TCTAP 2014, Main Session IV, Main Arena,

Seoul, Korea, April 23, 2014

What is the Future of Coronary Stenting?

Spencer B. King III, M.D., M.A.C.C., F.E.S.C.

Andreas Gruentzig Cardiovascular Center

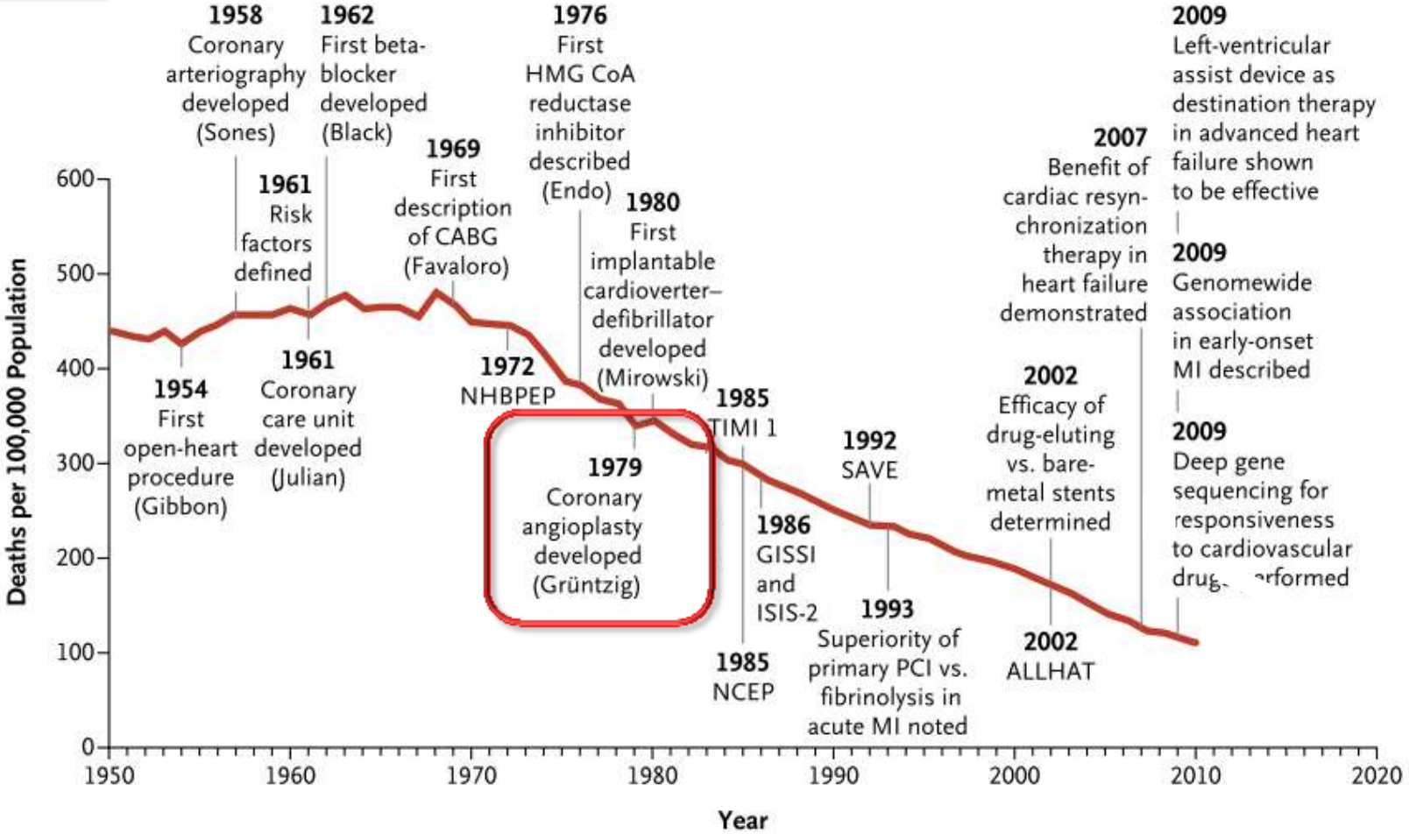
Professor of Medicine, Emeritus

Emory University

Atlanta

A Tale of Coronary Artery Disease and Myocardial Infarction

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



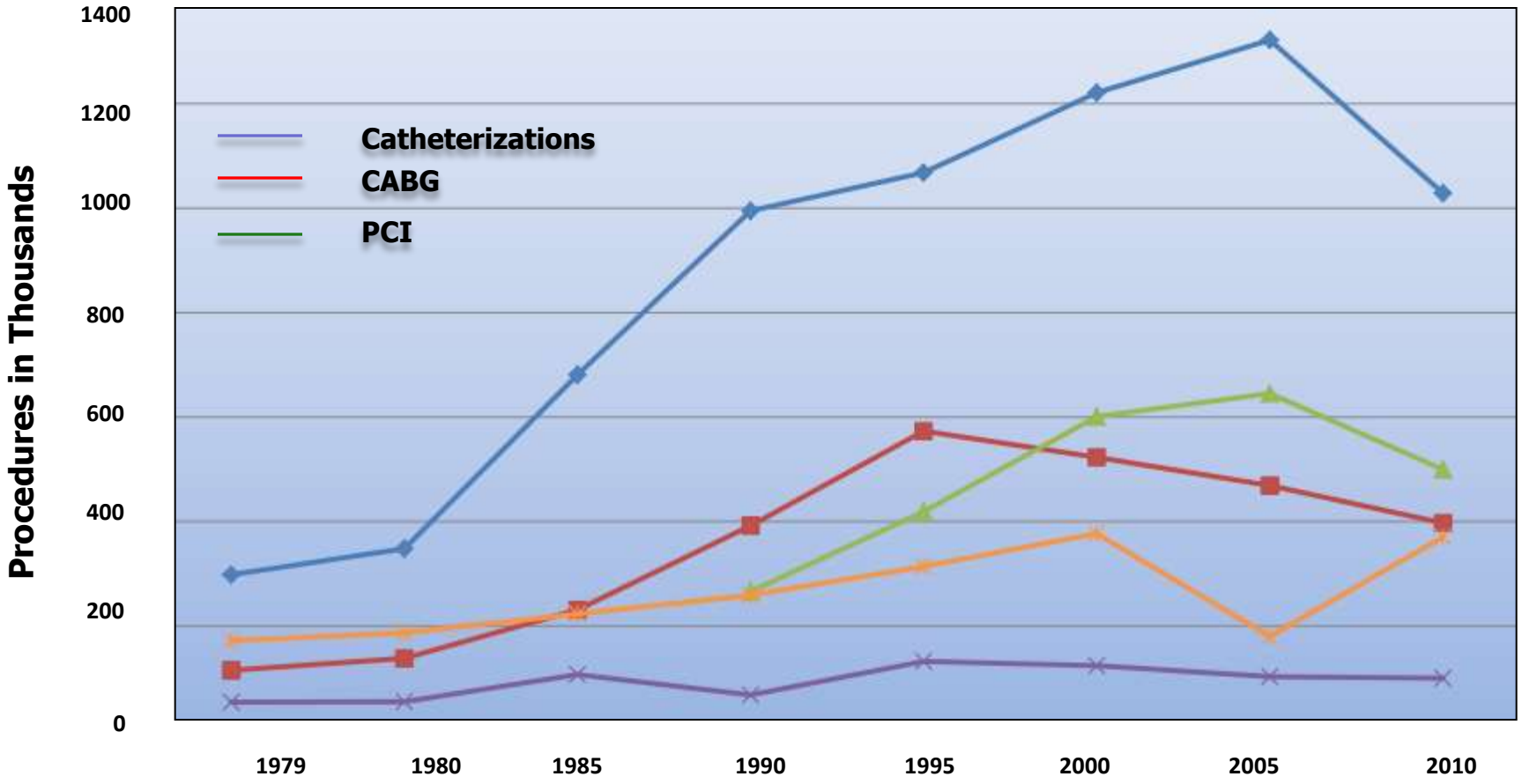
Circulation

Heart Disease and Stroke Statistics—2013 Update

A Report From the American Heart Association

rican Heart Association
Learn and Live

Trends in Cardiovascular Procedures, United States of America: 1979 to 2010



Go AS et al. Circulation 2013; 127:e6-e245

What are the major problems with DES?

- **In-segment Restenosis,**
  - although dramatically reduced with newer generation DES still remains an issue, (especially in complex lesions and specific clinical subsets)
- **Stent Thrombosis,**
  - although reduced with newer generation DES, still remains an issue

Where are we going with-

- **Technology**
- **Clinical Application**
- **Industry**

Patterns of Vascular Responses after PCI

Angiographic Patterns of In-Stent Restenosis
Classification and Implications for Long-Term Outcome

Mehran R. et al. Circulation 1999; 100(18): 1872-8

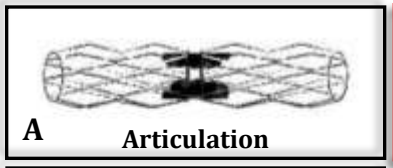
Circulation

American Heart Association. Learn and Live.

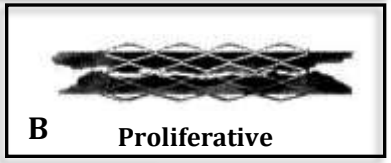
Patterns of restenosis after drug-eluting stent implantation: insights from a contemporary and comparative analysis of sirolimus- and paclitaxel-eluting stents

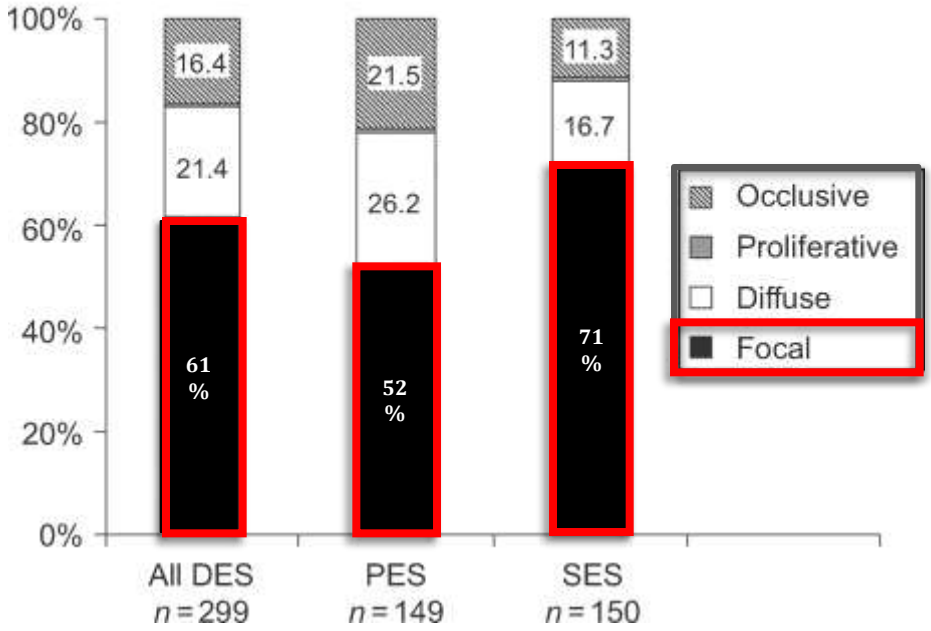
Corbett SJ. et al. Eur Heart J. 2006; 27 (19): 2330-7

Focal pattern of in-stent restenosis



Diffuse pattern of in-stent restenosis



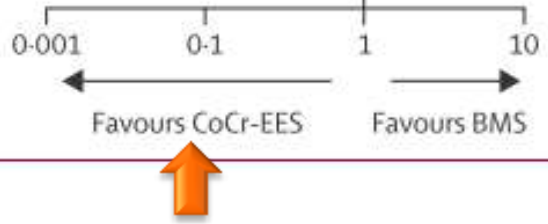


Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

Lancet 2012; 379: 1393–402

49 RCT with > 50.000 pt.
2nd generation CoCr EES emerged as the device with the lowest rate of ST compared with BMS or other DES

	log (odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
(A) Definite thrombosis				
Direct estimate	−1·427	0·519	32·4%	0·24 (0·09–0·66)
Indirect estimate	−1·421	0·359	67·6%	0·24 (0·12–0·49)
Total (95% CI)			**100·00%**	**0·24 (0·14–0·43)**
Test for overall effect Z=4·82 (p<0·00001)				
(B) Definite or probable thrombosis				
Direct estimate	−0·968	0·377	39·4%	0·38 (0·18–0·80)
Indirect estimate	−1·122	0·304	60·6%	0·33 (0·18–0·59)
Total (95% CI)			**100·00%**	**0·35 (0·22–0·55)**
Test for overall effect Z=4·48 (p<0·00001)				



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Total (95% CI)			**100·00%**	**0·24 (0·14–0·43)**
Test for overall effect Z=4·82 (p<0·00001)				

The risk of ST (ARC criteria) has been reduced but not eliminated…

0·001 0·1 1 10

Favours CoCr-EES Favours BMS

Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

Sarno G. et al. Eur Heart J. 2013;127:e6-e245

EUROPEAN SOCIETY OF CARDIOLOGY

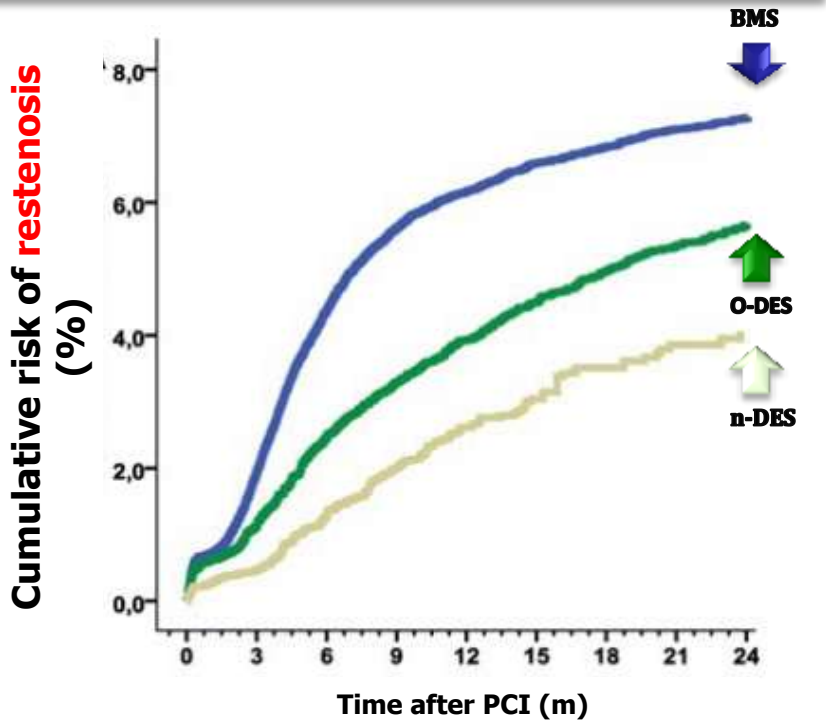
94.384 stent implantations/ BMS: 64.631, o-DES: 19.2012, n-DES: 10.551

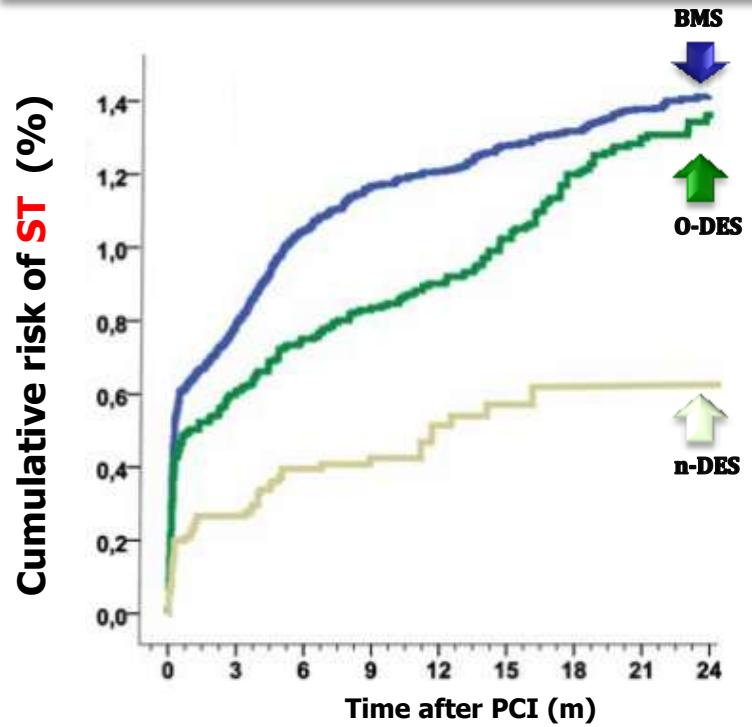
Older generation DES (o-DES):

Cypher and Cypher Select
Taxus Express,Taxus Liberte´ &
Endeavor

Newer generation DES (n-DES):

Endeavor Resolute
Xience V, Xience Prime &
Promus, Promus Element





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Taxus Express,Taxus Liberte´ &
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Newer generation DES (n-DES):

Endeavor Resolute
Xience V, Xience Prime &
Promus, Promus Element

PCI with n-DES was associated with:

38% lower risk of clinically meaningful restenosis,

43% lower risk of definite ST,

in this observational study from a large real-world population.

The risk has been reduced but not eliminated…

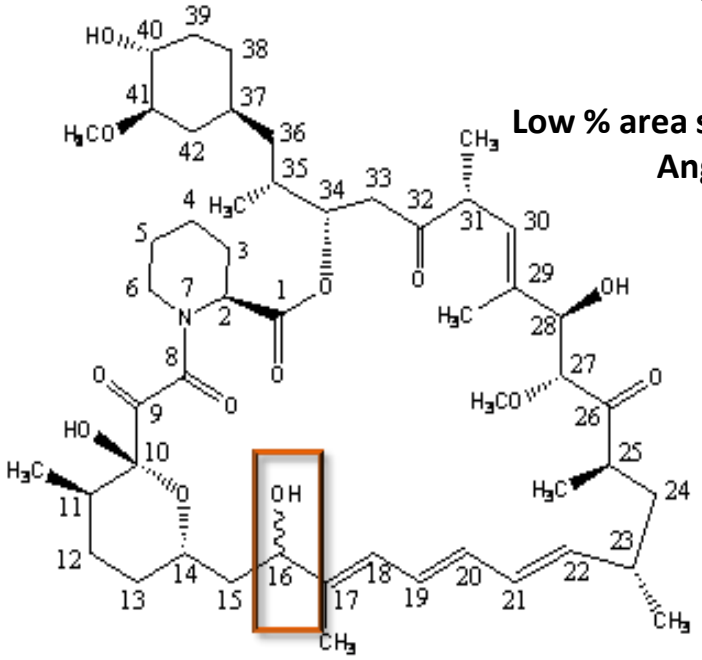
Where are we going with Technology?

- **Drug**
  - Novel Antiproliferative Drugs
- **Polymer**
  - Bioresorbable polymer
  - Polymer composition
  - No polymer
- **Selective Drug Delivery**
  - Abluminal Coating
- **Alloy**
  - Metallic, Durable
  - Metallic, Bioresorbable
  - Polymeric, Bioresorbable
- **Alloy Design**
  - Longitudinal Integrity
  - Strut Cross Linkage
- **Strut Design and Thickness**
  - Open/Closed cells
  - Hybrid cells
  - Thinner struts
  - Mesh covered struts
- **Dedicated Stents**
  - Bifurcation stenting

Novel Antiproliferative Agents: Novolimus

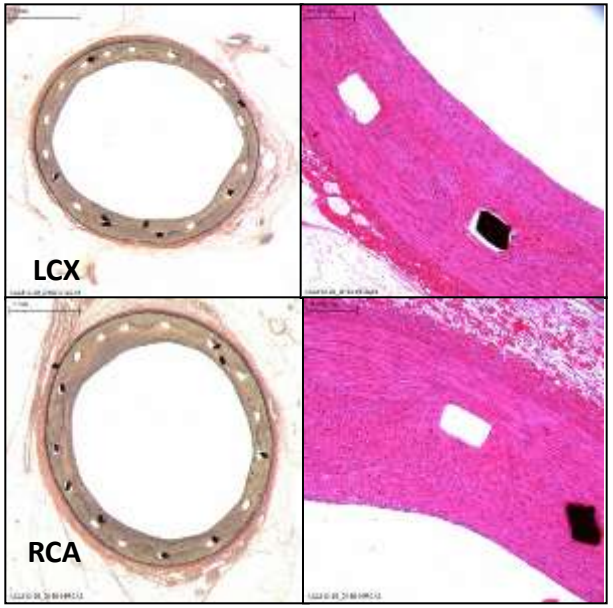
A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study

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



2. Histomorphometry and histopathology at 90 d:

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 with 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.

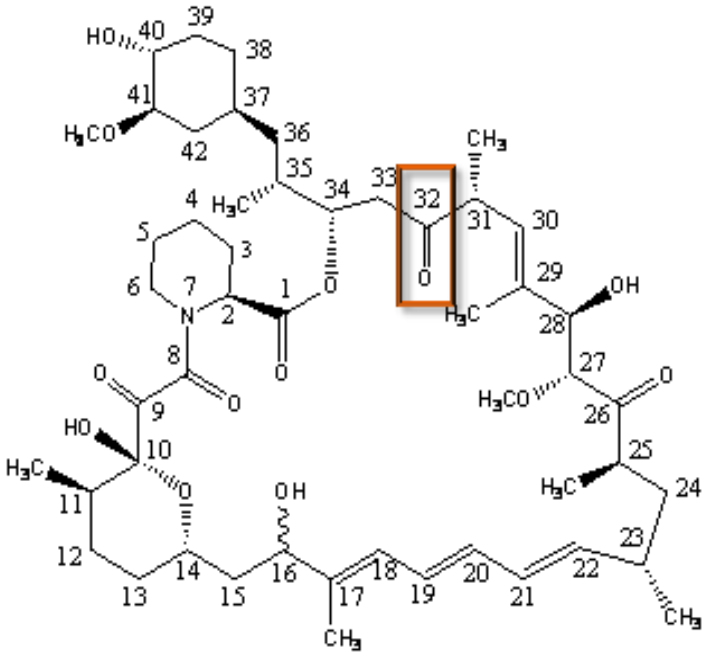
Novel Antiproliferative Agents: Myolimus

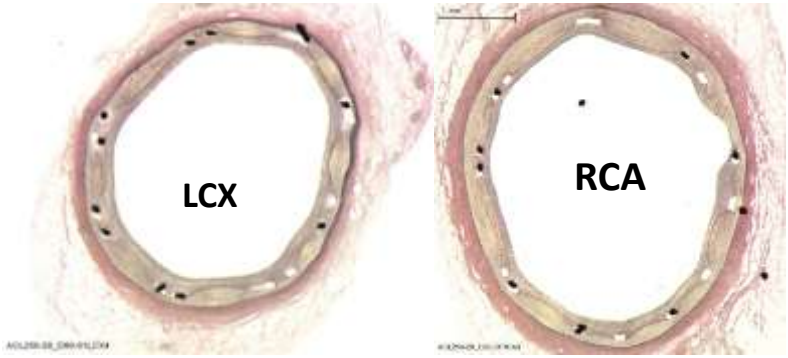
Multi-center first-in-man study with the lowest known limus dose on the Elixir medical Myolimus™ eluting coronary stent system with a durable polymer: 12-month clinical and six month angiographic and IVUS follow-up

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.





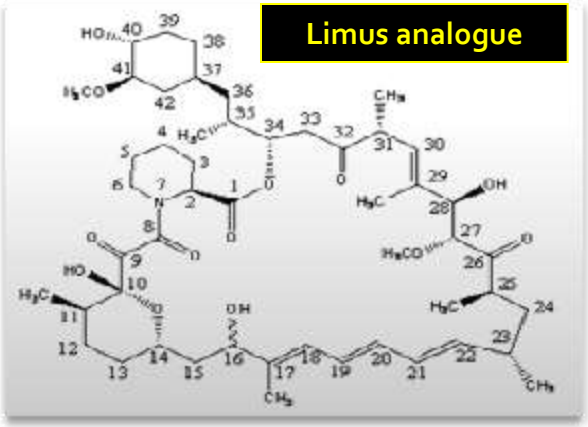
2. **Histomorphometry and histopathology at 90 days demonstrated safety:**
   Low % area stenosis & Low inflammation

3. **LLL by quantitative coronary angiography at 6m was 0.15±0.11mm; IVUS % neointimal volume was 1.4±1.2mm³**

Biodegradable Polymer DES
BioMatrix® stent (Biosensor)

Biodegradable Coating

1. Abluminal Coating
2. Controlled Biodegradability
3. Precise Drug Release Kinetics
4. Simultaneous Polymer Degradation and Drug Release



Biolimus A9™ (rapamycin derivative)

1. A Potent New "Limus" Designed for Stent Applications
2. Powerful anti-proliferative & anti-inflammatory properties
3. Prevents Smooth Muscle Cell Proliferation
4. Highly Lipophilic with Optimal Local Tissue Uptake

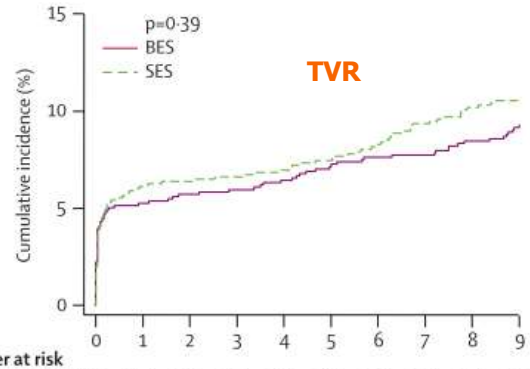
Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial

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

ELSEVIER

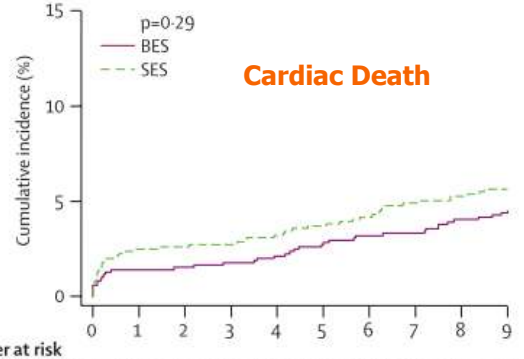
Interpretation Our results suggest that a stent eluting biolimus from a biodegradable polymer represents a safe and effective alternative to a stent eluting sirolimus from a durable polymer in patients with chronic stable coronary artery disease or acute coronary syndromes.

A



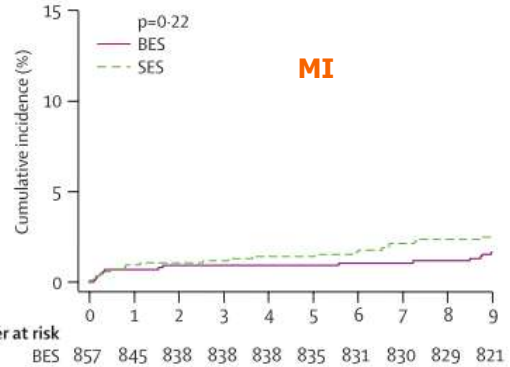
Number at risk

BES	857	806	798	796	792	784	779	777	771	761
SES	850	791	786	784	781	777	771	758	751	746



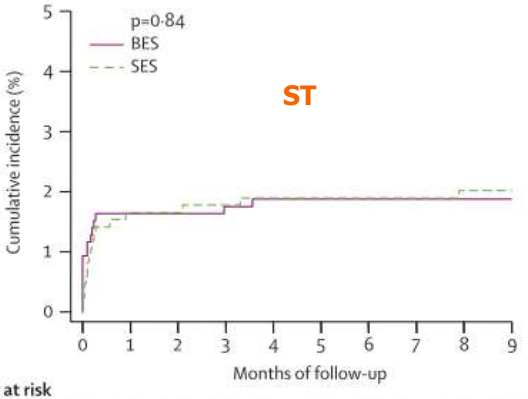
Number at risk

BES	857	835	827	825	822	814	808	806	800	791
SES	850	815	810	808	804	800	794	781	776	770



Number at risk

BES	857	845	838	838	838	835	831	830	829	821
SES	850	835	831	830	828	828	826	819	817	813



Number at risk

BES	857	833	826	825	824	821	818	817	816	808
SES	850	822	818	816	815	815	813	806	803	799

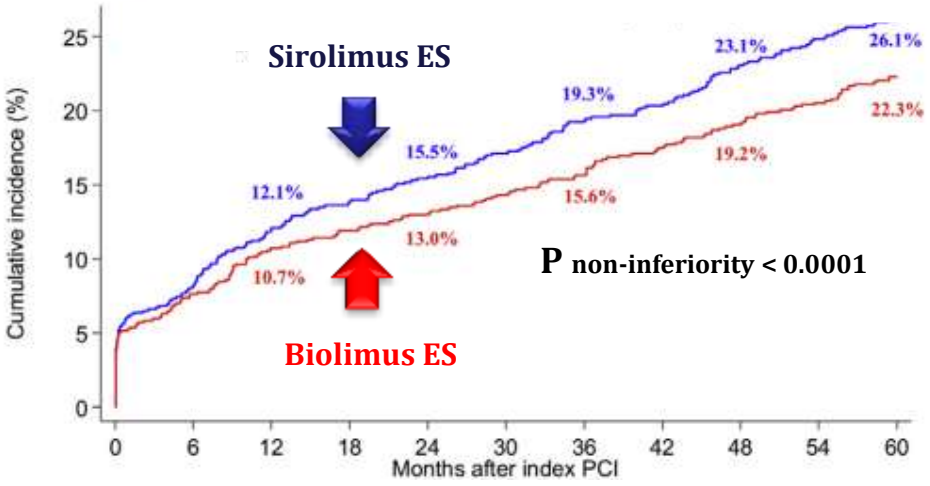
	Biolimus-eluting stent	Sirolimus-eluting stent	Difference	
			Estimate (95% CI)	p value
Late loss (mm)‡				
In-stent	0·13 (0·46)	0·19 (0·50)	−0·05 (−0·14 to 0·05)	0·34
In-segment	0·08 (0·45)	0·15 (0·46)	−0·07 (−0·16 to 0·02)	0·12
Binary restenosis				
In-stent	14/253 (5·5%)	20/231 (8·7%)	3·2 (−1·7 to 7·9)	0·20
In-segment	17/253 (6·7%)	25/231 (10·8%)	4·1 (−1·5 to 9·7)	0·15

Improved Safety and Reduction in Stent Thrombosis Associated With Biodegradable Polymer-Based Biolimus-Eluting Stents Versus Durable Polymer-Based Sirolimus-Eluting Stents in Patients With Coronary Artery Disease

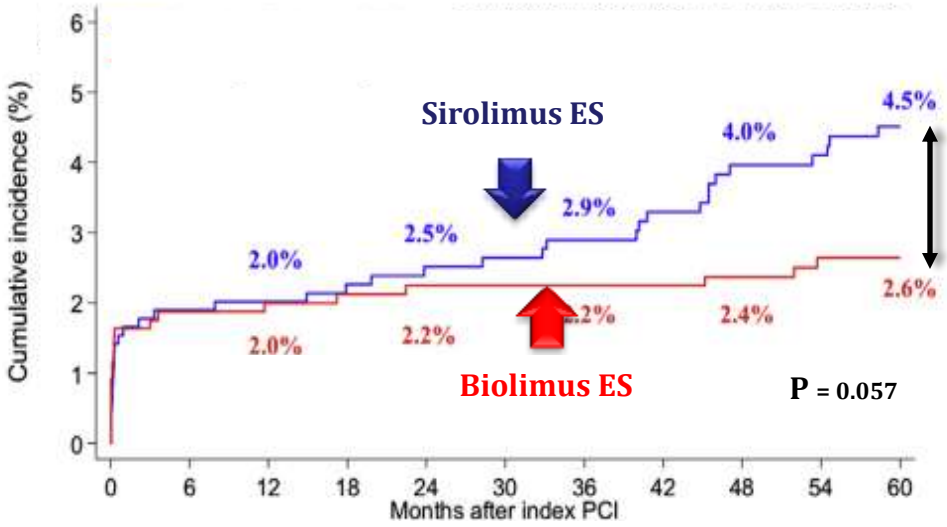
Final 5-Year Report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) Randomized, Noninferiority Trial

Serruys PW. et al. JACC Interv. 2013; 777-89

All cause Death, any MI, All cause revascularisation



Definite Stent Thrombosis (ARC criteria)



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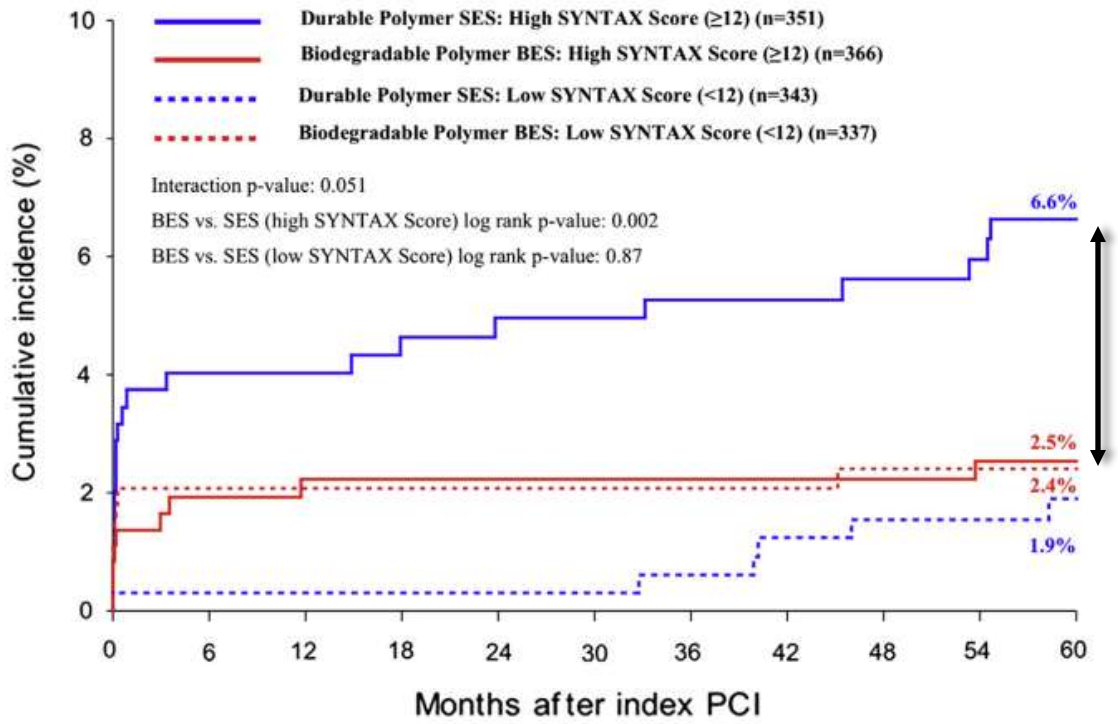
The 5-Year Time-to-Event Analyses for Definite Stent Thrombosis Stratified by Complexity of Coronary Artery Disease

High SYNTAX Score >12

Low SYNTAX Score <12



Sx Score>12:

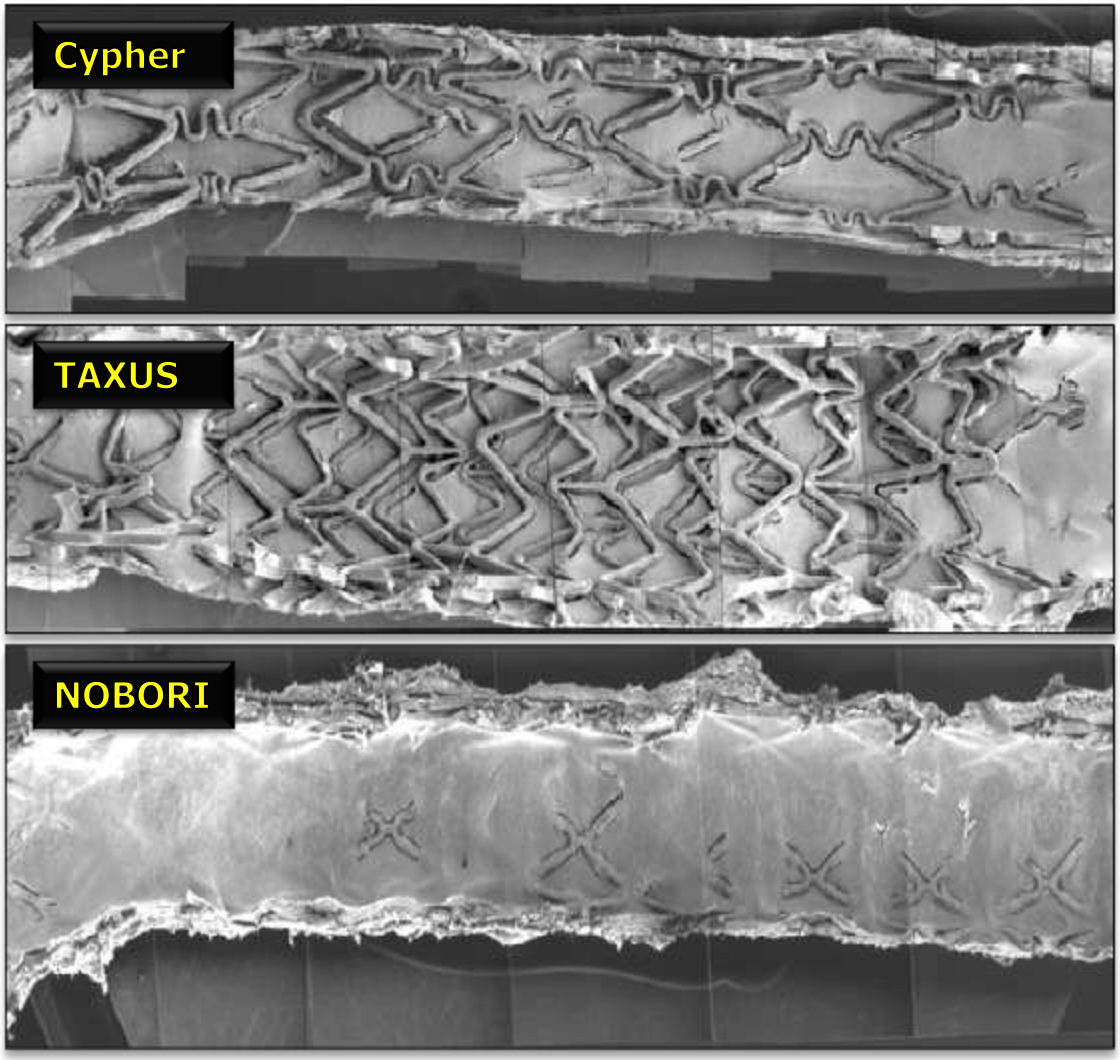
BES vs. SES,

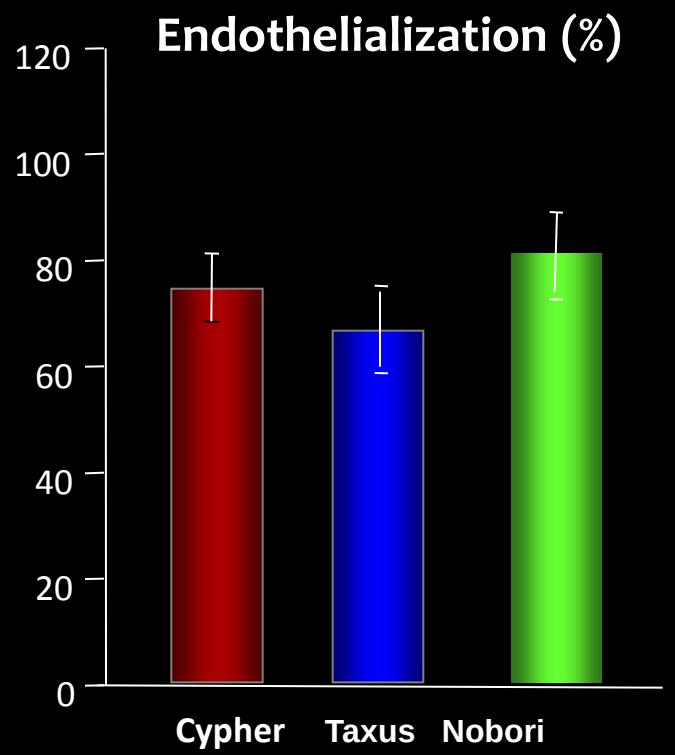
p-value < 0.002

Biodegradable Polymer DES

Nobori® stent (TERUMO)

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





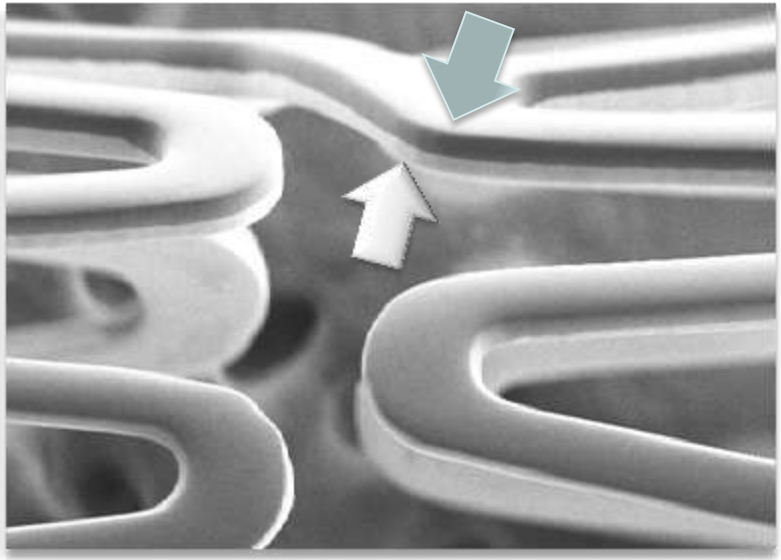
Finn A, et al. Circulation 2005

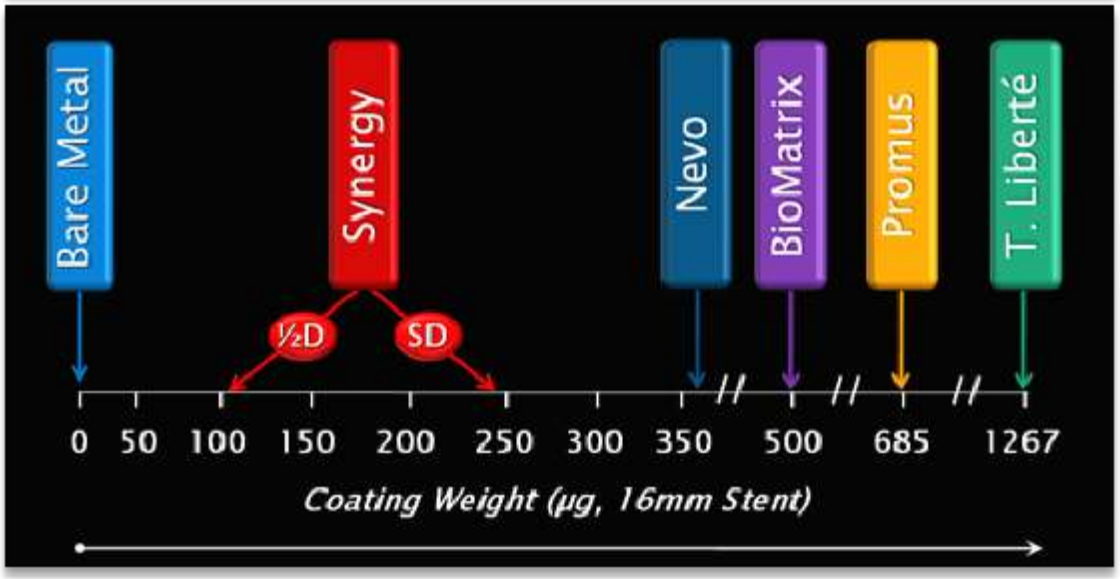
Biodegradable Ultrathin Polymer DES

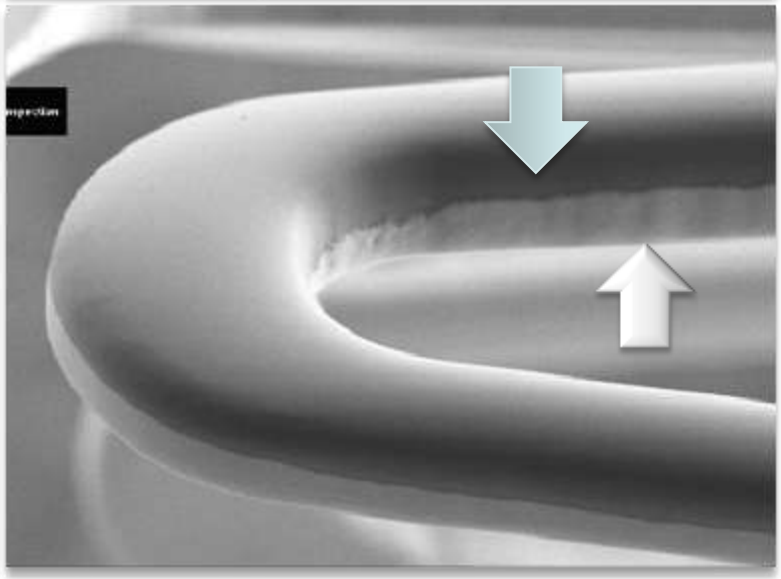
Synergy® stent (Boston Scientific)

- Bioerodable polymer is only applied at the abluminal surface of the stent
- Maximum coating thickness 3µm (low dose) and 4µm (high dose)

(Ultrathin coating)





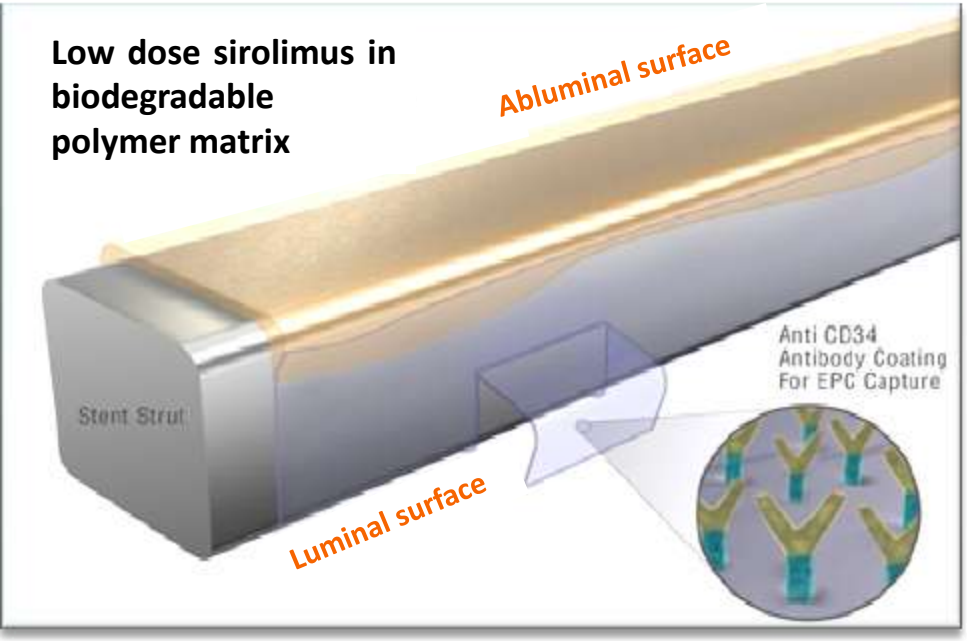


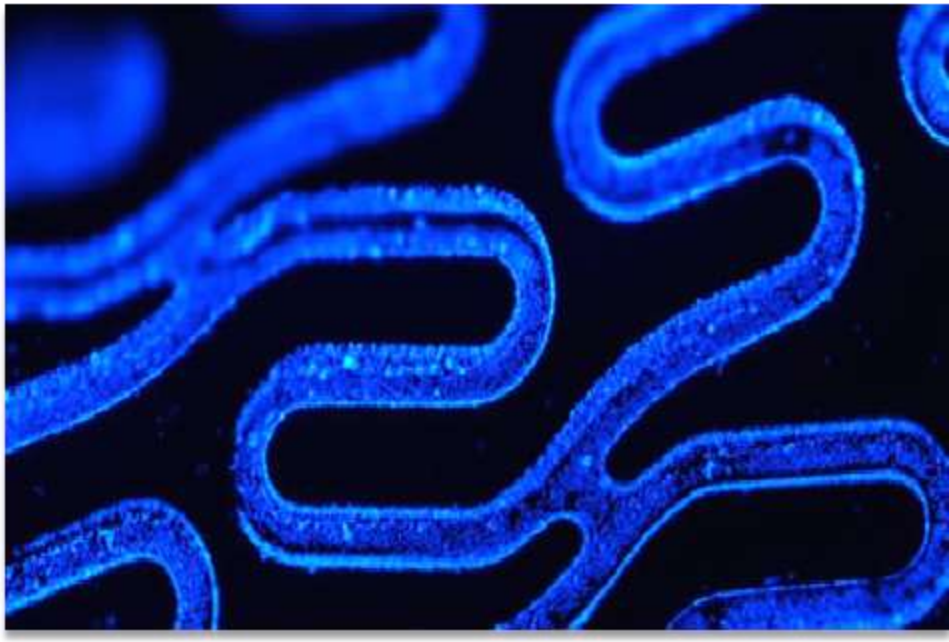
Selective Drug Delivery

Combo ® stent (Orbus Neich)

Rapamycin (5 µg/mm) applied in biodegradable SynBiosys polymer on the abluminal side

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



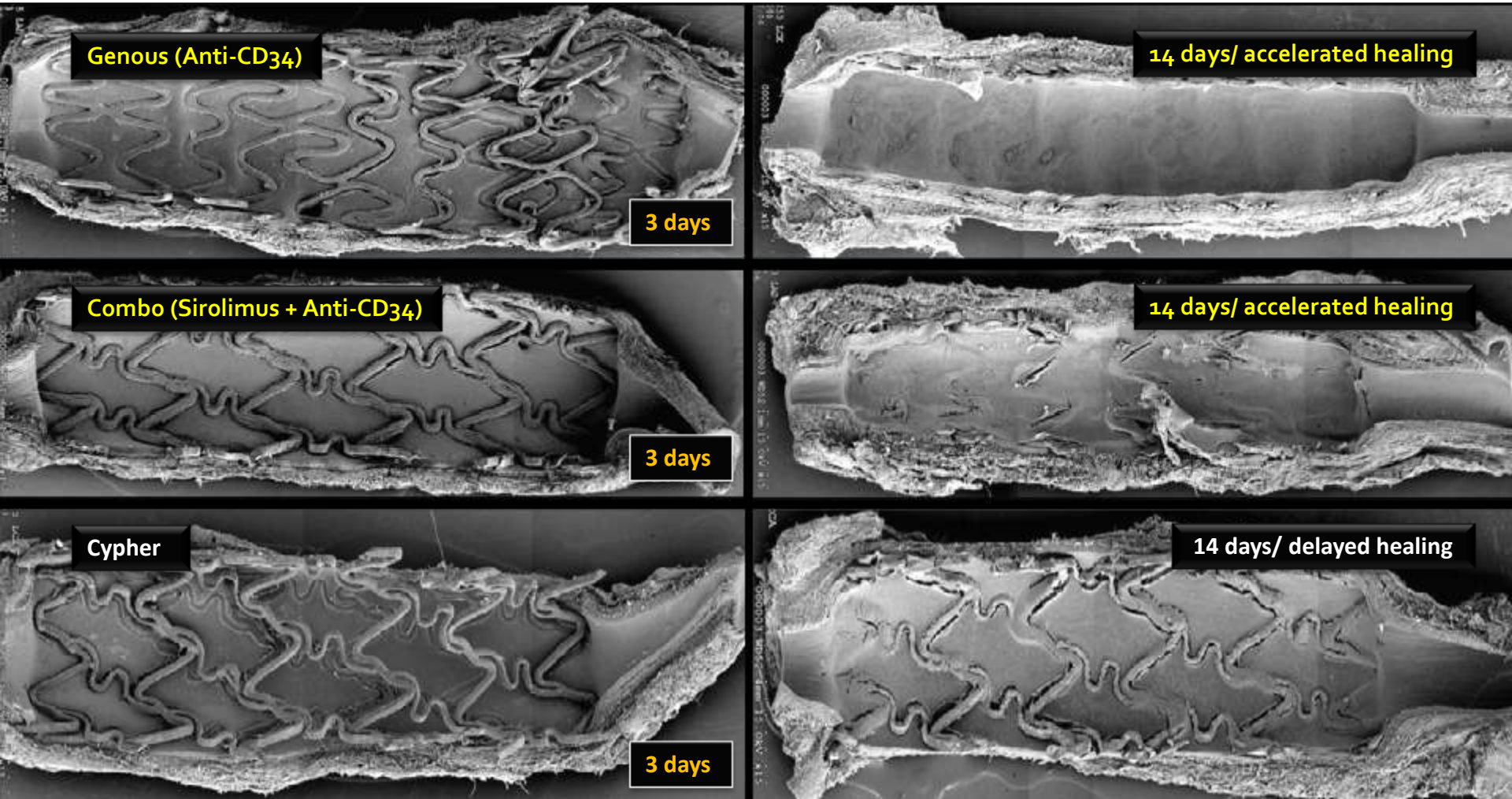


Development of a Novel Prohealing Stent Designed to Deliver Sirolimus From a Biodegradable Abluminal Matrix

Granada J. et al. Circ. Cardiovasc Interv. 2010; 257-66

American Heart Association
Learn and Live

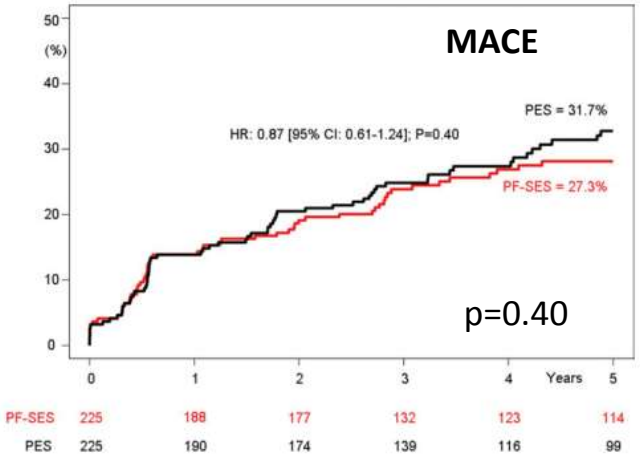
Both optical coherence tomography and histology demonstrate that Combo stents (anti-CD34 sirolimus-eluting stents) promote endothelialization while reducing neointimal formation and inflammation.

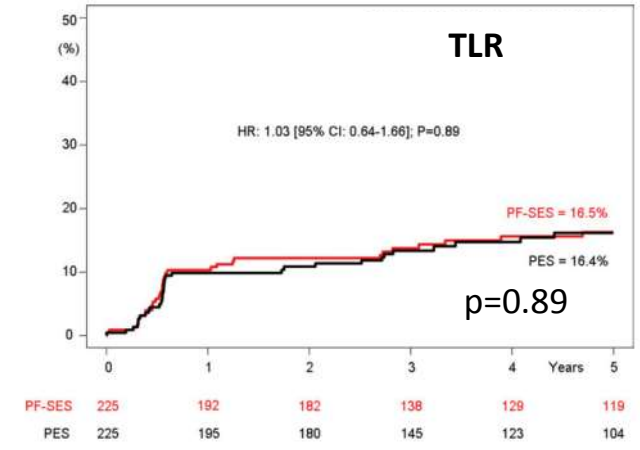


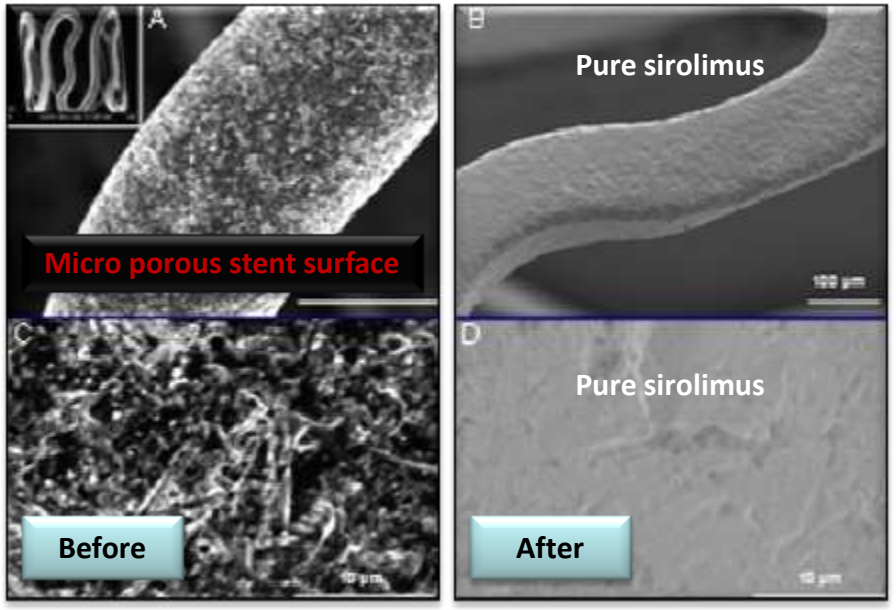
Polymer free (PF) DES
YUKON CHOICE ® stent (Translumina)

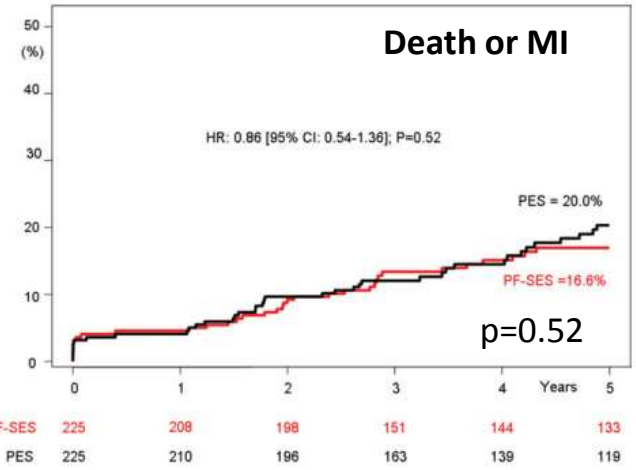
Five-Year Clinical Outcomes of a Polymer-Free Sirolimus-Eluting Stent Versus a Permanent Polymer Paclitaxel-Eluting Stent: Final Results of the Intracoronary Stenting and Angiographic Restenosis – Test Equivalence Between Two Drug-Eluting Stents (ISAR-TEST) Trial

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









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?

Mitsu	BioMime	XIENCE PRIME	ENDEAVOR RESOLUTE	TAXUS Liberte	CYPHER
					
Strut Thickness:	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**
40 µm	**65 µm**	**81 µm**	**91 µm**	**97 µm**	**140 µm**
Alloy:	**Alloy:**	**Alloy:**	**Alloy:**	**Alloy:**	**Alloy:**
Cobalt Chromium	**Cobalt Chromium**	**Cobalt Chromium**	**Cobalt Nickel**	**316L Stainless Steel**	**316L Stainless Steel**
Polymer Thickness:	**Polymer Thickness:**	**Polymer Thickness:**	**Polymer Thickness:**	**Polymer Thickness:**	**Polymer Thickness:**
< 2 µm	**2 µm**	**7.8 µm**	**6.2 µm**	**17.8 µm**	**12.6 µm**

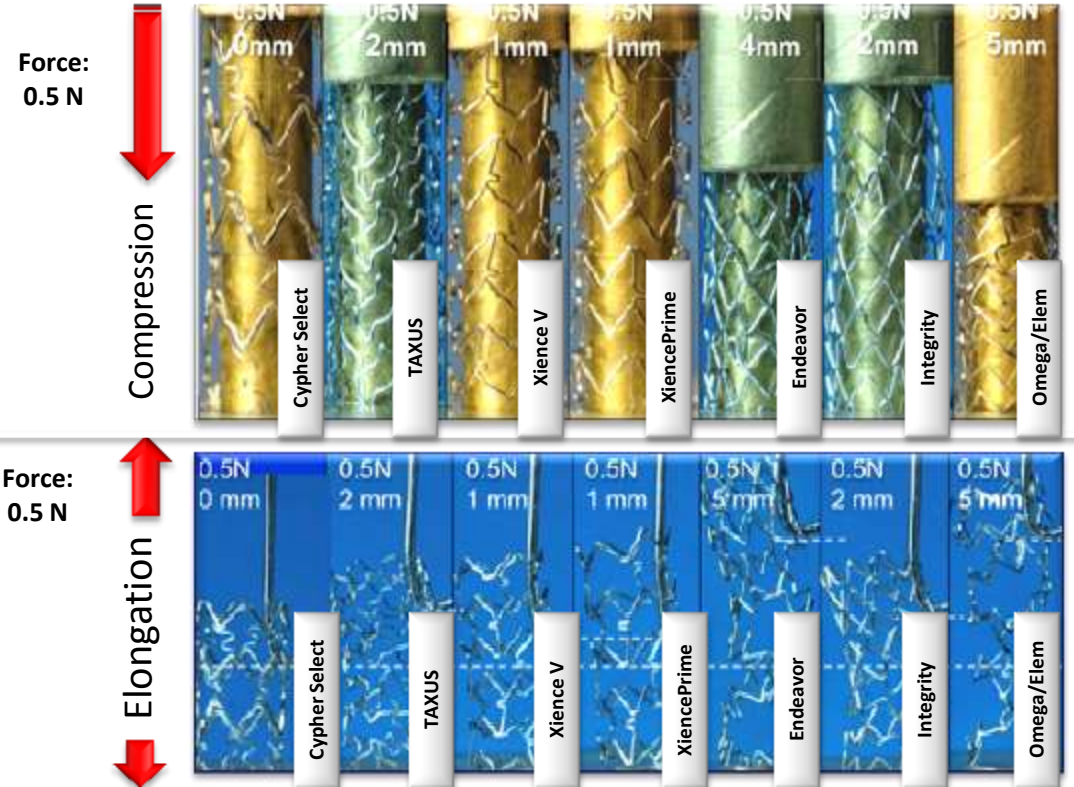
Alloy Design,
Importance of Strut Cross Linkage

Stent Longitudinal Integrity

Ormiston J. et al. JACC Cardiovasc Interv. 2011; 4(12):1310-7

Stents with **2 connectors** between hoops have **less longitudinal strength** when exposed to **compressing or elongating forces** than those with more connectors

Cypher Select was not compressed and appeared to have the greatest longitudinal stability



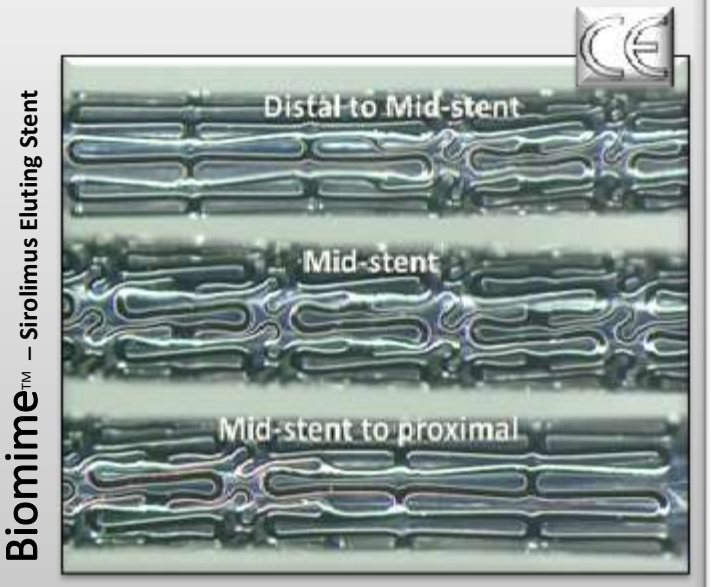
Alloy Design,
Thinner Struts

Not commercially available yet

Closed cells at the edges

Open cells in the middle parts of the stent

Hybrid Design



Despite Numerous Innovations…

The permanent drug-eluting metallic prosthesis remains a precipitating factor for:

1. **sustained vascular inflammation,**
2. **neoatherosclerosis &**
3. **impaired vasomotor function**

Where are we going with Technology?

From **Permanent Metallic Implants** with
Durable or
Bioresorbable Polymer Coatings
to
Bioresorbable Vascular Scaffolds
with
Bioresorbable Polymer Coatings

Vascular Restoration Therapy:

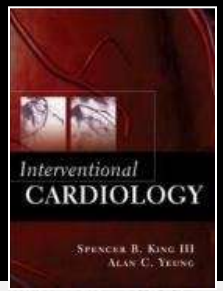
A Novel Field in

Interventional Cardiovascular Medicine

Potential Advantages:

- Restoration of vessel physiology
- Restoration of vessel anatomy
- Restoration of a low thrombogenic milieu
- Facilitates DAPT interruption
- Elimination of the risk of neoatherosclerosis
- Allowance of non-invasive imaging
- Pediatric applications

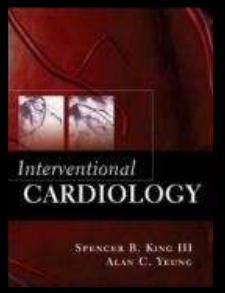
The Family of Bioresorbable Scaffolds in the Clinical Setting:

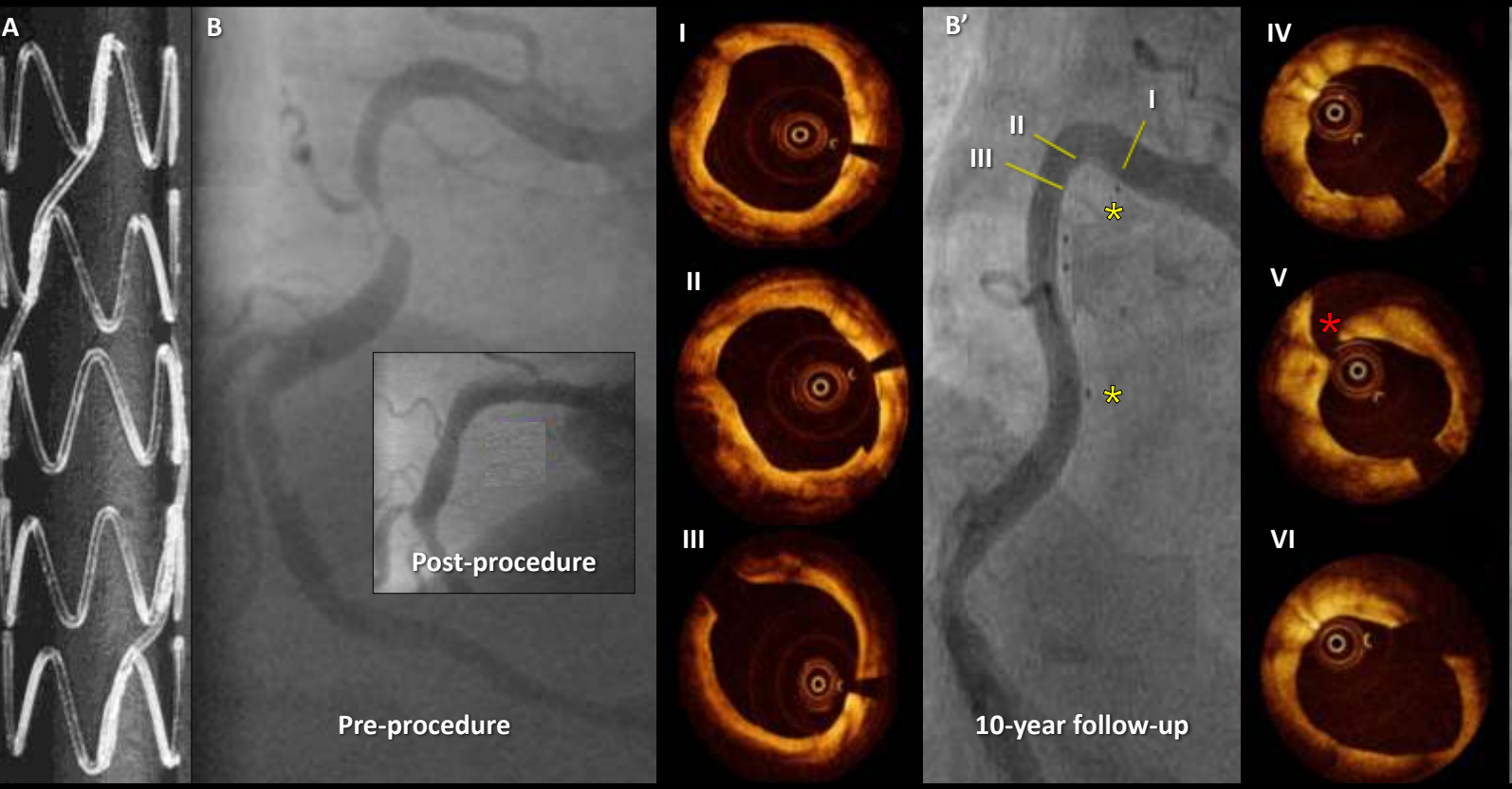


Igaki-Tamai Scaffold/ Kyoto Medical	DREAMS I/ Biotronik	Bioresorbable Vascular Scaffold/ Abbott Vascular	DESolve scaffold/ Elixir	BTI scaffold/ (-)	ReZolve scaffold/ REVA Medical	ART 18Z scaffold/ ART
						
FIM Trial:	**FIM Trial:**	**FIM Trial:**	**FIM Trial:**	**FIM Trial:**	**FIM Trial:**	**FIM Trial:**
Igaki-Tamai FIM	BIOSOLVE-1	Absorb Cohort B	DeSolve 1	Whisper	RESTORE	ARTDIVA
Strut Thickness:	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**	**Strut Thickness:**
170 µm	150 µm	150 µm	150 µm	200 µm	150 µm	170 µm
Alloy:	**Alloy:**	**Alloy:**	**Alloy:**	**Alloy:**	**Alloy:**	**Alloy:**
Poly-L-lactic acid	Magnesium+rare metals	Poly-L-lactic acid	Poly-L-lactic acid	Poly-salicylic acid	Tyrosine poly-carbonate	Poly-D-L-lactic acid
Drug-elution:	**Drug-elution:**	**Drug-elution:**	**Drug-elution:**	**Drug-elution:**	**Drug-elution:**	**Drug-elution:**
(-)	Paclitaxel	Everolimus	Myolimus	Sirolimus	Sirolimus	(-)
Radiopacity:	**Radiopacity:**	**Radiopacity:**	**Radiopacity:**	**Radiopacity:**	**Radiopacity:**	**Radiopacity:**
Gold markers	Platinum markers	Platinum markers	Platinum markers	(-)	Iodination of tyrosine	(-)
Loss Index	**Lumen Loss (mm)**	**Lumen Loss (mm)**	**Lumen Loss (mm)**	**Lumen Loss (mm)**	**Lumen Loss (mm)**	**Lumen Loss (mm)**
0.48 mm (6m)	0.64 mm (6m) & 0.52 (12m)	0.19 mm (6m) & 0.29 (36m)	0.19 mm (6m)	(-)	0.29 (12m)	(-)
Resorption time	**Resorption time**	**Resorption time**	**Resorption time**	**Resorption time**	**Resorption time**	**Resorption time**
Up to 2-years	Up to 2-years	Up to 3-years	Up to 1-year	Up to 1-year	Up to 1,5 year	Up to 2-years
Regulatory approval: EU CE mark / US FDA	**Regulatory approval: EU CE mark / US FDA**	**Regulatory approval: EU CE mark / US FDA**	**Regulatory approval: EU CE mark / US FDA**	**Regulatory approval: EU CE mark / US FDA**	**Regulatory approval: EU CE mark / US FDA**	**Regulatory approval: EU CE mark / US FDA**
EU CE / -	**- / -**	**EU CE / PMA***	**EU CE / -**	**- / -**	**- / -**	**- / -**

Gogas BD, Samady H. Textbook, Interventional Cardiology 2014, Mc Graw Hill, 2014 Editions

Igaki-Tamai Vascular Scaffold: 10-year follow-up





"The Golden Tube"

Gogas BD, Samady H. Textbook, Interventional Cardiology 2014, Mc Graw Hill, 2014 Editions

Bioresorbable Metallic & Bioresorbable Polymeric Scaffolds

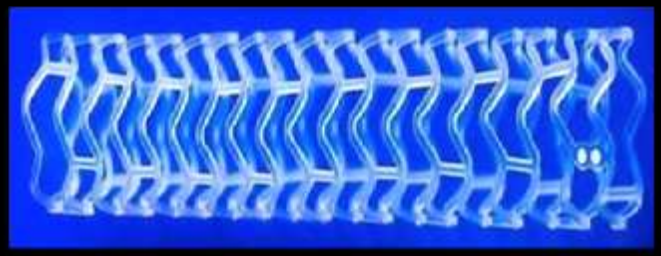
Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial

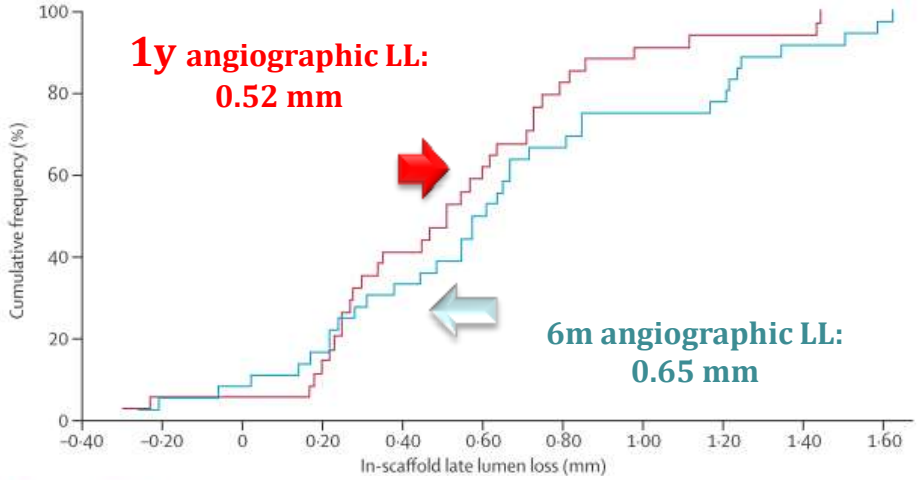
Haude M. et al. Lancet. 2013, Jan 14

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

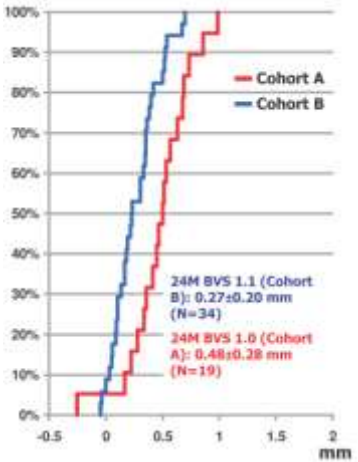
Ormiston J. et al. Circ Cardiovasc Interv. 2012; 5: 620-632





2y angiographic LL: 0.27 mm

(with the 2nd generation BVS, BVS 1.1)



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.

Late Lumen Loss
is comparable to conventional DES…

but

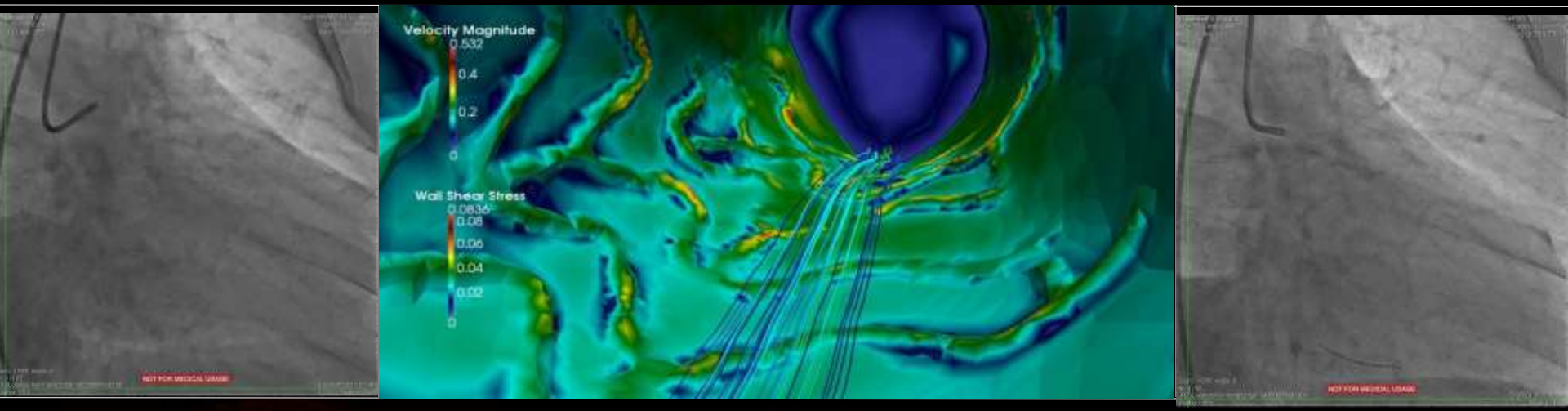
Is it all about LLL?

The Biomechanical Assessment of Bioresorbable Scaffolds may show superior performance compared to Permanent Metallic Stents

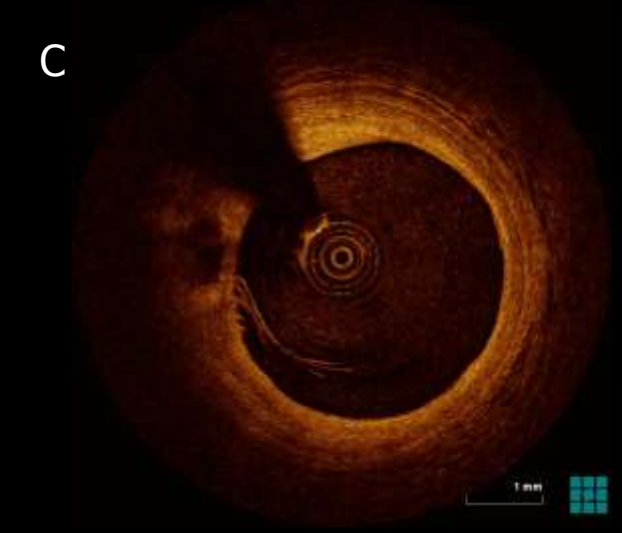
EMORY UNIVERSITY SCHOOL OF MEDICINE

Andreas Gruentzig Cardiovascular Center of Emory University

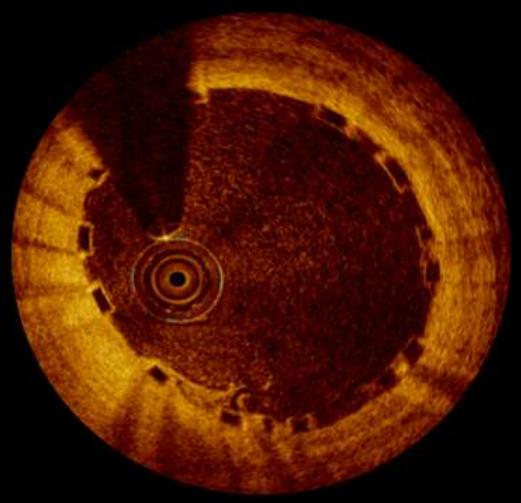
Integrated 3-D Multimodality Imaging Assessment Following BRS PCI



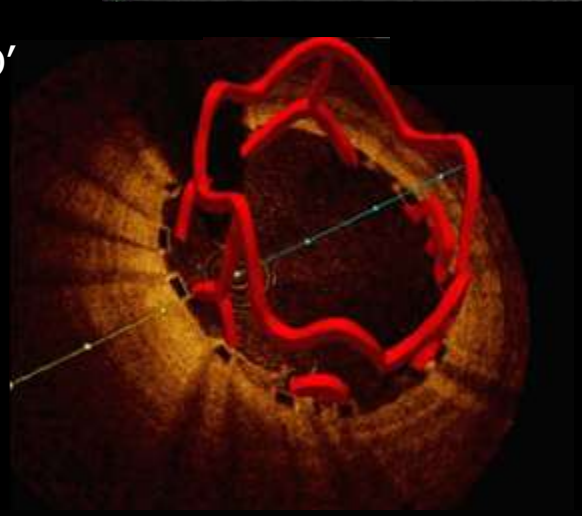
C



D



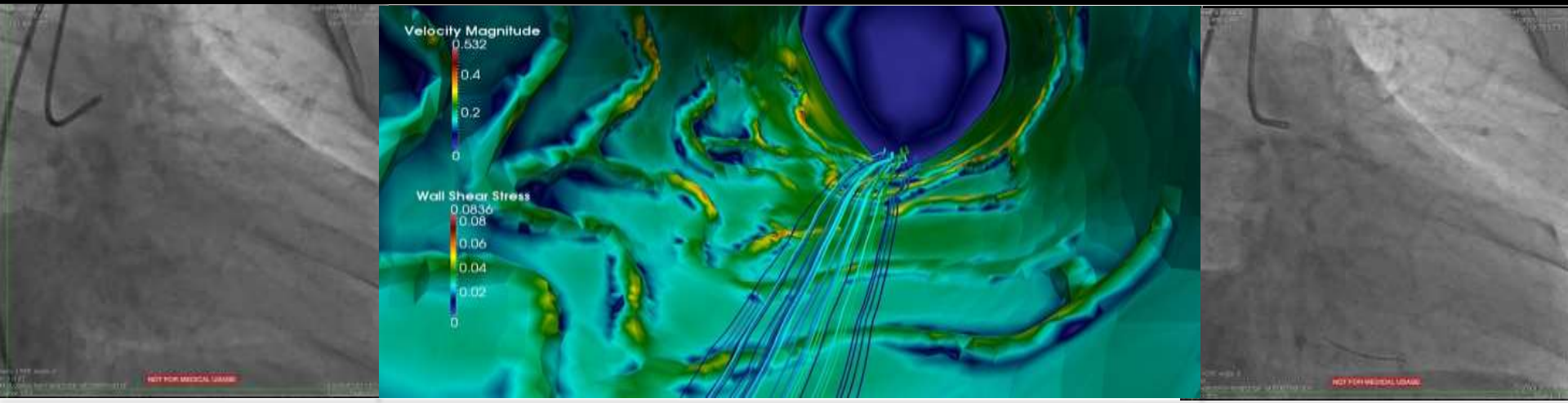
D′

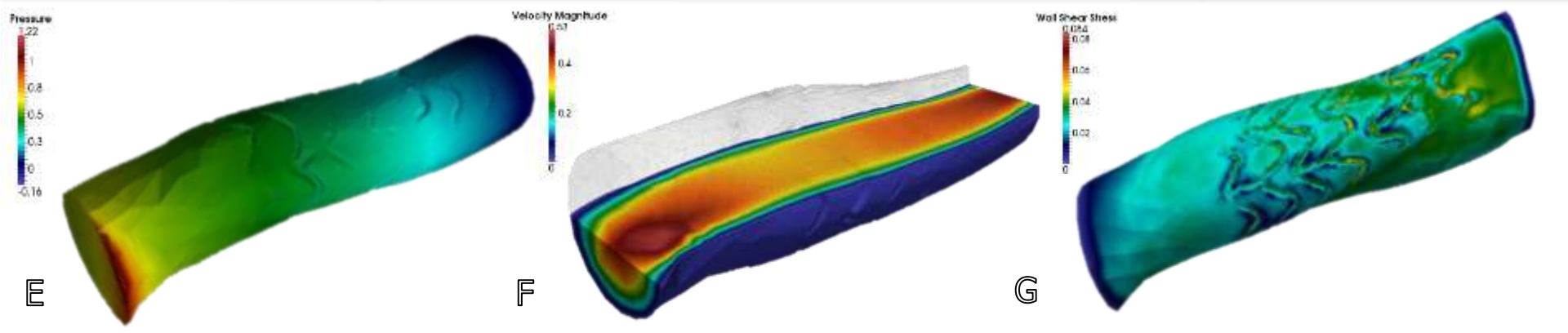


EMORY UNIVERSITY SCHOOL OF MEDICINE

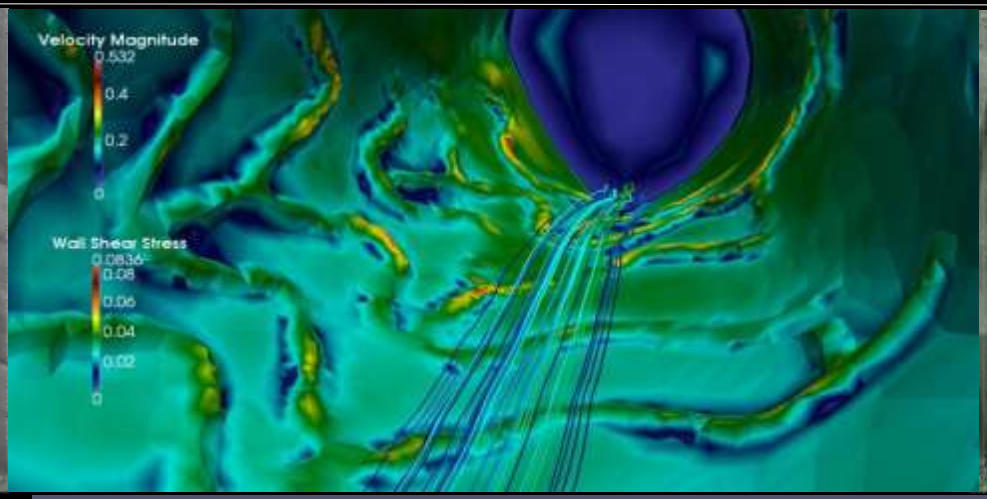
Andreas Gruentzig Cardiovascular Center of Emory University

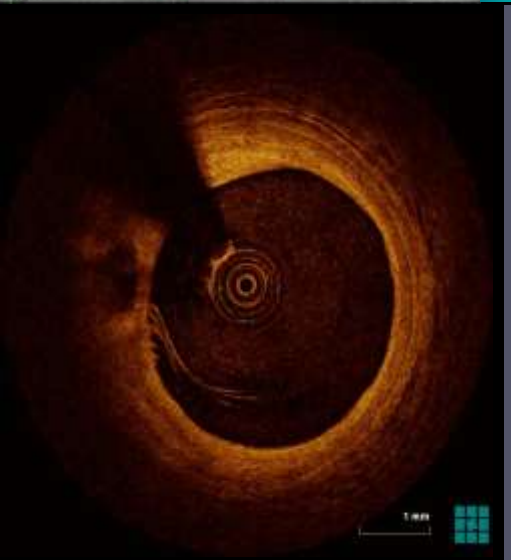
Integrated 3-D Multimodality Imaging Assessment Following Bioresorbable Scaffold Implantation

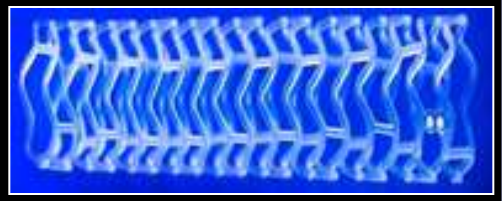


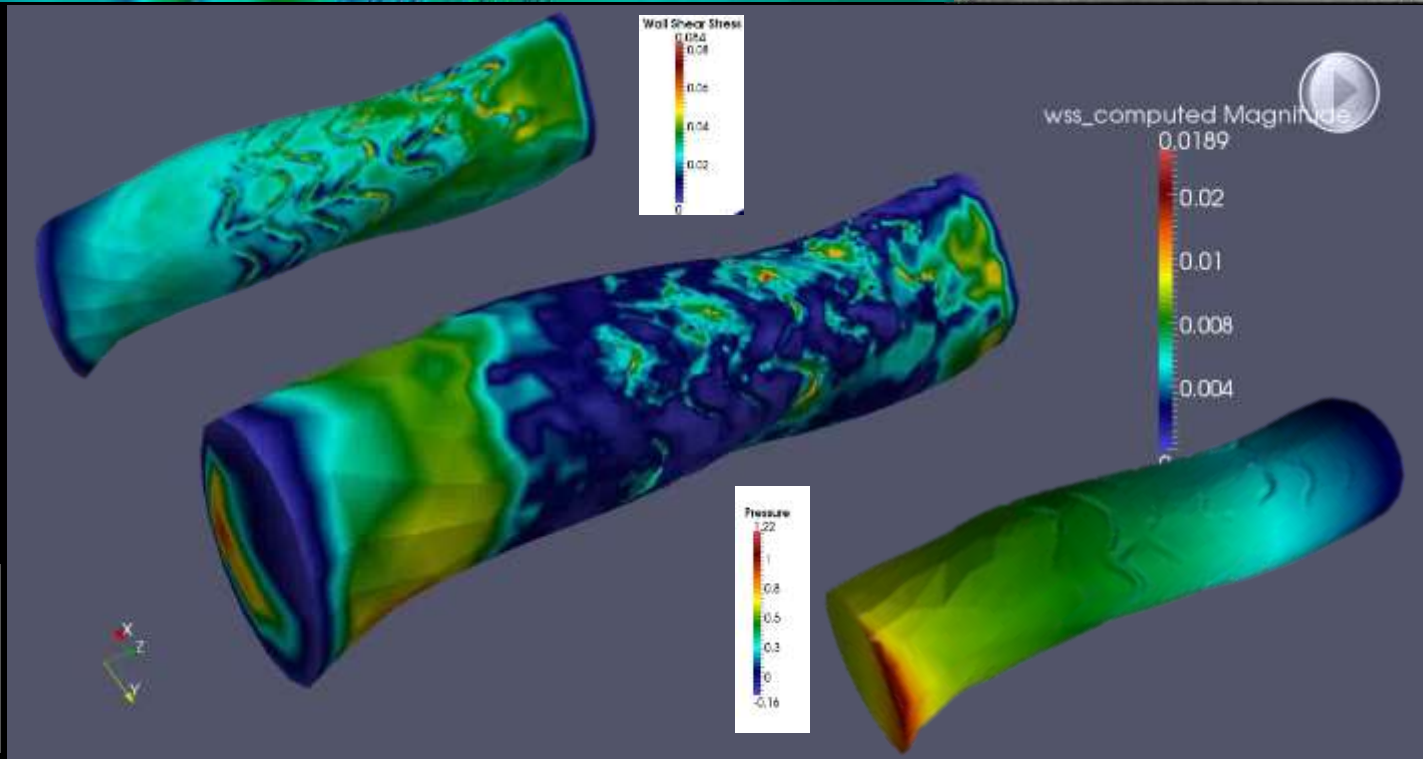


Integrated 3-D Multimodality Imaging Assessment Following BRS PCI

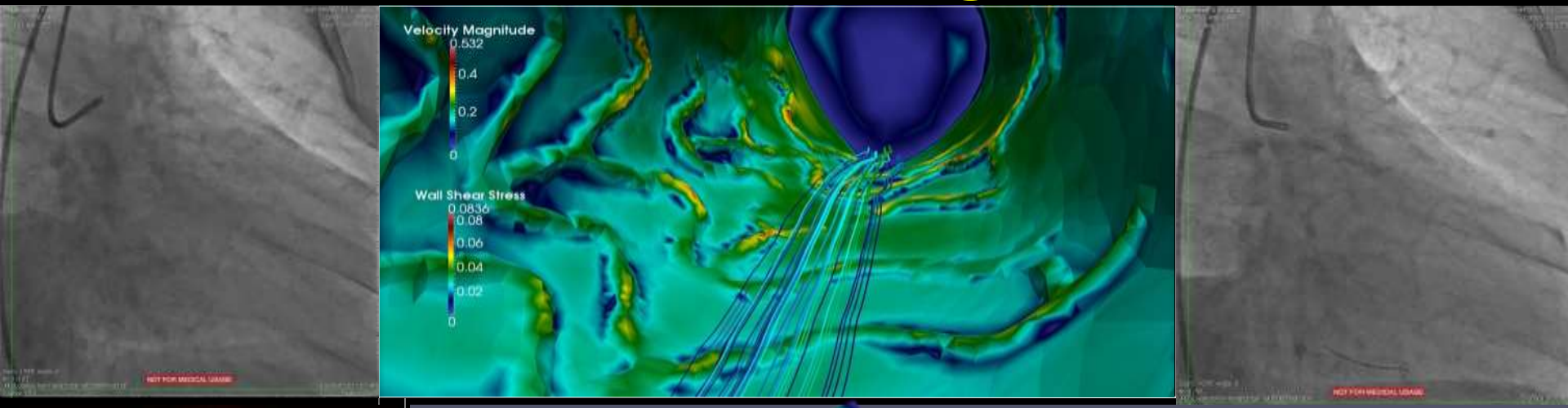


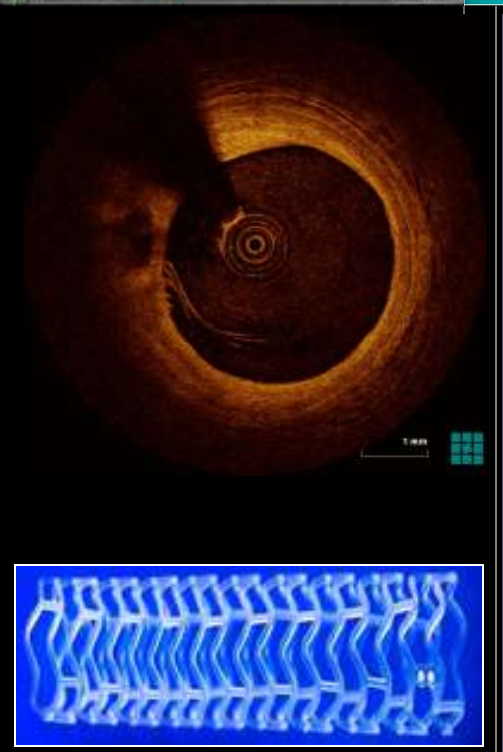






Integrated 3-D Multimodality Imaging Assessment Following BRS PCI





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of Emory University

Evaluation and Comparison of Three-Dimensional Wall Shear Stress Patterns & Neointimal Healing Following Percutaneous Coronary Intervention with Absorb™ Everolimus-Eluting Bioresorbable Vascular Scaffold Compared to Xience V® or Xience Prime™ Everolimus-Eluting Metallic Stent

Although Bioresorbable Technologies are appealing, there is still a lot of space for improvement…

Will bioresorbable scaffolds be as good as metal for scaffolding complex and calcified lesions ?

Will they be suitable for bifurcation lesions ?

Will thick struts present problems ?

Will preemptive stenting of "vulnerable" but non obstructive plaques occur ?

Will improvements in medical therapy trump invasive prevention in trials ?

Can bioresorbable technology become cost competitive with low cost DES ?

Where are we going with Clinical Application?

Stent Utilization in stable CAD

- Influence of guidelines recommending OMT, FAME I suggesting that stents be limited
- Influence of FAME II suggesting that stenting improves outcomes

Stenting or CABG?

- Influence of SYNTAX Score in treating LM or MV disease
- Influence of FREEDOM trial in treating DM + Multivessel (Better with CABG, but is it for all?)

Where are we going with Industry?

FACTS:

1. The global market for coronary stent devices reached $7.1 billion in 2011
2. By 2016 it is expected that total market value will reach $10.6 billion
3. American Revenue: 40% share and is expected to grow by 8.9% (2016)
4. European Revenue: 37% share and is expected to grow by 5.2% (2016)

Data provided by BCC Research, 2013

What is the Future of Coronary Stenting?

1. Advances in coronary stenting have been dramatic and some say: "Stents have completely evolved".

2. Appropriate selection for revascularization and method of revascularization (PCI + stent vs. CABG) will respond to the accumulating evidence.

3. Future disruptive technologies may significantly alter the value of endovascular therapies.

4. …However, Interventional Cardiovascular Medicine is here to stay.

TCTAP 2014, Main Session IV, Main Arena,

Seoul, Korea, April 23, 2014

What is the Future of Coronary Stenting?

Thank You