

# **Metallic DES: Is There Room for Further Progress?**

**Spencer B. King III, MD, MACC, FESC**

**President St. Joseph's Heart and Vascular Institute  
Professor of Medicine Emeritus  
Emory University**



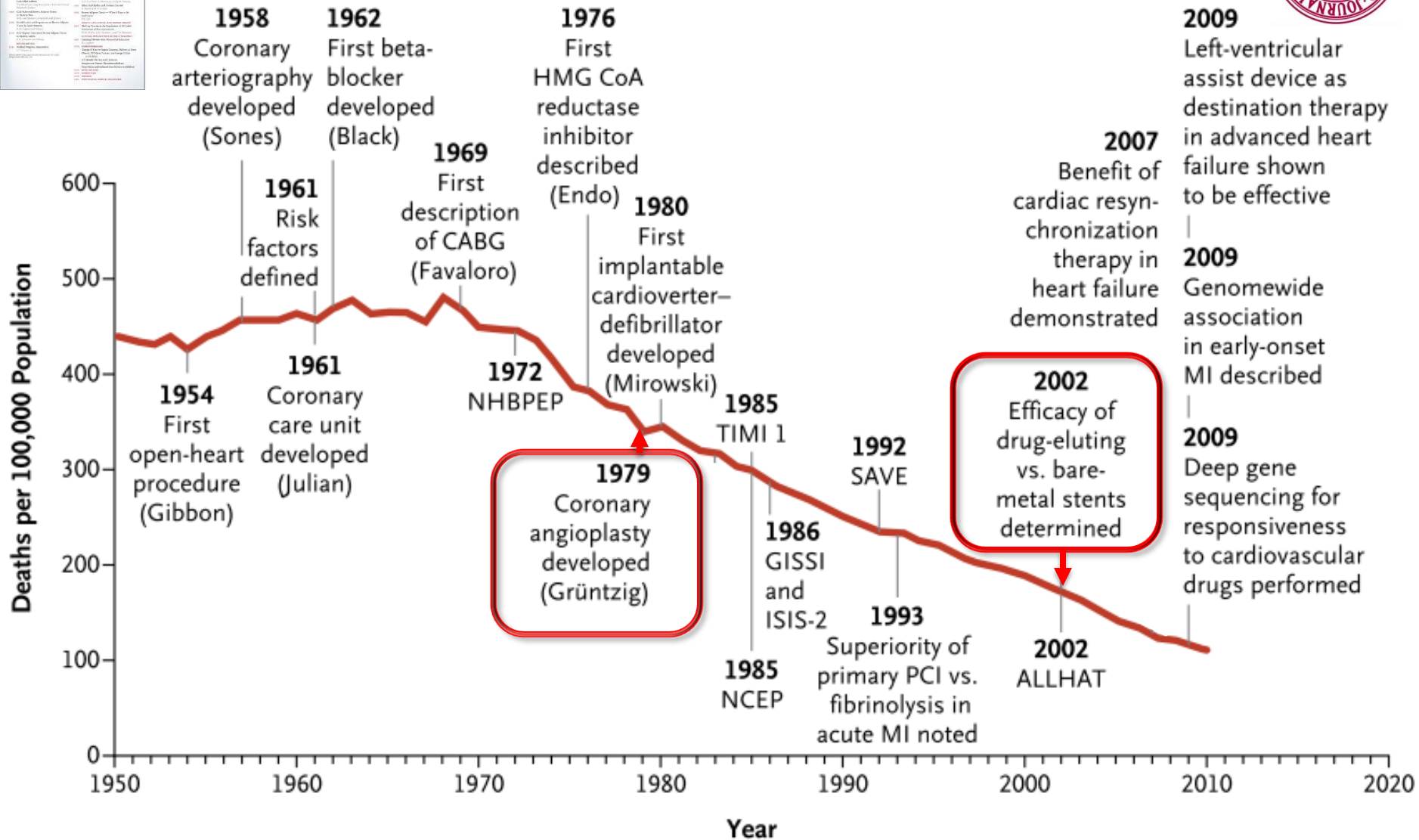
**EMORY**  
UNIVERSITY

**TCTAP 2013, 18<sup>th</sup> ANGIOPLASTY SUMMIT, Seoul, S. Korea  
April 25, Room 3-2, Level 3, 07:20 - 07:32 am**

# 20<sup>th</sup> NEJM ANNIVERSARY ARTICLE

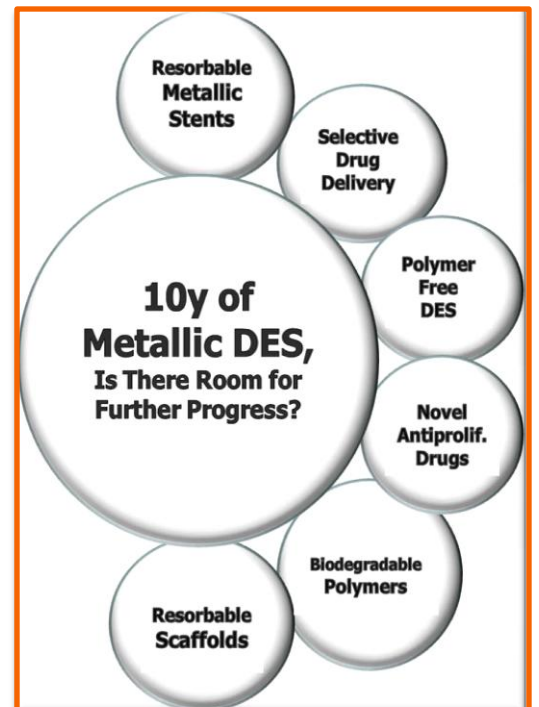
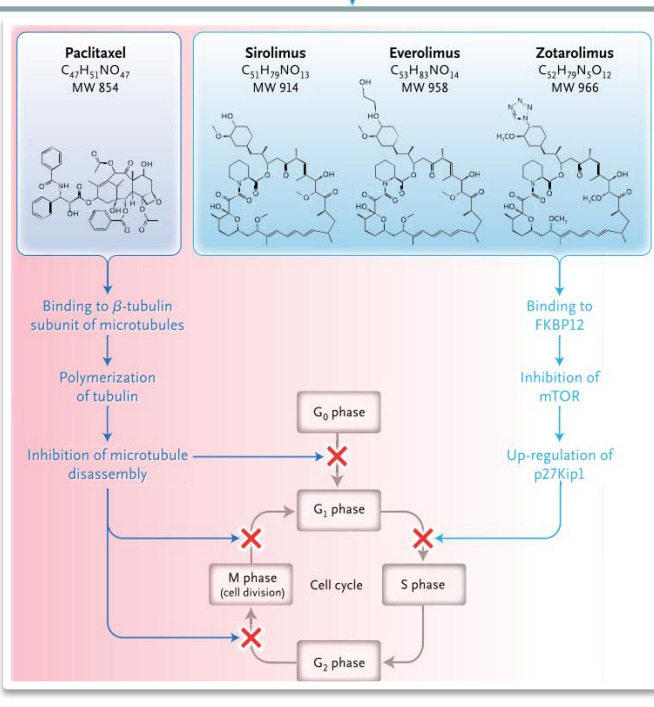
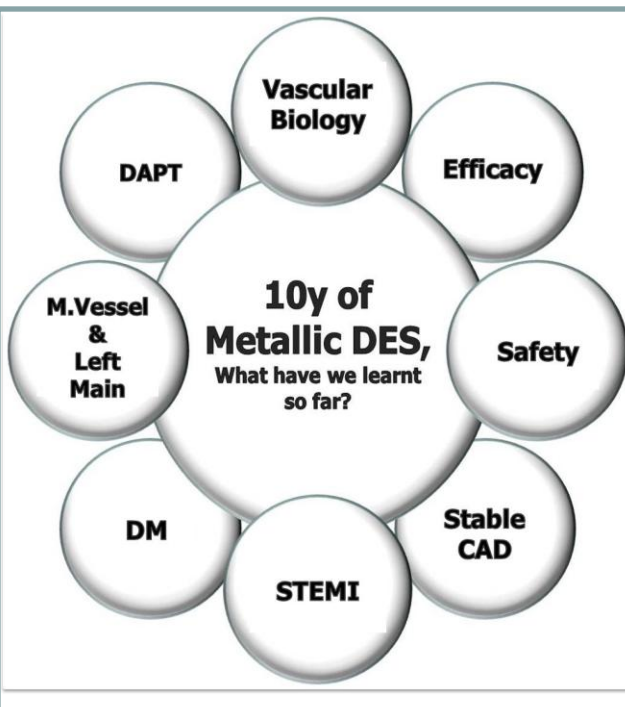
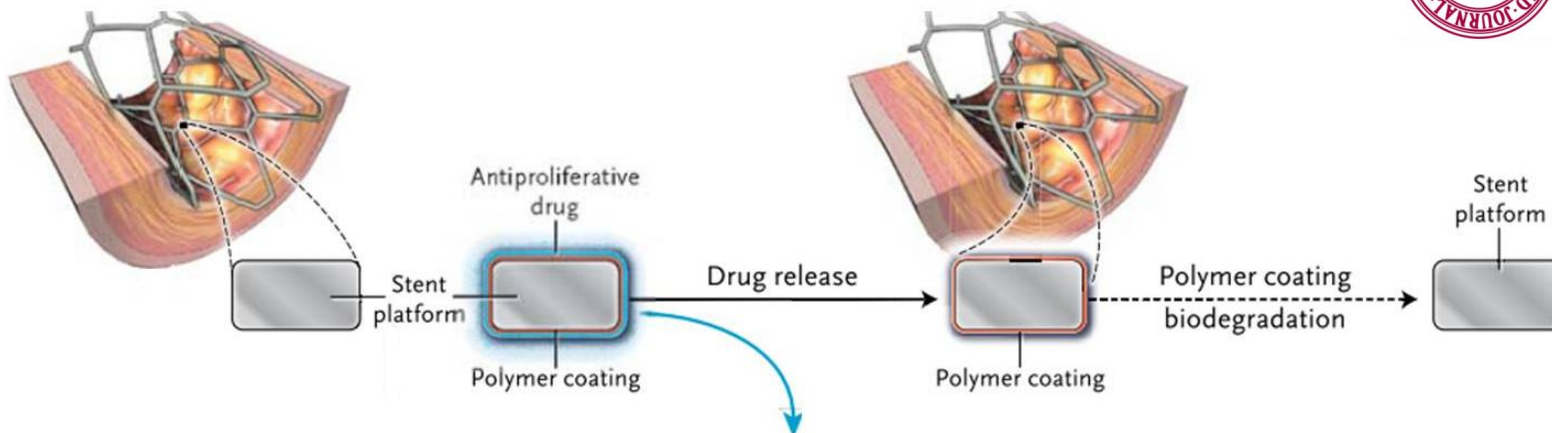
Elizabeth G. Nabel, M.D., and Eugene Braunwald, M.D.

N Engl J Med 2012;366:54-63.



# Drug-Eluting Coronary-Artery Stents

N Engl J Med 2013;368:254-65.

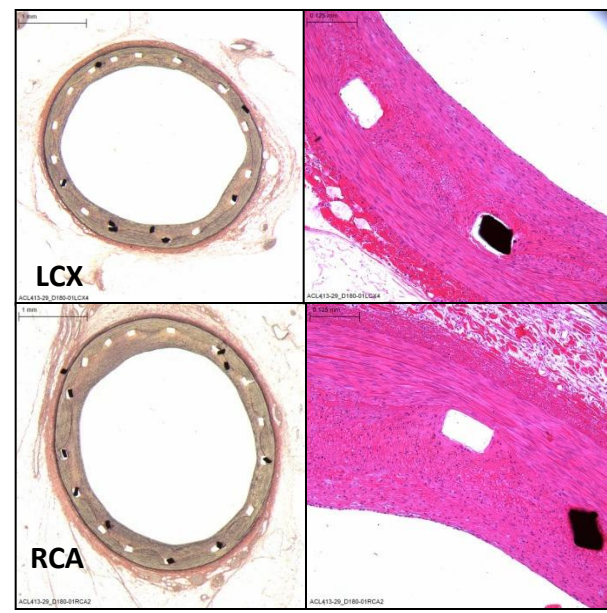
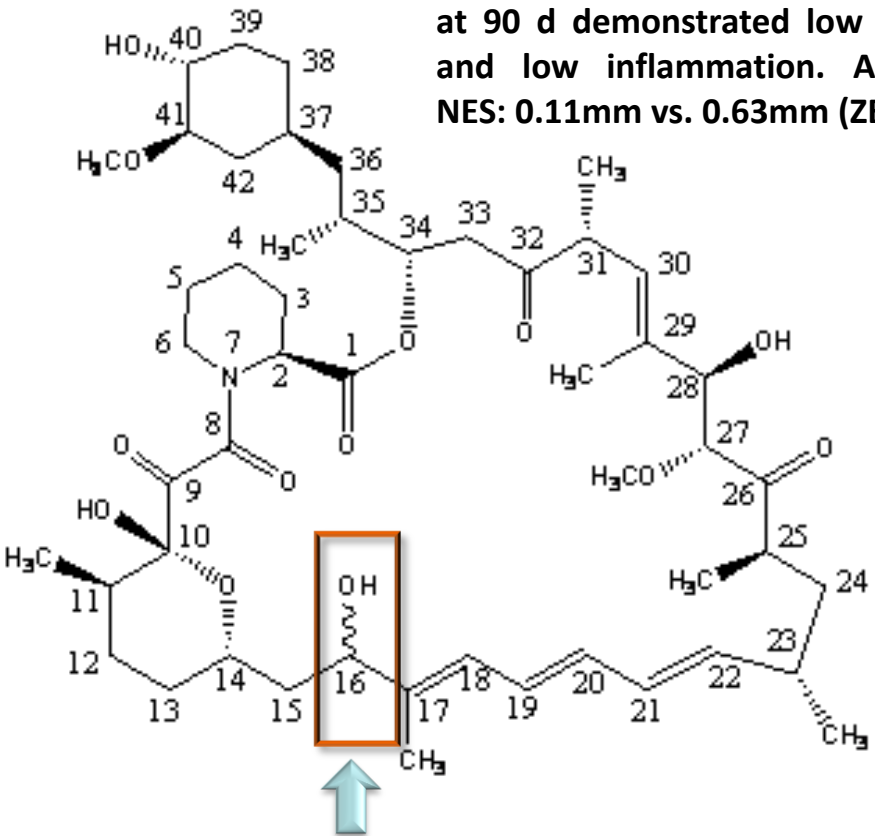




# A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study

Serruys PW. et al. EuroIntervention. 2010; 6; 195-205

2. Histomorphometry and histopathology at 90 d demonstrated low % area stenosis and low inflammation. Angiographic LLL NES: 0.11mm vs. 0.63mm (ZES) ( $p < 0.0001$ )



1. Modification that aims to create a drug with similar efficacy to current agents but requires a lower dose and polymer load.

The purified durable methacrylate polymer controls the elution of Novolimus (a sirolimus analogue), which is produced via removal of a methyl-group from C16, as opposed to modification of C40 on the macrocyclic ring.

**Novel Antiprolif. Drugs**

**10y of Metallic DES,**  
Is there room for further progress?

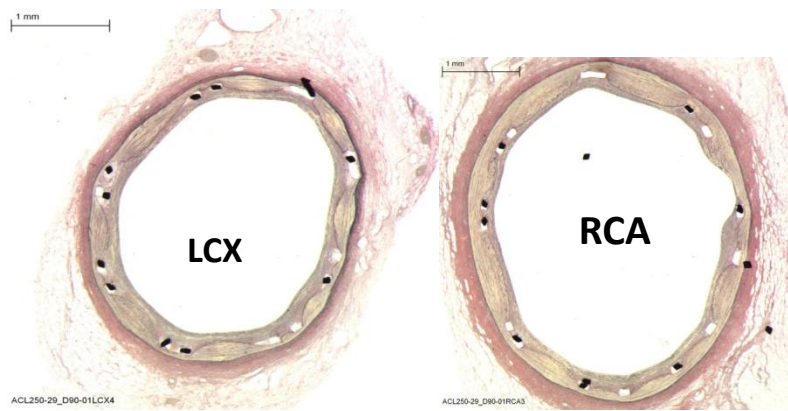
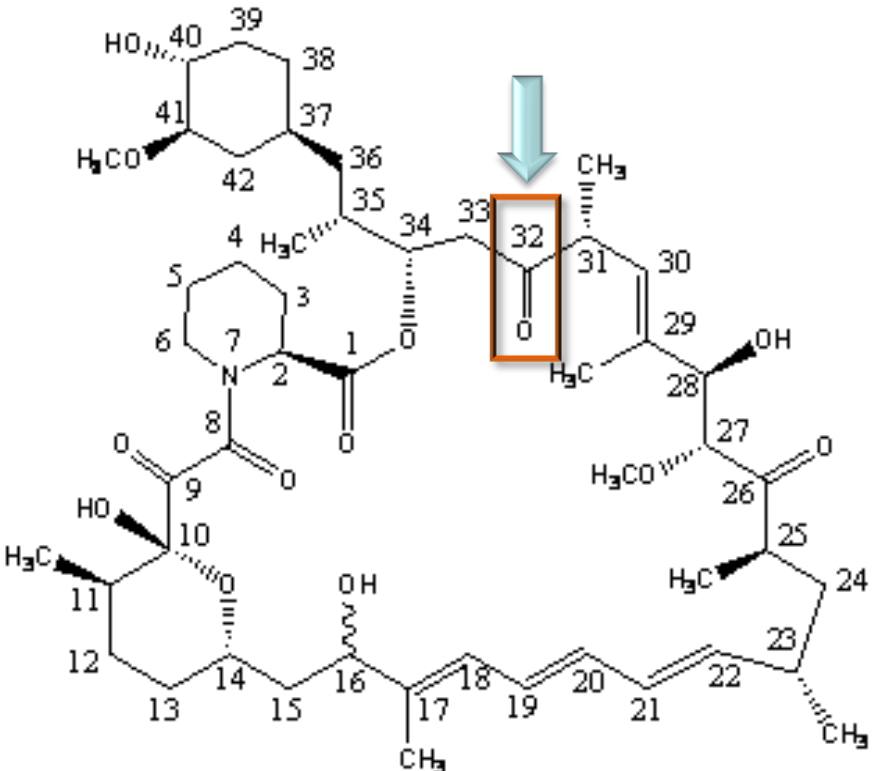


# Multi-center first-in-man study with the lowest known limus dose on the Elixir medical Myolimus™ eluting coronary stent system with a durable polymer: 12-month clinical and six month angiographic and IVUS follow-up

Rutsch W. et al. EuroPCR , abstract, 2010

## 1. Modification that aims to create a drug with similar efficacy to current agents but requires a lower dose and polymer load.

The polylactide polymer coating controls the elution of Myolimus which is produced via **removal of an oxygen from C32**, as opposed to **modification of C40** on the macrocyclic ring.



2. Histomorphometry and histopathology at 90 days demonstrated safety: Low % area stenosis & Low inflammation

3. LLL by quantitative coronary angiography (QCA) at 6m was  $0.15 \pm 0.11 \text{ mm}$ ; IVUS % neointimal volume was  $1.4 \pm 1.2 \text{ mm}^3$  (Comparable to conventional DES)

**Novel Antiprolif. Drugs**

**10y of Metallic DES,**  
Is there room for further progress?

# Selective Drug Delivery

Combo<sup>®</sup> stent (Orbus Neich)

Rapamycin (5  $\mu\text{g}/\text{mm}$ ) applied in biodegradable SynBiosys polymer on the abluminal side

Anti-CD34 surface to promote healing through rapid stent endothelialization.

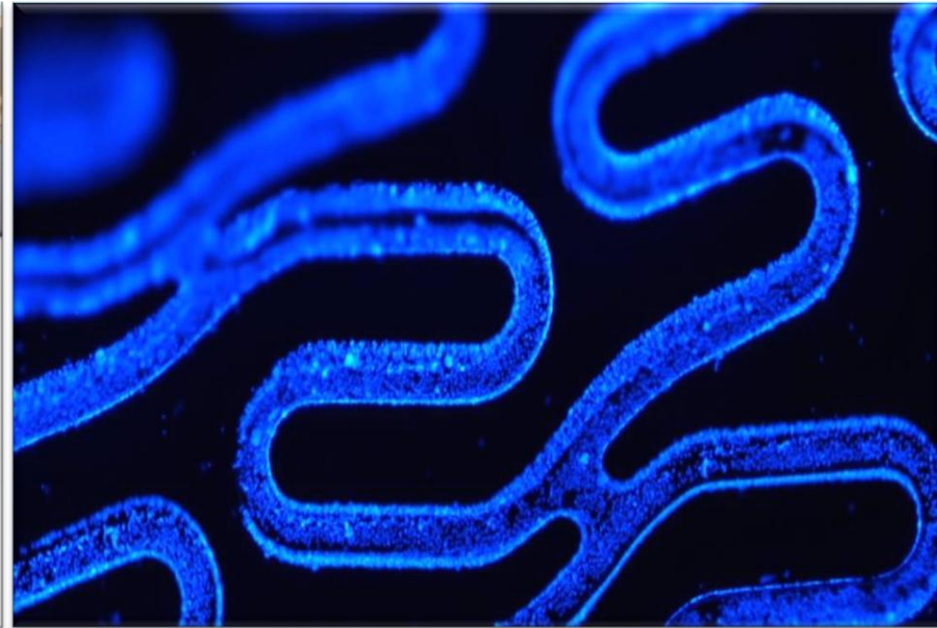
Low dose sirolimus in biodegradable polymer matrix

Abluminal surface

Stent Strut

Luminal surface

Anti CD34 Antibody Coating For EPC Capture



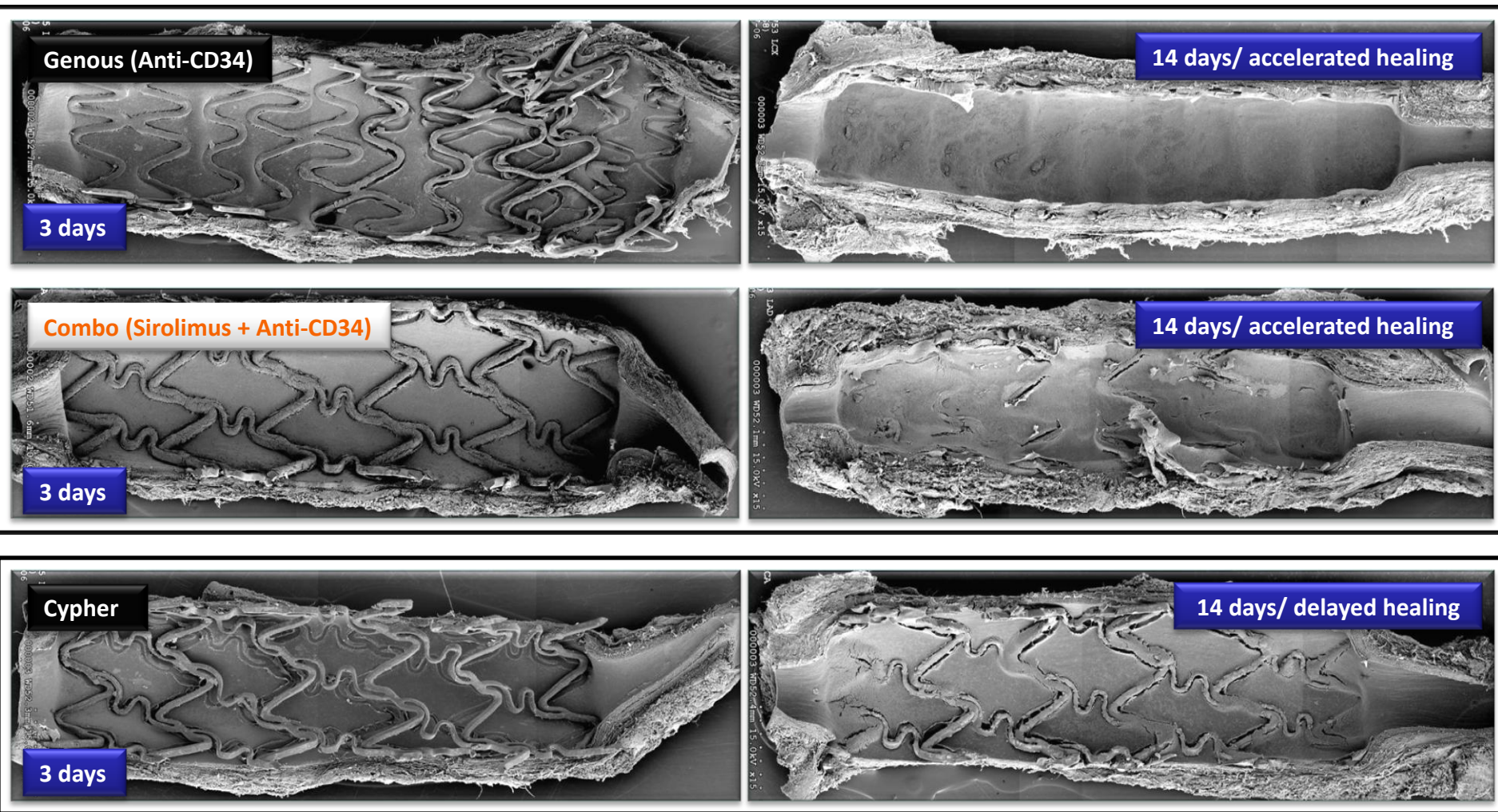
Selective Drug Delivery

10y of Metallic DES,  
Is there room for further progress?

# Development of a Novel Prohealing Stent Designed to Deliver Sirolimus From a Biodegradable Abluminal Matrix

Granada JF et al. Circ Cardiovasc Interv. 2010; 3: 257-66

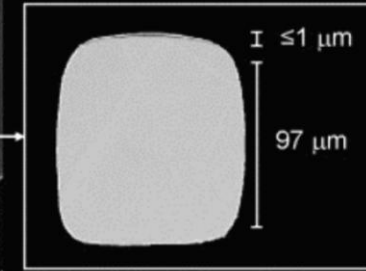
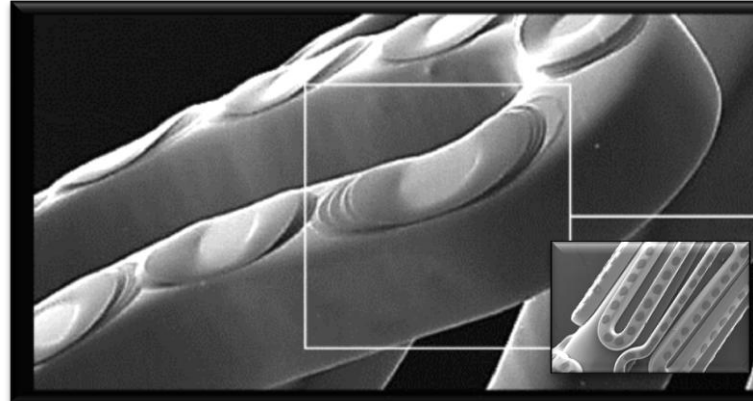
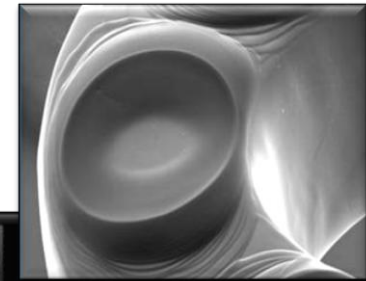
Both optical coherence tomography and histology demonstrate that **Combo stents (anti-CD34 sirolimus-eluting stents)** promote endothelialization while reducing neointimal formation and inflammation.





# Selective Drug Delivery

## JACTAX<sup>®</sup> stent (Boston Scientific)



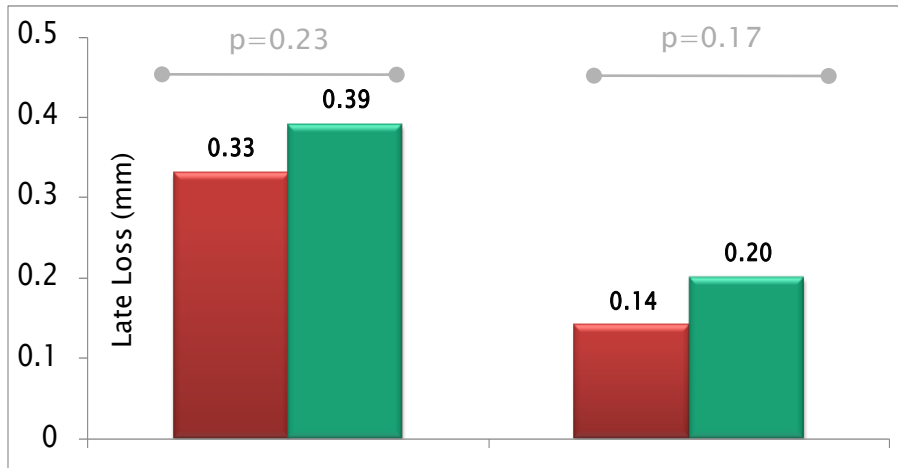
### A Novel Paclitaxel-Eluting Stent With an Ultrathin Abluminal Biodegradable Polymer

#### 9-Month Outcomes With the JACTAX HD Stent

Grube et al. JACC Cardiovasc Interv. 2010; 3:431-8

- Droplets of polymer-drug coating on the abluminal surface of the stent
- Reduced amount of drug and polymer
- BMS surface on three sides after completion of elution and bioresorption of the polymer

JACTAX HD stent (Labcoat Liberté) vs. TAXUS Liberté stent @ 9months



Labcoat Liberté (n=97) Taxus Liberté (n=215)

In-Stent

Labcoat Liberté (n=97) Taxus Liberté (n=215)

In-Segment

Labcoat Liberté (n=97) Taxus Liberté (n=215)

In-Stent

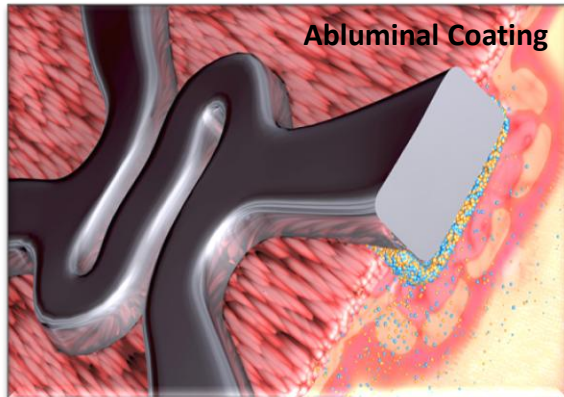
Labcoat Liberté (n=97) Taxus Liberté (n=215)

In-Segment



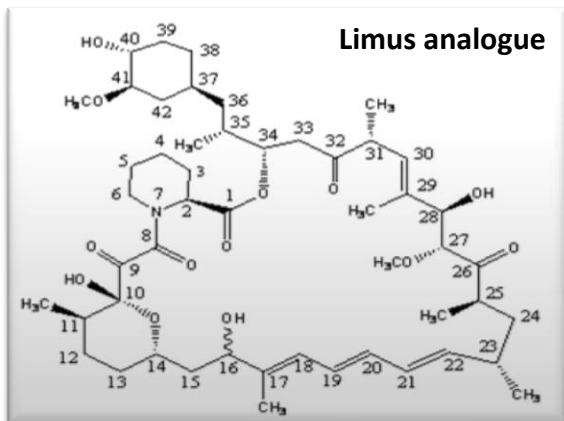
# Biodegradable Polymer DES

## BioMatrix<sup>®</sup> stent (Biosensor)



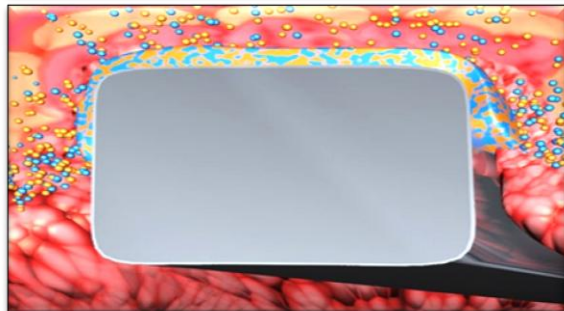
### Biodegradable Coating

- Abluminal Coating
- Controlled Biodegradability
- Precise Drug Release Kinetics
- Simultaneous Polymer Degradation and Drug Release



### Biolimus A9<sup>™</sup> (rapamycin derivative)

- A Potent New “Limus” Designed for Stent Applications
- Powerful anti-proliferative and anti-inflammatory properties
  - Prevents Smooth Muscle Cell Proliferation
- Highly Lipophilic with Optimal Local Tissue Uptake

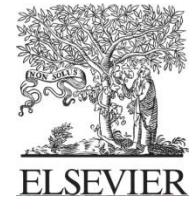


Biodegradable  
Polymer

10y of  
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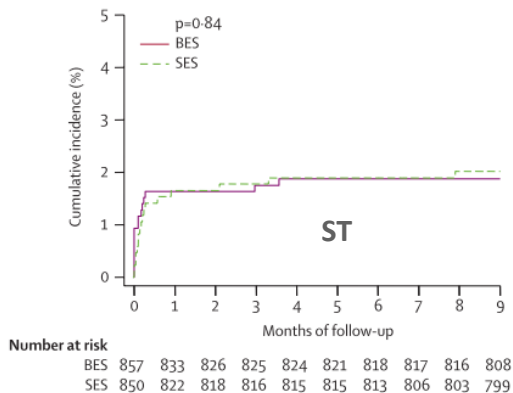
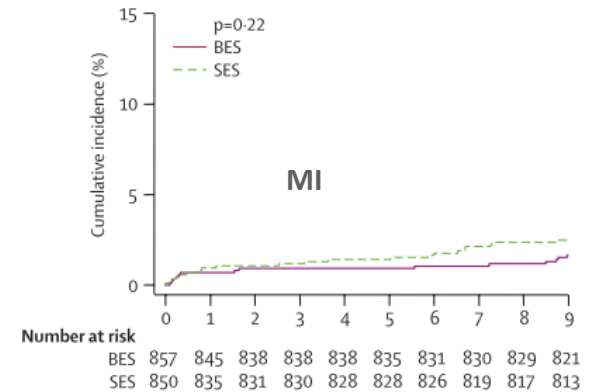
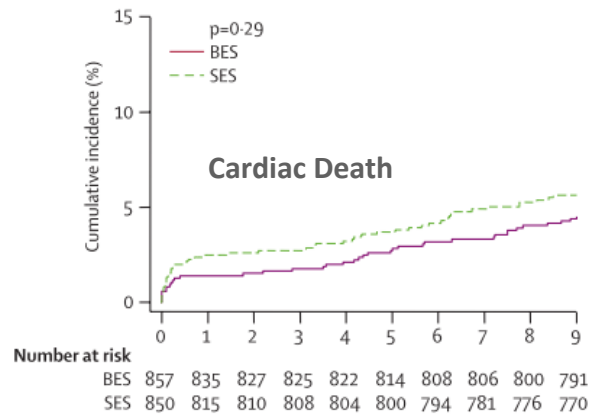
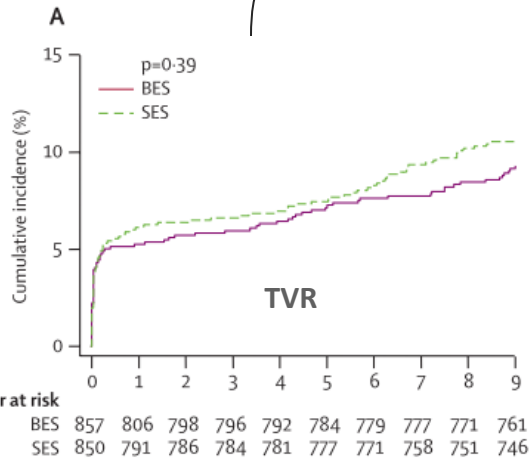
# Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial



Windecker S. et al. Lancet 2008; 372:1163-73

**Interpretation** Our results suggest that a stent eluting biolimus from a biodegradable polymer represents a safe and effective alternative to a stent eluting sirolimus from a durable polymer in patients with chronic stable coronary artery disease or acute coronary syndromes.

All p-values for superiority

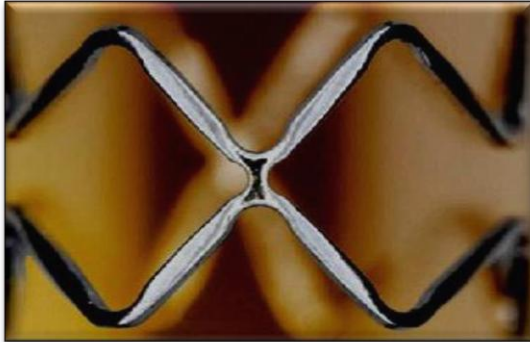


	Biolimus-eluting stent	Sirolimus-eluting stent	Difference	
			Estimate (95% CI)	p value
<b>Late loss (mm)‡</b>				
In-stent	0.13 (0.46)	0.19 (0.50)	-0.05 (-0.14 to 0.05)	0.34
In-segment	0.08 (0.45)	0.15 (0.46)	-0.07 (-0.16 to 0.02)	0.12
<b>Binary restenosis</b>				
In-stent	14/253 (5.5%)	20/231 (8.7%)	3.2 (-1.7 to 7.9)	0.20
In-segment	17/253 (6.7%)	25/231 (10.8%)	4.1 (-1.5 to 9.7)	0.15



# Biodegradable Polymer DES

Nobori<sup>®</sup> stent (TERUMO)

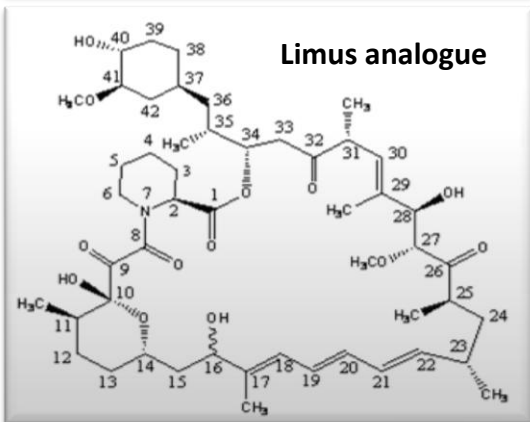


BMS (SUS 316L) Platform



Poly(DL lactic acid) Biodegradable Polymer

- Abluminal Coating
- Controlled Biodegradability
- Precise Drug Release Kinetics
- Simultaneous Polymer Degradation and Drug Release



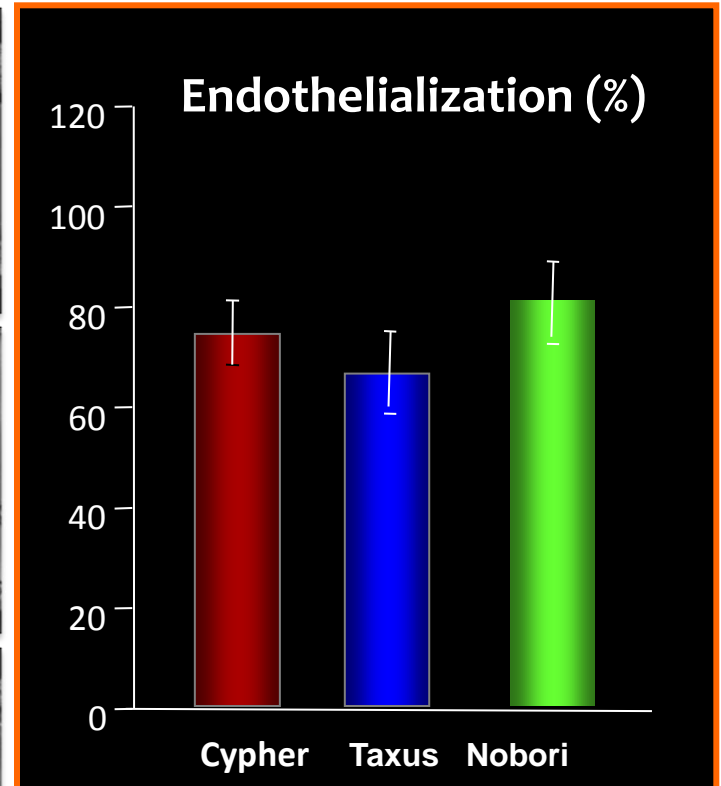
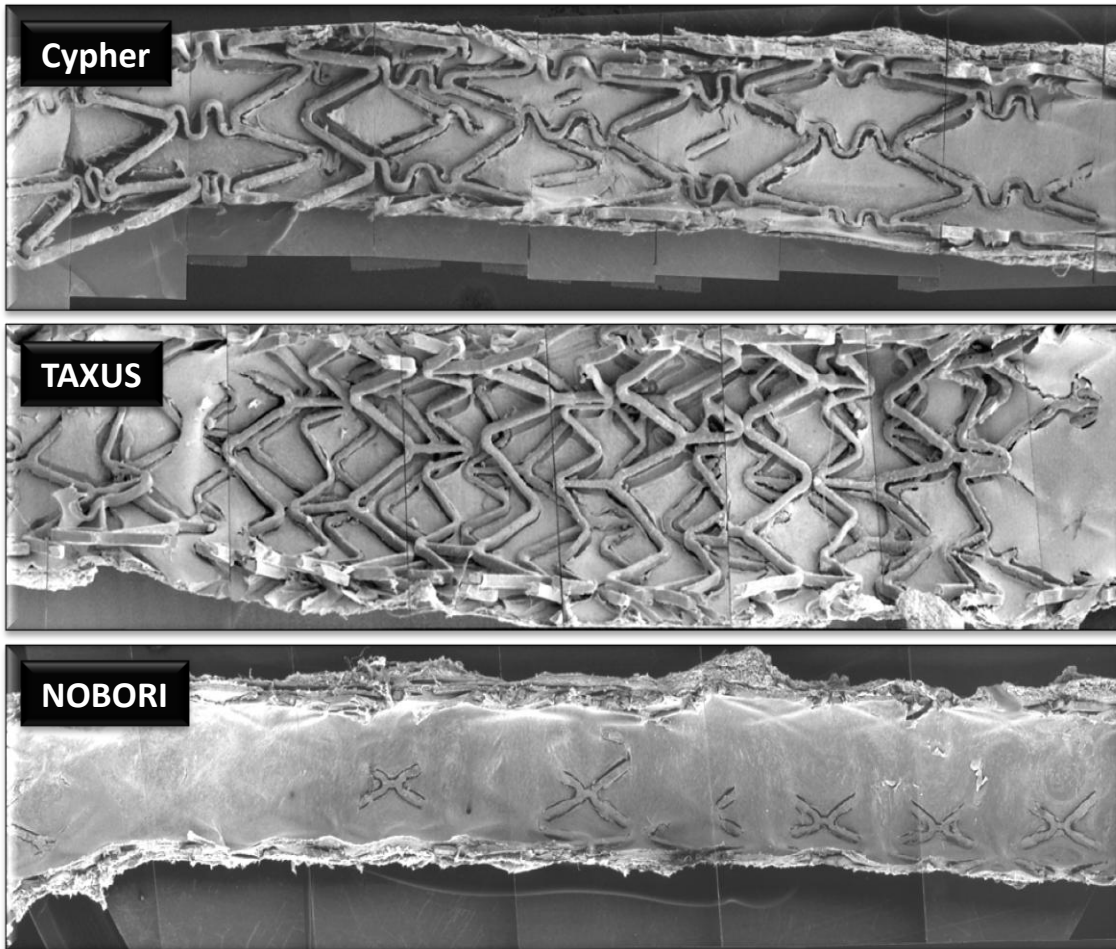
Biolimus A9<sup>™</sup> (rapamycin derivative)

- A Potent New “Limus” Designed for Stent Applications
- Powerful anti-proliferative and anti-inflammatory properties
  - Prevents Smooth Muscle Cell Proliferation
- Highly Lipophilic with Optimal Local Tissue Uptake

# Biodegradable Polymer DES

## Nobori<sup>®</sup> stent (TERUMO)

### Comparison of Various overlapped DES in Rabbit Iliac Arteries at 28-days



Finn A, et al. Circulation 2005

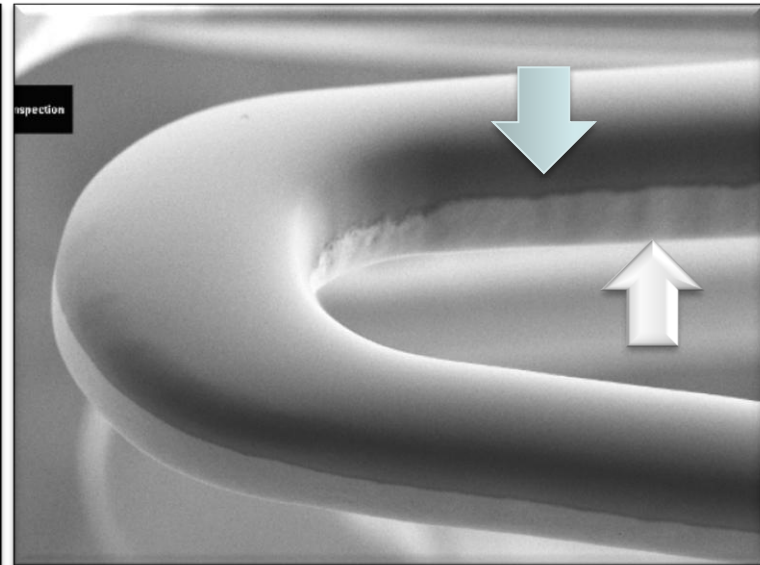
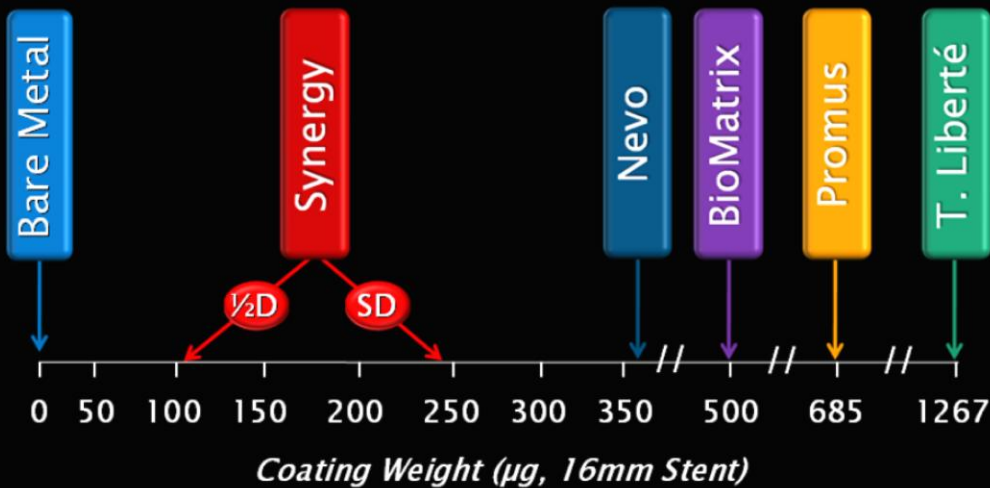
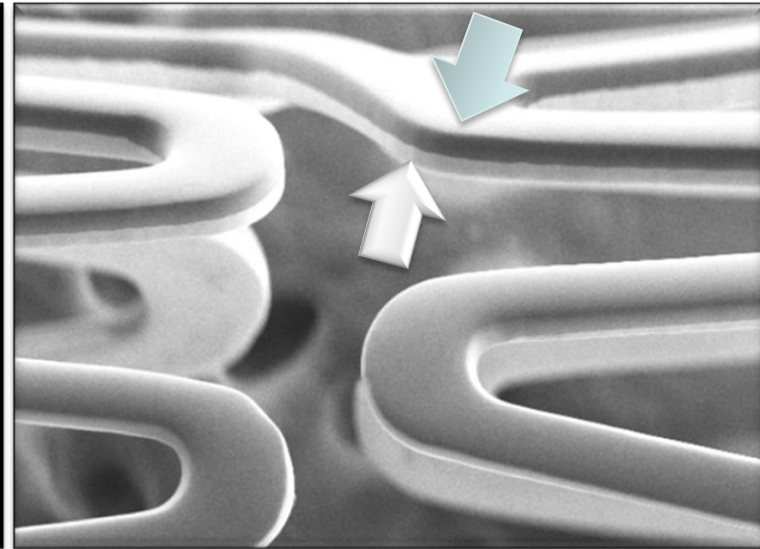
**Bio  
degradable  
Polymer**

**10y of  
Metallic  
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Is there room  
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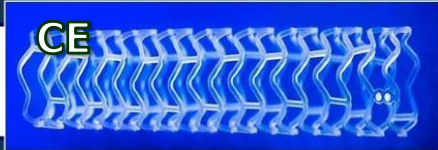



# Biodegradable Ultrathin Polymer DES

## Synergy<sup>®</sup> stent (Boston Scientific)

- Bioerodable polymer is only applied at the abluminal surface of the stent
- Maximum coating thickness 3 $\mu$ m (low dose) and 4 $\mu$ m (high dose) (Ultrathin coating)



# Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds

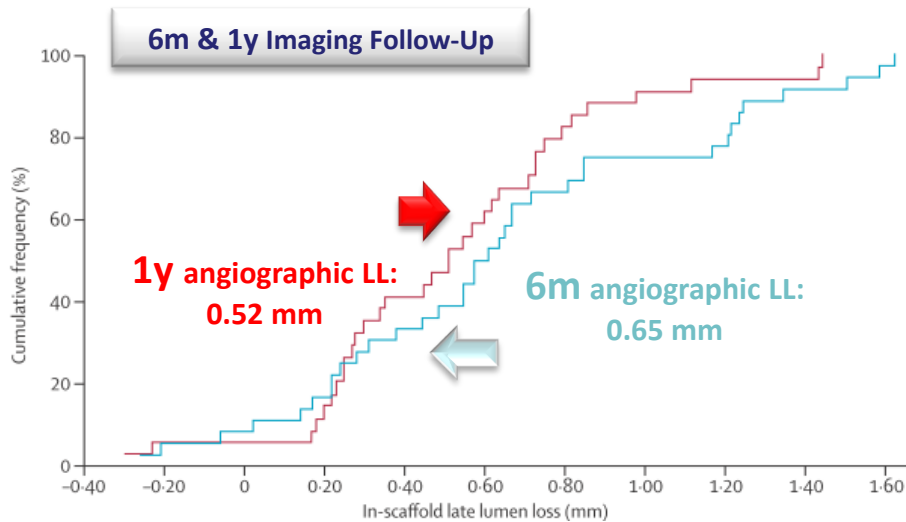
Company / Device	Design of the bioresorbable device	Strut thickness, ( $\mu$ m)	Polymer / Drug	Absorption time	Late loss, (mm)
Kyoto Medical / Igaki-Tamai		170	PLLA	2 years (y)	0.48 (6 m)
Biotronik / DREAMS		125	Mg alloy (AMS-4) / sirolimus	4 to 6 months (m)	0.68 (6 m)
Abbott / ABSORB BVS*		150	PLLA/ everolimus	2 y	0.19 (6 m)
Reva Medical / ReSolve		200	Tyrosine poly carbonate with iodine / sirolimus abluminal	2 y	1.81 (6 m)
- / BTI		200	Salicylic acid into polymer (PLA or adipic acid)/ sirolimus	6 m	NA
Elixir / DESolve		150	PLLA/ novolimus	1 to 2 y	0.19 (6m)

# Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds

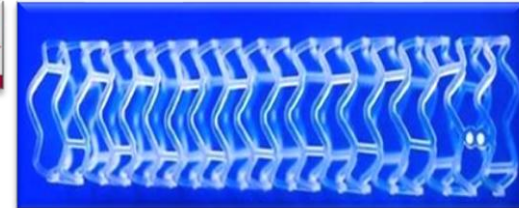


Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial

Haude M. et al. Lancet. 2013, Jan 14 [Epub ahead of print]

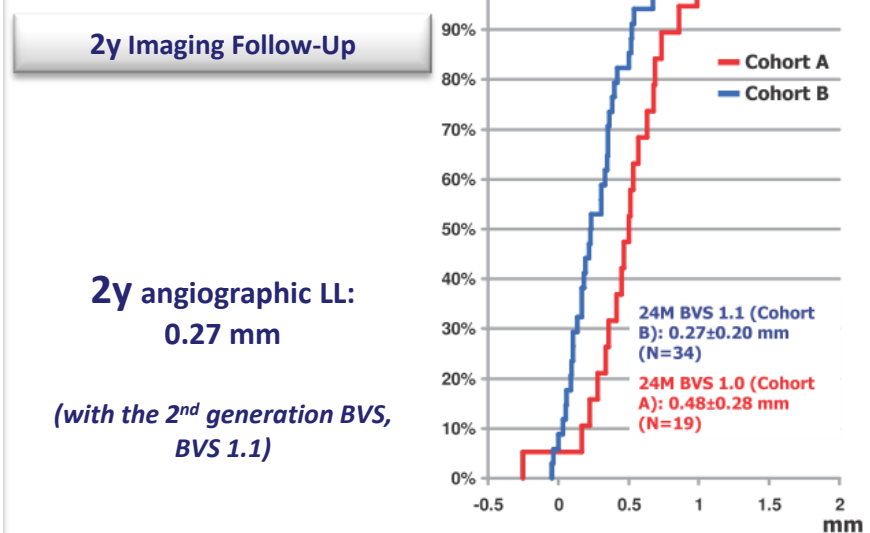


**Interpretation** Our results show feasibility, a good safety profile, and promising clinical and angiographic performance results up to 12 months for DREAMS. Our promising clinical results show that absorbable metal scaffolds might be an alternative to polymeric absorbable scaffolds.



First Serial Assessment at 6 Months and 2 Years of the Second Generation of Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold  
A Multi-Imaging Modality Study

Ormiston J. et al. Circ Cardiovasc Interv. 2012; 5: 620-632

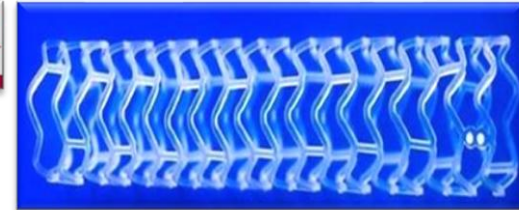




# Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds



Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial



First Serial Assessment at 6 Months and 2 Years of the Second Generation of Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold  
A Multi-Imaging Modality Study

**There is still a lot of work to be done for further improvement of these promising technologies.**

**The main *Question* that has to be answered:**

**Why shall we use a device with triple the cost of a metallic DES if there is no superiority in terms of strong end points?**

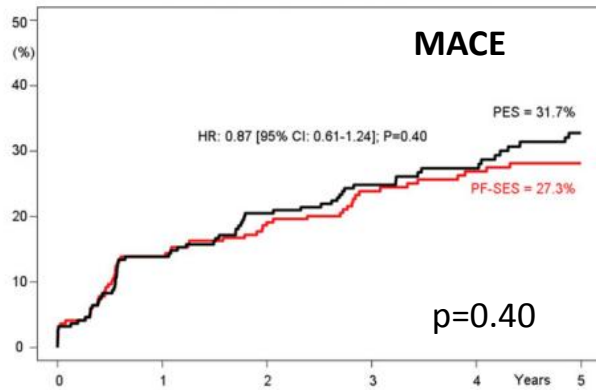
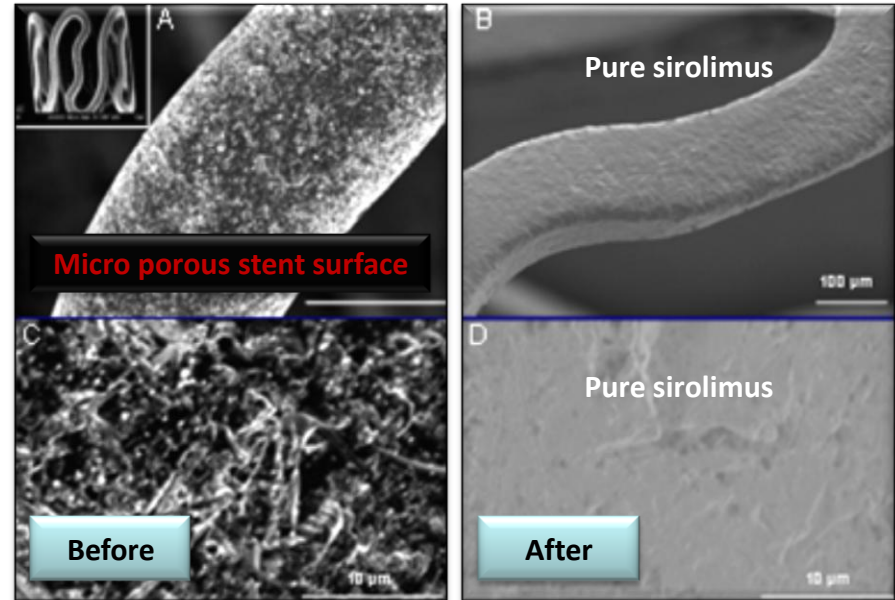
**Hopefully future randomized trials will answer this Q....**

# Polymer free (PF) DES YUKON CHOICE<sup>®</sup> stent (Translumina)

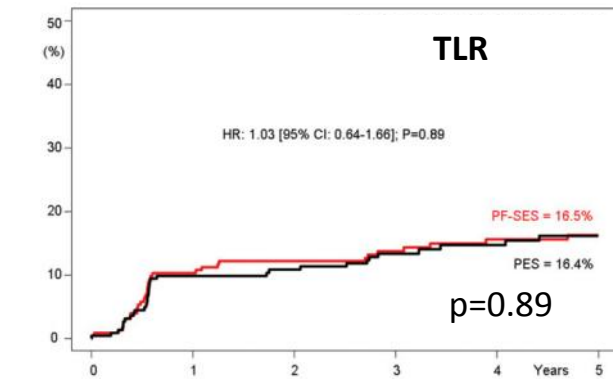


**Five-Year Clinical Outcomes of a Polymer-Free Sirolimus-Eluting Stent Versus a Permanent Polymer Paclitaxel-Eluting Stent: Final Results of the Intracoronary Stenting and Angiographic Restenosis – Test Equivalence Between Two Drug-Eluting Stents (ISAR-TEST) Trial**

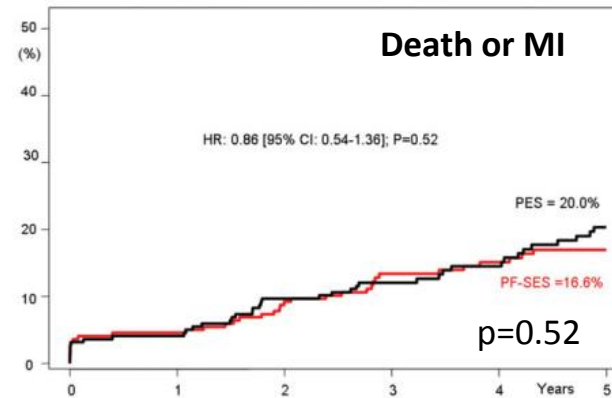
King L. et al. Cath Card Interv. 2013, E 23-28



PF-SES	225	188	177	132	123	114
PES	225	190	174	139	116	99



PF-SES	225	192	182	138	129	119
PES	225	195	180	145	123	104



PF-SES	225	208	198	151	144	133
PES	225	210	196	163	139	119

Overall there was no signif. difference in clinical outcomes between PF SES and PES at 5 years. This supports the durability and efficacy of PF DES.

# Reducing strut thickness... What have we achieved?

	BioMime	XIENCE PRIME	ENDEAVOR RESOLUTE	TAXUS Liberte	CYPHER
<b>Mitsu</b>					
<b>Strut Thickness:</b>	<b>Strut Thickness:</b>	<b>Strut Thickness:</b>	<b>Strut Thickness:</b>	<b>Strut Thickness:</b>	<b>Strut Thickness:</b>
40 $\mu\text{m}$	65 $\mu\text{m}$	81 $\mu\text{m}$	91 $\mu\text{m}$	97 $\mu\text{m}$	140 $\mu\text{m}$
<b>Alloy:</b>	<b>Alloy:</b>	<b>Alloy:</b>	<b>Alloy:</b>	<b>Alloy:</b>	<b>Alloy:</b>
Cobalt Chromium	Cobalt Chromium	Cobalt Chromium	Cobalt Nickel	316L Stainless Steel	316L Stainless Steel
<b>Polymer Thickness:</b>	<b>Polymer Thickness:</b>	<b>Polymer Thickness:</b>	<b>Polymer Thickness:</b>	<b>Polymer Thickness:</b>	<b>Polymer Thickness:</b>
<2 $\mu\text{m}$	2 $\mu\text{m}$	7.8 $\mu\text{m}$	6.2 $\mu\text{m}$	17.8 $\mu\text{m}$	12.6 $\mu\text{m}$

# Future Progress for DES :

Deliverable, Visible,  
Trackable,  
Conformable device



## Reduced Polymer Load

- Abluminal polymer
- Bioerodable polymer
- No polymer

No stent thrombosis,  
BMS like



## Reduced Drug Load

Shortened DAPT  
requirement



## Stent Delivery System

- Stent material
- Thinner struts
- Stent geometry
- Surface coating

Low TLR, Low clinical  
symptom recurrence



**...and there is still room for  
Future progress & Innovation**