Biodegradable Stent Update

2014. 12. 13 JCR

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Presenter Disclosure Information

Presenter: Eun-Seok Shin, MD/PhD

Title: Biodegradable Stent Update

No relationships to disclose

No industry sponsorship

Case Review

Patient Demographics

Age: 63

Gender: M

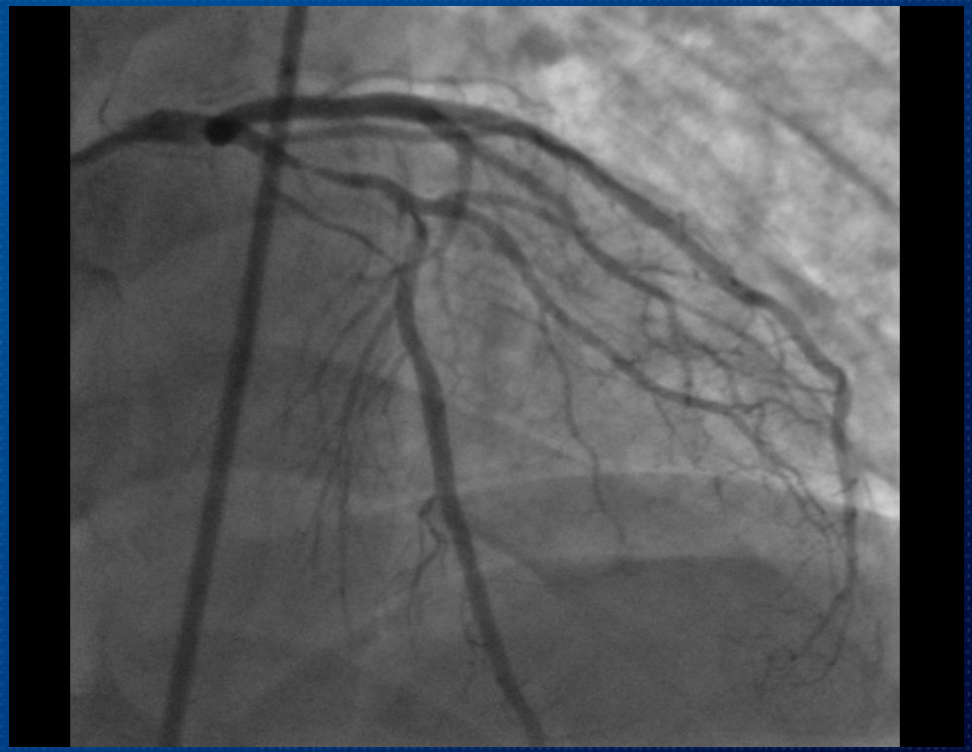
Risk factors: None

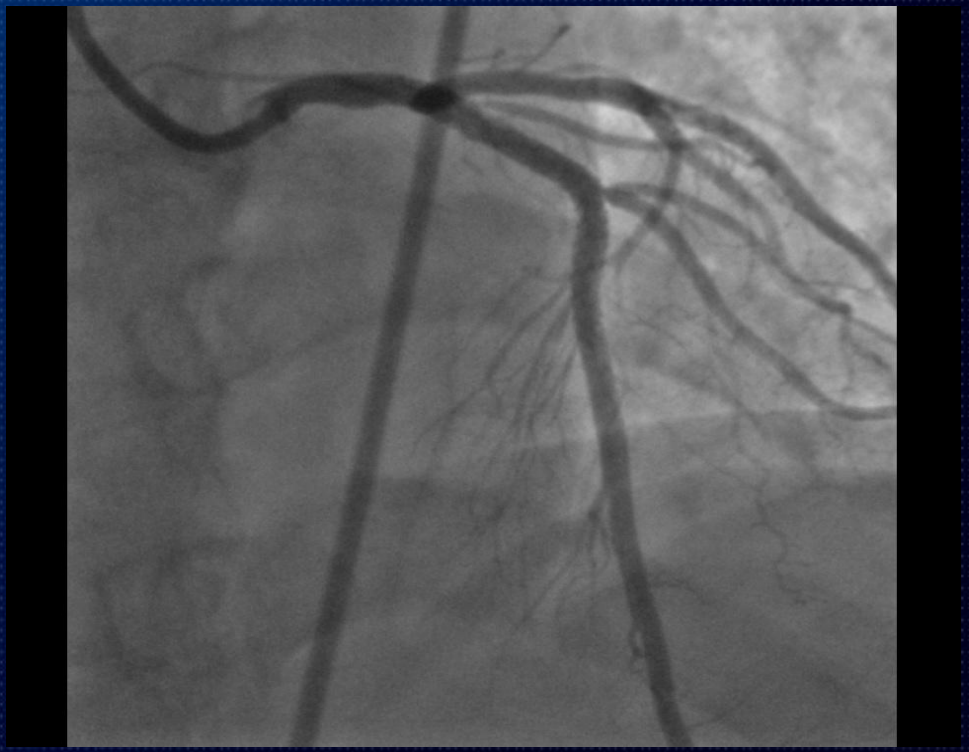
Clinical Presentation

Effort Chest pain 2 weeks ago

2007. 10. 9

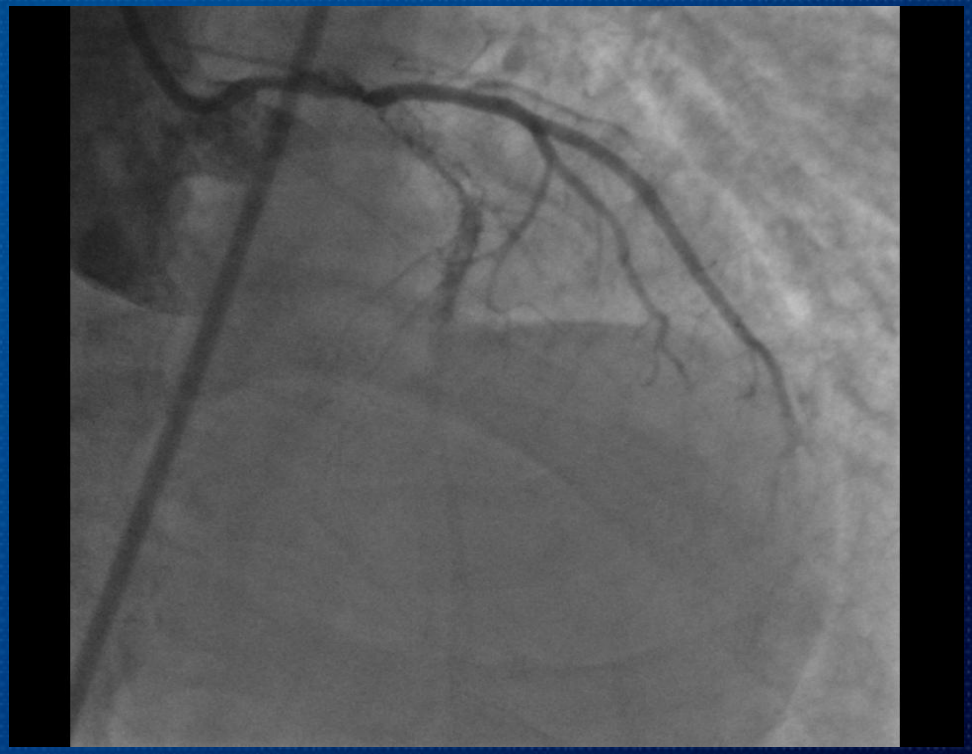
Cypher 3.5/30





2012. 5. 31

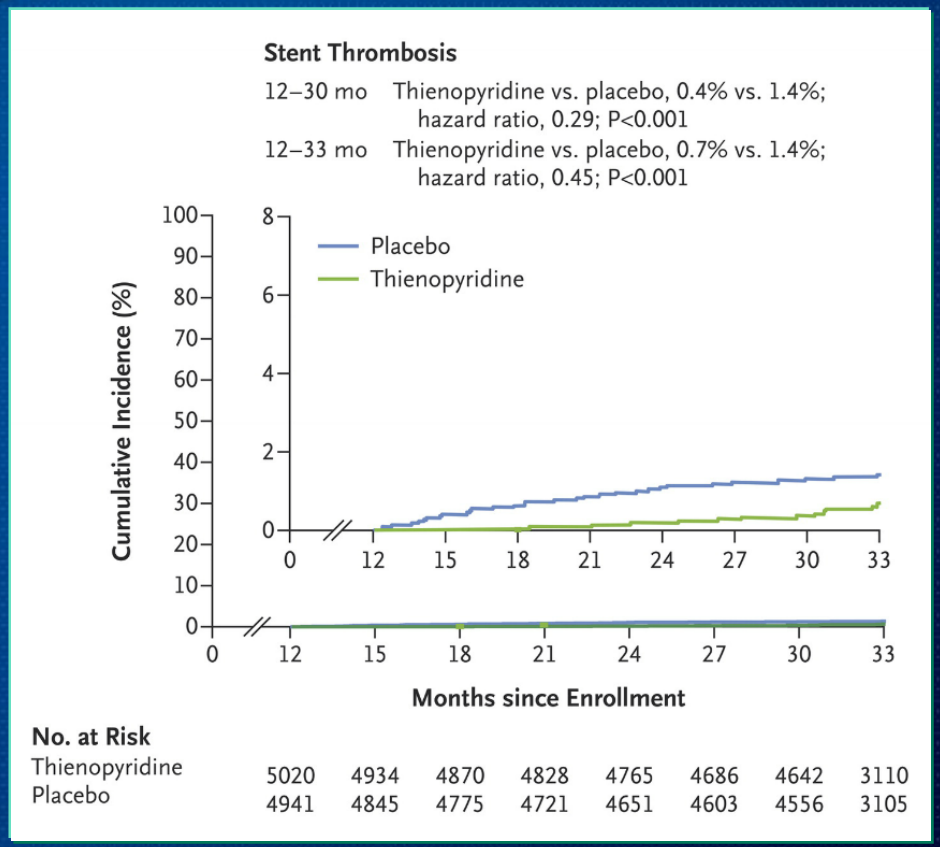
Stop aspirin for 5 days



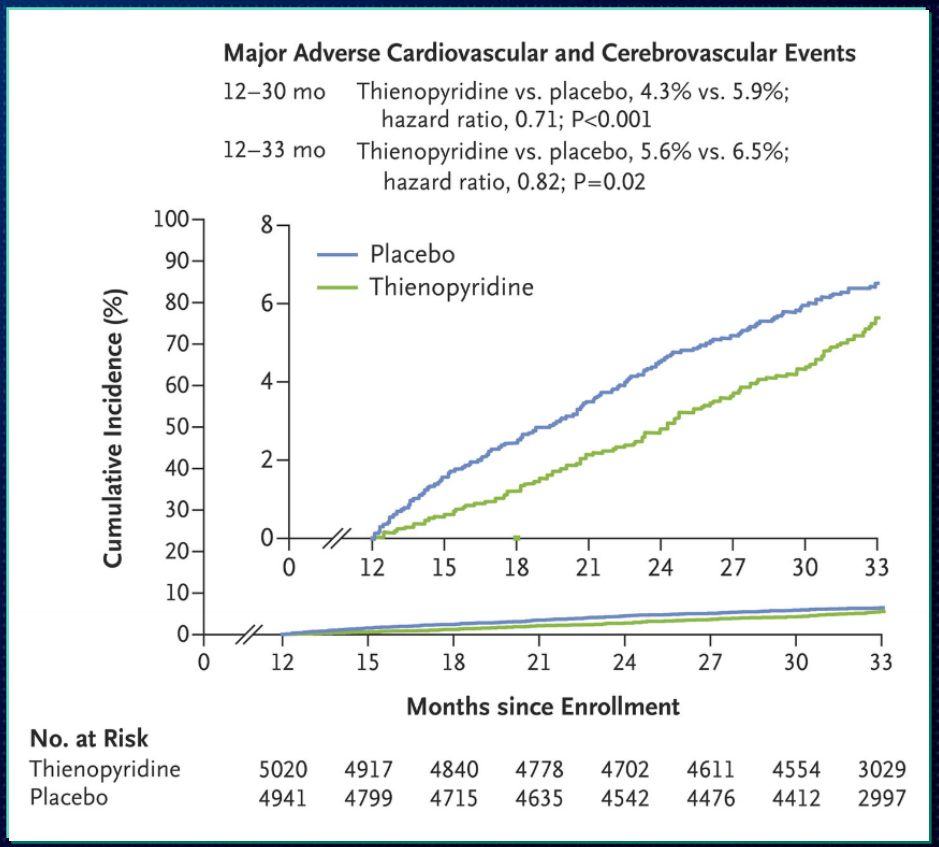
Cardiogenic shock after OP

12-month or 30-month of Dual Antiplatelet Therapy after DES

Stent Thrombosis



MACE



N Engl J Med 2014;371:2155-66.

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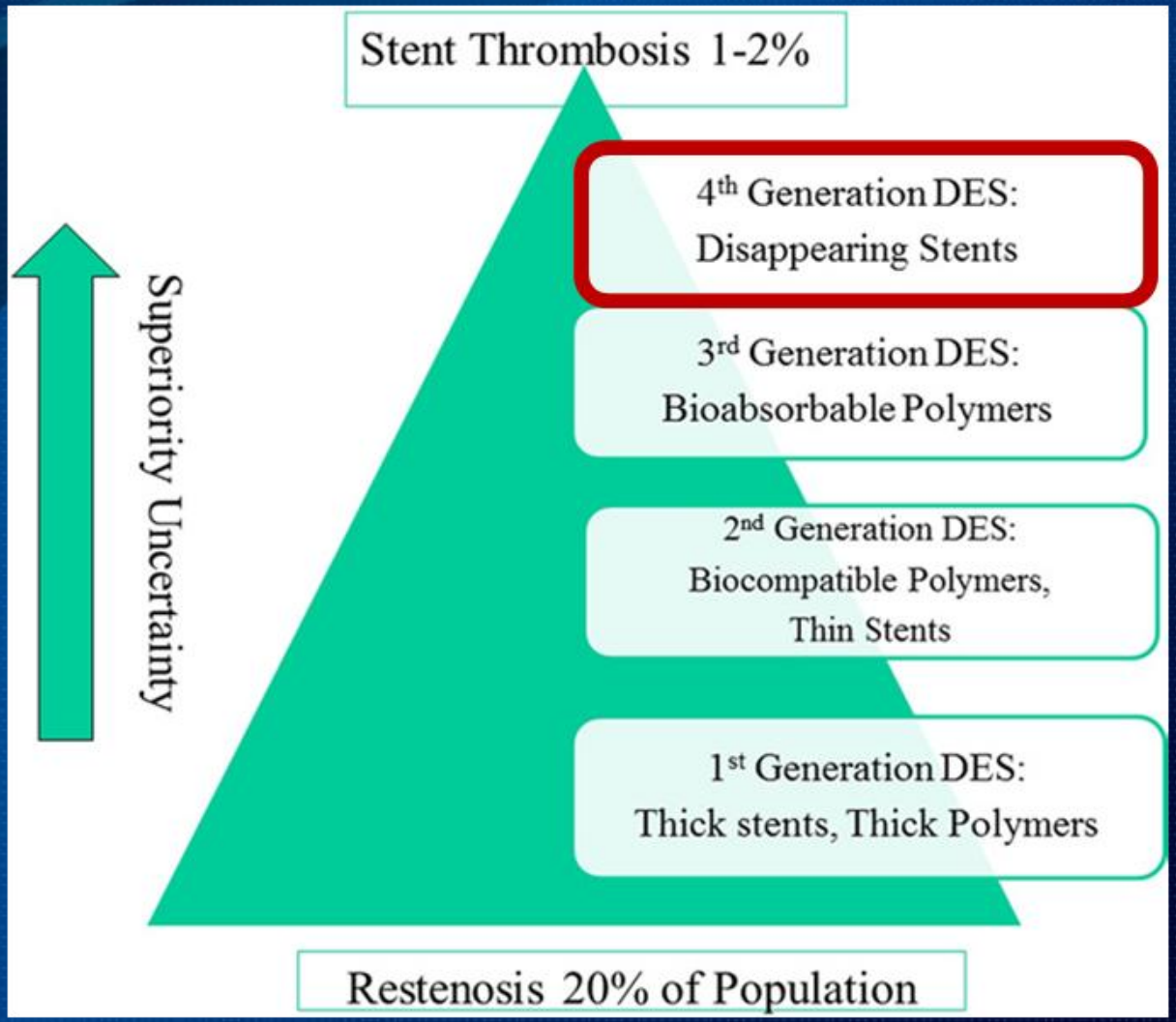
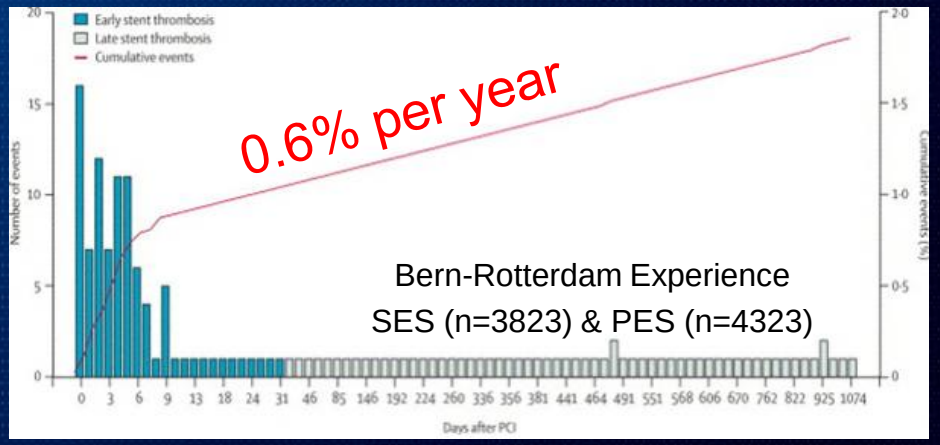
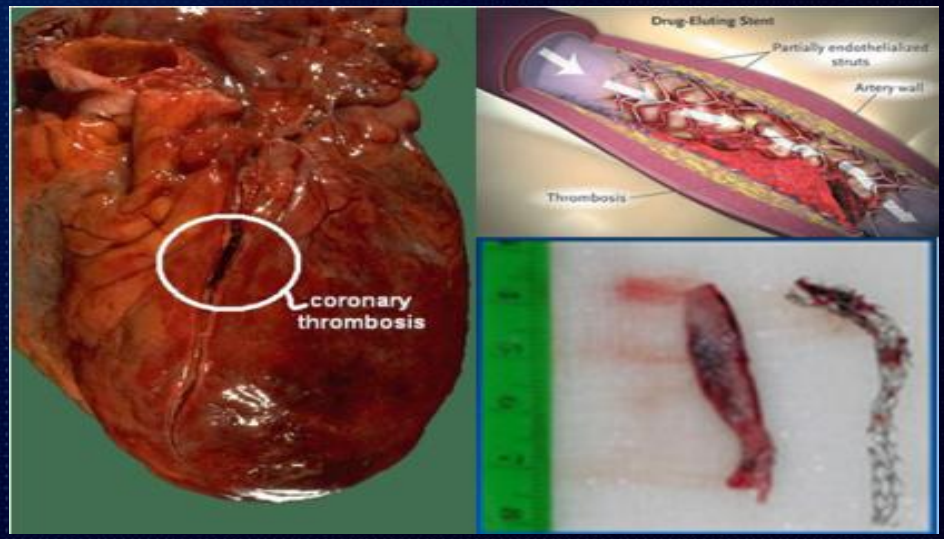
Evolution of PCI

1977	1988	2001
		
1	2	3
Balloon angioplasty	**Bare metal stent**	**Drug-eluting stent**

Evolution of DES & limitation







Stent thrombosis

JACC 2011

Evolution of PCI

1977

1

Balloon angioplasty

1988

2

Bare metal stent

2001

3

Drug-eluting stent

Today

4

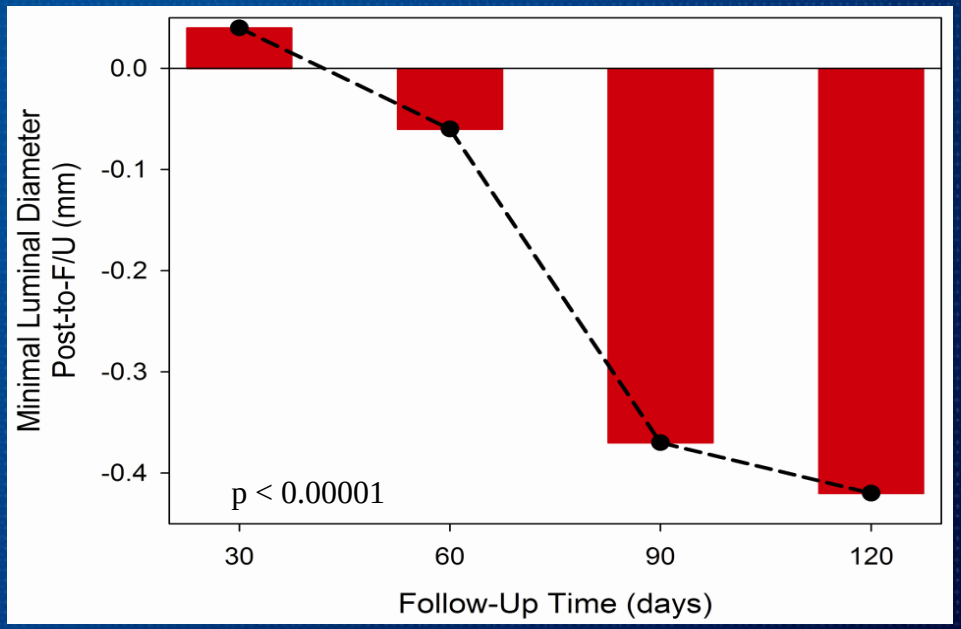
Biodegradable Vascular Scaffolds

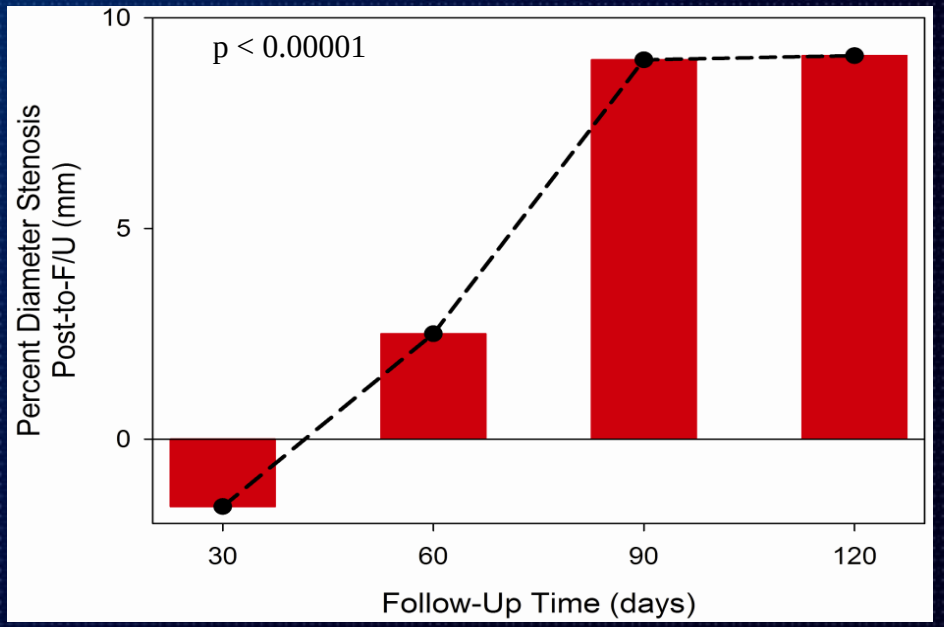
After implant.

After resorption.

Scaffolding of the Vessel is Only a Transient Need

n = 342 patients (n = 93 at 30-day F/U; n = 79 at 60-day F/U; n = 82 at 90-day F/U; n = 88 at 120-day F/U)





The lumen appears to stabilize approximately three months after PTCA

P. W. Serruys, Circulation 1988; 77: 361.

Conceptual Strength of BVS

- **No metal implant behind**
- **No sources of vessel irritation or chronic inflammation**
- **Restoration of natural physiologic vasomotor function**

→ Future re-interventions, particularly in younger patients

→ Potentially reduce the need for prolonged DAPT

→ Non-invasive imaging (CT/MRI) without “blooming artifact”

Vascular Reparative Therapy

1. **Revascularization with Transient Support**

2. **Restoration of Physiological Environment**
   (shear stress, multidirectional motion, morphology)

3. **Resorption**

Revascularization – Restoration - Resorption

Cohort B OCT images - courtesy of RJ van Geuns, Erasmus Medical Center, Netherlands

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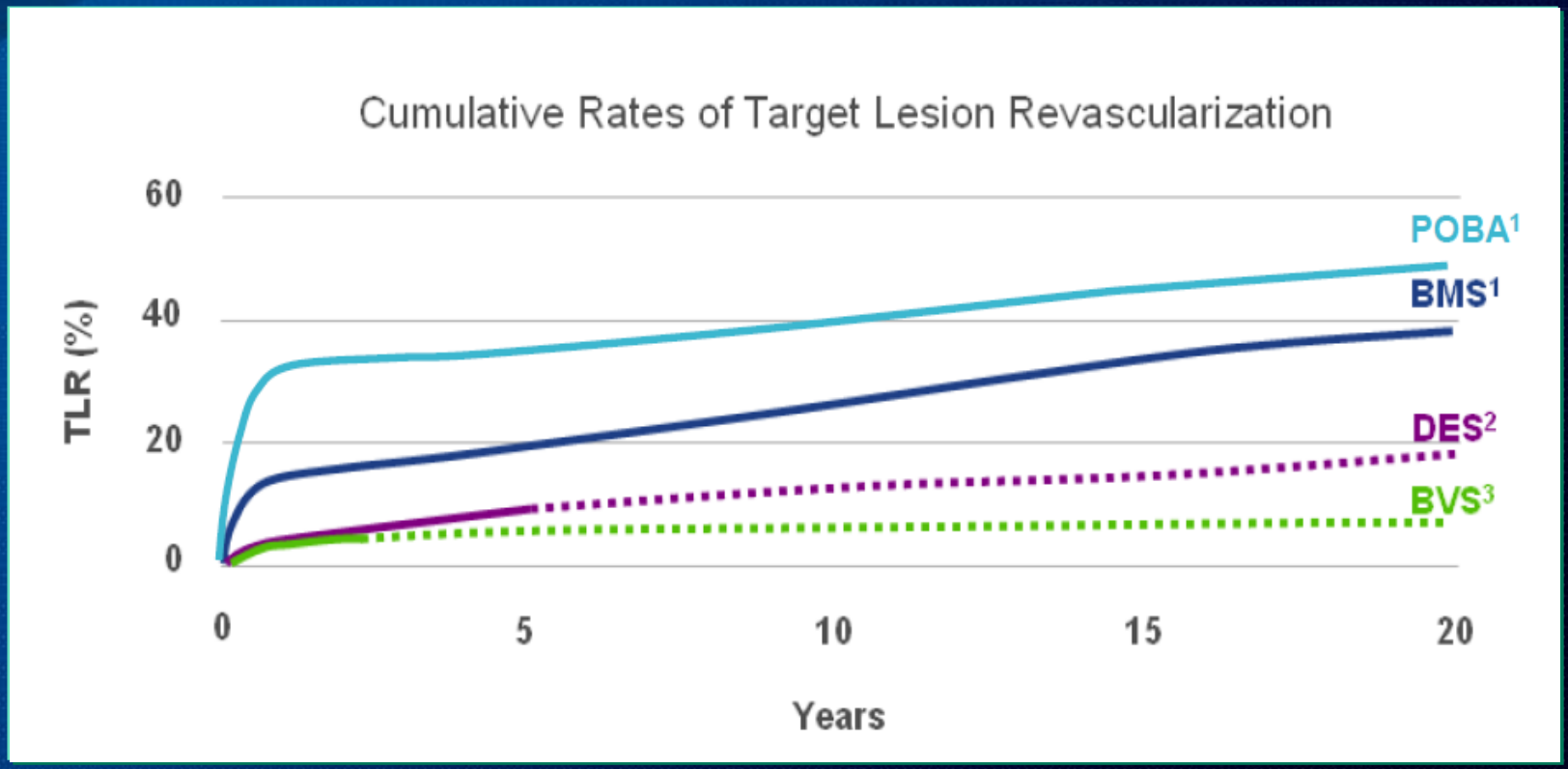
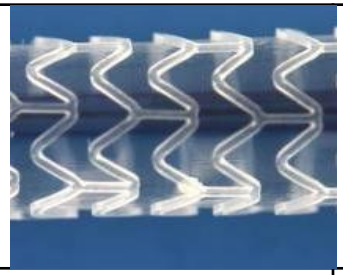
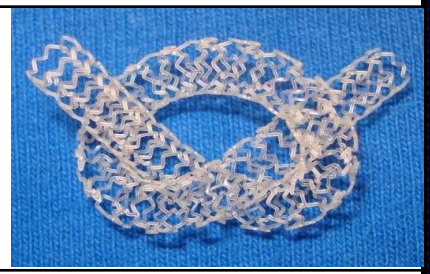
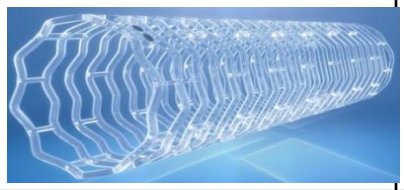
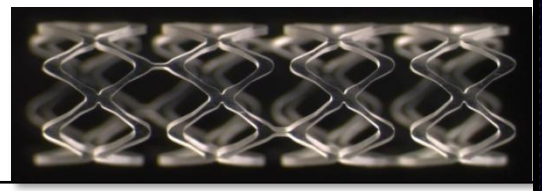
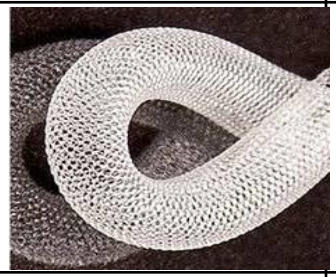
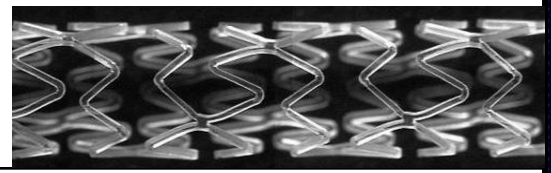
Potential for Improved Long-Term Outcomes



The goal of bioresorbable vascular scaffolds is to achieve the early benefits seen with DES, but improve on long-term outcomes by eliminating the implant

Essential Materials in Bioresorbable Scaffolds

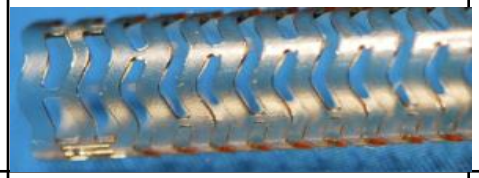
Aliphatic Polymers

	PRODUCT DEVELOPMENT PROGRAMS	
LEADING COMPOUND: **Poly (lactic acid) = PLLA and copolymers** DEGRADATION END PRODUCTS: **Lactic and glycolic acid (metabolites)**	**ABBOTT"ABSORB""** PLLA Everolimus 	AMARANTH "FORTITUDE" Layered PLLA No drug 
	ELIXIR "DESolve" PLLA Myolimus/ Novolimus 	ART "ART18AZ" R+D PLLA No drug 
	480 BIOMEDICAL "STANZA" Peripheral, self-expandable PLLA 	ORBUS CD34 EPC-capturing, sirolimus-eluting 
	MERIL "MeRes" PLA, Merilimus-eluting	HUAAN BIOTECH "XINSORB" PLA, PCL, PGA, Sirolimus-eluting

Gabriel Maluenda, TCT 2013

Essential Materials in Bioresorbable Scaffolds

Other Chemical

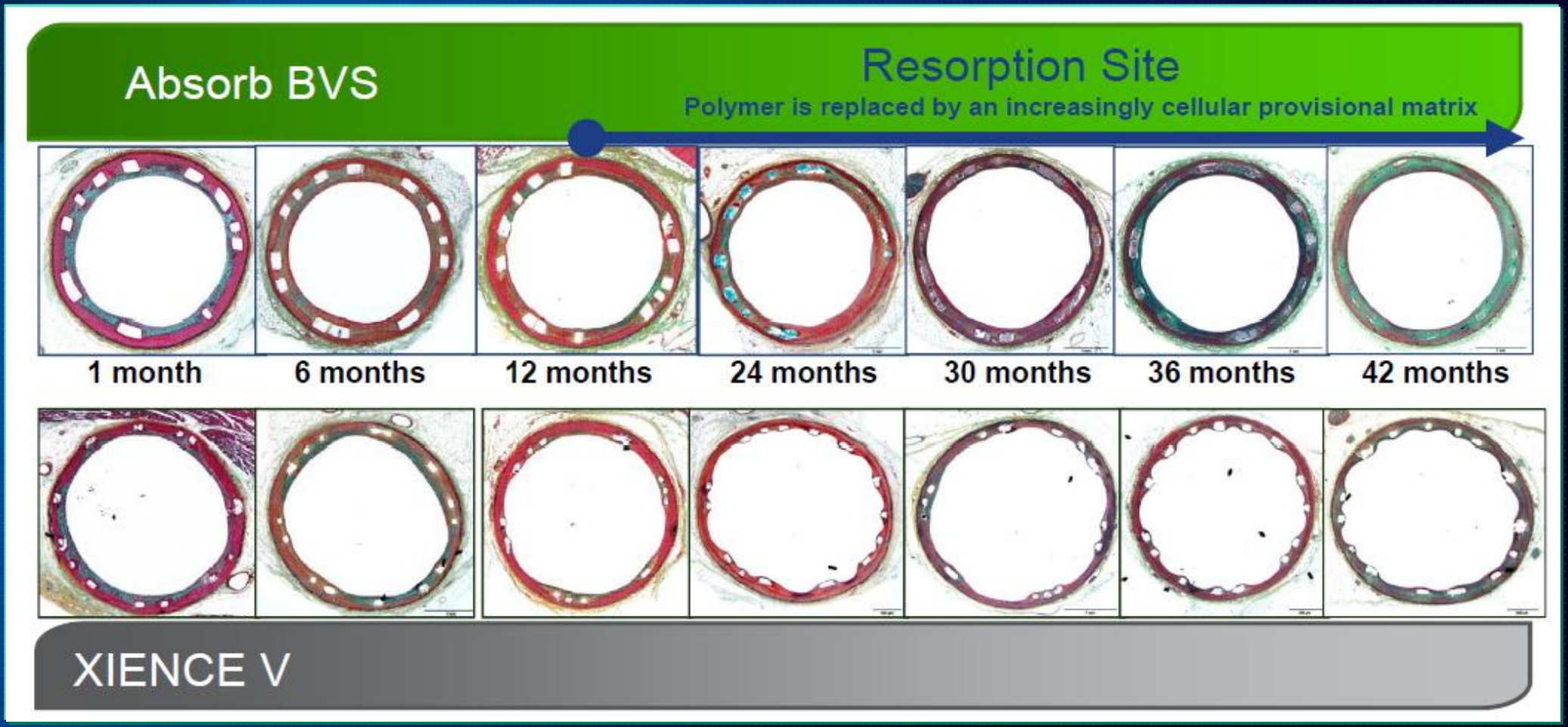
MATERIAL GROUP	LEADING COMPOUNDS/ DEGRADATION END PRODUCTS	COMPANY	PRODUCT
Polycarbonates	Aminoacids (e.g. tyrosine)/ Chemicals, metabolites, and oligomers	REVA MEDICAL 	ReZolve 2 Slide-and-lock, Sirolimus eluting BVS
Poly-anhydrides	Salicylic acid and Adipic acid/ Chemicals	BTI 	NONE – program not active
Metals	Magnesium/ Salts and ions (hydroxyapatite)	**BIOTRONIK** 	**Biosolve** Magnesium BVS, paclitaxel eluting (sirolimus expending)
"Hybrid"	Magnesium and PLGA/ Salts, ions, metabolites	ZORION MEDICAL	Fades BVS No drug

Gabriel Maluenda, TCT 2013

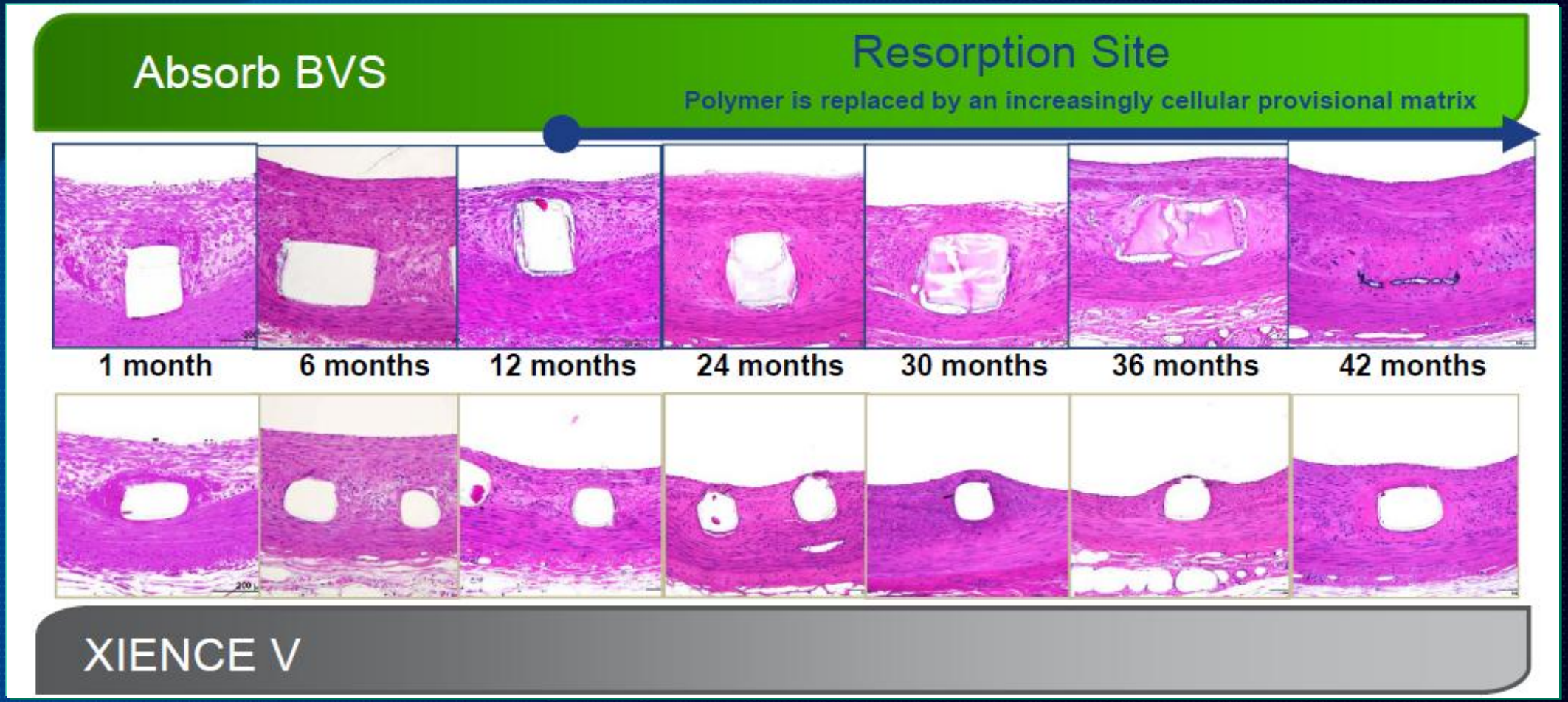
Development of BVS

Company	BVS	Pre-clinical	Clinical	CE
Kyoto Medical	Igaki-Tamai	✓		
Biotronic	Dreams	✓	✓	
Abbott	Absorb	✓	✓	✓
Art	Art18AZ	✓	✓	
Reva Medical	Resolve	✓	✓	
Amaranth	Amaranth PLLA			
Xenogenics	Ideal biostent			
Orbus Neich	Acute	✓		
Elixir	DESolve	✓	✓	√
Amaranth	Amaranth PLLA	✓		
Huaan Biotech	Xinsorb	✓	✓	
S3S3V	Avatar	✓		
MerilNeril	MeRes	✓		
Zorion Medical	Zorion BRS	✓		

Resorption: Vascular response



Resorption: Vascular response

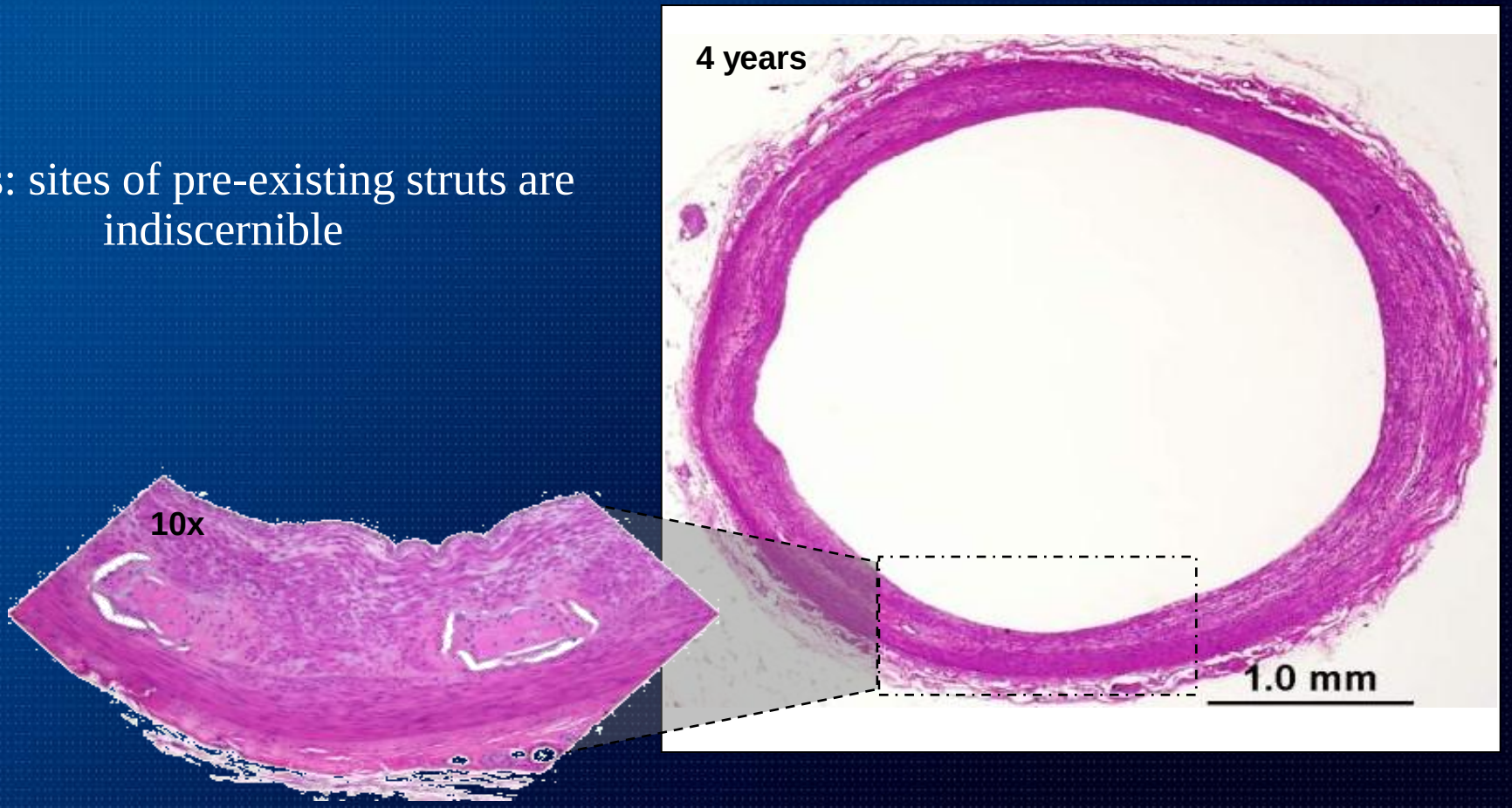


Resorption: Mostly Achieved by 2 Years

- Mass loss data suggests near completion of material mass loss at 2 years
- The shape of struts is still apparent at 2 years, although the device is fully resorbed
- No inflammation around the pre-existing strut regions

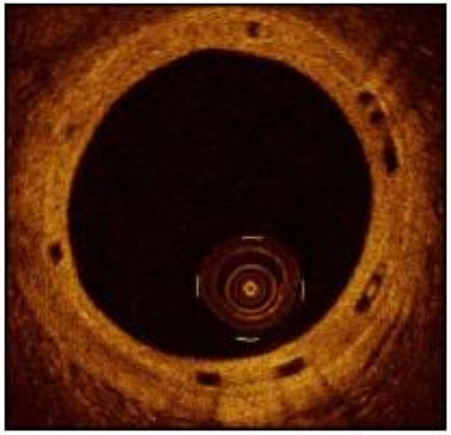
Resorption: Histology 4 Years

- 4 years: sites of pre-existing struts are indiscernible

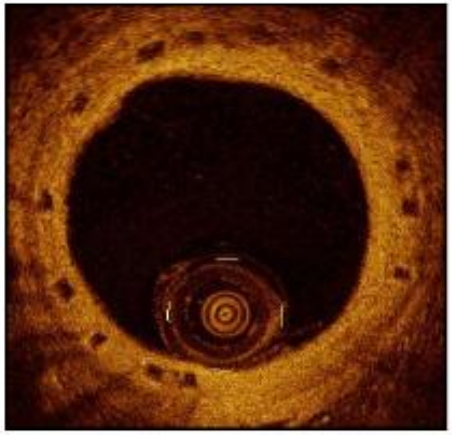


Resorption: Vascular response

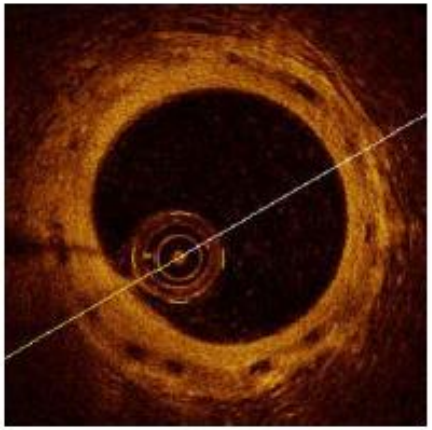
Cohort B, Preclinical OCT Images



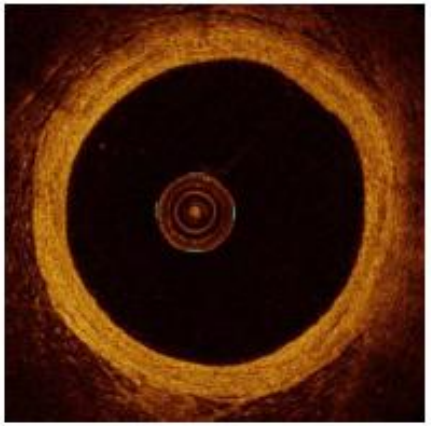
6 months



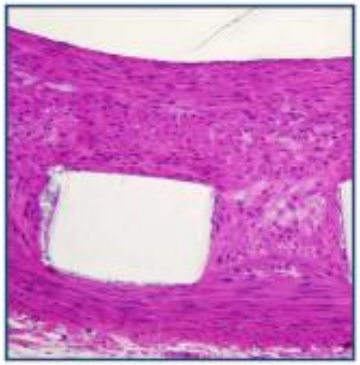
24 months

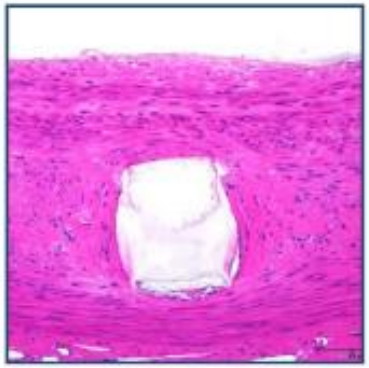


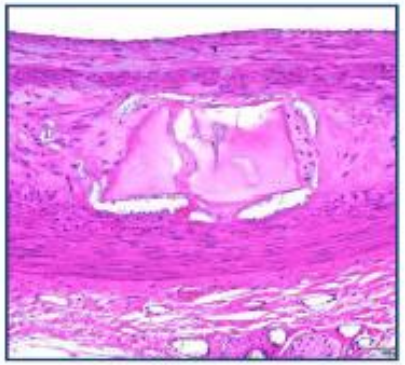
36 months

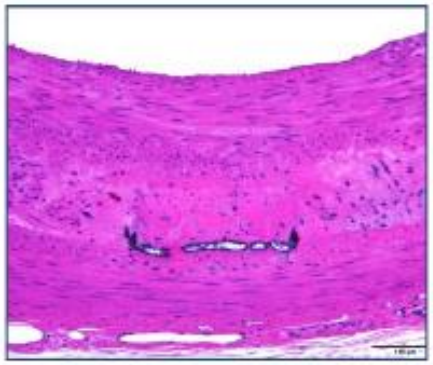


42 months

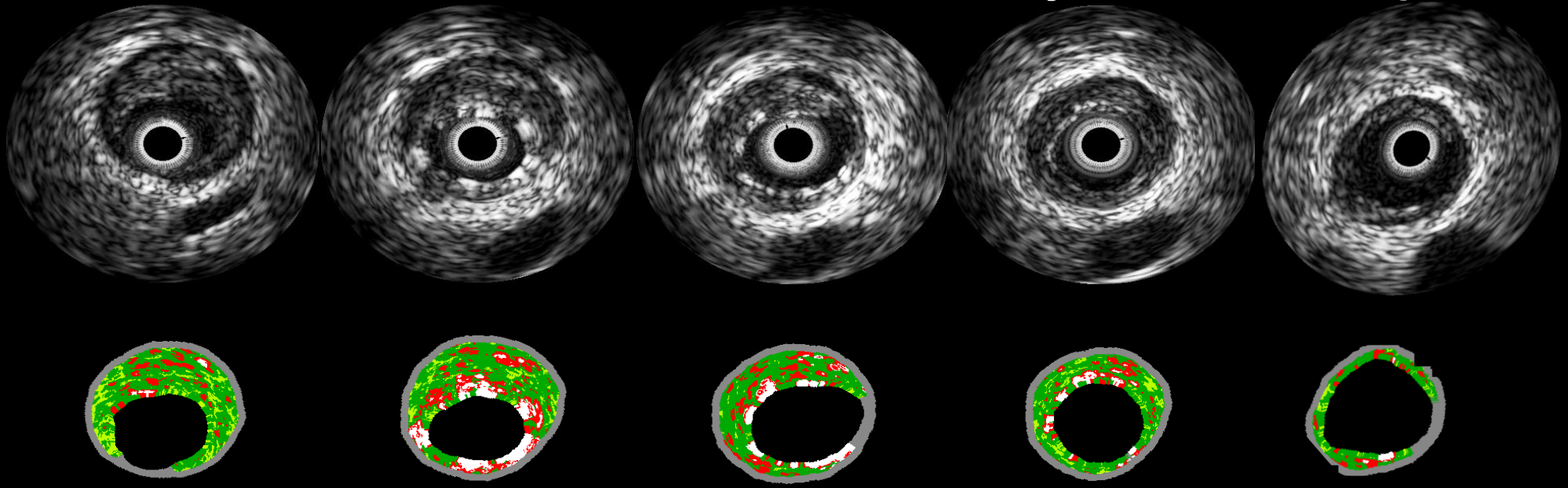








IVUS/ VH at 5Y follow up : Plaque media Reduction, Late lumen Enlargement and adaptive remodeling

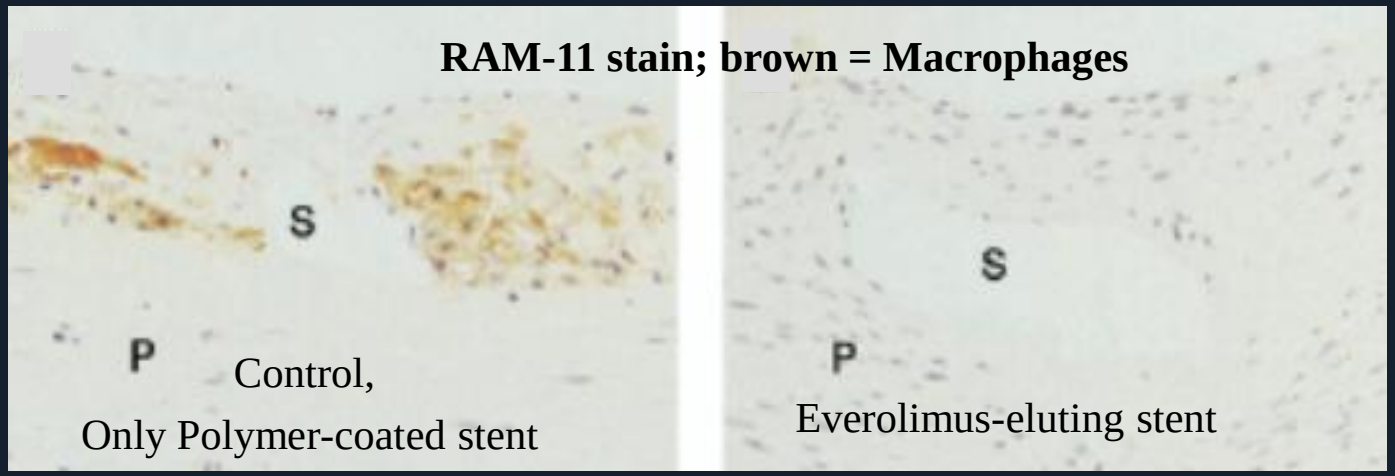


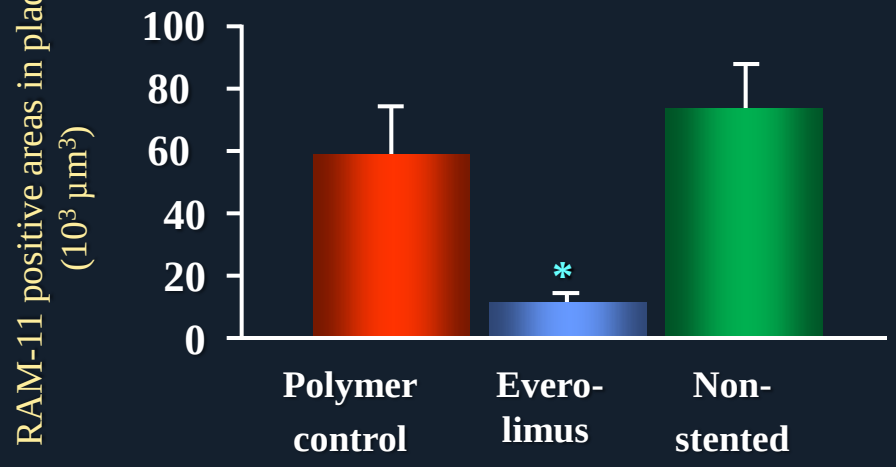
	Post-PCI	6 months	2 years	5 years
Mean lumen area (mm^2)	6.95	6.17	6.56	6.96
Plaque area (mm^2)	8.78	9.17	7.54	7.57
Vessel area (mm^2)	15.72	15.34	14.09	14.52

Simsek et al. Eurointervention 2013

Everolimus Induced Autophagy of Macrophages

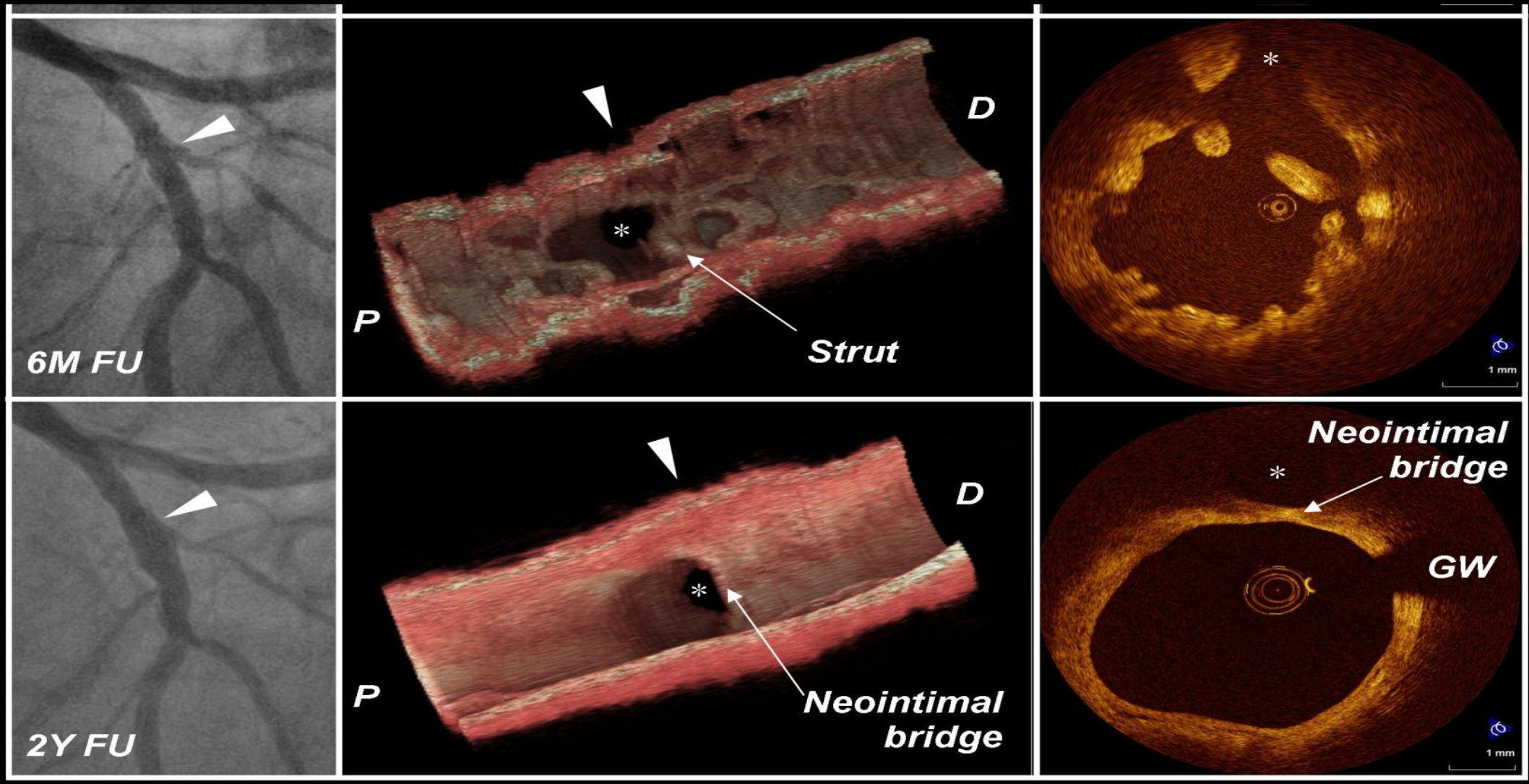
Atherosclerotic arteries of cholesterol-fed rabbits



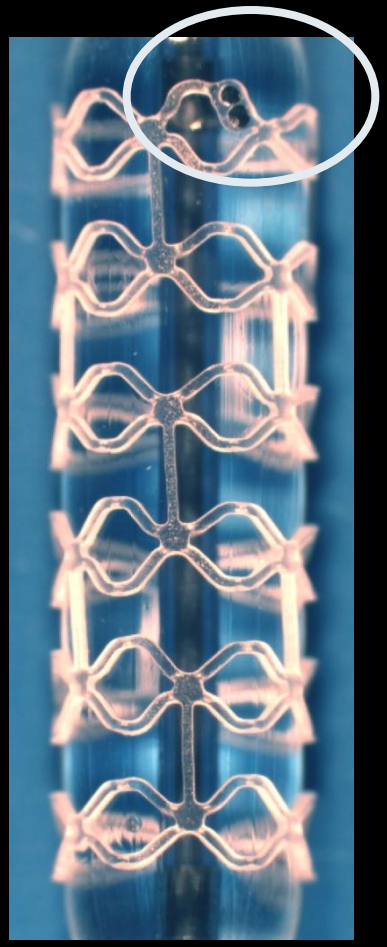


EES resulted in marked reduction of macrophage content, with preservation of SMC, *which can stabilize the plaque vulnerability*

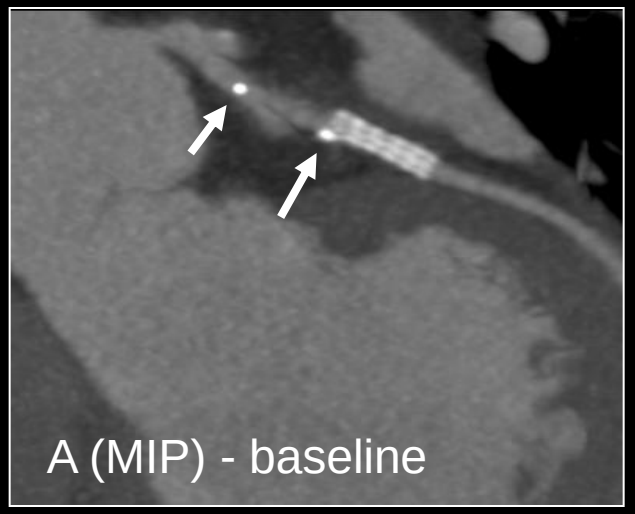
Verheye S et al. JACC 2007;49:706-15

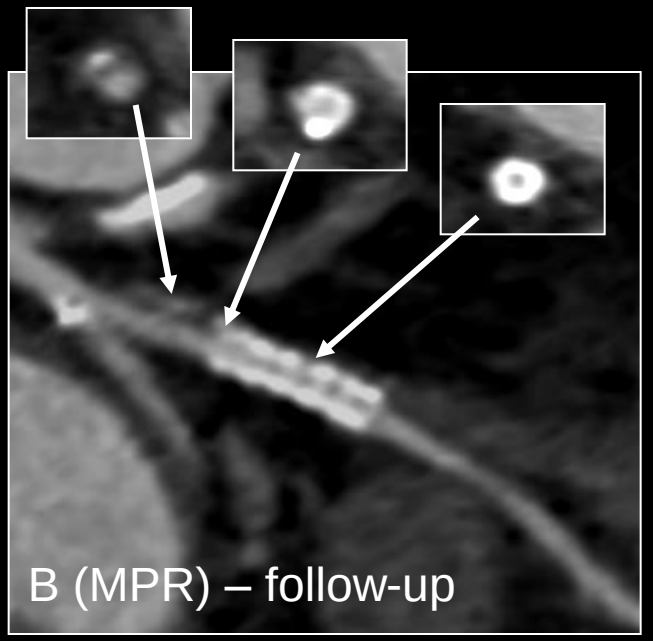

6M FU
D
P
Strut
1 mm
2Y FU
D
P
Neointimal bridge
Neointimal bridge
GW
1 mm

Metal vs BVS by MSCT



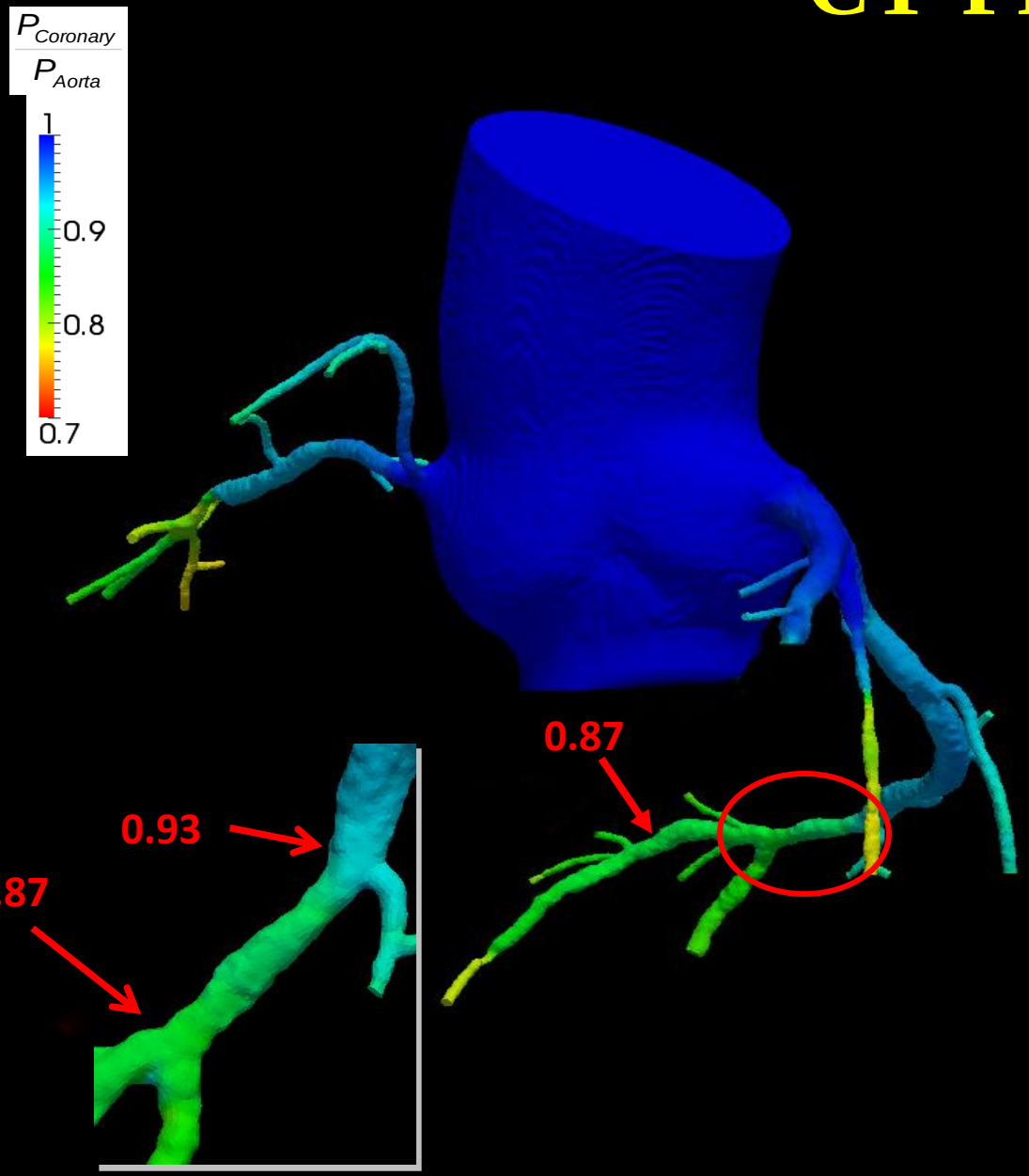
*marker



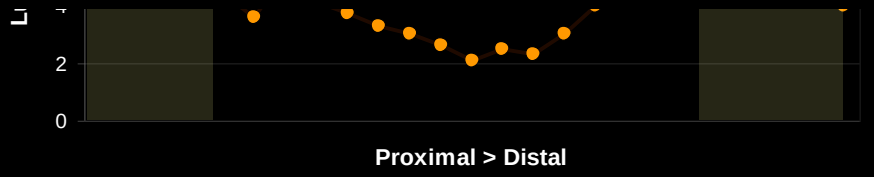


- Absorbable and metal stent implantation (bail-out)
- Highly attenuating distal metal stent well visible
- Only prox./dist. markers absorbable stent detectable
- In-stent plaque remains visible

CT-FFR

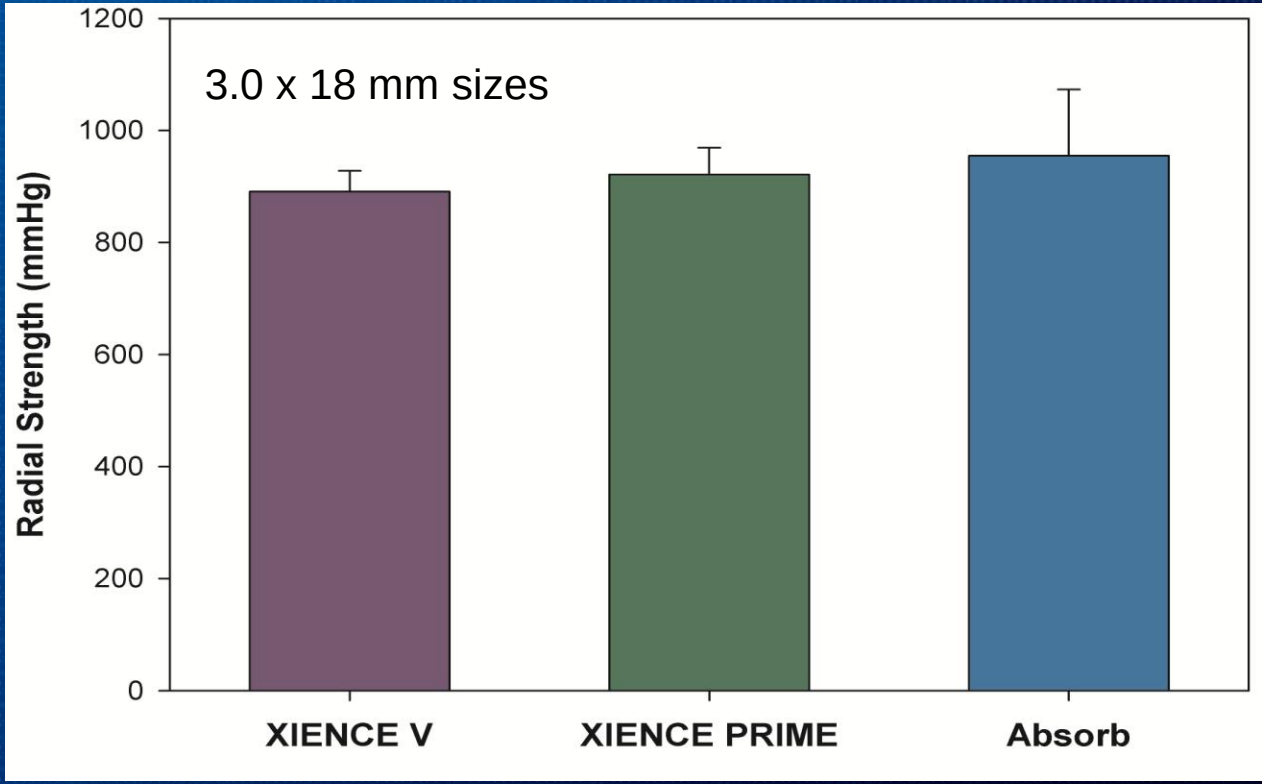


Non-invasive FFR could further improve the interpretation of quantitative MSCT results.



Onuma et al. JACC interv 2013

Mechanical Strength of BVS



Absorb acute radial strength is comparable to that of XIENCE V and XIENCE PRIME.

n = 6

Dobrin PB, Am. J. Physiol. 1973; 225: 659.

Agrawal CM, Biomaterials 1992; 13: 176.

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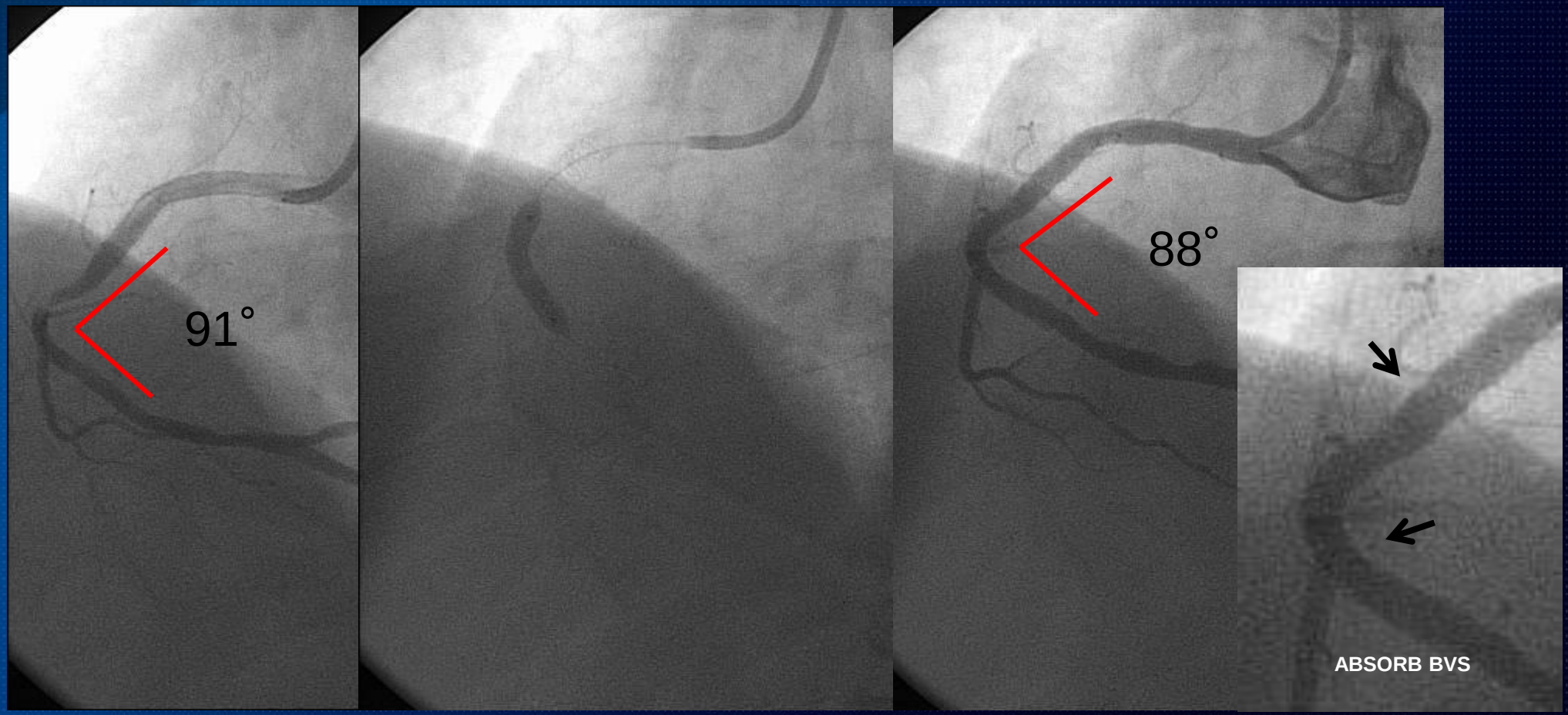
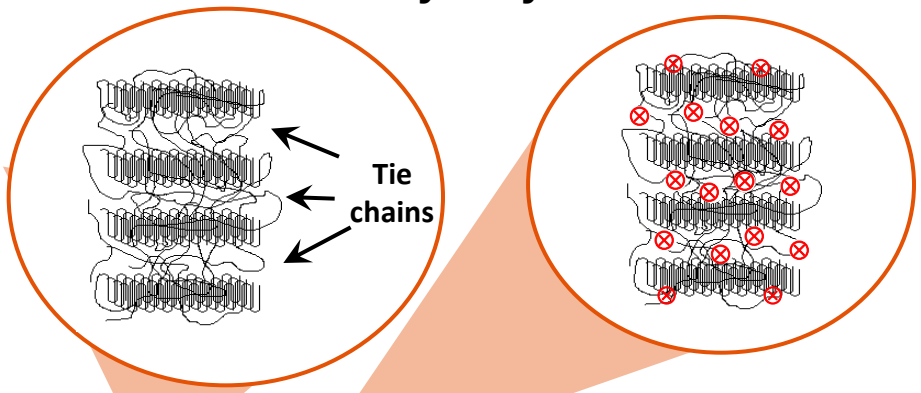
Deliverability/Conformability of BVS

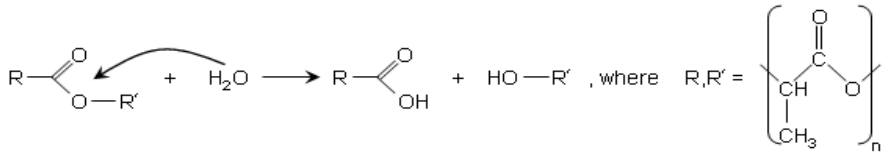


Serruys, PW. , TCT 2009

Polylactide Resorbtion → Losing Radial Support after 6 months

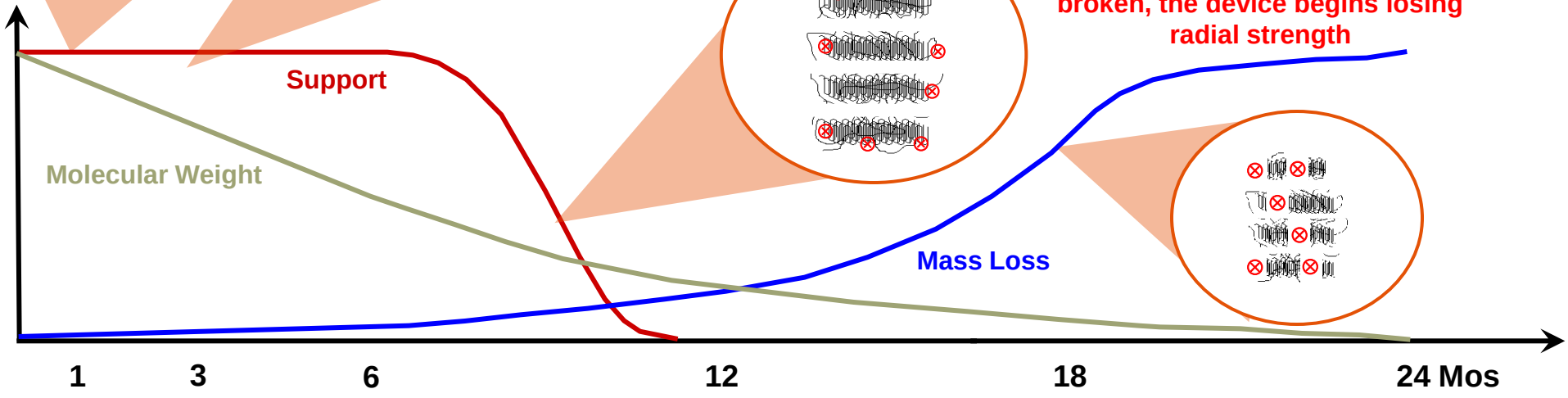
Hydrolysis occurs via random chain scission of the ester bond



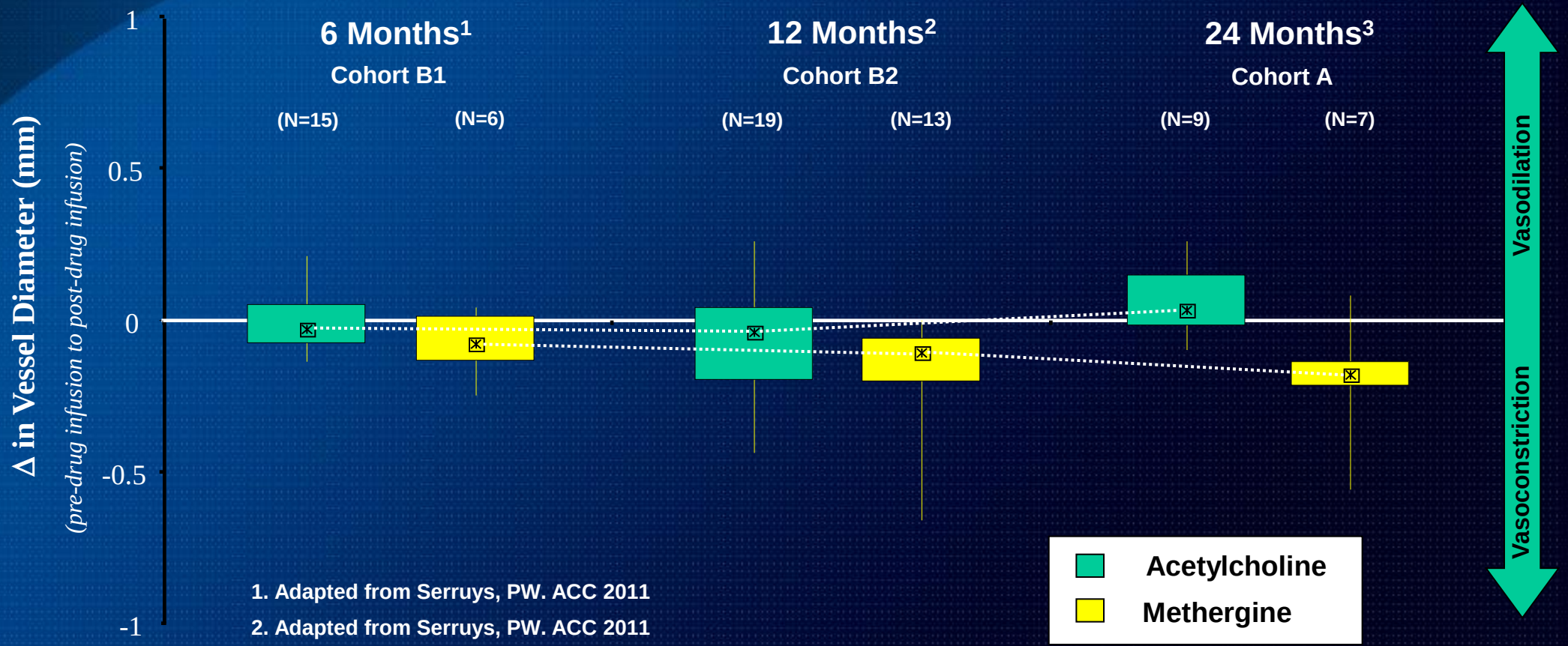


Hydrolysis randomly cleaves amorphous tie chains, leading to a decrease in molecular weight without altering radial strength

When enough tie chains are broken, the device begins losing radial strength



Vasomotor Function Testing

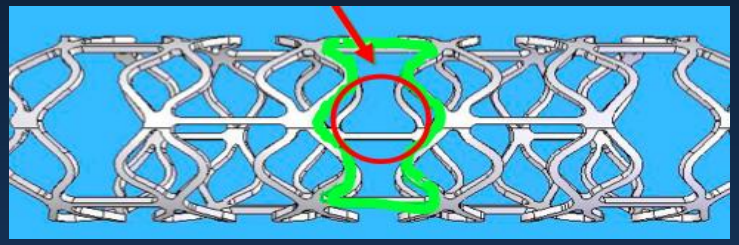


1. Adapted from Serruys, PW. ACC 2011
2. Adapted from Serruys, PW. ACC 2011
3. Adapted from Serruys, PW, et al. *Lancet* 2009; 373: 897-910.

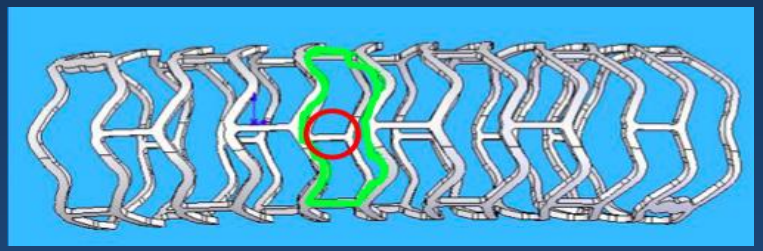
BVS 1.0 vs. BVS 1.1

The second generation (ABSORB BVS1.1) has a modified platform design and a different manufacturing process of the polymer.

Larger Maximum Circular Unsupported scaffold area (MCUSA)



ABSORB BVS 1.0 (Cohort A)

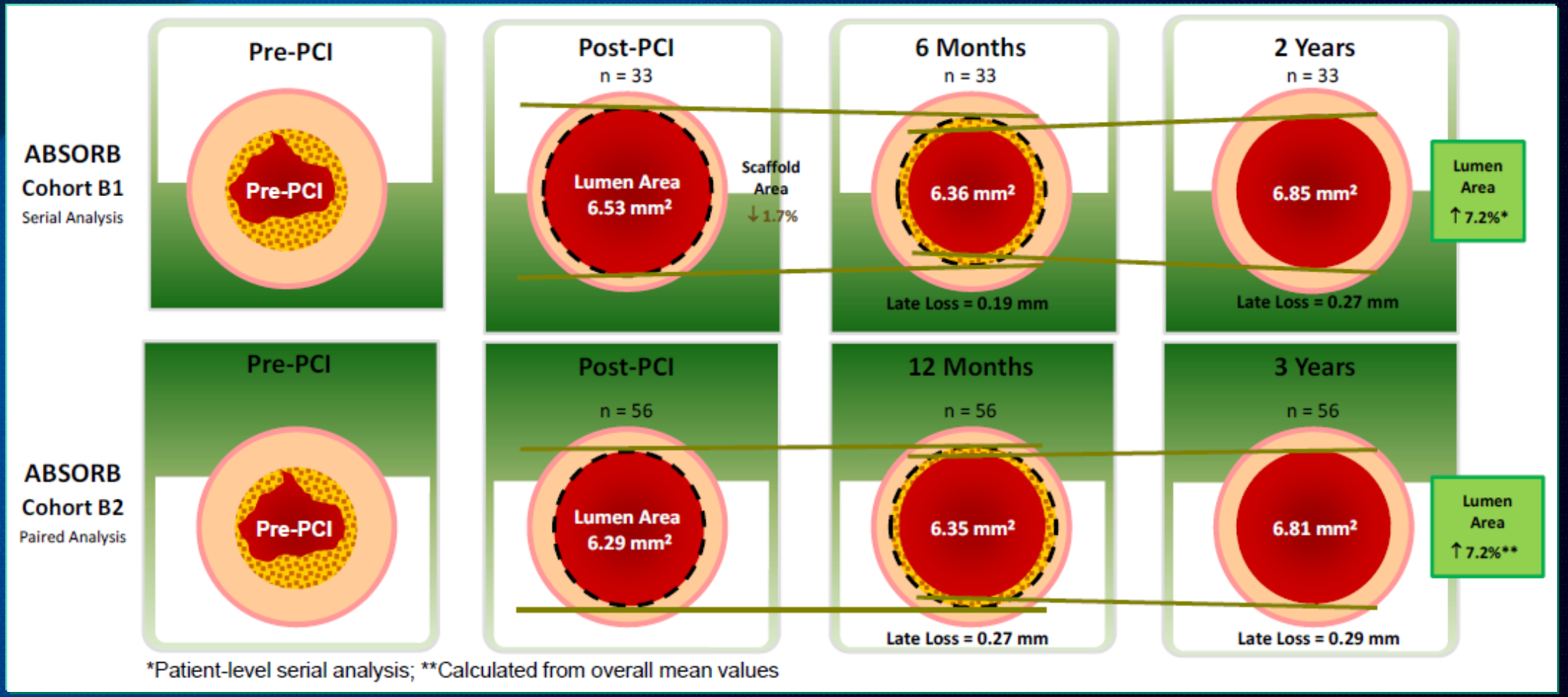


ABSORB BVS 1.1 (Cohort B)

ABSORB BVS1.1 has

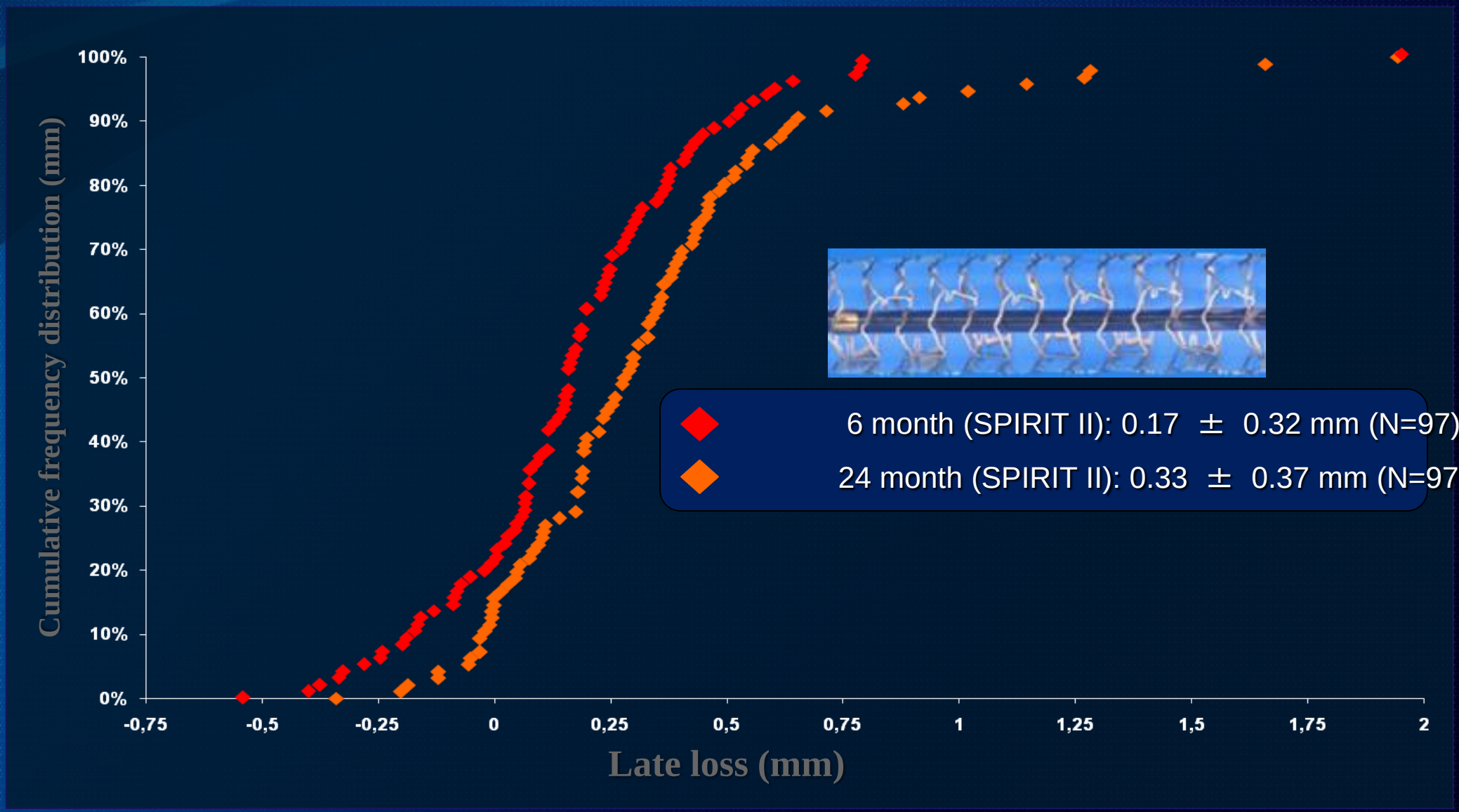
- More radial strength
- More uniform support and drug application
- Longer duration of support
- Profile less than Cypher
- Track test better than ML Vision
- No change in strut thickness

ABSORB Cohort B Trial: IVUS Vessel Area, Lumen Area, and Scaffold Area Comparison



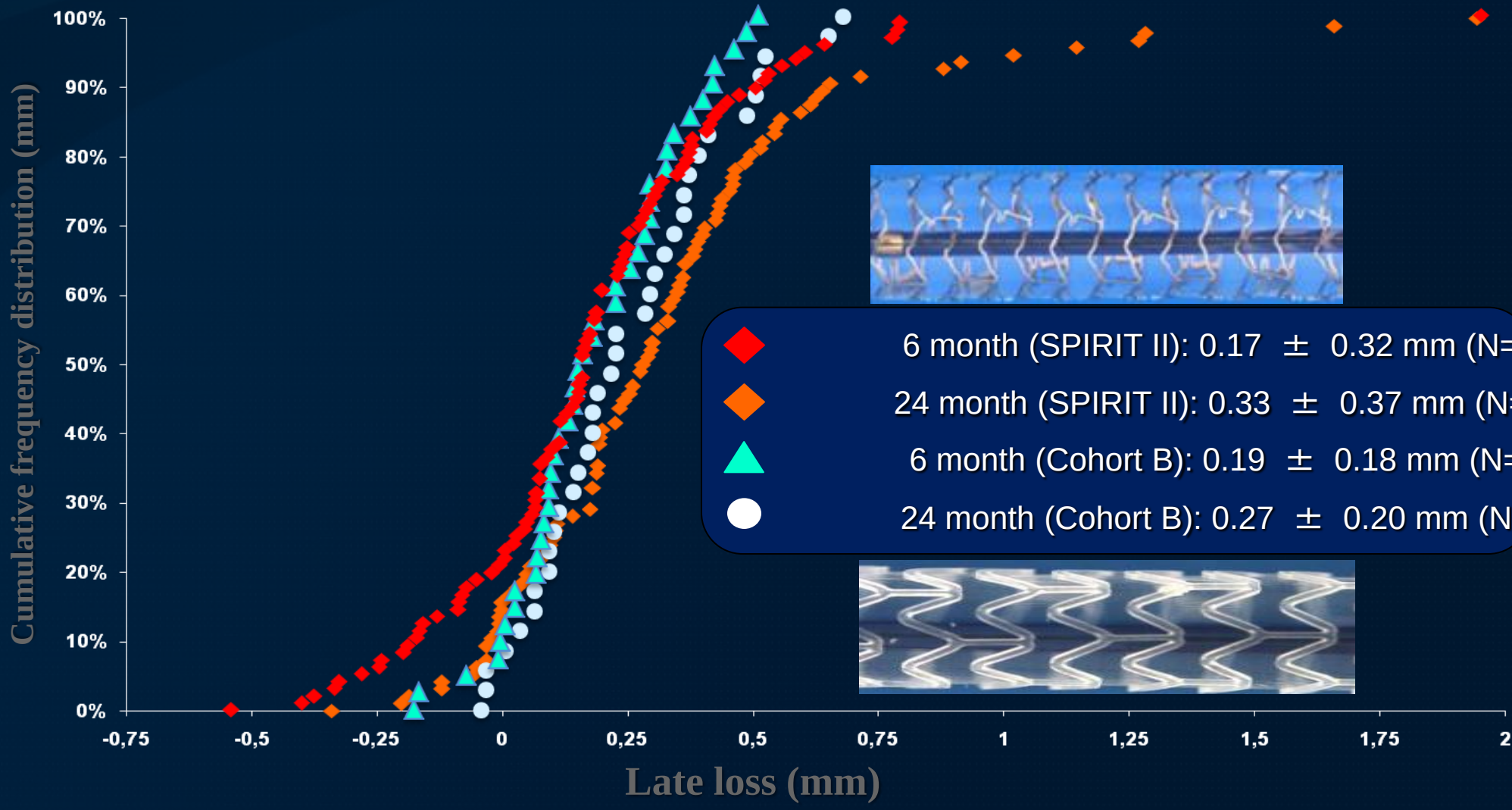
*Patient-level serial analysis; **Calculated from overall mean values

Late Loss with Absorb Cohort B vs. Xience V



Claessen BE et al. Circ CV Int. 2009;2:339-47

Late Loss with Absorb Cohort B vs. Xience V



Claessen BE et al. Circ CV Int. 2009;2:339-47
Serruys PW. ESC 2012

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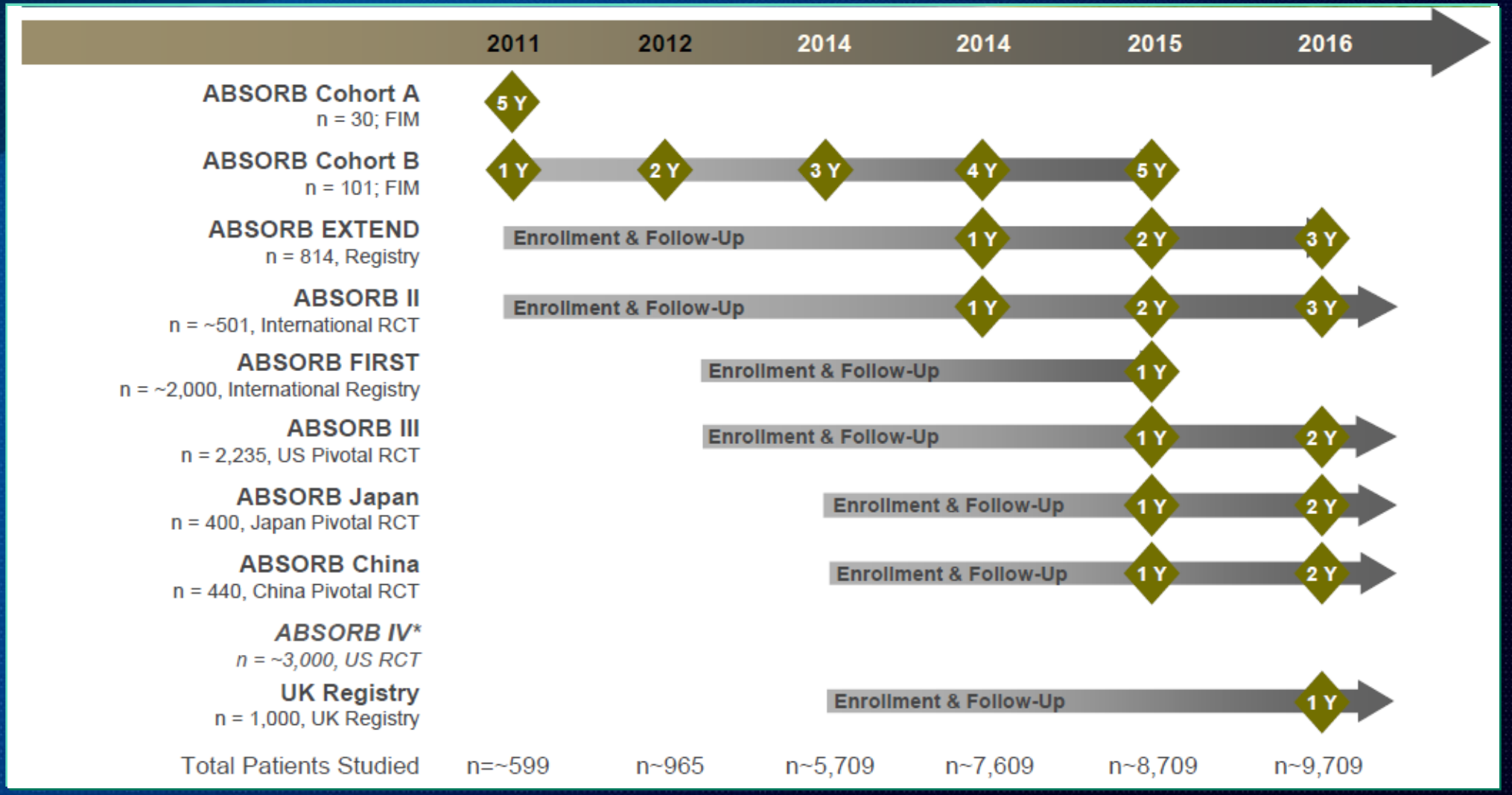
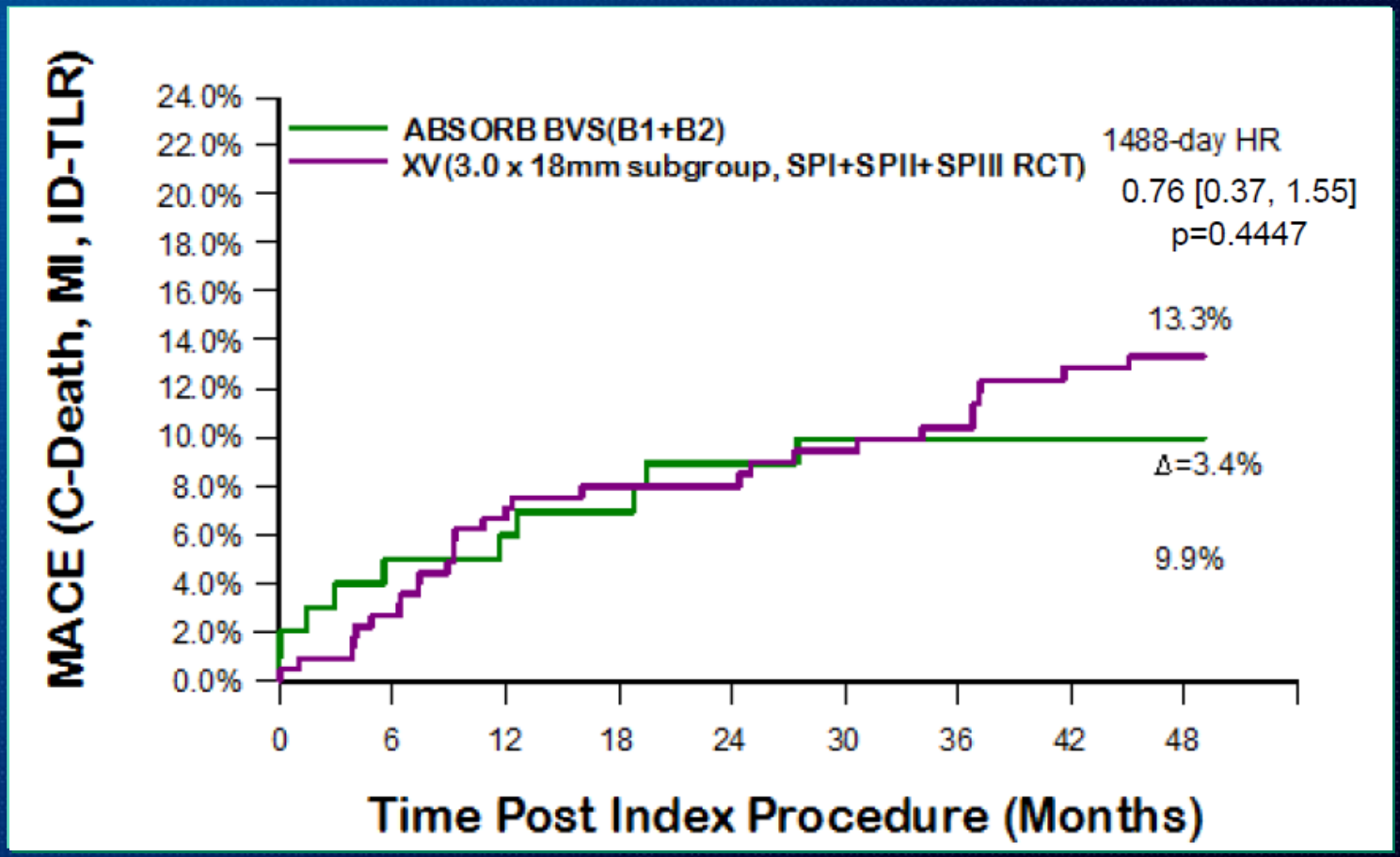
ABSORB™ Clinical Trial Program



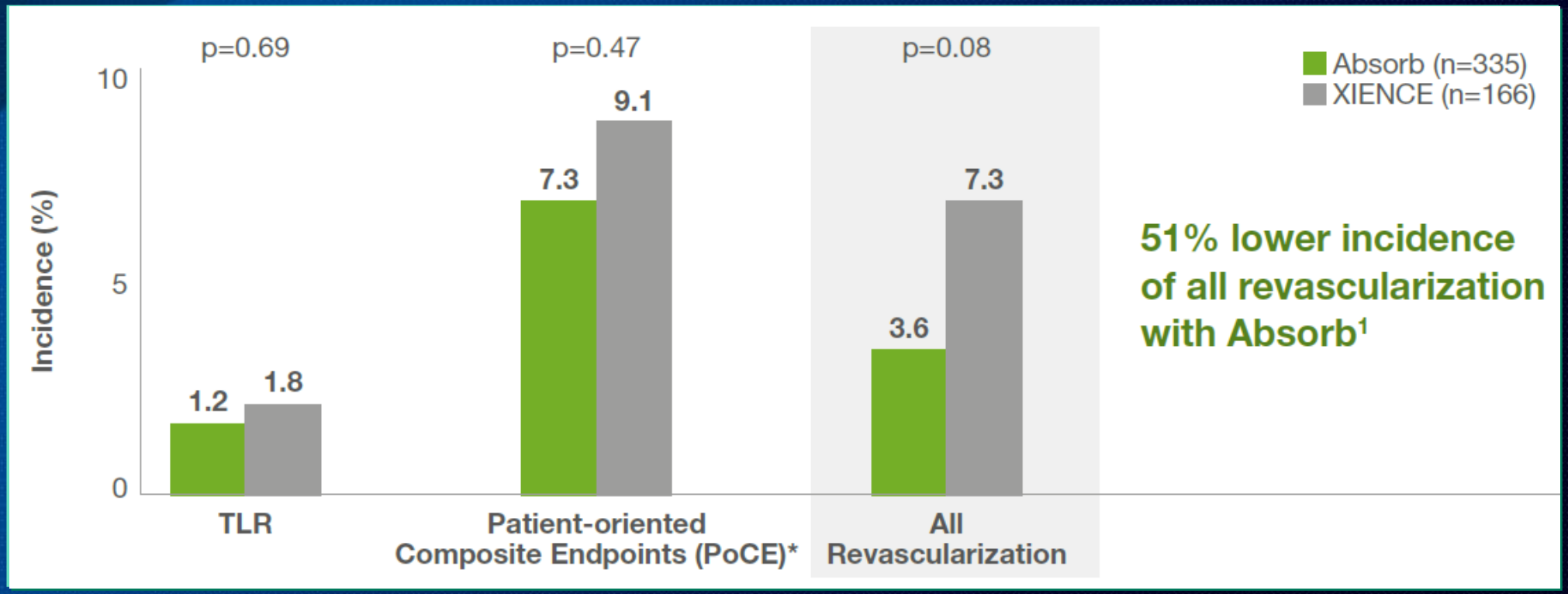
BVS and XIENCE V: 4-year MACE



ABSORB EXTEND Clinical Results

	12 Months	24 Months	36 Months
Non-Hierarchical	n=250	n=250	N=250
Cardiac Death %	0.4	0.4	0.8
Myocardial Infarction %	2.8	4.0	4.0
Q-wave MI	1.2	1.2	1.2
Non Q-wave MI	1.6	2.8	2.8
Ischemia driven TLR %	2.0	4.0	6.0
CABG	0.0	0.4	0.4
PCI	2.0	4.0	6.0
Hierarchical MACE %	4.4	7.3	9.3
Scaffold Thrombosis %	0.8	0.8	1.2

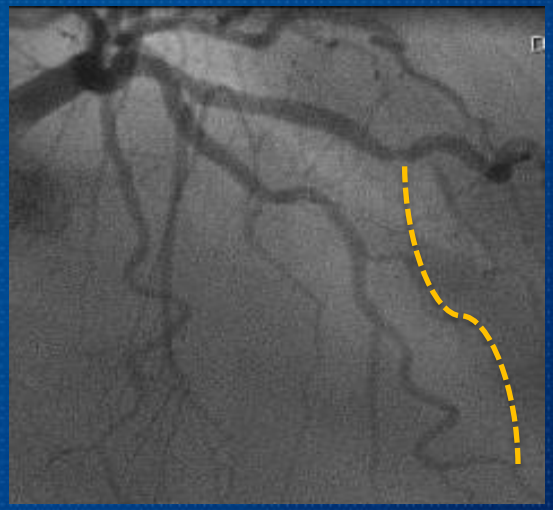
ABSORB II 1-year results



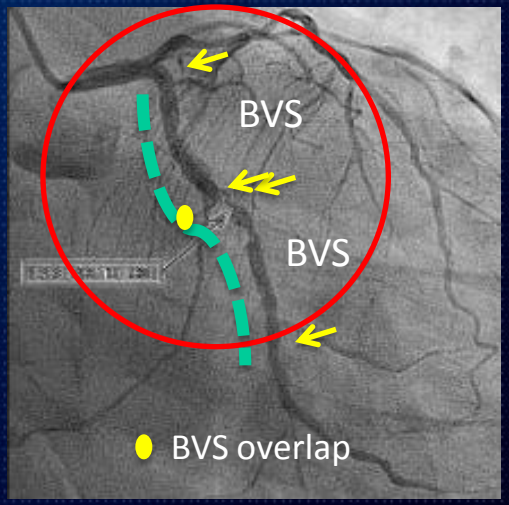
Definite scaffold/stent thrombosis:
0.6% in BVS vs. 0% in the Xience

ABSORB II & ABSORB Extend registry

Non-Hierarchical % (n)	6 Months* (N=450)	12 Months* (N=450)
Scaffold Thrombosis (ARC Def/Prob)	0.7 (3)	0.9 (4)



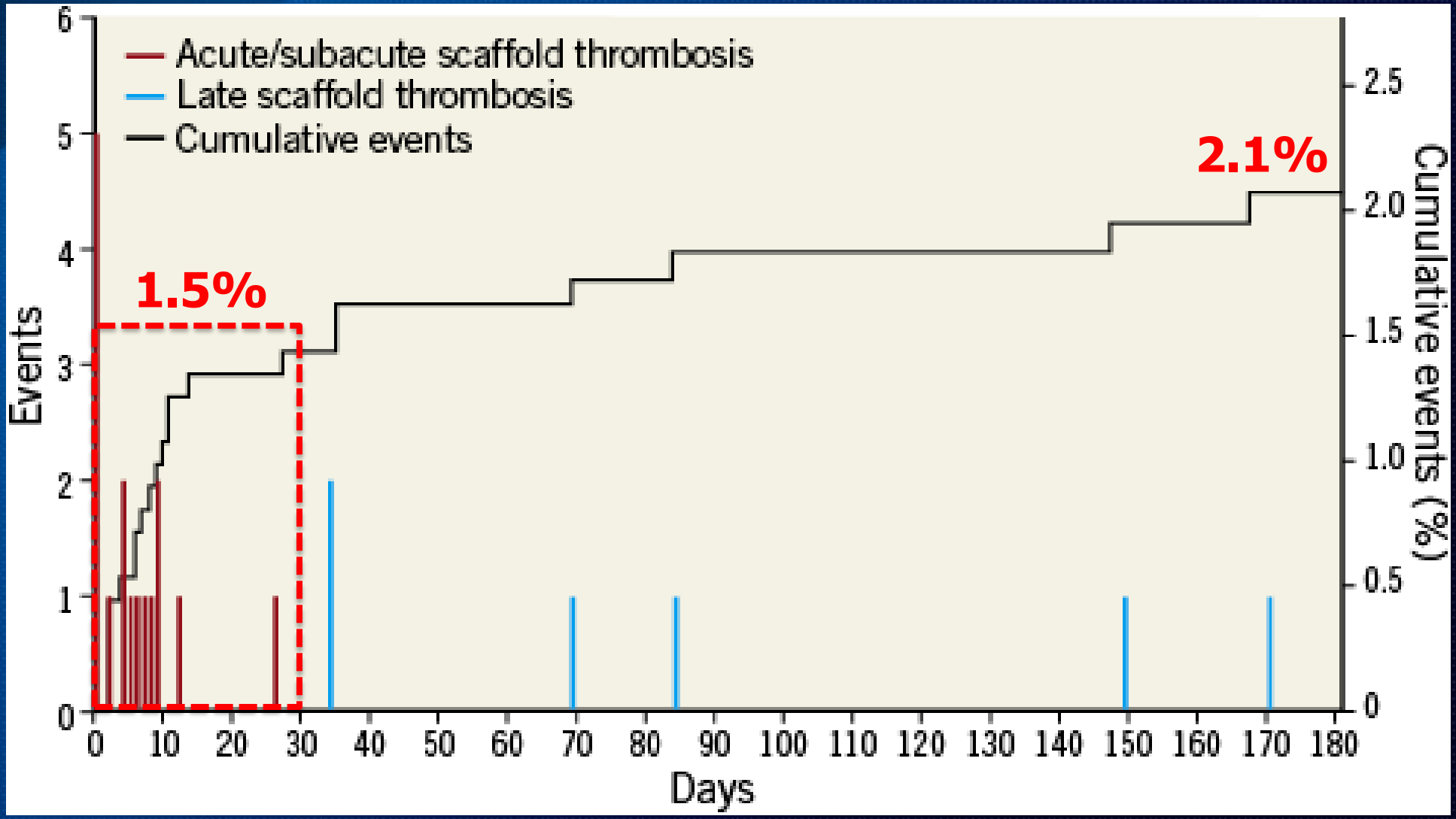
- 2 cases related to interruption of/ or resistance to DAPT



- 1 related to overlap
- 1 unknown cause

2 subacute (day 6 and 29), 2 late (day 75 and 239)

Def/Prob ST Ghost-EU registry
1.189 patients treated with BVS



Capodanno et al. Ghost EU registry, EuroIntervention 2014, ahead of print

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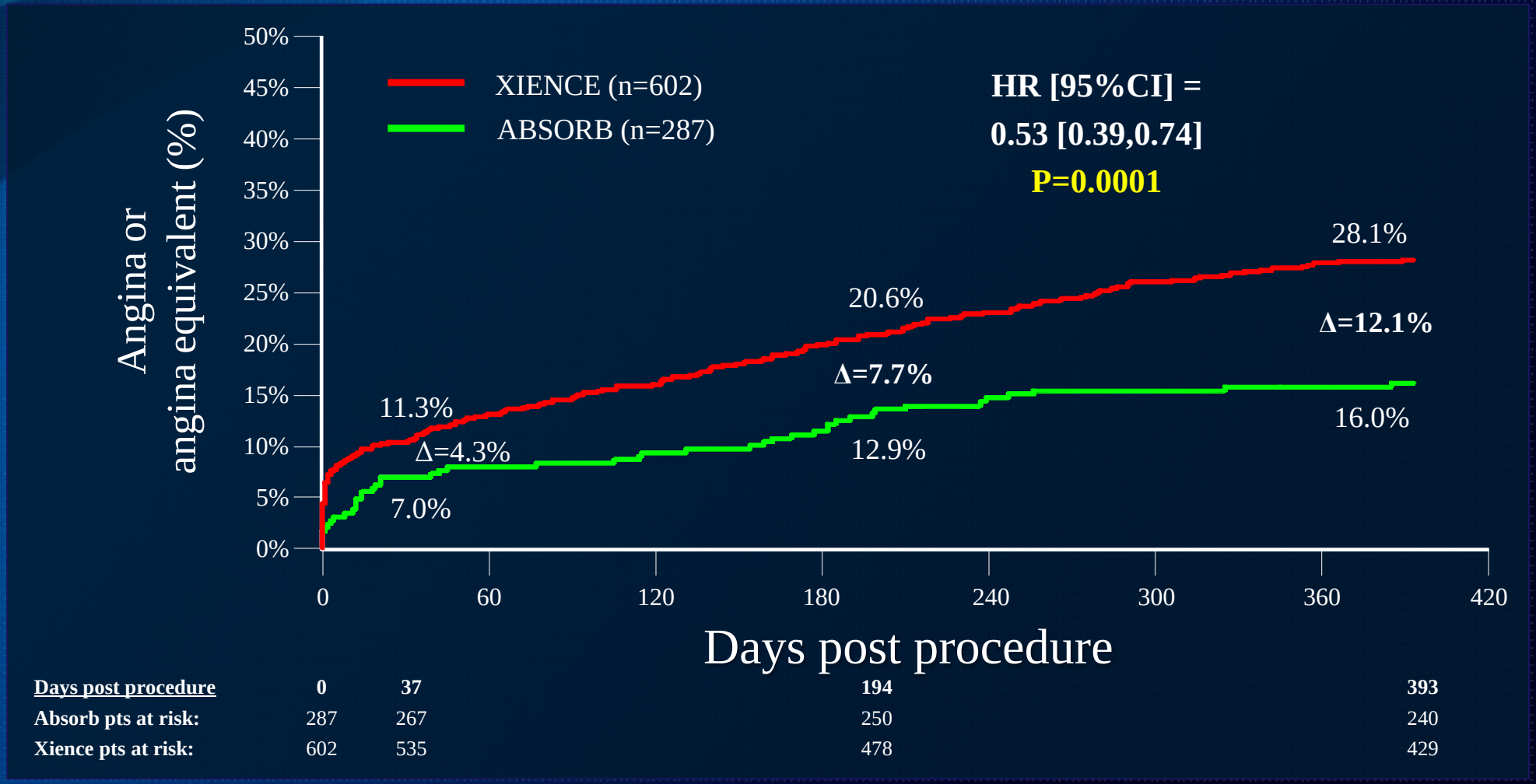
Cox proportional hazard analysis of TLF

	Univariate		Multivariate*	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	0.99 (0.97-1.01)	0.49	–	–
Male	0.64 (0.38-1.09)	0.10	0.66 (0.32-1.35)	0.26
Current smoker	1.71 (1.05-2.82)	0.03	1.80 (0.91-3.58)	0.09
Diabetes mellitus	2.51 (1.55-4.06)	<0.001	2.41 (1.28-4.53)	0.006
History of PCI	1.04 (0.63-1.71)	0.90	–	–
History of CABG	0.86 (0.27-2.74)	0.80	–	–
History of renal disease	1.70 (0.84-3.46)	0.14	1.60 (0.74-3.47)	0.24
ACS at presentation	1.50 (0.93-2.45)	0.10	1.45 (0.74-2.84)	0.28
ACC/AHA B2/C lesion type	0.91 (0.56-1.48)	0.70	–	–
In-stent restenosis	1.97 (0.72-5.44)	0.19	2.42 (0.81-7.22)	0.11
Chronic total occlusion	0.80 (0.29-2.19)	0.66	–	–
Ostial lesion	1.86 (0.85-4.07)	0.12	2.03 (0.60-6.82)	0.25
Bifurcation treatment	1.37 (0.82-2.31)	0.23	–	–
Thrombus present	1.43 (0.82-2.48)	0.21	–	–
Number of scaffolds per patient	1.18 (0.94-1.48)	0.16	1.02 (0.61-1.71)	0.94
Total scaffold length per patient	1.01 (1.00-1.02)	0.13	1.01 (0.99-1.03)	0.41
Average scaffold diameter per patient	0.80 (0.48-1.34)	0.40	–	–
Received both Absorb BVS and stents	1.30 (0.73-2.31)	0.38	–	–
Intravascular ultrasound use	0.84 (0.43-1.65)	0.61	–	–
Optical coherence tomography use	1.31 (0.67-2.58)	0.43	–	–
Post-dilation	0.92 (0.57-1.49)	0.74	–	–
Prasugrel or ticagrelor use¶	1.42 (0-85-2.38)	0.18	1.61 (0.85-3.06)	0.15

EuroIntervention. 2014 Jul 18

Angina Status: EXTEND* vs. SPIRIT IV**

Propensity matched cohorts



Days post procedure	0	37	194	393
Absorb pts at risk:	287	267	250	240
Xience pts at risk:	602	535	478	429

*Excludes non-Japanese Asian pts because of low event reporting rates; **Excludes complex pts and lesions (3 vessel PCI; PCI of 2 lesions per vessel; RCA aorto-ostial lesions; bifurcation lesions)

c/o Stone GW TCT2013

Clinical Update: Transition in Clinical Endpoints

Interventional Cardiology is Shifting Focus onto Patient-Oriented Outcomes

Device Oriented Endpoints	Patient Oriented Endpoints
• Target Lesion Failure (TLF) • Target Lesion Revascularization (TLR) • Myocardial Infarction (MI) • Restenosis	• All Death, All MI, All Revascularization • Angina • Quality of Life

ABSORB III Randomized Controlled Trial

Principal Investigators: Dean Kereiakes & Stephen Ellis,

Study Chair: Gregg Stone

Prospective, single blind, randomized 2:1 Absorb BVS vs. XIENCE

Up to 2250 patients in up to 220 US and non-US sites

- ABSORB III is the pivotal trial to support the US post-market approval of Absorb BVS.

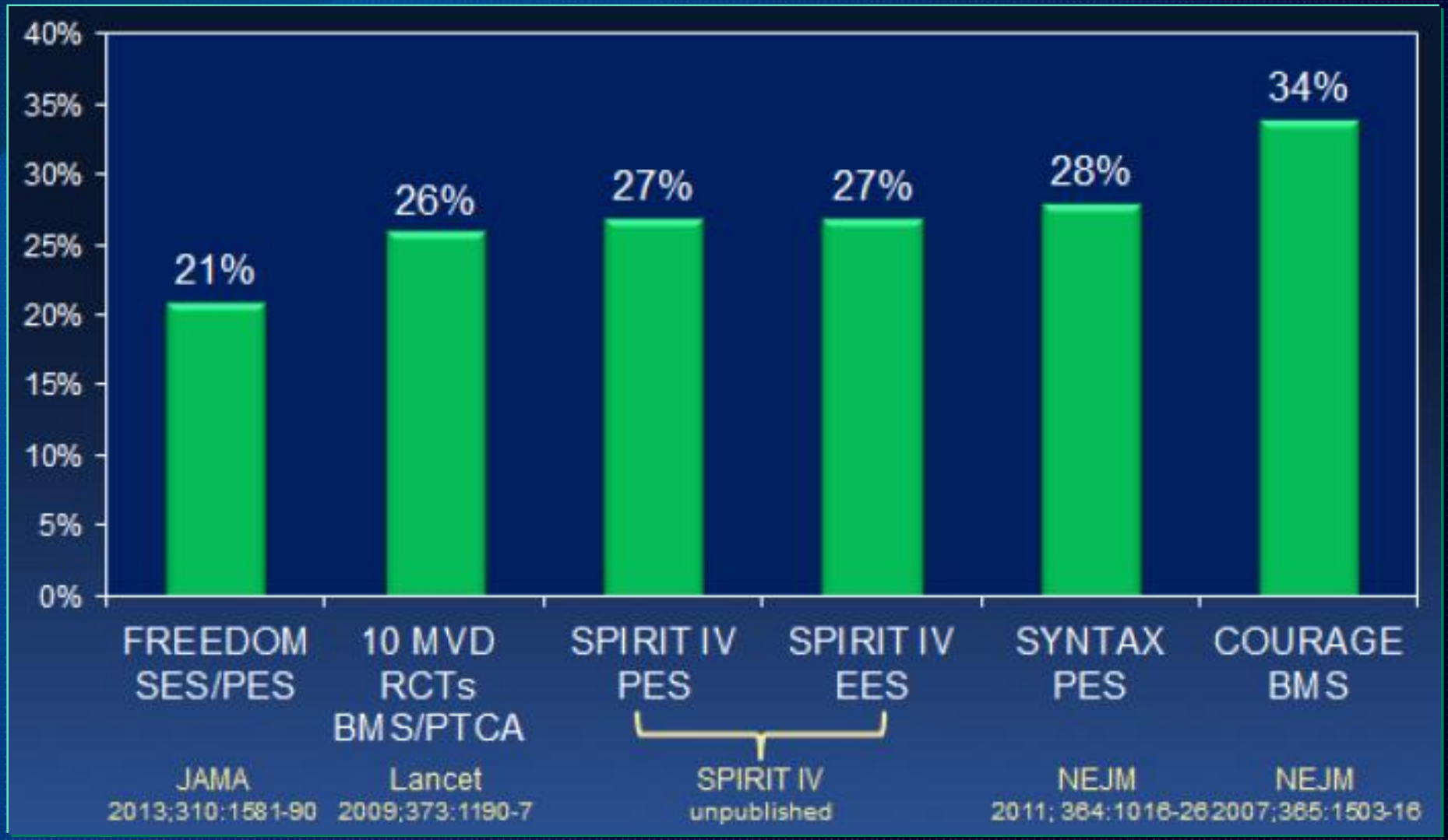
- The primary objective of ABSORB III is to evaluate the safety and effectiveness of the Absorb BVS System compared to the XIENCE in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels.

Background of ABSORB IV

- 2 issues
  1) Recurrent angina
  2) Accumulation of very late adverse events

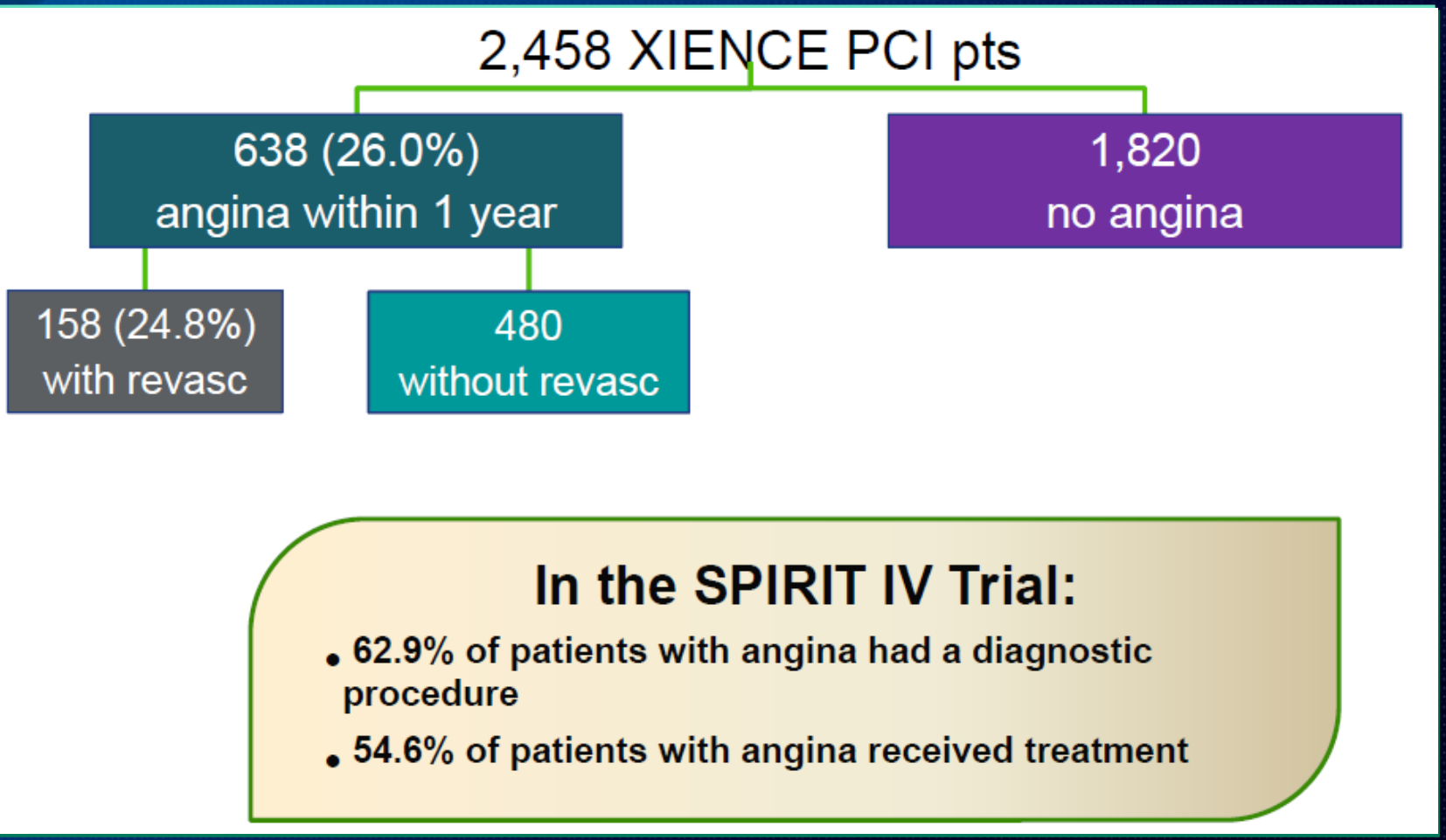
Dr Stone, TCT 2013

Angina at 1 year after PCI



Dr Stone, TCT 2013

Post PCI angina: potential area of improvement



In the SPIRIT IV Trial:

- **62.9% of patients with angina had a diagnostic procedure**
- **54.6% of patients with angina received treatment**

ABSORB IV

~3,000 pts randomized 1:1 ABSORB v XIENCE

RVD: 2.50 - 3.75 mm; Lesion length: ≤24 mm

Scaffold diameters: 2.5, 3.0 and 3.5 mm
Scaffold lengths: 12, 18, and 28 mm

~5,000 total pts (ABSORB III + IV) with up to 2 de novo lesions in different epicardial vessels randomized, with FU for at least 5 years, at up to 160 US and non-US sites

Primary endpoints:

1. Angina at 1 year (ABSORB IV)
2. TLF between 1 and 5 years (landmark analysis)

PI: GW Stone
Co-PIs: SG Ellis, DJ Kereiakes

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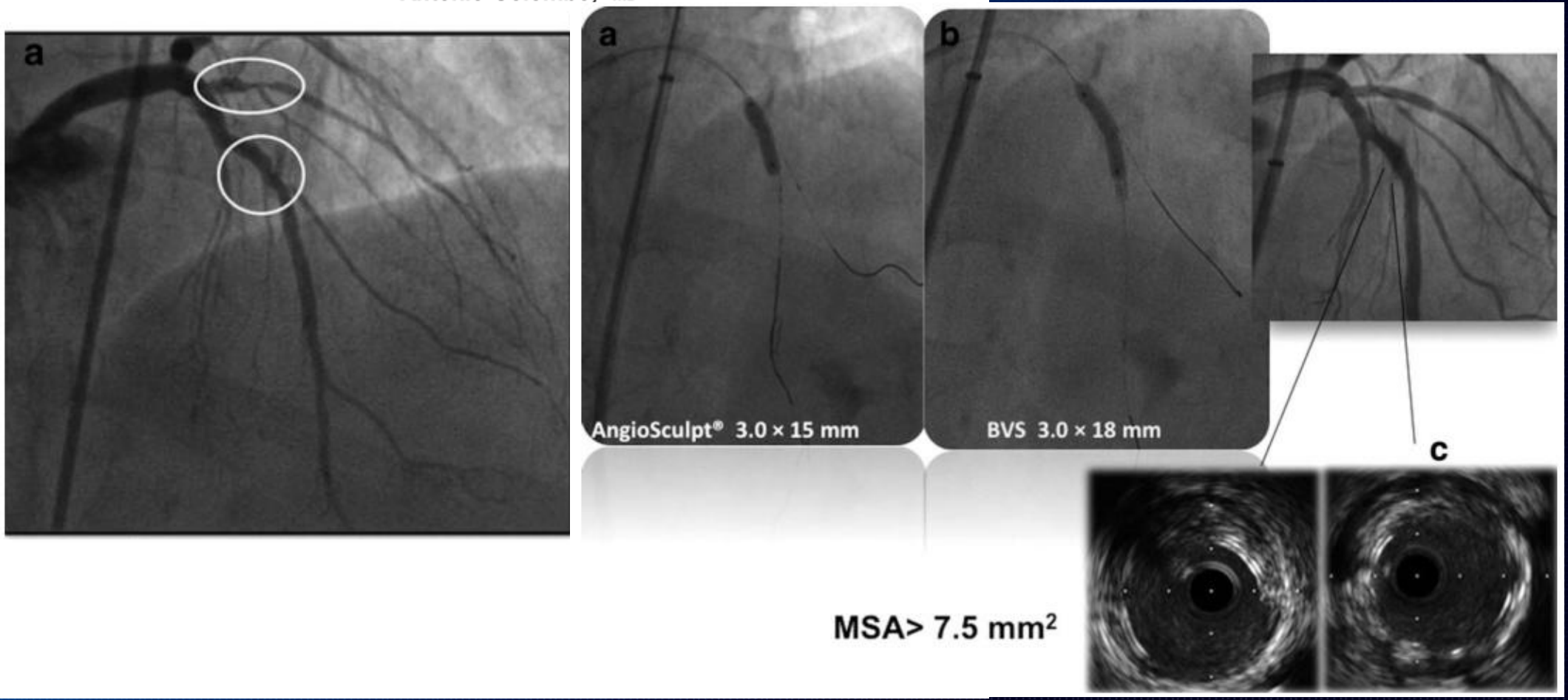
Case Report

Can Bioabsorbable Scaffolds Be Used in Calcified Lesions?

Sandeep Basavarajaiah,[1,2*] MBBS, MRCP, MD, Toru Naganuma,[1] MD, Azeem Latib,[1] MD, and Antonio Colombo,[1] MD



Catheterization and Cardiovascular Interventions (2013)

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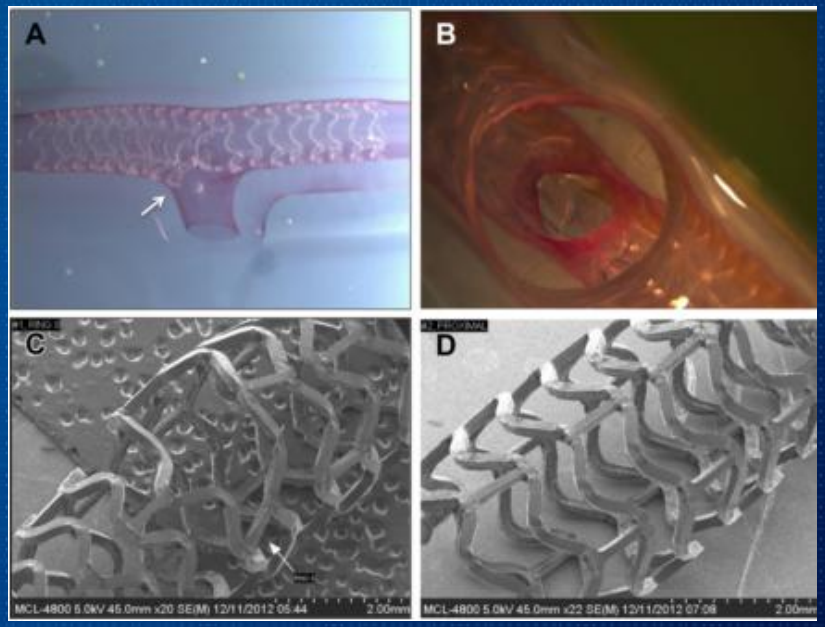
The Absorb Bioresorbable Vascular Scaffold in Coronary Bifurcations

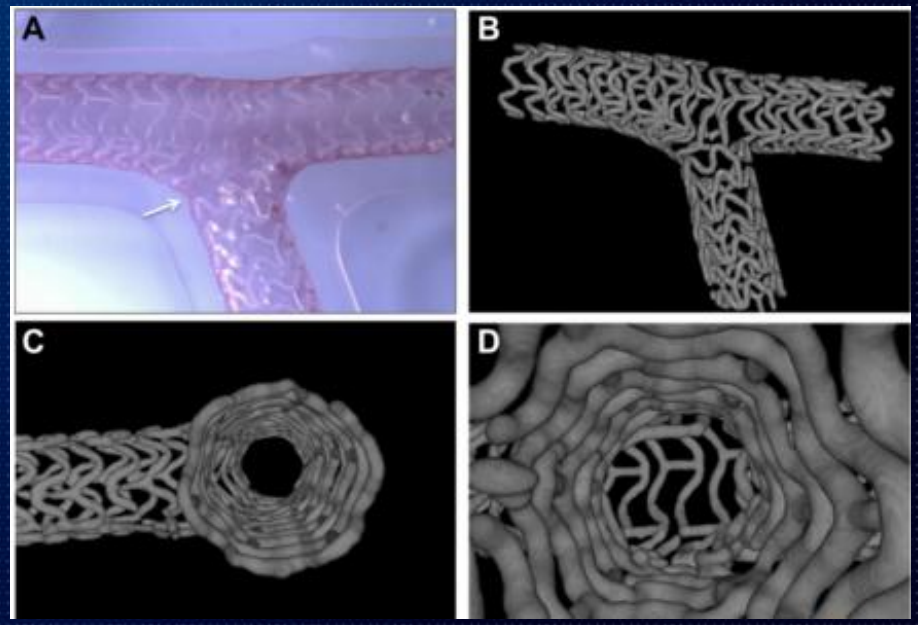
Insights From Bench Testing

Vladimír Džavík, MD,* Antonio Colombo, MD†

Toronto, Ontario, Canada; and Milan, Italy



Main-Vessel Stenting



T- Stenting

Bifurcation techniques appears feasible

J Am Coll Cardiol Intv 2014;7:81–8

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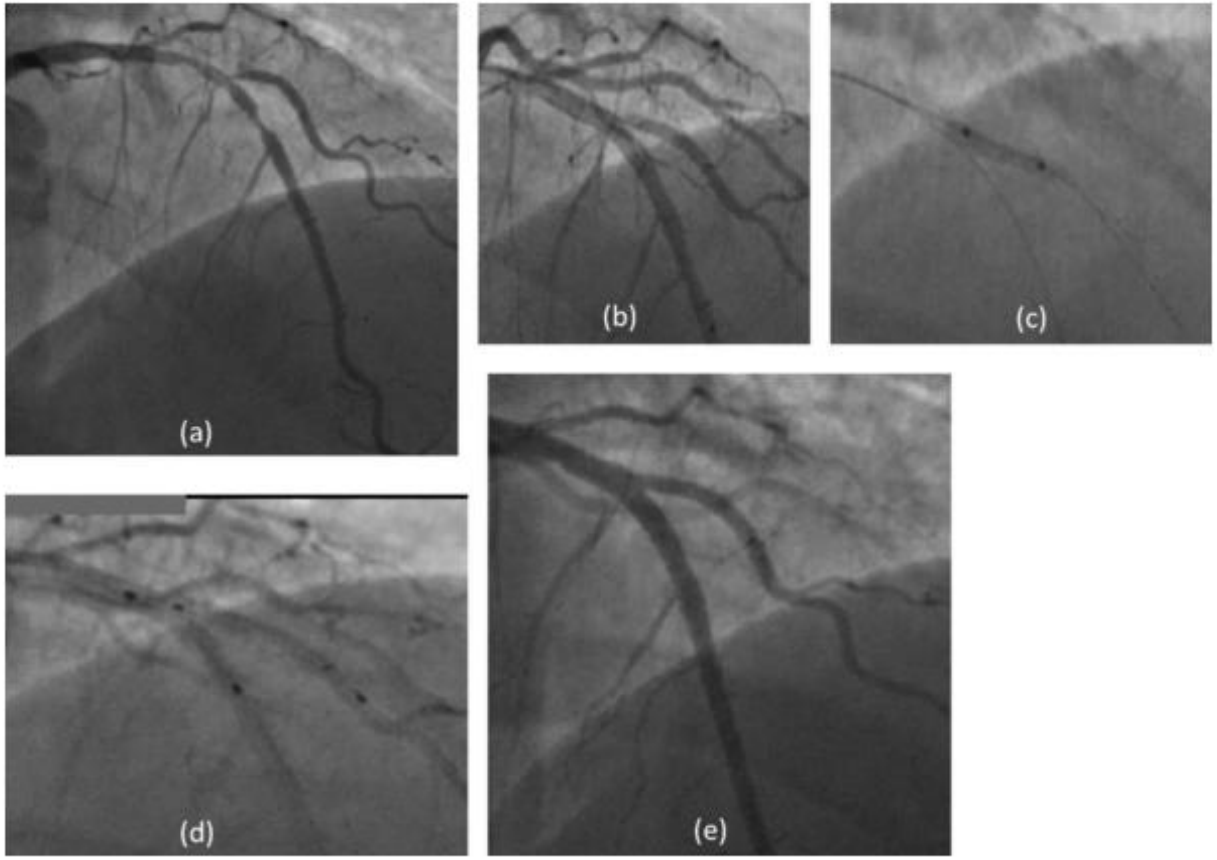
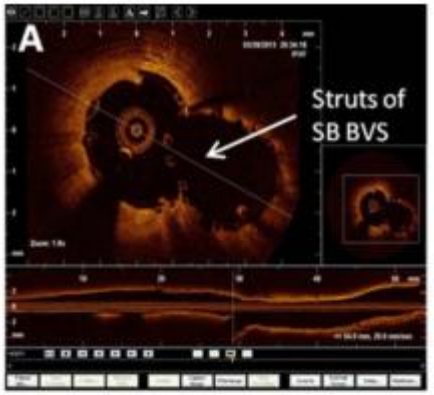
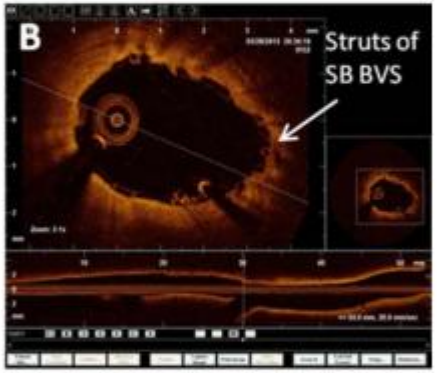
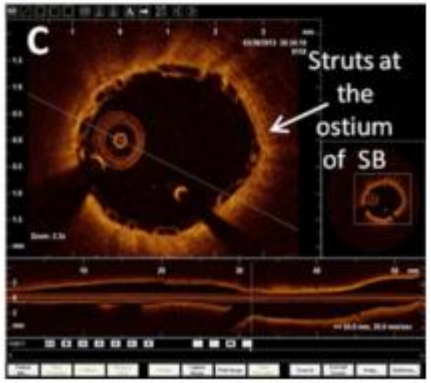
Case Report

Salvage of Side Branch by Provisional "TAP Technique" Using Absorb™ Bioresorbable Vascular Scaffolds for Bifurcation Lesions: First Case Reports with Technical Considerations









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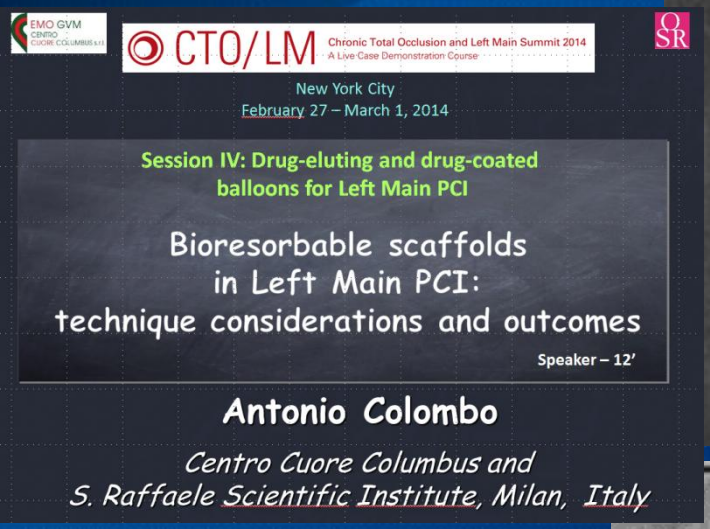
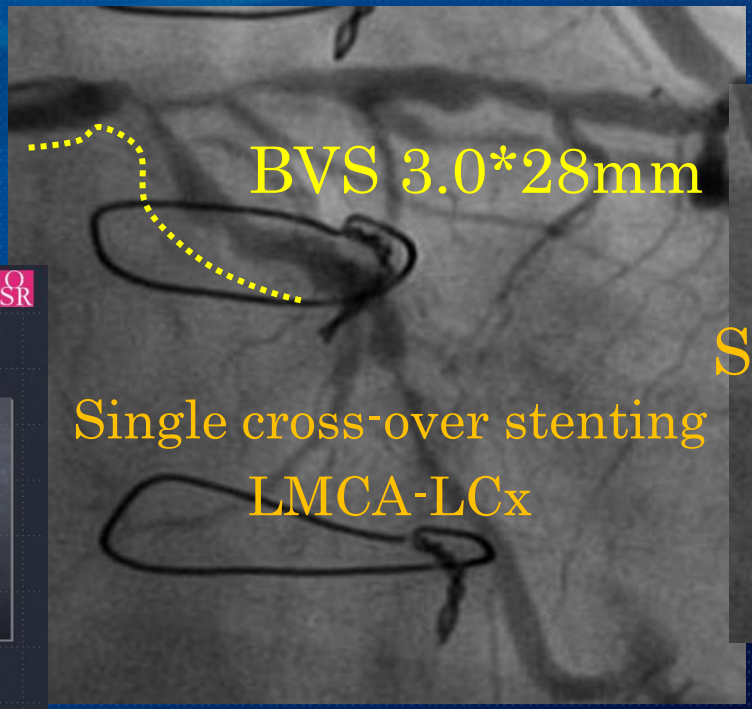
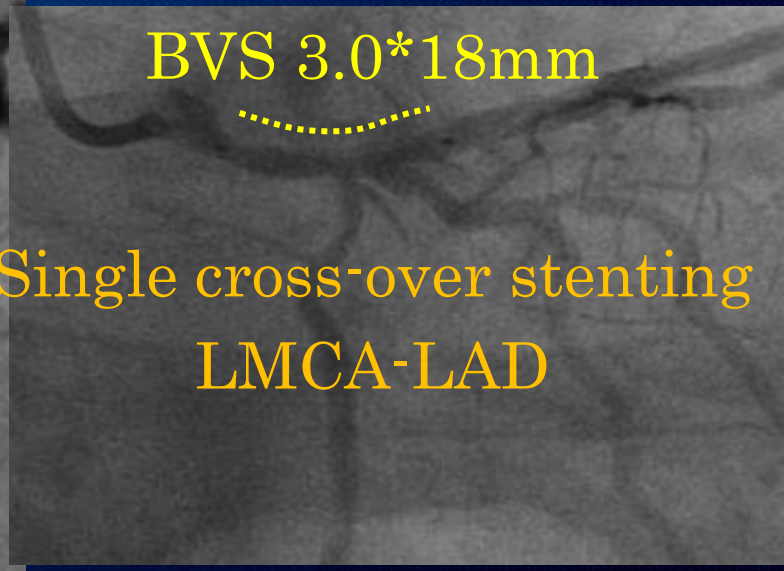
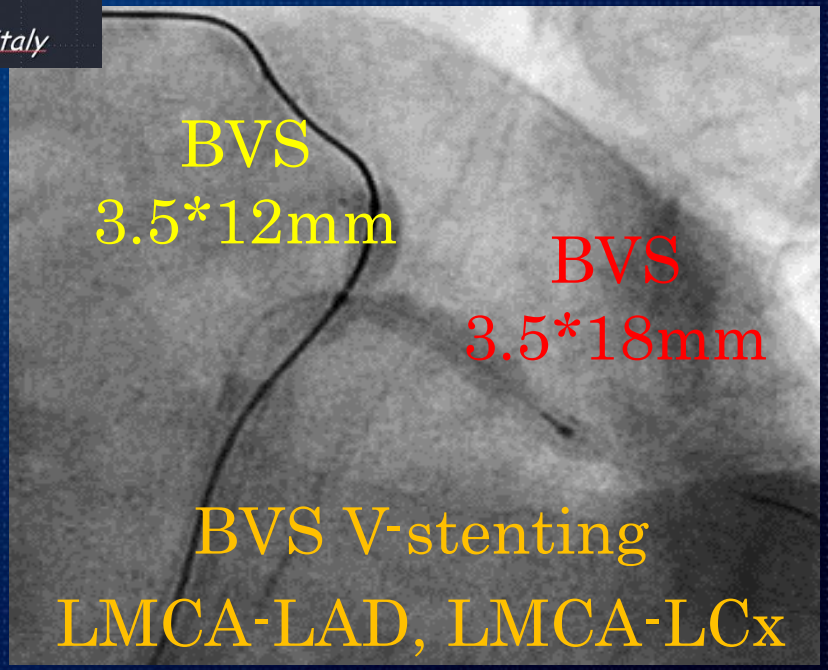
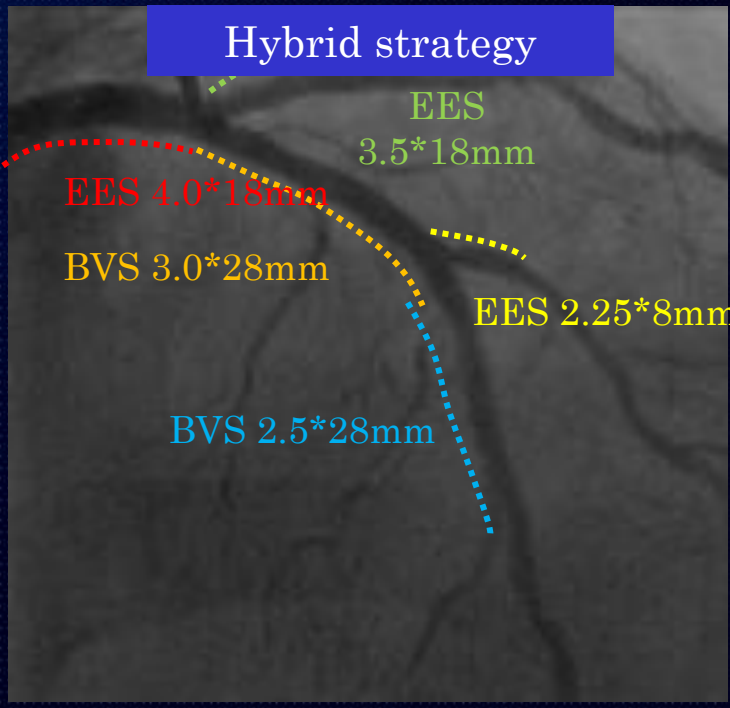
Catheterization and Cardiovascular Interventions (2014)


EMO GVM
CENTRO CUORE COLUMBUS S.r.l.
CTO/LM
Chronic Total Occlusion and Left Main Summit 2014
A Live Case Demonstration Course
OSR
New York City
February 27 – March 1, 2014
Session IV: Drug-eluting and drug-coated balloons for Left Main PCI
Bioresorbable scaffolds in Left Main PCI: technique considerations and outcomes
Speaker – 12'
Antonio Colombo
Centro Cuore Columbus and S. Raffaele Scientific Institute, Milan, Italy

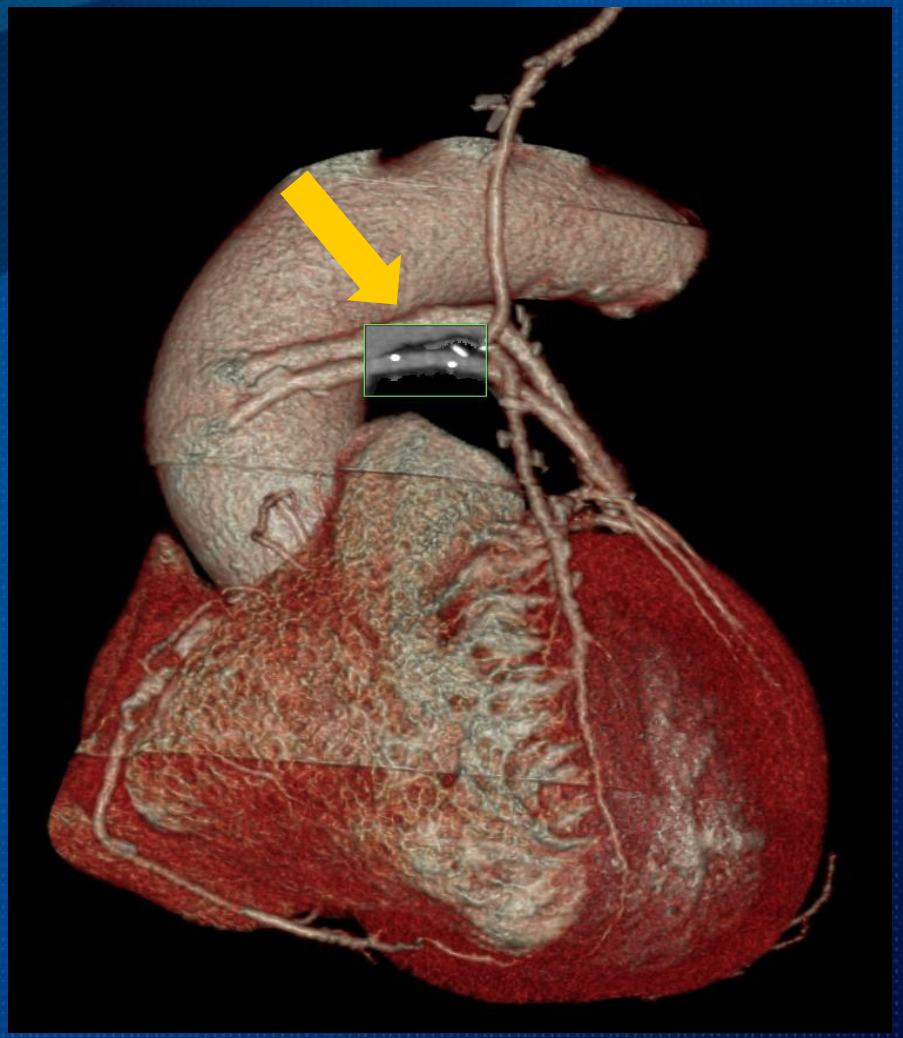

BVS 3.0*28mm
Single cross-over stenting
LMCA-LCx

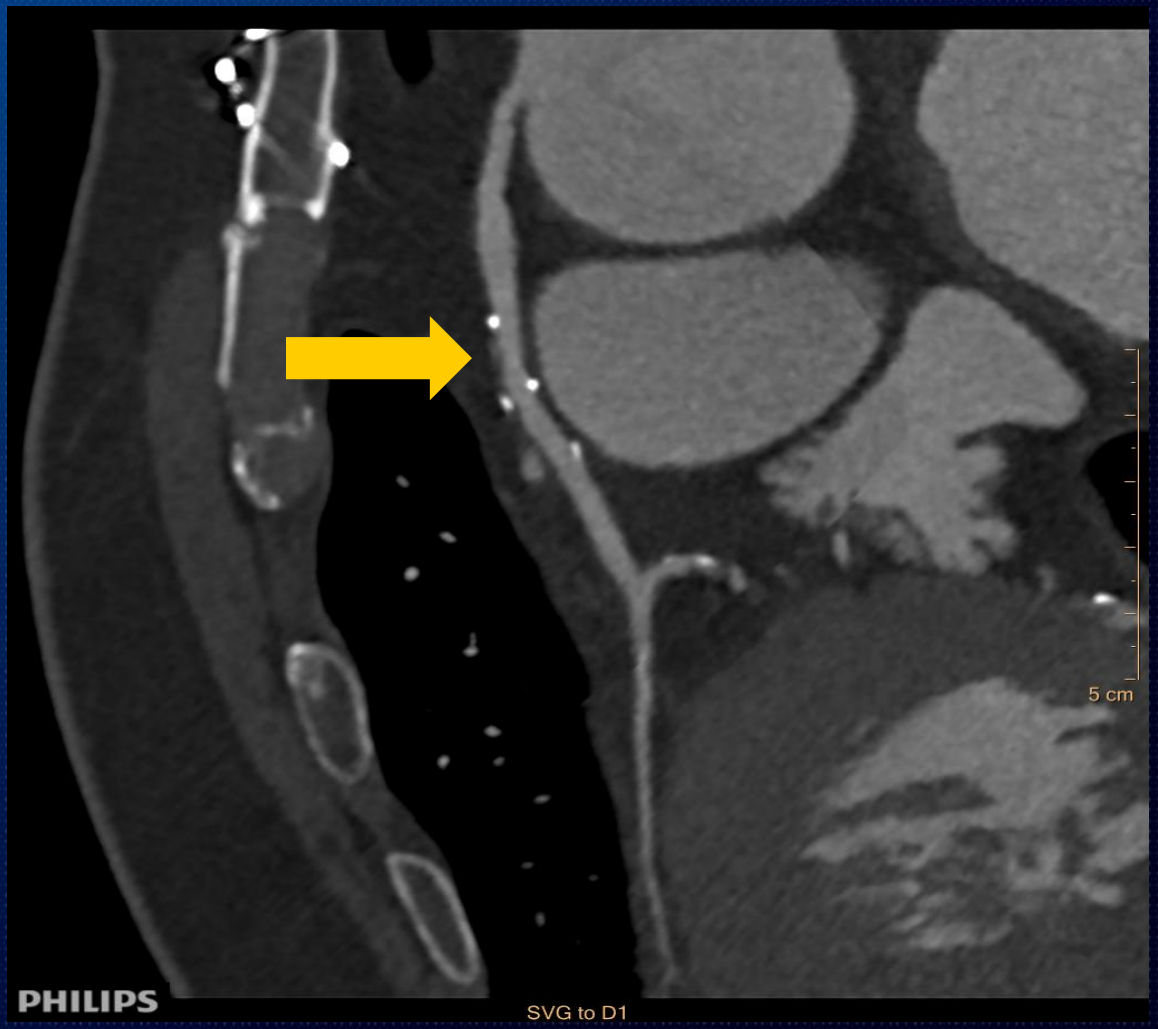

BVS 3.0*18mm
Single cross-over stenting
LMCA-LAD


BVS
3.5*12mm
BVS
3.5*18mm
BVS V-stenting
LMCA-LAD, LMCA-LCx


Hybrid strategy
EES
3.5*18mm
EES 4.0*18mm
BVS 3.0*28mm
EES 2.25*8mm
BVS 2.5*28mm

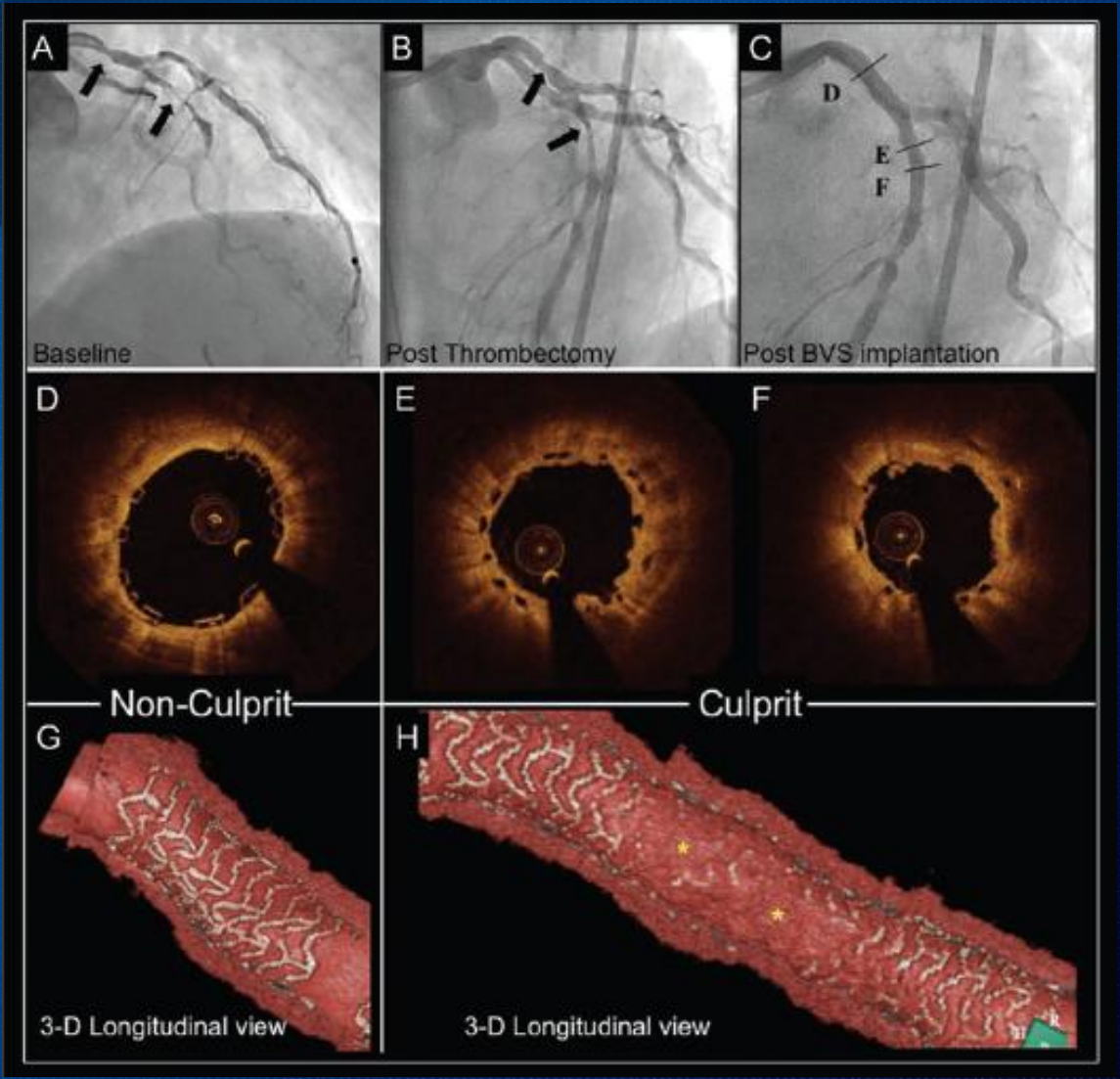
Venous graft stenting with BVS





Coronary CTA at ninety days

BVS for STEMI



Scaffolds with >5% malapposed struts 7/31 **(22.6%)**

The strategy of scaffold oversizing in primary PCI results in good results with low rate of strut malapposition demonstrated by OCT

R Diletti et al Eur Heart J Advance Access 6 Jan 2014

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In registries, the device success was 98.2% in complex lesions

Till Oct 2013	All (N=200, L=275)
MVD	77 (38.5%)
Bif	80 / 275 (29.1%)
Total Occlusion	33 / 275 (12.0%)
CTO	16 / 275 (5.8)
B2 or higher	113(41.1%)
Calcification	126/ 275 (45.8%)
Lesion Length	25.41 ± 13.52 mm
Range	5.32, 80.01 mm
Overlap	88 / 275 (32.0%)
Total scaffolds	390
Scaffolds per procedure	1.95
Failure to deliver	7 (3.7%)
Device succes	269 / 274 (98.2)

Procedural data 171 patient

Erasmus MC

BVS-Expand: 234 lesions

- Radial approach: 76.6%
- Supportive wire: 7.7%, buddy wires 8.3%
- Direct stenting: 19/234 (8.1%)
- Prep: 215/234 (91.9%)
  - Rotablator (1.9%)
  - Aspiration (7.8%)
  - Balloon: non-compl: 28.1%, semi-compl: 71.9%
  - balloon/artery ratio ≦ 1.0: 99.6%.
  - Balloon 0.5 mm ≤ scaffold size: 85.1%.

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The Absorb Potential: Unique Benefits Not Possible with a Metallic Implant


DIARIO MEDICO

MEDICINA

El Clínico de Madrid implanta el primer 'stent' bioabsorbible


Les Echos

LES STRATÉGIES

La nouvelle chirurgie s'habille en high-tech


De Telegraaf

GEZOND & WEL

OPLOSBAAR IMPLANTAAT


BBC NEWS HEALTH


la Repubblica.it

in diretta con l'Italia

Cuore

Quel piccolo tubo che ridà il sangue al muscolo vitale


CORRIERE DELLA SERA

La gabbietta che riapre le coronarie, salva il cuore e poi sparisce

Due «stent riassorbibili» impiantati per la prima volta a Milano


Handelsblatt

Die Zukunft der Stents ist unsichtbar


La Libre BELGIQUE

L'ère du stent bioabsorbable est ouverte


EL PAÍS

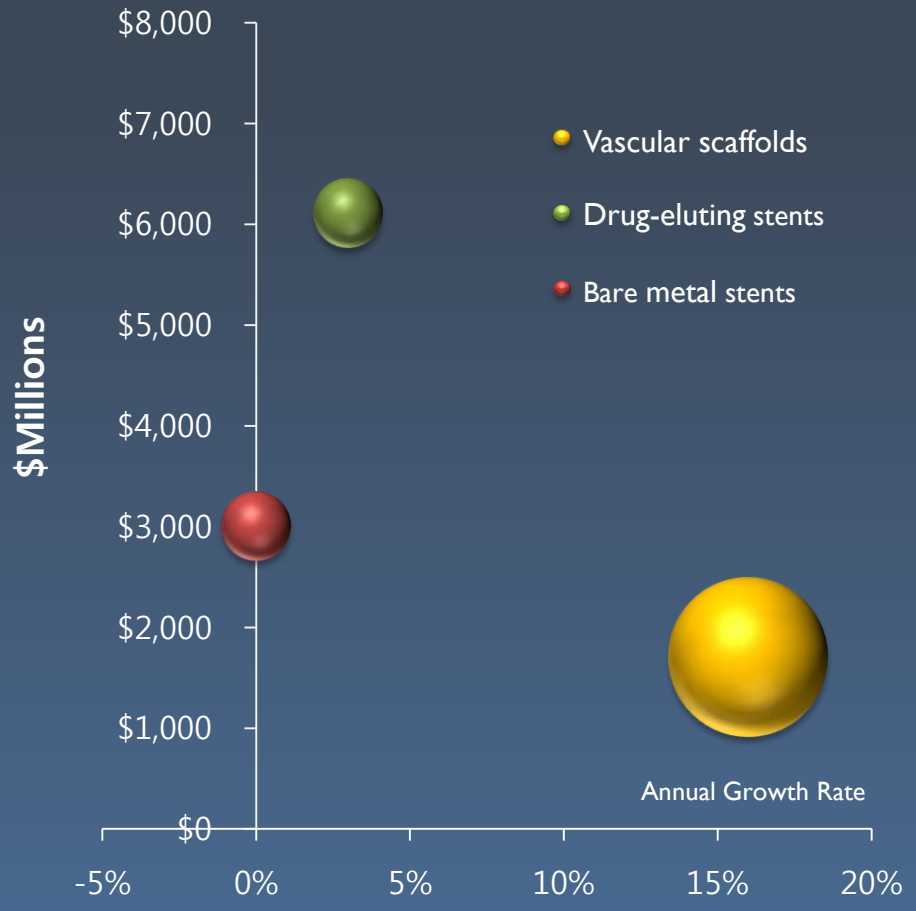
Una prótesis arterial que se esfuma

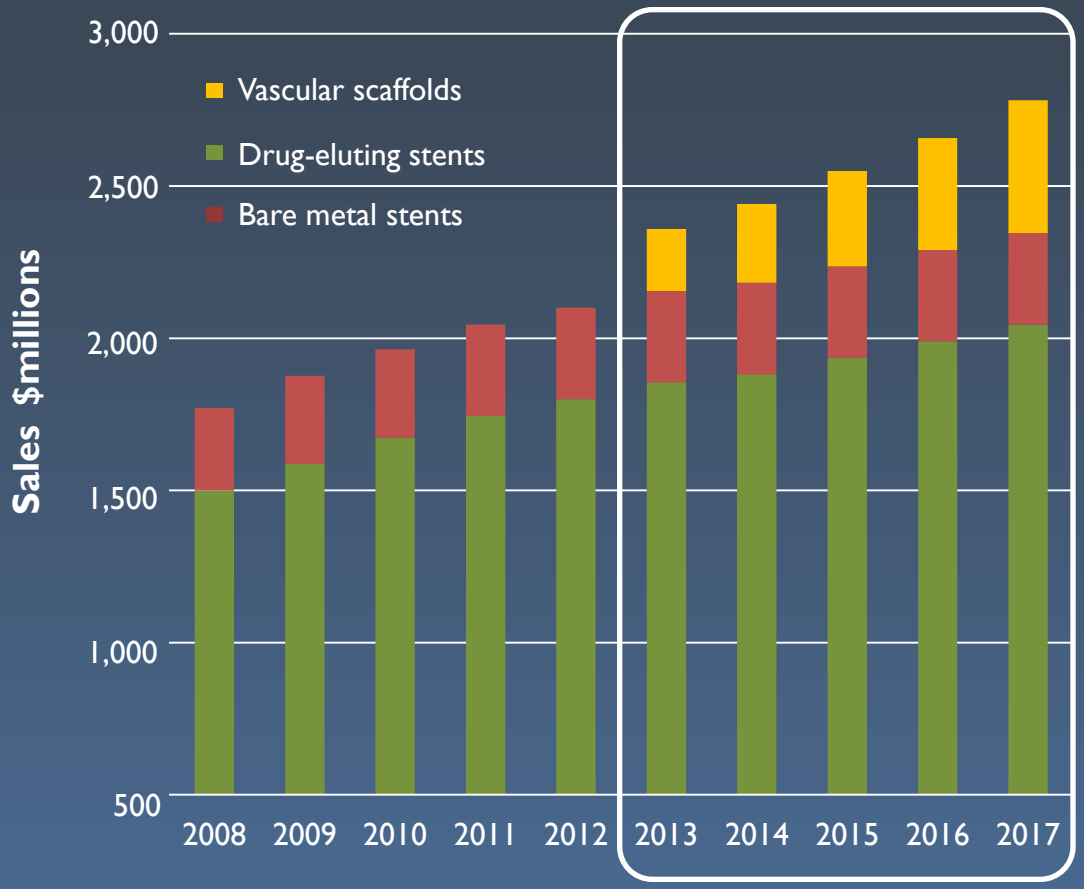

London Evening Standard

standard.co.uk

Heart saver that clears arteries then dissolves

Stent market





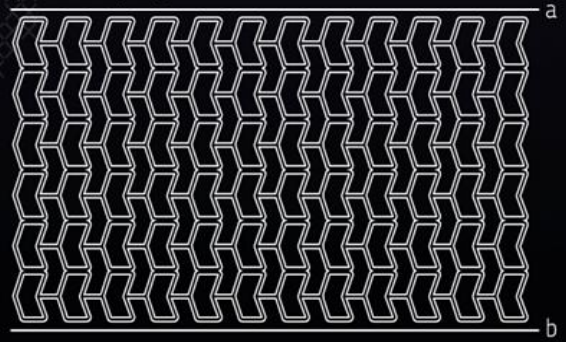
MedMarket Diligence, "Worldwide Coronary Stents Market, 2008-2017

Suntech vs. Abbott

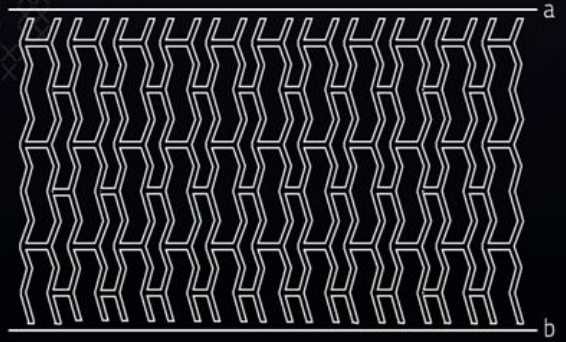
- Same PLLA backbone
  but different stent design

- **Different drug-coated layer**
  PDLLA / ***PC polymer** / sirolimus **vs.** PDLLA / everolimus
  (US 13/120,507, US 13/730,434)

V Suntech **pattern.**
(US 13/929,237)



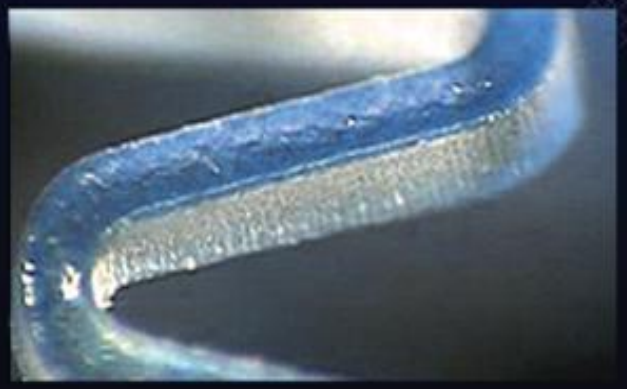
W Abbott **pattern.**
(US 8,002,817)



***PC polymer**: phosphorylcholine-based polymer

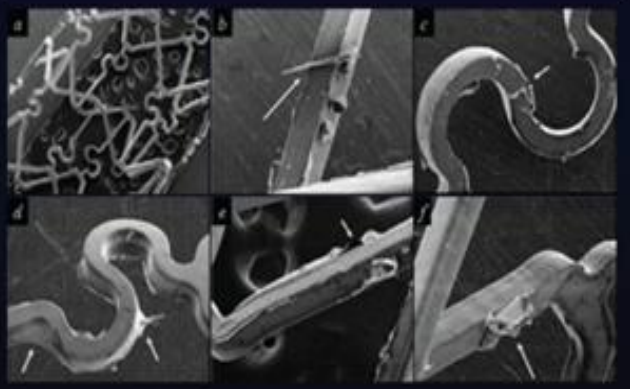
Suntech vs. Biocompatible

Suntech



- **Bioabsorbable** PC coating
- **High** density of phosphorylcholine (PC) groups on surface:
  phosphorous /carbon > 0.80 %
- **Bioabsorbable** stents

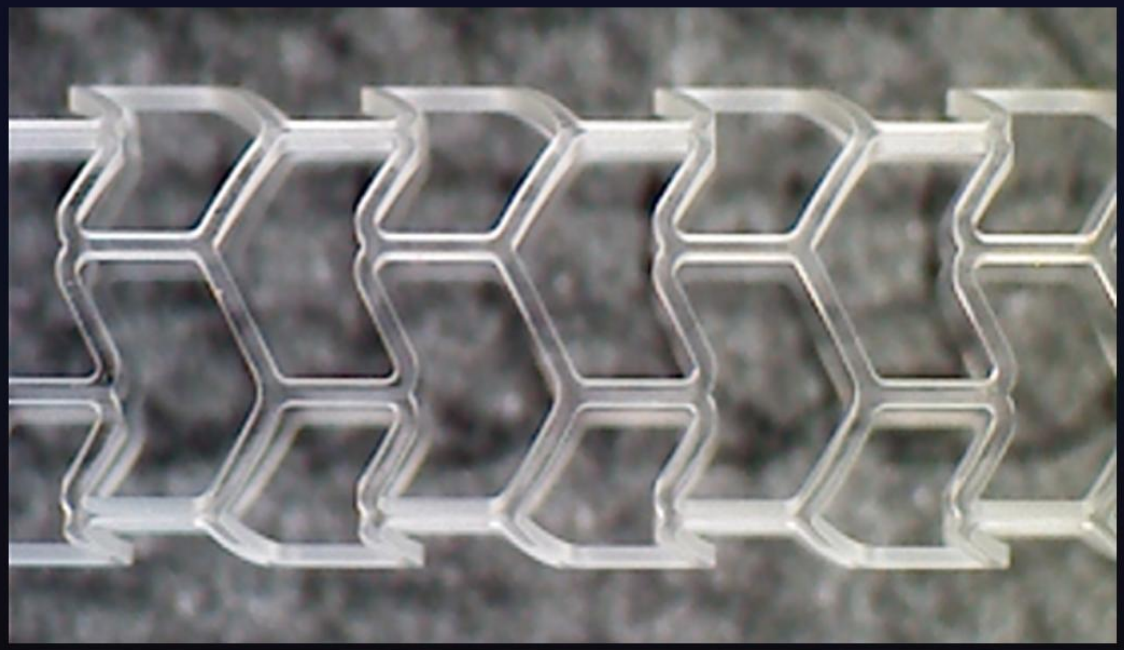
Biocompatible, inc



Source : J Invasive Cardiol ©2007 Health Management Publications.Inc.

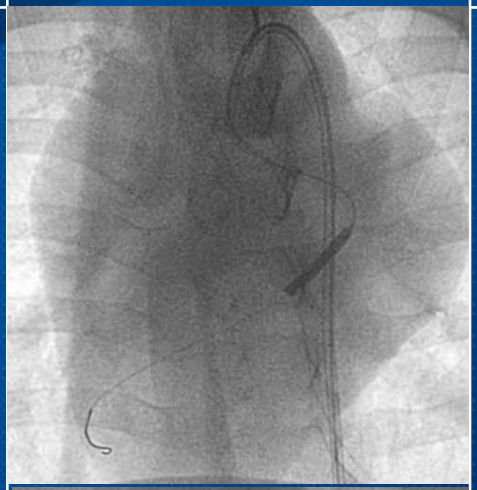
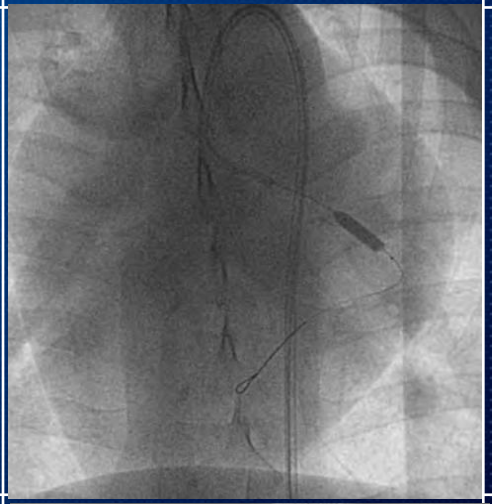
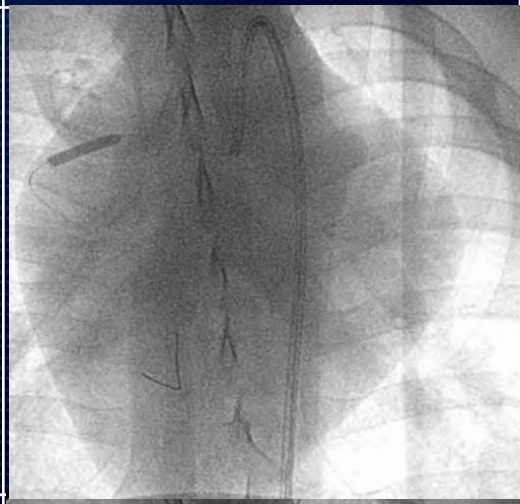
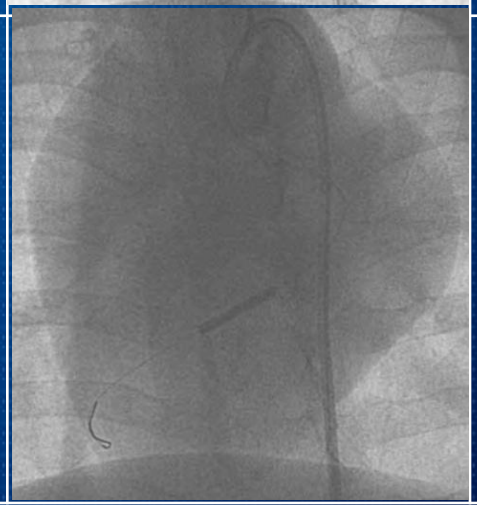
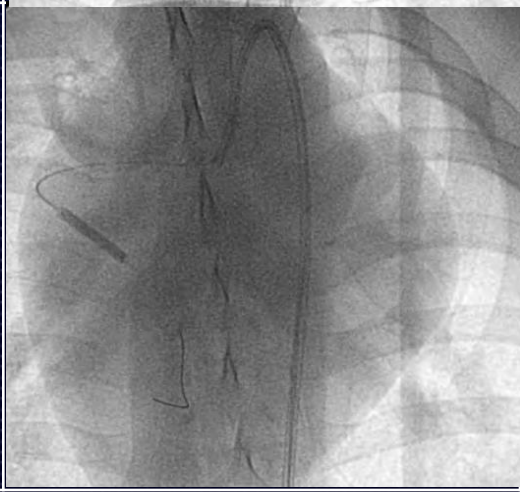
- **Non-degradable** PC coating
- **Low** density of phosphorylcholine (PC) groups on surface:
  phosphorous/carbon < 0.01 %
  (below the threshold of XPS)
- **Permanent metal** stents
  (BiodivYsio, Endeavor)

V type

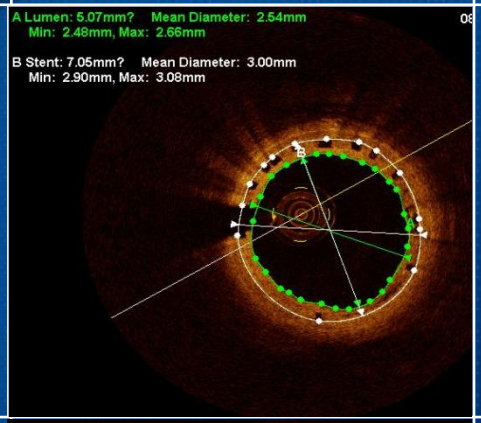
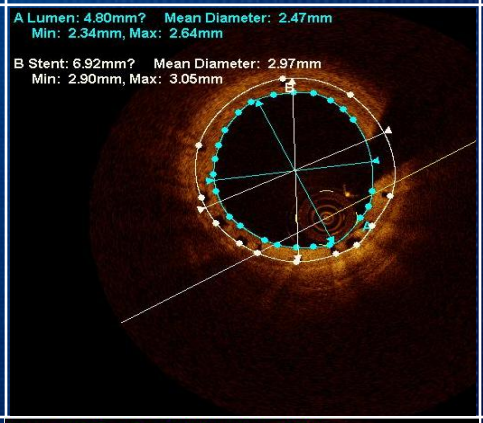
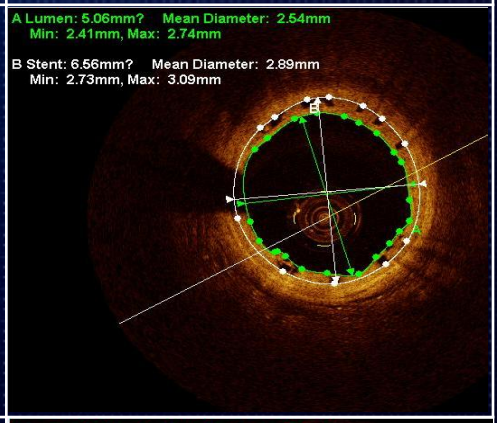
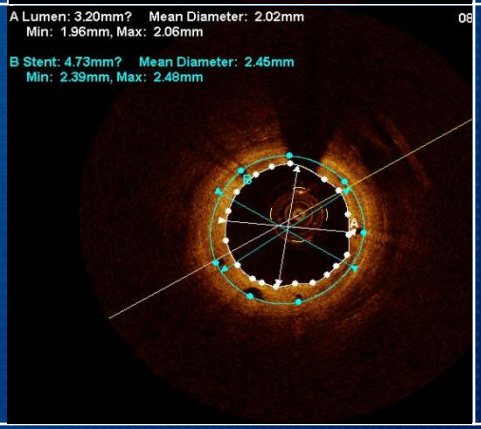
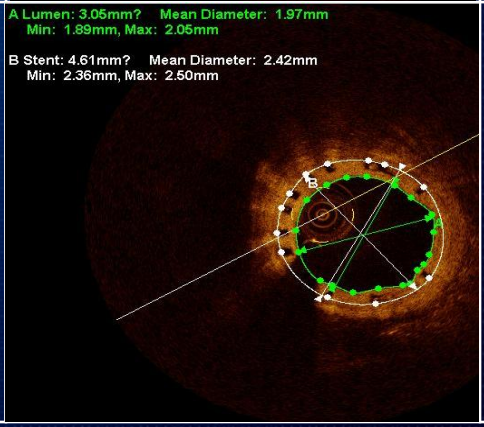
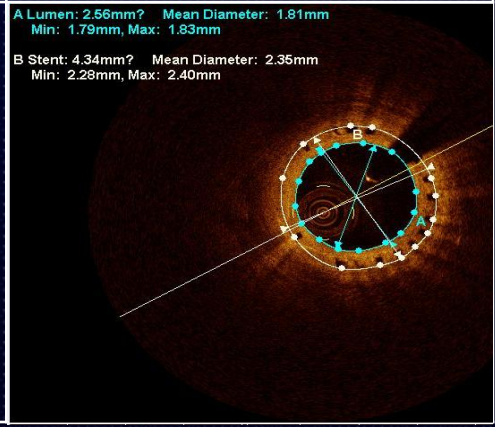


- Had **higher radial forces.**
- Can make **thin struts (<120 μm).**
- Led to **simple processing.**

UUH 003 (45Kg) Scaffold implantation

LAD	Cine images	LCX	Cine images	RCA	Cine images
mLAD Sirolimus Eluting 3.5/18 mm		pLCX Everolimus Eluting 3.5/18 mm		pRCA Sirolimus Eluting 3.5/18 mm	
dLAD Sirolimus Eluting 3.0/20 mm		mLCX No drug 3.0/20 mm		mRCA Everolimus Eluting 3.0/20 mm	

UUH 003 (45Kg) Day 28 after implantation

LAD	OCT images	LCX	OCT images	RCA	OCT images
mLAD Sirolimus Eluting 3.5/18 mm		pLCX Everolimus Eluting 3.5/18 mm		pRCA Sirolimus Eluting 3.5/18 mm	
dLAD Sirolimus Eluting 3.0/20 mm		mLCX No drug 3.0/20 mm		mRCA Everolimus Eluting 3.0/20 mm	

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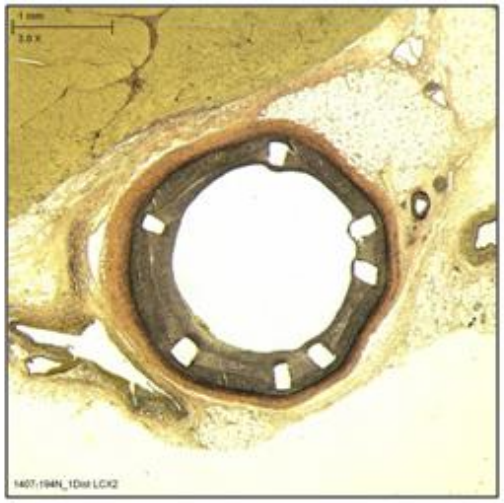
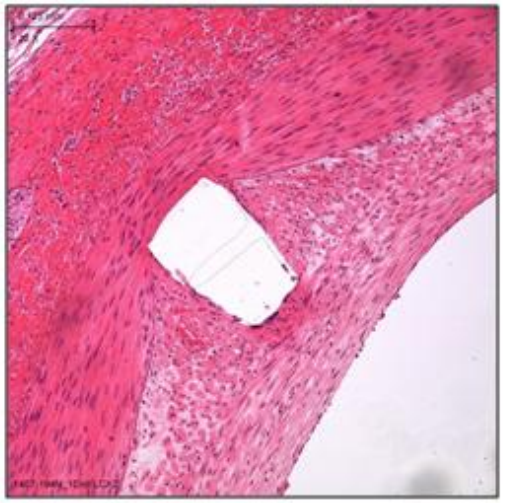


S2 VVG 3x

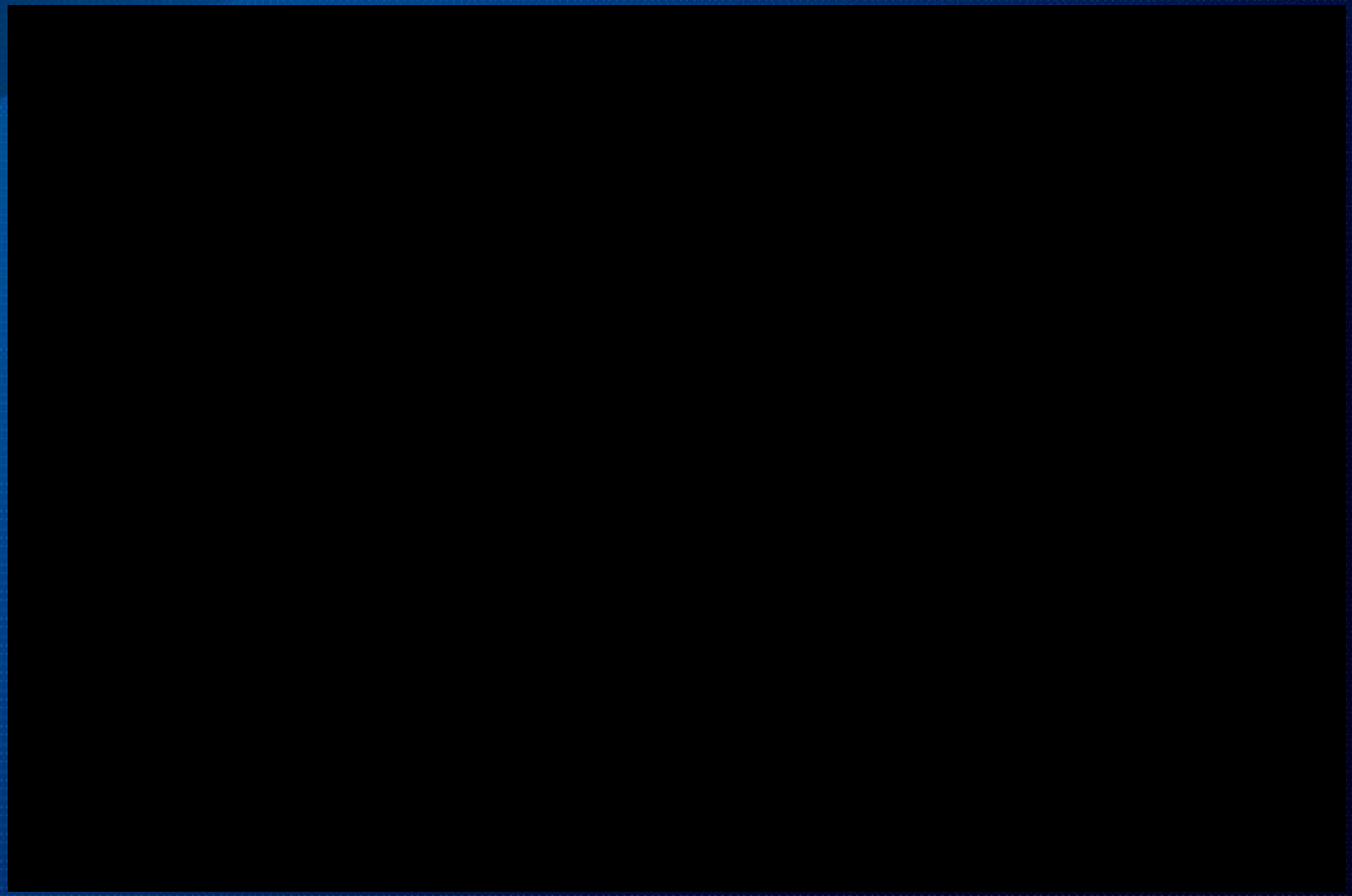


S2 H&E 20x

S3 VVG 3x

S3 H&E 20x

UUH 003 (45Kg) Micro-CT on Day 28



Bioresorbable Vascular Scaffolds for Angioplasty

- BVS is the revolution in PCI.
- BVS does completely dissolve and potentially restore vessel function in a way not possible with permanent implants.
- The registry data shows acceptable results compared to metal stent except concern about stent thrombosis.
- We need understand BVS characteristics and implantation technique.
- Still, a larger body of long-term data is needed.

Thank you for your attention !