Biodegradable Stents

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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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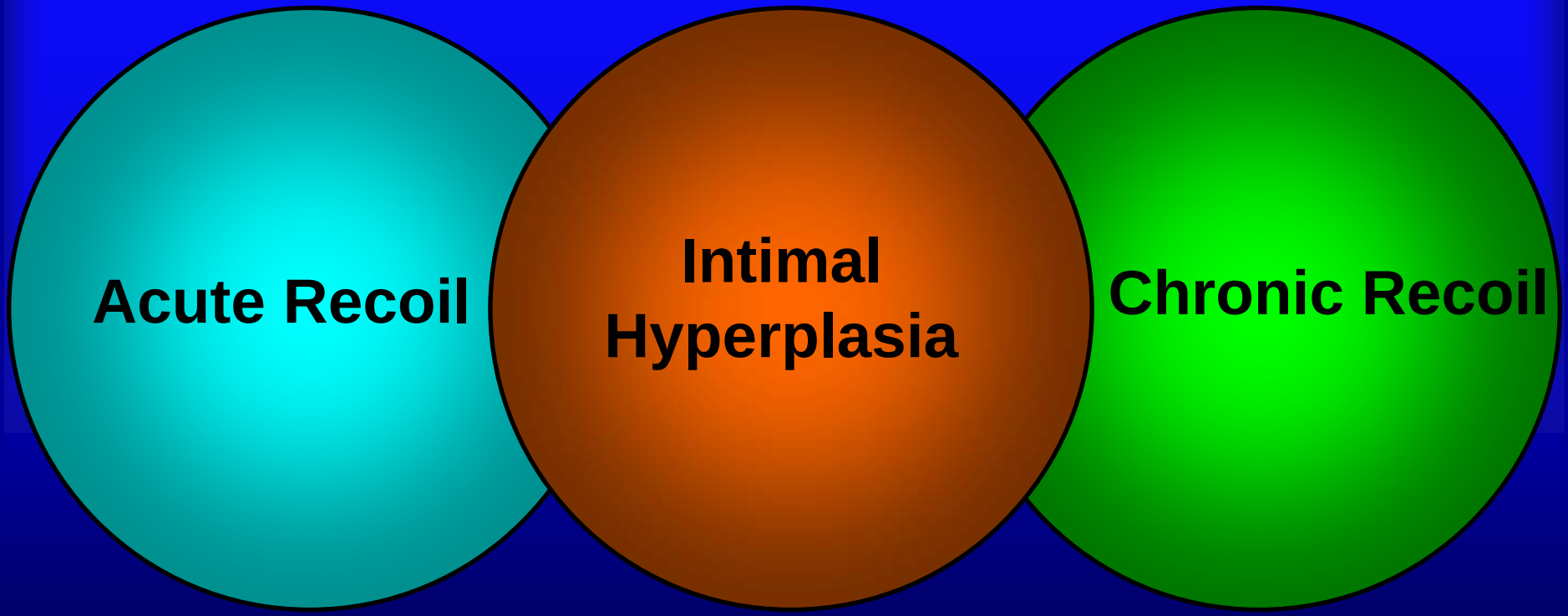
Mechanism of Restenosis



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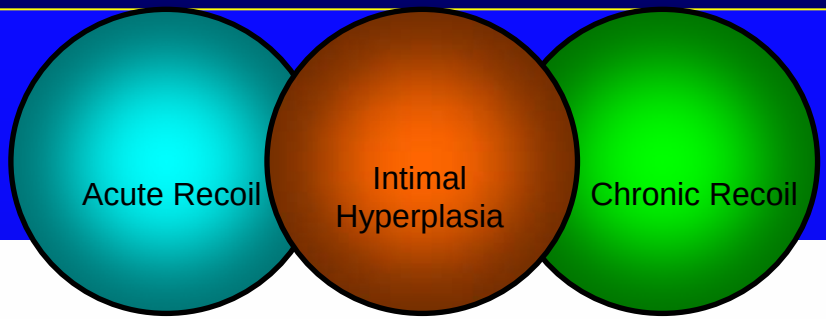
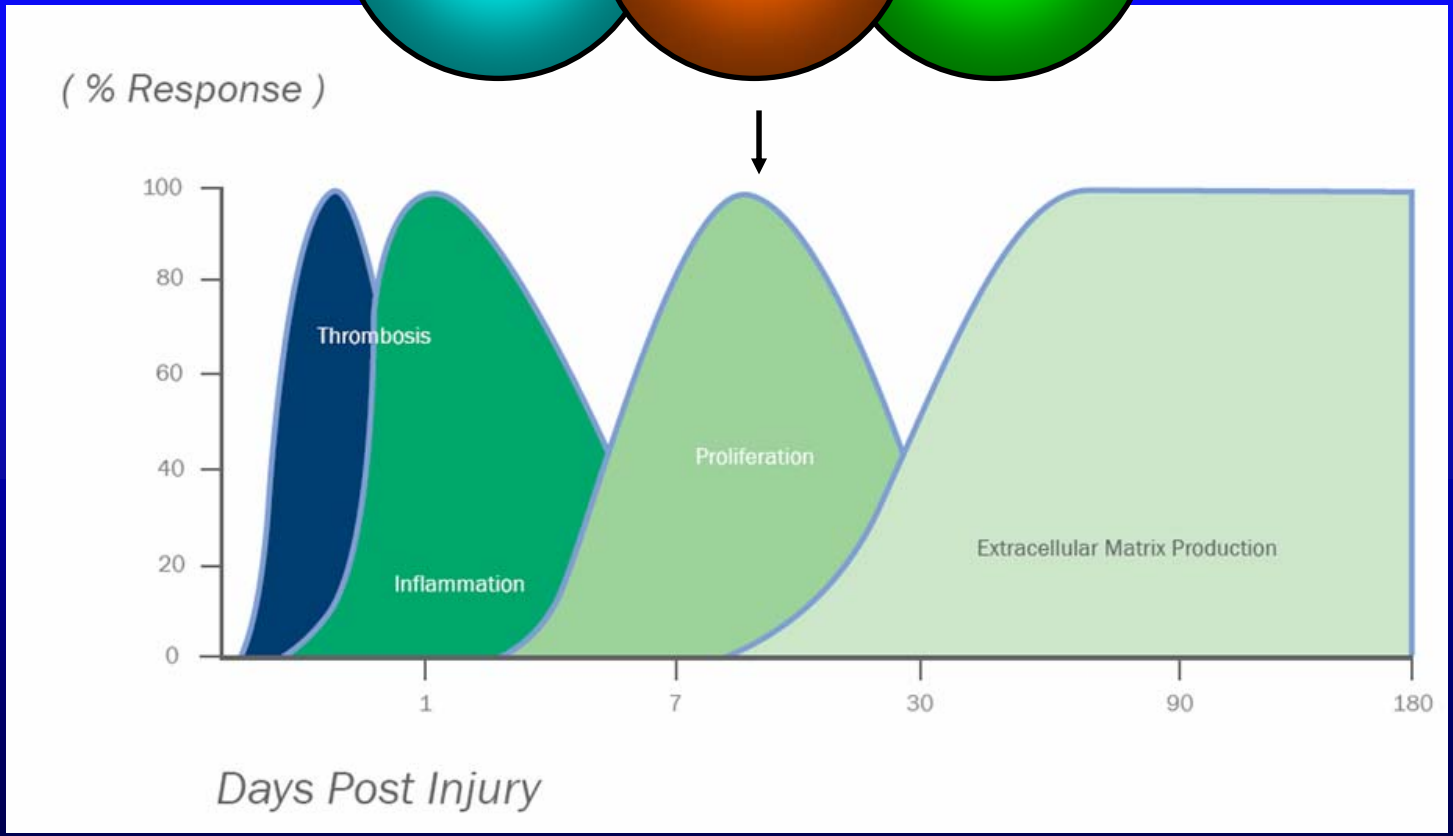
Intimal Hyperplasia





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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

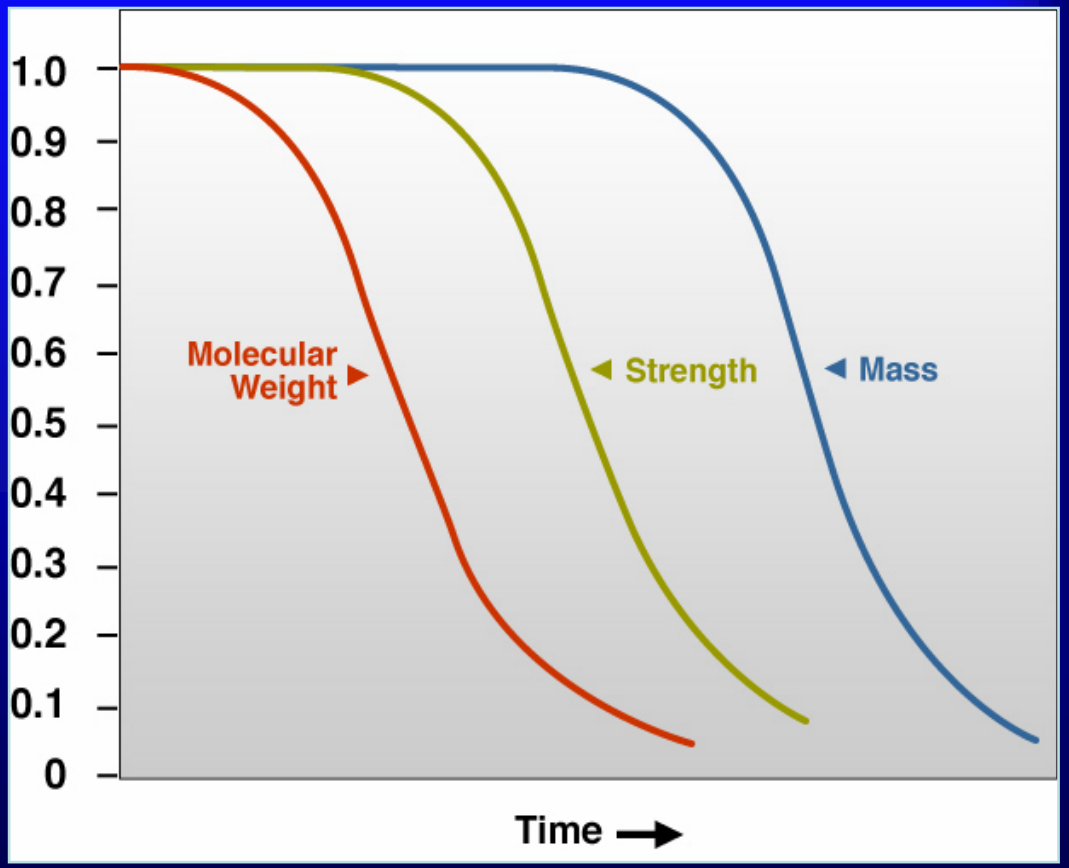
Lactic Acid

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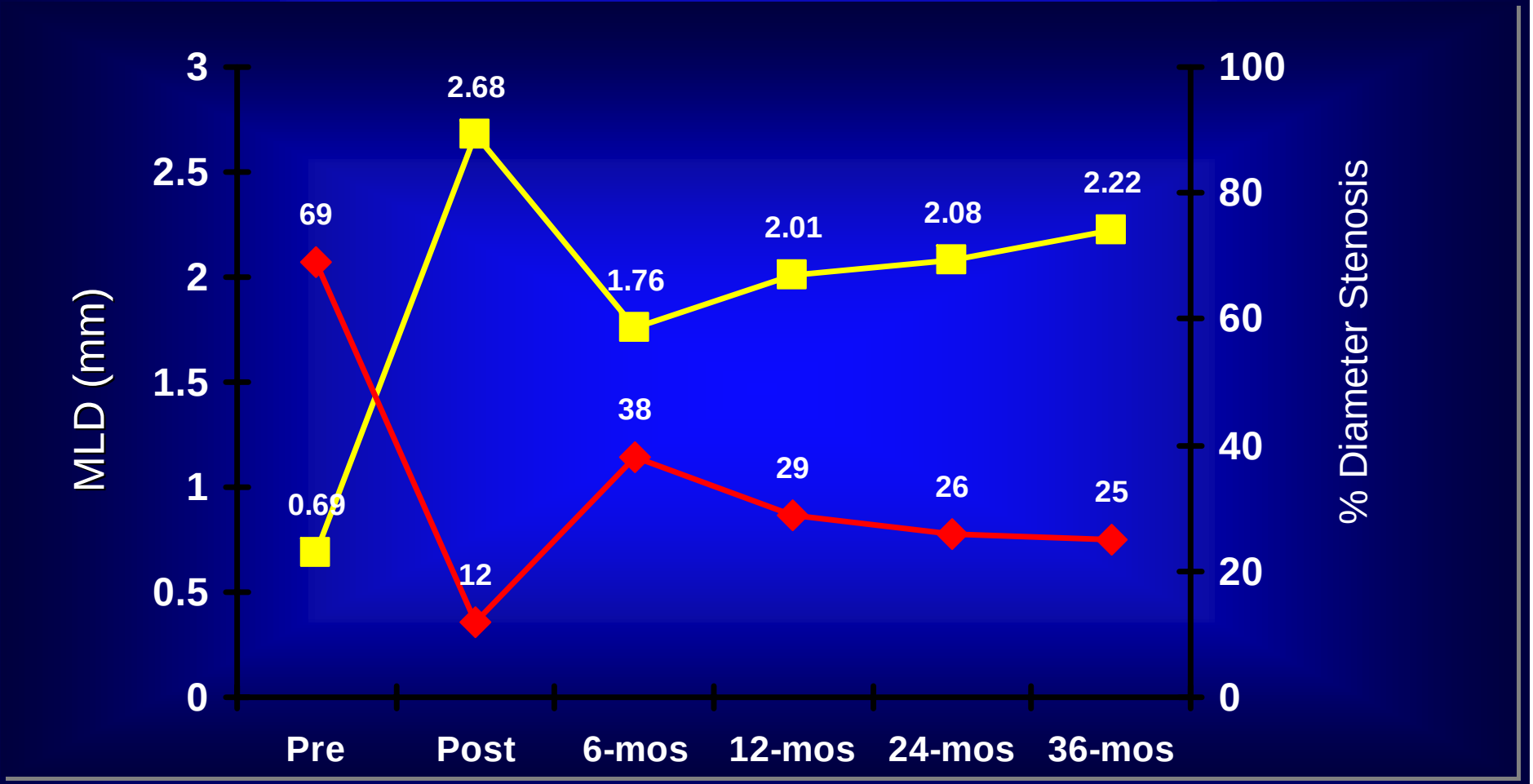
"Biodegradable Stents An update and work-in-progress" Presentation, Hideo Tamai CCT 2003
**ABRR (Angiographic Binary Restenosis Rate) per lesion.

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



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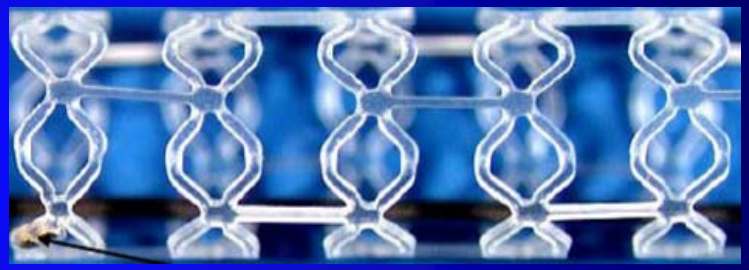
Tamai CCT 2004

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 Study Design

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

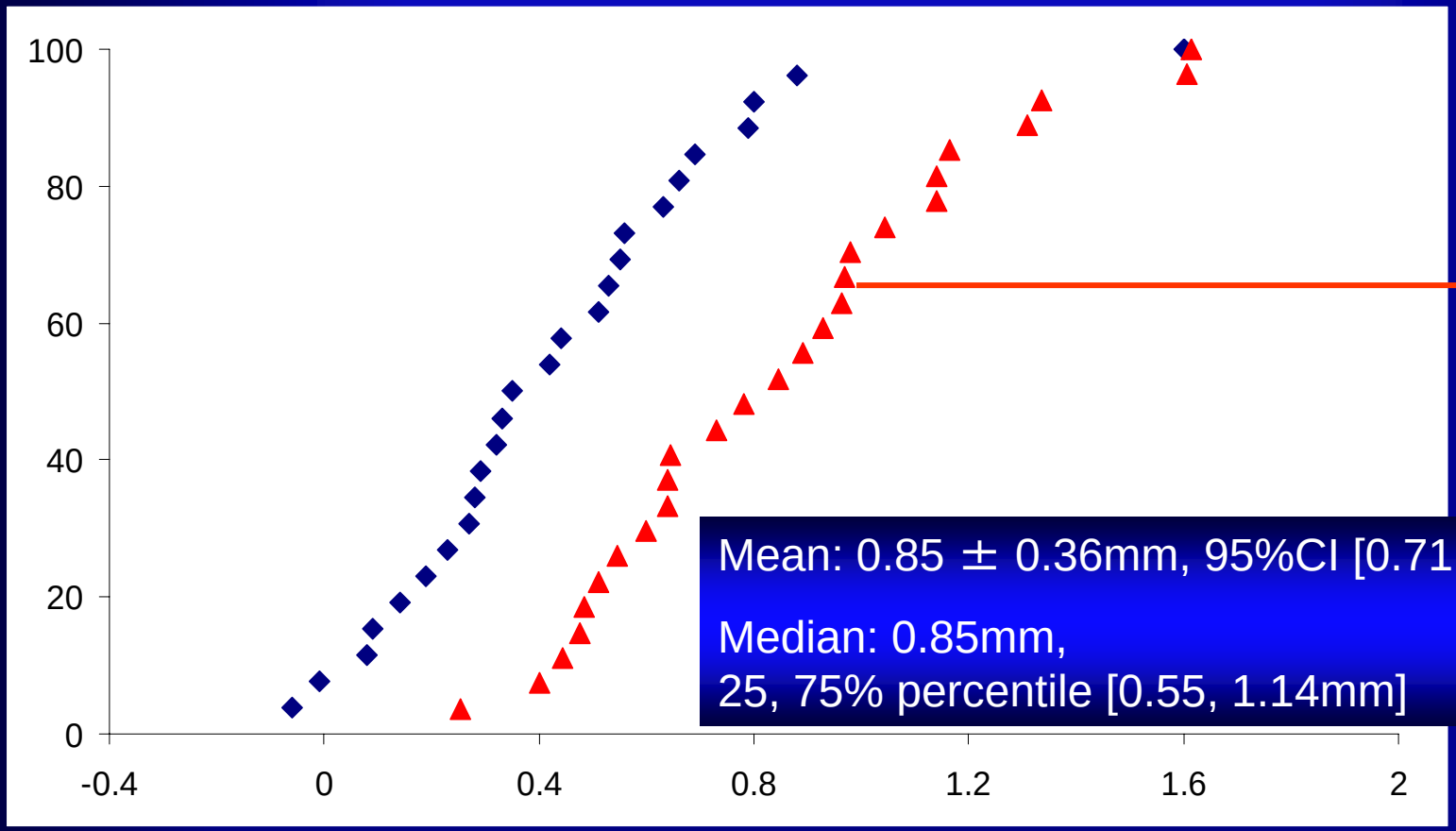
- Sponsor: Abbott Vascular
- Primary Investigators:
  - J Ormiston MD
  - PW Serruys MD, PhD
- DSMB: J Tijssen PhD, T Lefèvre MD, P Urban MD
- CEC: C Hanet MD, D McClean MD, V Umans MD
- Angiographic and IVUS Corelab: Cardialysis (Rotterdam, NL)

- 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

Serruys at al. ACC 2007

ABSORB
Late Loss (26 pts)



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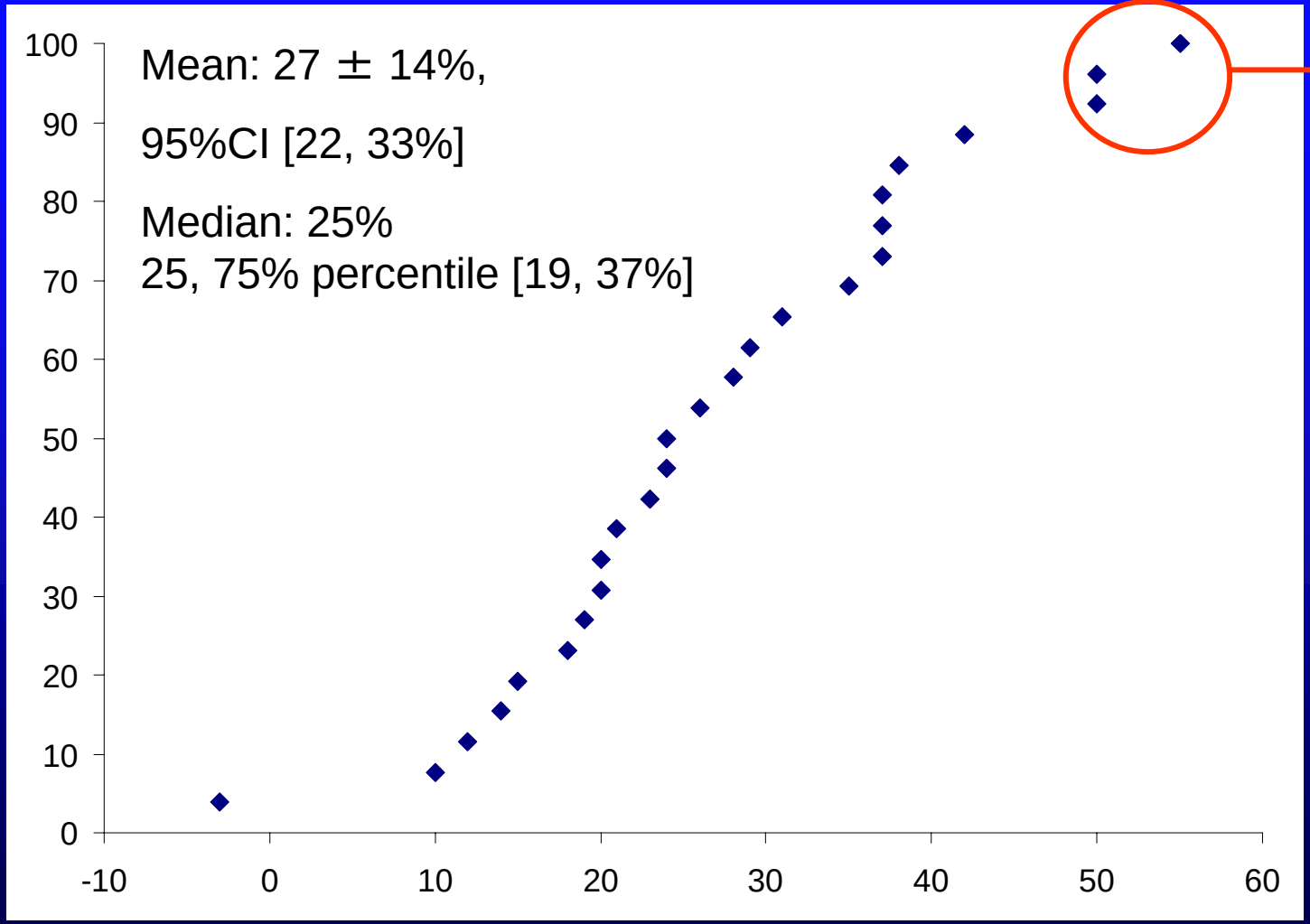
Diameter stenosis at follow-up (26pts)



Binary restenosis: 11.5 % (3/26)

No TLR

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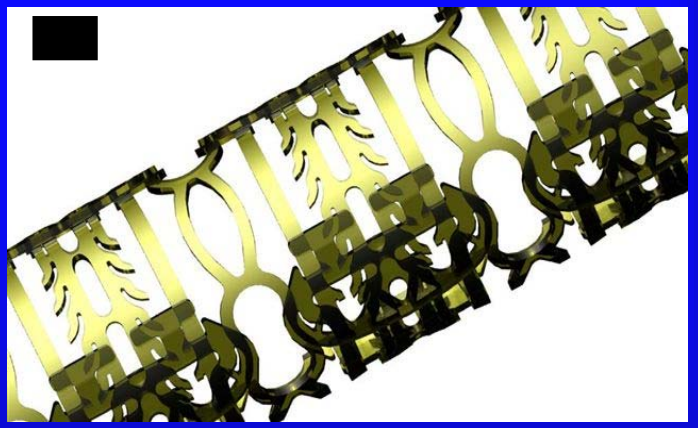
ABSORB:IVUS results (24 pts)

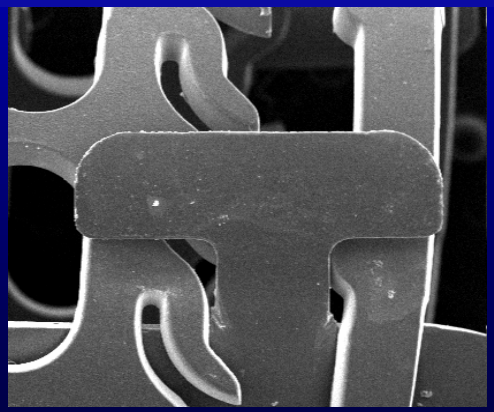
	Post-PCI	Follow-up	% Difference	p-value
Vessel area (mm^2)	13.55	13.49	-0.4	NS
EEM-Stent Area (mm^2)	7.47	8.08	+8.2	0.003
Stent area (mm^2)	6.08	5.37	-11.7	<0.001
Neointimal hyperplasia area (mm^2)	0	0.30	NA	NA
Lumen area (mm^2)	6.08	5.07	-16.6	<0.001
Stent area obstruction (%)	0	5.55	NA	NA

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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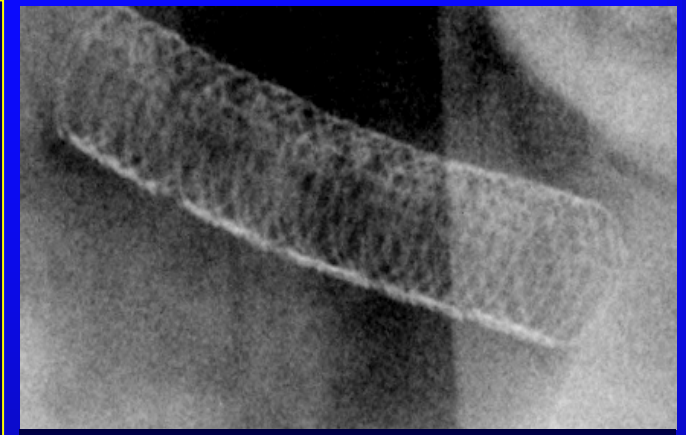
REVA
Bioresorbable Polymer Material

- 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

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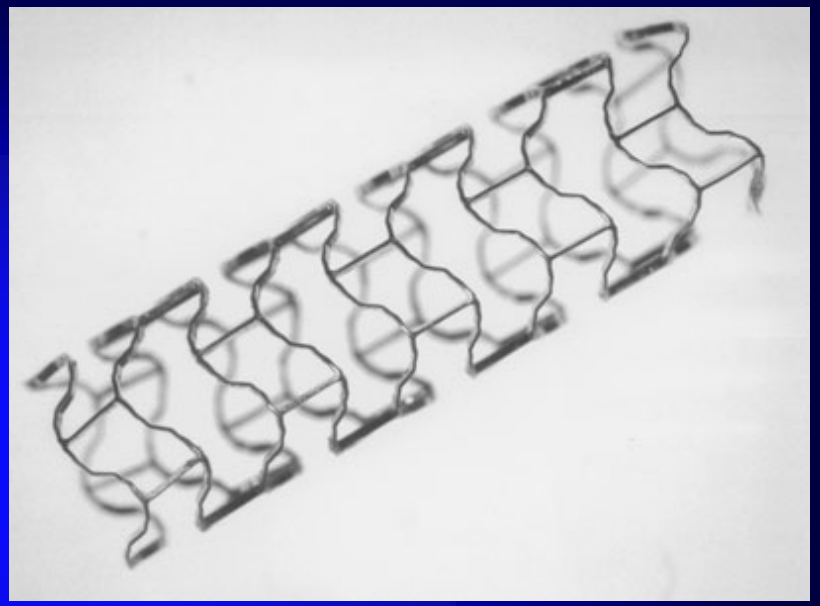
AMS, Biotronik
Magnesium Alloy Biodegradable Stent

Magnesium and the Human Body

- Essential element for human body involved in the synthesis of more than 300 enzymes (4th most common mineral)
- Quantity in human body: ~ 20 g
- Daily need (adult) : ~ 350 mg
- Quantity in the intracellular space: > 40%



3.0 x 10 mm stent: ~ 3 mg

- Degradation by replacement with Calcium and Phosphorous (2 months)

Bioabsorbable Therapeutics, BTI PAE Polymers

- Anti-inflammatory:
  - Salicylic acid (active ingredient in aspirin) chemically incorporated into polymer backbone

- Combination therapy:
  - Anti-neoplastic (sirolimus)
  - Plus anti-inflammatory (salicylic acid)
  - Elution over first month post-implant

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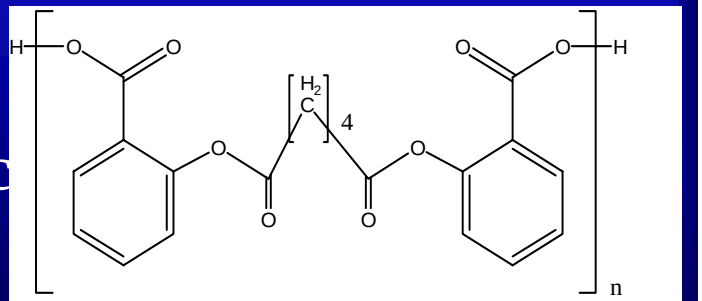
Polyanhydride Polymers (PAE)

Polymer A:

Salicylic acid — Polylactide Anhydride (Linker) — Salicylic acid

Polymer B:

Salicylic acid — Adipic acid — Salicylic acid



Poly(anhydride based on salicylic acid and adipic acid anhydride)

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Bioabsorbable Stent Design

Topcoat: Polymer B

Drug Layer: Polymer B + Sirolimus

Undercoat: Polymer B

Core: Polymer A

Coating Layers

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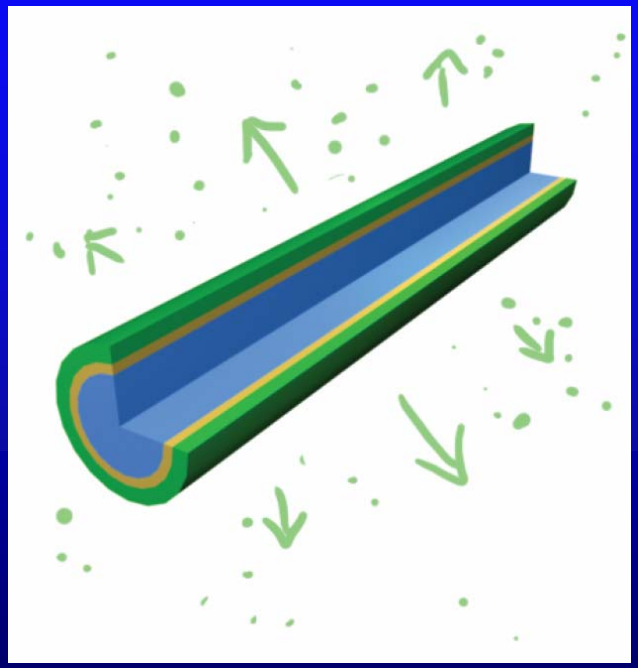
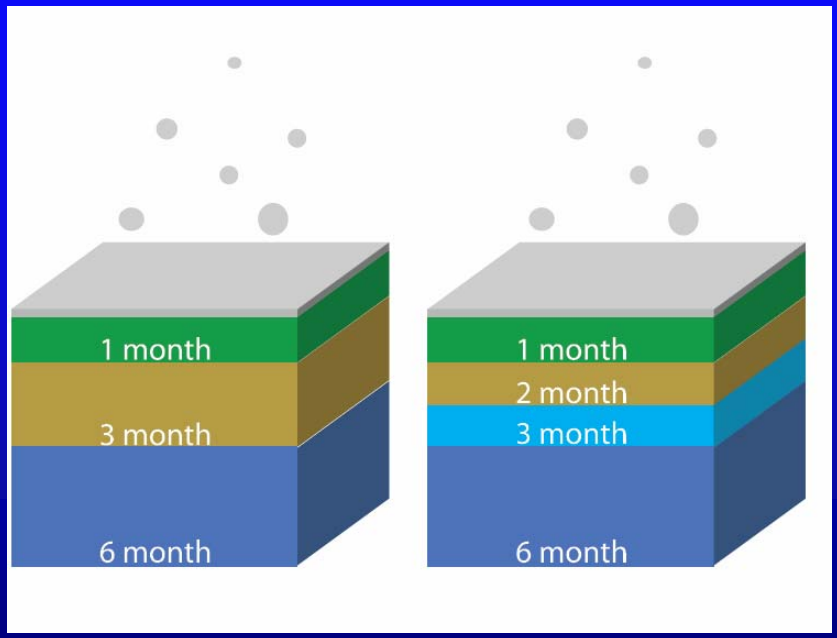
Multi-Layer, Combination Drug Delivery





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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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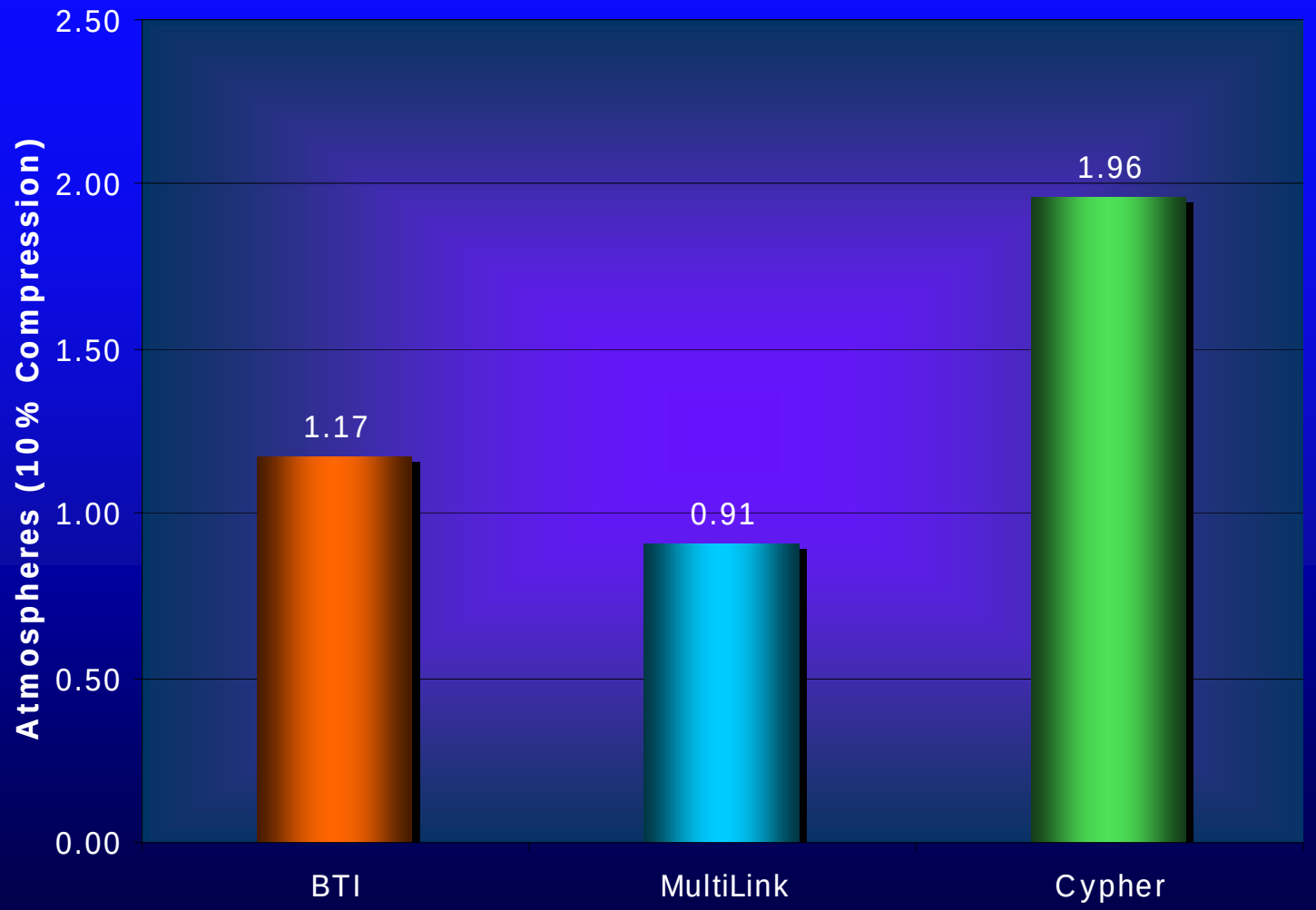
Radial Strength



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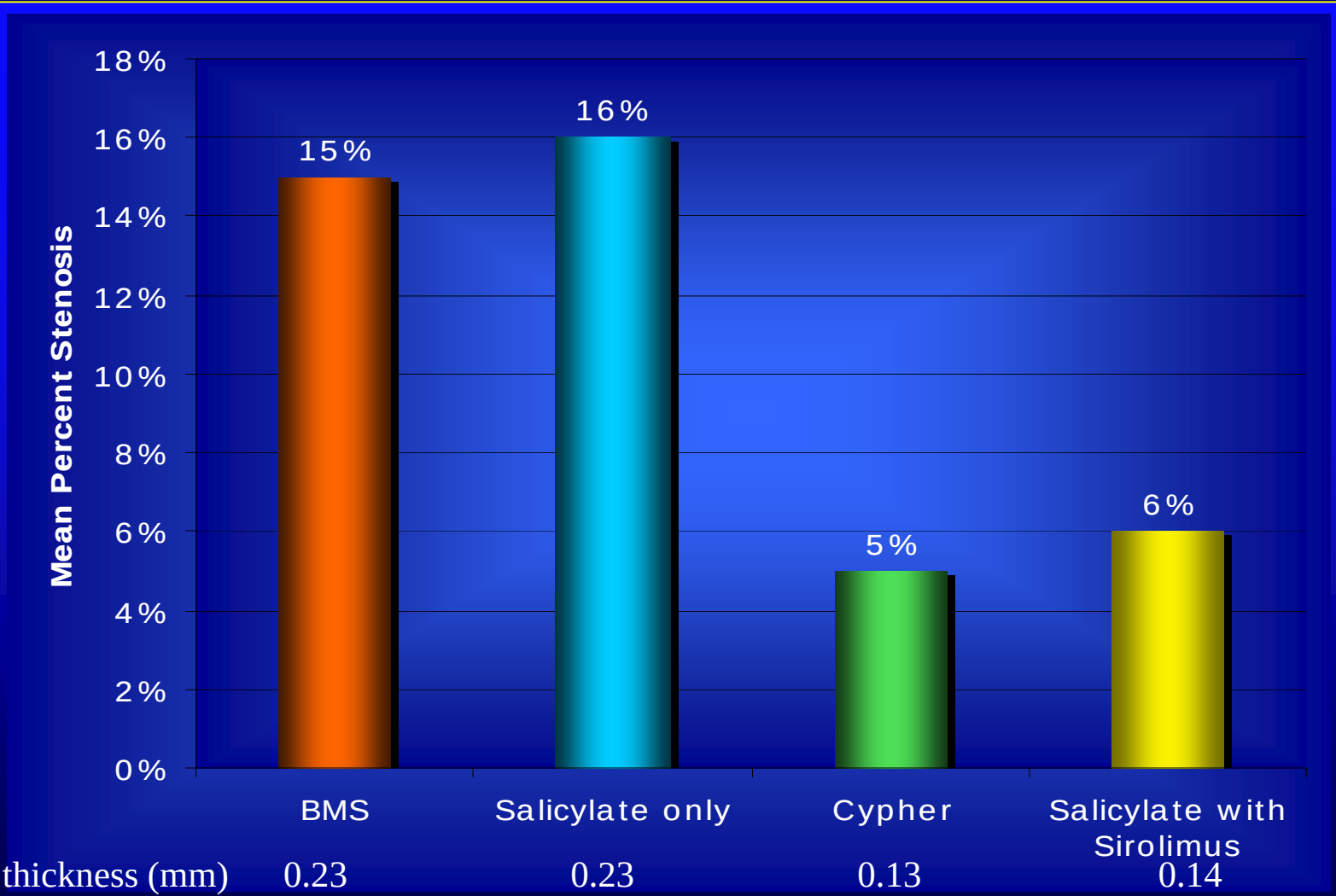
Mean Percent Stenosis in Pig Coronary Arteries One Month after Stent Implant



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

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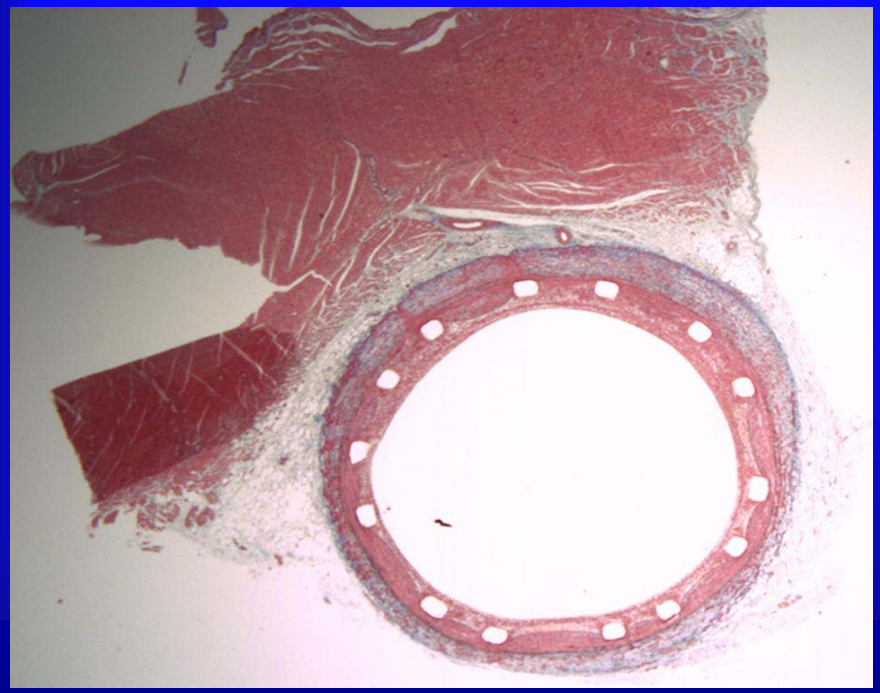
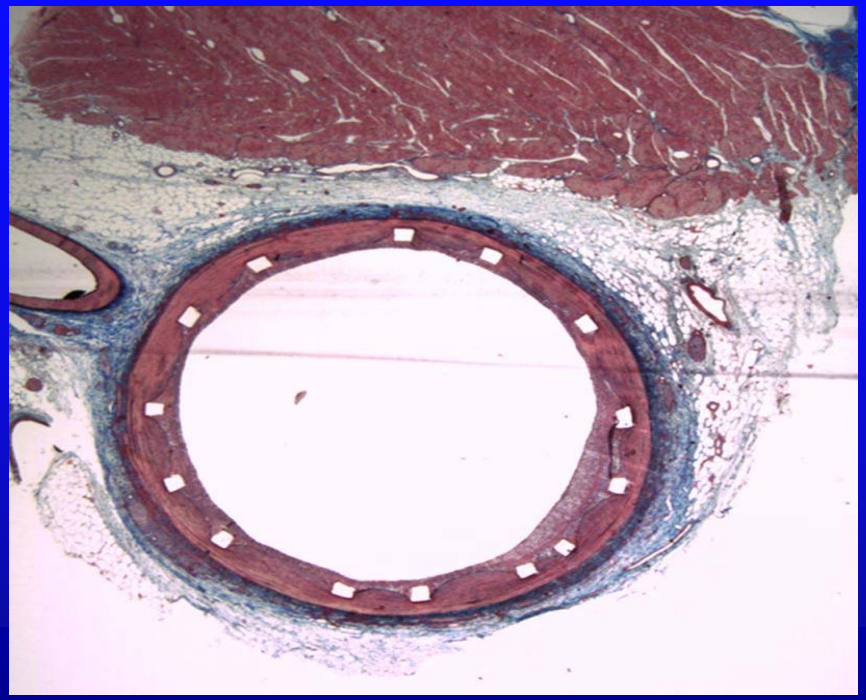
30-Day Histology





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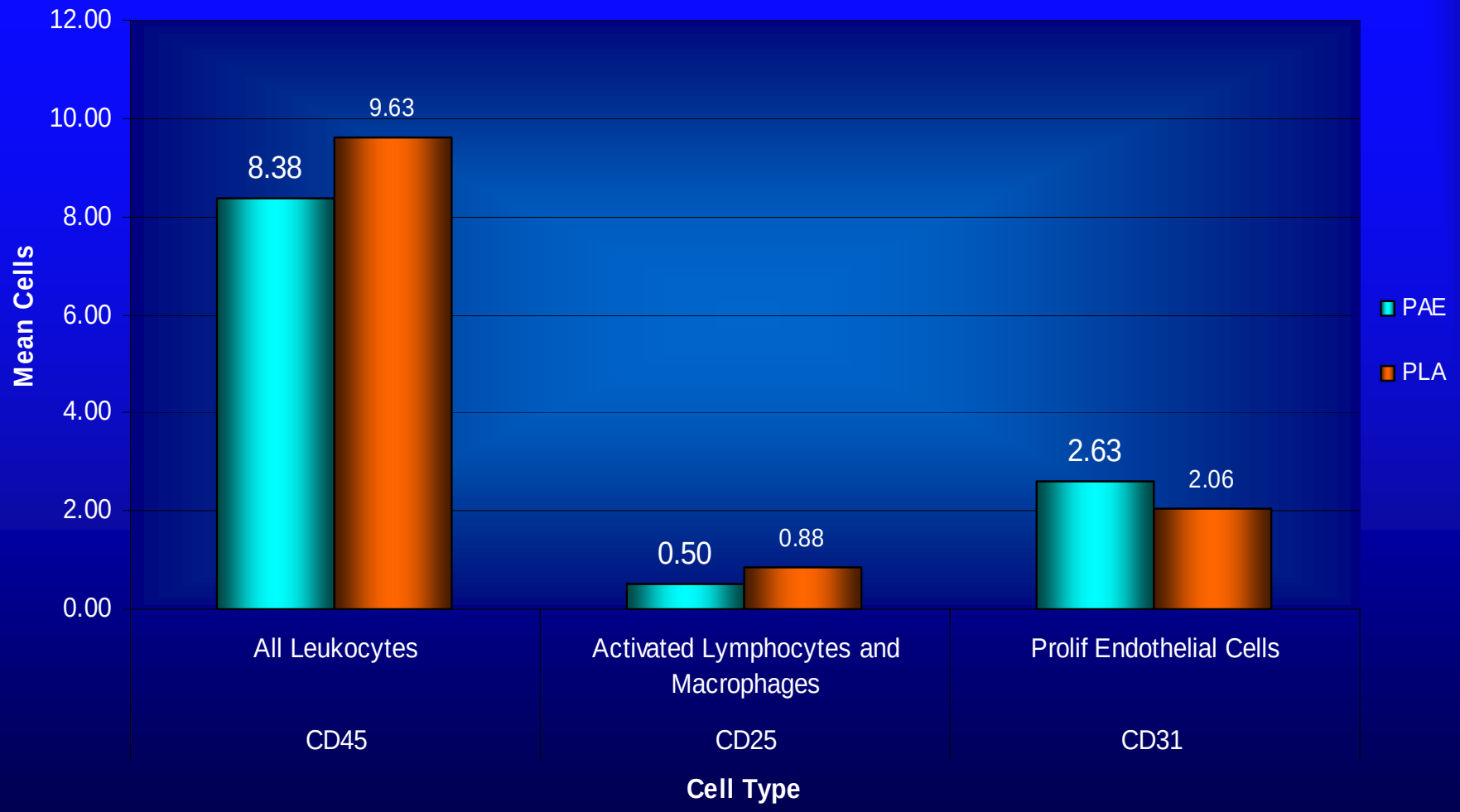
Day 3 Flow Cytometry



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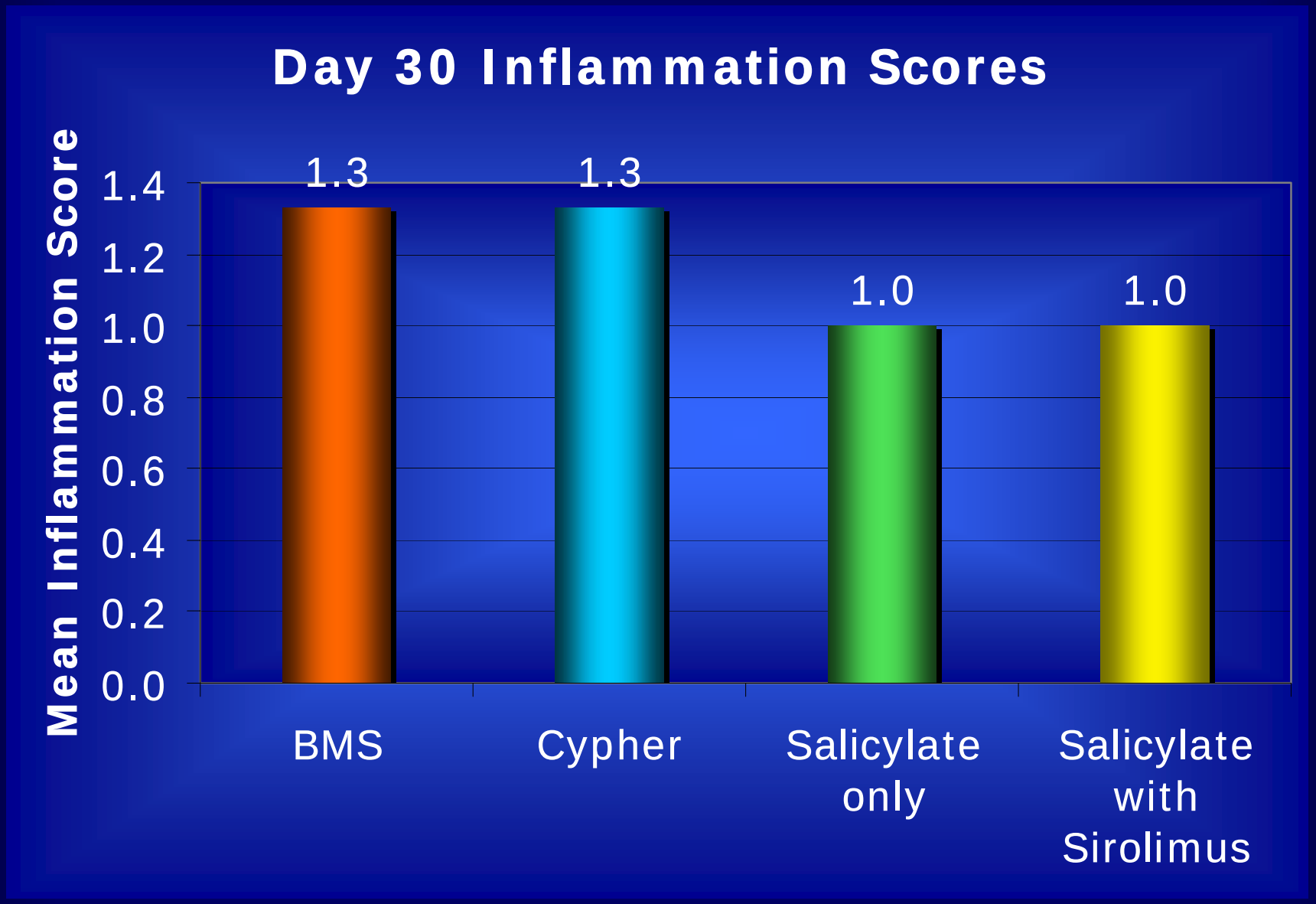

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Conclusion

- 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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“Biodegradable Stents: They Do Their Job and Disappear”

- Ron Waksman

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