CATH LAB SYMPOSIUM 2010

Stent Technology 2010

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Cath Lab Director
Memorial Regional Hospital

First Report of Coronary Stenting in 1987

The NEW ENGLAND JOURNAL of MEDICINE

INTRAVASCULAR STENTS TO PREVENT OCCLUSION AND RESTENOSIS AFTER TRANSLUMINAL ANGIOPLASTY

Ulrich Sigwart, M.D., Jacques Puel, M.D., Velimir Mirkovitch, M.D., Francis Joffre, M.D., and Lukas Kappenberger, M.D.

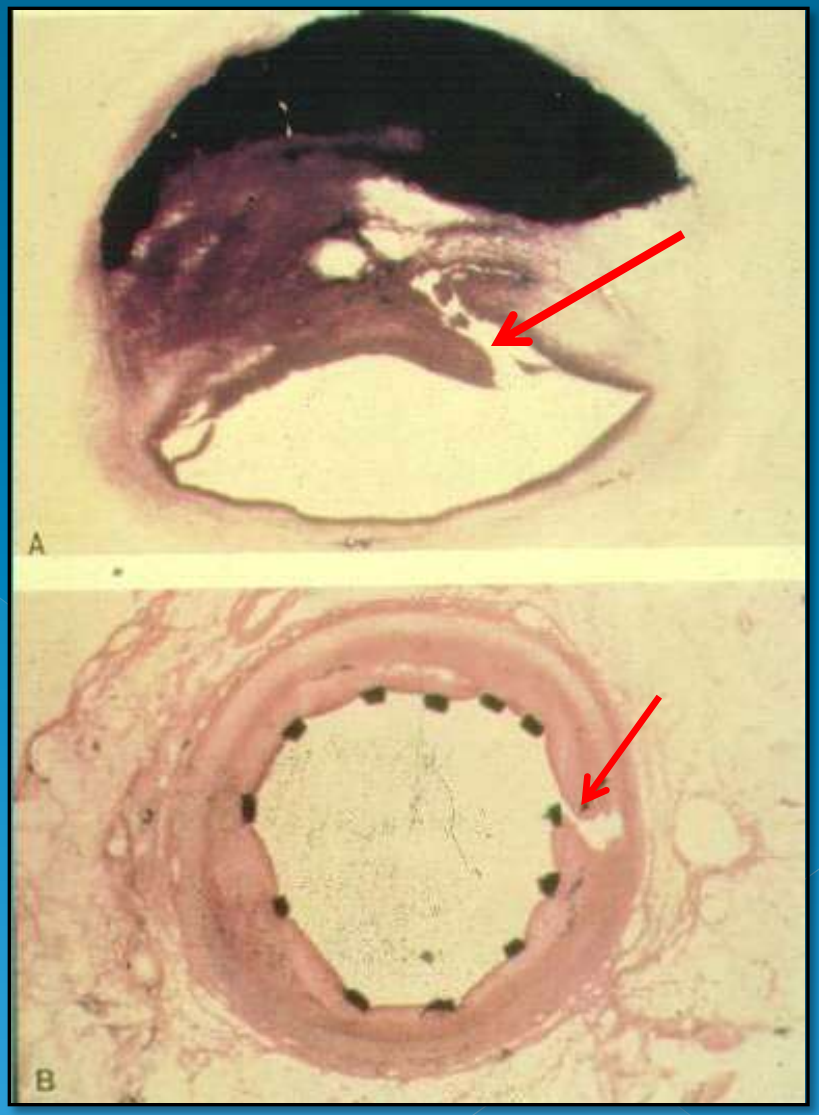
N Engl J Med 1987; 316:701-6

Ulrich Sigwarth (Lausanne 1986)

First human coronary implantation

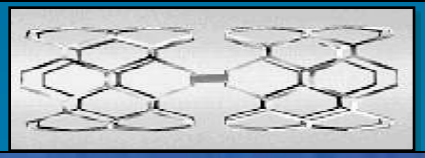
Why to Stent?

- Mechanically scaffold the artery and create a larger lumen predictably
- Prevent abrupt vessel closure
- Prevent restenosis

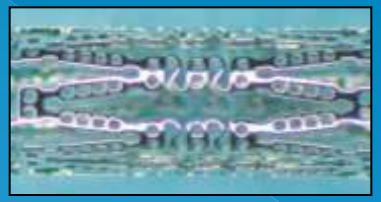


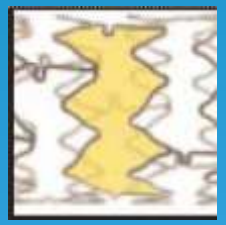
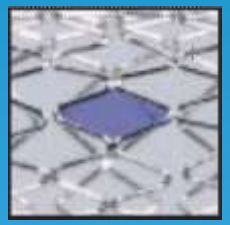
Stent Design

- Coil (Gianturco-Roubin)
- Slotted-tube (Palmaz-Schatz)
- Self-expanding mesh (Wallstent)
- multicellular or corrugated ring with flexible connections (majority of current stents)
- Open-cell or closed cell design

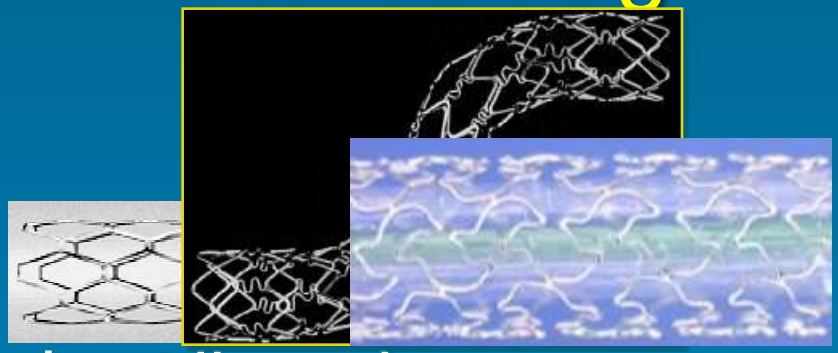


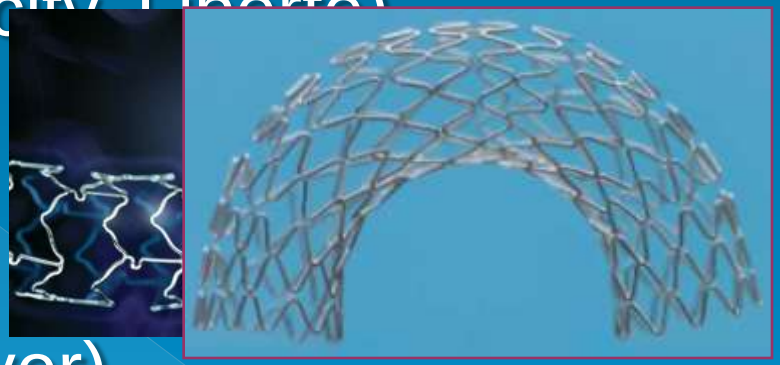



Features & Variables of Stent Design

Strut material

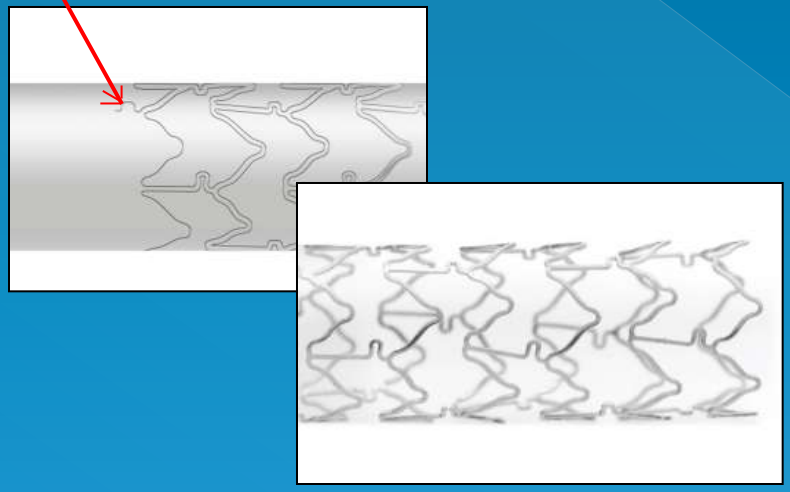




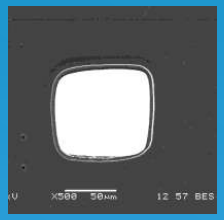
- Stainless steel 316 L (Palmaz-Schatz, Velocity, Liberte)
- Tantalum (Wiktor)
- Nitinol (ACT-One)
- Cobalt chromium (Multilink VISION, Driver)
- Platinum chromium (Taxus & Promus Element)
- New Alloy DES (Xience)

Basic strut types / Construction

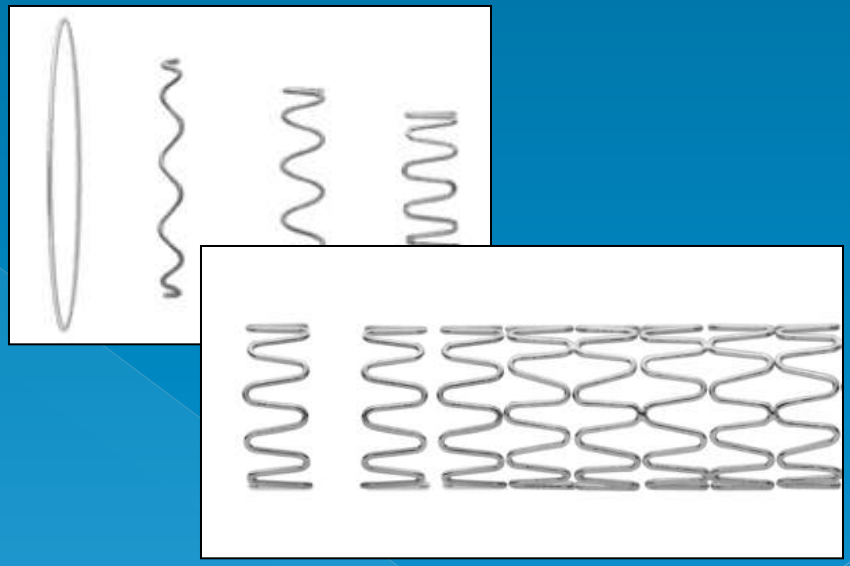
1. Laser-cut stents start as a tube, a laser removes material and a stent remains. Laser-cut stent production leaves square (blunt) edges.



Squared edges

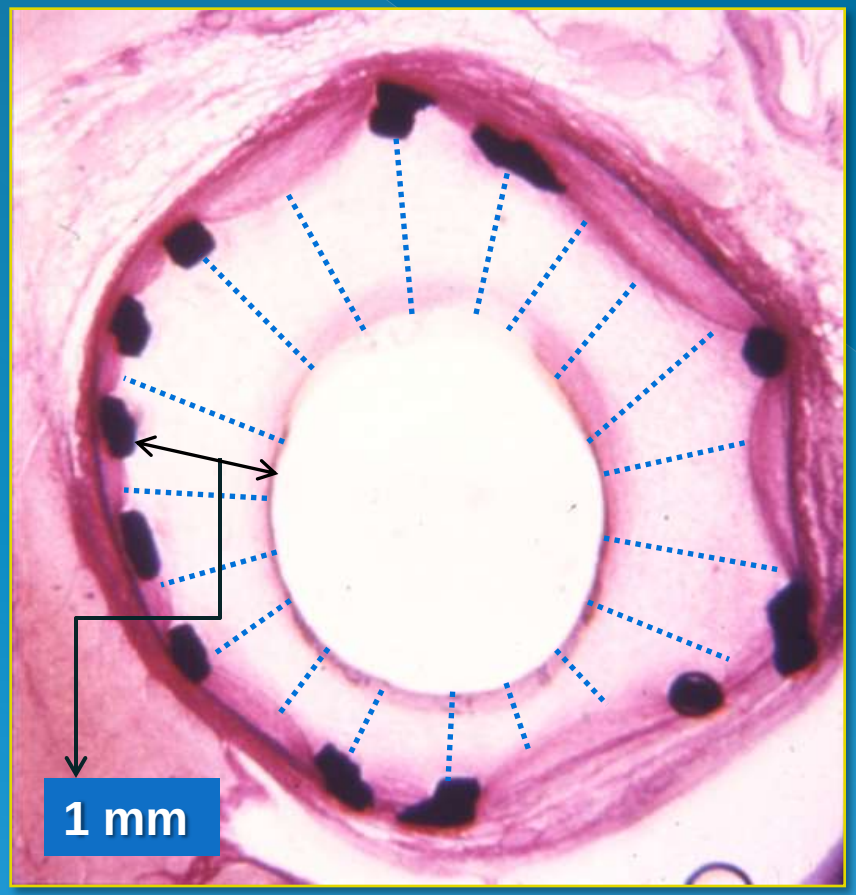


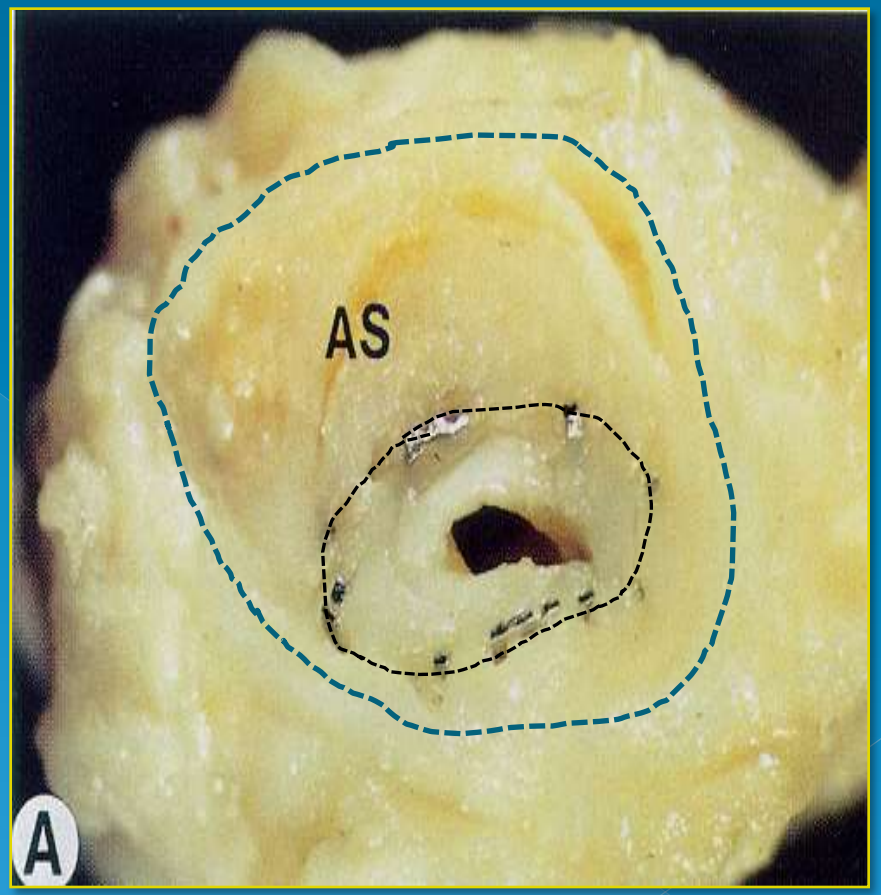
2. Metallic rings are formed into sinusoidal elements that are fused together to comprise a modular stent.



Ultrathin, smooth, edgeless struts

The Limitation of Bare Metal Stents

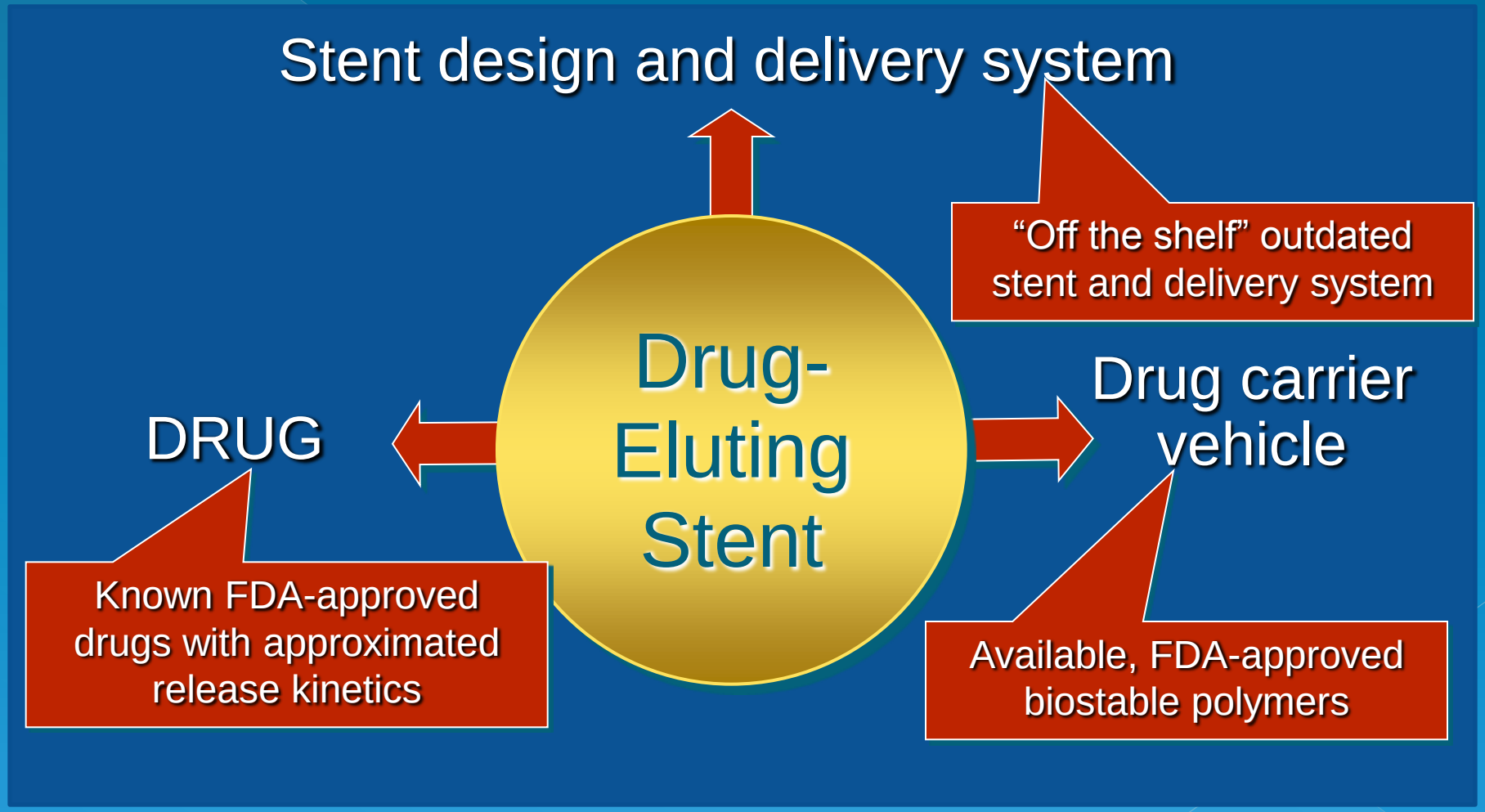




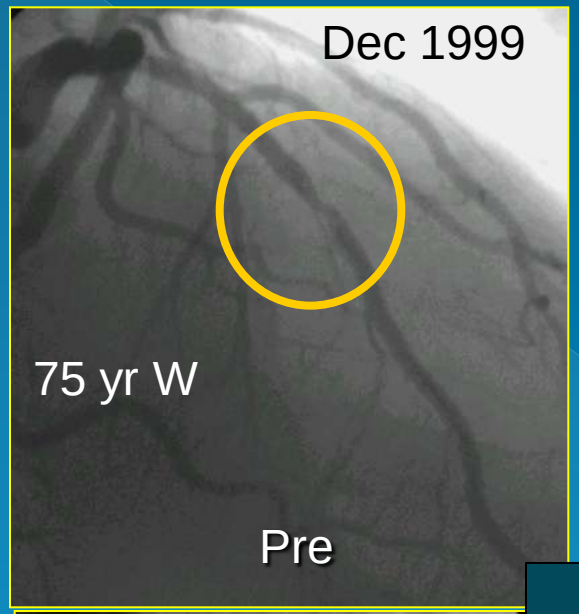
In-stent Restenosis = Intimal Hyperplasia

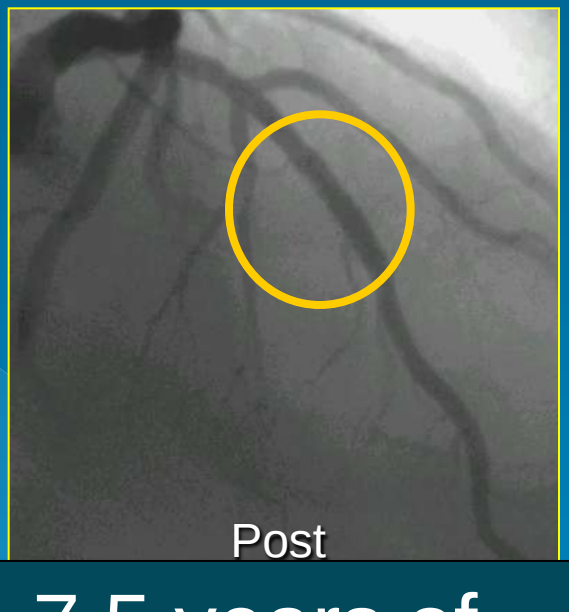
Drug-Eluting Stents

First Generation

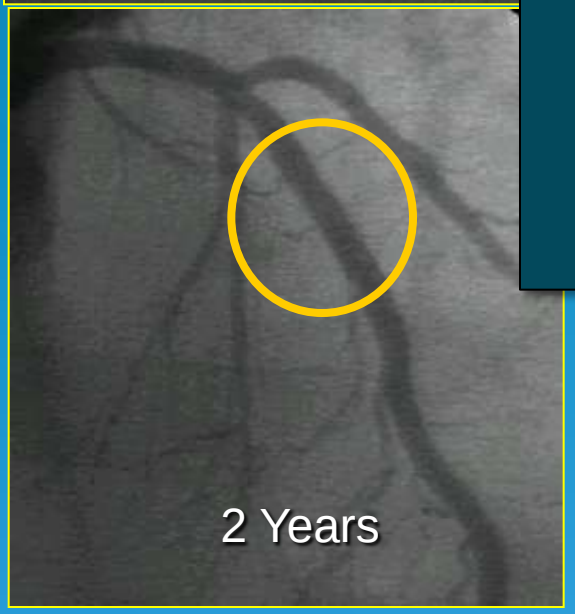


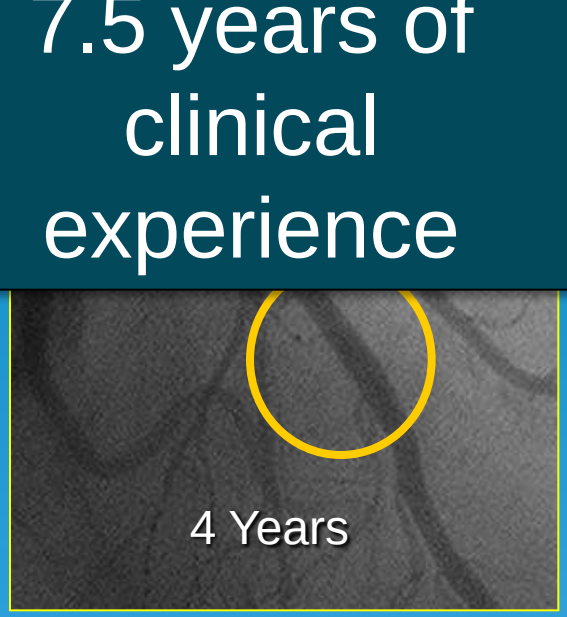
CYPHER Stent: First patient 10 Years FU





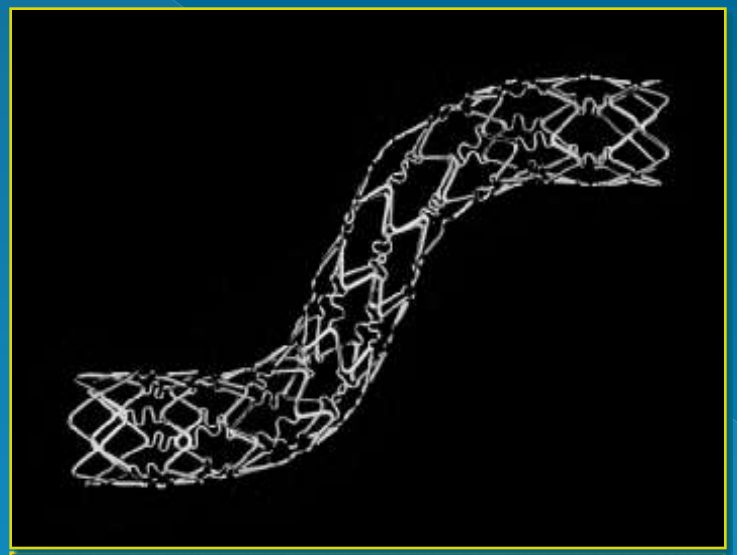
7.5 years of clinical experience

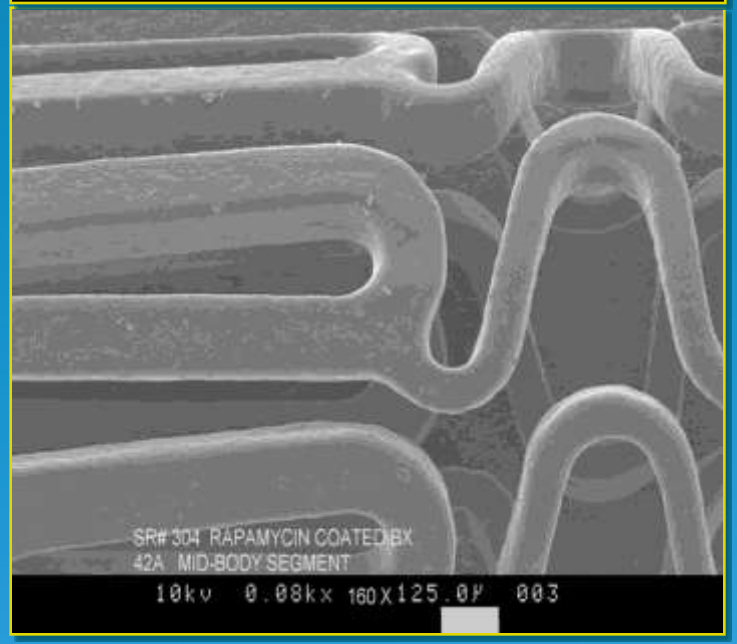





Success over
In-Stent
Restenosis!!

The Sirolimus-Eluting Stent (Cypher)





- ***Bx VELOCITY™ Stent***

  Stainless steel stent

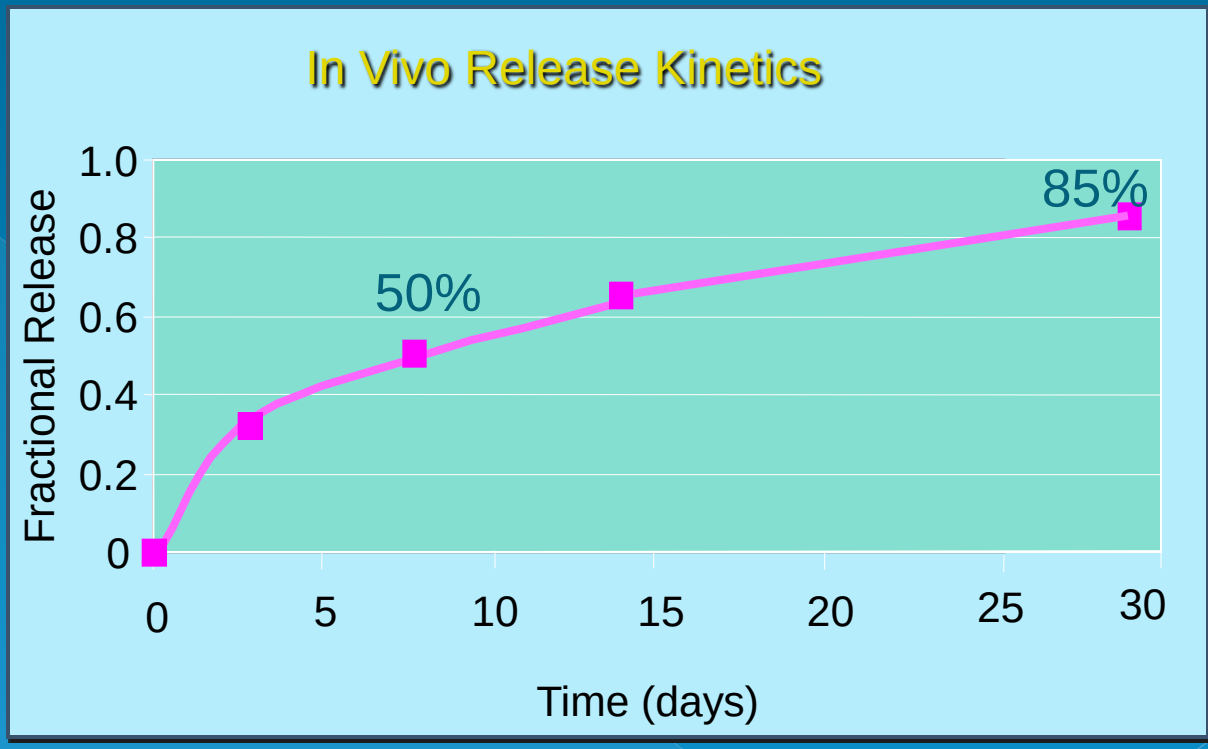
- Coating:

  Blend of 2 polymers (PEVA + PBMA) containing Drug: Sirolimus (~ 10um thick)

Sirolimus Eluting Cypher Stent

Topco

Basecoat = polymer/drug
+
Topcoat = polymer only
(diffusion barrier)



Sirolimus (Rapamycin): Cytostatic Agent

Released in a controlled manner from the polymer matrix (PEVA + PBMA)
ALL of the drug is released within 3 months

One Year later: TAXUS Stent

Drug

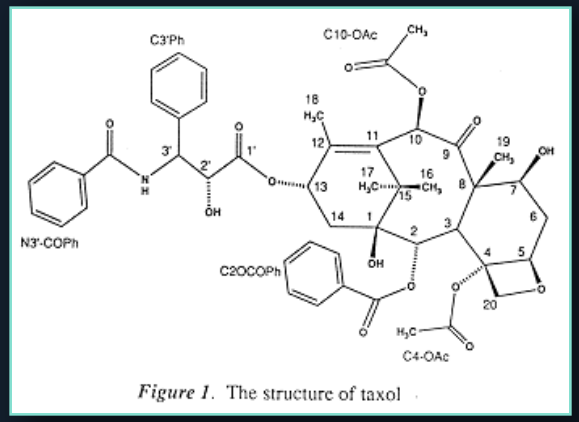
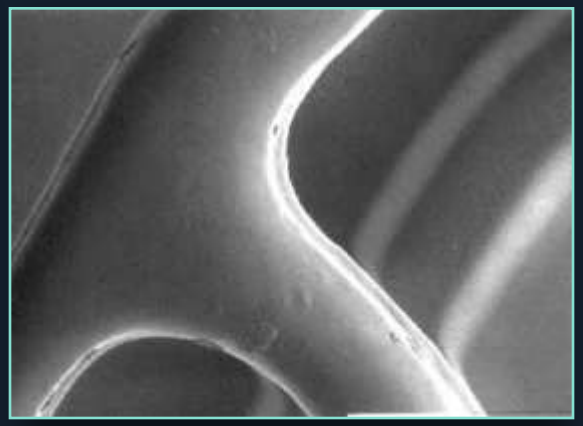


Figure 1. The structure of taxol

Paclitaxel

- Binds tubulin
- Stabilizes microtubular deconstruction
- Multi-cellular
- Multi-functional
- Cytostatic at low dose

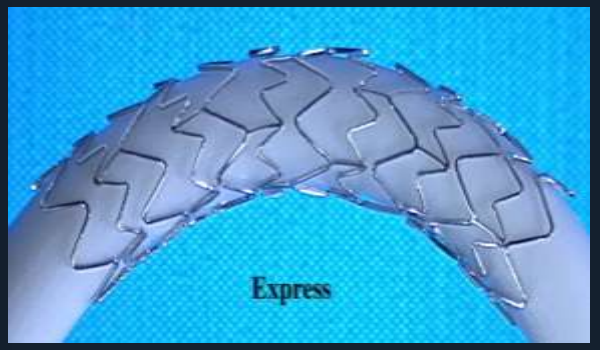
Polymer



Translute™

- **Polyolefin derivative**
- **Uniform**
- **Biocompatible**
- **Elastomeric**
- **Provides controlled release**

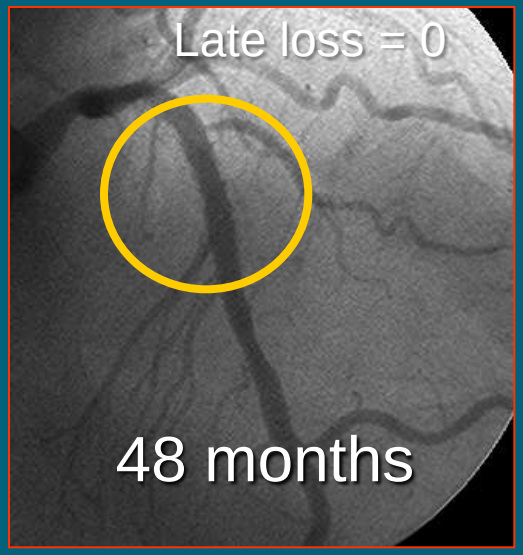
Stent

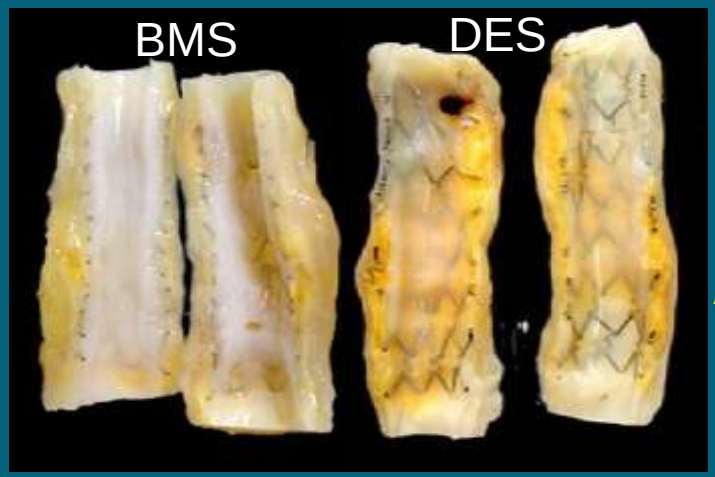


Express²

- **Stainless Steel**
- **Maverick balloon system**
- **Flexible**
- **Deliverable**

1st Generation DES…. the good, the bad, and the ugly!

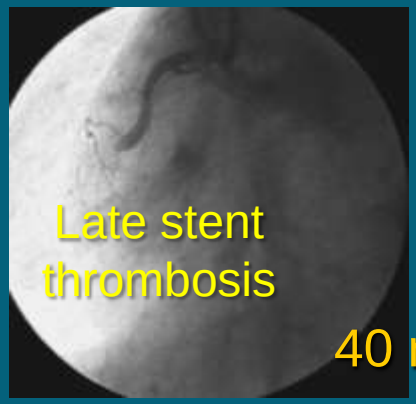


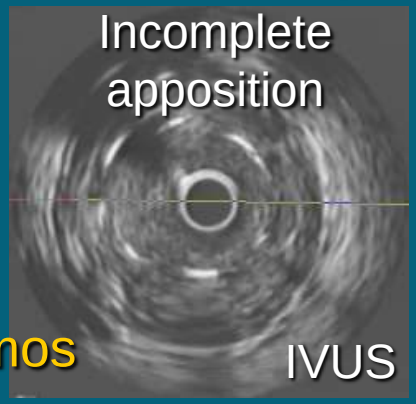


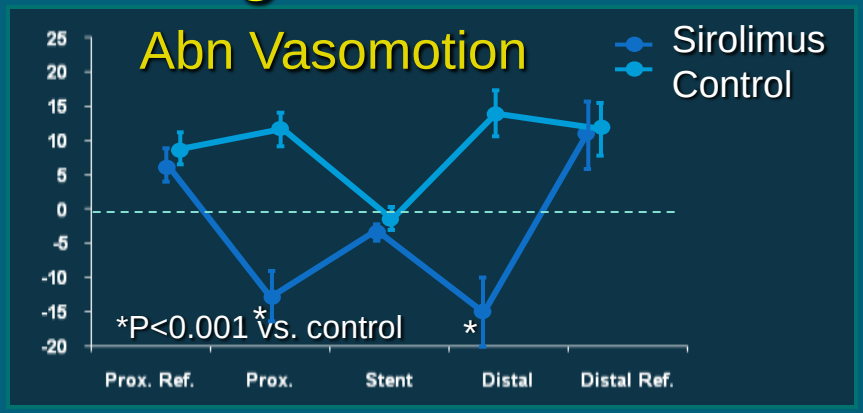
Delayed Healing!

Angioscopy

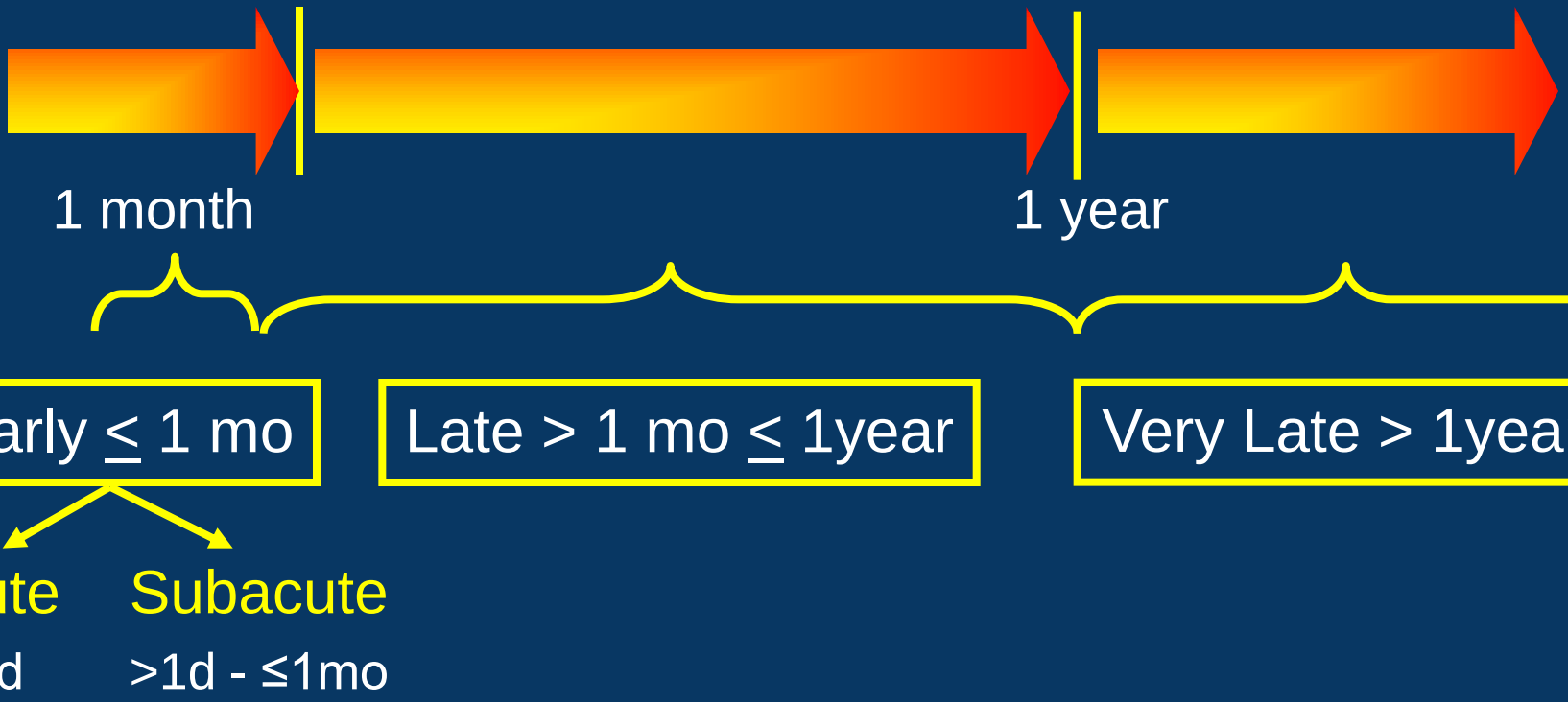
Inflammation





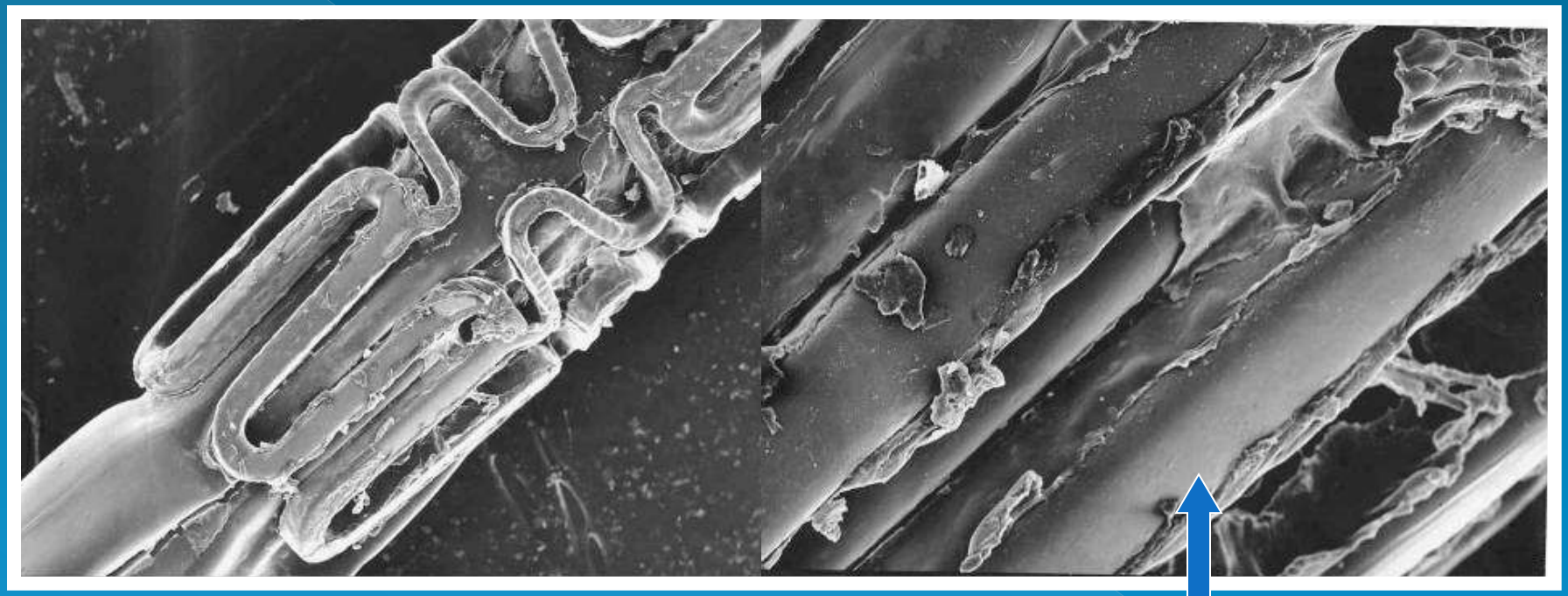


Stent Thrombosis

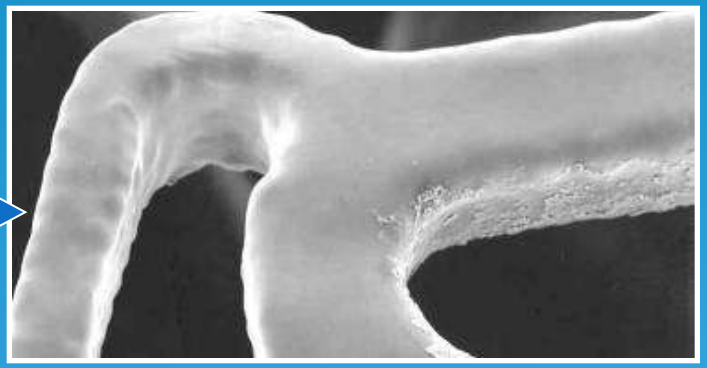


And still some restenosis…..

Polymer coating damage



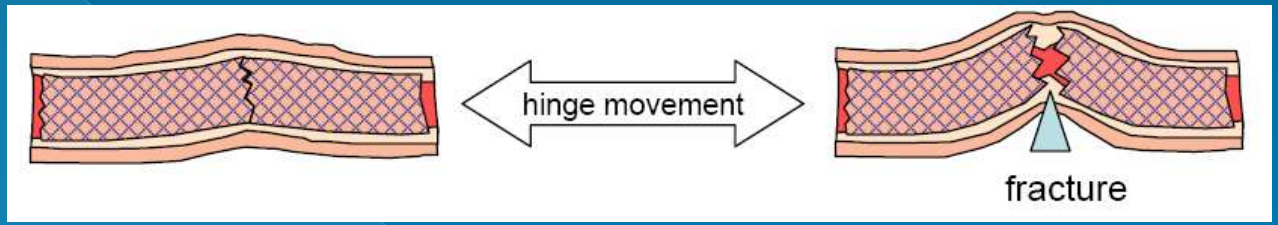
Failed to cross calcified lesion



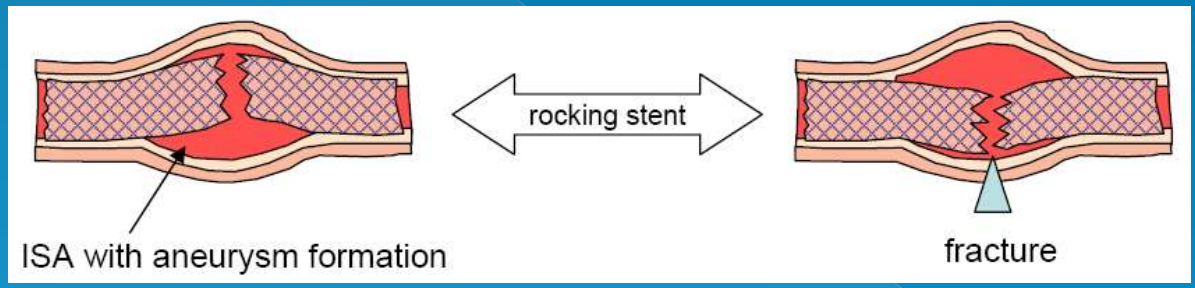
Undamaged polymer

Three patterns of Stent Fracture

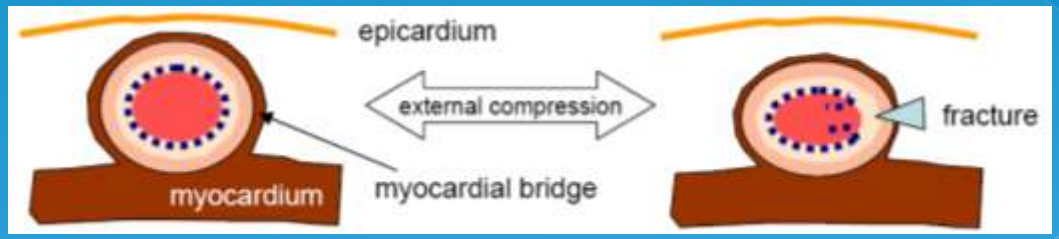
Type I; Stent Fracture in the lesion without either aneurysm or myocardial bridge (14 SF)



Type II; Stent Fracture in aneurysm with incomplete apposition (5 SF)



Type III; Stent Fracture in myocardial bridge (1 SF)



H.Doi SCAI/i2 2008

ACROSS CYPHER: n= 200

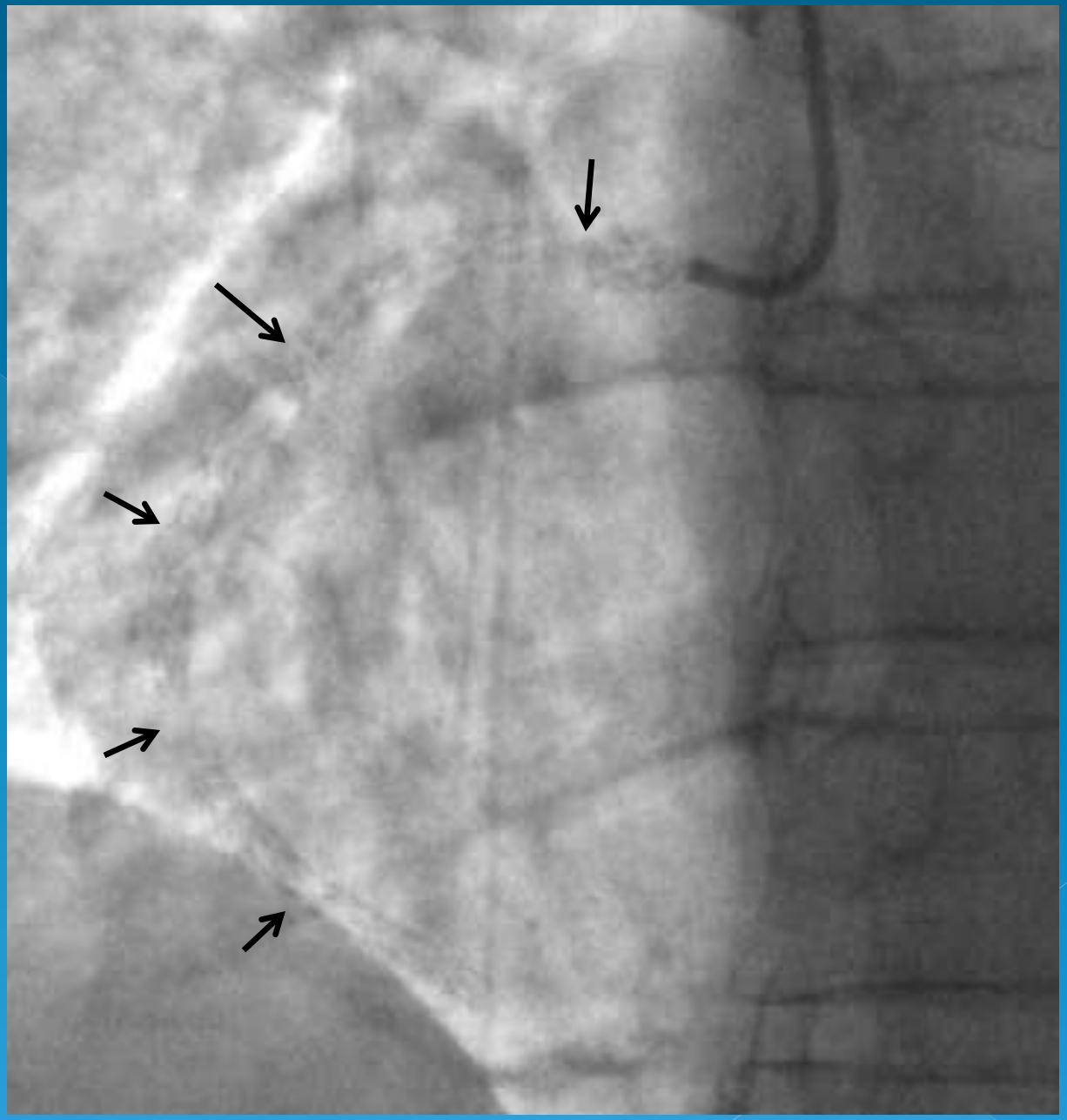
16% Angio Stent Fractures at 6 mos

	Patients with Stent Fracture N = 32	Patients w/o Stent Fracture N = 168	p-value
Mean Stent Length (mm)	69.7 ± 24.6	45.0 ± 22.2	<0.001
Overlapping Stents	100.0% (30/30)	89.9% (107/119)	0.06
Binary Restenosis			
In-segment	21.9% (7/32)	11.7% (16/137)	0.07
In-stent	15.6% (5/32)*	7.4% (10/136)	0.09
Stent Thrombosis	3.1% (1/32)	0.0% (0/165)	0.16

* Of the 5/32 fracture patients with in-stent restenosis, 2 patients had restenosis at the site of fracture (1 patient had restenosis at 2 separate fracture sites).

RCA STENT PLACEMENT FOR DIFFUSE DISEASE

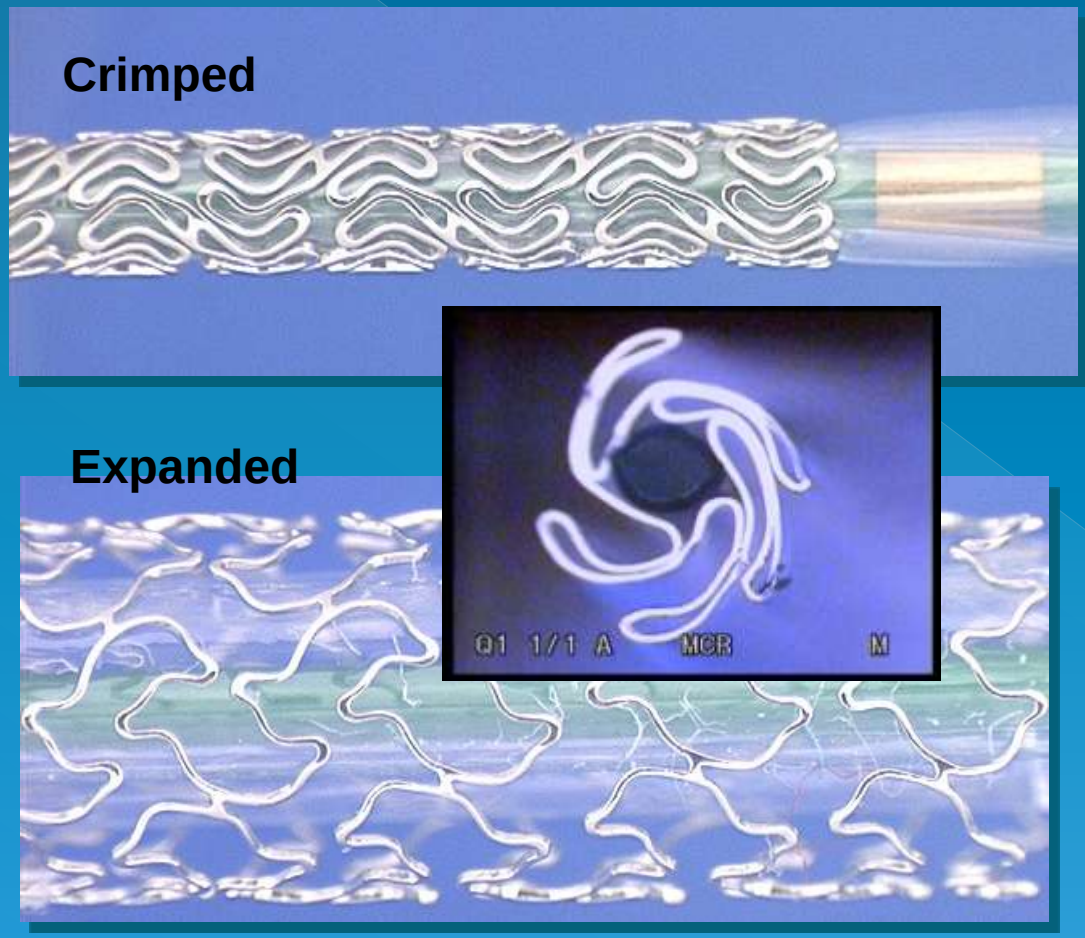
More than 2 yrs later, stops DAPT. One week later comes in with a inferior STEMI: Multiple Cypher stent Fractures



“Second” Generation DES:

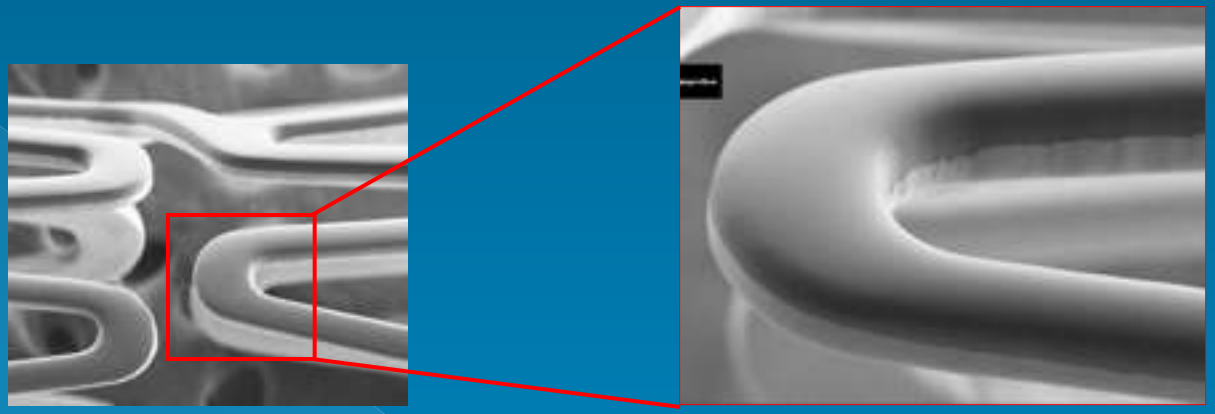
Better designed to be drug eluting stents

Second Generation TAXUS Stent:
TAXUS Liberté™



- *Polymer and drug are unchanged*
- *Maverick² balloon*
- *5-wing fold for improved re-wrap and less resistance to withdrawal*
- *Stainless steel 27%↓ in strut thickness - from 0.0052" (Express²) to 0.0038"*

Ultra-thin Abluminal Bioabsorbable Polymer



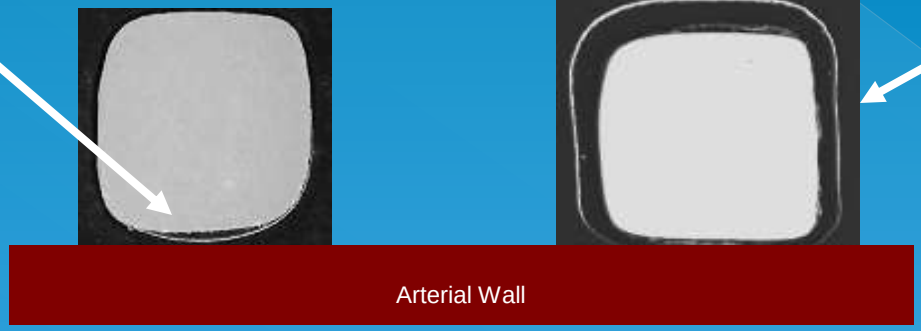
Bioabsorbable polymer (PLGA) is only applied to the abluminal surface of a thin strut (0.0028”) PtCr Stent

PLGA Bioabsorbable Polymer + Everolimus on Abluminal Side of Stent

Bioabsorbable Abluminal Polymer Stent

Current DES

Durable Permanent Polymer + Drug 360° Around Stent

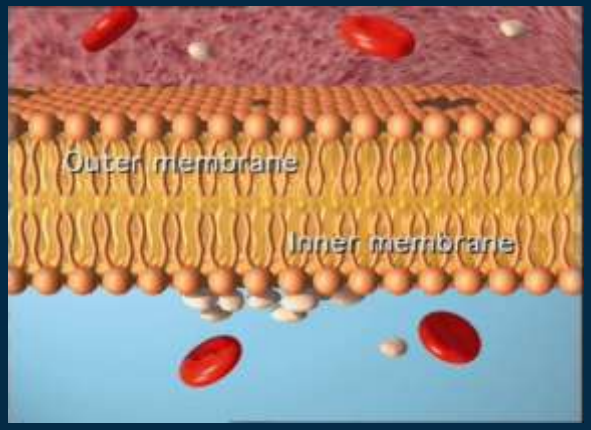


Endeavor DES System

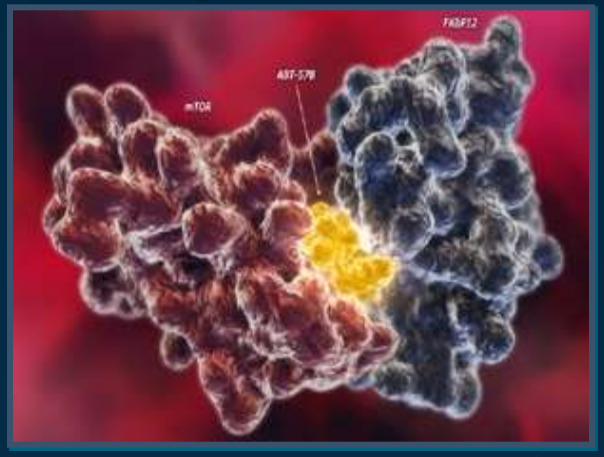
Driver Cobalt Alloy Stent

Stent Delivery

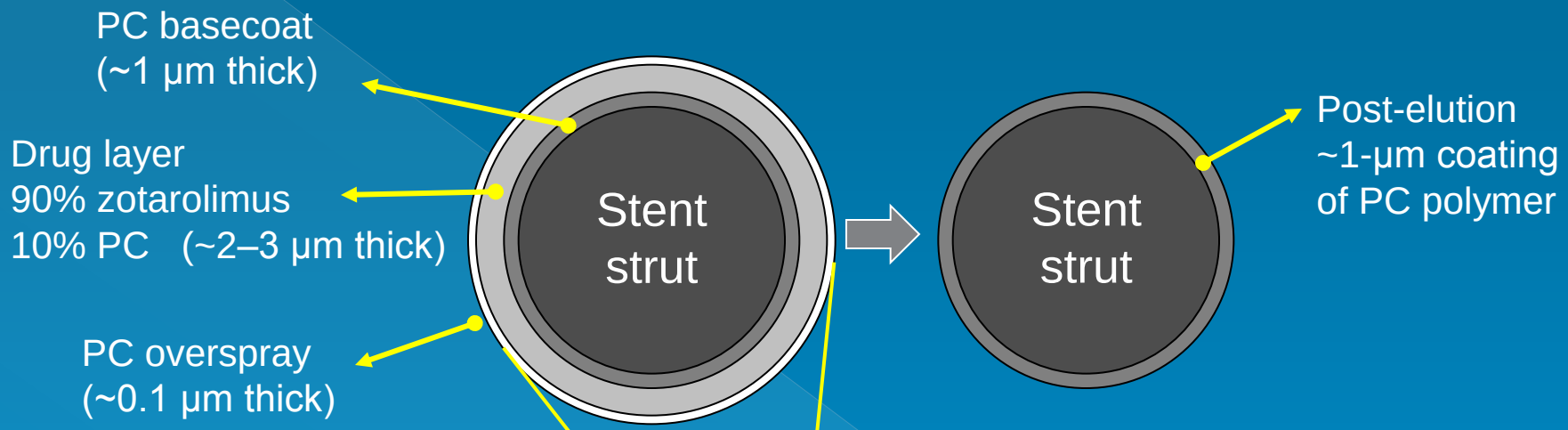
PC Technology



Drug: Zotarolimus



Endeavor Polymer + Drug Matrix

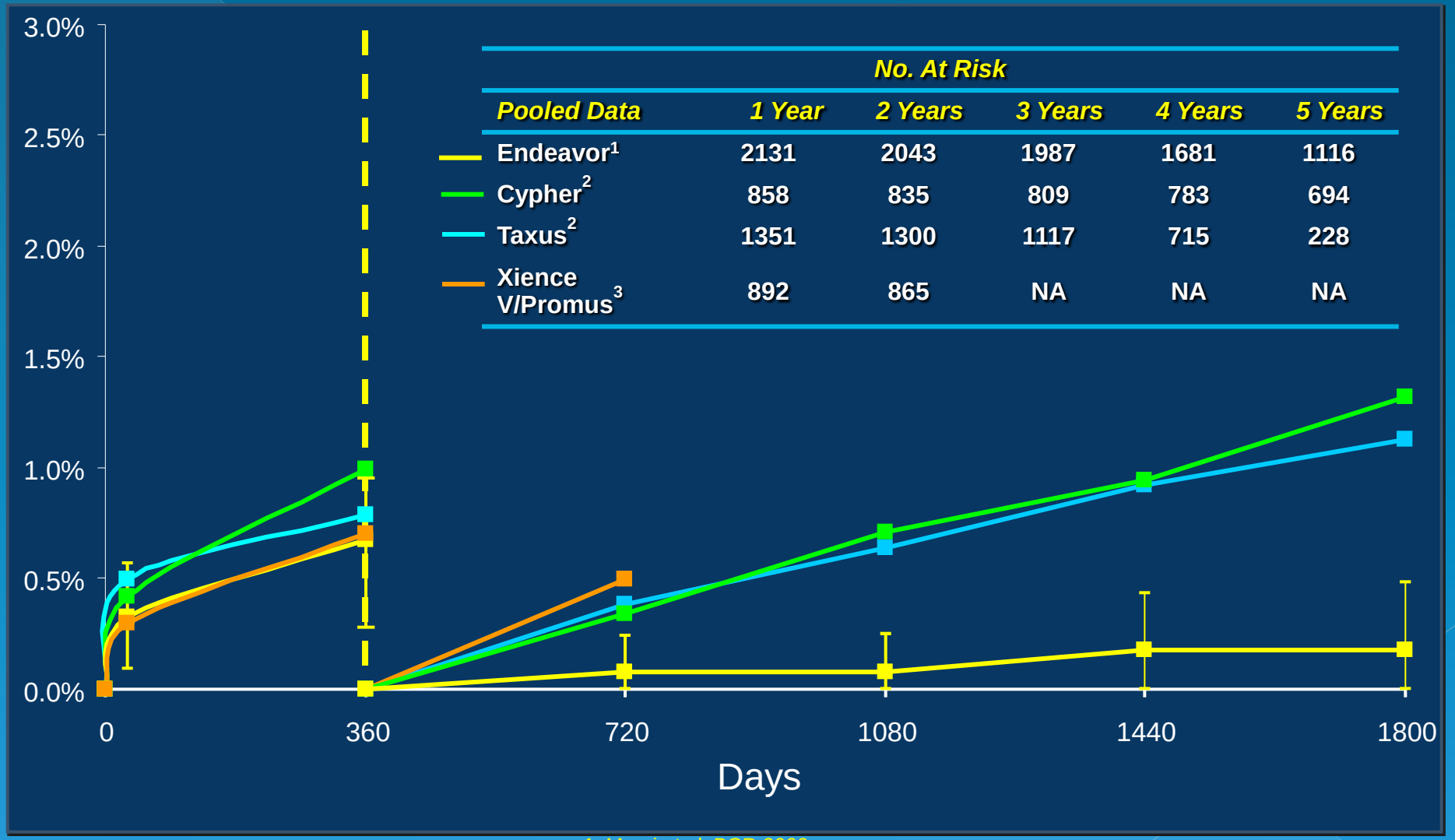


3.0-mm stents
500x magnification

	Endeavor	Taxus®	Cypher®
Drug/polymer	4 μm	16 μm	13 μm
Strut thickness	91 μm	132 μm	140 μm
Total thickness	95 μm	148 μm	153 μm

DES Pooled Programs

Definite/Prob ST* Landmark at 1 year to 5 Years



Pooled Data	No. At Risk 1 Year	2 Years	3 Years	4 Years	5 Years
Endeavor[1]	2131	2043	1987	1681	1116
Cypher[2]	858	835	809	783	694
Taxus[2]	1351	1300	1117	715	228
Xience V/Promus[3]	892	865	NA	NA	NA

*ARC Def

1. Mauri et al. PCR 2009.
2. 5 year Outcomes in the Sirius Trial, Weisz et al. JACC Vol. 53, No. 17, 2009
3. Mauri L et al. N Engl J Med. 2007;356:1020-1029.
4. Stone, G et al., New SPIRIT Clinical Data, ACC. 09.

OPTIMIZE (Brazil)

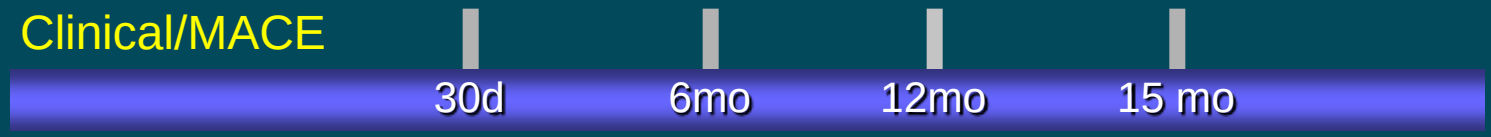
RCT 3 months DAPT vs 12 months

All comers (excluding STEMI)
Reference Vessel Diameter 2.25 mm-4.0 mm

Endeavor Stent
3 months DAPT
n = 1,600

N = 3,200 patients
in
Brazil

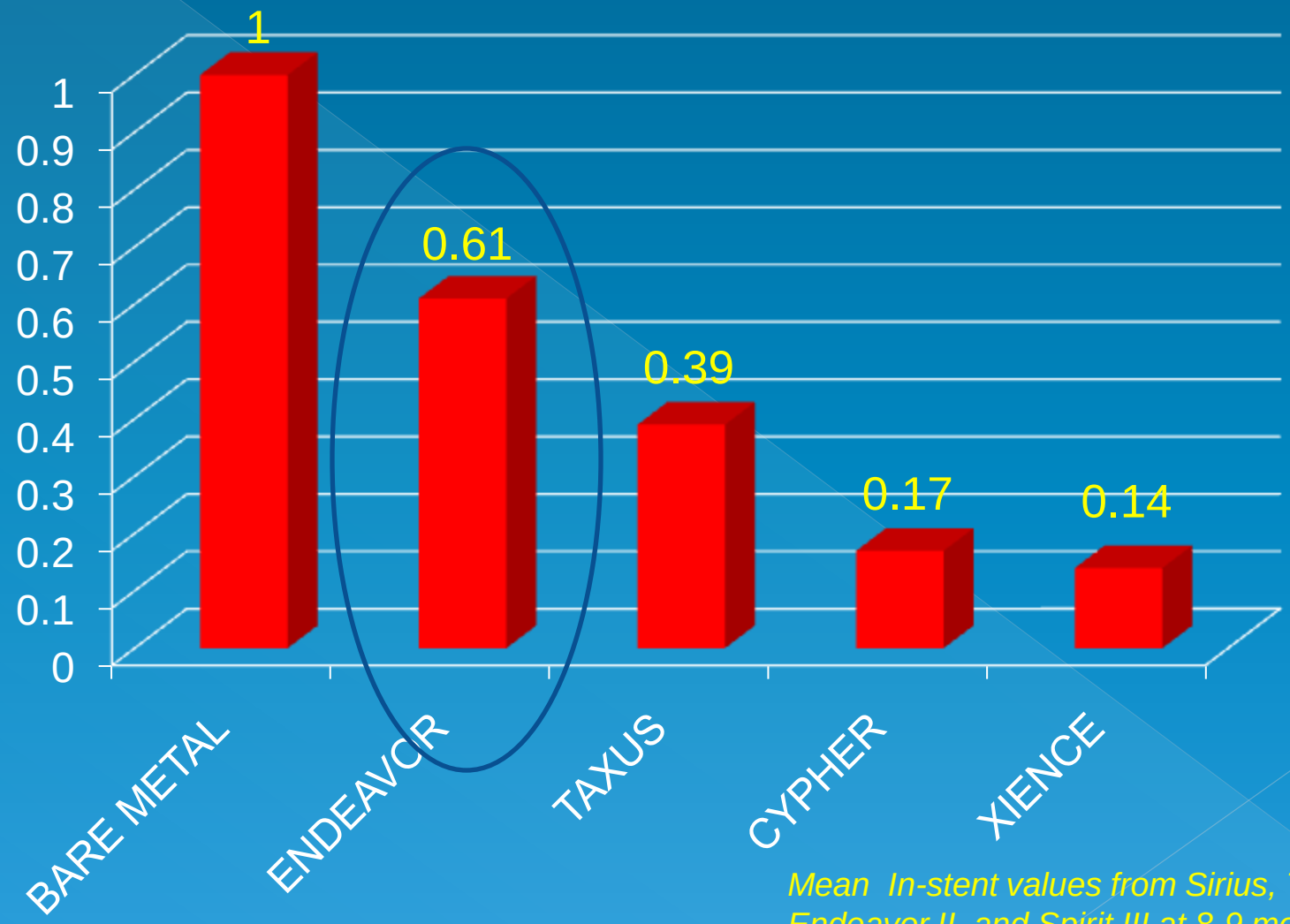
Endeavor Stent
12 months DAPT
n = 1,600



Primary Endpoint: TLF at 12 months
Secondary Endpoints: MI, Cardiac Death, ARC def/prob ST at 30 days, 6 months and 15 months
Drug Therapy: ASA and Clopidogrel 3 or 12 months

Late Loss* (mm)

An (imperfect) Index of Anti-restenotic Efficacy



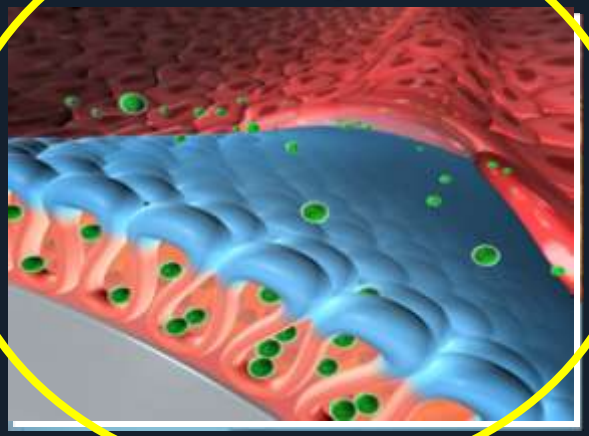
Mean In-stent values from Sirius, Taxus IV Endeavor II, and Spirit III at 8-9 months

Solution: Resolute DES System

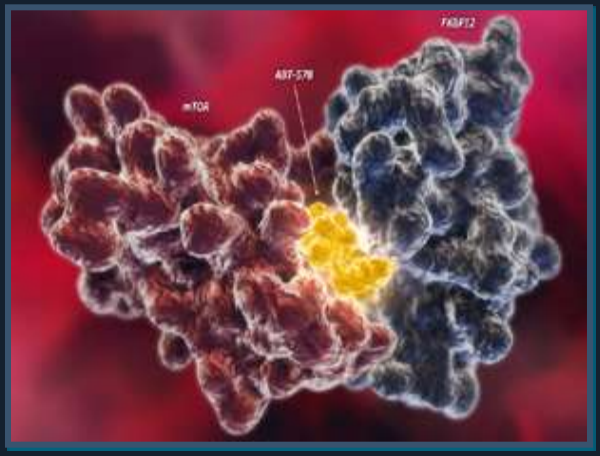
Driver Cobalt Alloy Stent

Stent Delivery System

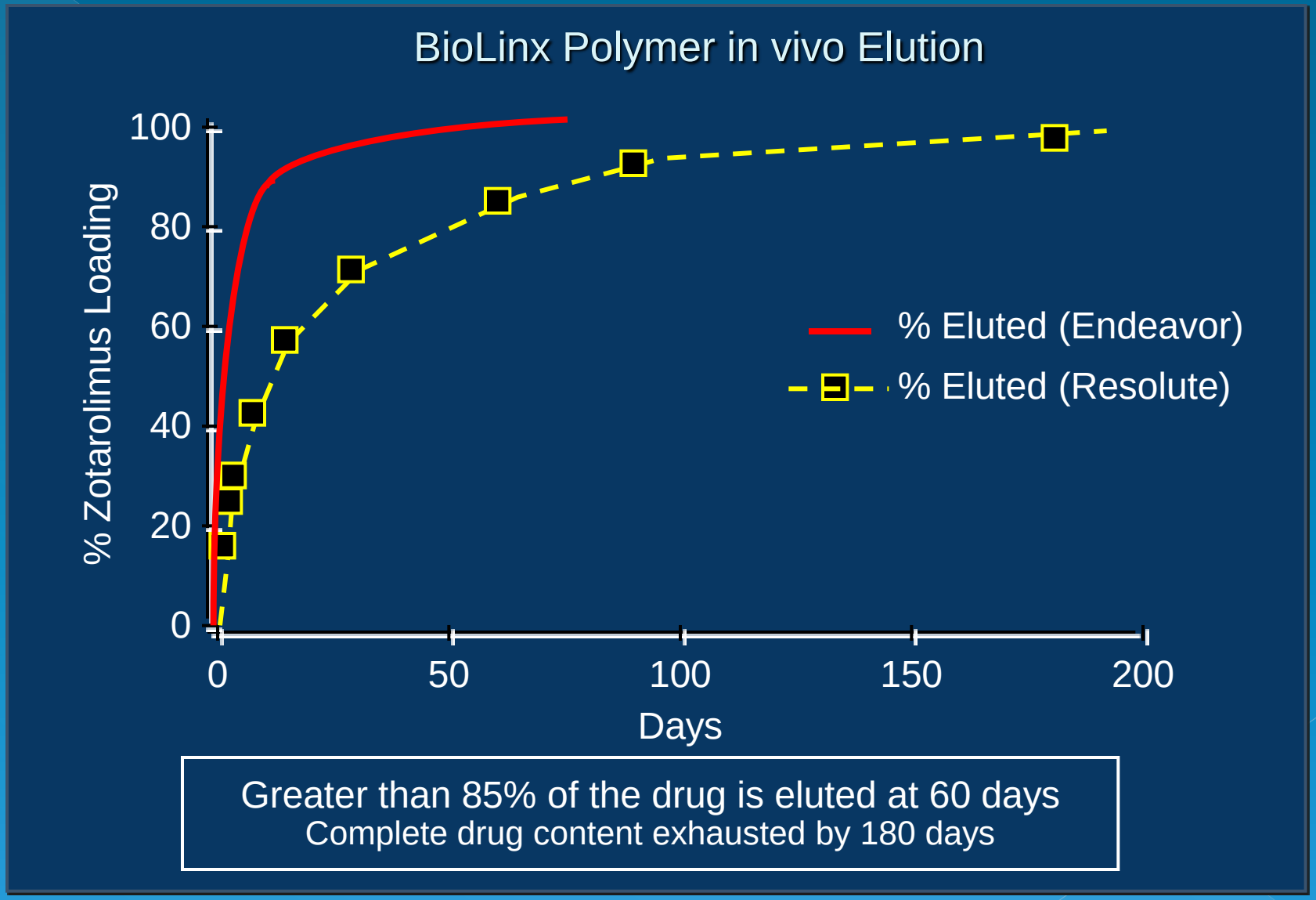
BioLinx Polymer



Drug: Zotarolimus



Resolute Elution Kinetics



Carter et al TCT 2006

Endeavor RESOLUTE

9 month Angiographic Results

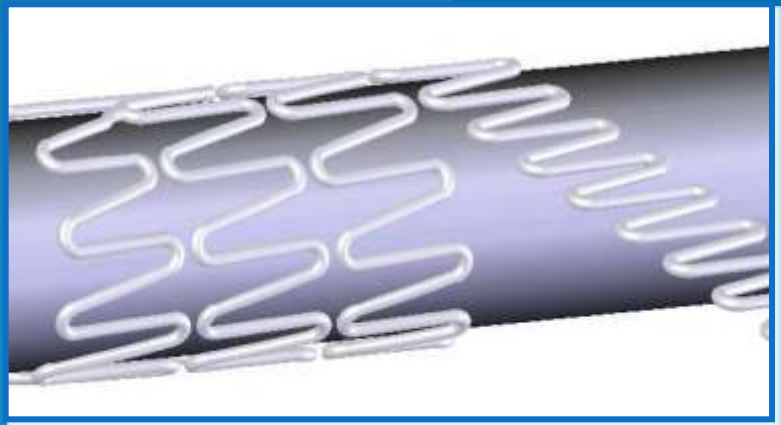
n=96	In-stent	In-segment
Pre-procedure RVD (mm)		2.79 ± 0.40
Lesion Length (mm)		15.87 ± 6.51
MLD (mm) pre		0.82 ± 0.35
post	2.74 ± 0.41	2.33 ± 0.44
Acute Gain	1.91 ± 0.47	1.51± 0.50
Late loss (mm) ENDEAVOR	0.67 ± 0.49	0.42 ± 0.50
Late Loss (mm)	0.22 ± 0.27	0.12 ± 0.27
Late Loss Index	0.12 ± 0.16	0.08 ± 0.21
9 mo f/u % DS	10.13 ± 12.63	21.08 ± 10.62
ABR n (%)	1 (1%)	2 (2.1%)

*Meredith et al: EuroInterv 2007; 3:50-53

COMING SOON……..

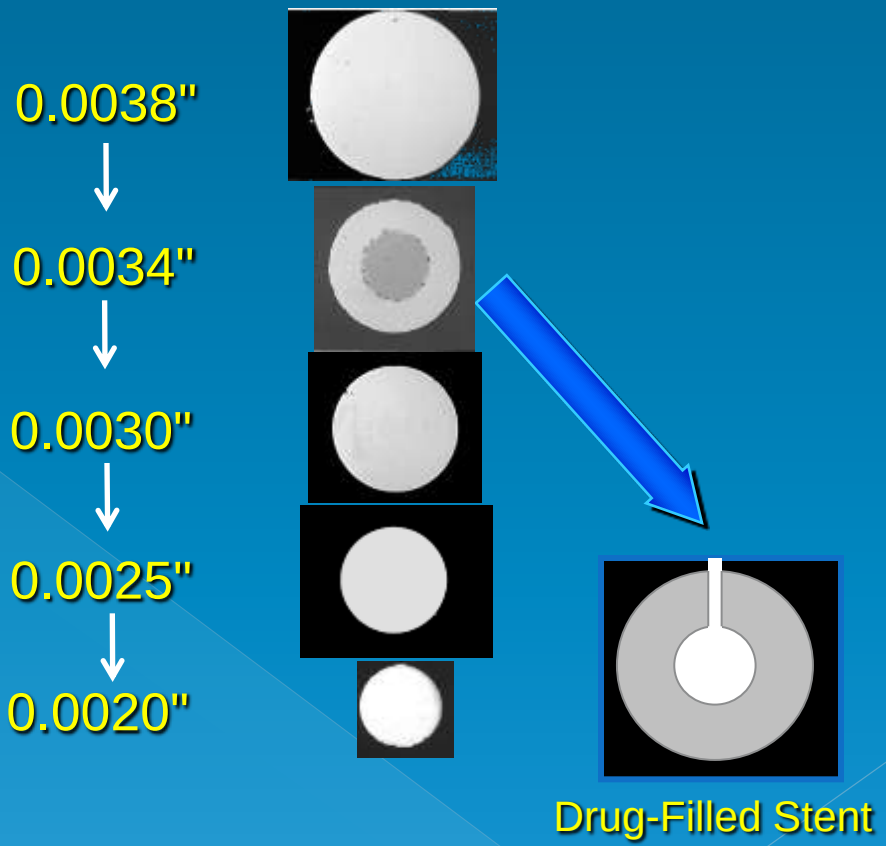
Continuous Sinusoid Technology and Stent strut construction

Continuous Sinusoid Technology



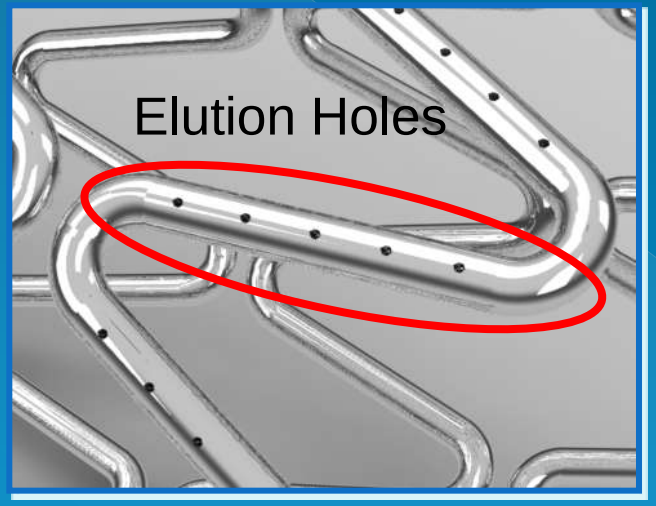
Program Targets:

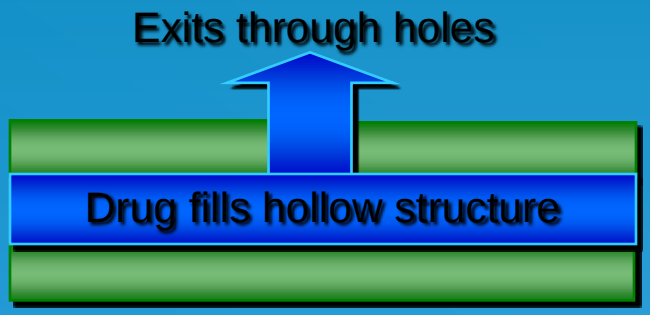
- Enhance deliverability and conformability without compromising strength & opacity
- Develop a platform for DES that enables optimized drug transmission



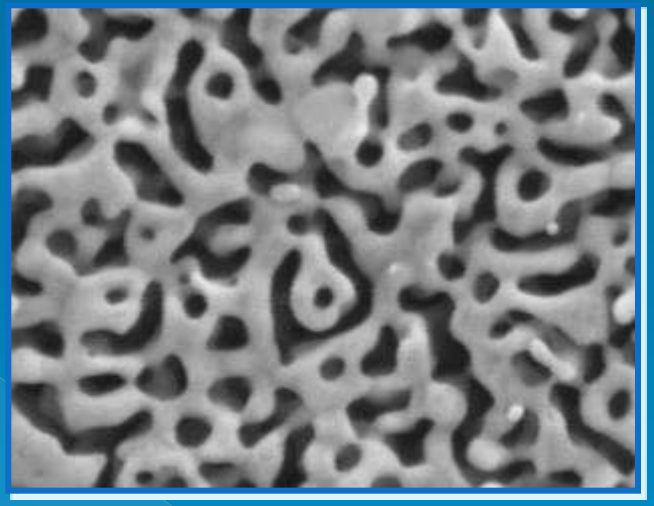
Non-Polymeric DES Approaches

Drug-Filled Stent





Nanoporous Surface Modification



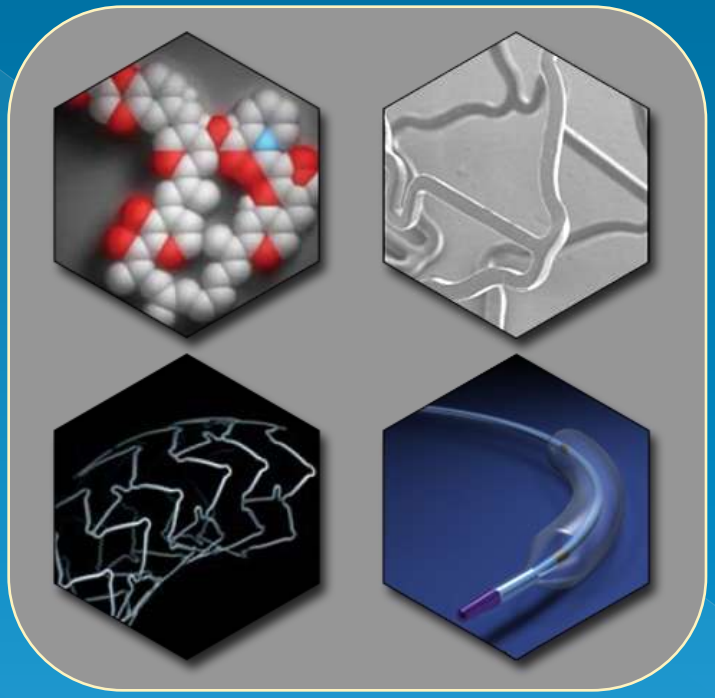
Development Targets:

- Inhibit restenosis and cell proliferation without the use of a polymer
- Provide for rapid, healthy endothelialization

XIENCE V / PROMUS
Everolimus-eluting Stent

Everolimus

ML VISION® Stent Platform



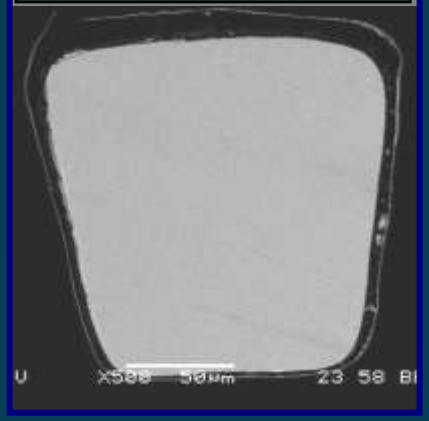
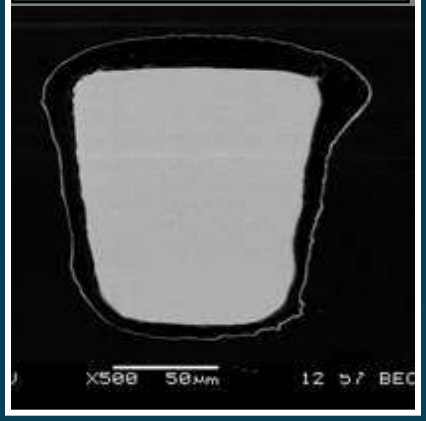
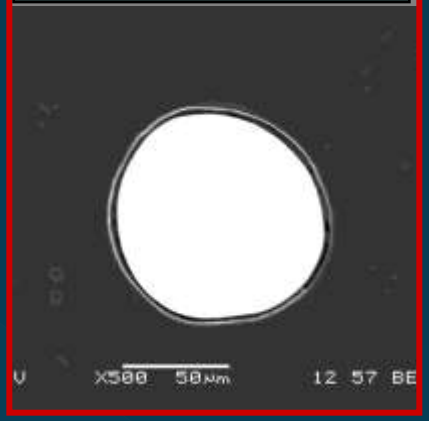
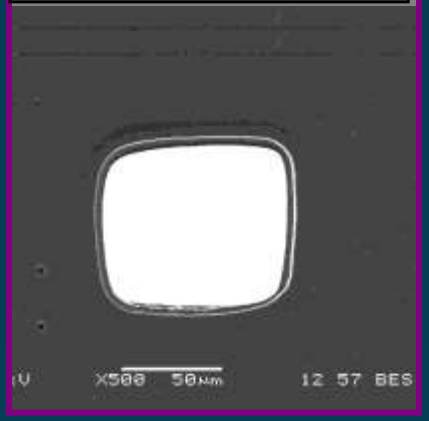
Durable Fluorinated Copolymer

ML VISION® Stent Delivery System

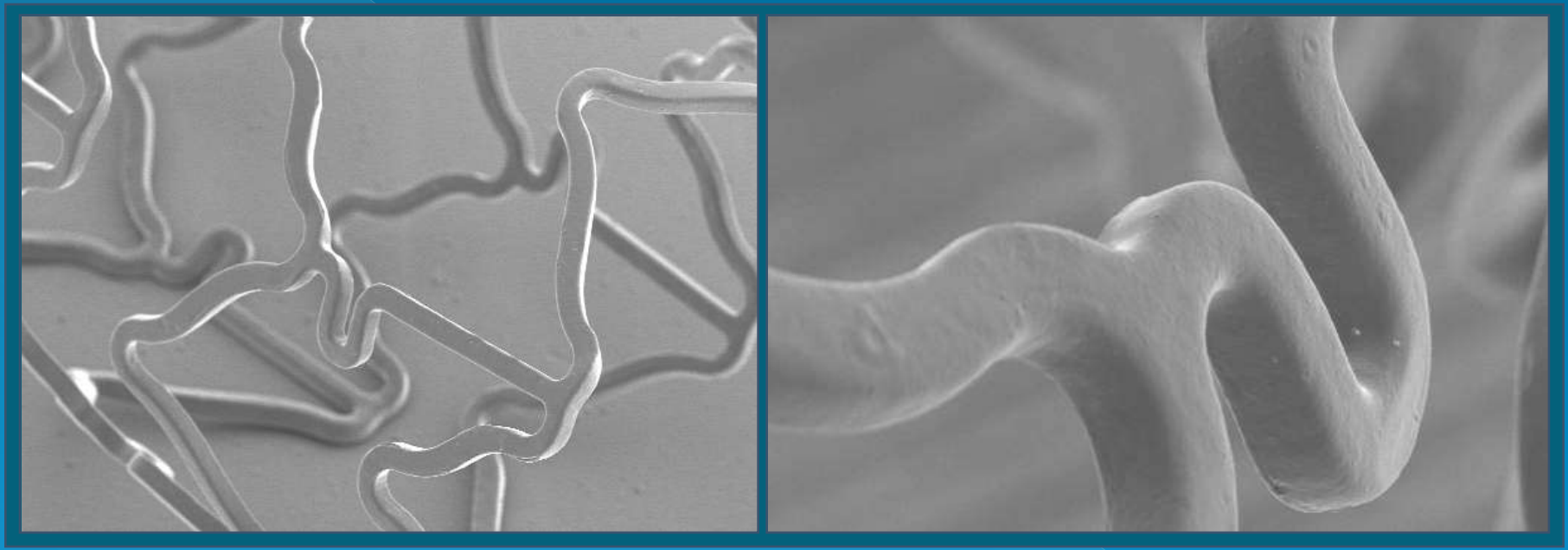
SPIRIT Clinical Trials

DES Strut and Polymer Thickness

3.0 mm diameter stents, 500x magnification

CYPHER®	TAXUS®	ENDEAVOR™	XIENCE™ V
			
Strut Thickness: **140 μm** Polymer Thickness: **12.6 μm** **Total:** **165.2 um**	Strut Thickness: **132 μm** Polymer Thickness: **16 μm** **Total:** **164 um**	Strut Thickness: **91 μm** Polymer Thickness: **5.3 μm** **Total:** **101.6 um**	Strut Thickness: **81 μm** Polymer Thickness: **7.8 μm** **Total:** **96.6 um**

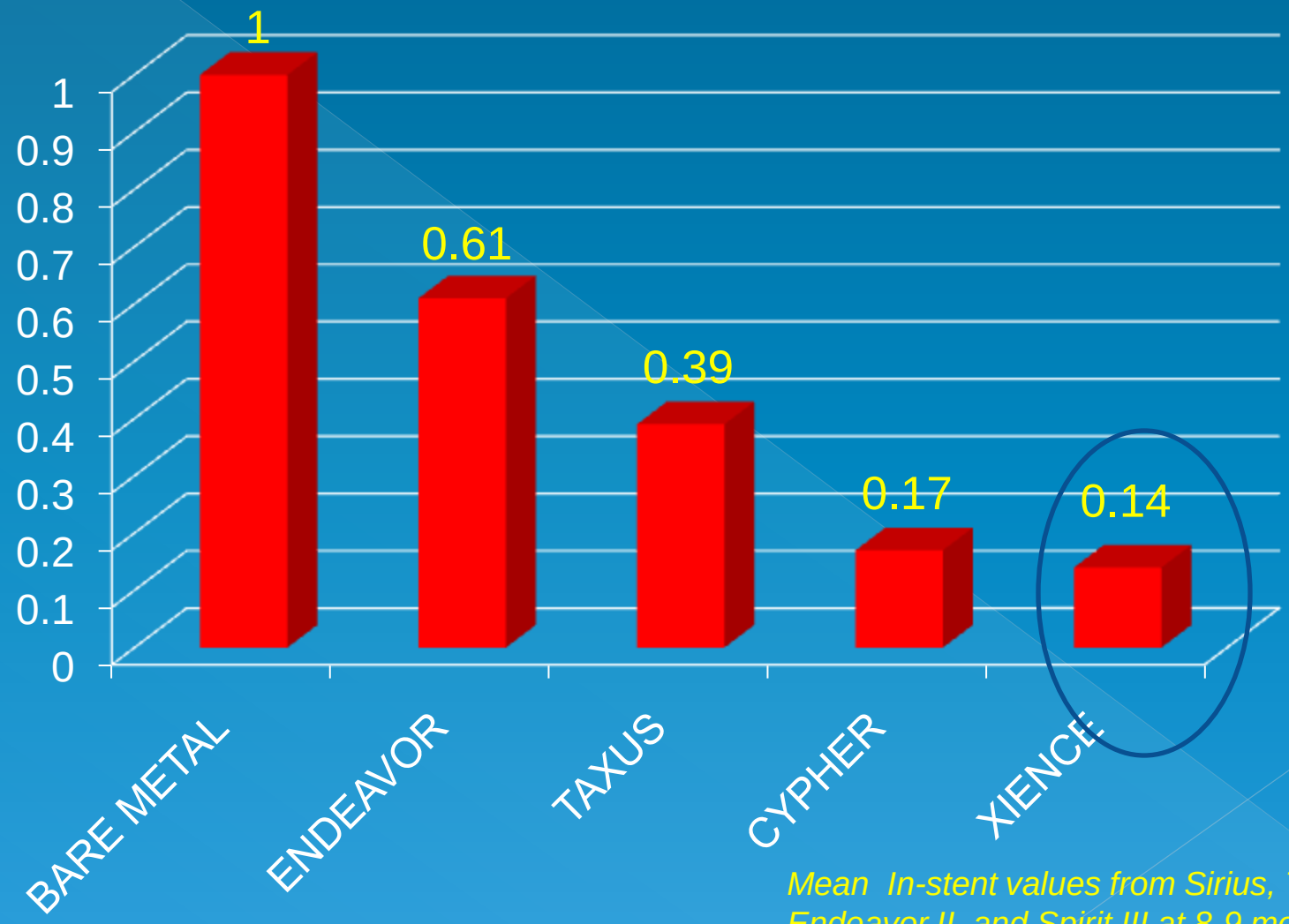
Coating Integrity – XIENCE™ V Fluoropolymer (7.8 um thick)



- Uniform, consistent coating integrity upon deployment
- Good adhesion to stent – no bonding, webbing, tearing
- Non-tacky drug matrix prevents “unwanted” adhesions

Late Loss* (mm)

An (imperfect) Index of Anti-restenotic Efficacy



Mean In-stent values from Sirius, Taxus IV Endeavor II, and Spirit III at 8-9 months

XIENCE PRIME : Next generation workhorse everolimus-eluting stent

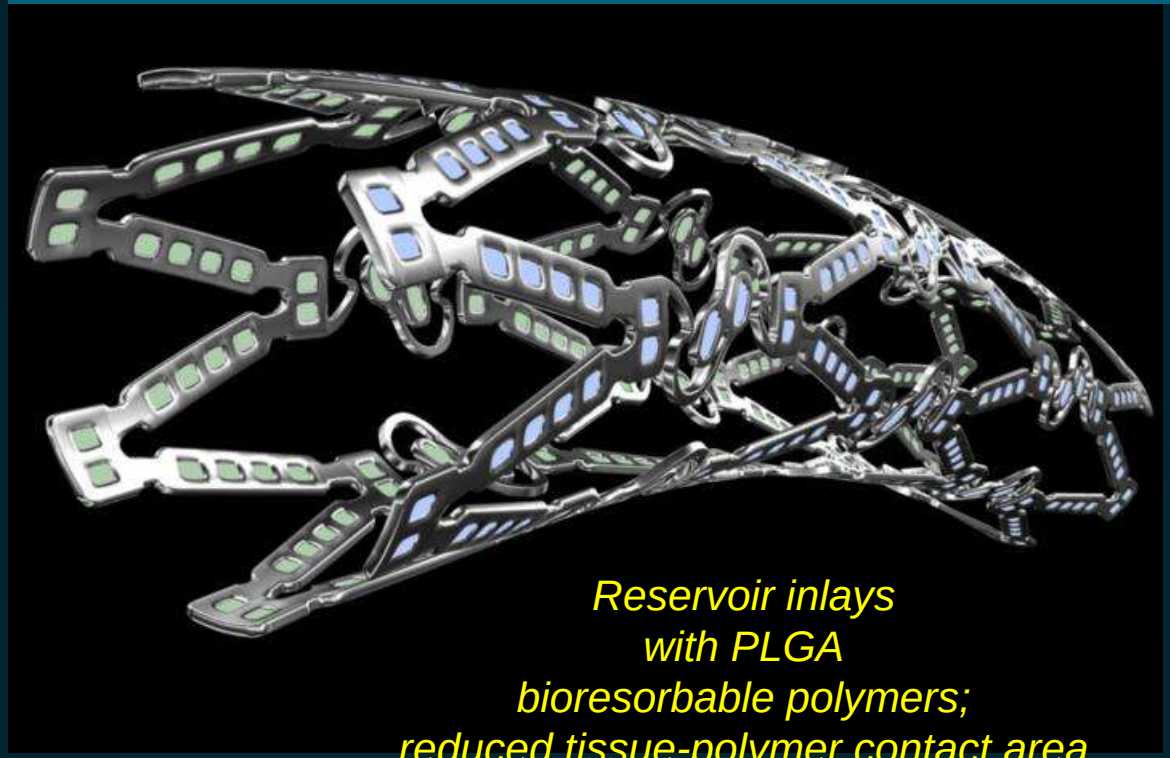
New Alloy DES for Xience

- Best-in-Class safety
  - Thinner stent struts for less vessel injury and faster re-endothelialization
  - Improved conformability
  - Low recoil
- Excellent acute performance
  - Superior deliverability in calcified vessels and tortuous anatomy
  - Better crossability
  - Enhanced visibility
- Same drug (everolimus) and polymer (fluorinated copolymer) as XIENCE V

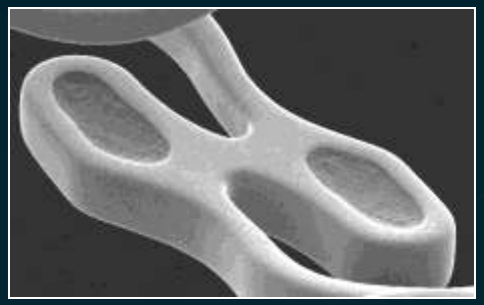
From Cypher to New Cordis RES Technology

CoStar® Sirolimus-Eluting Coronary Stent System

A Stent Specifically Designed for Controlled Drug Delivery from a Bioresorbable PLGA Polymer

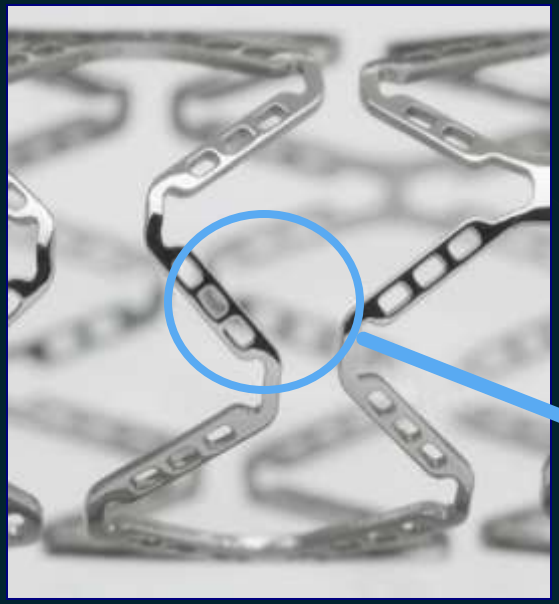


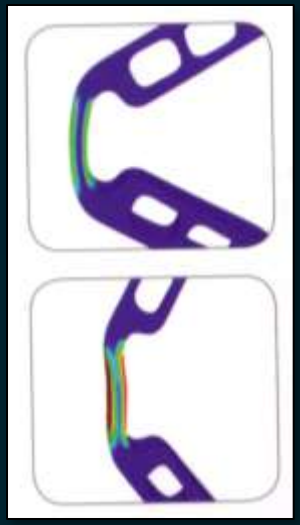
Reservoir inlays with PLGA bioresorbable polymers; reduced tissue-polymer contact area

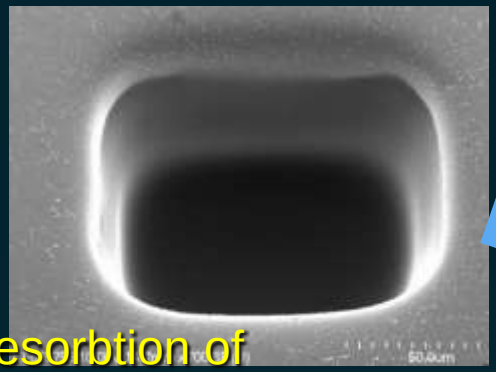


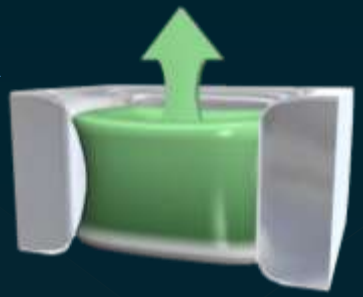
NEVO STENT: Low profile CoCr

Flexible Design with Non-Deforming Reservoirs





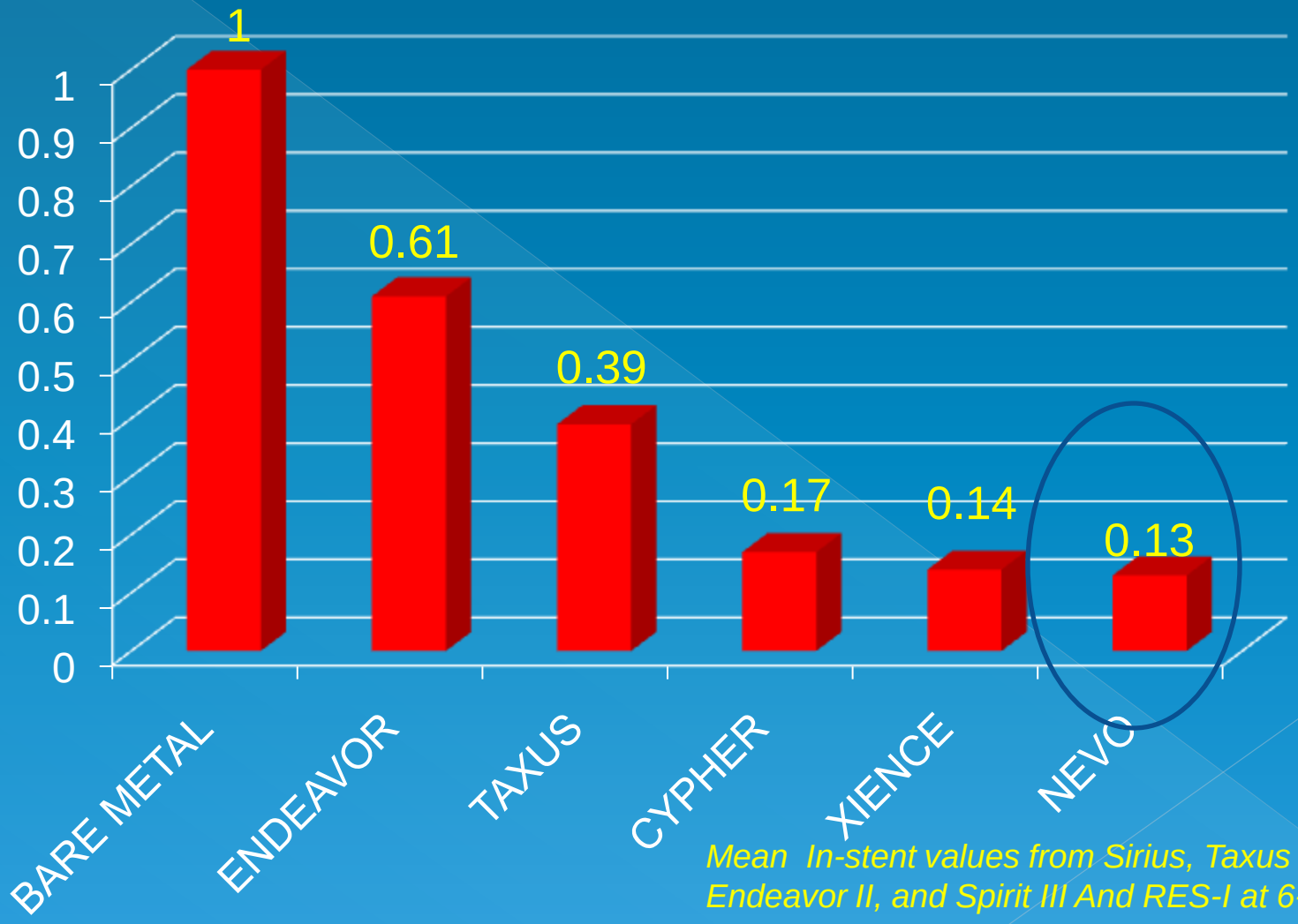




- Complete elution of the drug and resorbtion of the polymer from the reservoirs over time leave behind a bare metal stent

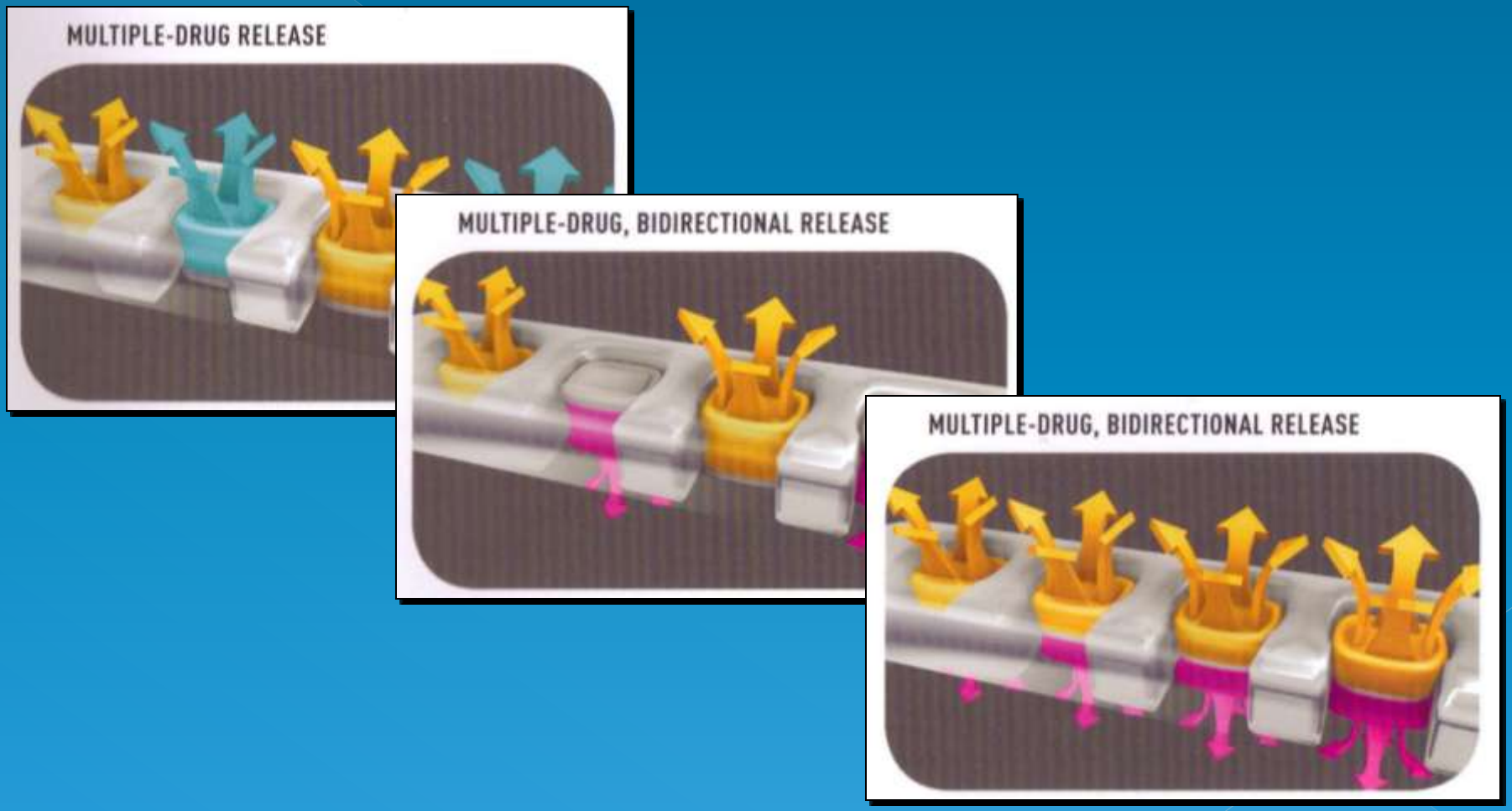
Late Loss* (mm)

An (***imperfect***) Index of Anti-restenotic Efficacy



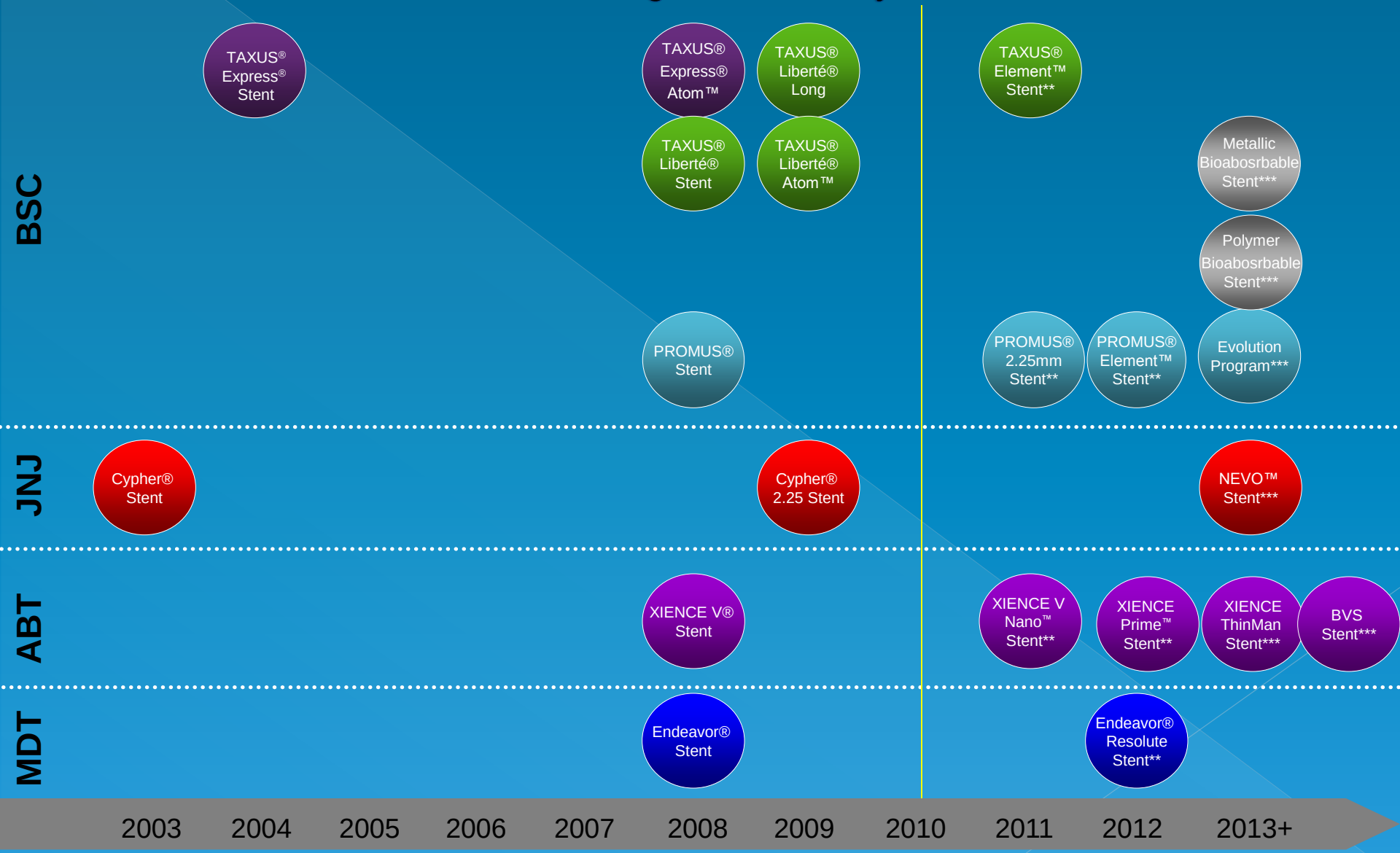
Mean In-stent values from Sirius, Taxus IV Endeavor II, and Spirit III And RES-I at 6-9 months

Nevo Stent: Future posibilities

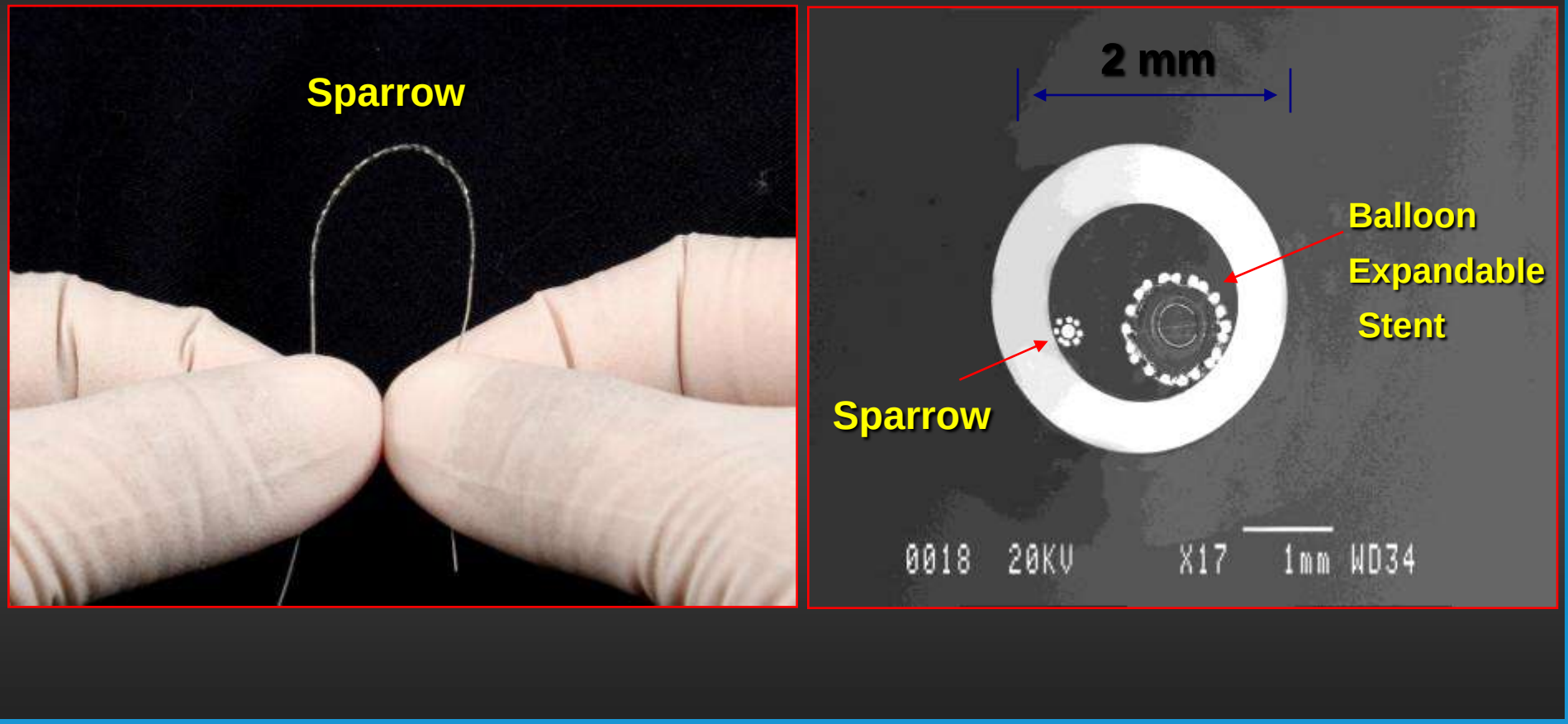


U.S. Drug-Eluting Stent Launches

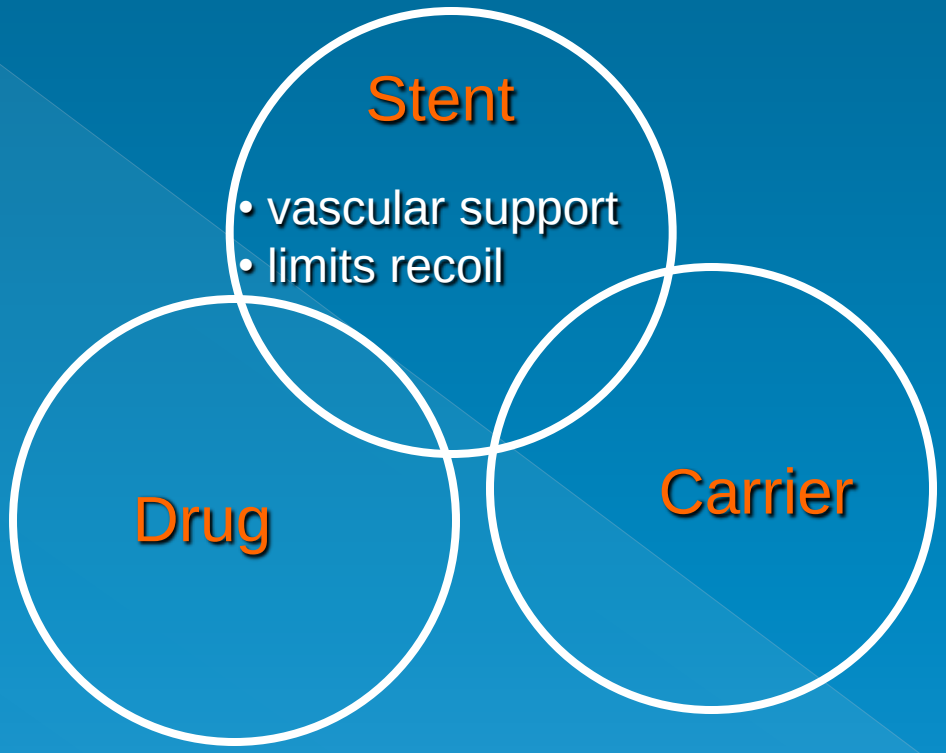
2003 through 2013+ Projections



The CardioMind Sparrow™:
Stent on a .014” Guide Wire Platform



WHICH NEEDS TO GO AND WHICH NEEDS TO STAY ?



• modulates vascular responses

• elute appropriate drug load
• control kinetic release

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY ?

Stent

- vascular support
- limits recoil

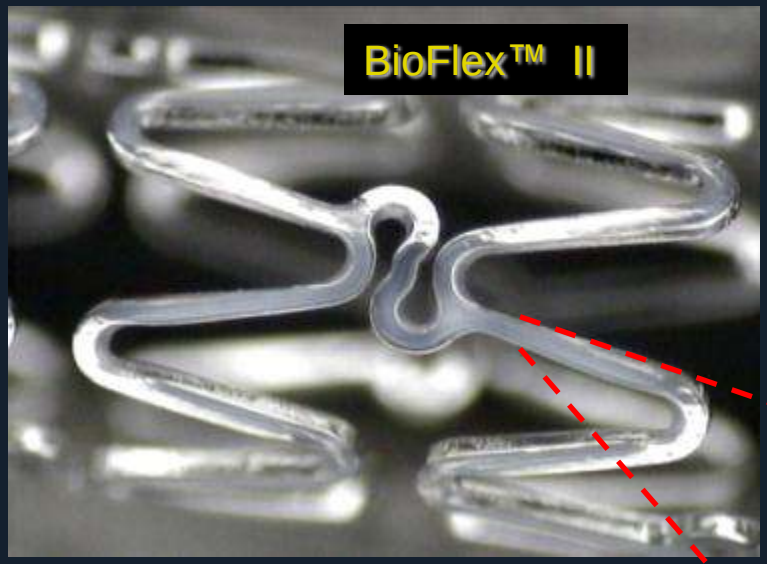
Future DES

New Drug Carrier Systems

- Bioabsorbable Polymers
- Polymer-Free Drug Delivery

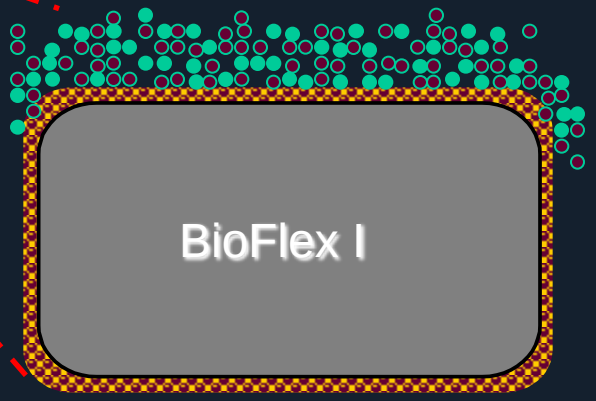
BioMatrix Stent Platform
Bioabsorbable Polymer DES

BIOMATRIX

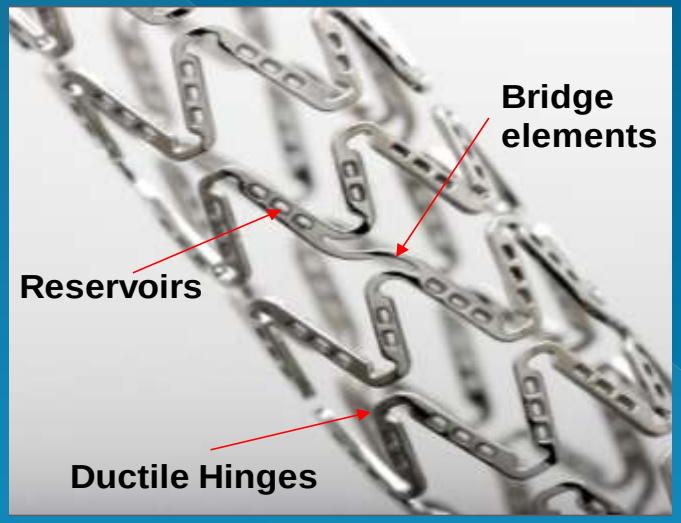


Biodegradable Drug Carrier:

- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 10 microns coating thickness
- degrades in 9 months releasing CO_2+ water



NEVO™ Stent Design



- *Chromium-Cobalt Platform*
  - Flexible, thin struts, open cell design
- *Novel Reservoir Technology*
  - Minimizes polymer - vessel wall contact
- *Biodegradable Polymer*
  - Achieves Cypher-like sirolimus tissue levels
  - Rapid endotheliazation

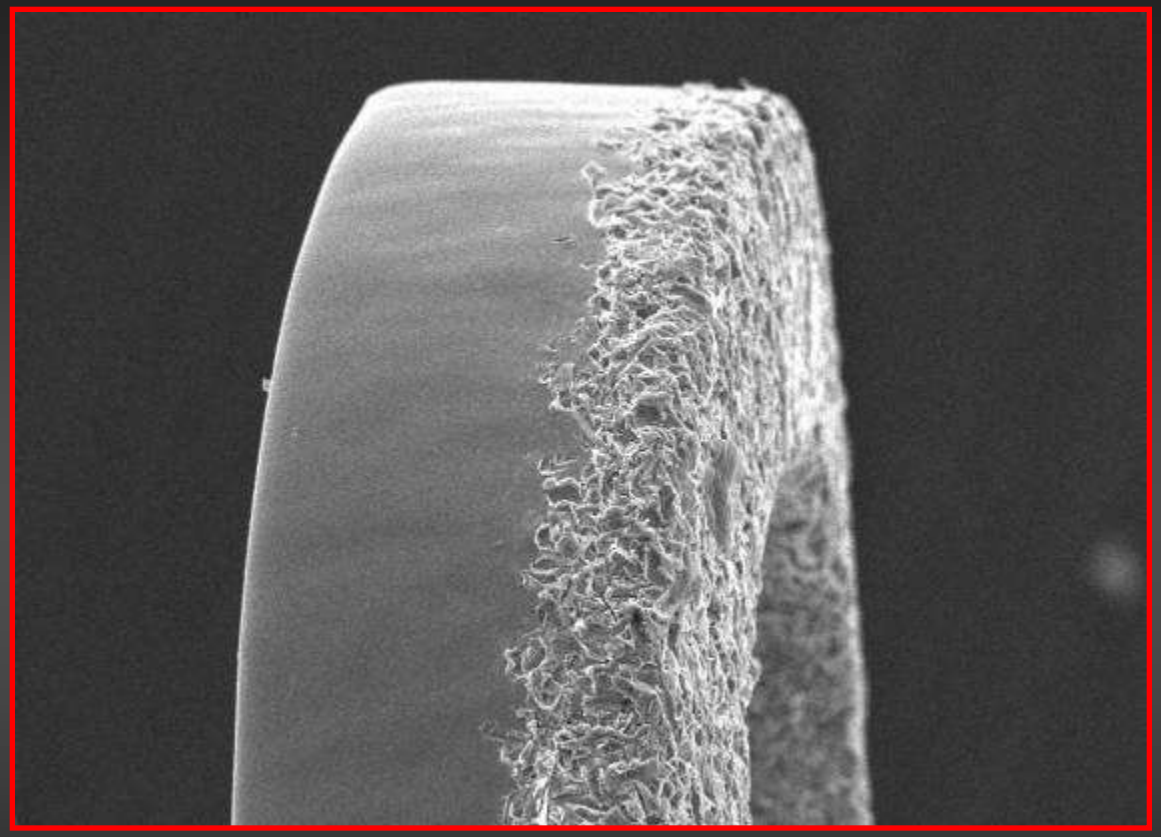
New DES Carrier Systems

Polymer-Free Drug Delivery

- Benefit – “essentially” BMS after drug delivery (maximal safety)
- Issues – difficulties in prolonging drug elution
- Examples – Translumina (Yukon), Biosensors (BioFreedom), MIV (Vestasync)

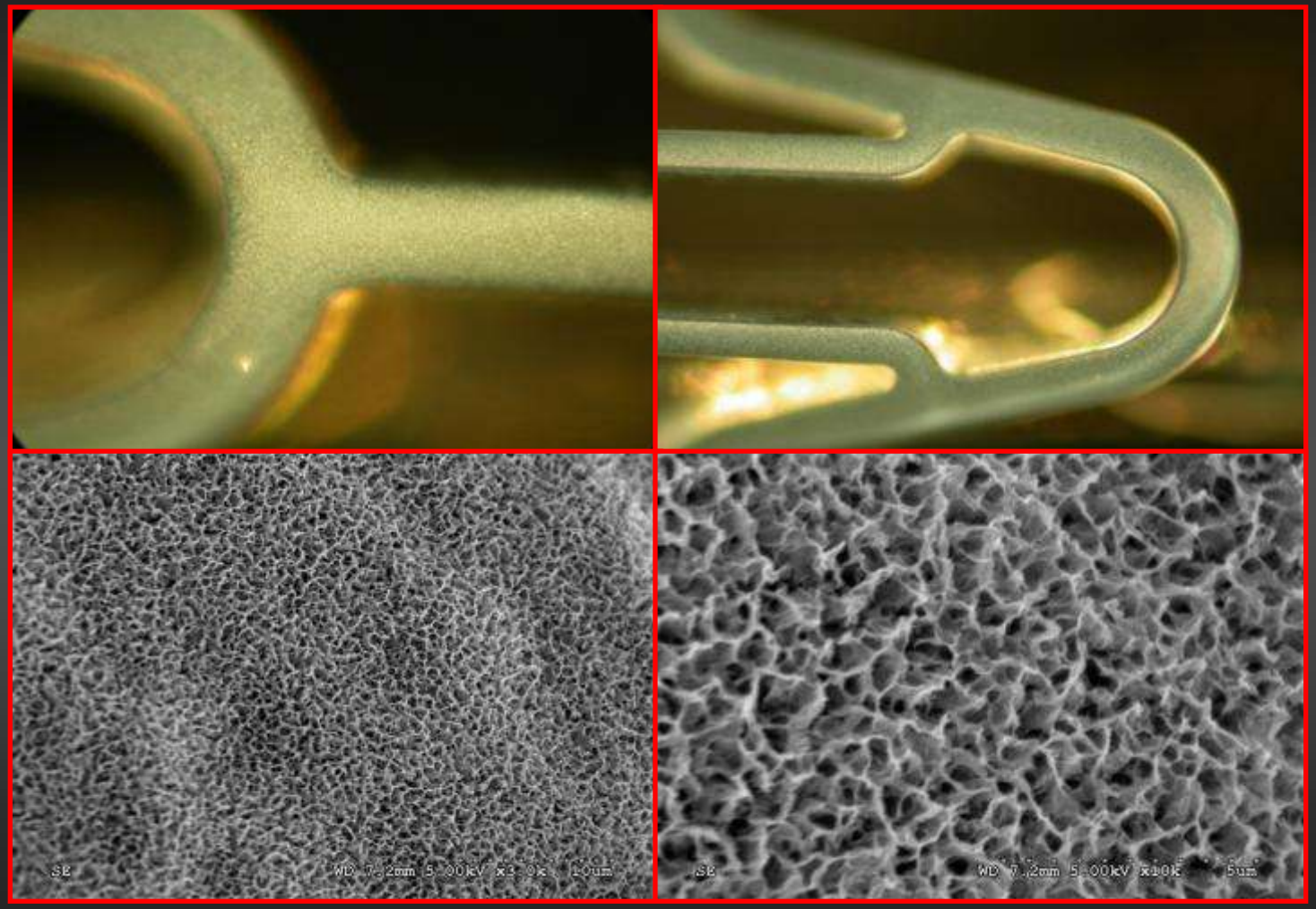
BioMatrix Freedom Stent

Micro-structured Surface



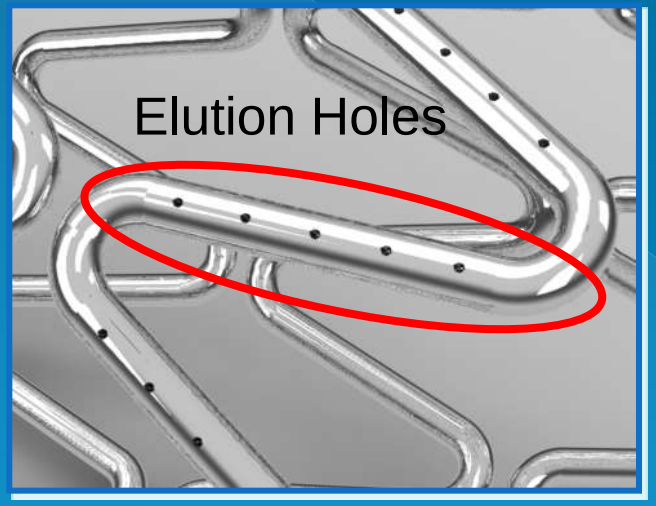
- Selectively micro-structured surface holds drug in abluminal surface structures

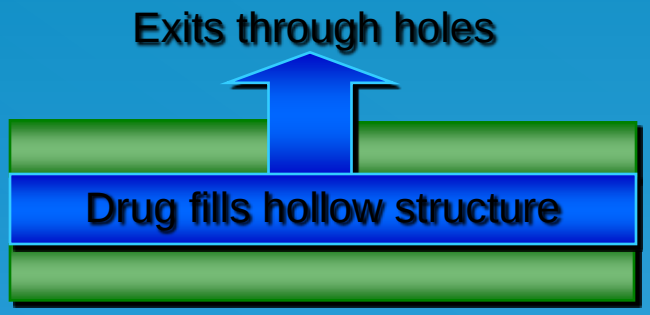
3D MicroPorous Nanofilm HAp



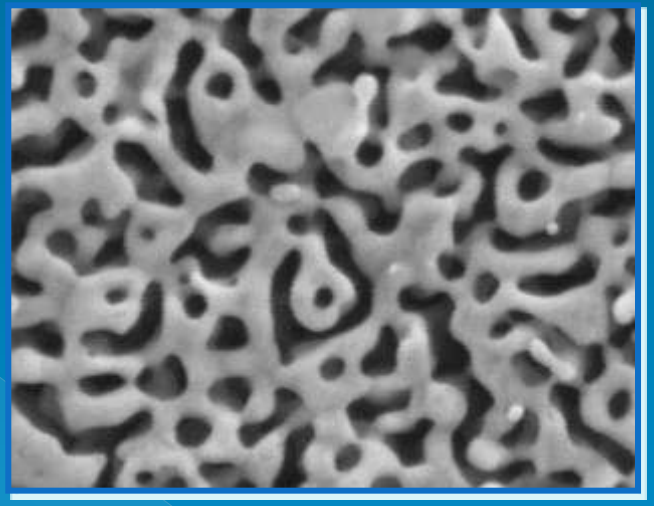
Non-Polymeric DES Approaches

Drug-Filled Stent





Nanoporous Surface Modification



Development Targets:

- Inhibit restenosis and cell proliferation without the use of a polymer
- Provide for rapid, healthy endothelialization

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY ?

Stent

- vascular support
- limits recoil

Bioabsorbable Stents

- Igaki-Tami (Igaki Medica Planning Co Ltd)
- Magnesium (Biotronik)
- REVA (REVA Medical)
- BTI (Bioabsorbable Therapeutics Inc)
- BVS (Abbott Vascular)

Igaki-Tamai stent

PLLA

Bioabsorbable Magnesium Stent

BVS (Abbott)

PLLA and
PDLLA
Everolimus

BSC's Fully Bioabsorbable Stent Programs

Design Goal: The drug & stent gone within 12 months

"Leave Nothing Behind"

BSC's Bioabsorbable Stent Projects

	Bioabsorbable Metal Stent (Magnesium)	Absorbed within ~6 months
	Bioabsorbable Metal Stent (Iron)	Absorbed within +24 months
	Bioabsorbable Polymer Stent (PLLA)	Absorbed within +24 months
	Bioabsorbable Polymer Stent (Tyrosine-derived Polycarbonate)	Absorbed within +24 months

How about DRUG ELUTING BALLOONS (no stent or provisional stenting)?

Local Drug Delivery: Paccocath-DEB vs. DES

Drug-Eluting Balloon	Drug-Eluting Stent
Immediate release	Slow release
Short-lasting exposure	Persistent drug exposure
~ 300 - 600 µg dose	~ 100 - 200 µg dose
No polymers	Polymer
Wiped off the balloon surface	Diffusion from stent struts
Premounted stent optional	Stent mandatory

- Conventional angioplasty balloon catheters
- Coated with paclitaxel

  (+ contrast medium as matrix builder and release supporting additive)
- Controlled dose, homogeneity of coating, non-toxic excipients

Scheller et al., Circulation 2004;110:810. Speck et al., Radiology 2006;240:411. unpublished data

Drug Coated Balloon

Design Goal: Provide balloon dilatation with a drug coated balloon without the use of a stent

Potential Indications

- ISR
- Bifurcation/Side Branch
- Small Vessels
- Unable to deliver stent
- Replace POBA
- Workhorse treatment for CAD
- Peripheral vascular use

Drug Coating Design

Paclitaxel + Excipient

- Similar drug tissue concentration as the TAXUS® Express® Stent at 45 days
- Paclitaxel is a highly lipophilic molecule
- Excipient used in other pharmaceutical technologies

PEPCAD II ISR - Outcome, 6 months FU

n=126

	SeQuent Please	Taxus	p
n	66	60	
Follow-up	6.2 ± 0.8	6.2 ± 0.8	0.7
Control angiography	58 (87.9 %)	54 (90.0 %)	0.8
Late lumen loss	0.19 ± 0.38	0.47 ± 0.71	0.03
Binary restenosis in segment	**2 / 58 (3.4 %)**	**11 / 54 (20.4 %)**	**0.007**
TLR	2 / 64 (3.1 %)	10 / 60 (16.7 %)	0.02
Myocardial infarction	0 / 64 (0.0 %)	1 / 60 (1.7 %) NSTEMI due to side branch occlusion	1
Death	2 / 64 (3.1 %) 1 non-cardiac, 1 cardiac but not lesion related	1 / 60 (1.7 %) non-cardiac death	1
MACE (w / o noncardiac death)	3 / 64 (4.7 %)	11 / 60 (18.3 %)	0.02

Much more to come…

Thanks