

# LE FUTUR DU STENT

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CHU TOULOUSE-RANGUEIL

APPAC, 08 Juin 2011

# Drug-eluting Stents in 2004

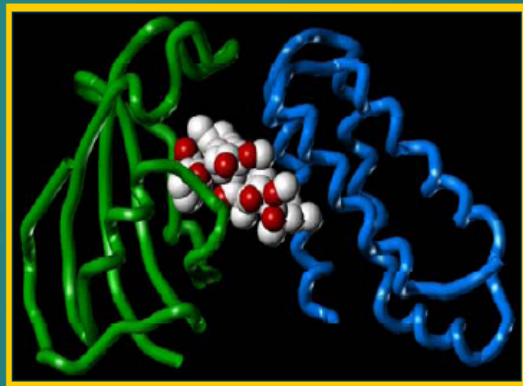
## Safety and Efficacy Proven

Drug

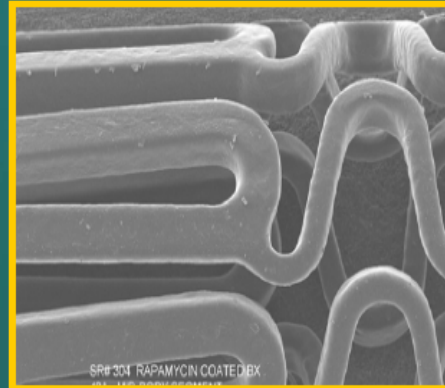
Polymer

Stent

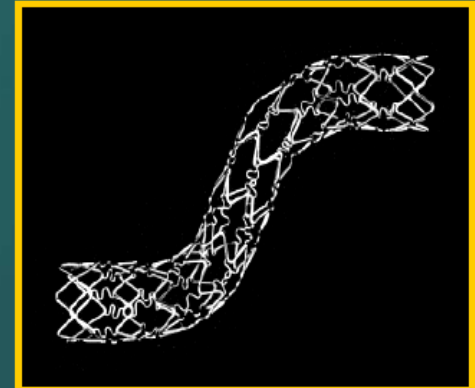
**Cypher**



Sirolimus

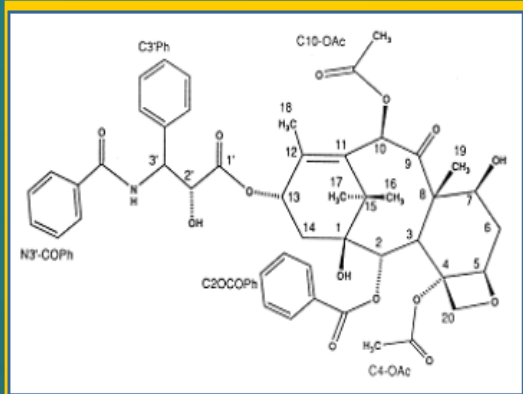


PEVA + PBMA blend

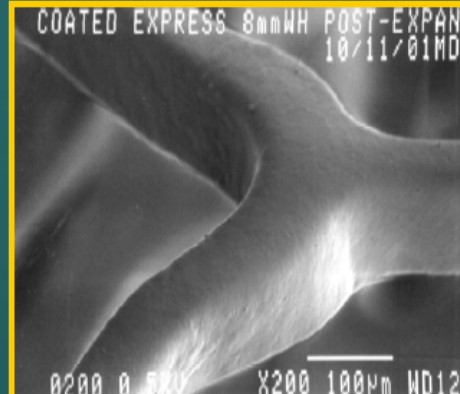


BX Velocity

**TAXUS**



Paclitaxel



Polyolefin derivative



Express<sup>2</sup>

# Next generation ?

Need to demonstrate a step forward in

- **Acute results** / functionality
- Maintain / improve **efficacy** – TLR
- Improve **safety** – Stent Thrombosis

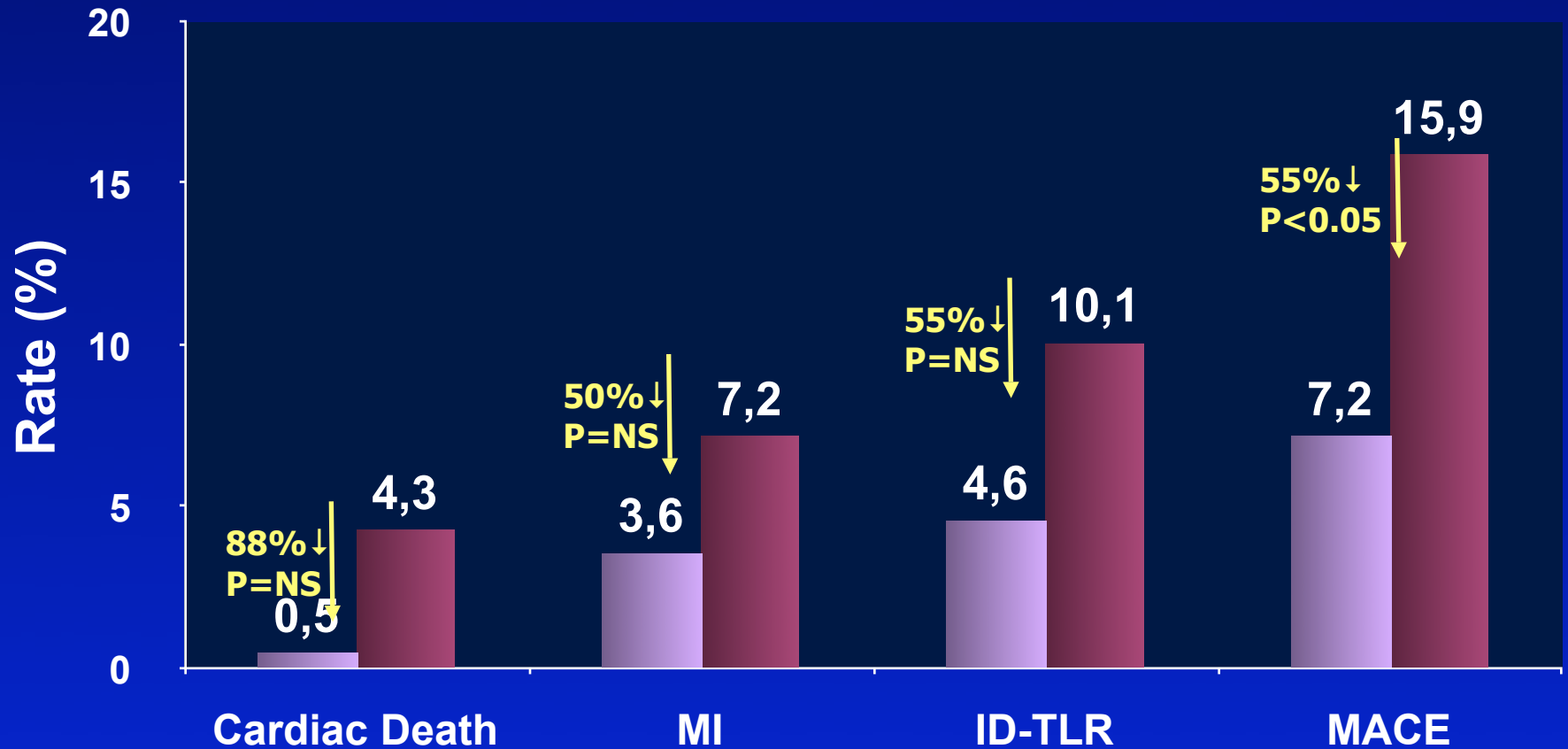
# SPIRIT II

## 3 Year Clinical Results

Non-hierarchical

XIENCE V (n=223)

TAXUS (n=77)



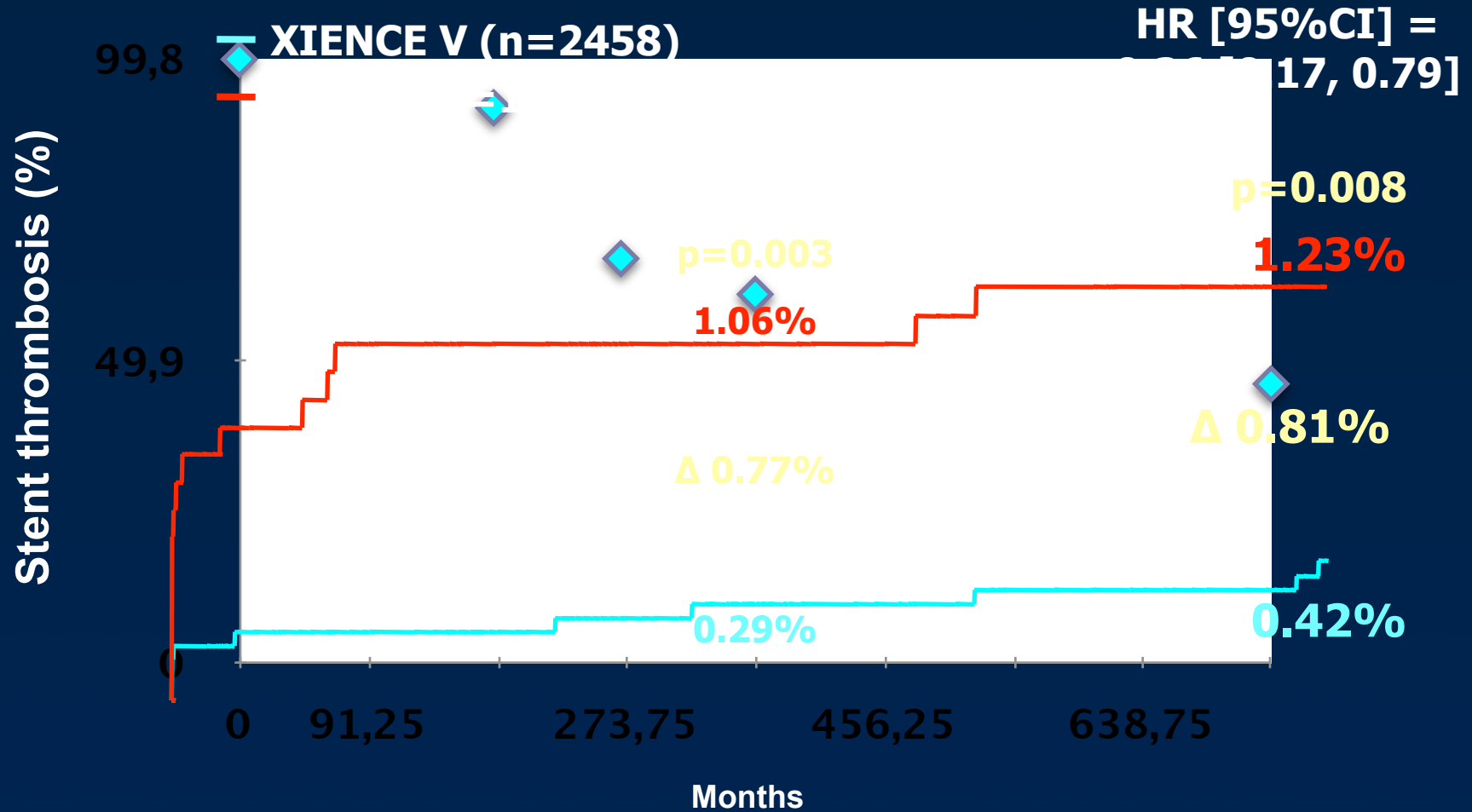
Serruys PW. EuroPCR 2009



Pôle Cardiovasculaire et Métabolique



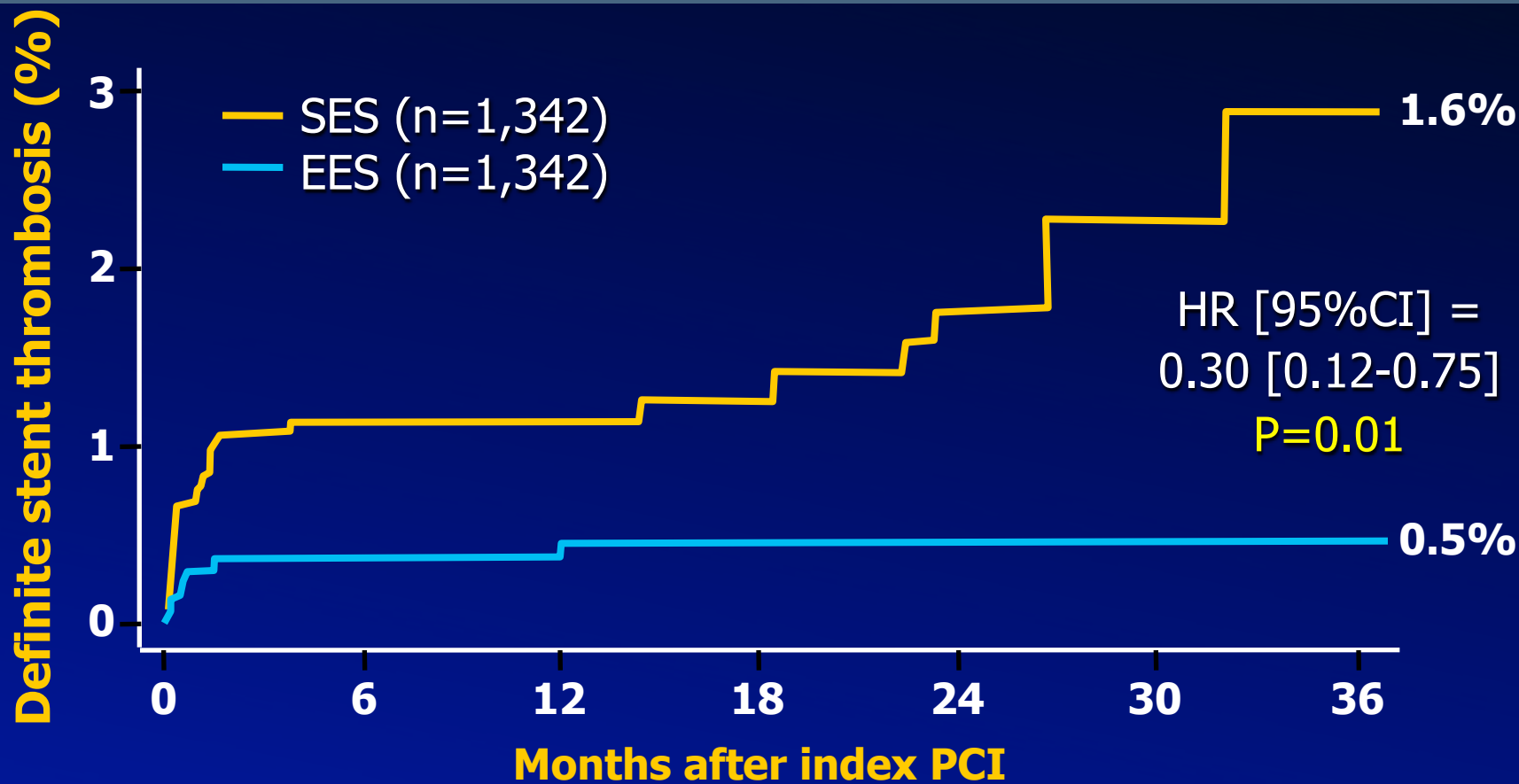
# Stent Thrombosis (ARC Def or Prob)



Number at risk

XIENCE V	2458	2426	2412	2386	2367	2354	2342	2334	2321
TAXUS	1229	1196	1186	1175	1166	1160	1156	1152	1139

# LESSON I: Definite Stent Thrombosis @ 3 Yrs



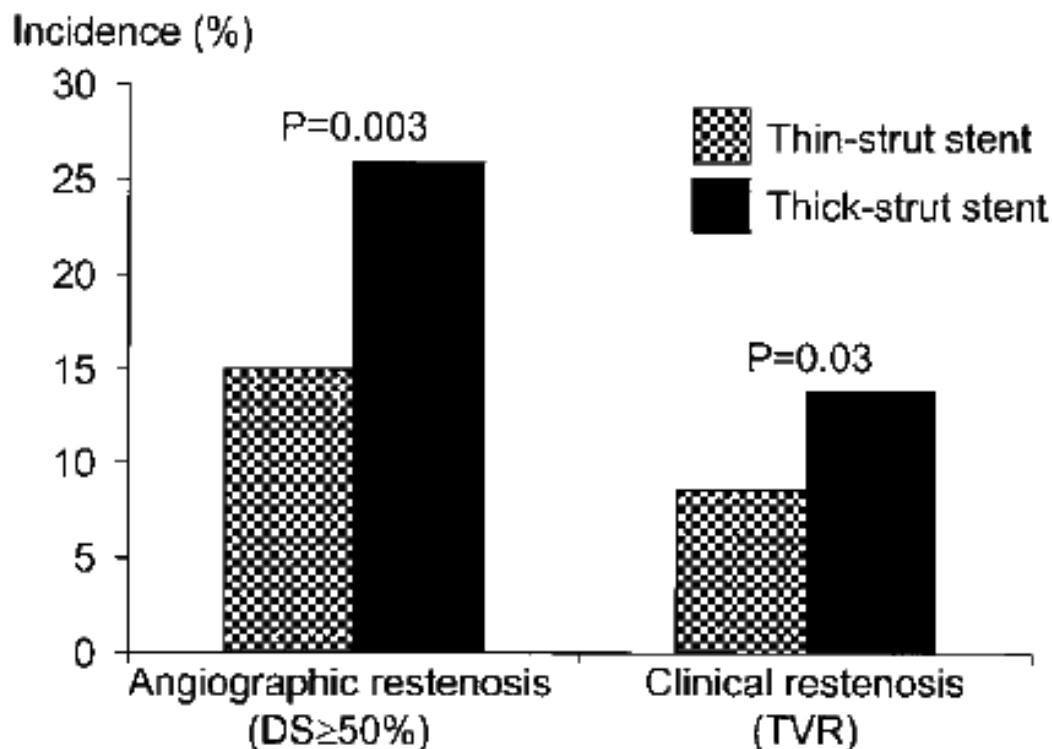
No. at risk

EES	1342	1296	1234	620	543	226	29
SES	1342	1271	1216	619	527	223	28

# Thinner is better

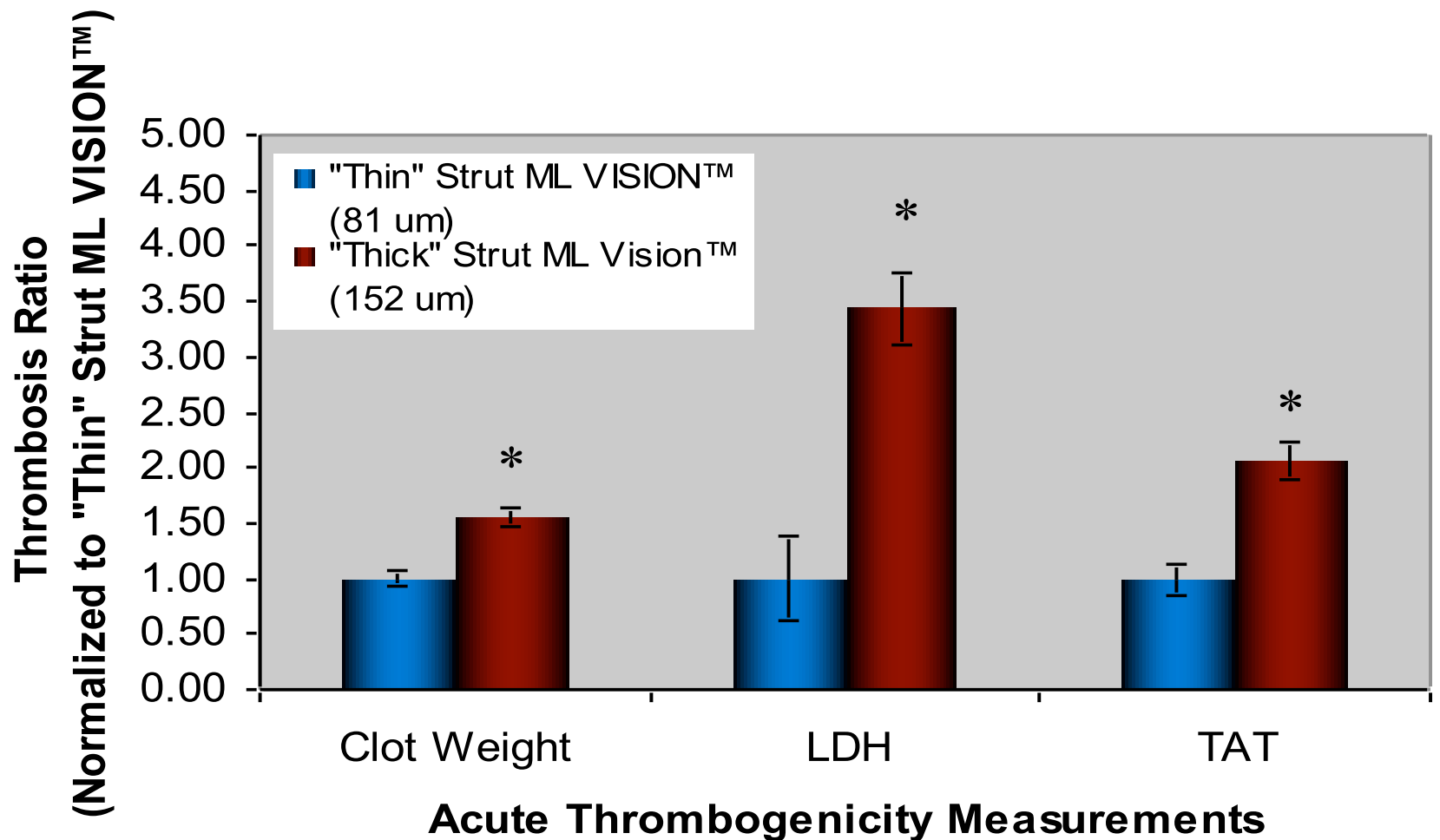


## Thickness of BMS strut and restenosis



**Figure 2.** Incidence of angiographic (left) and clinical (right) restenosis in each group. DS denotes diameter stenosis; TVR, target-vessel revascularization.

# Thickness of BMS strut and thrombotic markers



	Cypher	TAXUS Express	Biomatrix NOBORI	TAXUS Liberte	TAXUS Element	Endeavor	Resolute	PROMUS Xience V PRIME	PROMUS Element
<b>Platform</b>									
<b>material</b>	316L SS	316L SS	316L SS	316L SS	PtCr	MP35N	MP35N	CoCr L-605	PtCr
<b>Strut (mm)</b>	0.14	0.12	0.11	0.097	0.081	0.091	0.091	0.081	0.081
<b>Polymer</b>									
<b>material</b>	PEVA PBM A	SIBS	PLA	SIBS	SIBS	PC	C10 C19 PVP	PDVF-HFP	PDVF-HFP
<b>microns</b>	12.6	18	10	16	14	5.3	NA	7.6	7.6
<b>Drug</b>									
<b>Drug</b>	SIRO	(PTX)	BIO	(PTX)	(PTX)	ZOTA	ZOTA	EVERO	EVERO
<b>Load * mcg</b>	150	1mcg/mm <sup>3</sup>	280	1mcg/mm <sup>3</sup>	1mcg/mm <sup>3</sup>	180	180	88	88
<b>Kinetics Time to ~70% release</b>	28d	<10%	90d	<10%	<10%	2d	30d	30d	30d

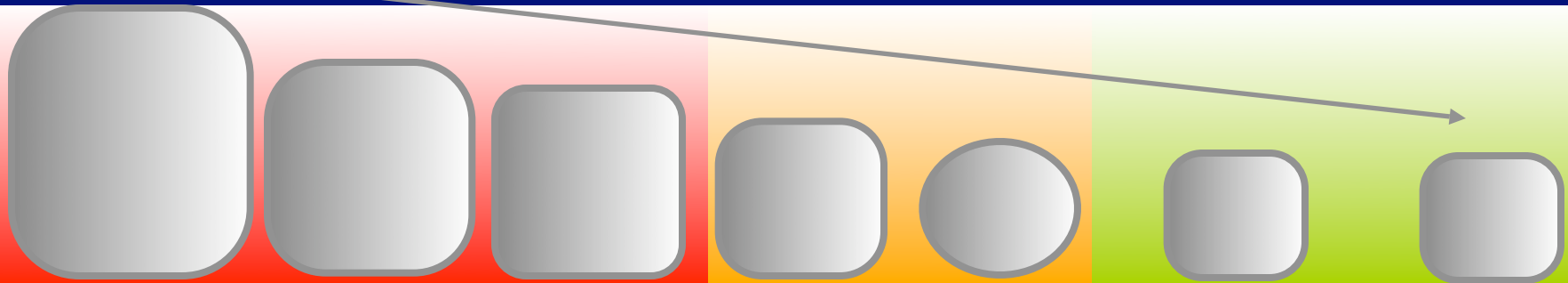


\*Load on a 3.0 x 18mm stent

# Strut Thickness of Contemporary DES

Thick Strut Stents

Thin Strut Stents



**Cypher  
Select Plus™  
Stent  
0.14mm**

**TAXUS™  
Express2™  
Stent  
0.12mm**

**BioMatrix  
Flex™  
Stent  
0.11mm**

**TAXUS™  
Liberte™  
Stent  
0.097mm**

**Resolute  
Integrity  
Stent  
0.091mm**

**PROMUS™  
Xience V™  
Stent  
0.081mm**

**PROMUS  
Element™  
Stent  
0.081mm**

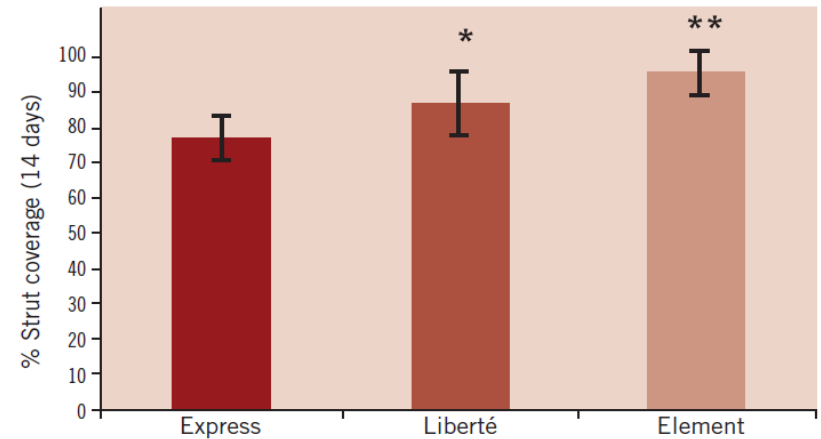
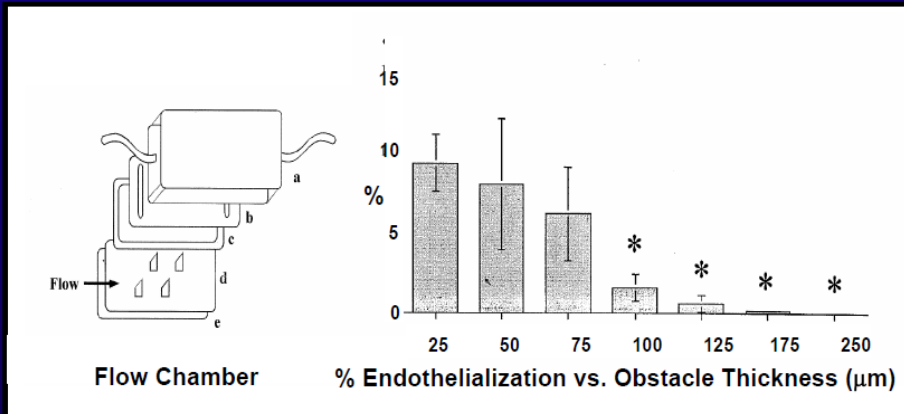


Figure 3. Effect of strut thickness on the kinetics of tissue coverage. At 14 days post-implant, 77±6% of bare metal Express stents struts had some form of tissue coverage compared to 88±7% of bare Liberté (\* P=0.05) and 95±4% of bare Element (\*\* P=0.001) stent struts.

**Endothelial coverage may be impaired for thicker stent struts**

# Polymer Evolution



## Durable Polymers

Fluoropolymer performance - (anti) thrombogenicity

Polymer integrity

Stent thrombosis

## Biodegradable Polymers

## Non-Polymeric

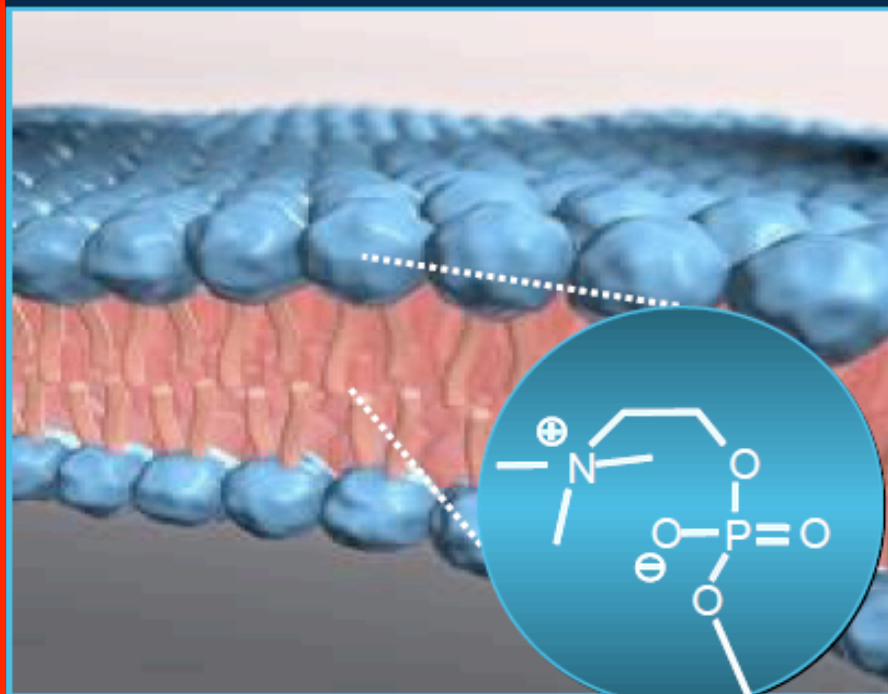


# Medtronic Polymer Technologies

## Medtronic PC and BioLinx Polymers

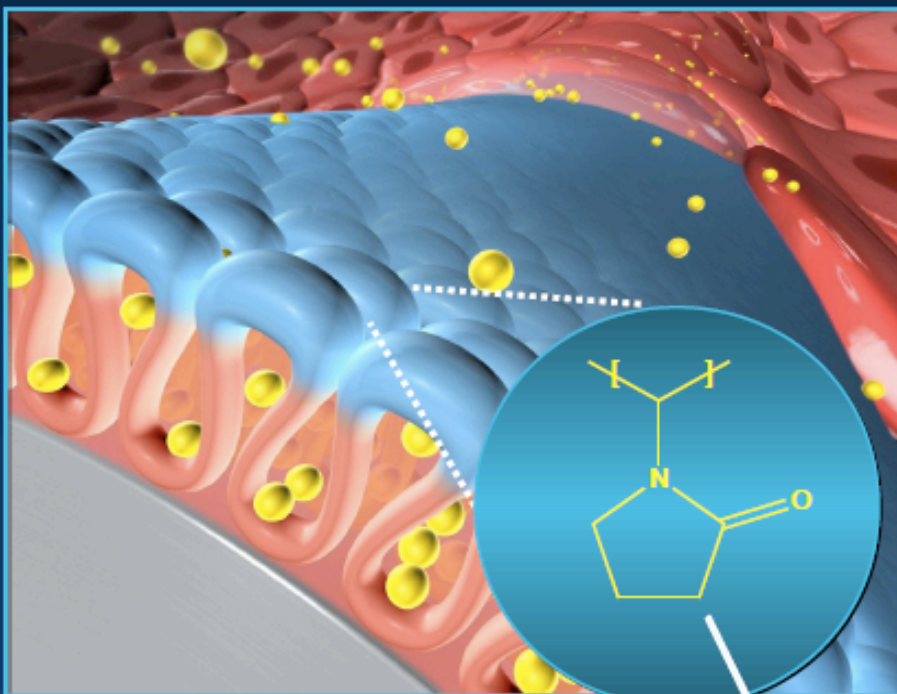
Hydrophilic Surface Chemistry Engineered for Biocompatibility

Endeavor DES: PC Technology



Phosphorylcholine  
(PC) Headgroup

Resolute DES: BioLinx



Vinyl pyrrolidinone  
groups

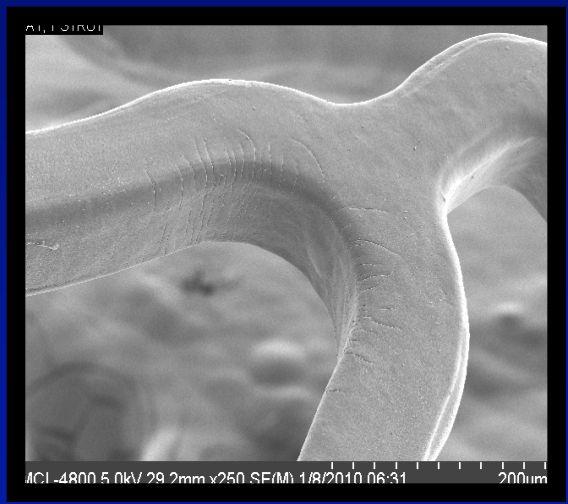
# Coating integrity as $f(t)$ during elution; Different Durable DES

Data generated in collaboration with Prof. Edelman's lab with Drs M Balcells, S Schubert and ER Edelman

$t = 0$



$t = 7 \text{ d}$

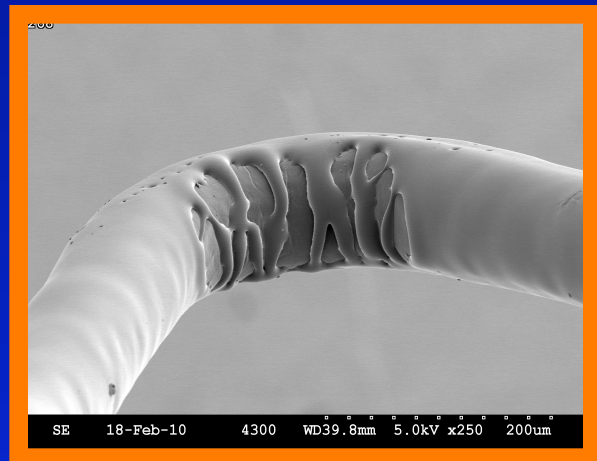


$t = 56$

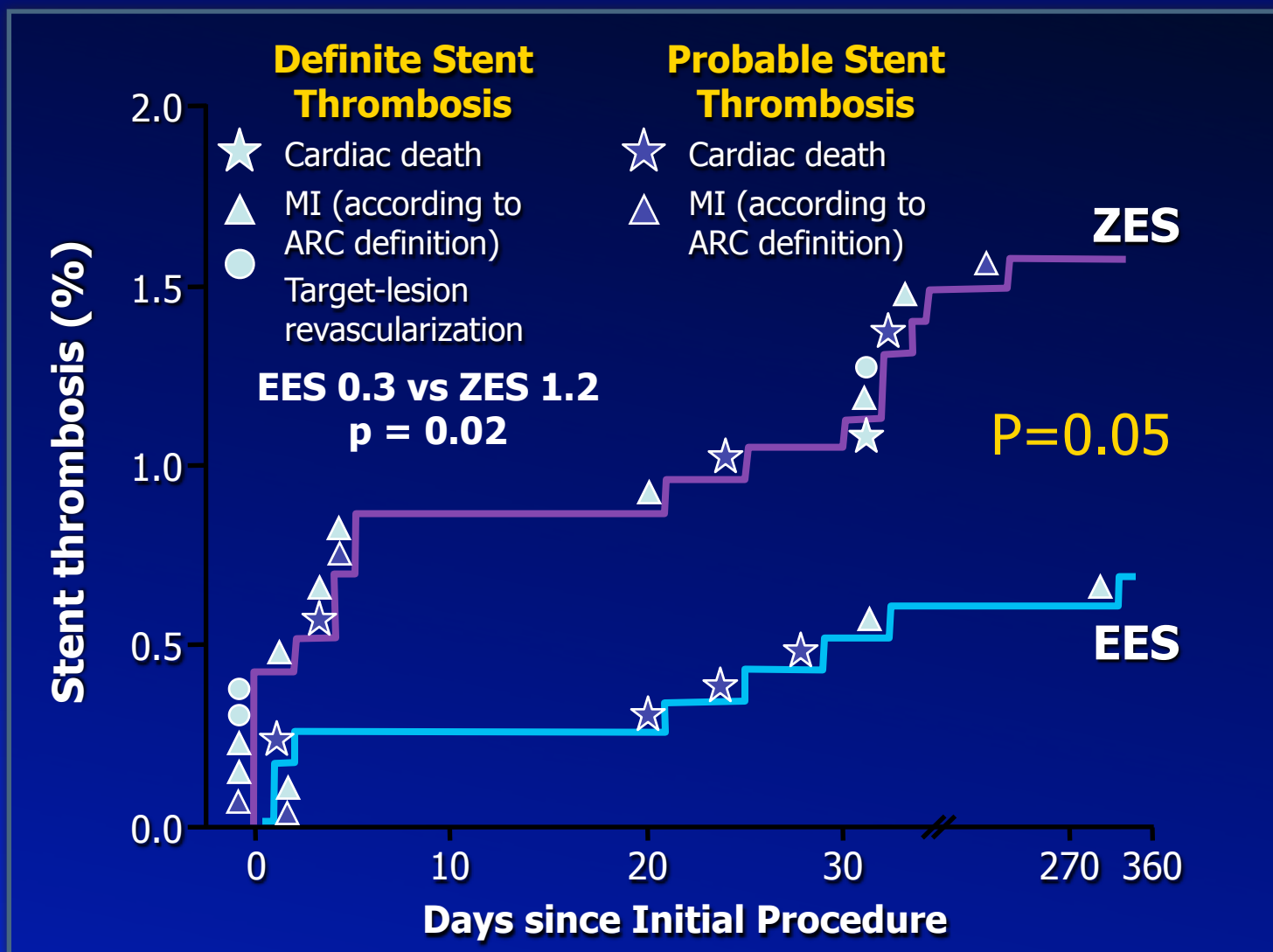


PROMUS / XIENCE V

Resolute Coating



# RAC: Stent Thrombosis (ARC Def/Prob)



Serruys PW et al. NEJM 2010

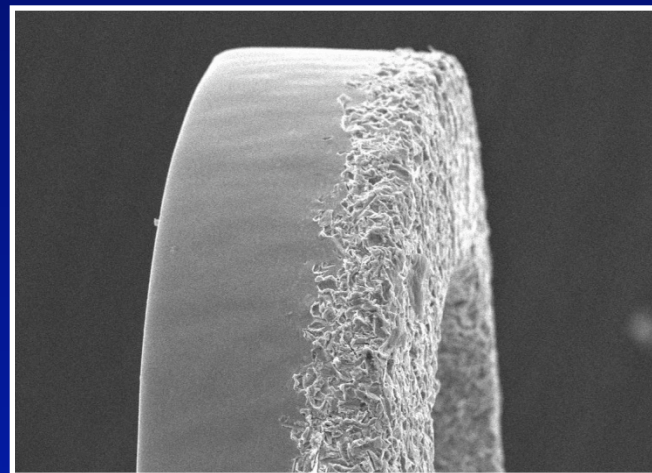
# BioFreedom™

**Hypothesis: Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings.**

## Potential advantage

- Avoid long term late adverse effects that might be attributable to the polymer
- Improved surface integrity since there is no polymer to be sheared or peeled away from the stent struts
- Possible Shorter need of dual antiplatelet therapy

Selectively micro-structured surface holds drug in abluminal surface structures

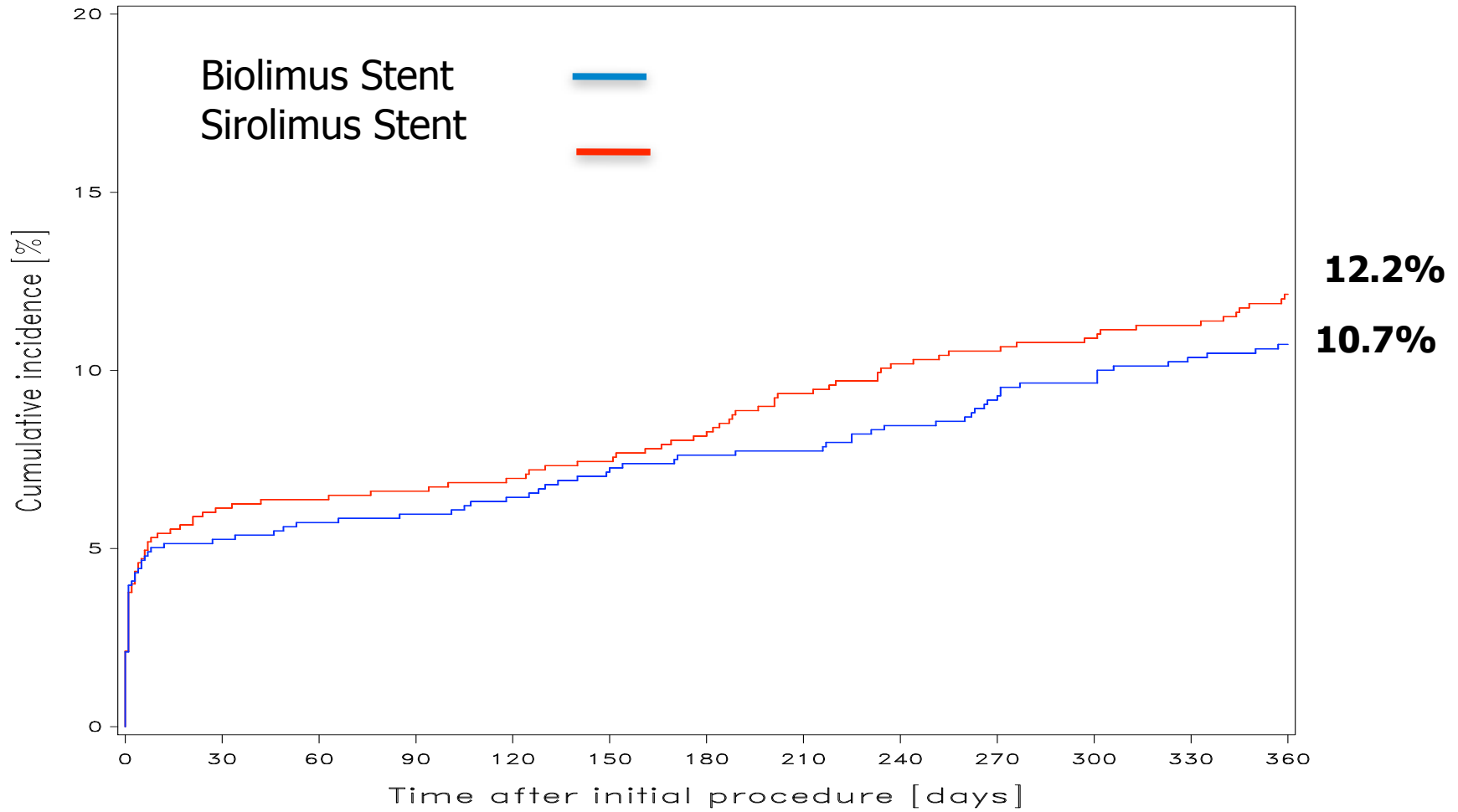


Proprietary Highly Lipophilic Limus drug

**'BA9™**



# CARDIAC DEATH, MI, OR TVR @ 12 MONTHS



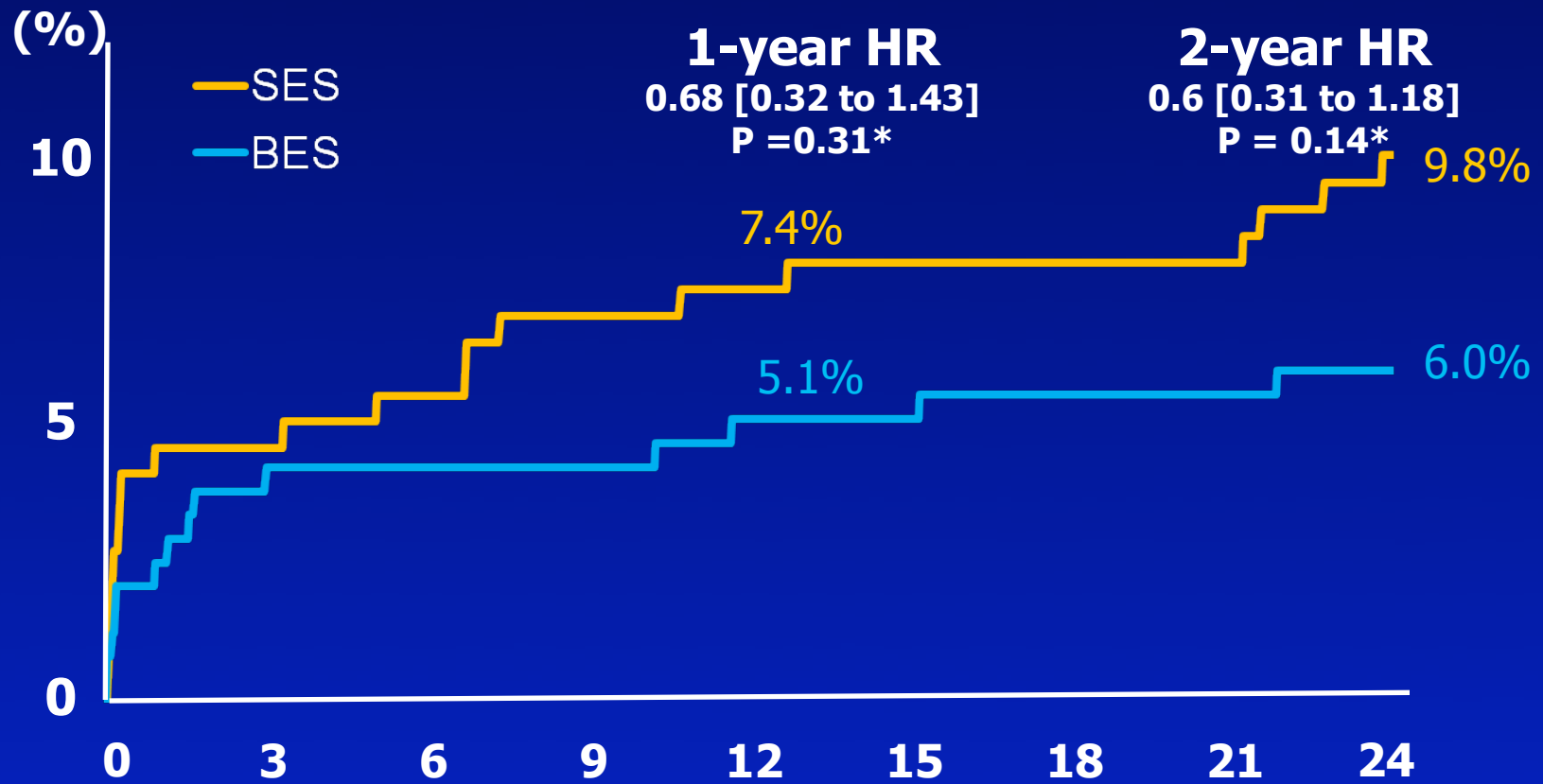
# Summary

	<b>Biomatrix</b>	<b>Cypher</b>	<b>p value*</b>
	Bifurcations		
MACE	15.6	18.9	0.37
TLR	7.2	13.2	0.03
Definite/probable stent thrombosis	2.7	4.3	0.37
	Multivessel disease		
MACE	15.0	23.5	0.05
TLR	6.0	15.1	0.005
Definite/probable stent thrombosis	2.9	5.2	0.27
	STEMI		
MACE	8.4	19.7	0.01
TLR	6.2	10.4	0.20
Definite/probable stent thrombosis	3.8	8.8	0.10

\*P values for superiority



# Stent Thrombosis in High Syntax Score (>16)



Number at risk

Months

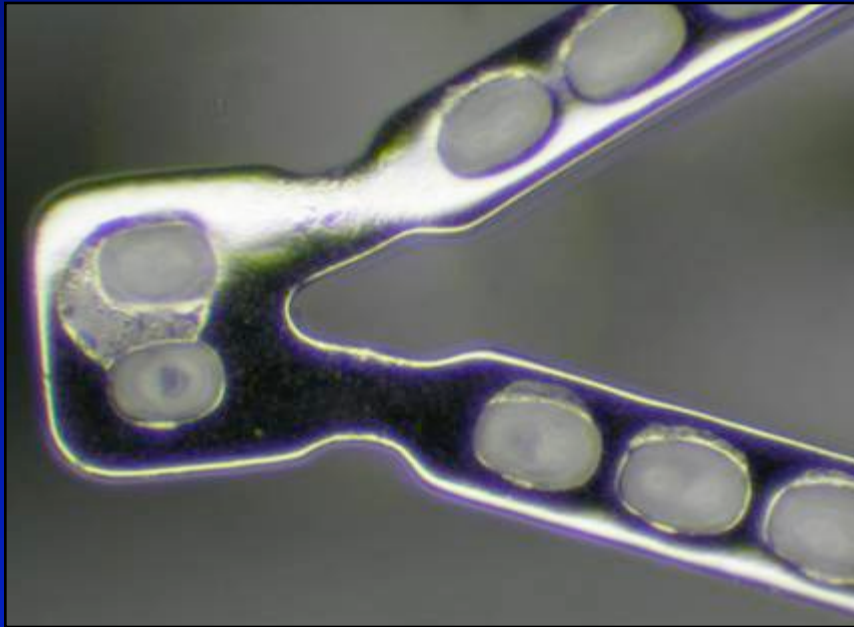
BES	239	230	226	223	221	218	217	216	215
SES	222	205	204	200	196	194	192	192	190

\*P values for superiority

# PLGA Polymer Bio-Erosion

## Polylactide-co-glycolide (PLGA)

*7 Day Porcine Explant*



*180 Day Porcine Explant*



**Following Tissue Removal  
Evidence of Polymer Bio-Erosion**



## Polymer-Free platform

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall

## Abluminal Reservoir Technology (ART)



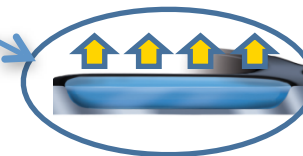
Controlled and directed elution to the vessel wall

## Bio Inducer Surface (BIS) = 2<sup>nd</sup> generation pure carbon coating

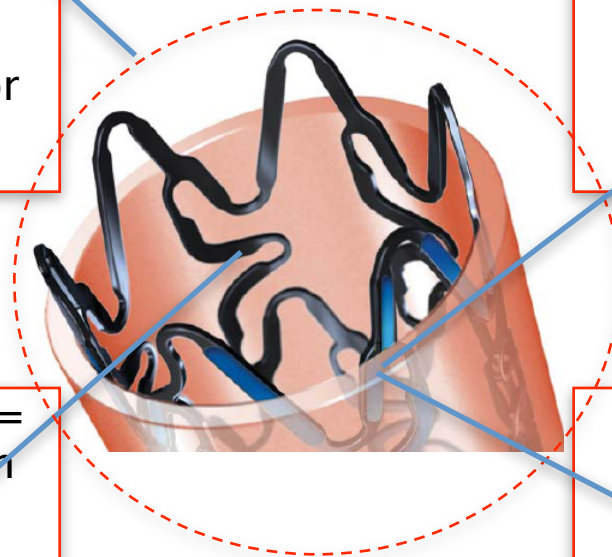


Optimal haemo-compatibility vs. lumen blood flow

## Amphilimus Formulation = Formulated Sirolimus with an organic acid



Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy



323 enrolled patients  
(377 lesions)

Randomisation  
1:1

**Cre8**  
N=162 enrolled pts  
N=158 pts analyzed  
for f/u endpoints

**Taxus Liberté**  
N=161 enrolled pts  
N=157 pts analyzed  
for f/u endpoints

1-month clinical f/u  
N=158 pts **100%**

1-month clinical f/u  
N=155 pts **98.7%**

6-month clinical f/u  
N=154 pts **97.5%**  
6-month  
angiographic f/u  
N=141 pts **89.2%**

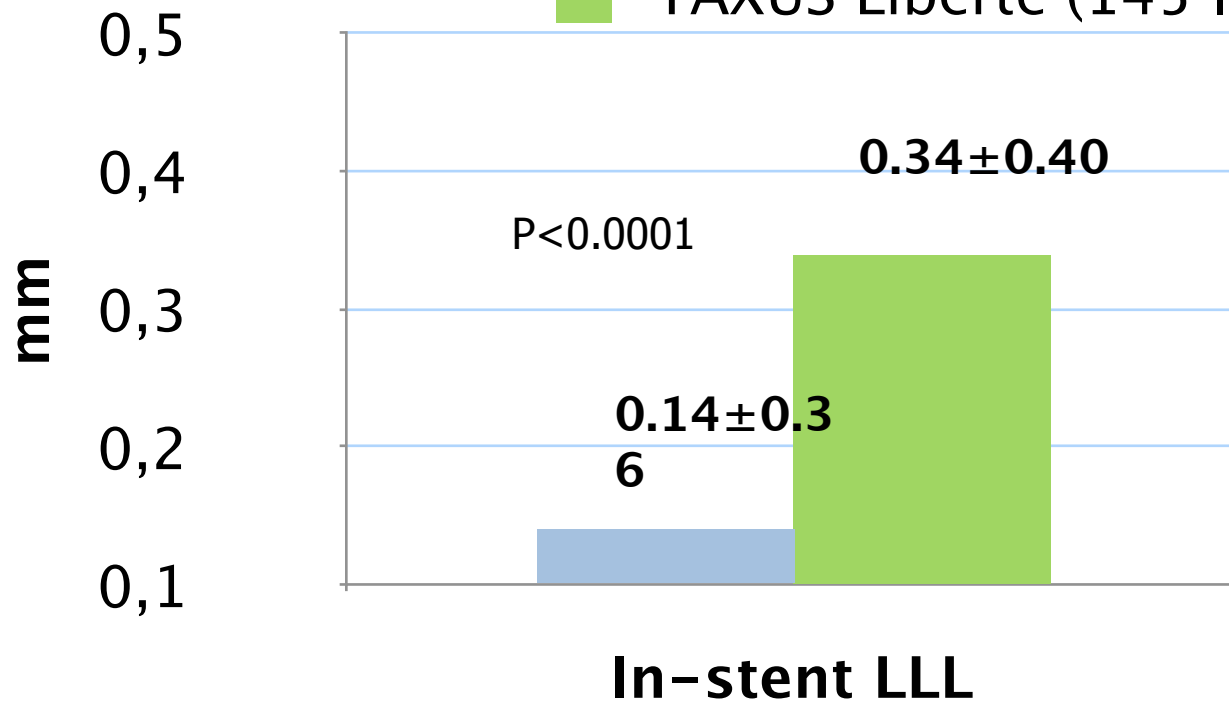
6-month clinical f/u  
N=150 pts **95.5%**  
6-month  
angiographic f/u  
N=135 pts **86.0%**

1 pt withdrawn and 3 pts treated with additional non-study device

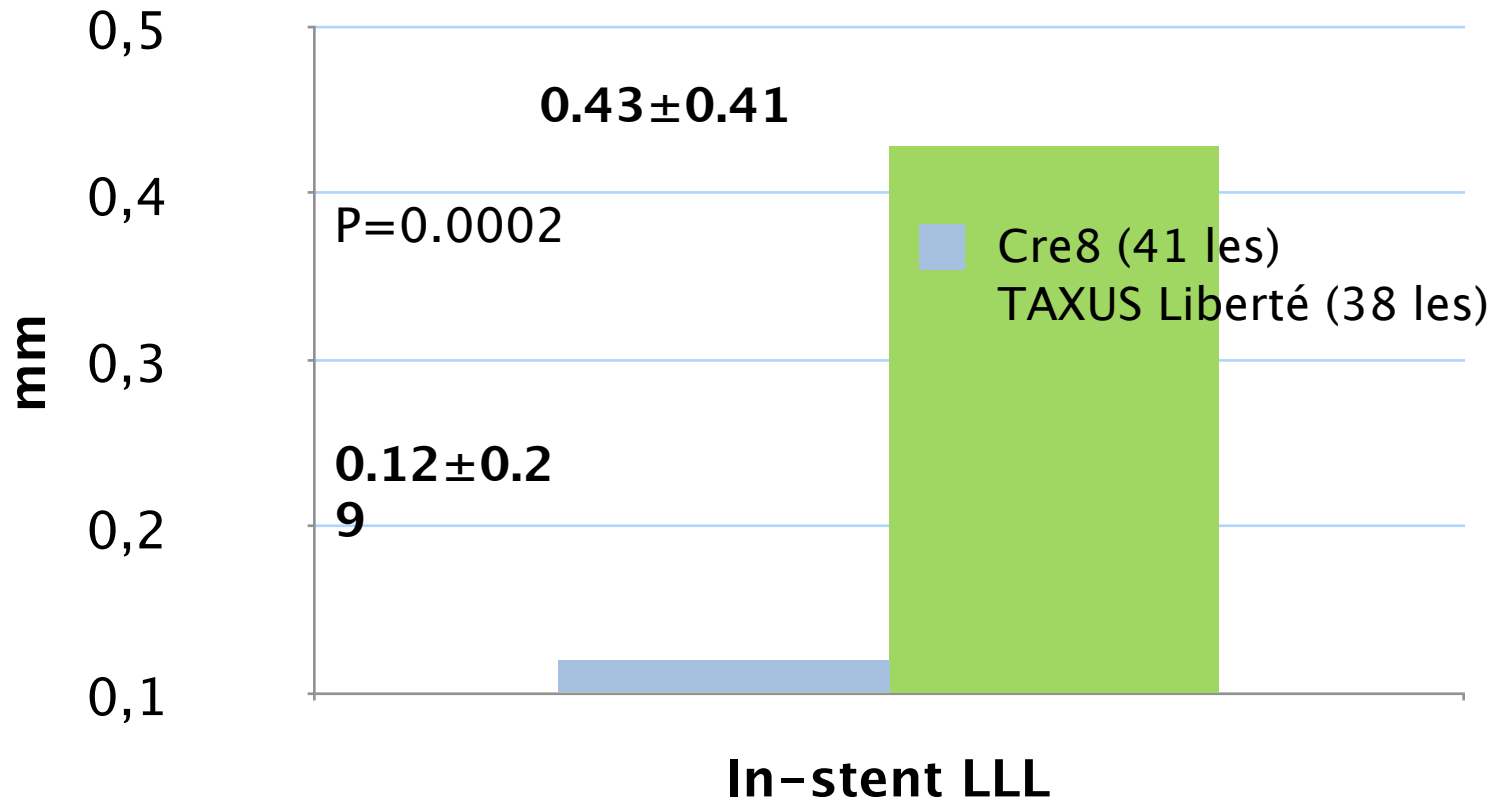
4 pts treated with additional non-study device

# Primary Endpoint: 6-month in-stent Late Lumen Loss

■ Cre8 (148 les)  
■ TAXUS Liberté (145 les)



# Diabetic Subgroup: 6-month Late Lumen Loss



# ARC Stent Thrombosis

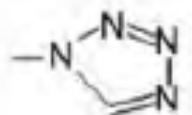
	Cre8 (158 pts)	TAXUS Liberté (157 pts)	p value
<b>Definite Stent Thrombosis</b>			
Acute Thrombosis (0-1 day)	0	0	-
Sub-acute Thrombosis (2-30 days)	0	0.6% (1/157)*	0.4984
Late Thrombosis (31-180 days)	0	0	-
<b>Probable Stent Thrombosis</b>			
All (0-180 days)	0	0	-
<b>TOTAL (Definite + Probable)</b>	<b>0</b>	<b>0.6% (1/157)*</b>	<b>0.4984</b>

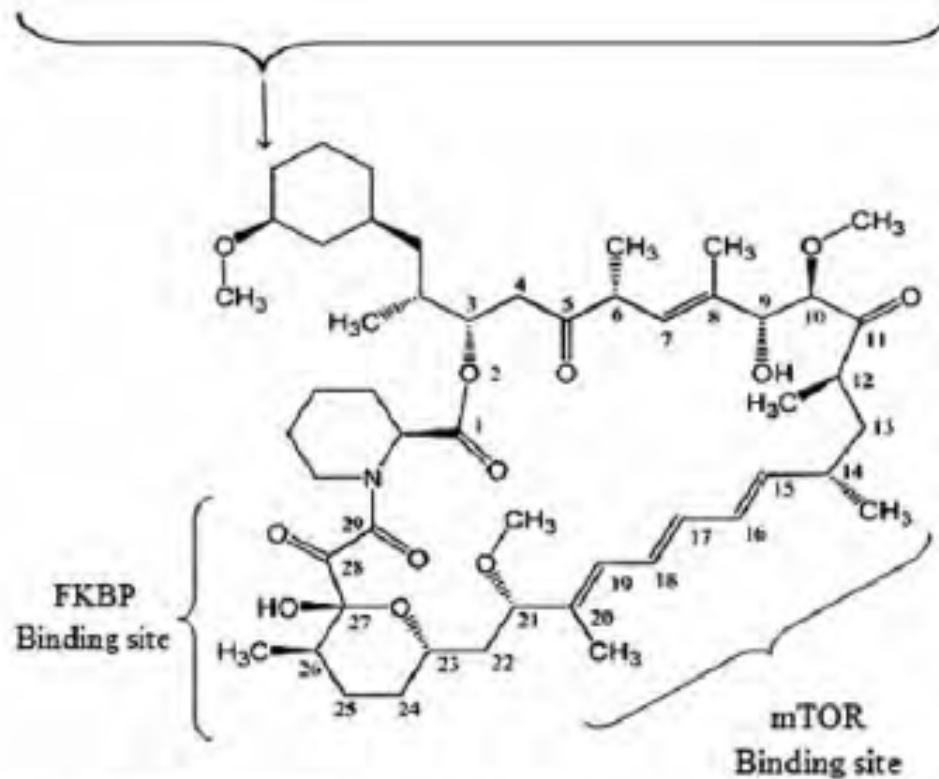
<b>Possible Stent Thrombosis</b>			
All (0-180 days)	0.6 % (1/158)#	0	1.0000

\* Definite sub-acute thrombosis: 48 hours after the procedure the patient came back to hospital with MI. Angio control showed a stent thrombosis. Blood exams revealed clopidogrel not responsiveness. The patient was submitted to medical treatment.

# Possible late thrombosis (Late): 3 months from the procedure the patient suddenly died.

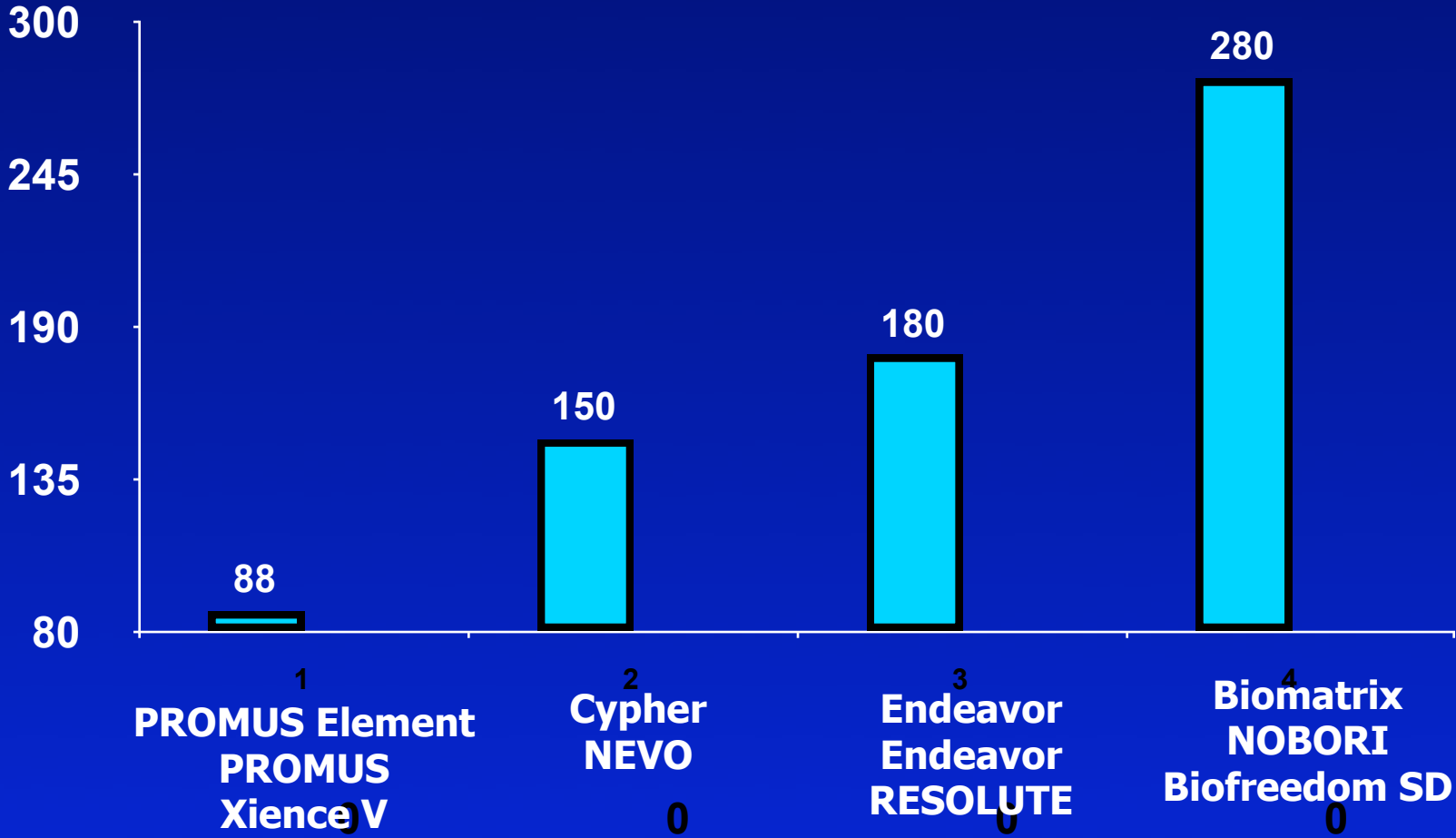
# 'limus end chain differences only

<b>A Sirolimus</b>	<b>-OH</b>
<b>Everolimus</b>	<b>-OCH<sub>2</sub>CH<sub>2</sub>OH</b>
<b>Biolimus</b>	<b>-OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub></b>
<b>Zotarolimus</b>	



# Comparative Drug Loads across (similarly potent) 'limus DES

## Drug Load mcg on 3.0 x 18mm stent



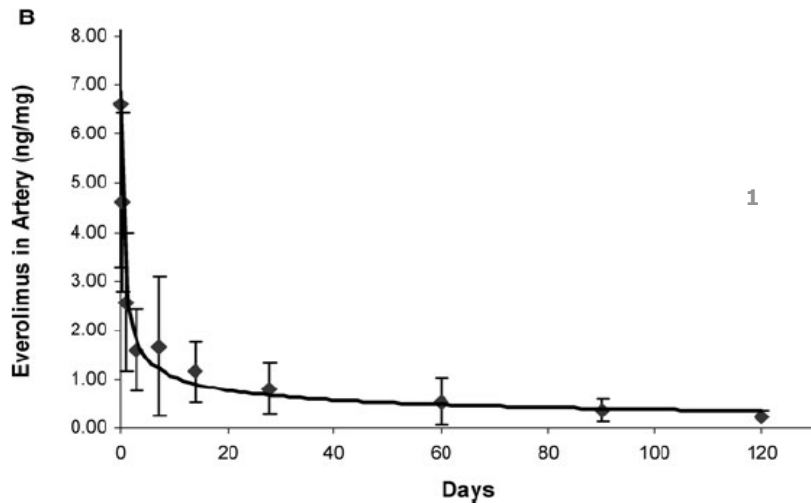
# Drug Dose and Release Kinetics

## Drug Dose Across 'olimus Stents

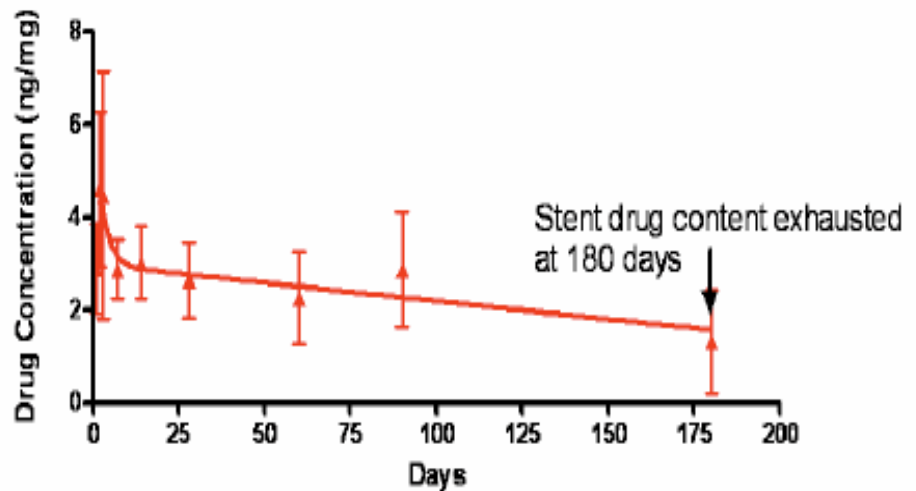


## Everolimus and Zotarolimus drug release kinetics

### PROMUS™ Stent



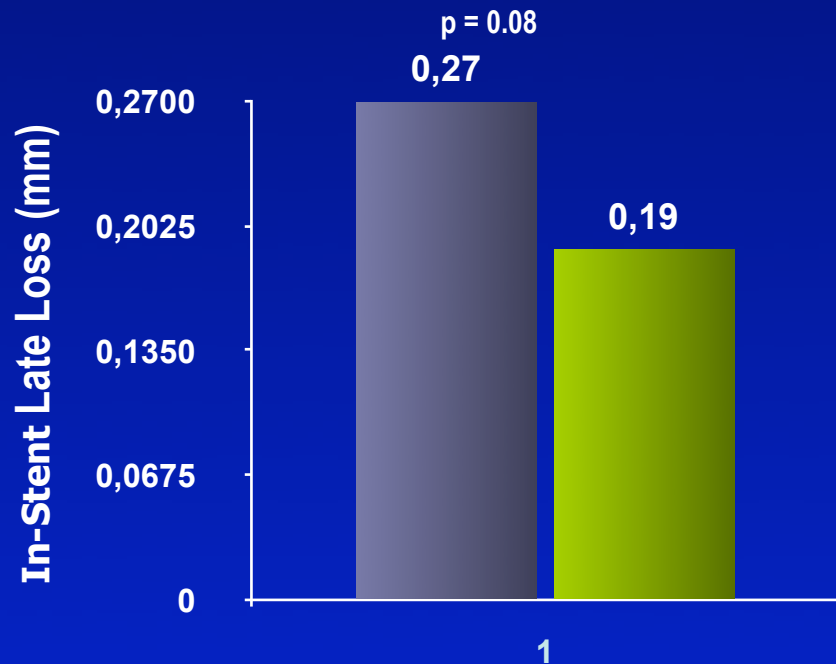
### Resolute™ Stent





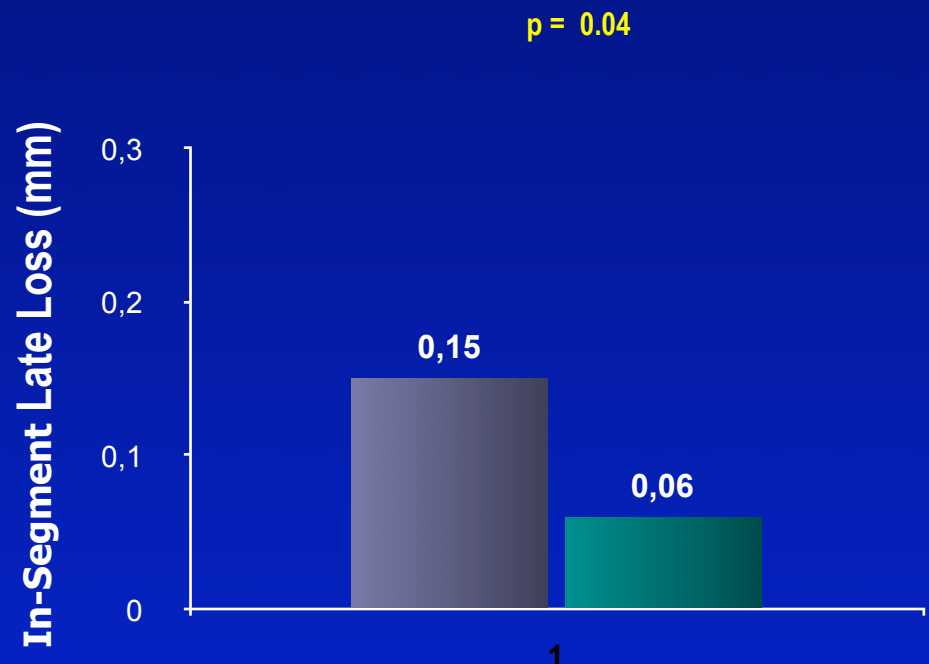
# RESOLUTE All-Comers Trial: 13-Month Late Loss

## 13-Month In-stent Late Loss



Resolute™ Stent  
(n = 183 lesions)

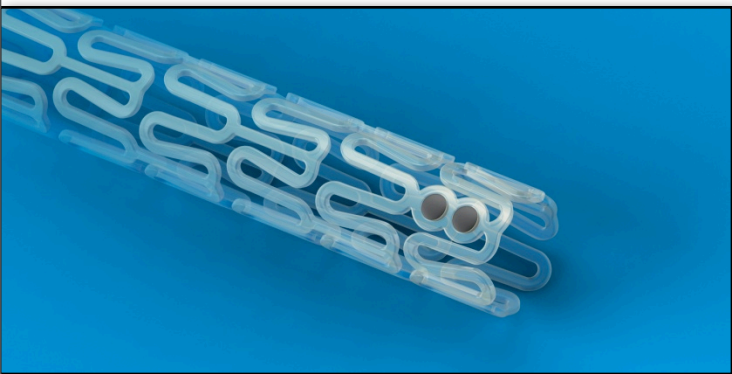
## 13-Month In-segment Late Loss



PROMUS™ Stent  
(n = 177 lesions)

# UNE INNOVATION DE RUPTURE

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- **Bioresorbable**
- **Vascular**
- **Scaffold**
- ... **BVS**

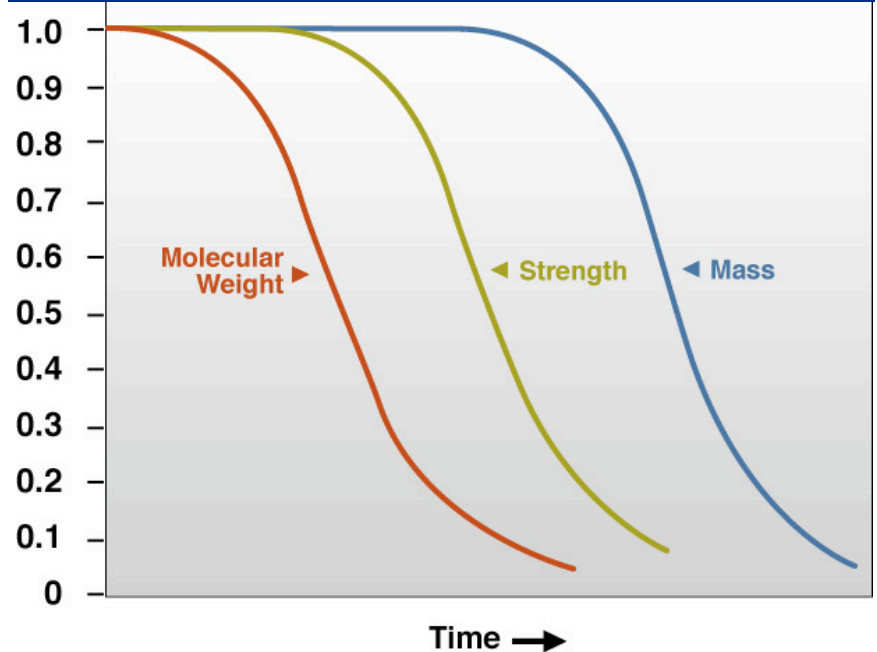
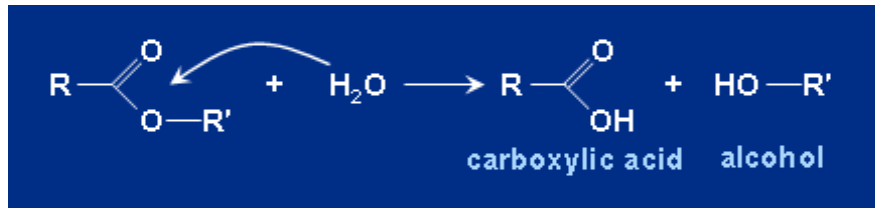
# Dispositif résorbable – Rationnel et Objectifs

## Etayage du vaisseau est nécessaire seulement de manière transitoire

- Revascularise comme un stent métallique, actif ou non actif, puis se résorbe naturellement dans le corps.
- Plus d'implant permanent.
  - Pas d'étayage permanent – permet de restaurer une réponse naturelle et physiologique du vaisseau avec un remodelage tardif positif.
  - Pas de réponse inflammation chronique – permettrait de réduire la bi-thérapie anti aggrégante plaquettaire?
  - Possibilité re-interventions (dilatations ou pontages) à distance facilitées.
- Compatible avec des examens non invasifs (IRM, CT)

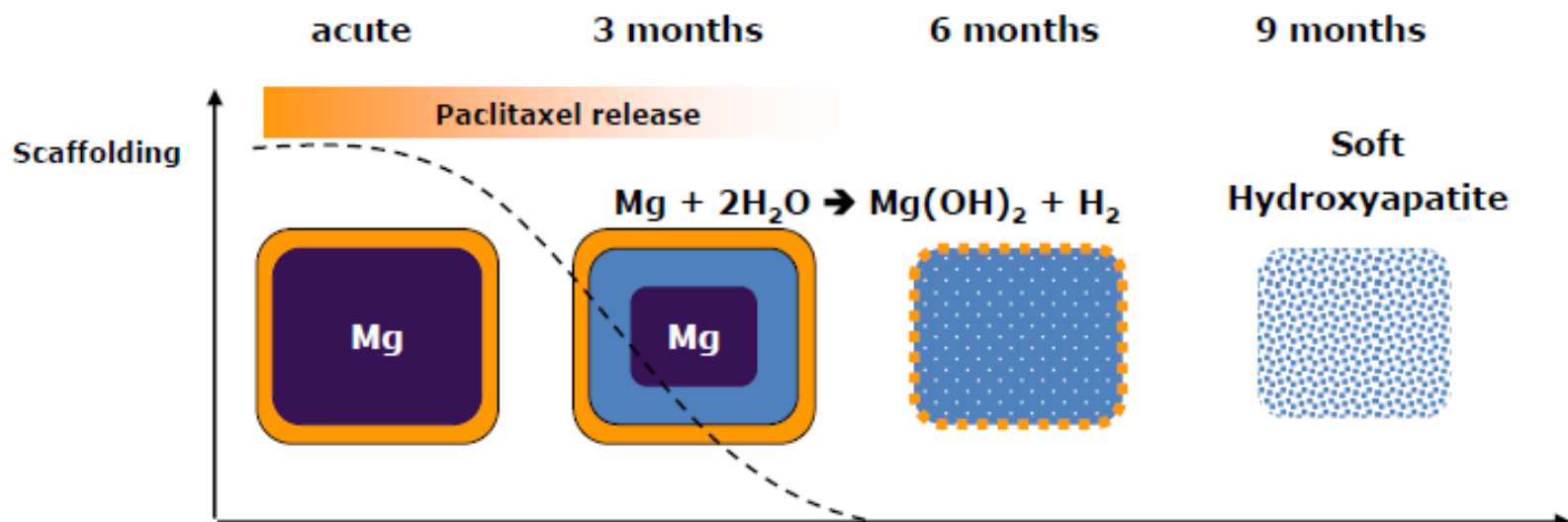
# Polylactide Degradation by Hydrolysis

- Primary mode of degradation is by hydrolysis of ester bonds
- Water preferentially penetrates amorphous regions of the polymer matrix
- Hydrolysis initially results in a loss of molecular weight, but not radial strength, as the strength comes from crystalline domains
- Once crystalline domains are hydrolyzed, there is mass loss



<sup>1</sup>Pietrzak WS, et al. J. Craniofacial Surg, 1997; 2: 92-96.  
Middleton JC, Tipton AJ, Biomaterials, 21 (2000) 2335-2346.




# DREAMS provides scaffolding and paclitaxel release up to 3 months



- Initial Mg degradation
- Stable drug carrier layer
- Controlled drug release

- Mg degradation completed
- Drug release completed
- Absorption of polymer ongoing

- Conversion of degradation product completed
- Drug carrier layer completely absorbed
- Beginning of structural disintegration and bioabsorption

-  Mg alloy
-  Mg degradation product
-  Polymer

# Results: procedural and primary endpoints for cohort 1 up to 6 months

	n	%
Device success	22	100
Procedural success	22	100
<b>6-month clinical results</b>	<b>22</b>	<b>100</b>
TLF	2	9.1
Death	0	0.0
MI	0	0.0
Scaffold thrombosis	0	0.0
TLR (clinically-driven)*	2	9.1

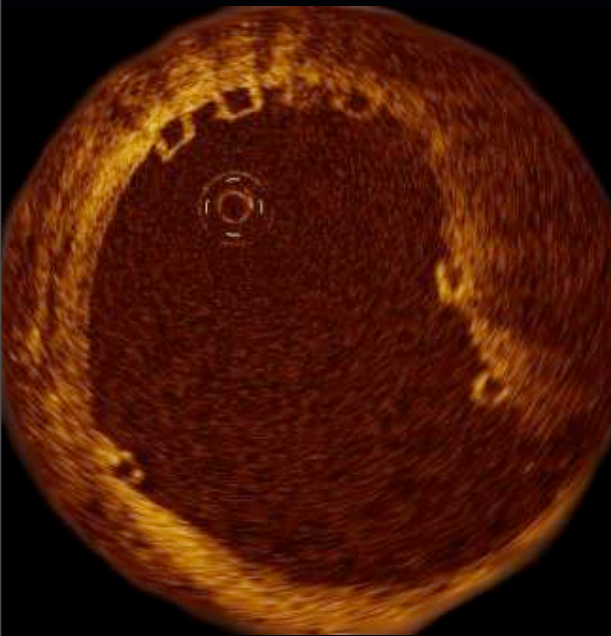
\*TLR occurred during 6 M FUP, both pts had angina, 1 pt received an additional DREAMS in the target lesion during the initial procedure because of a flow-limiting bailout situation

# ABSORB Cohort A

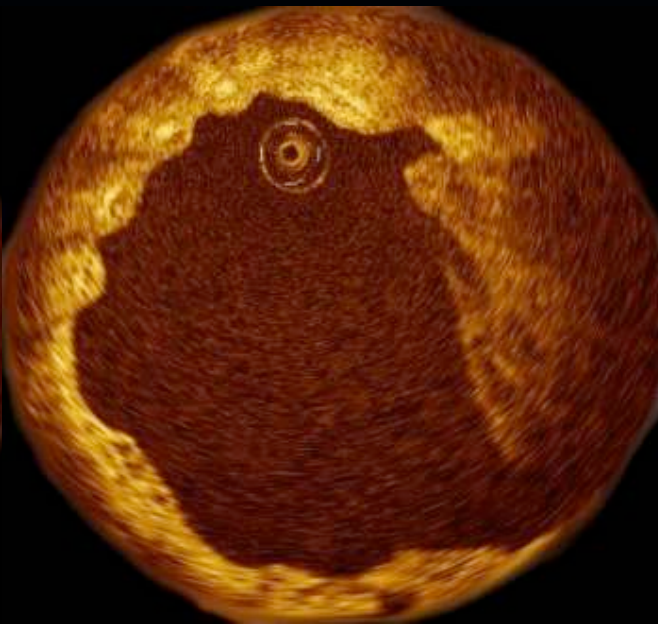
## OCT Images on ABSORB-treated Segment

### Case Example

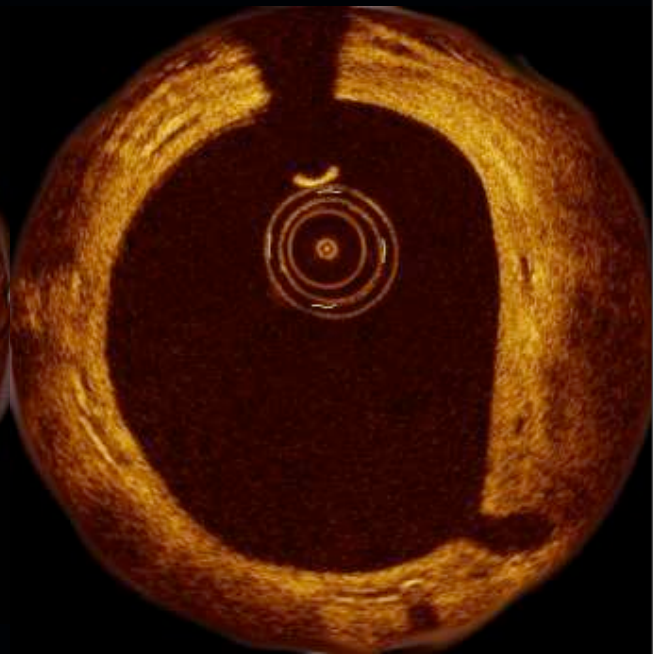
**Baseline**



**6 Months**



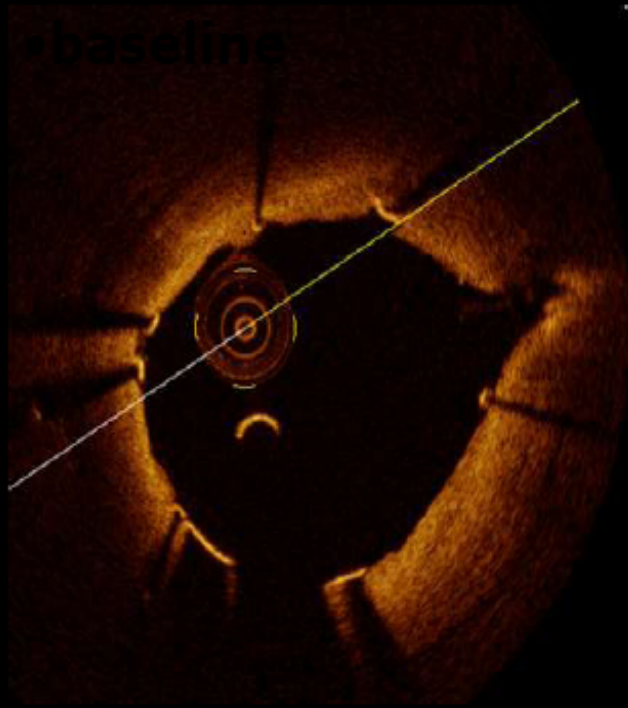
**2 Years**



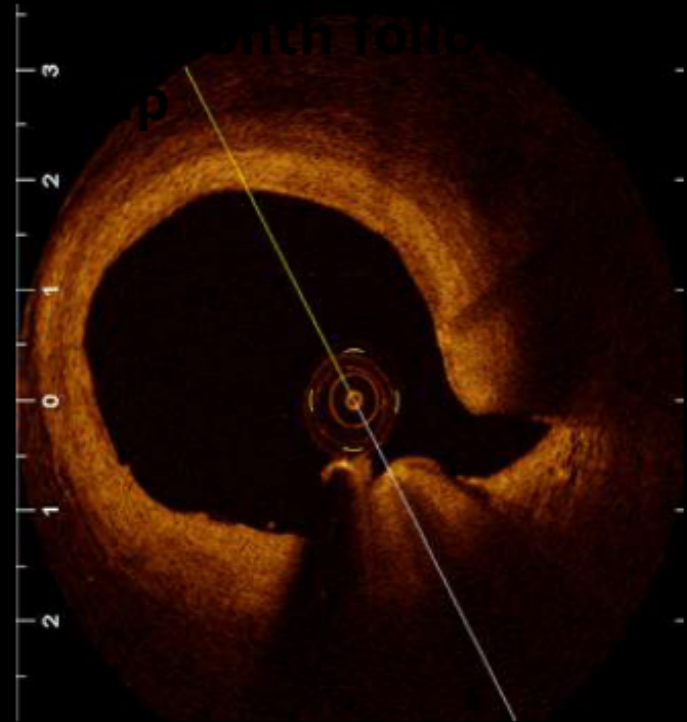
SE2928753 REV. A. Pipeline product. Currently in development at Abbott Vascular. Not available for sale.



# BIOSOLVE-I: OCT shows strut absorption



- Appearance like a permanent metallic stent
- Very good wall apposition



- Complete tissue coverage
- Absorbing Magnesium core
- Strut remnants depicted as shadows



# CONCLUSION

- ✓ 1<sup>st</sup> or 2<sup>nd</sup> or 3<sup>rd</sup> generation DES ?
- ✓ Clinical end-points (safety, efficacy) +++
- ✓ Platform (thinner is better)
- ✓ Polymer (bio-erodible, fluoropolymer, no polymer)
- ✓ Drug (vessel exposure)
- ✓ Bio-absorbable stent