What are the Targets to Further Improve Coronary Stent Technologies:

A Look into Emerging Technologies

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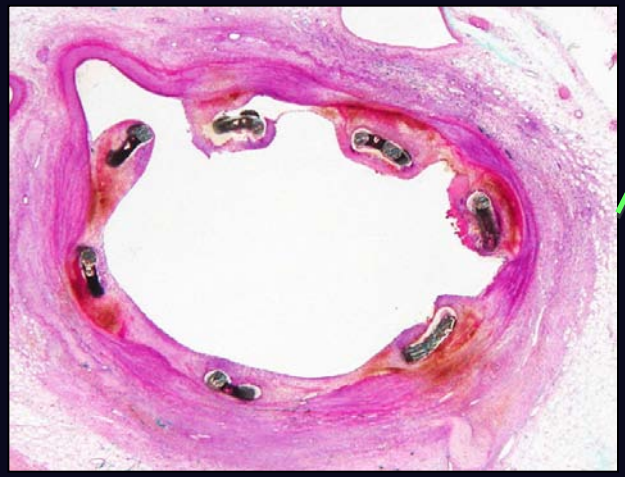
Technological Strategies to Improve Vessel Healing Following DES Implantation

DES: Controlled drug release (polymer based)

Cellular drug effect

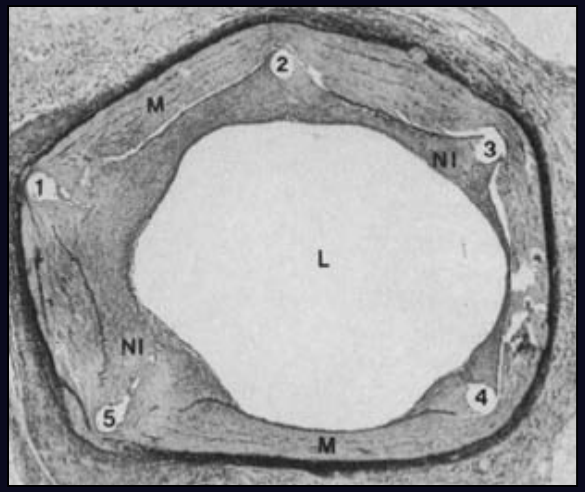
New issue= delayed healing and stent thrombosis

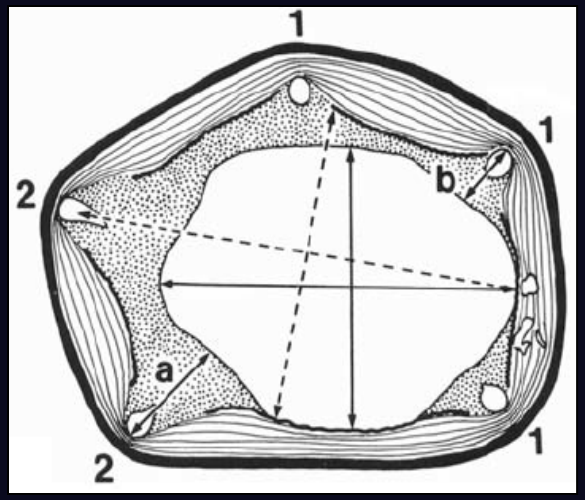


Minimize Injury at the time of implantation

- Stent design
- Mechanism of expansion
- Strut thickness

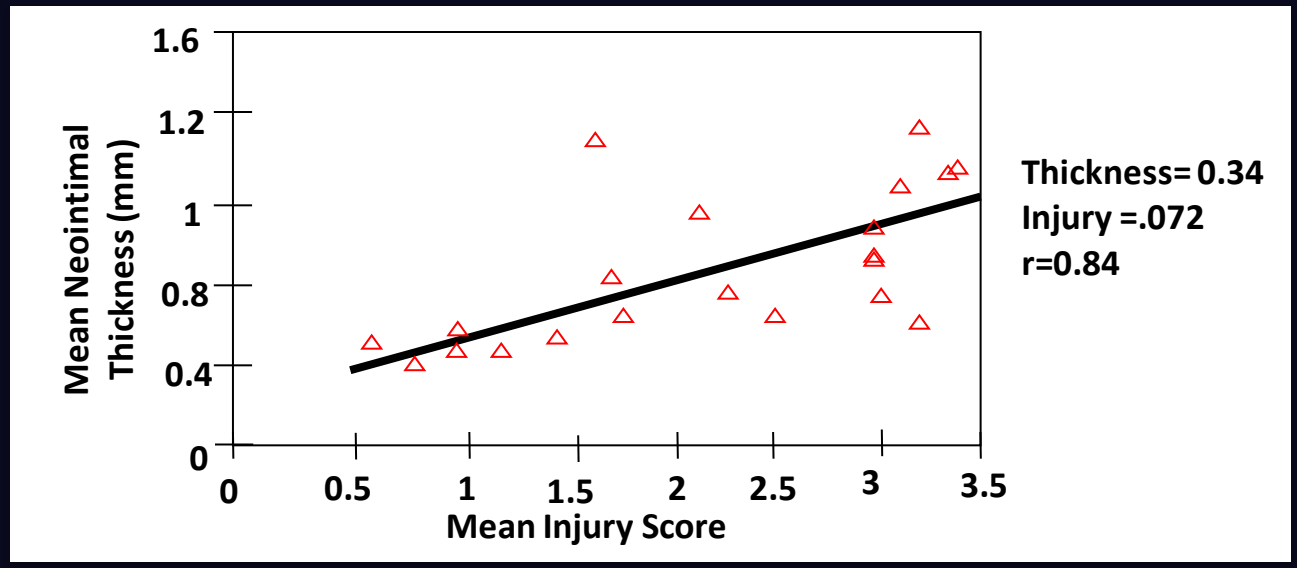
Impact of Vessel Injury on Vascular Healing and Restenosis





Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model

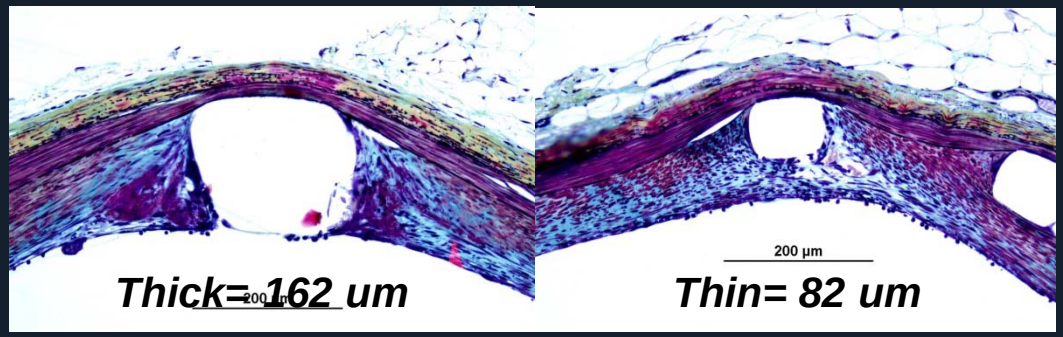
ROBERT S. SCHWARTZ, MD, FACC, KENNETH C. HUBER, MD, JOSEPH G. MURPHY, MB, WILLIAM D. EDWARDS, MD, FACC, ALLAN R. CAMRUD, RN, RONALD E. VLIETSTRA, MB, BCh, FACC, DAVID R. HOLMES, MD, FACC



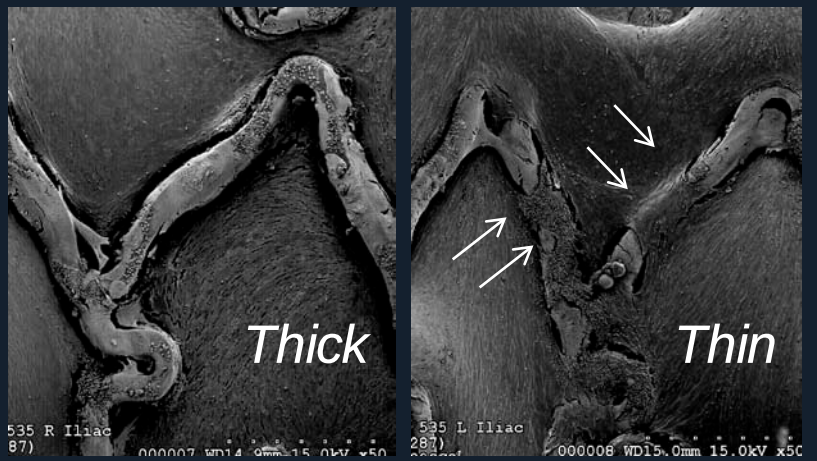
Schwartz, R. J Am Coll Cardiol. 1992 Feb;19(2):267-74

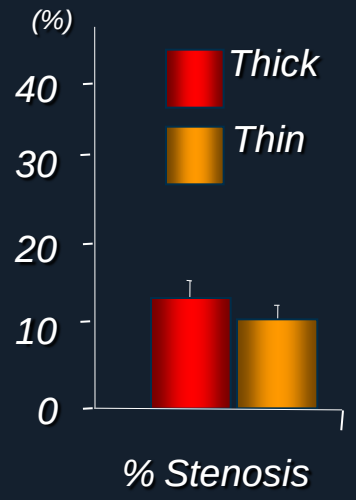
Strut Thickness Influences Neointimal Formation and Inflammation

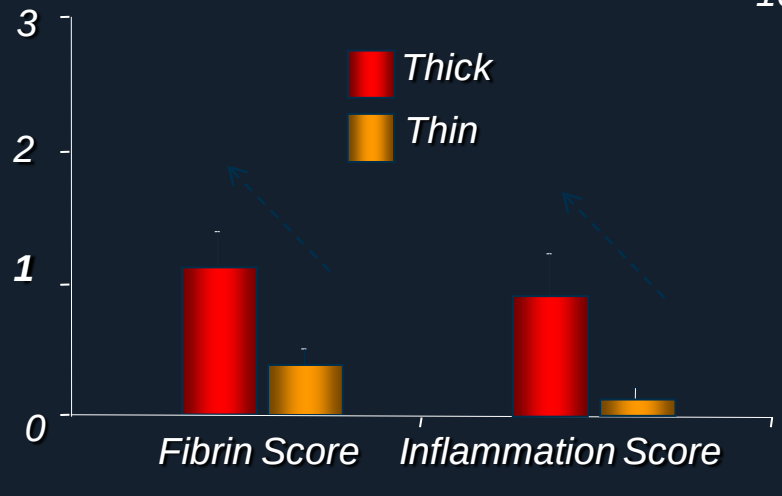
Enhanced surface coverage and healing in struts ~80 micron thickness

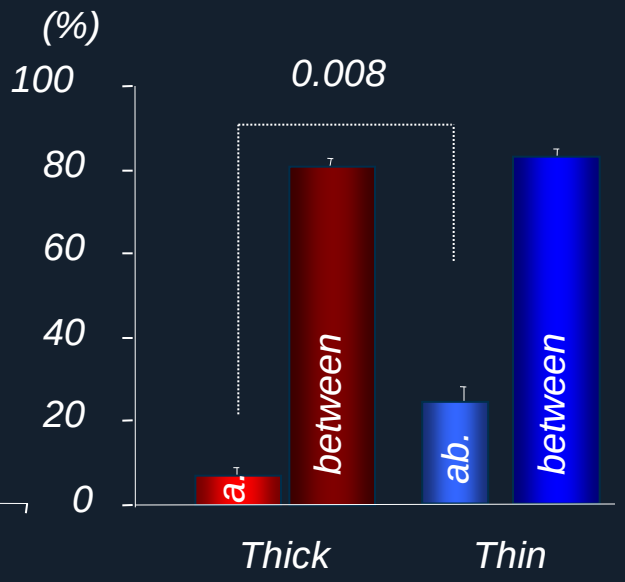


SEM of 7-Day Implants









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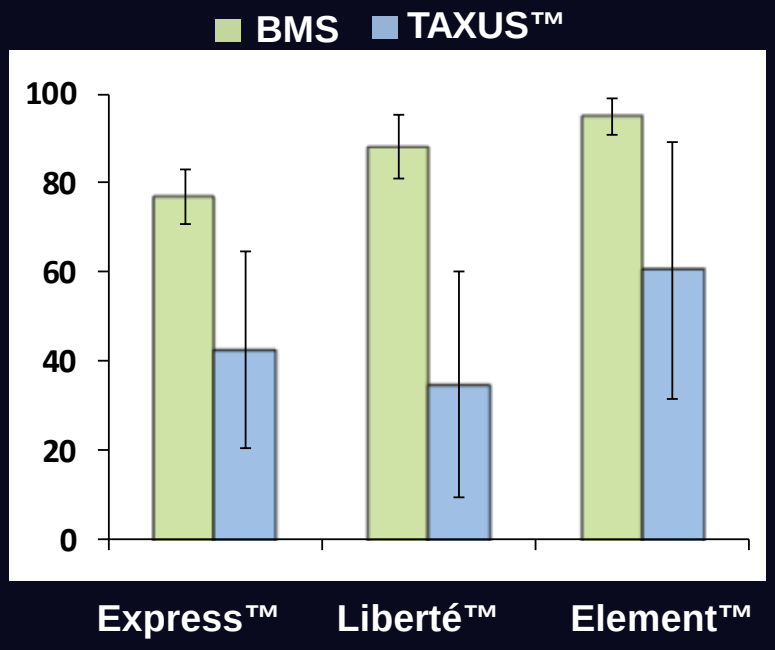
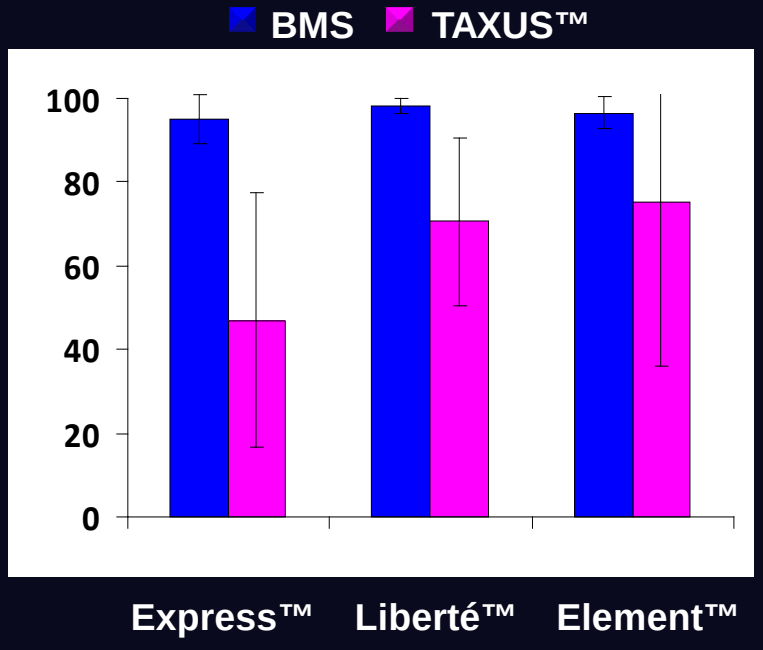
Slide courtesy (adapted) of Renu Virmani

Delayed Healing Caused by Drug Elution is Mitigated by Platform Modification

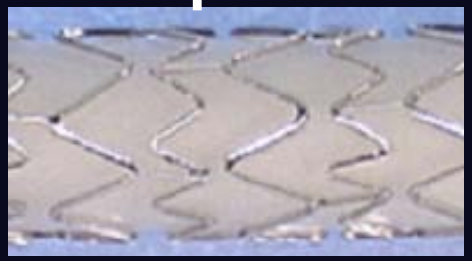
%Strut Coverage at 14 days in Rabbits



%Strut Coverage at 21 days in Rabbits

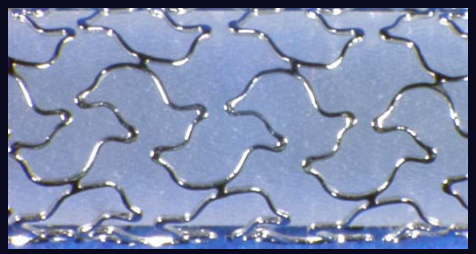


Express



Strut Thickness = 132µm

Liberte



Strut Thickness = 97µm

Element

Strut Thickness = 81µm

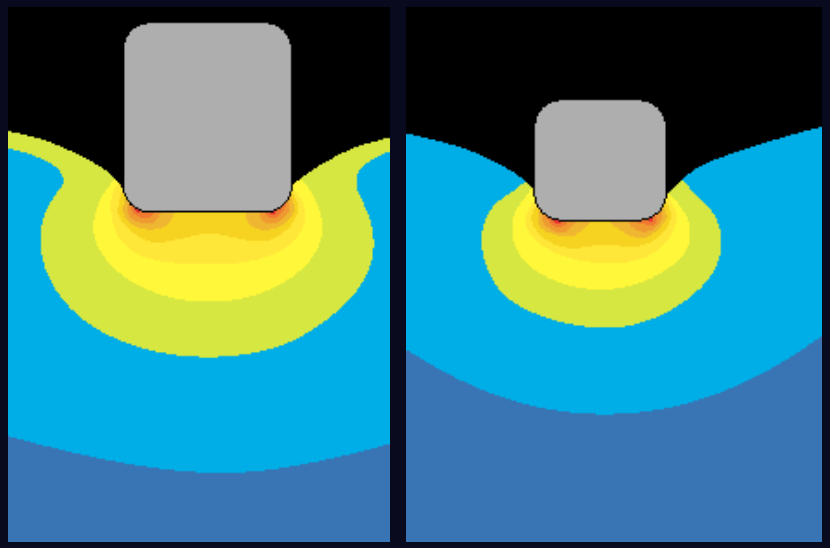
Data on file Boston Scientific

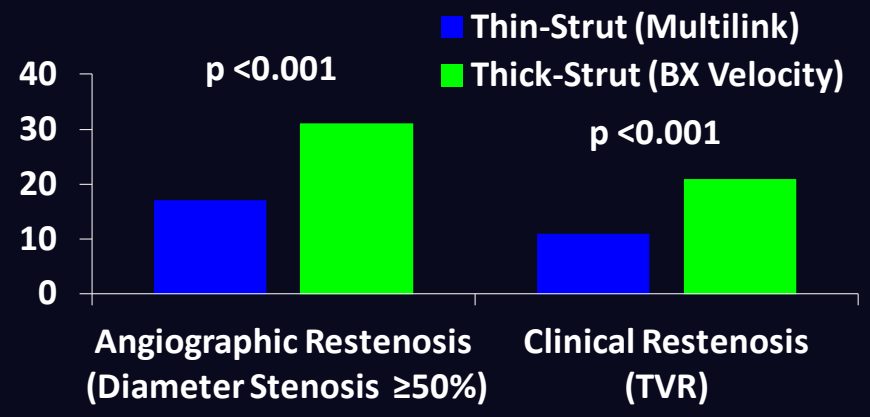
Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO-2) Trial

Jürgen Pache, MD,* Adnan Kastrati, MD,* Julinda Mehilli, MD,* Helmut Schühlen, MD,† Franz Dotzer, MD,‡ Jörg Hausleiter, MD,* Martin Fleckenstein, MD,‡ Franz-Josef Neumann, MD,† Ulrich Sattelberger, MD,§ Claus Schmitt, MD,* Martina Müller,* Josef Dirschinger, MD,* Albert Schömig, MD*†

Munich, Garmisch-Partenkirchen, and Ingolstadt, Germany

	Thin-Strut (n = 309)	Thick-Strut (n = 302)	p Value
B2/C Lesions	255 (82)	213 (70)	< 0.001
Chronic Occlusions, n (%)	15 (5)	26 (9)	0.06
Restenotic Lesions, n (%)	10 (3)	13 (4)	0.49
Lesion Length, mm	13.9 ± 7.8	14.1 ± 7.8	0.77
Vessel Size, mm	2.93 ± 0.50	2.91 ± 0.51	0.68
Diameter Stenosis, %	68.2 ± 18.9	70.8 ± 20.4	0.11





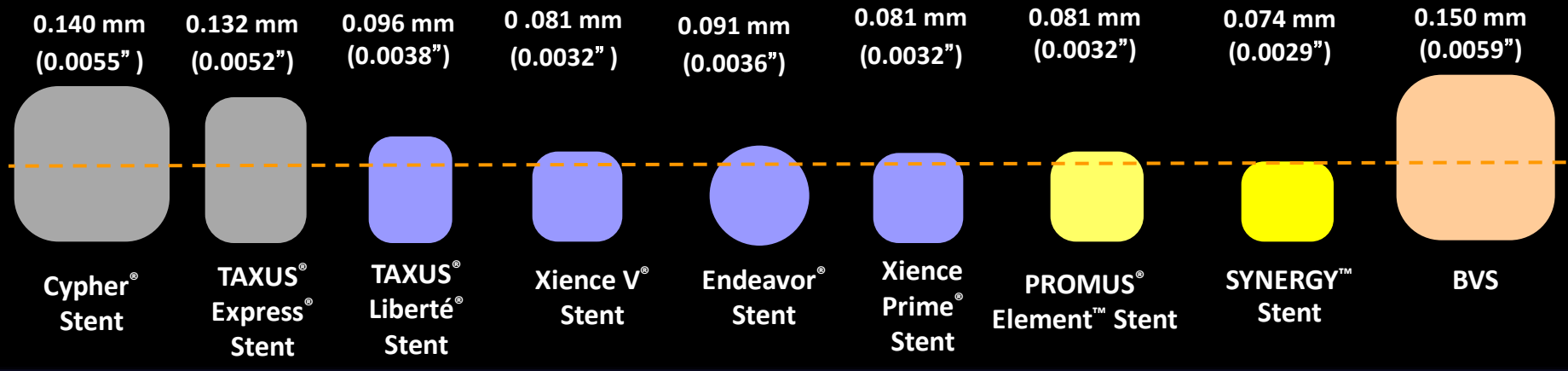
	Thin-Strut (n = 229)	Thick-Strut (n = 236)	p Value
MLD, mm	1.96 ± 0.76	1.70 ± 0.83	< 0.001
DS, %	33.4 ± 21.5	42.4 ± 24.1	< 0.001
LL, mm	0.93 ± 0.61	1.19 ± 0.69	< 0.001
LL index	0.51 ± 0.37	0.65 ± 0.44	< 0.001
Restenosis, n (%)	41 (17.9)	74 (31.4)	< 0.001

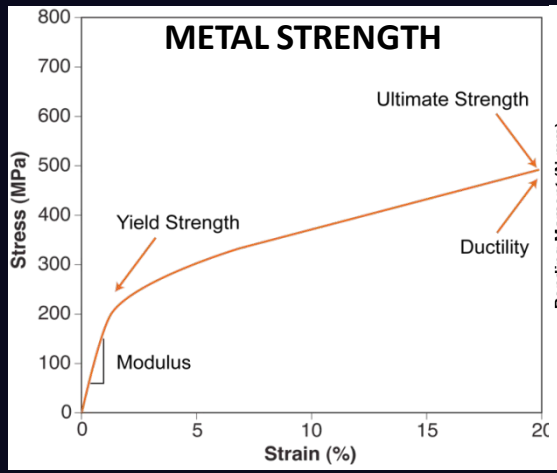
Pache J. JACC. 2003 Apr 16;41(8):1283-8

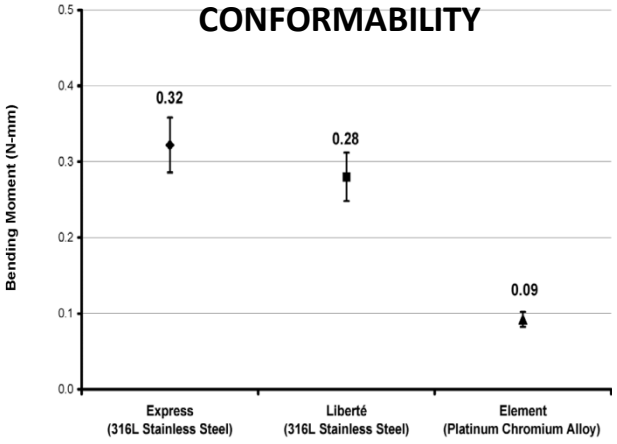
Progression in Stent Platform Design

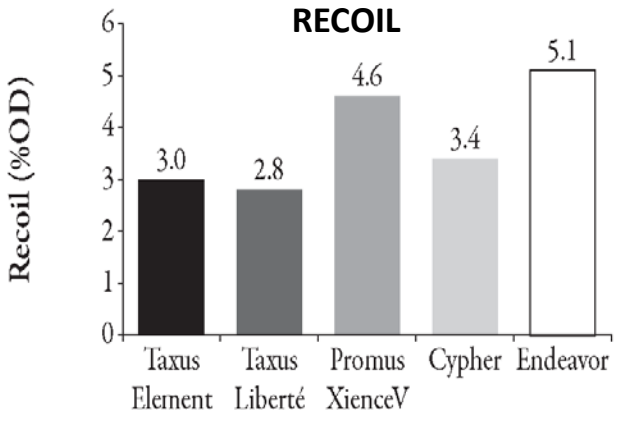
Strut Thickness and Biomaterials

1st Generation	2nd Generation	3rd Generation	4th Generation	1st Gen BVS
Stainless Steel	Cobalt Alloys	Platinum Chromium		PLLA

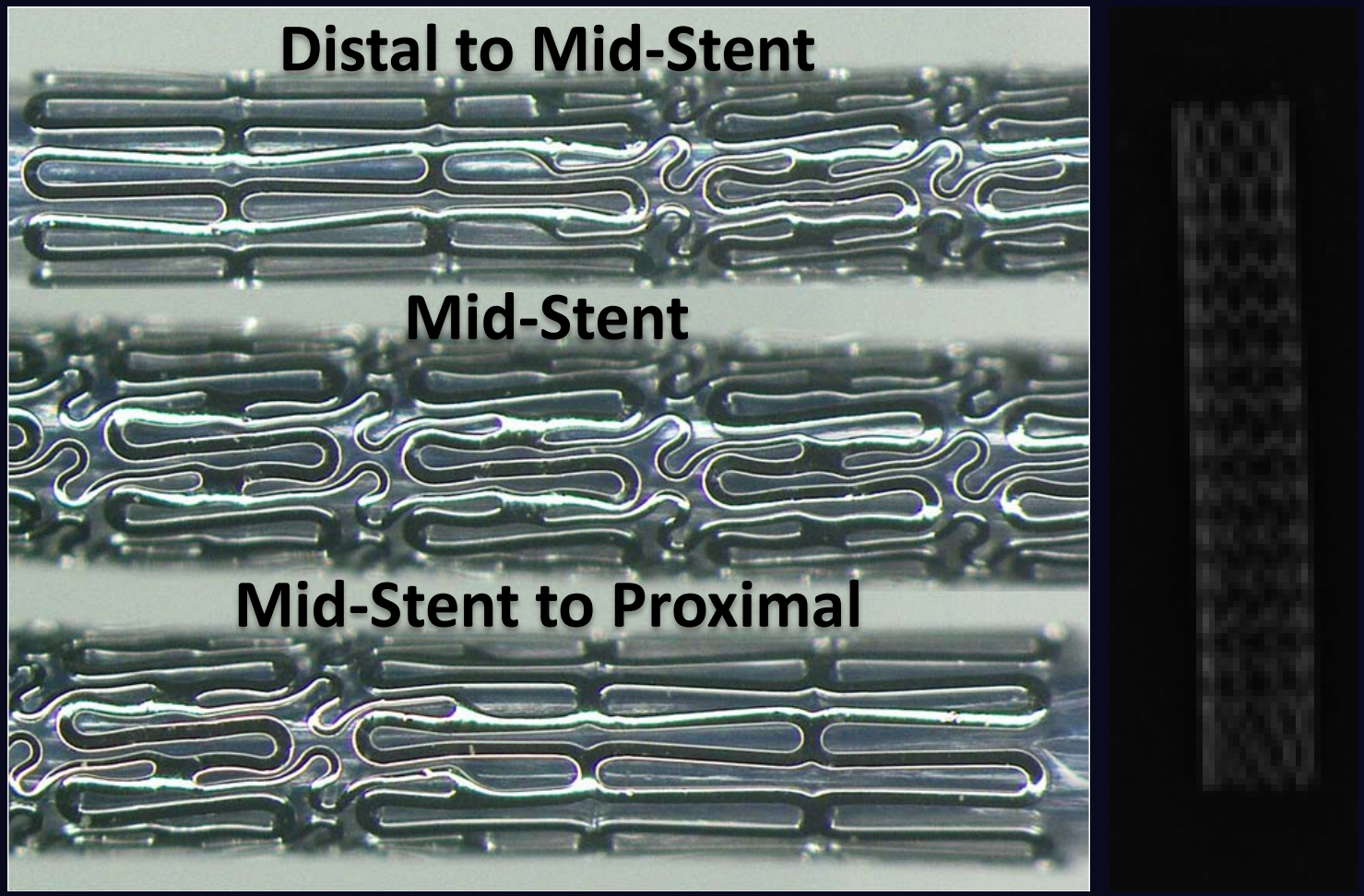








Mitsu (Meril LifeSciences) Ultra-Thin (40 Microns) DES CoCr Platform



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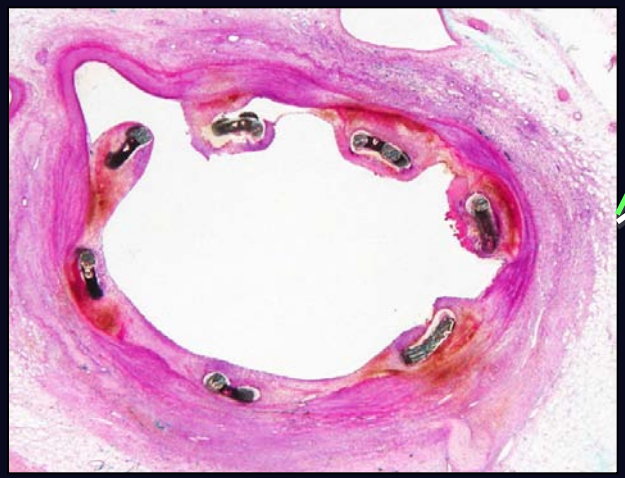


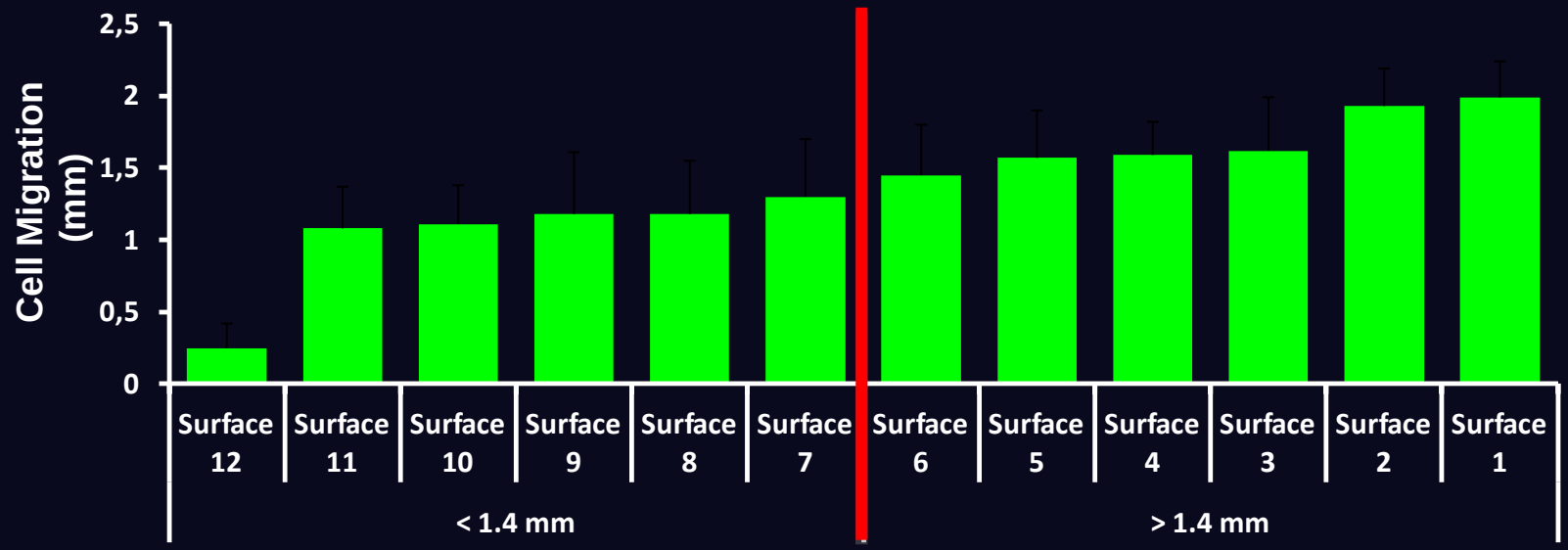
Minimize Injury at the time of implantation

- Stent design
- Mechanism of expansion
- Strut thickness

Adluminal stent surface modification

- Material biocompatibility
- Surface modification

Endothelial Cell Migration Correlates with Surface Coverage and Morphology



Metallic Surface	Cell Migration (mm)	Cell Morphology	Cell Size	Cell Confluence	Cell Concentration
Surface 1	1.99 ± 0.25	++	Normal	++	++
Surface 2	1.93 ± 0.26	++	Normal	++	++
Surface 3	1.62 ± 0.37	++	Normal	++	++
Surface 4	1.59 ± 0.23	++	Normal	++	++
Surface 5	1.57 ± 0.33	++	Normal	++	++
Surface 6	1.45 ± 0.35	++	Normal	++	++
Surface 7	1.3 ± 0.4	+	Elongated	-	+
Surface 8	1.18 ± 0.37	-	Elongated	+	+
Surface 9	1.18 ± 0.43	-	Elongated	-	+
Surface 10	1.11 ± 0.27	+	Elongated	+	-
Surface 11	1.08 ± 0.29	+	Elongated	-	-
Surface 12	0.25 ± 0.17	-	Elongated	-	-

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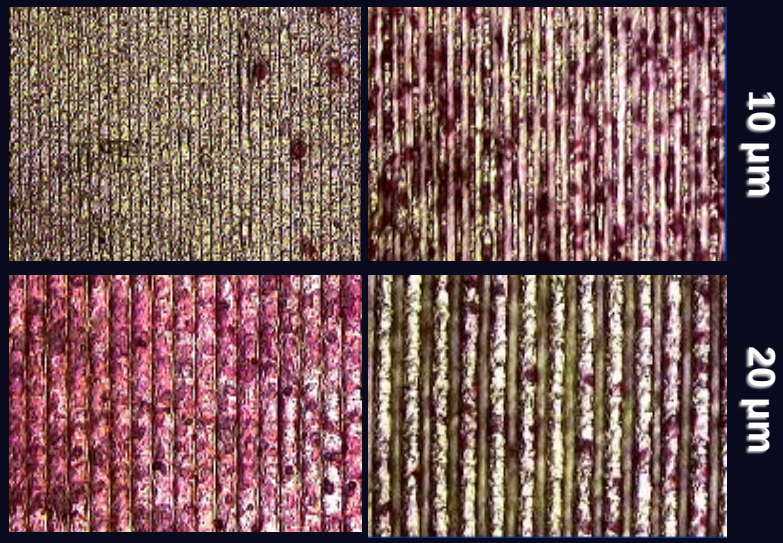
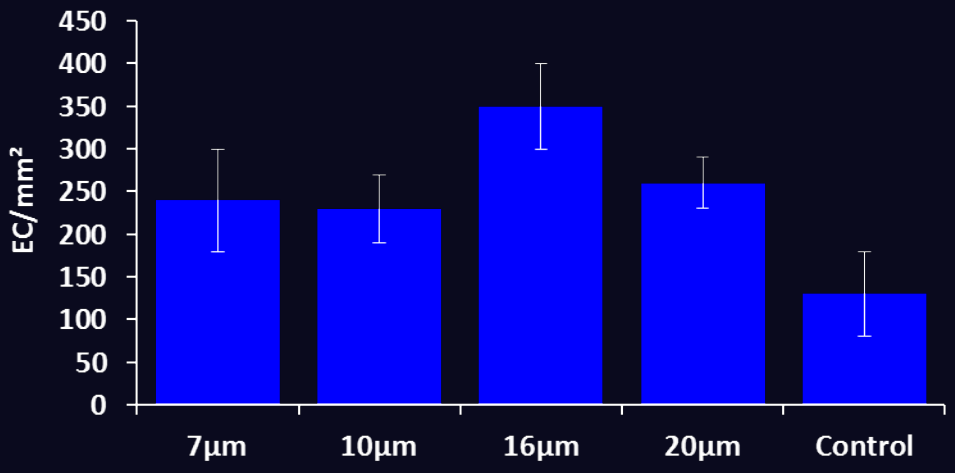
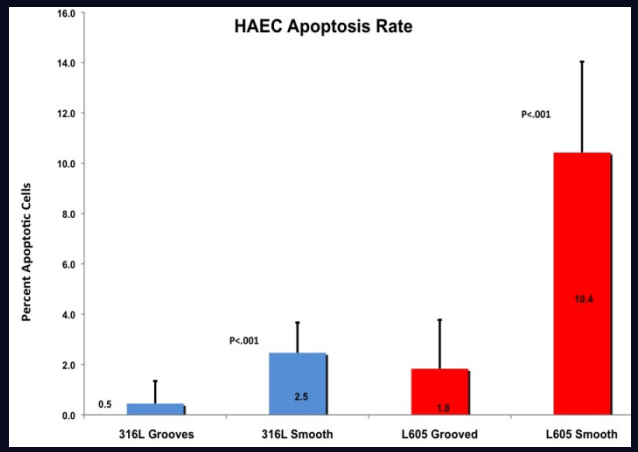
Picture (modified) courtesy of A. Tellez, SCCR

Endothelial Migration on Surfaces with Different Sized Grooves







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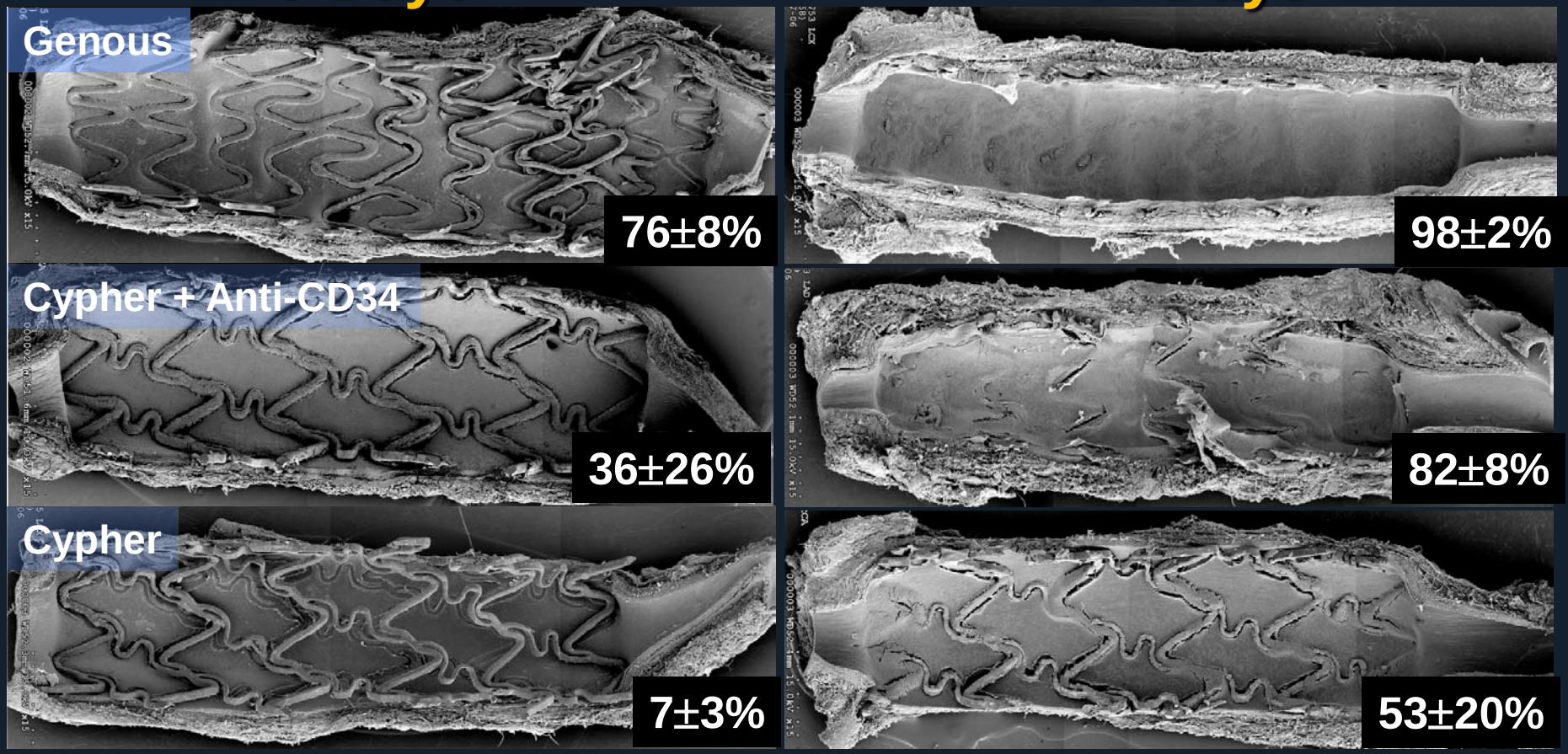
Picture (modified) courtesy of G. Sprague and J. Palmaz

Anti-CD34 Antibodies on Cypher Stents Enhance Surface Coverage



Nakazawa G, Granada JF. JACC Cardiovasc Interv. 2010 Jan;3(1):68-75

Combo Bio-engineered Sirolimus Eluting Stent

Granada JF. Circ Cardiovasc Interv. 2010 Jun 1;3(3):257-66

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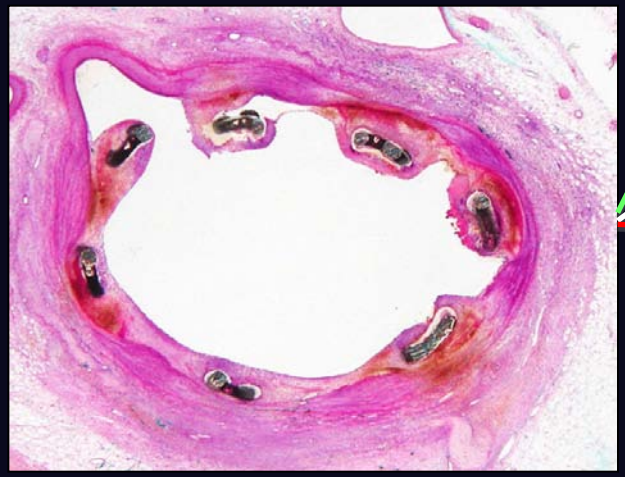


Minimize Injury at the time of implantation

- Stent design
- Mechanism of expansion
- Strut thickness

Adluminal stent surface modification

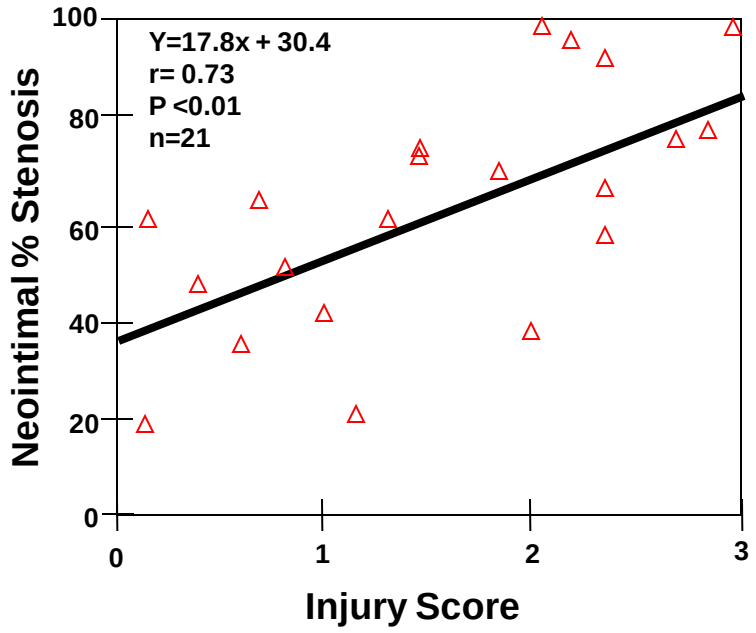
- Material biocompatibility
- Surface modification

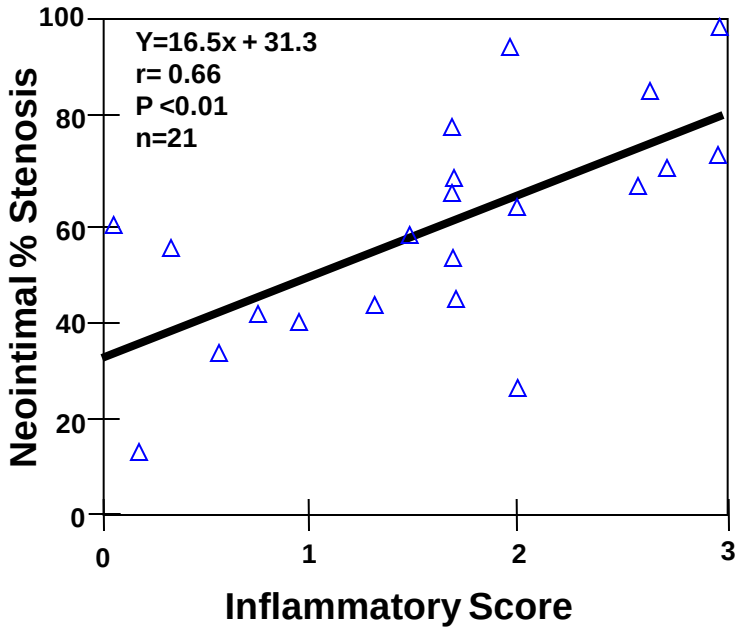
Polymeric carrier modification

- Amount, location, type
- Bioresorbable carriers

In-Stent Restenosis: Contributions of Inflammatory Responses and Arterial Injury to Neointimal Hyperplasia

RAN KORNOWSKI, MD, MUN K. HONG, MD, FACC, FERMIN O. TIO, MD,*
ORVILLE BRAMWELL, HONGSHENG WU, PHD, MARTIN B. LEON, MD, FACC
Washington, D.C. and San Antonio, Texas





Score 0 | Score 1 | Score 2 | Score 3

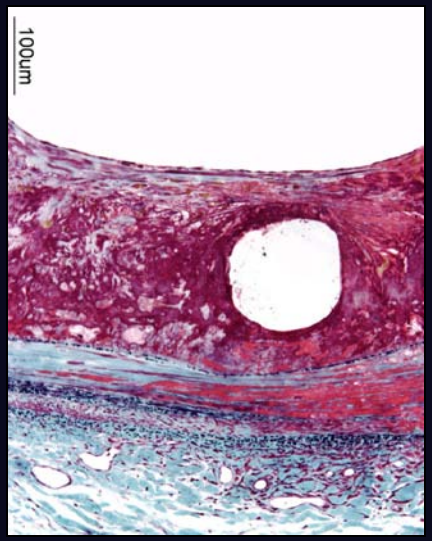
Kornowski, R. J Am Coll Cardiol. 1998 Jan;31(1):224-30

Evolution of Durable Polymers

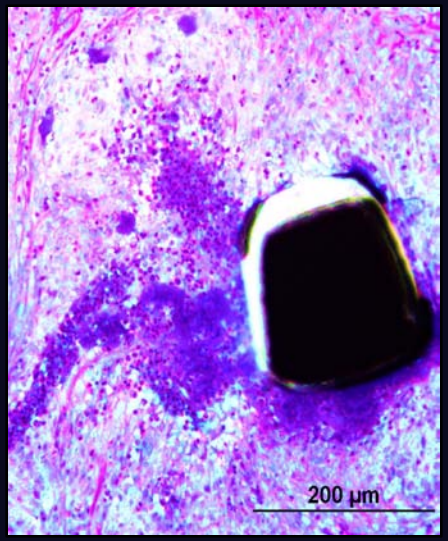
Biocompatibility and Thrombogenicity

First Generation Durable Polymers

TAXUS Liberte

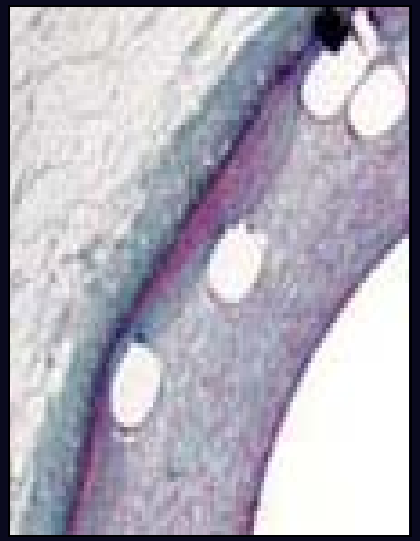


CYPHER

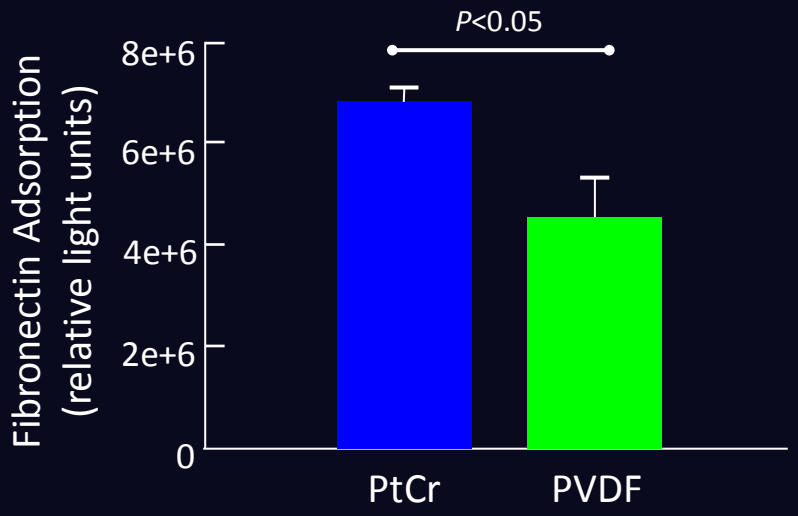


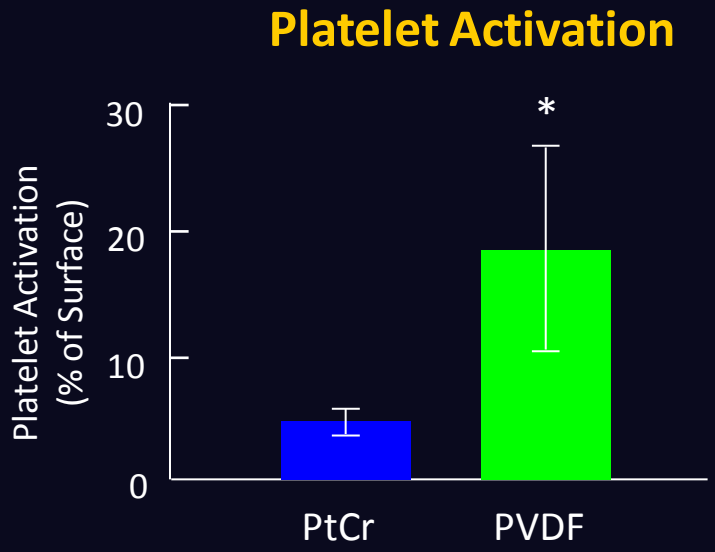
Emerging Polymers

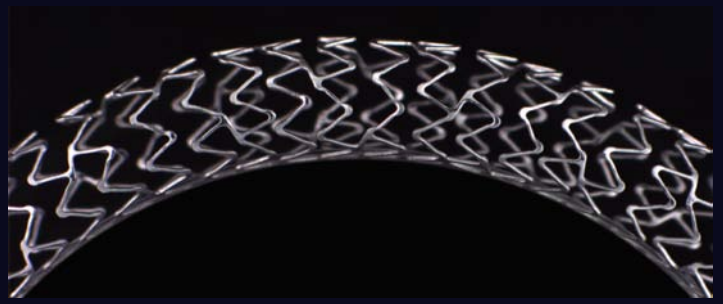
XIENCE -RESOLUTE

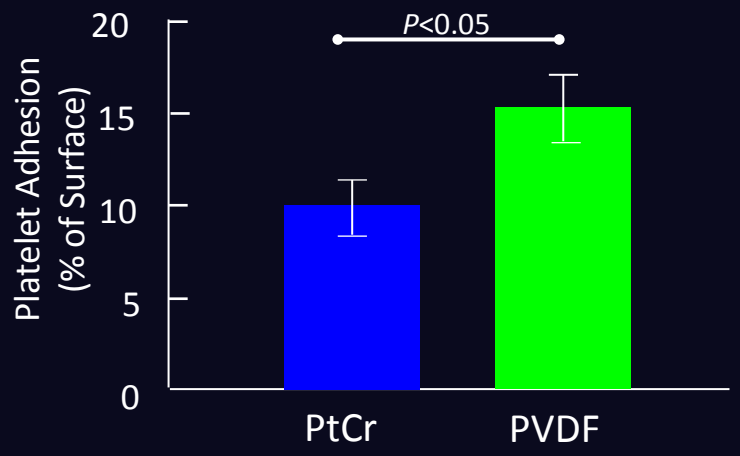


Impact of PVDF on Protein Absorption and Platelet-Surface Interaction



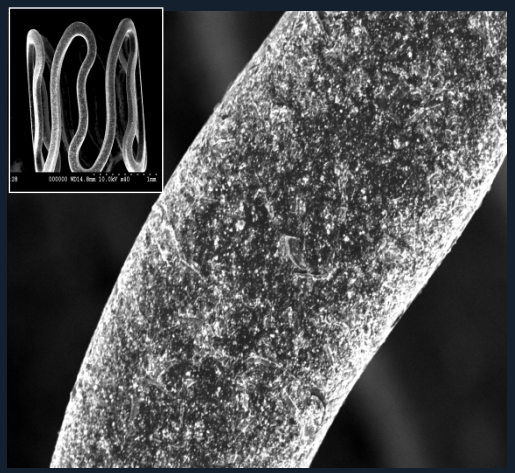




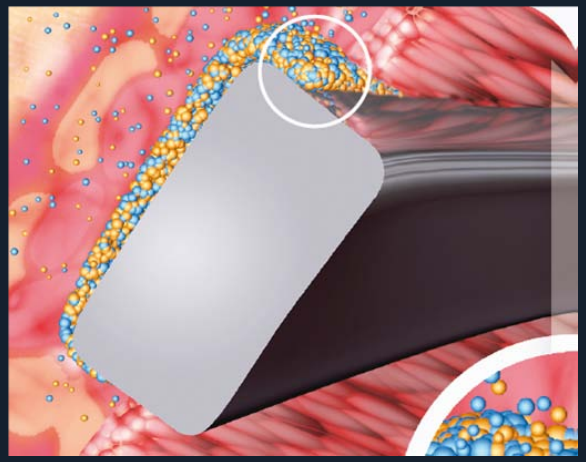


Bioabsorbable Polymer DES

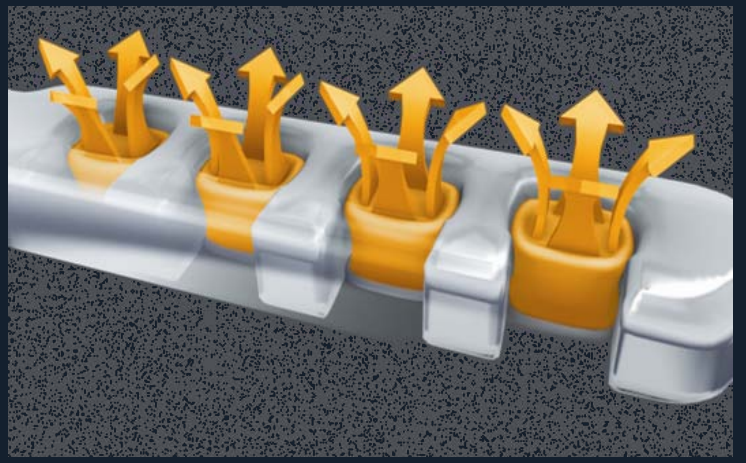
Sirolimus – ISAR TEST



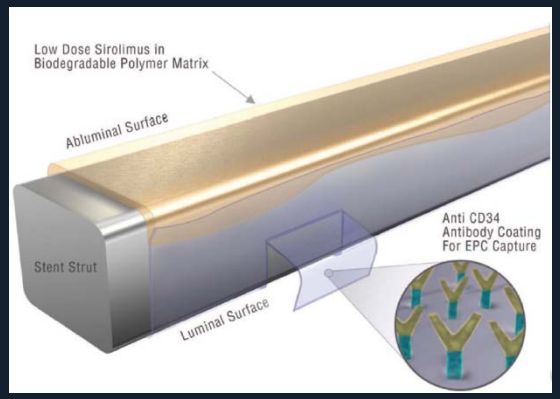
Biolimus A9 – BioMatrix Nobori, Axxess, XTENT



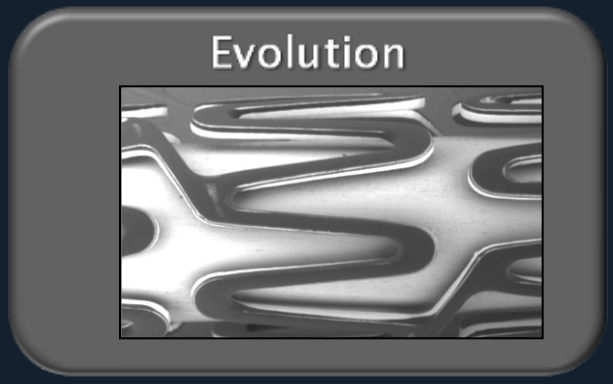
Sirolimus – NEVO



Sirolimus – Genous Bioengineered R Stent



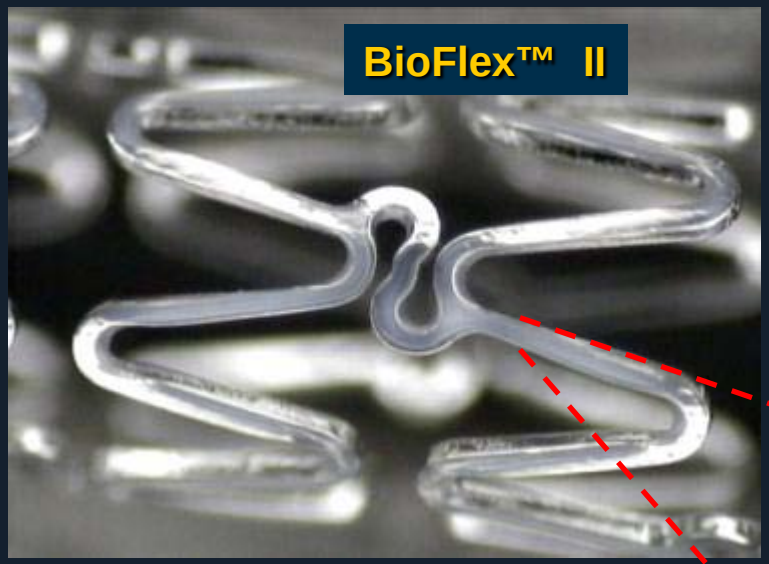
Everolimus – BSC (Synergy)



Sirolimus – Meril (Biomime)

Bioresorbable Polymers as Drug Carriers

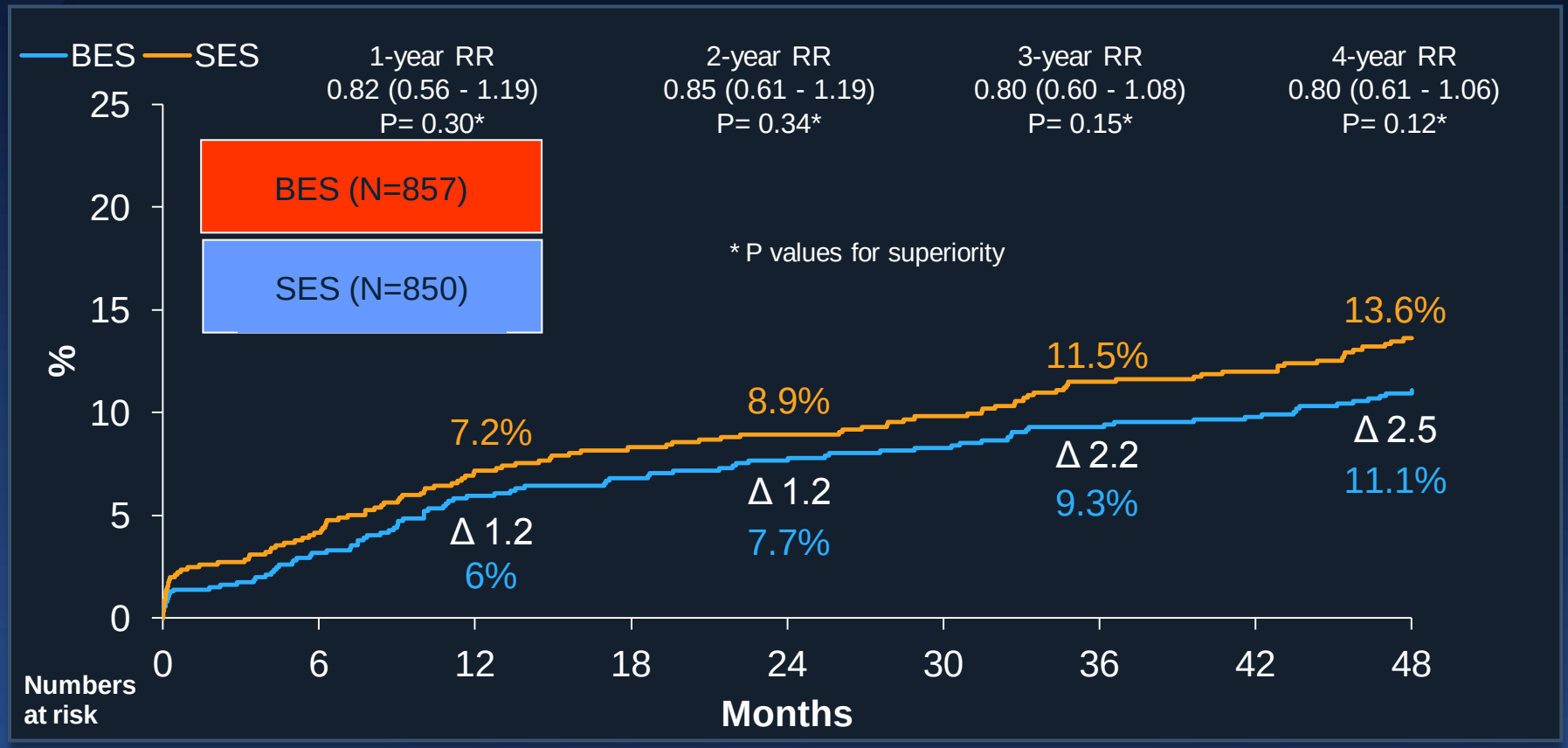
BioMatrix™ Stent Platform



Biodegradable Drug/Carrier:

- Biolimus A9® / Poly Lactic Acid 50:50
- 15.6 μg/mm drug = 250 μg /16mm
- 500 mcg drug+polymer)
- Abluminal surface only
- 10 microns coating thickness
- Degrades in 9 months

Clinically-Indicated TVR in the Leaders Trial (BES versus SES)



BES	857	809	776	758	748	736	725	707	688
SES	850	797	760	741	727	704	685	666	644

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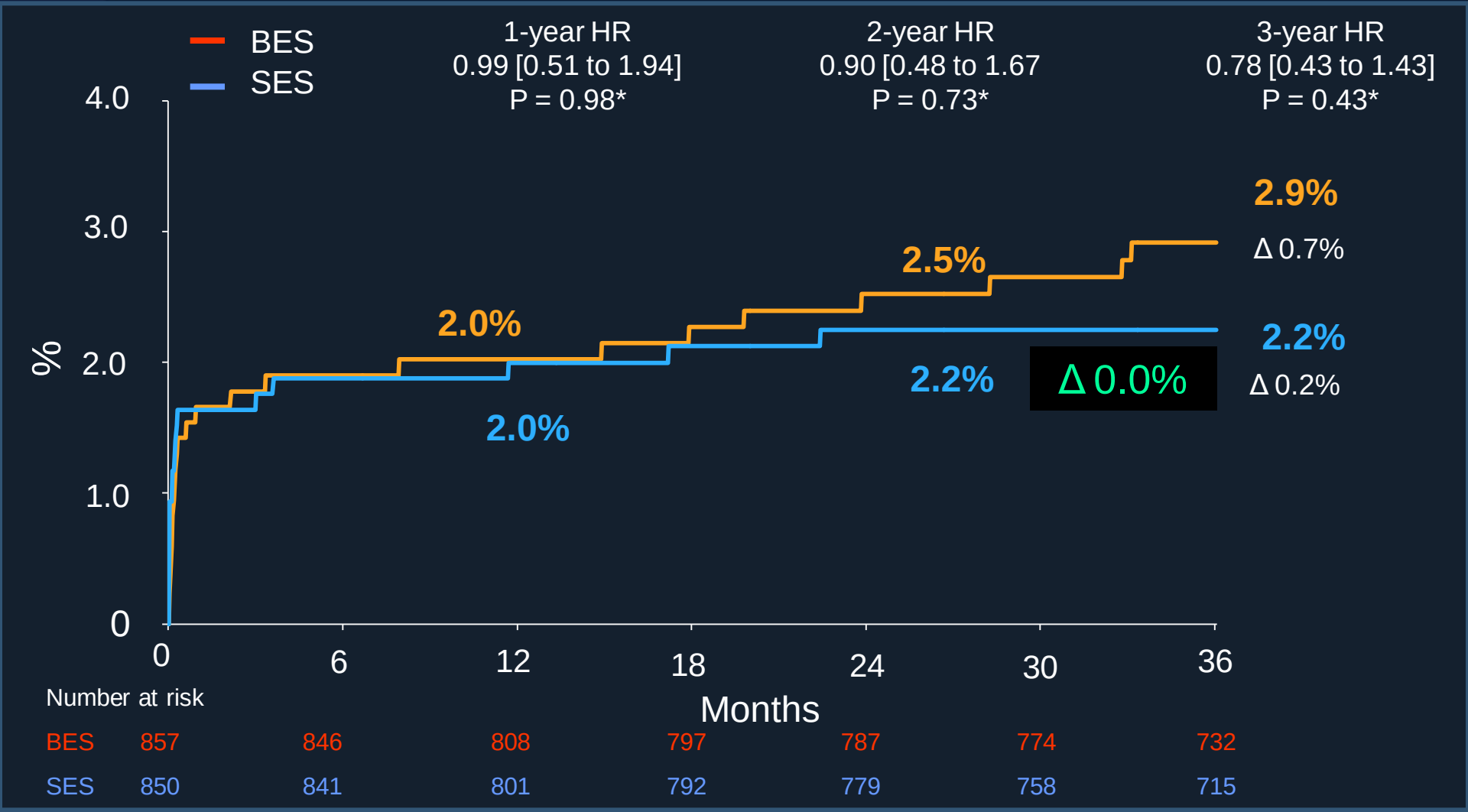
*P values for superiority
Serruys, P. W., oral presentation ,TCT 2011

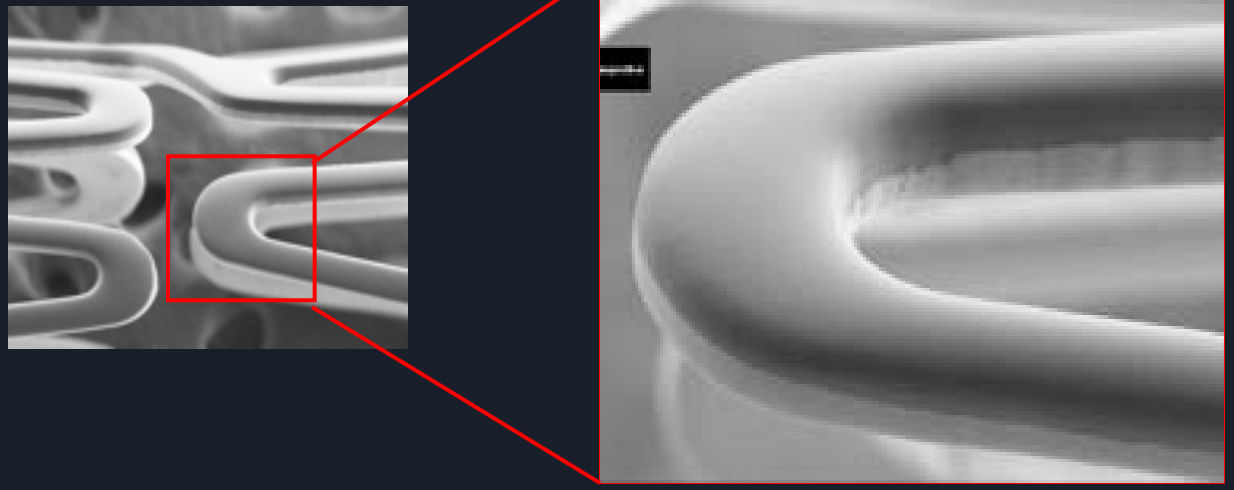
Definite ST Through 3 Years in the Leaders Trial (BES versus SES)



*P values for superiority

Serruys, P. W., oral presentation ,TCT 2011

SYNERGY™ Stent Platform
Abluminal Bioabsorbable Polymer



Bioabsorbable polymer (PLGA)

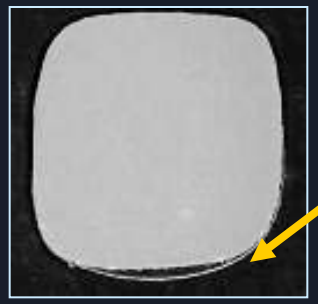
Applied only to the abluminal surface (rollcoat)

Thin strut PtCr Stent

Durable Permanent Polymer + Drug 360° Around Stent

Current Durable Polymer

Abluminal Bioabsorbable Polymer

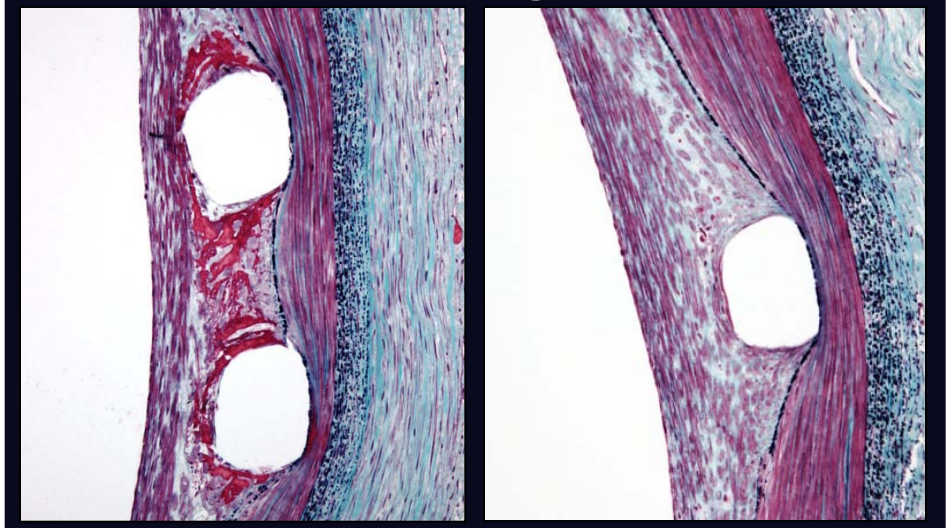


PLGA Bioabsorbable Polymer (3 µm) + Everolimus* on Abluminal Side of Stent

****2 doses of everolimus evaluated: one similar to PROMUS™ stent and one that is half the dose***

Long Term Vascular Healing of Fourth Generation Drug Eluting Stents

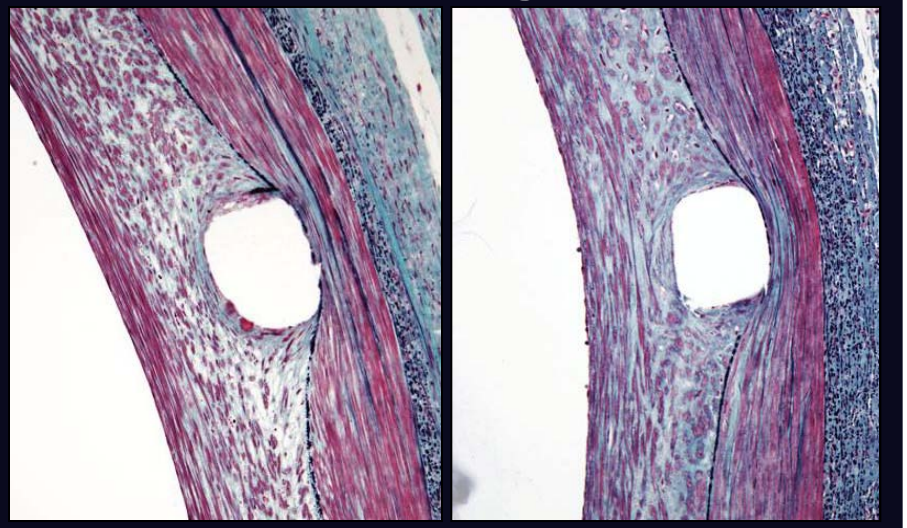
30 Days



SYNERGY™ Bare Element

Short term healing effect due to the anti-proliferative effect of Everolimus on cell proliferation

90 Days



SYNERGY™ Bare Element

Long term healing effect following the inhibitory effect leaving behind only BMS platform

EVOLVE Study Design

SYNERGY™ Stent Primary Endpoint

EVOLVE

Single-Blind, Non-Inferiority Design

Patients with de novo native coronary lesions
≤28 mm length, RVD 2.25-3.5mm, %DS ≥50
Exclusions: LM disease, CTO, AMI or recent MI

↓

Randomized 1:1:1 at 29 sites
(EU, Australia, New Zealand)

SYNERGY™ Stent (81µm PtCr platform) PROMUS™ Dose (N=97)	SYNERGY™ Stent (81µm PtCr platform) ½ PROMUS™ Dose (N=97)	PROMUS Element™ Stent (N=97)

Primary Clinical Endpoint: TLF* at 30 days
Primary Angiographic Endpoint: In-stent Late Loss at 6 months
Additional analyses: IVUS at baseline & 6 months

Angiographic Outcomes at 6 Months in the Evolve Trial (Synergy DES)

In-stent values	PROMUS Element N=98	SYNERGY N=94	*P* value	SYNERGY ½ Dose N=99	*P* value
MLD	2.29 ± 0.50	2.41 ± 0.42	0.08	2.45 ± 0.44	0.02
Late Loss	0.15 ± 0.34	0.10 ± 0.25	0.19	0.13 ± 0.26	0.56
Diameter stenosis	8.95 ± 14.97	6.59 ± 9.90	0.18	7.27 ± 9.47	0.34
Binary restenosis	3.2%	0.0%	0.25	0.0%	0.25

Assessed by QCA
Values are mm or percent
Intent-to-treat; P values are versus PROMUS Element

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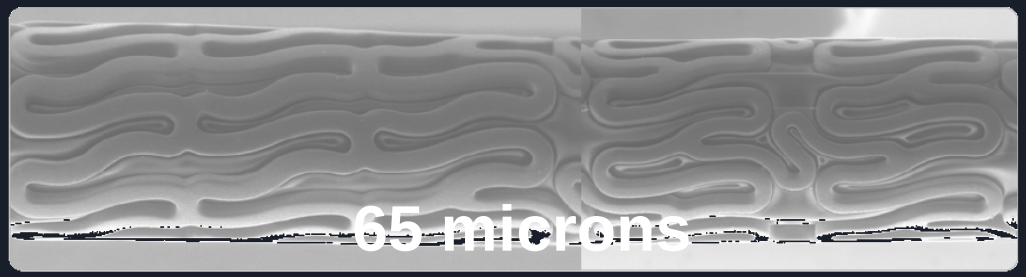
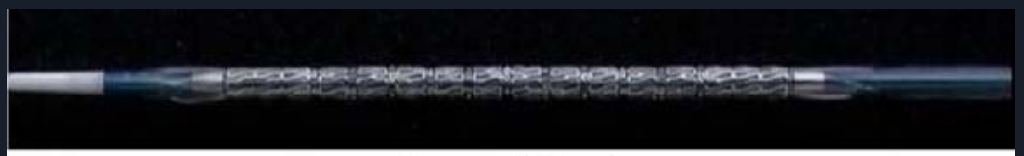
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

J Am Coll Cardiol. 2012 Apr 10;59(15):1362-70

Biomime Sirolimus Based DES Program (Meril Life Sciences)

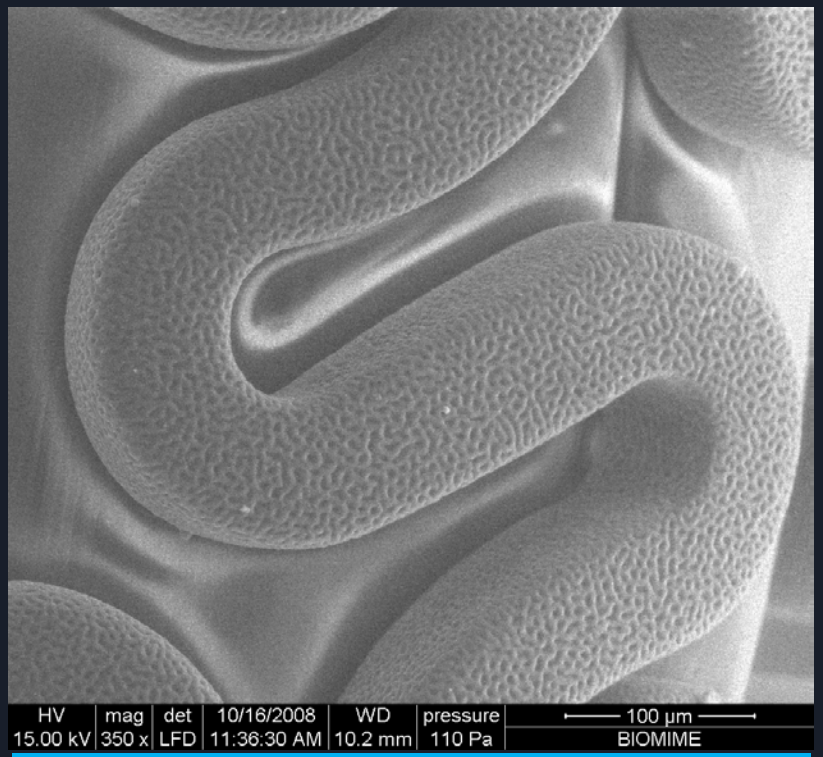




Crimped Stent

Mid-segment Expansion

Fully Expanded Stent



PLLA + PLGA

Sirolimus
1.25 µg/mm^2

MeriT-2 Trial (250 Patients): Key Results

Follow-Up Time Point	Patients Available	Death		MI		Revascularization TLR / TVR	
		Cardiac	Non-Cardiac	Q-Wave	Non-Q-Wave	Re-PCI	CABG
30-days	248 (99%)	0 (0%)	1* (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6-m	237 (96%)	2# (0.8%)	0 (0%)	0 (0%)	0 (0%)	3 (1.3%)	0 (0%)
8-m	231 (93%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9$ (3.9%)	1 (0.4%)
1-year	211 (86%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cumulative 1Y MACE 16 (7.6%)		**2 (0.8%)**	**1 (0.4%)**	**0 (0%)**	**0 (0%)**	**12 (5.2%)**	**1 (0.4%)**

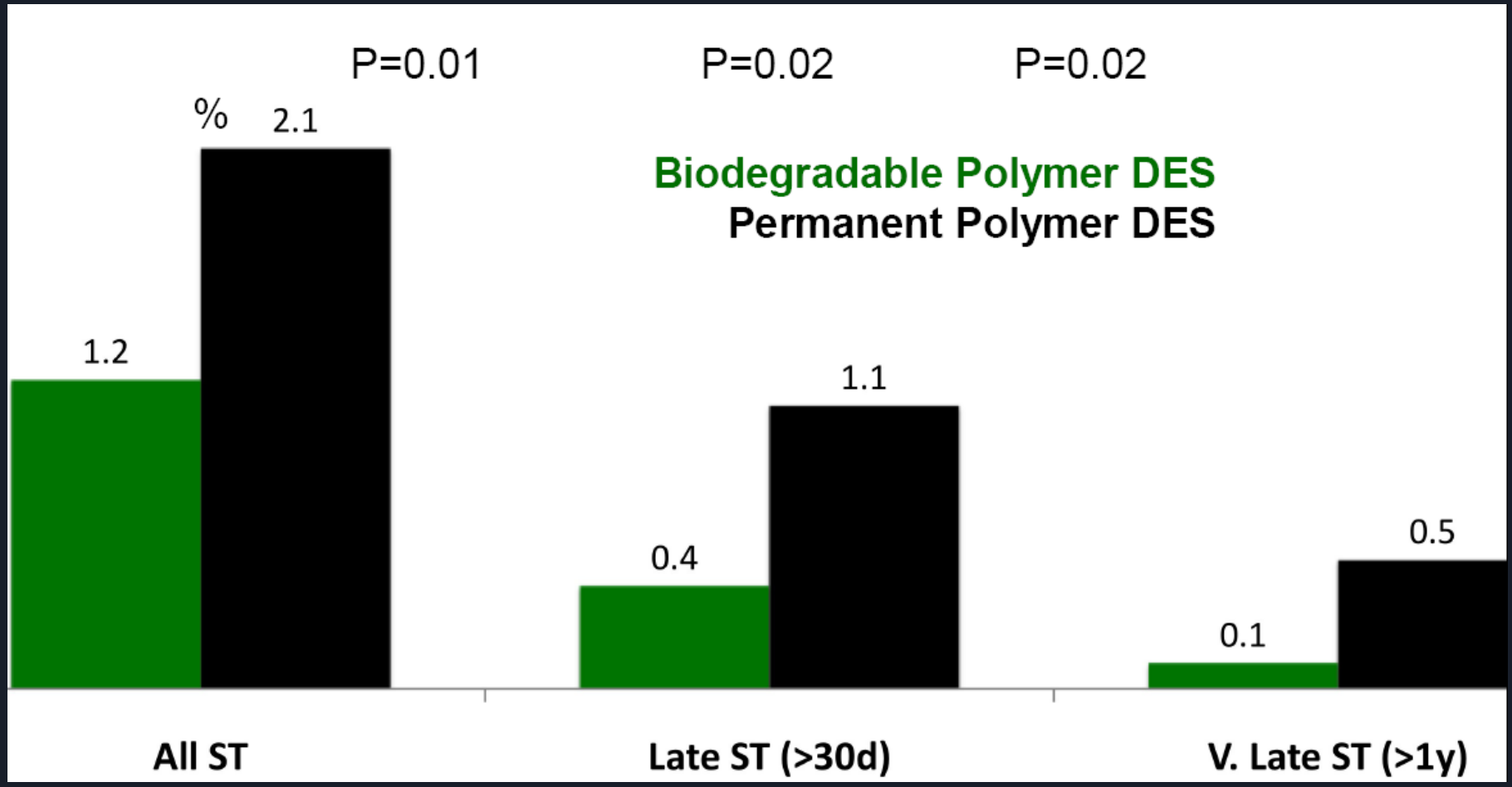
Acute ST (0h – 1D)	Sub-Acute ST (>1D – 30D)	Late ST (>30D – 1Y)	V. Late ST (> 1Y)
1*/250 (0.4%)	1#/250 (0.4%)	0 (0%)	1/211 (0.5%)

Angiographic Follow Up (97 patients, 8 Months):

- **Late Loss: In-segment: 0.13 [0.09, 0.31], In-stent: 0.15 [0.09, 0.33]**
- **Binary Restenosis: In-segment: 6 / 132 (4.5%), In-stent:1/ 132 (0.8%)**

Biodegradable Polymer DES versus Permanent Polymer Sirolimus DES

ISAR-TEST 3, ISAR-TEST 4, LEADERS (n= 4052)



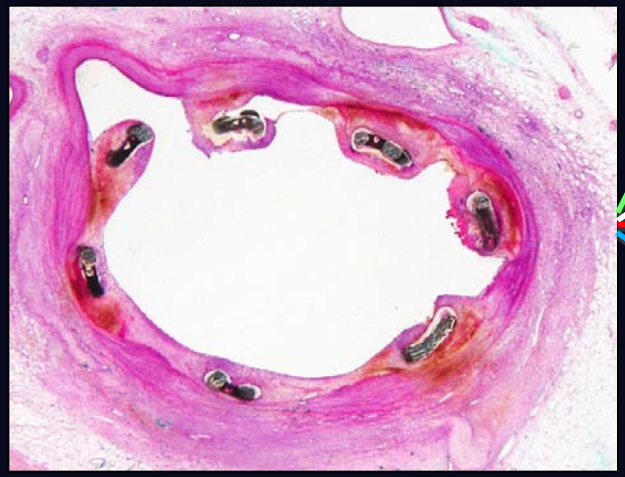
Stefanini GG. Eur Heart J. 2012 Mar 24

Strategies to Improve Vessel Healing Following DES Implantation?

DES: Controlled drug release (polymer based)

Cellular drug effect

New issue= delayed healing and stent thrombosis



Minimize Injury at the time of implantation

- Stent design
- Mechanism of expansion
- Strut thickness

Adluminal stent surface modification

- Material biocompatibility
- Surface modification

Polymeric carrier modification

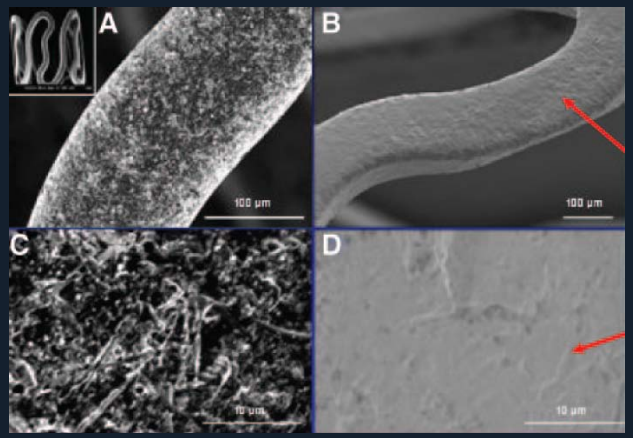
- Amount, location, type
- Bioresorbable carriers

Polymer-free delivery systems

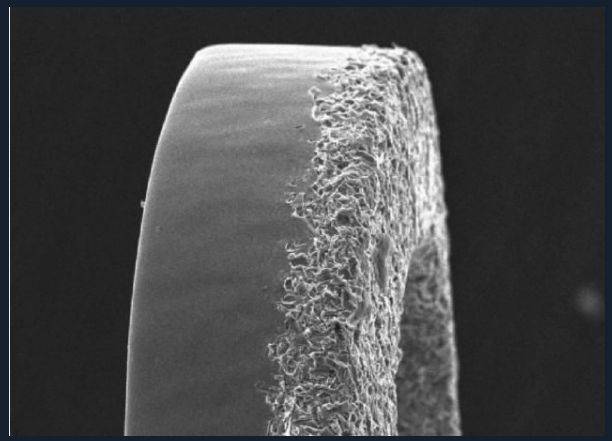
- Surface versus filled stents
- Local drug delivery (DEB)

Polymer-Free DES Platforms

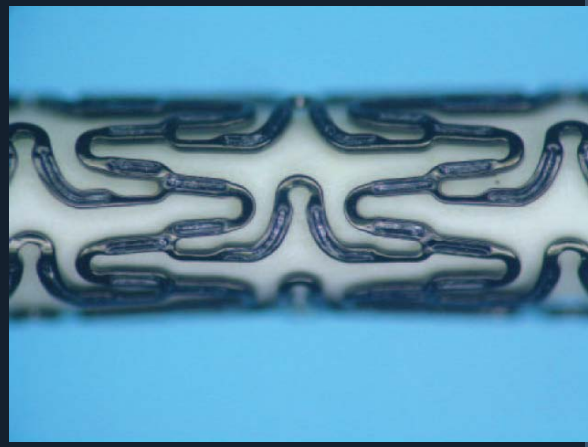
YUKON
Various Drugs



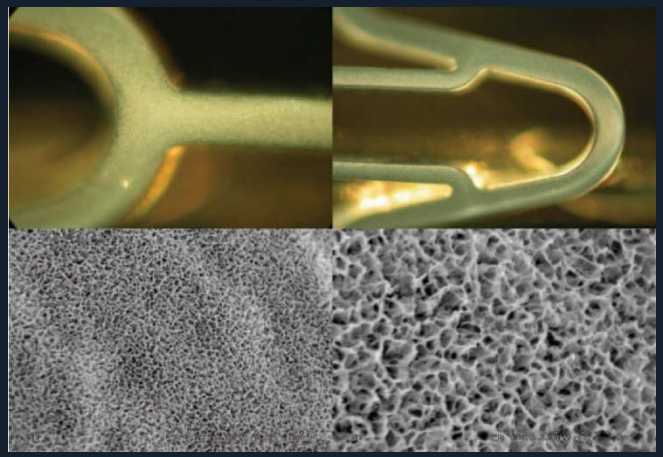
BioFreedom
Biolimus A9



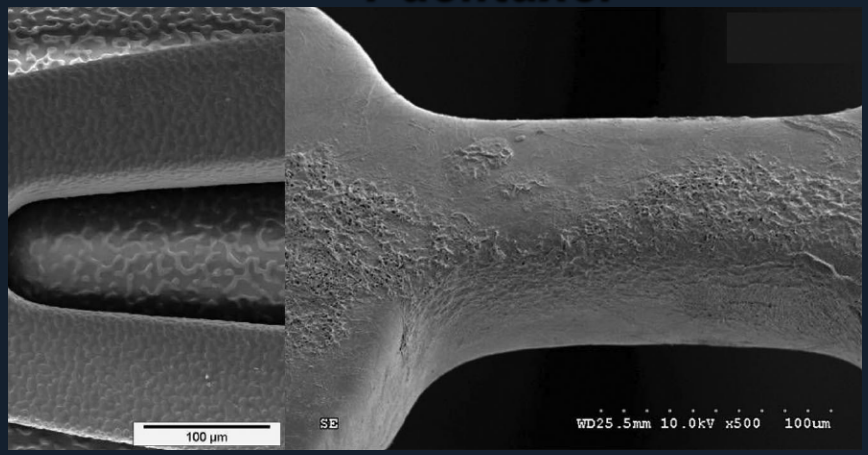
Optima
Tacrolimus



VESTAsync
Sirolimus



Amazon Pax
Paclitaxel

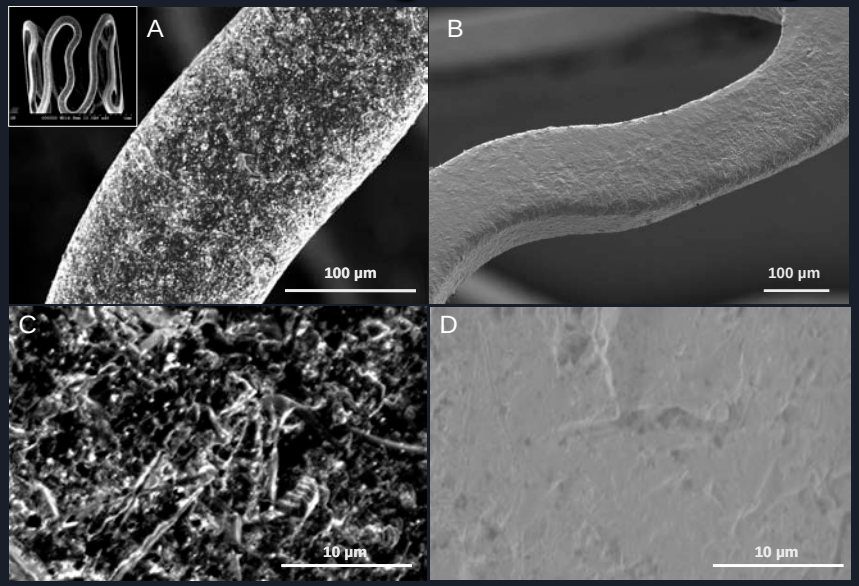


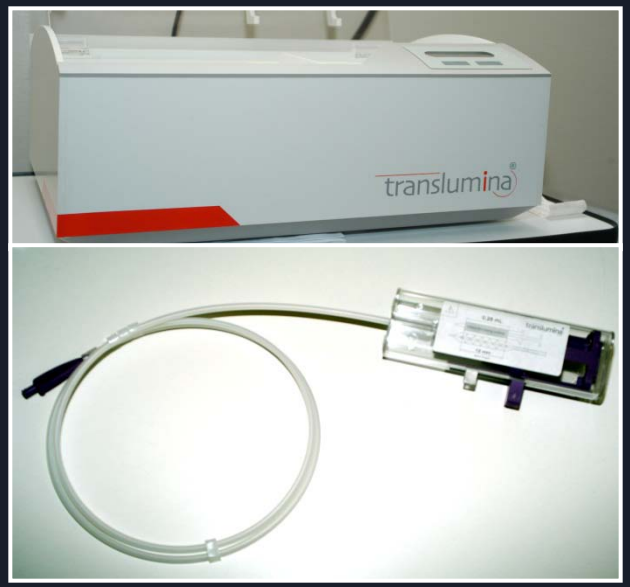
ISAR : Individualized Drug–Eluting Stent System to Abrogate Restenosis Project

Design, development and clinical implementation of novel microporous DES without permanent polymer

- **ISAR Generation 1 (No polymer at all)**
- **ISAR Generation 2 (Biodegradable polymer)**
- **ISAR Generation 3 (Dual-drug, no polymer)**

Before Coating **After Coating**

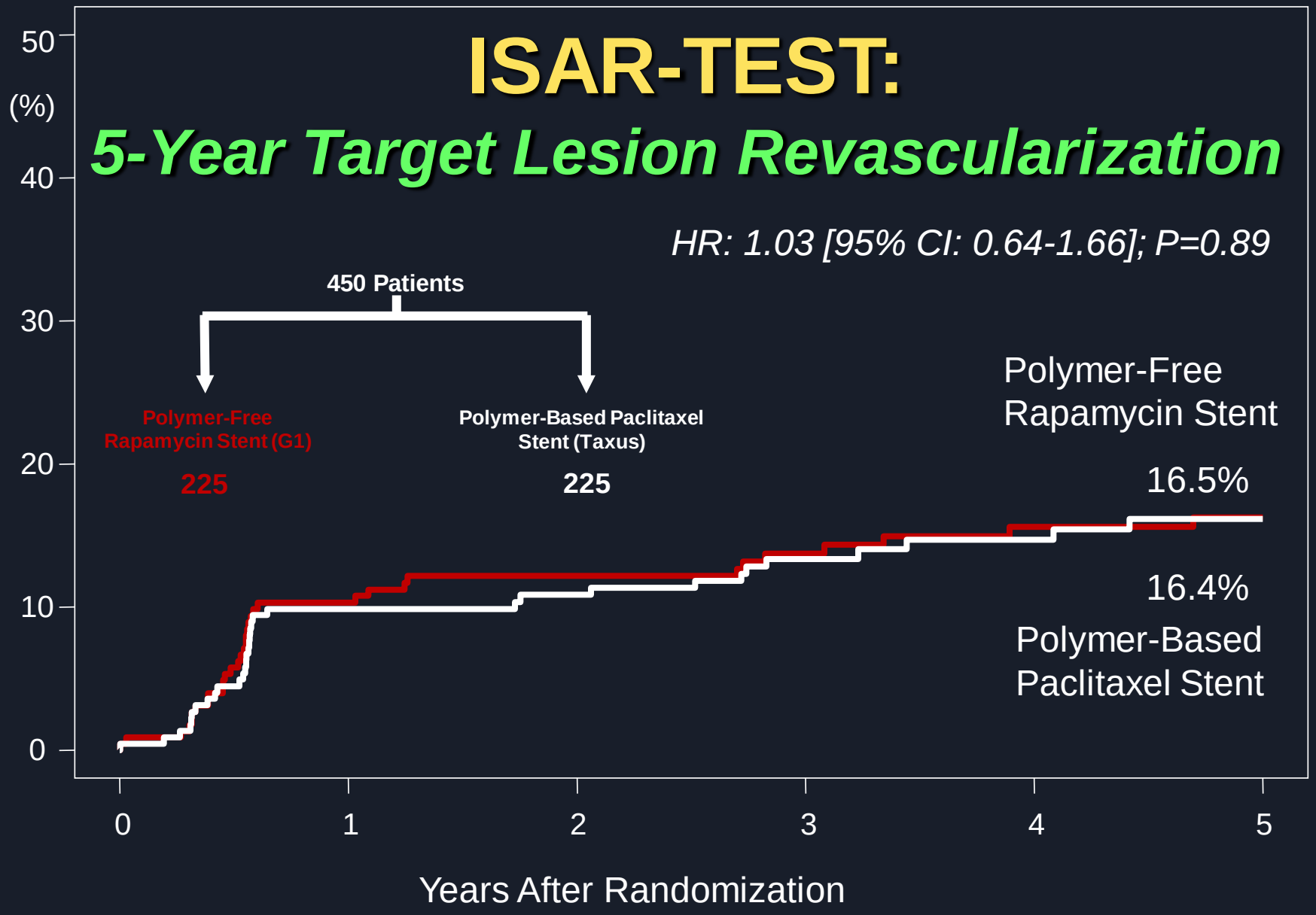




ISAR-TEST:

5-Year Target Lesion Revascularization

HR: 1.03 [95% CI: 0.64-1.66]; P=0.89



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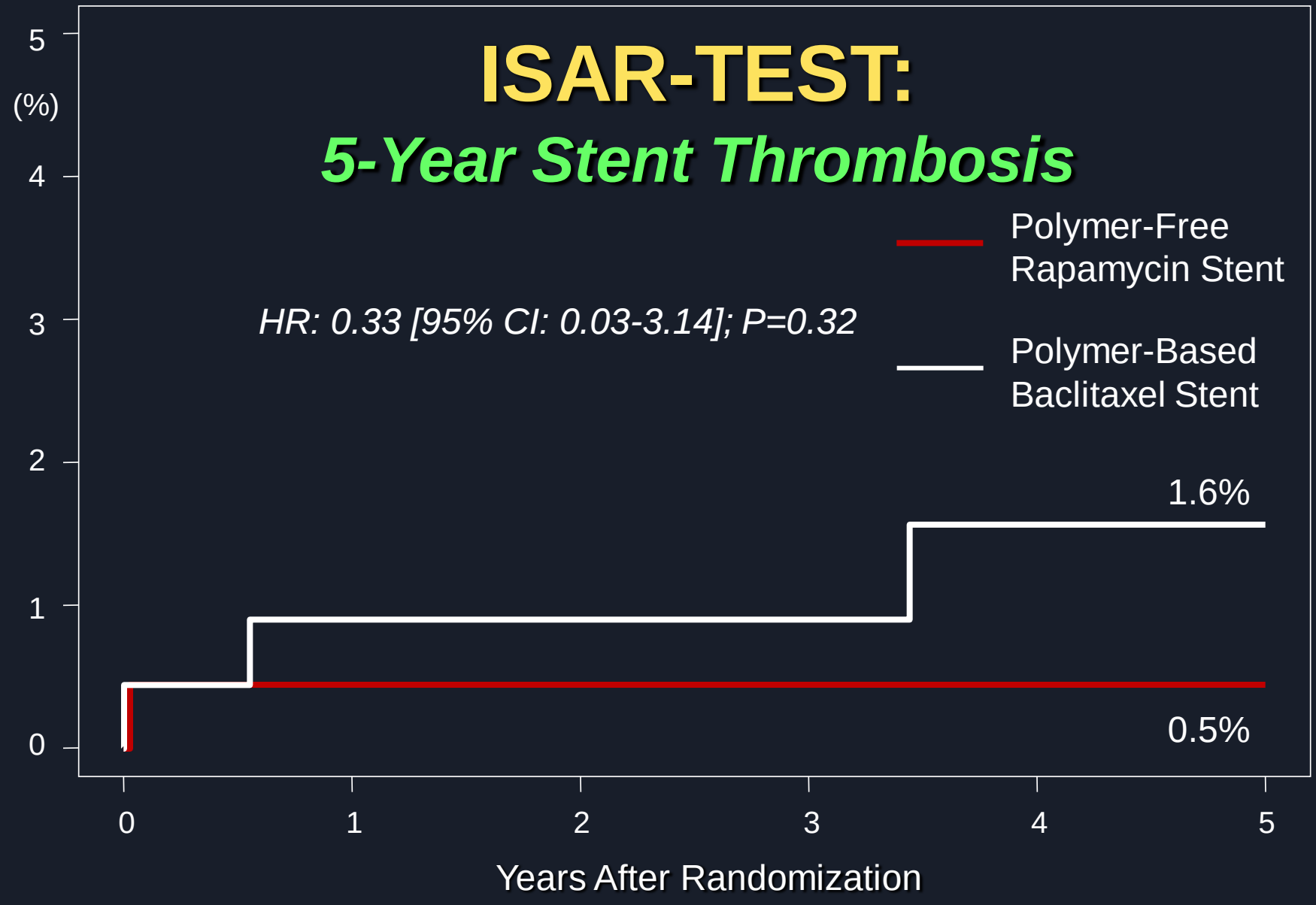
ISAR-TEST, Circulation 2006

ISAR-TEST:

5-Year Stent Thrombosis

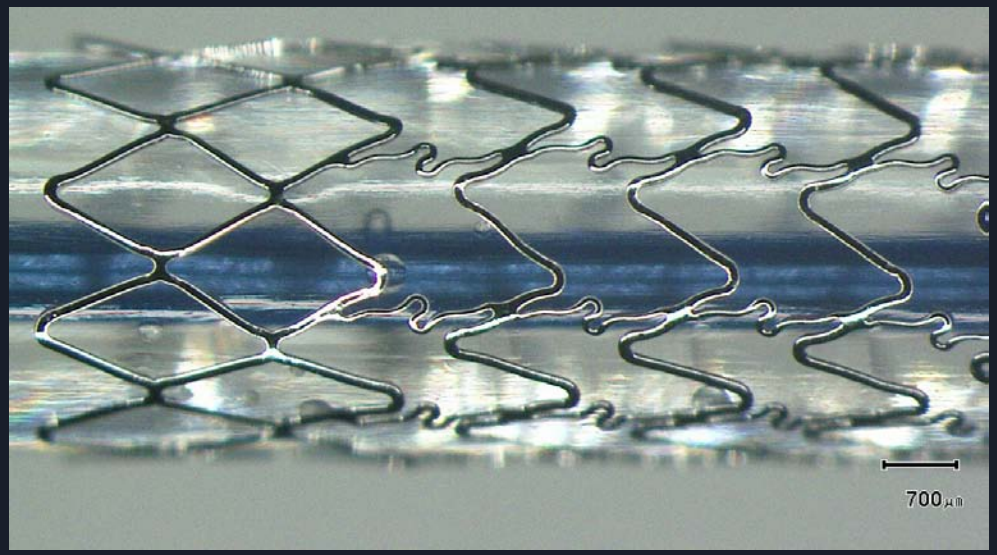


Nanocoating DES Technology

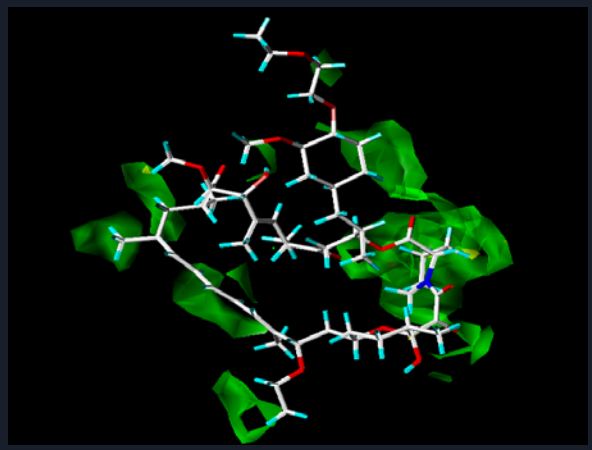
Polymer Free Drug Delivery

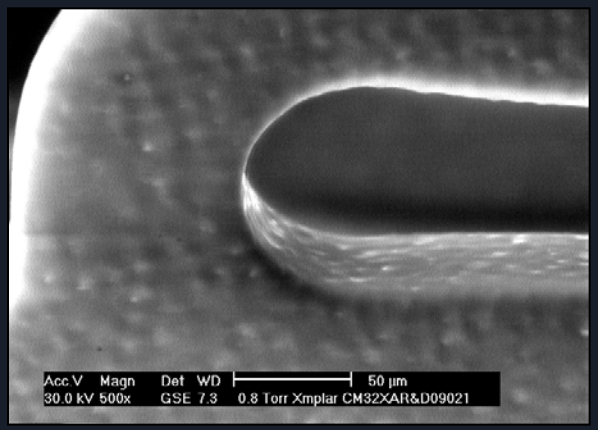
Meril Life Science Mitsu

The 40µm Hybrid Stent



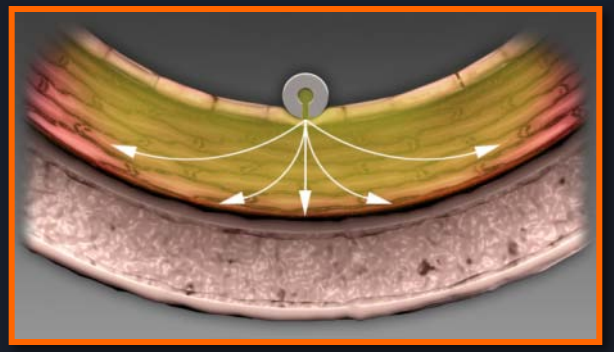
Merilimus

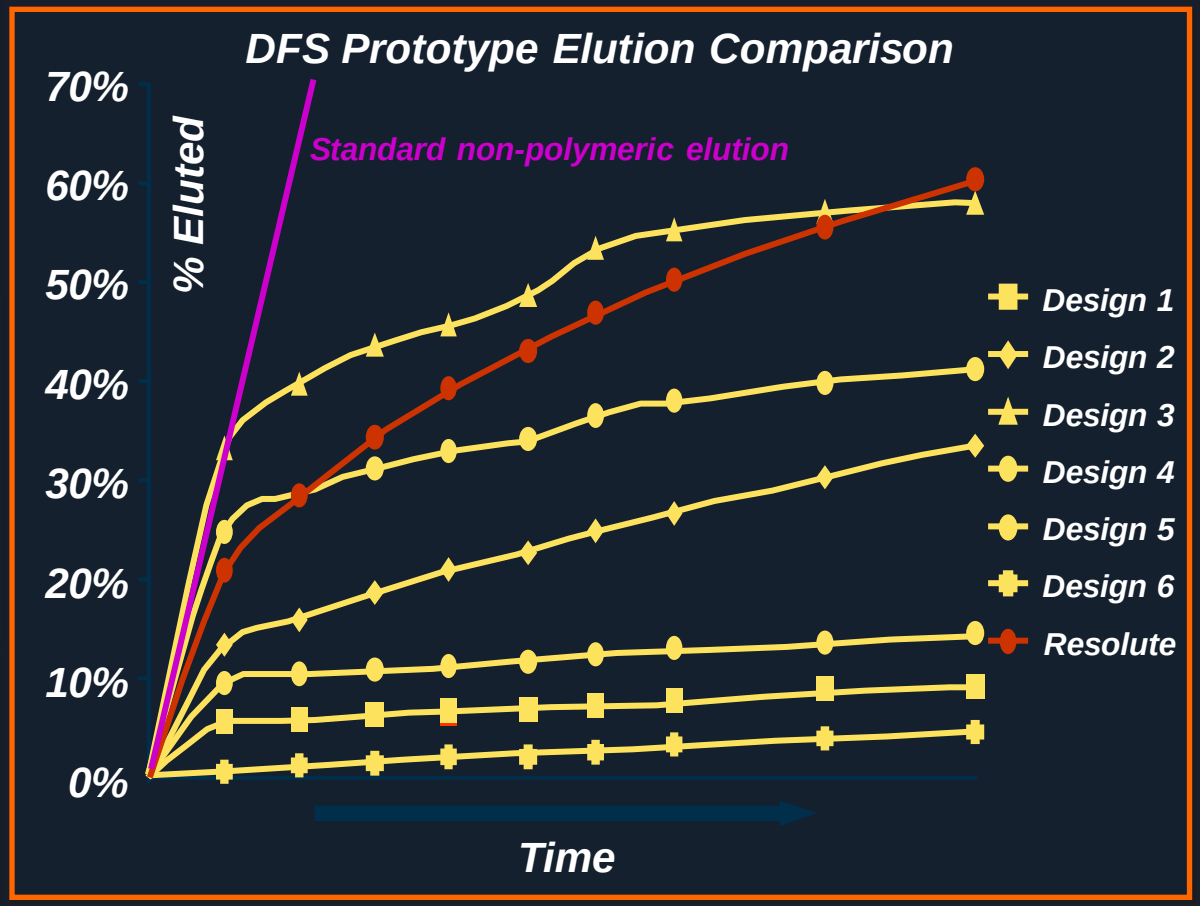




Drug Filled Stent (DFS) Technology

Polymer Free Drug Delivery





Conclusions

- Despite the excellent clinical results achieved with current generation DES, the potential for technological improvement still remains
- DES technologies continue to evolve by decreasing strut size, polymeric load and the use of more biocompatible polymers
- DES using bioabsorbable polymers (as drug carriers) have demonstrated similar clinical efficacy compared to 2nd generation DES However, their potential to decrease LST needs to be tested in large head to head RCTs
- The absence of polymer beyond the drug delivery period creates the potential to reduce the dependency on DAPT for long-term safety while maintaining best-in-class DES efficacy