

# BioMatrix™ :

The New Biodegradable Abluminally Coated DES  
BioMatrix™ Clinical Program

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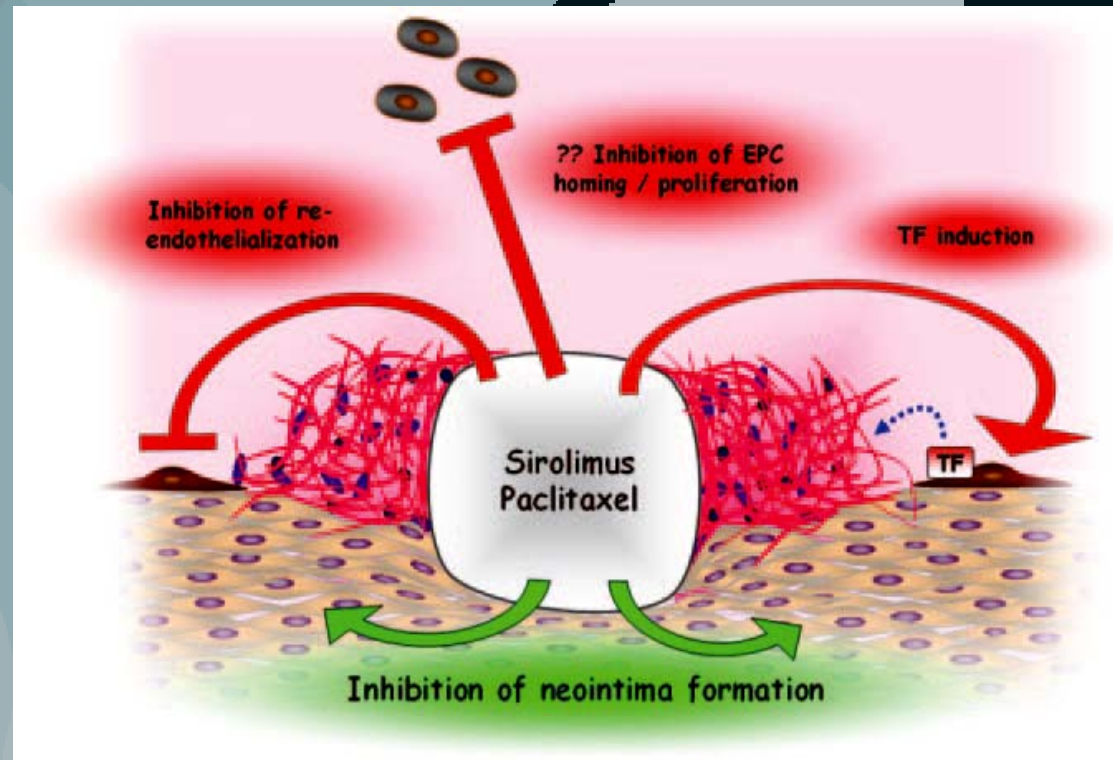
# Biodegradable Abluminally Coated DES:

## Why do we need it ?

- Several studies in the preclinical & clinical scenarios have documented **local inflammatory reactions (delayed healing & hypersensitivity)** after 1<sup>st</sup>-generation DES deployment, which have been considered one of the possible mechanisms of **late & very late stent thrombosis**.
- Because the **drugs are the 1<sup>st</sup> to disappear usually < 3 months** after stent deployment, **durable polymers** are speculated to be the main DES components to instigate this untoward local reaction.
- Possible solution: **Biodegradable polymer & stents**

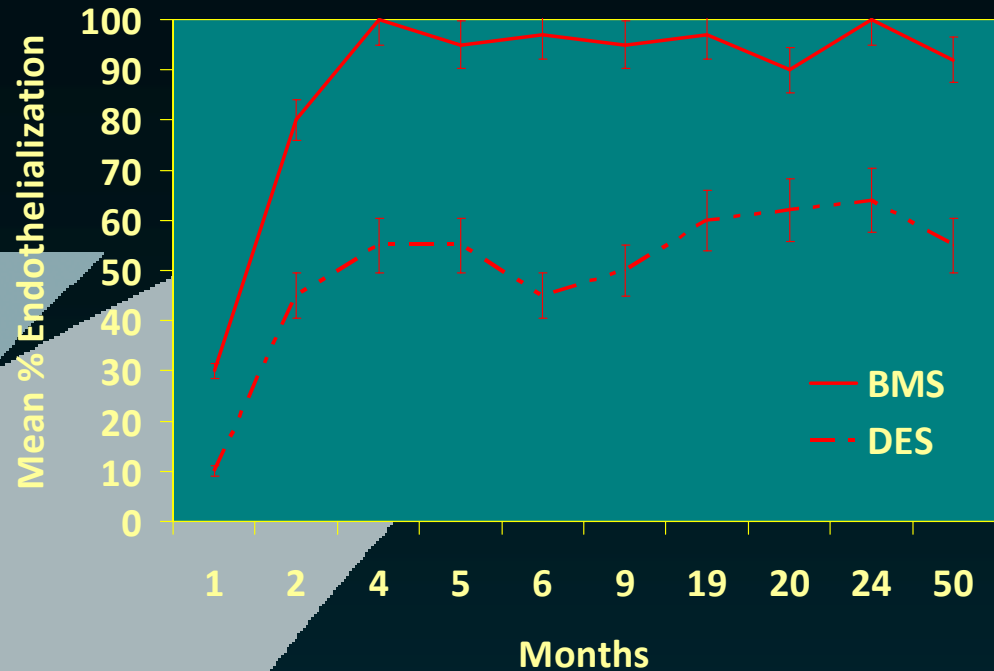
# DES reduce Neointima Formation, but may increase Stent Thrombogenicity:

Effect of sirolimus-eluting / paclitaxel-eluting stent strut on the local vessel wall

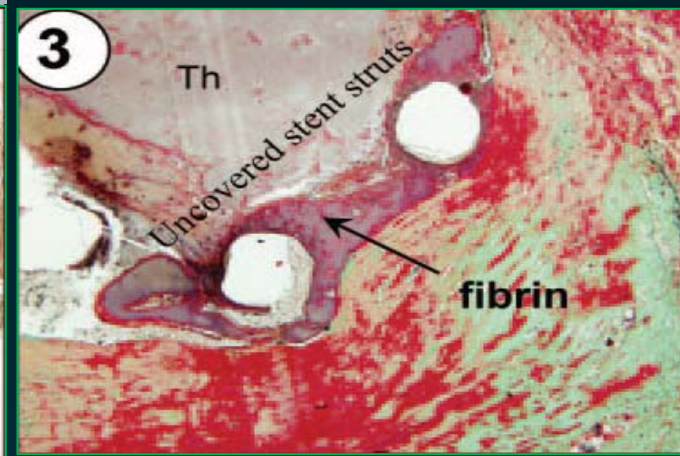
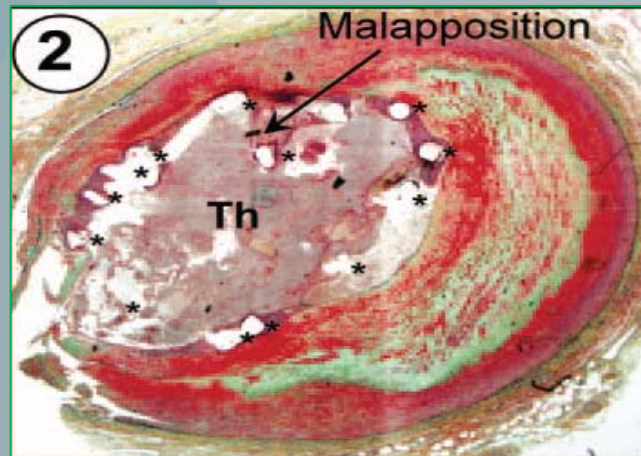


Sirolimus / paclitaxel reduces neointima formation by inhibiting vascular smooth muscle migration & proliferation (green arrows). However, the drugs also **inhibit reendothelialization**, **induce tissue factor (TF)**, & may **prevent homing & proliferation of endothelial progenitor cells (EPCs; red arrows/bars)**.

# Temporal sequence of reendothelialization in BMS & DES in man.



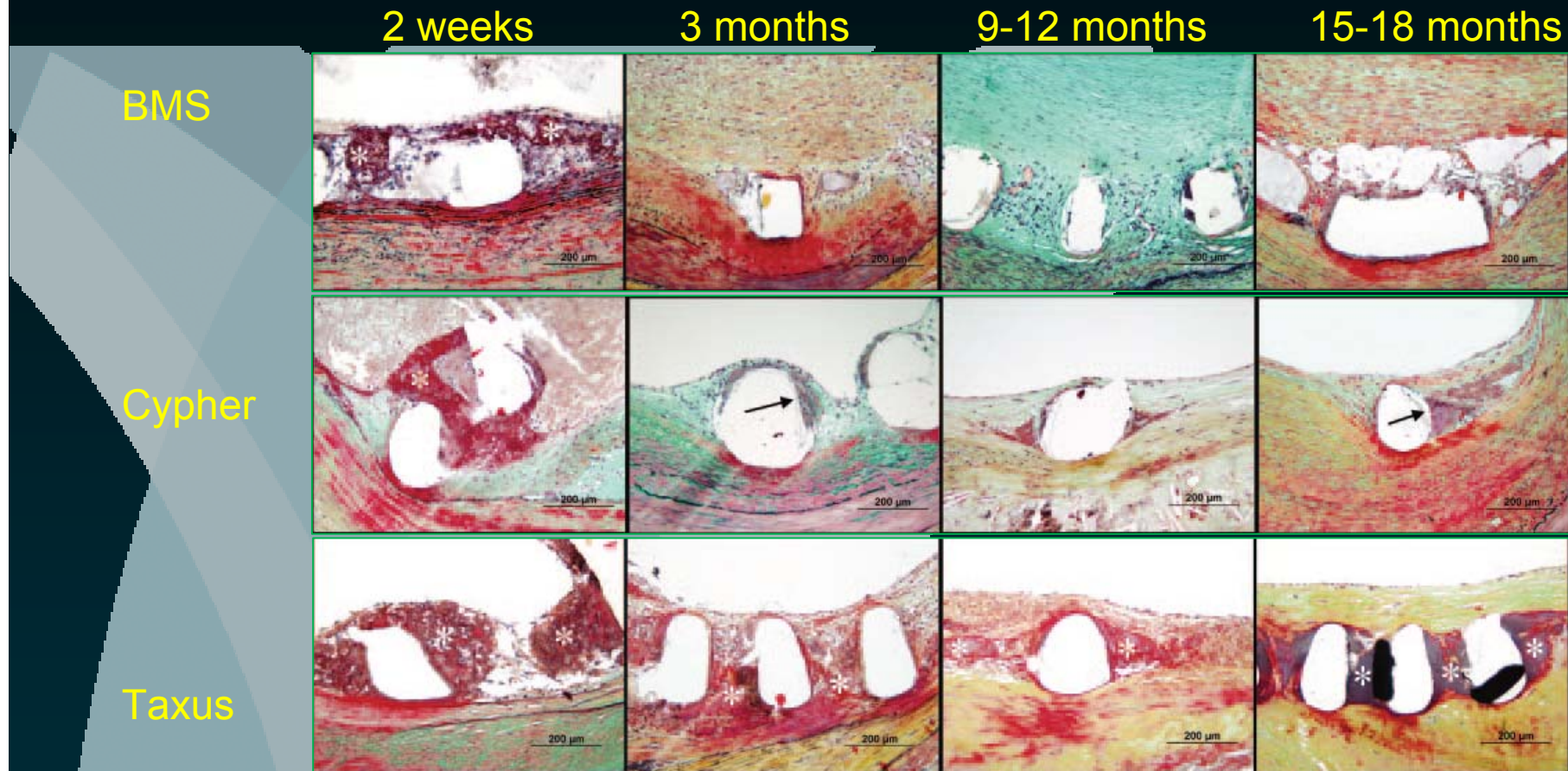
Radiograph of the stented LAD from a 38-yr-old woman who had undergone **stenting of the prox. LAD** with a 3.0/12-mm Taxus stent 6 mo's before death



Low & high (respectively) power magnification of sections (Movat stain). There is **total occlusion of the lumen by a platelet-rich thrombus (Th)** with **absence of healing of the stent strut regions, which are surrounded by fibrin**. Note a single stent strut is malapposed (arrow). High-power view of the stent struts shows **uncovered struts surrounded by fibrin with absence of endothelium & inflammatory cells**.

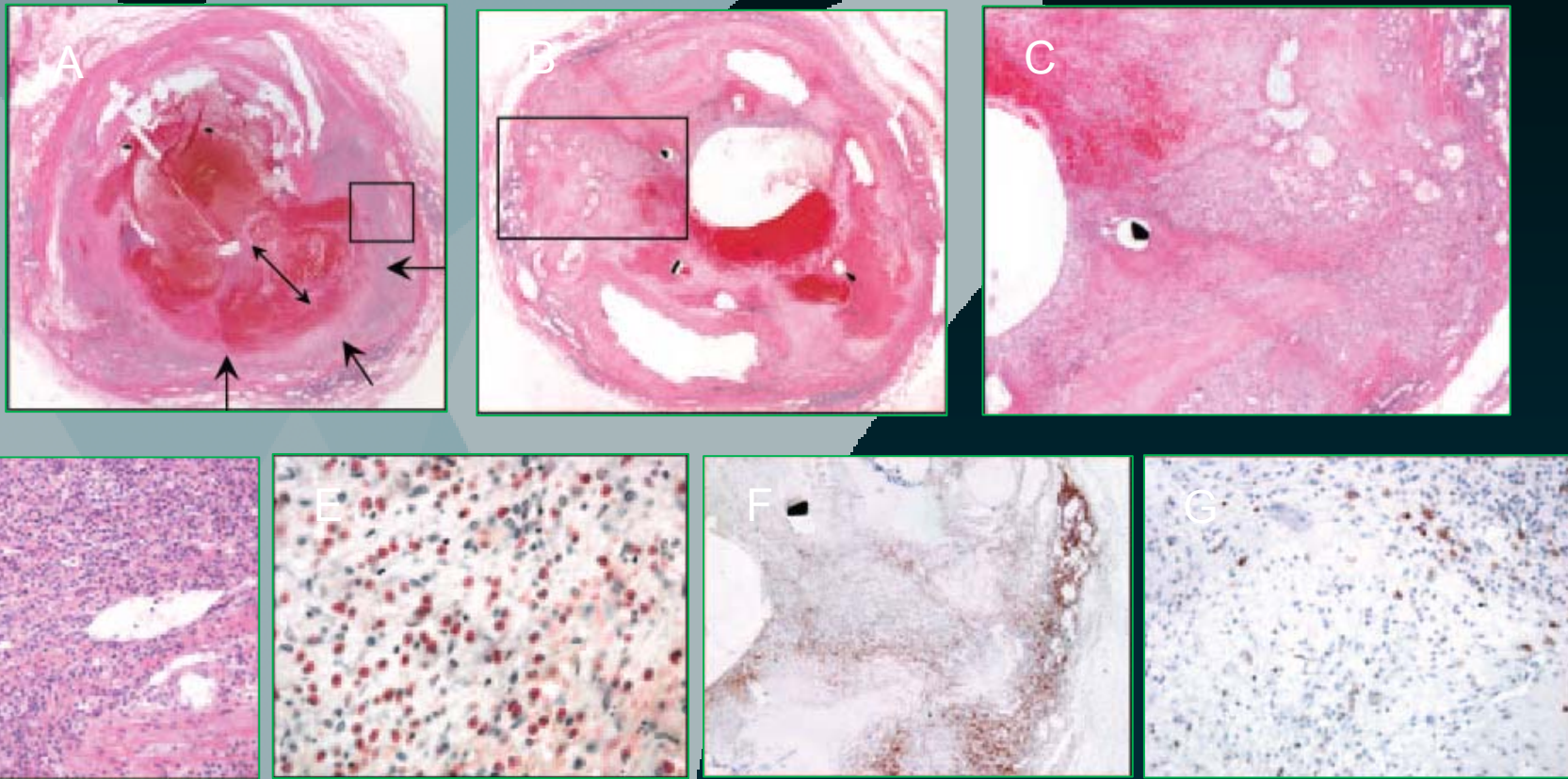
# Morphological changes after DES & BMS implantation

Human pathologic specimens from 2 wk's to 18 mo's after stenting.



Peristut fibrin thrombus is most prominent at 2 wks' (no difference in BMS vs DES). At 3 mo's, complete arterial healing, incl. a well-established neointimal layer, with neointimal thickness peaking around 9 to 12 mon's & regression is seen thereafter in BMS. **Cypher** stents show an inflammatory infiltrate, fibrin deposition, & only rare smooth muscle & endothelial cells at 3 mo's with minimal to no significant increase in neointima at 15 to 18 mo's. **Taxus** stents show more fibrin deposition surrounding stent struts (\*), which persists up to 18 mo's. **Cypher** DES shows predominance of inflammatory cells, including giant cell formation (black arrowheads), at early & late time points with less fibrin deposition than in **Taxus** stents.

# Histological findings from a patient who died of late stent thrombosis



Two Cypher stents had been placed in the LCX for unstable angina 18 mo's before presentation with chest pain. A focal malapposition with aneurysmal dilatation (double arrow) & stent malapposition with **occlusive thrombus** in the lumen. B, The **vessel wall is highly inflamed** & high power images show an **extensive inflammatory infiltrate consisting mostly of eosinophils** (C & D). E shows Luna stain for **eosinophils**, F **T-lymphocytes (CD45Ro)**, & G **macrophages (CD 68)**. (Reproduced with permission from Virmani et al.)

Are All DES  
with Biodegradable Polymer  
created the same?

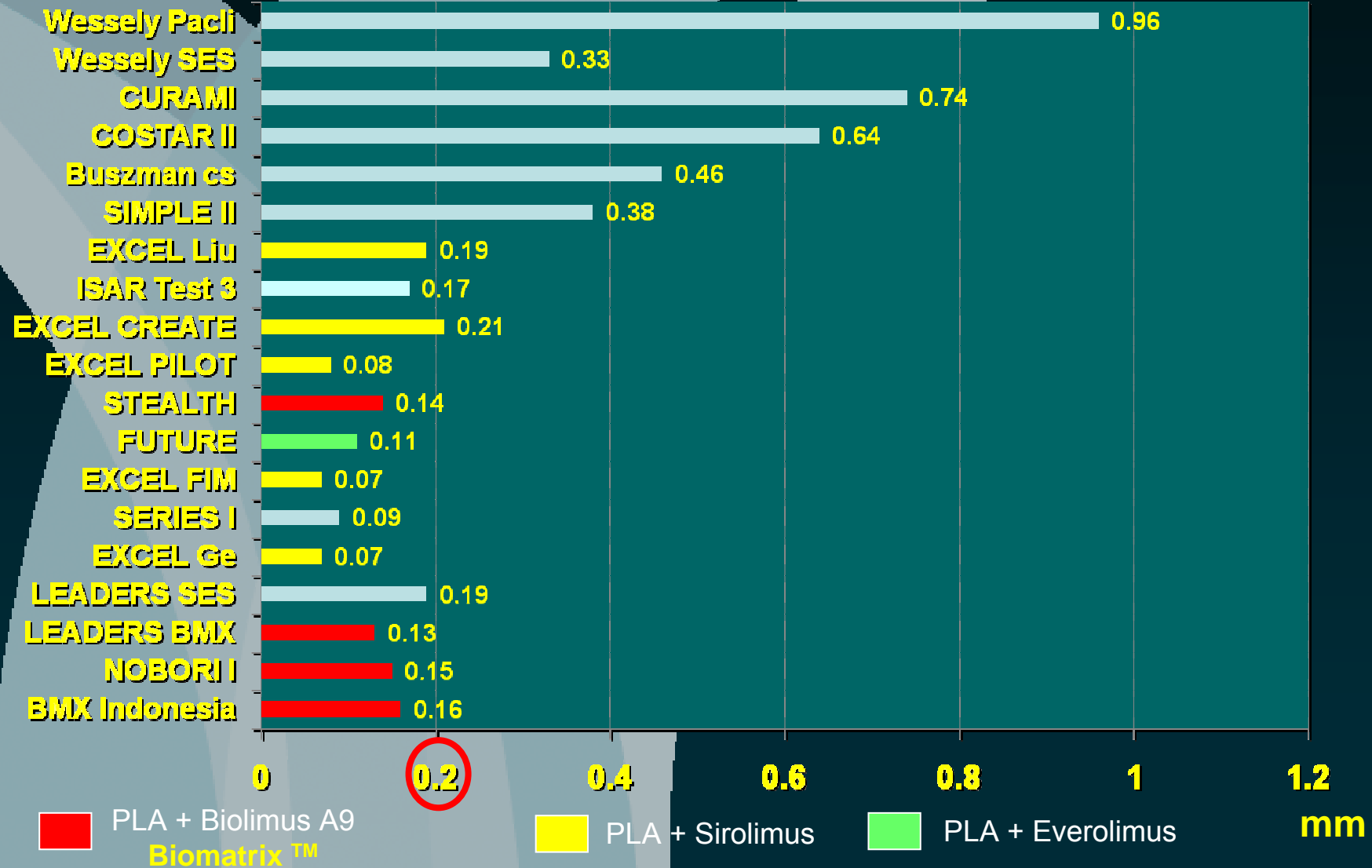
# Bioabsorbable Polymer Based DES Trials

Study	Type	Stent Type (Polymer+Platform)	No. of Patients	Drug	Primary Endpoint	Late loss (InStent)(mm)	BAR (%)
Biomatrix Indonesia	Registry	PLA+SS	302	Biolimus A9	TVR at 6-12 mo	0.16	3.1
NOBORI I	Rand 2:1	PLA+SS vs SS	360	Biolimus A9	Instent LL	0.15 vs 0.32	NA
LEADERS	Rand	PLA+SS vs DP+SS	1700	Biolimus A9 vs Sirolimus	MACE at 9 mo	0.13 vs 0.19	5.5 vs 8.7
EXCEL Ge	Registry	PLA+SS	31	Sirolimus	LL at 6 mo	0.07	0
SERIES I	Registry	PLA/PLGA/PVP+SS	126	Sirolimus	BAR at 6 mo	0.09	1.70
EXCEL FIM	Registry	PLA+SS	357	Sirolimus	TLR at 6-12 mo	0.07	3.2
STEALTH	Rand 2:1	PLA+SS vs SS	80 vs 40	Biolimus A9	LL at 6 mo	0.14 vs 0.74	3.9 vs 7.7
FUTURE 1	Rand 2:1	PLA+SS vs SS	27 vs 15	Everolimus	MACE at 30 d	0.11 vs 0.85 *	0 vs 9.1†
EXCEL PILOT	Registry	PLA+SS	100	Sirolimus	MACE at 1 yr	0.08	4
CREATE	Registry	PLA+SS	2007	Sirolimus	MACE at 1 yr	0.21	3.8
Liu H et al	Registry	PLA+SS vs NEP+SS	93 vs 97	Sirolimus	Not specified	0.19 vs 0.14 †	0 for both
ISAR-Test-3	Rand	BDP/NEP/PF	625	Sirolimus	LL at 6–8 mo	0.17/0.23/0.47	NA
CURAMI	Registry	PLA/PLGA	49	Sirolimus	6-month LL	0.74±0.89	22
SIMPLE II	Registry	PLC/PVP + SS	103	Paclitaxel	MACEs at 30 d	0.38	8.30
Buszman cs	Registry	LA/GA+SS	116	Paclitaxel	9-mo BAR/ 12-mo TLR	0.46	11.9
Wessely cs	Rand	BDP+SS vs BDP+SS	45 vs 46	Paclitaxel vs Sirolimus	LL at 6-8 mo	0.96 vs 0.33 *	39 vs 12.2 P=.005
COSTAR II	Rand	PLGA+CC vs PP+SS	989 vs 686	Paclitaxel	8 mo MACE	0.64 vs 0.26 mm*	17.9% vs 4.1%*

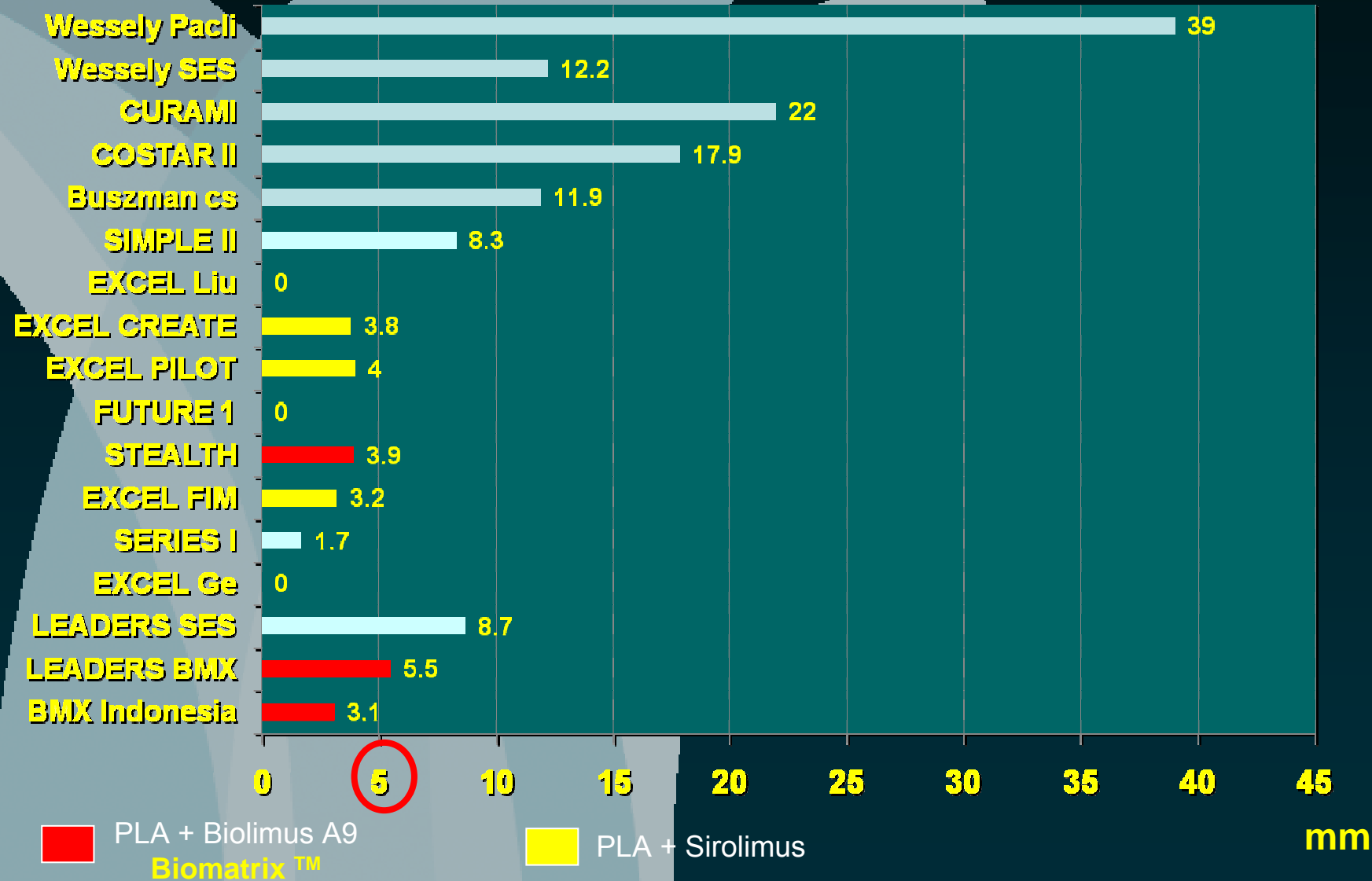
SS, stainless steel; CC, cobalt chromium; PLA, polylactic acid; NEP, nonerodible polymer; BDP, biodegradable polymer; PF, polymer free; PLGA, poly-lactide-co-glycolide; PVP, polyvinyl pyrrolidone; PLC, poly-L-lactide-co-caprolactone; LA, lactic acid; GA, glycolic acid; \*P<.001; †P=NS.



# Late Loss in Various Studies with Biodegradable Polymer Based DES



# Binary Angiographic Restenosis in Various Studies with Biodegradable Polymer Based DES



# Stent Thrombosis in Various Studies with Biodegradable Polymer Based DES



# BioMatrix® Drug Eluting Coronary Stent System

## Stent:

- Stainless steel platform
- Strut thickness 112 µm
- Quadrature link design: Biomatrix I, II, III

## Polymer:

- **Biodegradable PLA** – safe, nontoxic, degrades & co-released into CO<sub>2</sub> & H<sub>2</sub>O in ~ 6-9 months
- **Higher drug carrying capacity** of PLA polymer results in ½ to ⅓ the amount of carrier polymer used vs. durable coatings
- **10 µm coating thickness** / 1:1 drug/polymer ratio
- **Abluminal coating only**

## Drug

- Biolimus A9 – rapamycin derivative, **more lipophilic** than sirolimus or everolimus → **higher affinity into fatty tissue and is less available in blood**
- Dose 15.6 µg/mm stent length

# BioMatrix® Stent Platform Evolution

## S-STENT



**FUTURE 1 & 2**  
**STEALTH I**  
**BEACON Registry I & II**  
**Biomatrix Single Centre**  
**(Thailand, Indonesia)**

## BIOFLEX I



**STEALTH PK**  
**STEALTH II**

## BIOFLEX II



**LEADERS**

Platform for BioMatrix I

Laser cut stainless steel tube

QUADRATURE LINK design

**Straight connector link**

Strut thickness: 112µm

2.5 mm-4.0 mm diameters

8-28 mm lengths

6 & 9 crown design

Platform for BioMatrix II

Laser cut stainless steel tube

QUADRATURE LINK design

**Radius shaped connector link**

Strut thickness: 112µm

2.5 mm-4.0 mm diameters

8-28 mm lengths

6 & 9 crown design

Platform for BioMatrix III

Laser cut stainless steel tube

QUADRATURE LINK design

**"S" shaped connector link**

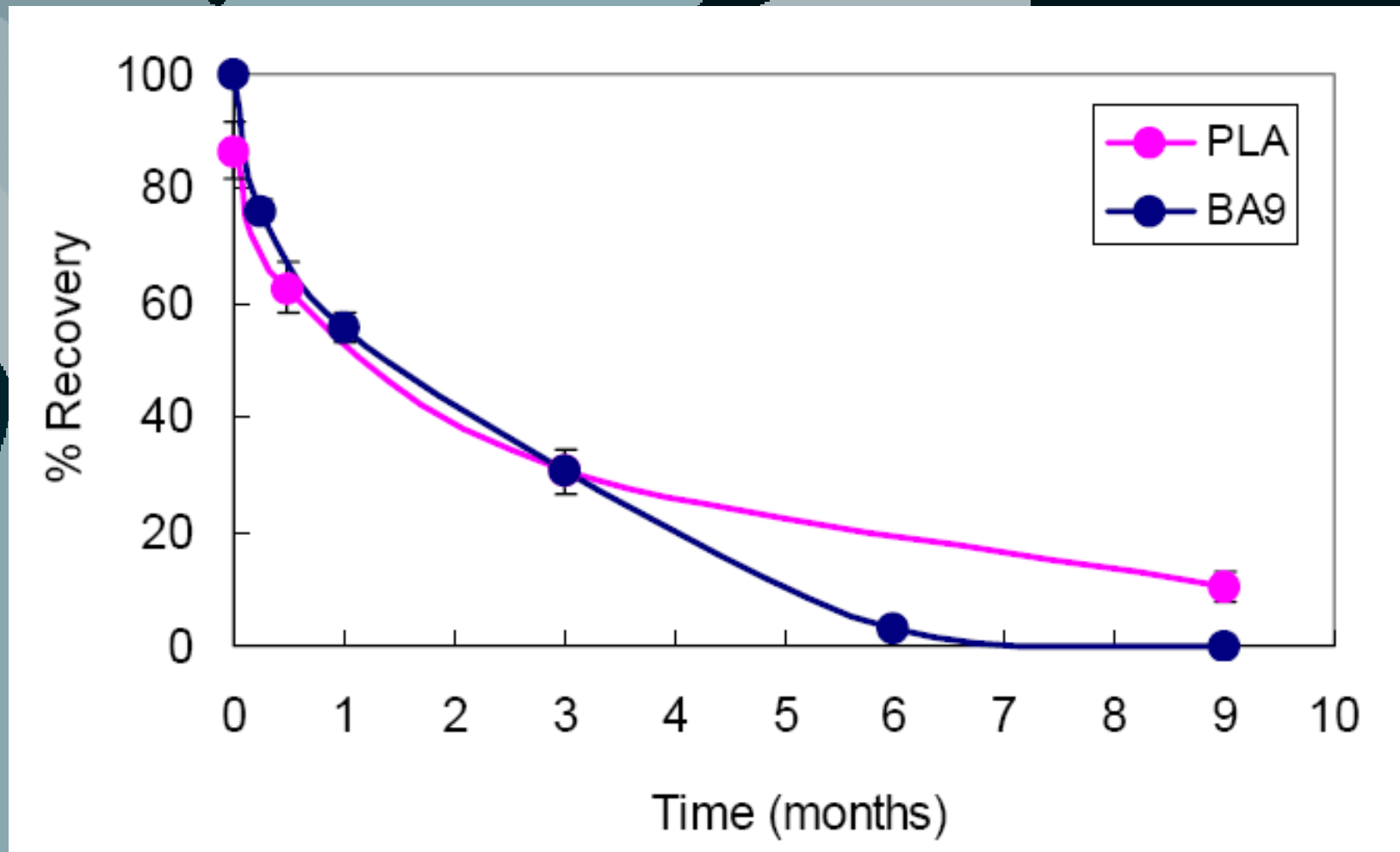
Strut thickness: 112µm

**2.25** mm-4.0 mm diameters

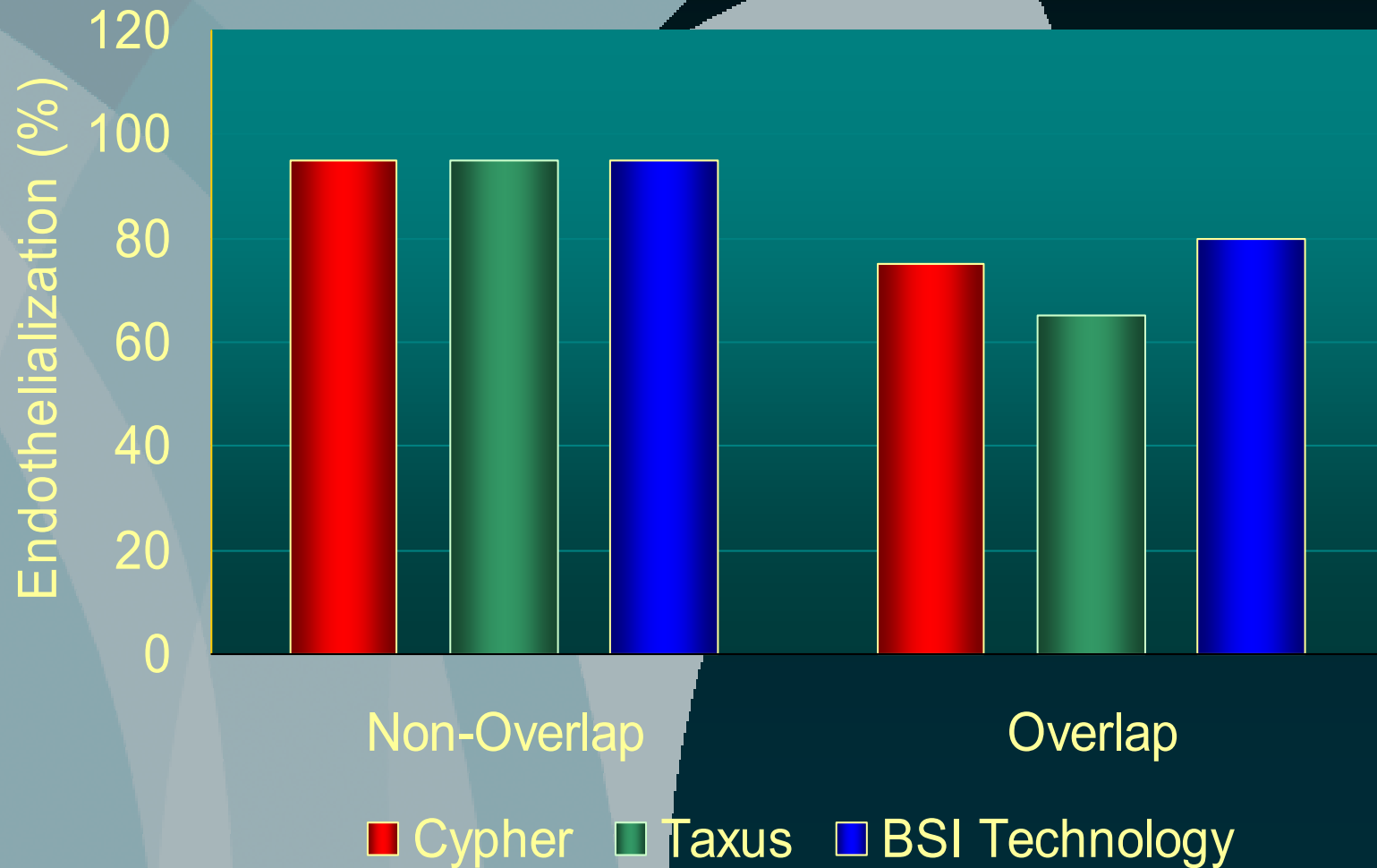
8-**36** mm lengths

6 & 9 crown design

# Release of Biolimus A9 & Degradation of Polymer Over Time in Porcine Coronary Arteries



# 28 Days Endothelialization



# 28 Days Endothelialization

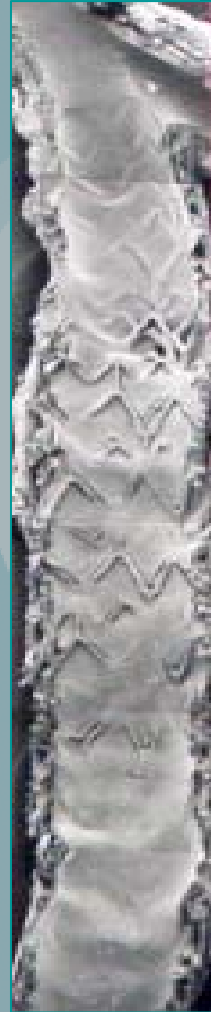
Bx Velocity



Cypher



Express



Taxus



S Stent



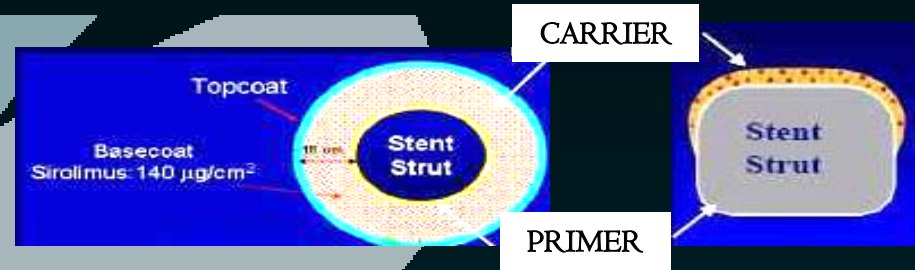
BSI Technol



Overlapped



# BioMatrix® : Less Polymer, Biodegradable Polymer



	<b>TAXUS® 3.5X16 mm</b>	<b>CYPHER® 3.5X13 mm</b>	<b>BIOMATRIX® 3.5x14 mm</b>
<b>Primer coating</b>	None	Paralyne C	Paralyne C
<b>Drug carrier</b>	Durable polymer, Poly (styrene-6- isobutylene-b-styrene) ca 1227µgrams	Durable polymer, Polyethylene co-vinyl Acetate / Polybutyl metacrylate blend, ca 301µgrams	Biodegradable polymer, Polylactic acid, 225µgrams
<b>Topcoat</b>	None	Polybutyl metacrylate	None
<b>Drug reservoir coating thickness</b>	Thickness not published, coated all sides, incl. blood contact area	10 µ all sides incl. blood contact area	10 µ, abluminal side only

TRIALS	Primary end point	Design (n=sample size)	Results & F/up durations
<b>STEALTH PK</b>	Safety & PK	Single arm registry (n=27)	Confirmation of BA9 PK (30 days & 6 mos). BA9 safe
<b>STEALTH FIM</b>	Safety & efficacy	RCT vs. BMS (n=120)	6 mos in lesion LL $0.14 \pm 0.45$ vs $0.40 \pm 0.41$ mm (BMS); similar clinical safety
<b>BEACON I Registry</b>	Safety & efficacy	Single arm registry (n=292)	TVR (6 mos) 2.1%, MACE 3.8% (1 mo), 6.5%(1 yr), no stent thrombosis
<b>Biomatrix Single Centre (Thailand)</b>	Safety & efficacy	Single arm registry, more complex lesions (n=169)	At 2 yr: death 8.28%, MI 6.50%, TLR 7.69%
<b>Biomatrix Single Centre (Indonesia)</b>	Safety & efficacy	Single arm registry, real world cases (n=302)	Instent LL 0.16 mm, BAR 3.1%; At 2 yr: death 1%, MI 0.3%, TLR 2%, MACE 3%
<b>BEACON II Registry</b>	Safety & efficacy	Single arm registry (n=497)	At 30 days: Death 0.6%, MI 0.8%, tlr 0.6%, early stent thrombosis 0.6%, MACE 1.6%
<b>NOBORI I</b>	Instent (ISt) LL at 9 mos	RCT "NOBORI" vs. <b>TAXUS</b> (n=120)	ISt LL $0.15 \pm 0.27$ vs. $0.32 \pm 0.33$ mm (TAXUS). More effective in ↓ neointimal proliferation. ↓ MACE 59%
<b>NOBORI CORE</b>	Instent (ISt) Late Loss (LL) at 9 mos	RCT "NOBORI" vs. <b>Cypher</b> (n=107)	Similar LL & MACE rates, but better recovery in endothelial function
<b>LEADERS</b>	Cardiac death, MI, or clinically-indicated TVR	RCT, Biomatrix vs. <b>Cypher select</b> , real world (except LM)	Biomatrix was noninferior in efficacy & safety vs. Cypher select

# BioMatrix™ – Abluminal DES (ADES)

## ABLUMINAL COATING

Improved healing  
More targeted tissue release  
Less systemic exposure

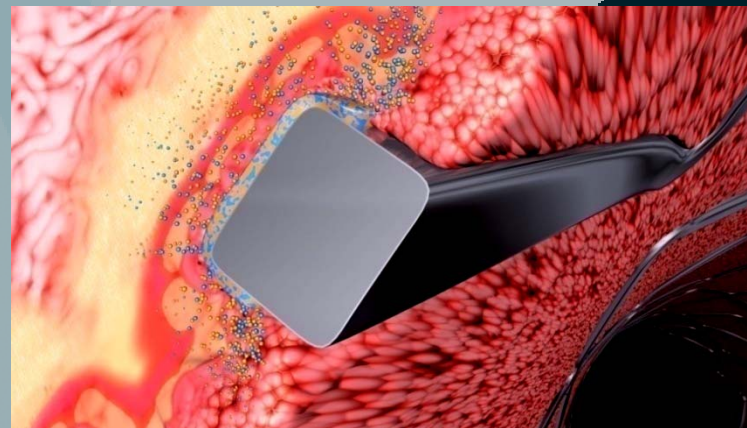


## BIOLIMUS A9™ DRUG

Biosensors' proprietary rapamycin derivative  
Highest lipophilic profile of all common limus drugs

## BIODEGRADABLE PLA

Co-released with BA9™  
Fully biodegrades from the stent in 6 months  
High drug carrier capacity



## S-STENT™ PLATFORM

Superior side branch access without compromising radial strength

(Data on file at BSI)

# BA9, Biodegradable Polymer & Abluminal Coating: A Good “Clinical’ Combination?

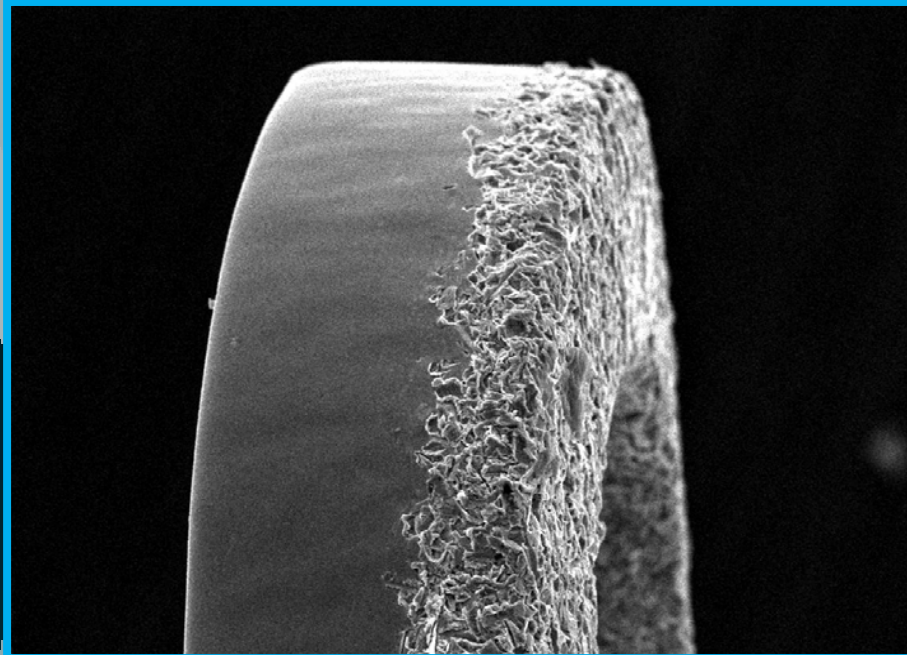
- The BioMatrix™ stent demonstrated to be **safe & efficacious** out to 12-24 months **even in real world cases.**
- In the **Asia Pacific Registries:**
  - BioMatrix™ resulted in very low rates of death, QMI, TLR, MACE & stent thrombosis (even in real world cases)
- In the **LEADERS Trial:**
  - BioMatrix™ resulted in a **12% reduction** compared to the sirolimus eluting stent in the **primary clinical endpoint.**
  - In the OCT subset the BioMatrix™ struts are **10 times more frequently apposed & neointimal coverage** of >95% of the stent struts is visualized with OCT **10 times more frequently** compared with the sirolimus eluting stents

# Ongoing Trials of Biolimus A-9 eluting-stent

	Purpose	Design (n=sample size)	PEP & F/up durations
<b>BEACON II</b>	Safety & effectiveness	Single arm registry, <b>real world</b> (n=497)	MACE & TVR at 12 months
<b>STEALTH II</b>	Safety & effectiveness	R, SB, <b>single de-novo, type A-B2</b> , DES control ( <b>TAXUS</b> ) (n=1,700)	TVF at 9 mos. Angiographic subset at 9 mos
<b>NOBORI 2</b>	Safety & effectiveness. Length of dual antiplatelet Rx & stent thrombosis	Single arm registry, <b>real world</b> (n>3000 in >20 countries)	MACE & TLR at 360 days

R=randomised; SB=single blind

# The Next Generation .....



***BioFreedom™***

**FIM started September 2008**

Selectively micro-structured  
surface holds drug in  
abluminal surface structures

# *BIOMATRIX*<sup>TM</sup>: Conclusion

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Not all Biodegradable polymer based DESs are the same.

BioMatrix<sup>TM</sup> stent with its' **unique features** has been demonstrated to be **safe and efficacious** to use in **real world patients** up to 12-24 month follow-up with a low incidence of MACE, TLR, stent thrombosis as well as low late loss and restenosis.

*Thank You*

