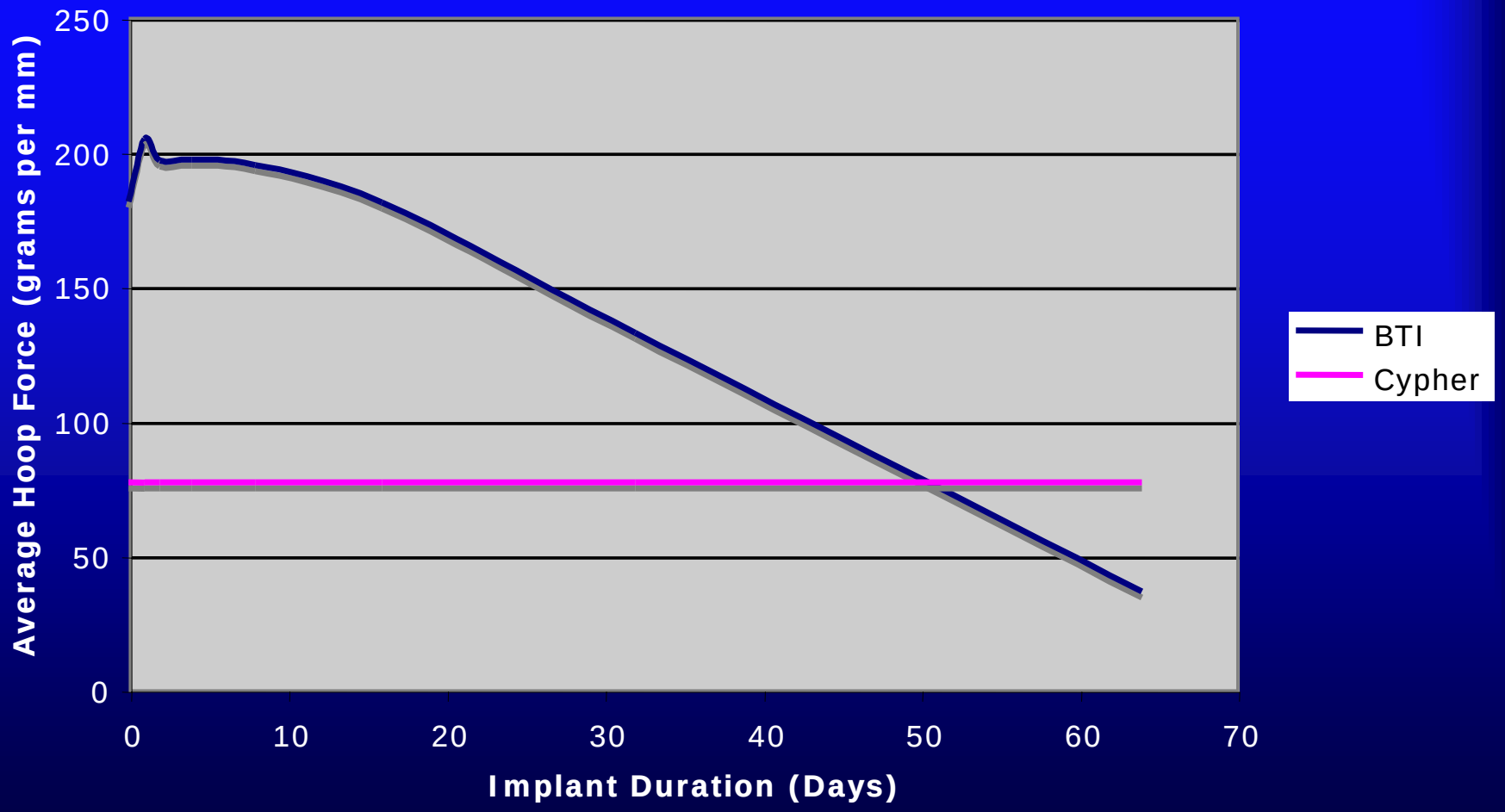
Radial Strength



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Pre-Clinical Results

Study	Arm 1	Arm 2	Arm 3	End points
PAE Vascular Compatibility	BMS (no coating)	PLA coated metal stent	PAE coated metal stent	3D: FC, 30D: A/H
PAE + Sirolimus Efficacy	Cypher	PLA + sirolimus coated BX Velocity	PAE + sirolimus coated BX Velocity	3D: FC, 30D: A/H, 90D: A/H
Fully Degradable Performance	-	-	IDEAL™ Stent	30D: A/H, 90D: A/H, 180D: A/H

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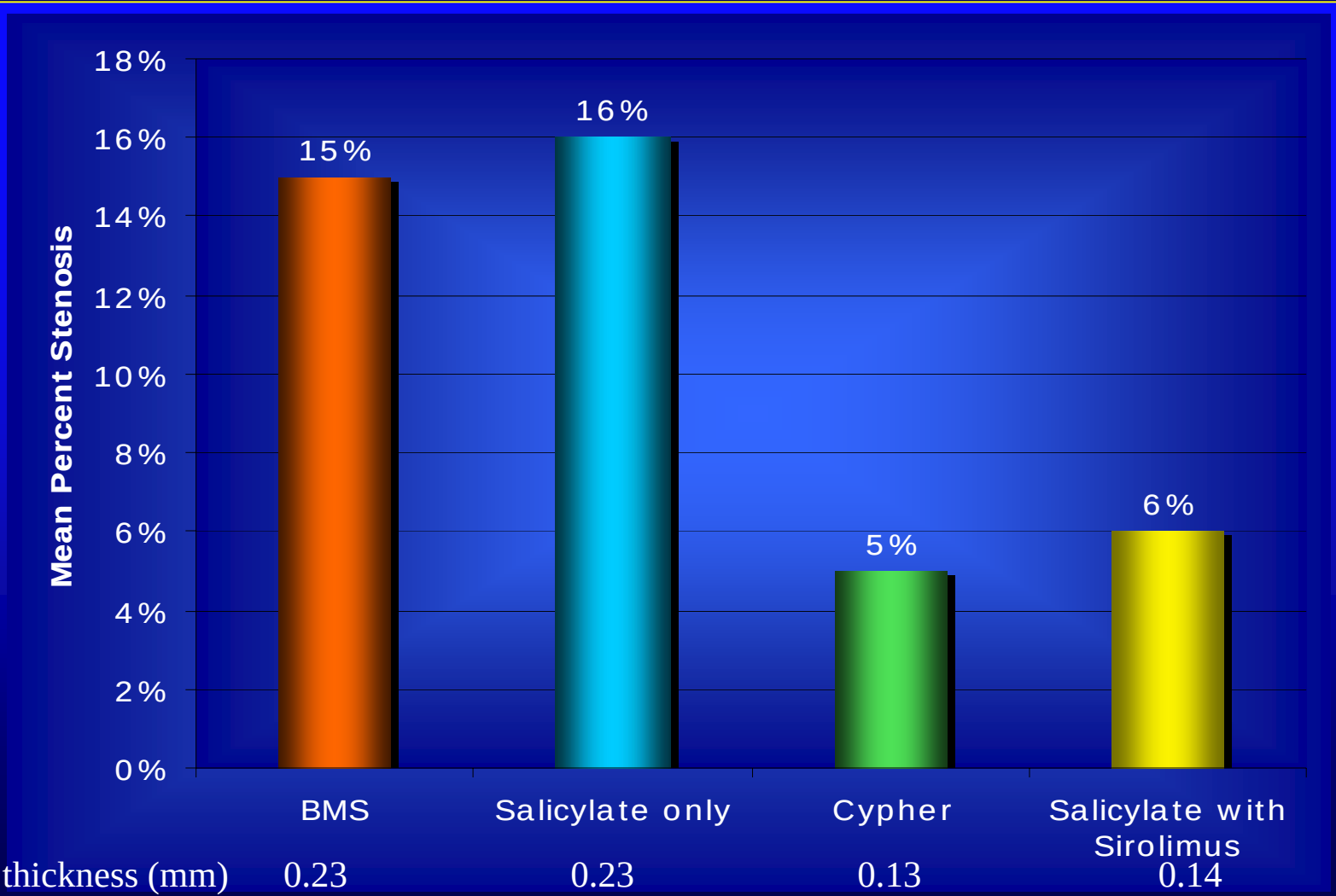
Mean Percent Stenosis in Pig Coronary Arteries One Month after Stent Implant



	BMS	Salicylate only	Cypher	Salicylate with Sirolimus
Intimal thickness (mm)	0.23	0.23	0.13	0.14

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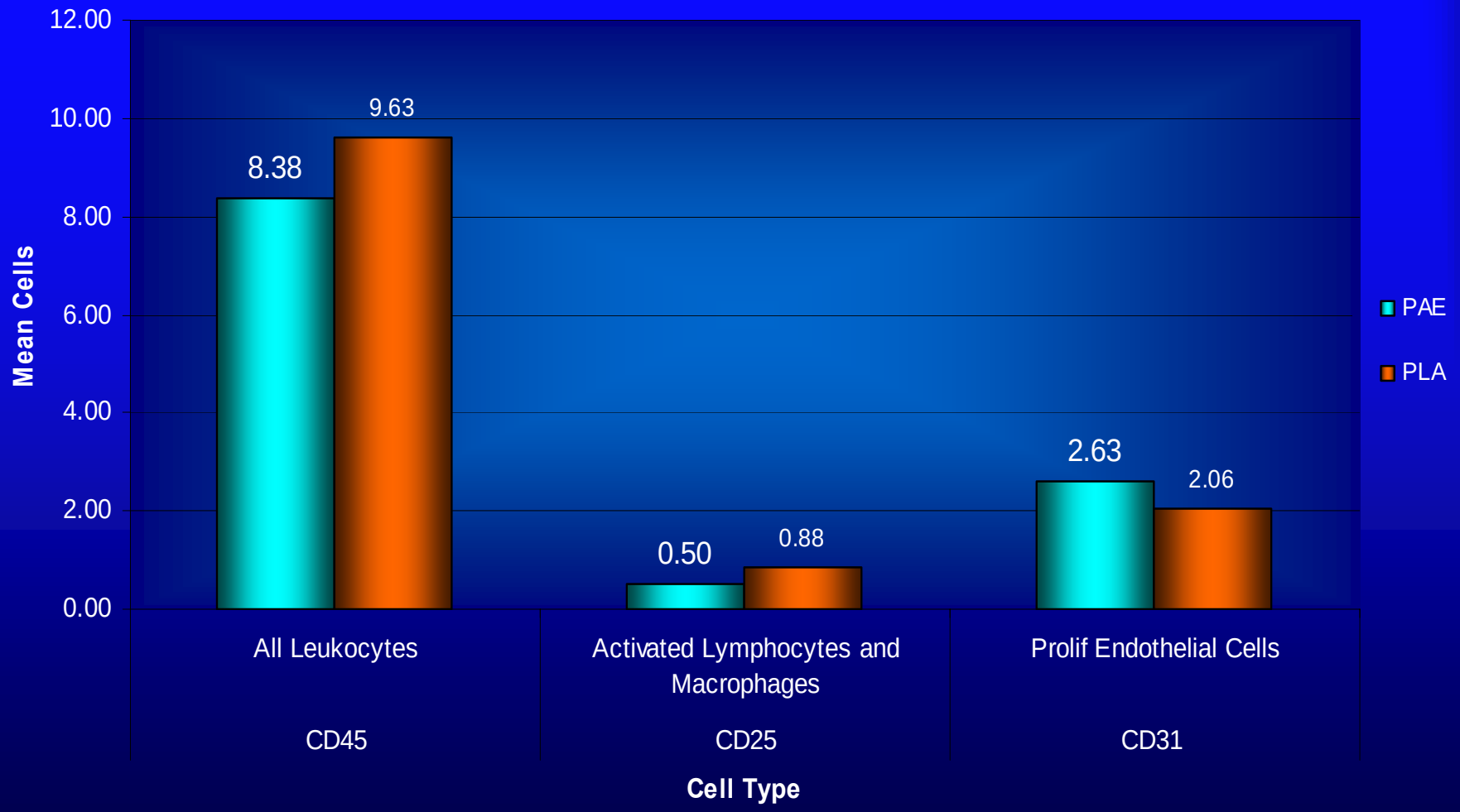
Day 3 Flow Cytometry



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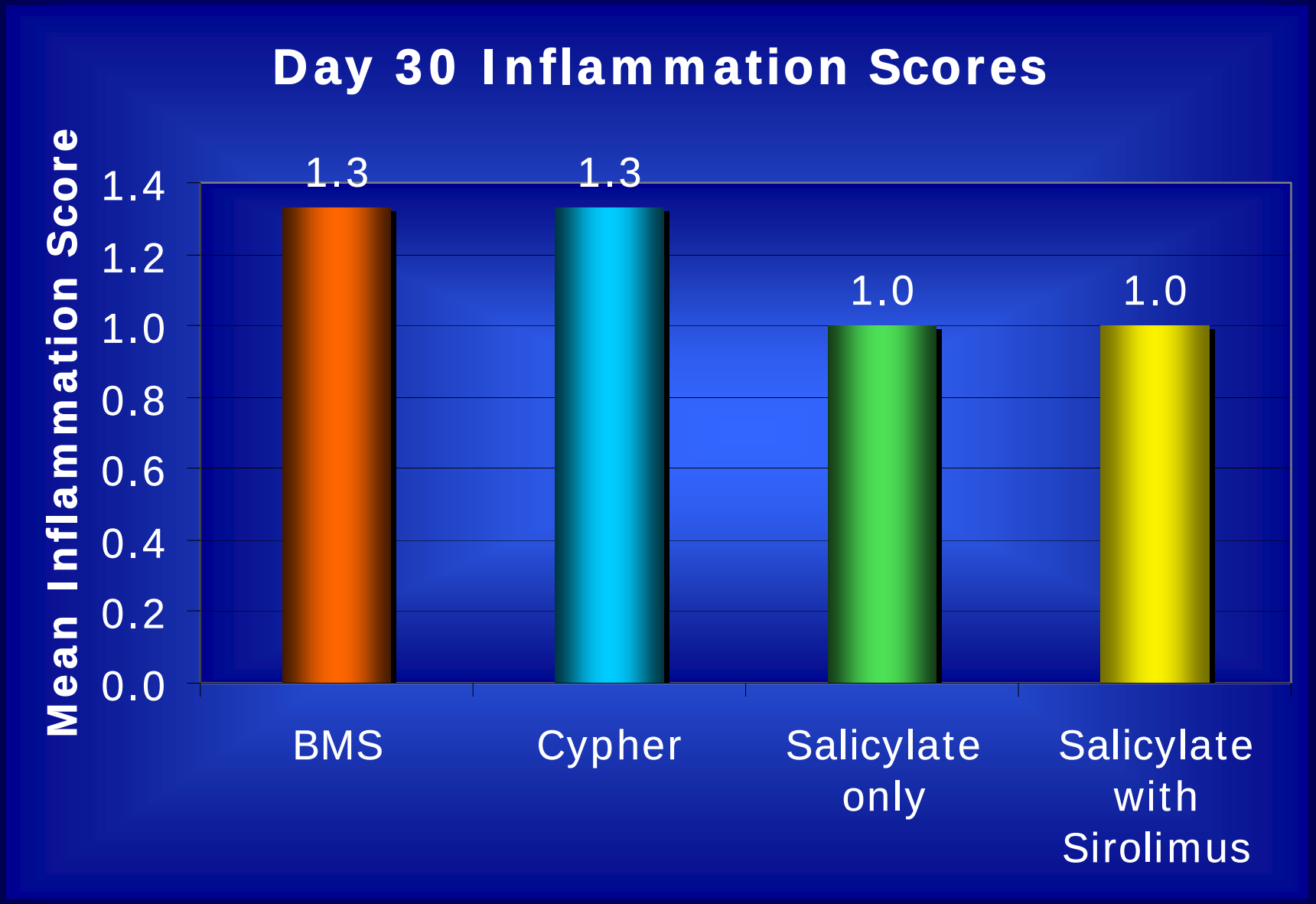

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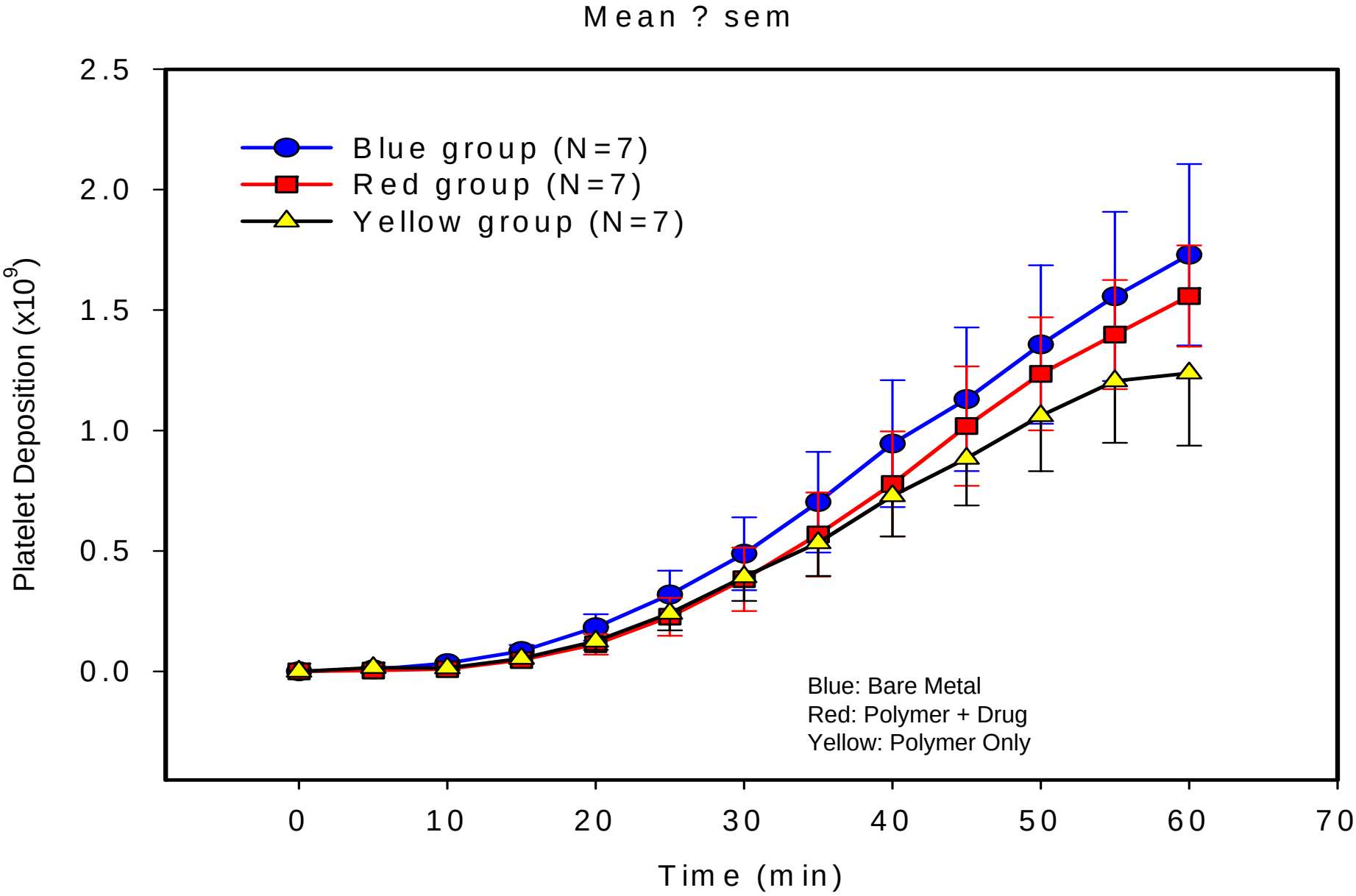
Stent Thrombosis in Baboons



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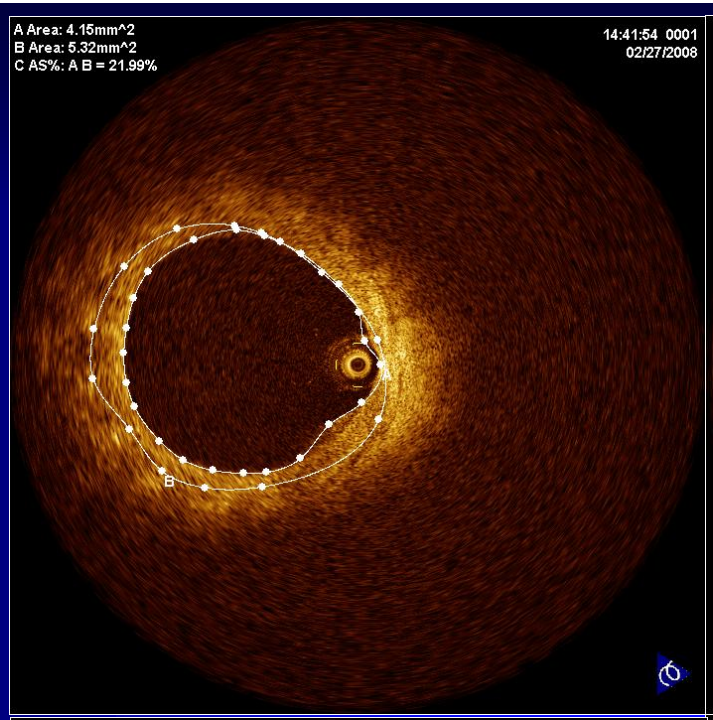
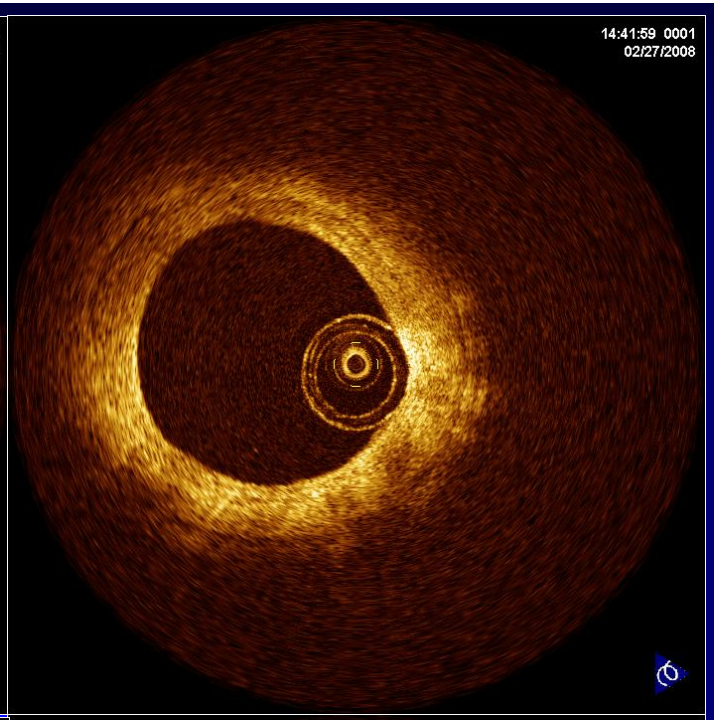
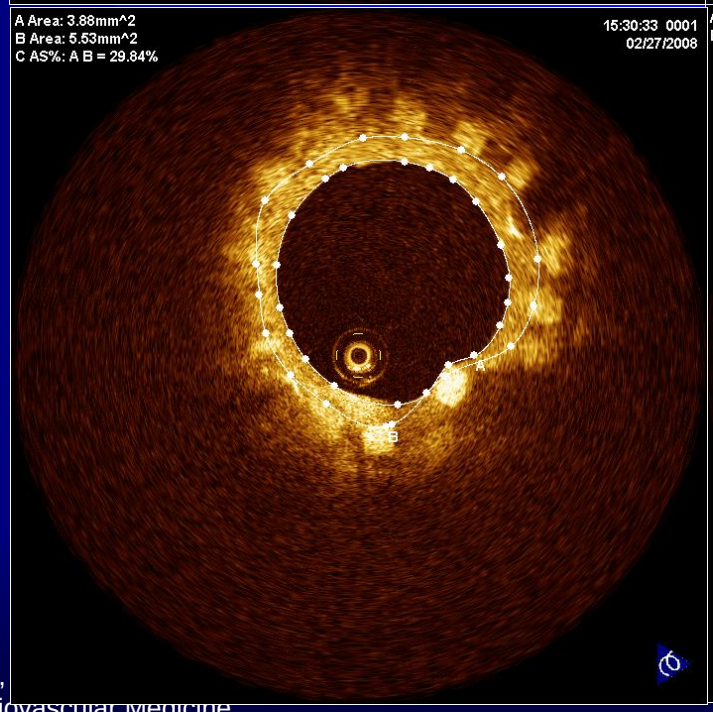
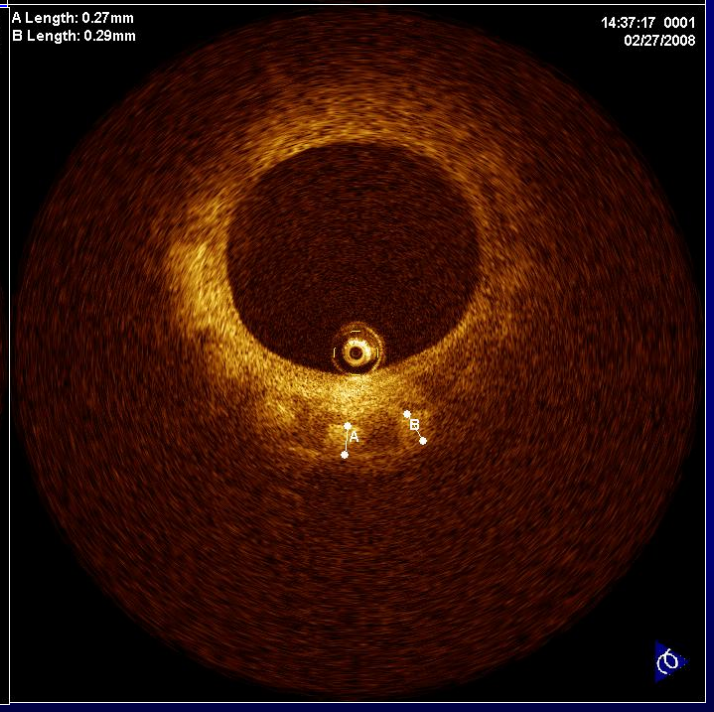




3-month





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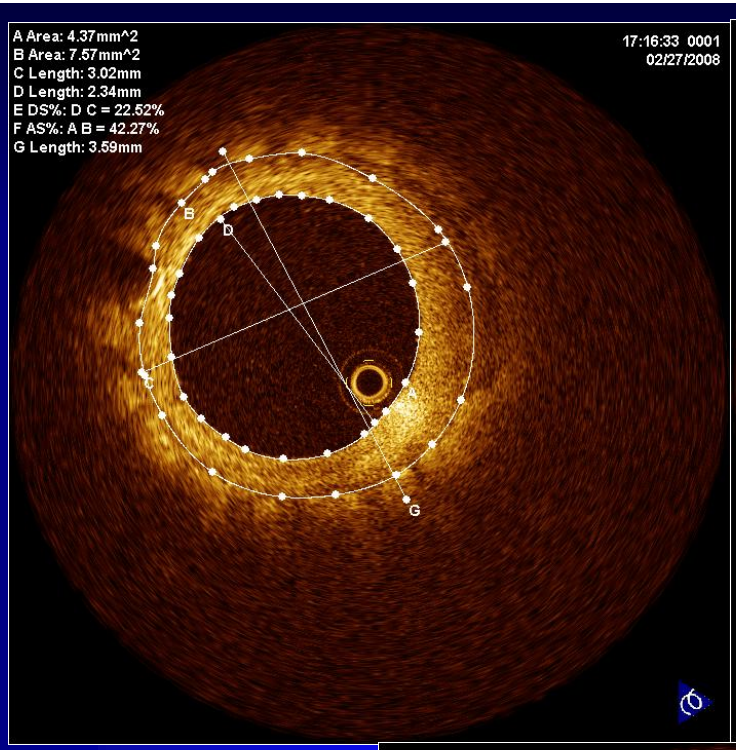

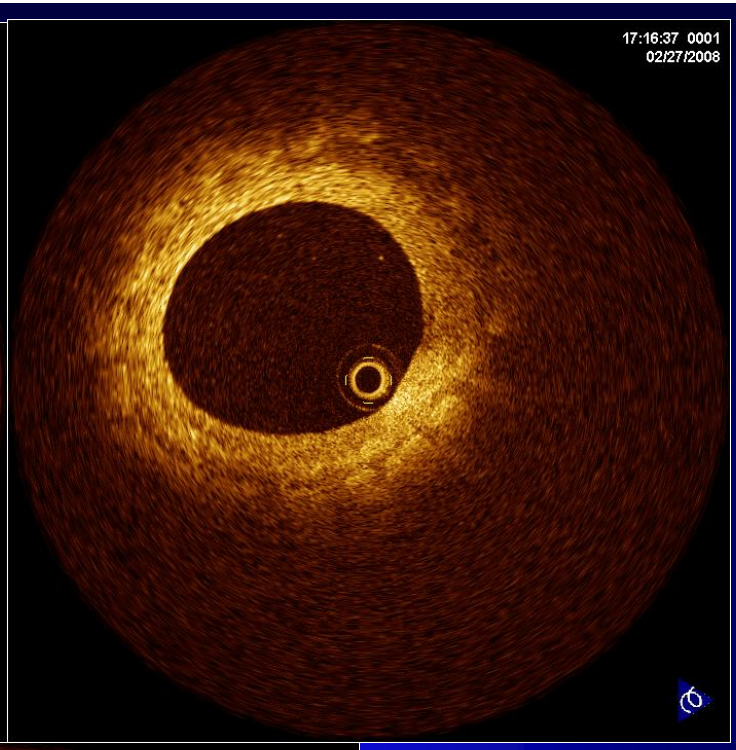

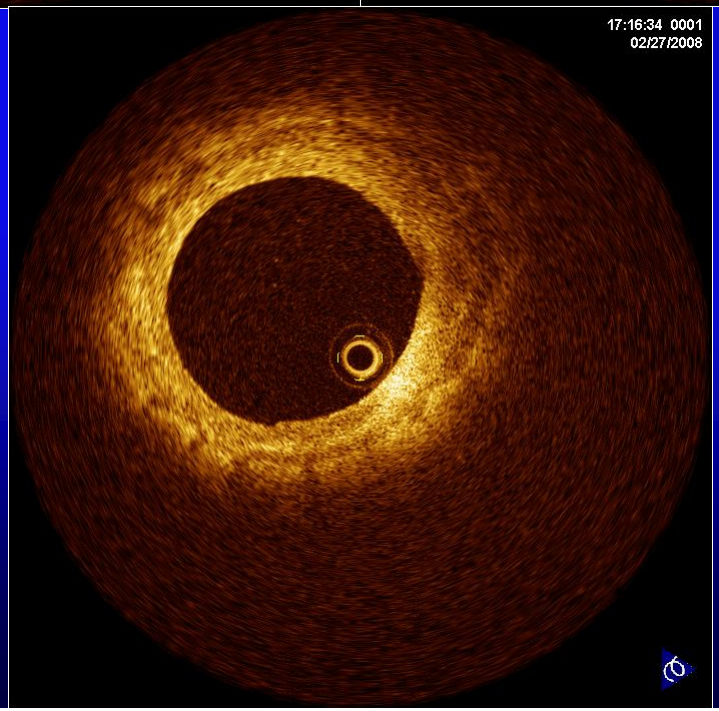

3-month

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3-month

animal #	vessel	Angio % stenosis	OCT DS%	OCT AS%
4106	RCA	26%	23	26
4106	LAD	27%	17	26
4106	LCX	31%	37	59
4107	RCA	29%	23	42
4107	LAD	22%	28	40
4107	LCX	19%	29	54
4108	RCA	23%	20	48
4108	LAD	18%	21	40
4108	LCX	24%	35	53
	Mean	24%	26%	43%
	SD	4%	7%	12%

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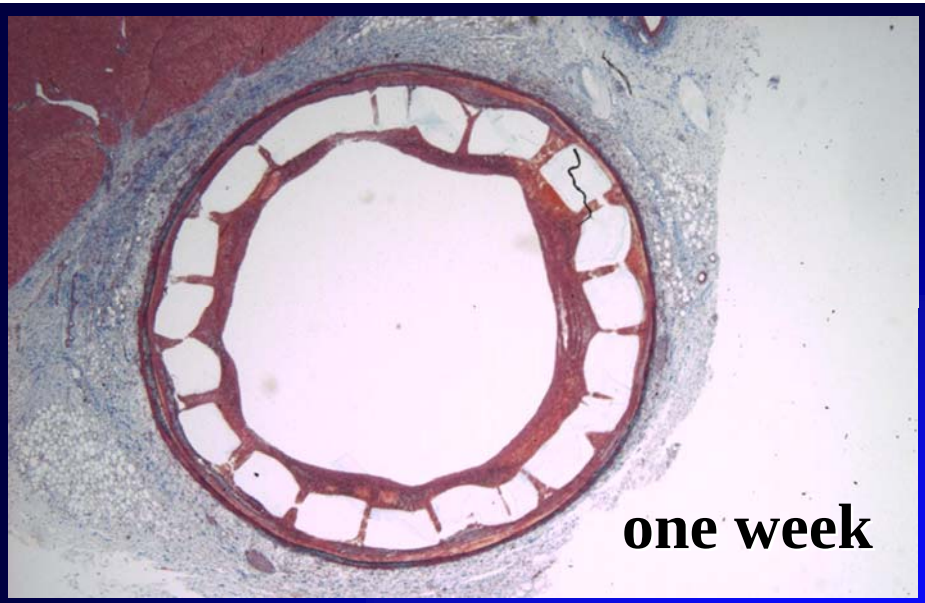
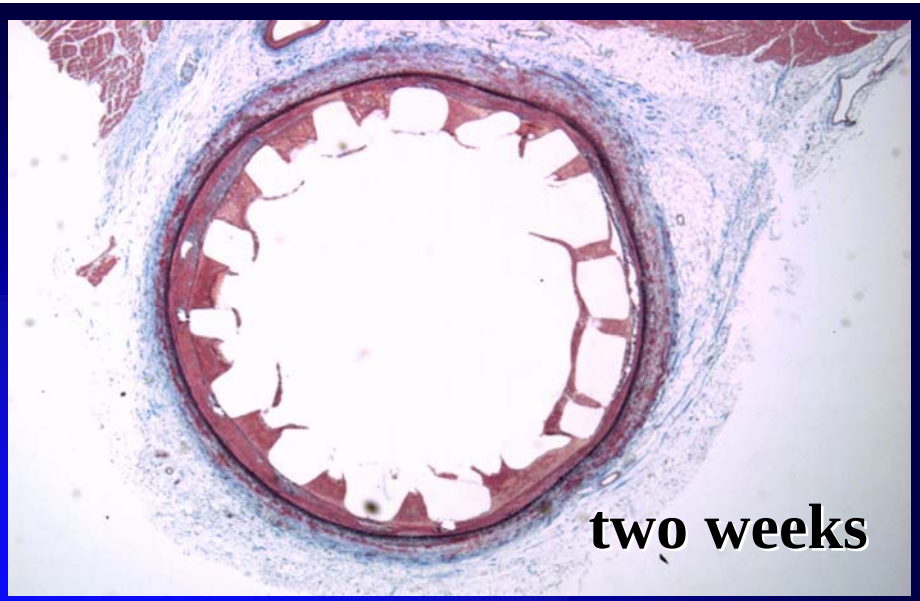
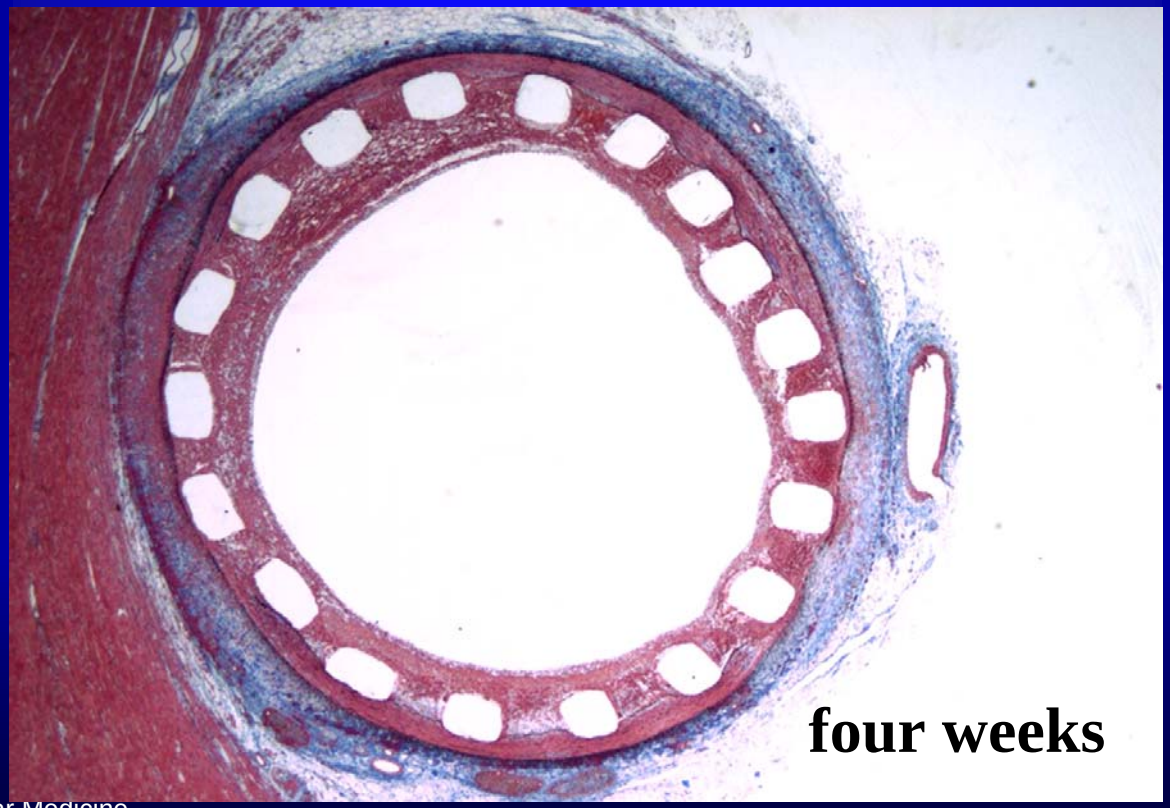




BTI
completely absorbable stent

eluting sirolimus



histology of pig coronary artery implants

VM stain 20X

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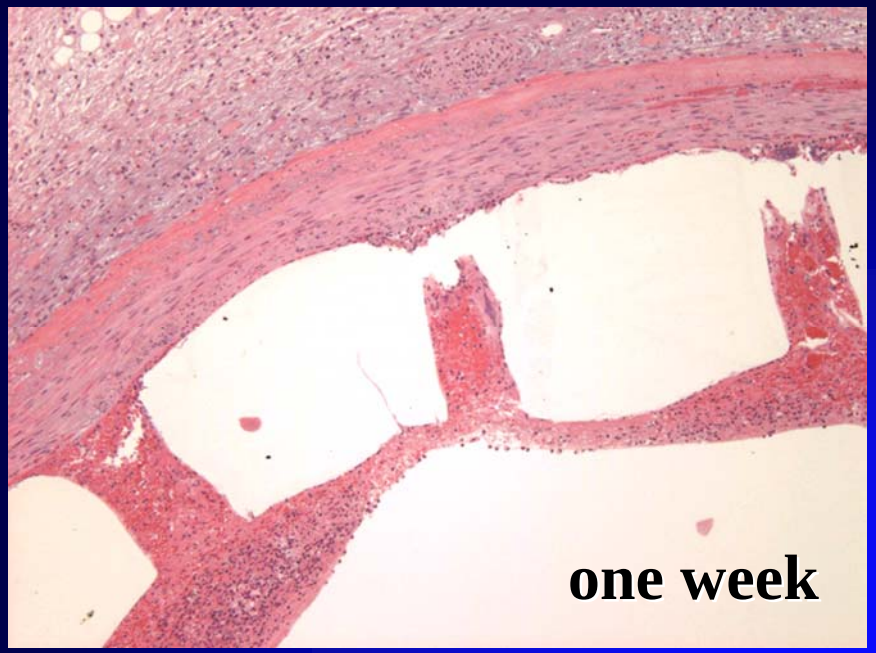
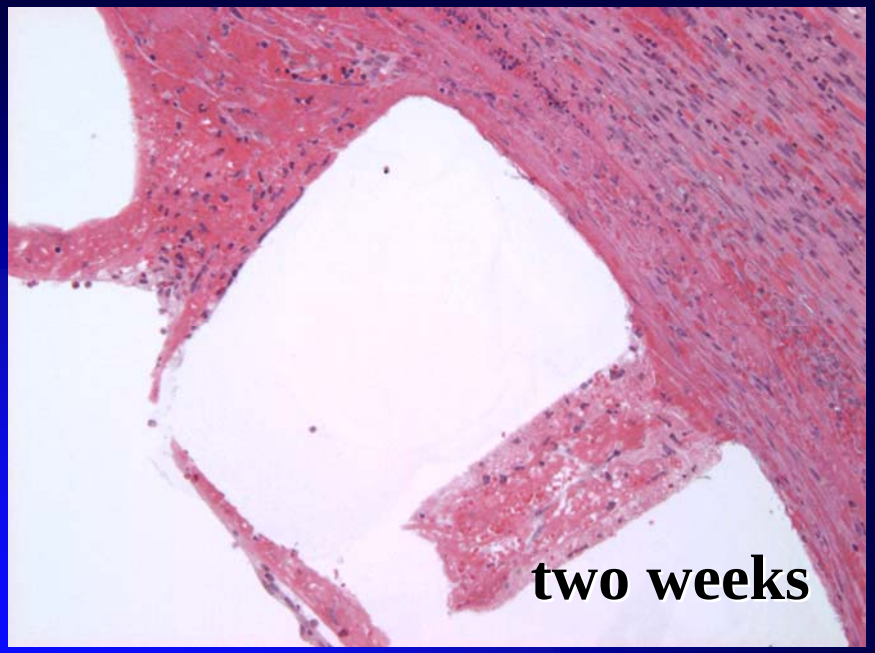
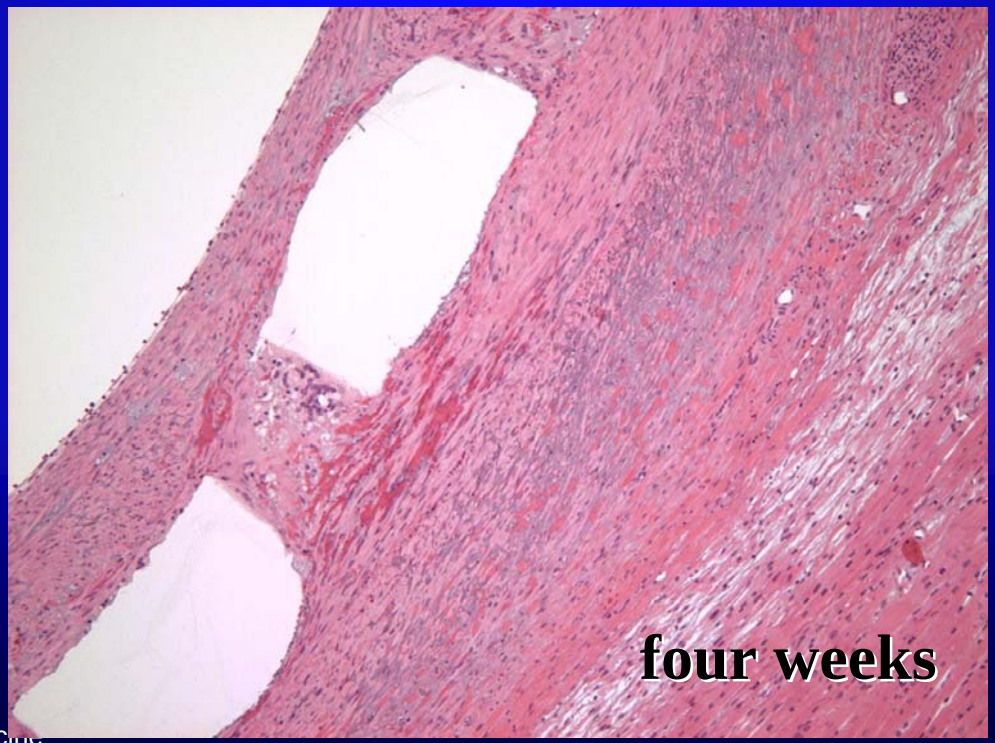




BTI
completely absorbable stent

eluting sirolimus



histology of pig coronary artery implants

H&E stain 200X

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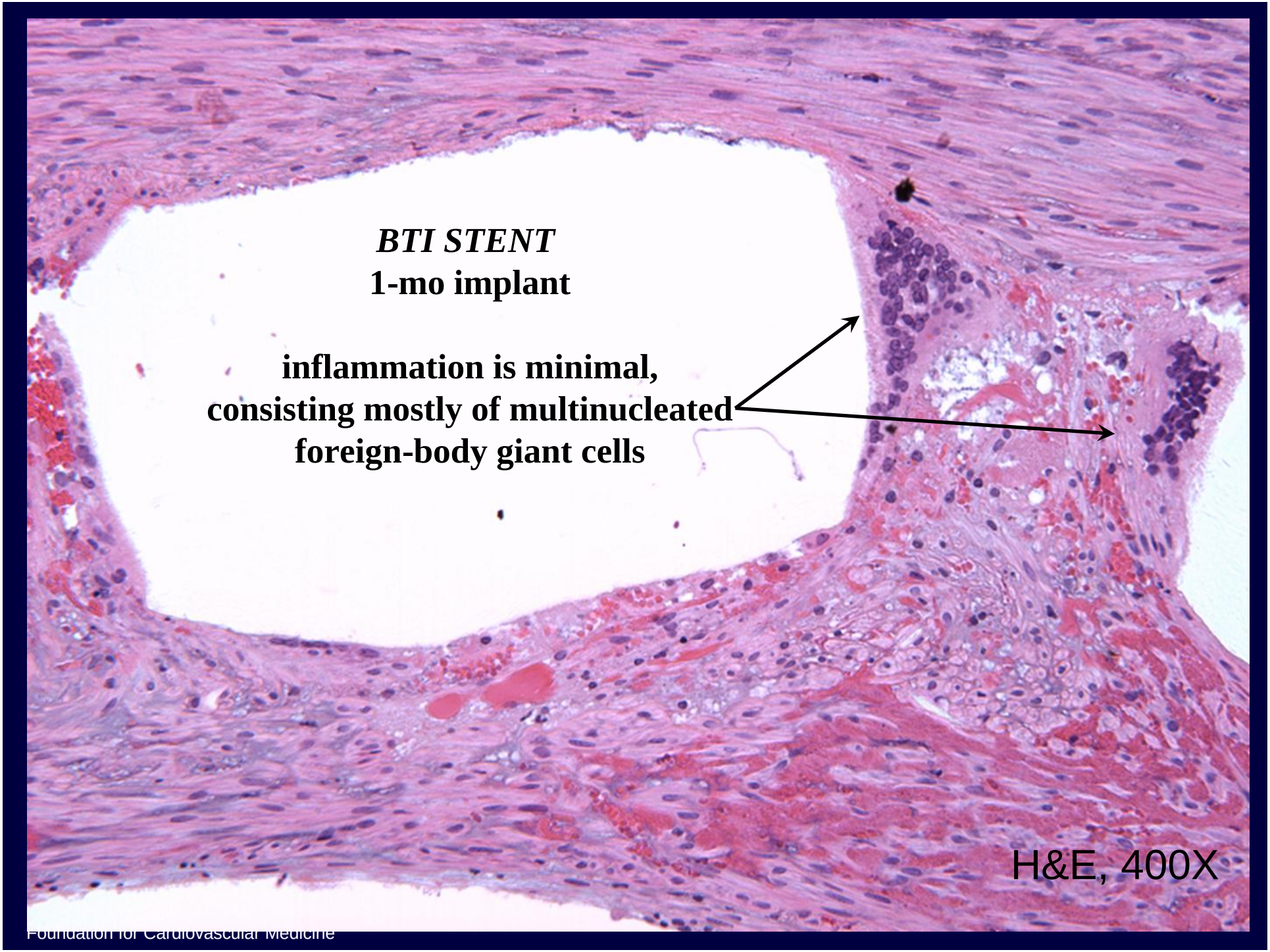
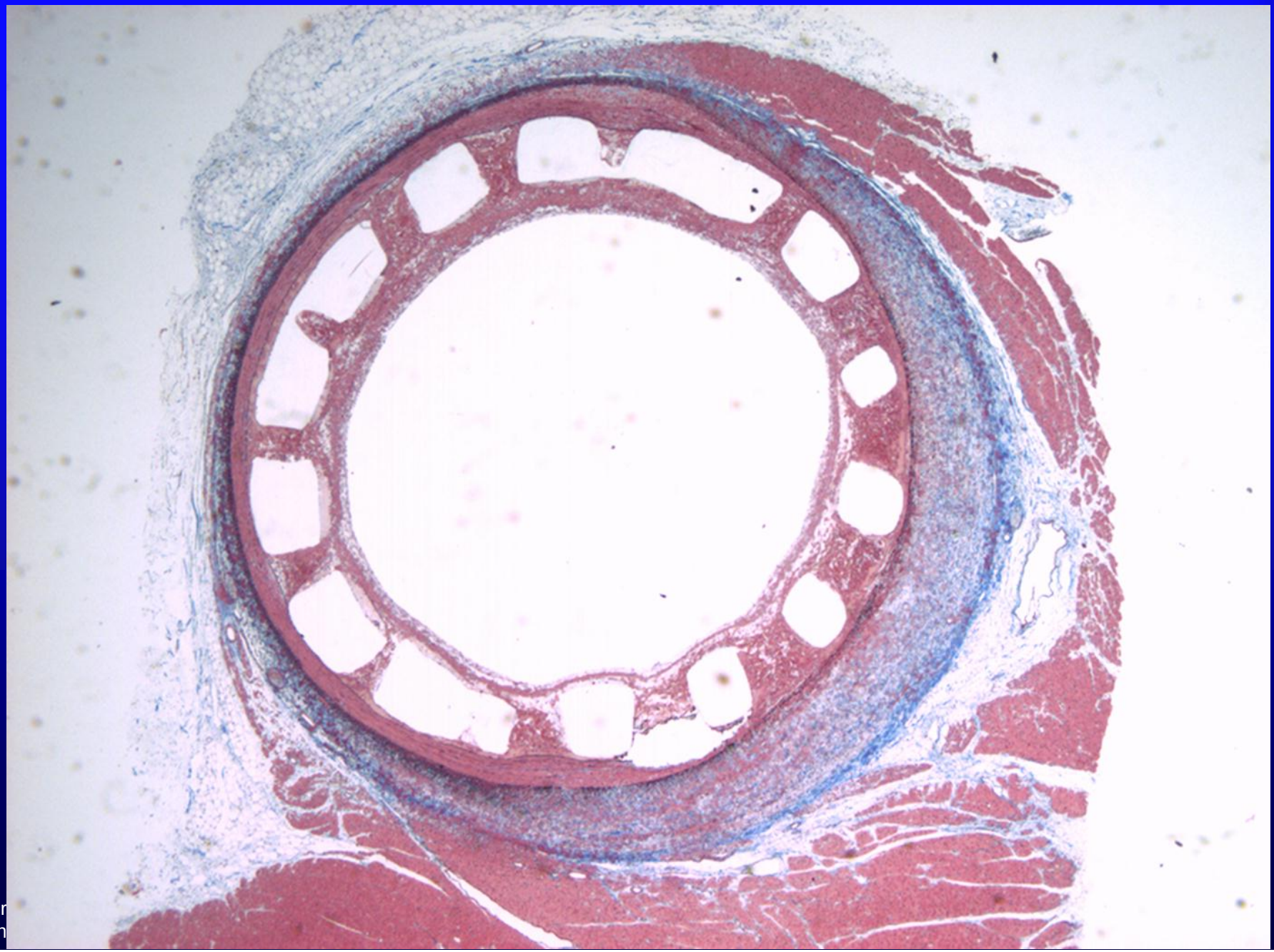
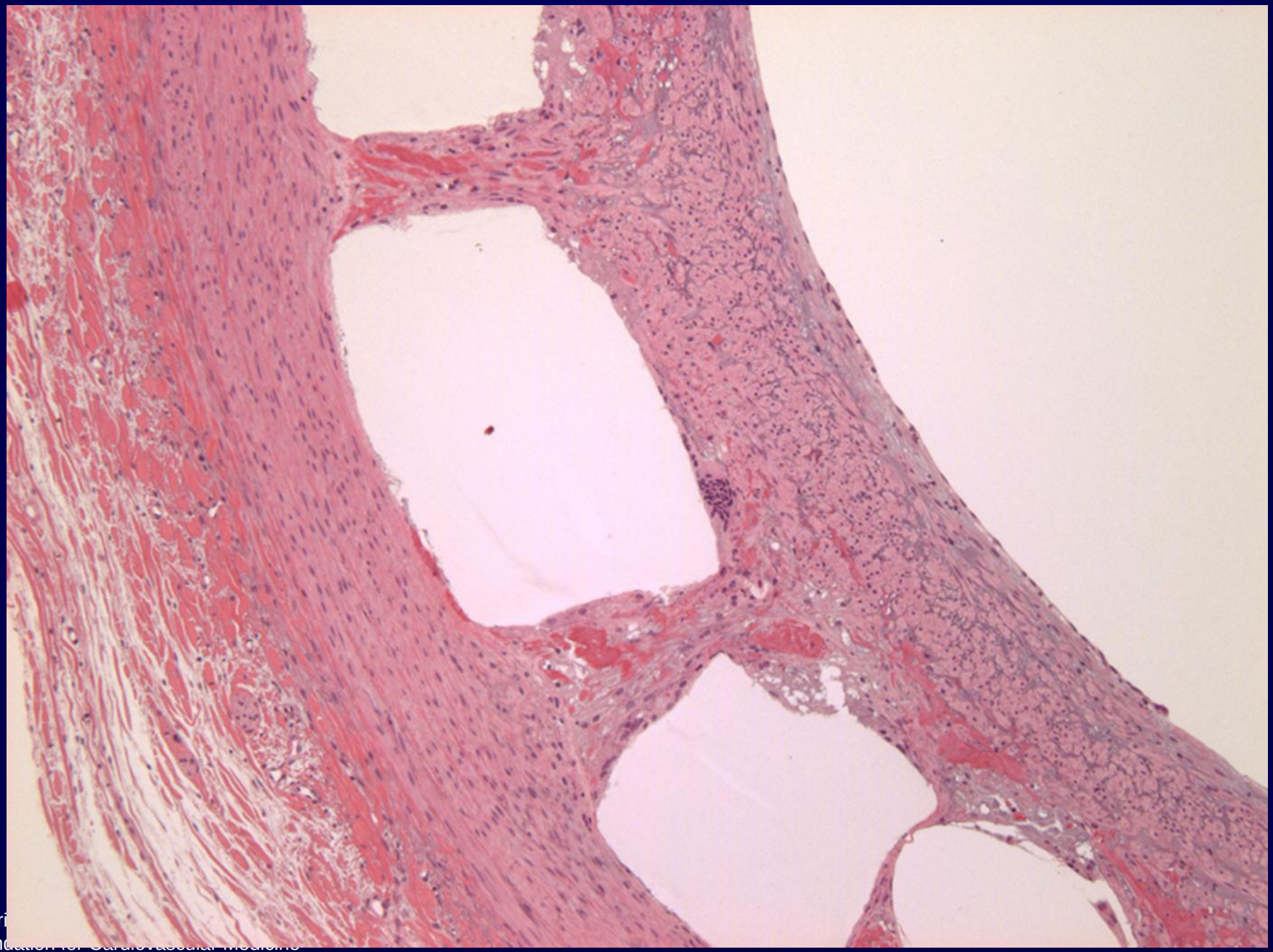

BTI STENT
1-mo implant
inflammation is minimal,
consisting mostly of multinucleated
foreign-body giant cells
H&E, 400X

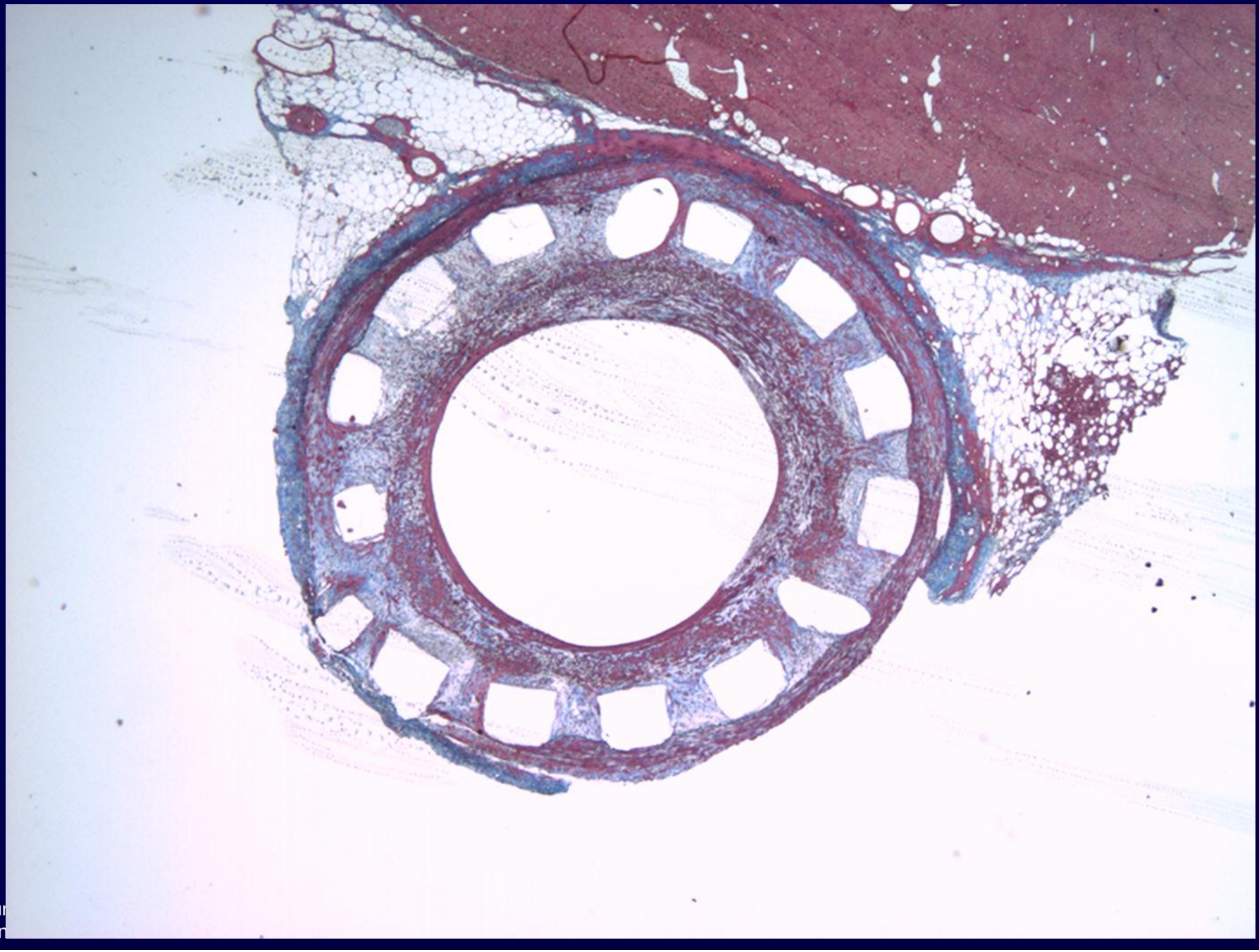
1-month



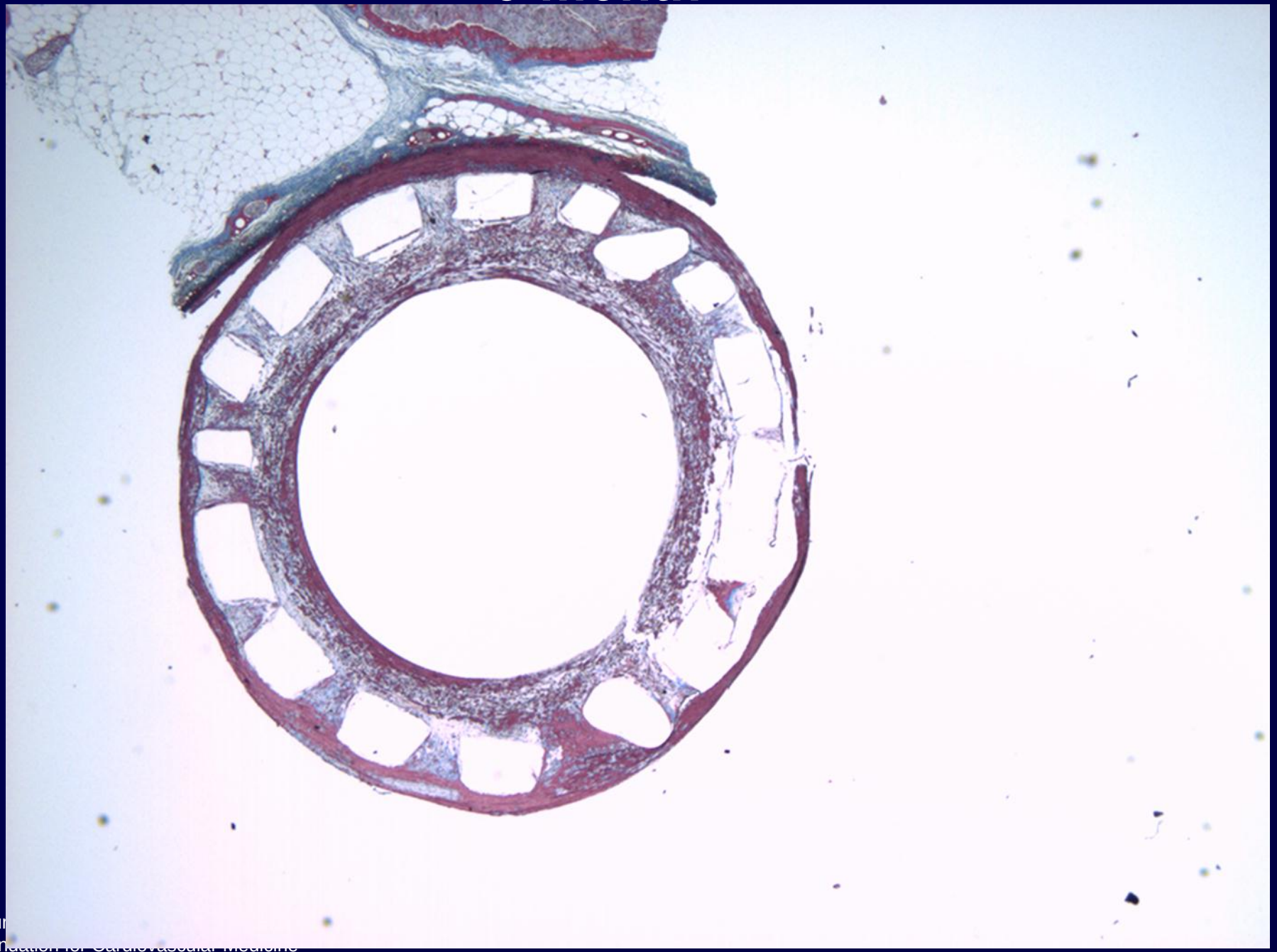
1-month



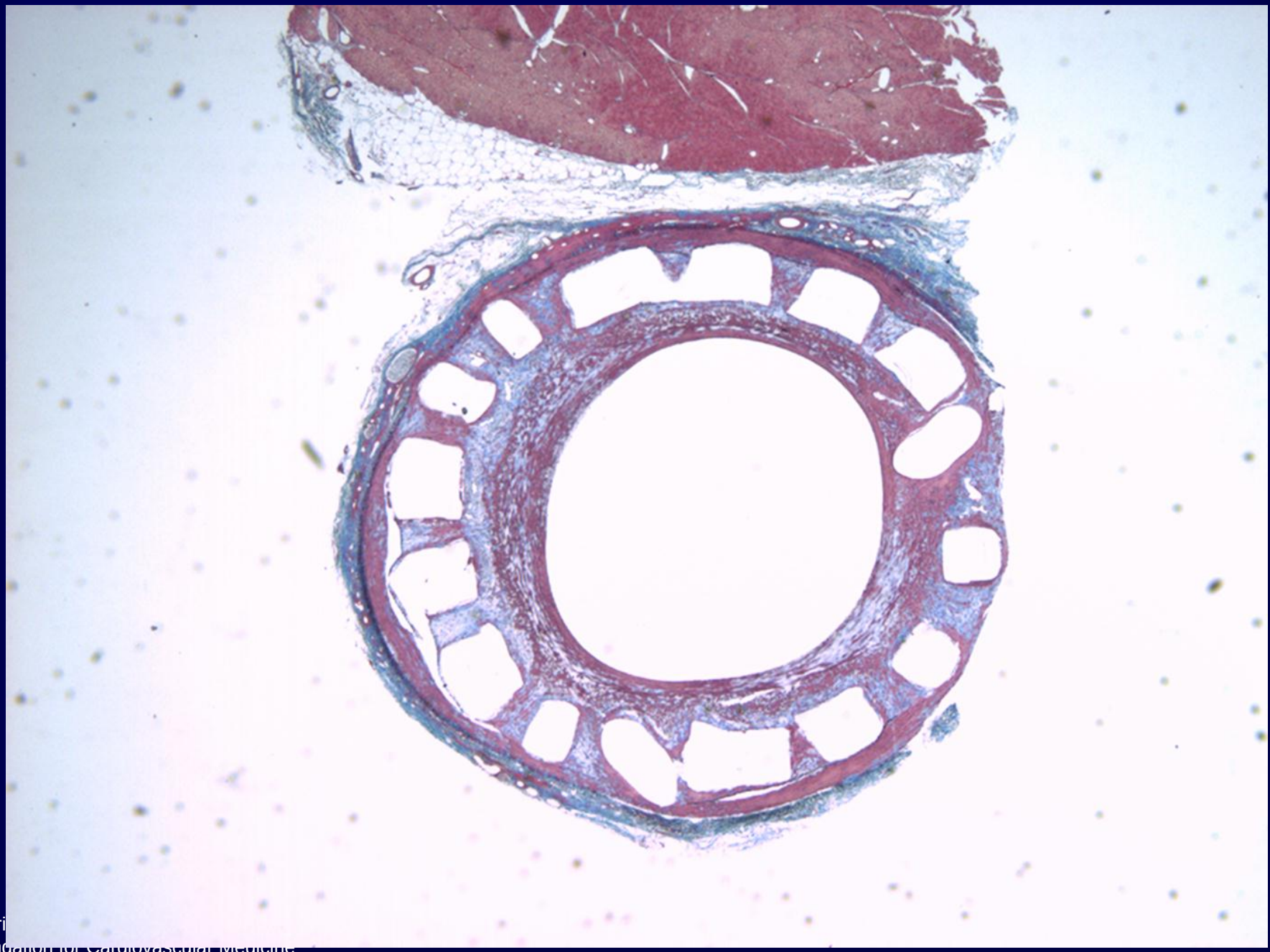
3-month



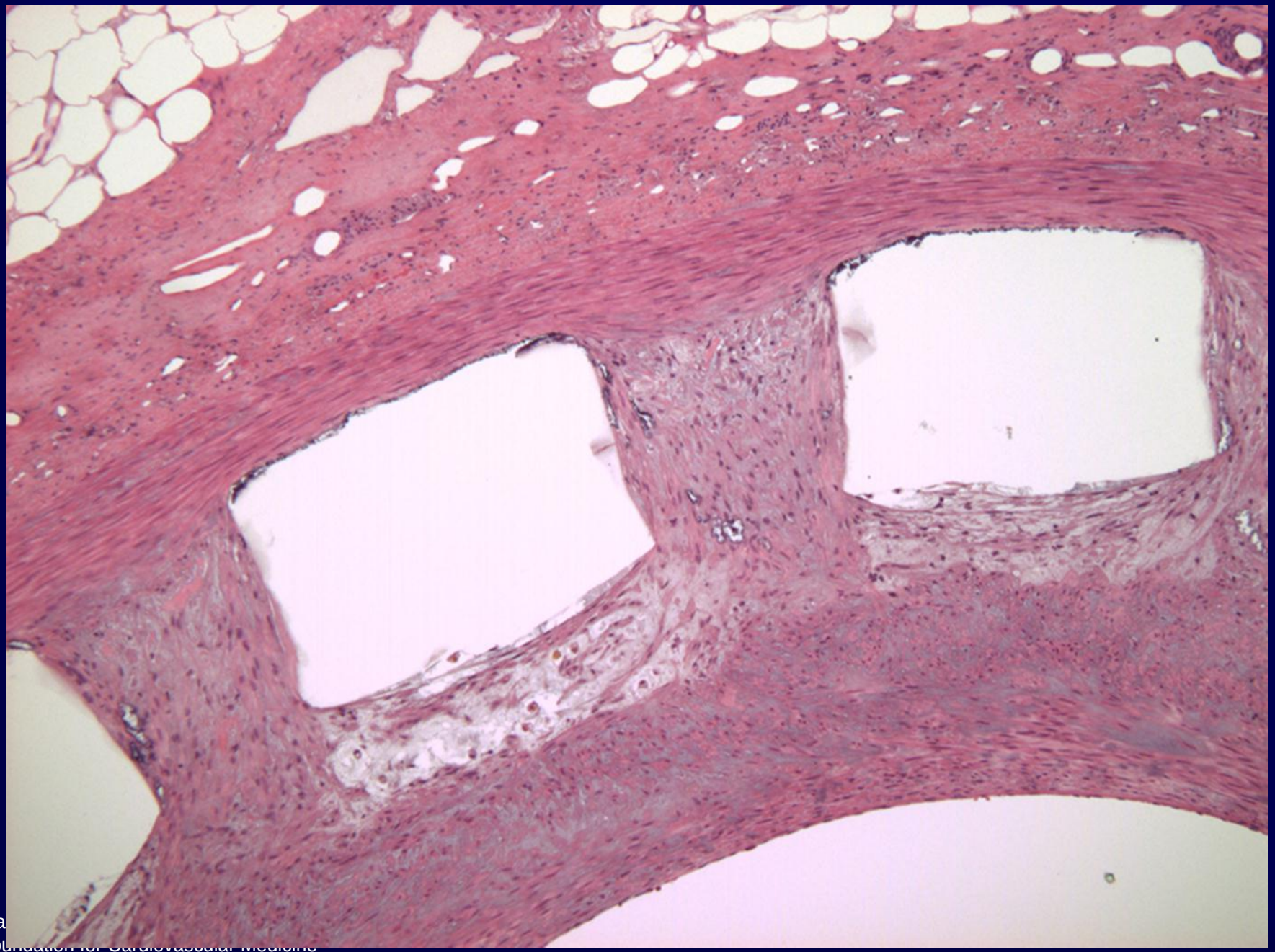
3-month



3-month



3-month



Ongoing & Upcoming Studies *(BTI STENT)*

- Preclinical - porcine coronary implants
  - Efficacy: 1, 3, 6 and 9 months follow up including IVUS and OCT
  - In vivo degradation (^{14}C label)
  - In vivo drug release pharmacokinetics
  - Flow cytometry (inflammatory & other markers)
  - Assay for inflammatory mediators (ROS, IL-1, etc.)
  - Thrombogenicity studies in baboon *ex-vivo* shunt
  - Vascular function proximal and distal to the stent
- First-in-man studies outside USA has been initiated

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Conclusion

- Though biodegradable polymer stents seem to be the ultimate candidate for the “ideal stent” further evaluation is needed to understand their role as a substitute for bare metal or present generation metallic drug eluting stents.
- They could also be the ideal vehicle for several other applications: non-obstructive vulnerable plaque, gene transfer for infract repair and angiogenesis…..

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