BVS (Bioabsorbable Vascular Scaffold): They Will Replace the Metal Stent?

Current Status and Future Perspective

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Heart Institute, University of Ulsan College of Medicine,

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Drug-Eluting Stents

Stefanini G, Holmes D.

N Engl J Med 2013

"PCI is the most frequently performed therapeutic intervention in medicine"

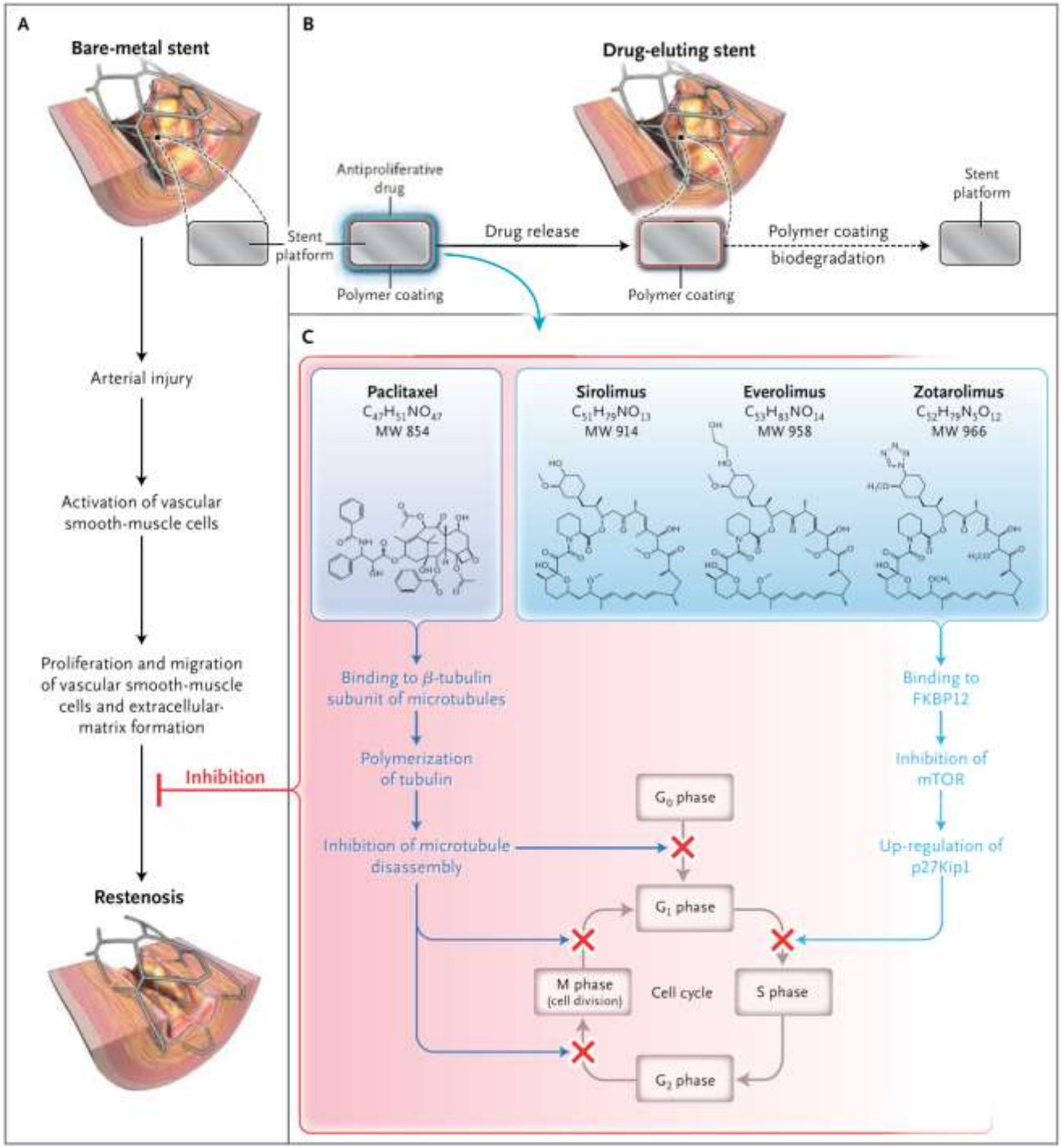
***Revolution of PCI;**

***1st – POBA**

***2nd – BMS**

***3rd – DES**

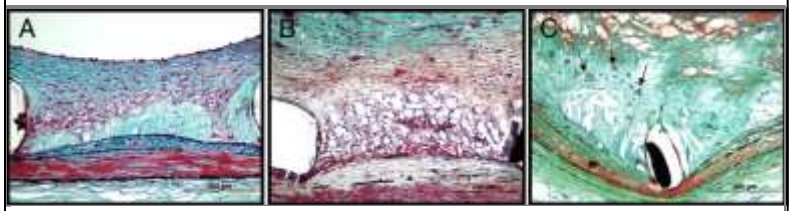
***4th – BRS**



Limitations and Unmet Needs of Metal Stents

Neoatherosclerosis

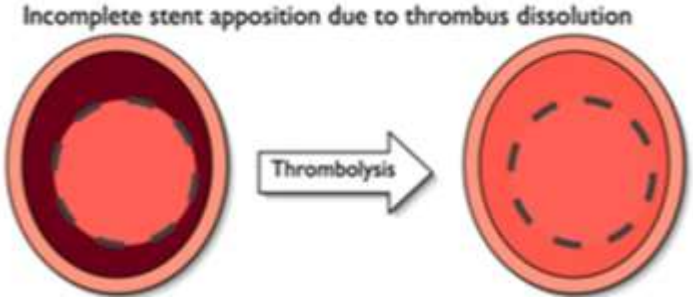
Nakazawa G et al. *JACC* 2011



Late Stent Thrombosis?
Late Restenosis ?

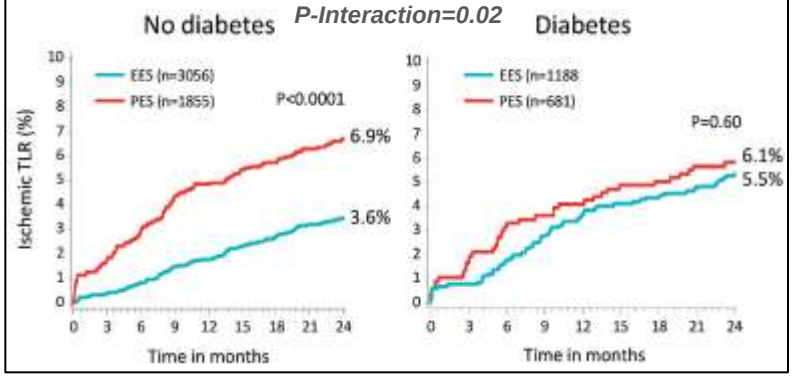
Acute MI

Cook S et al. *Circulation* 2009



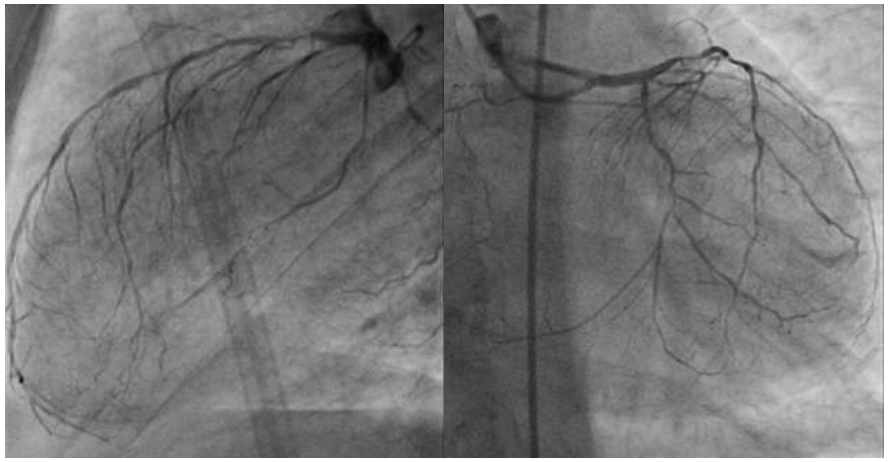
Diabetes

Stone GW et al. *Circulation* 2011



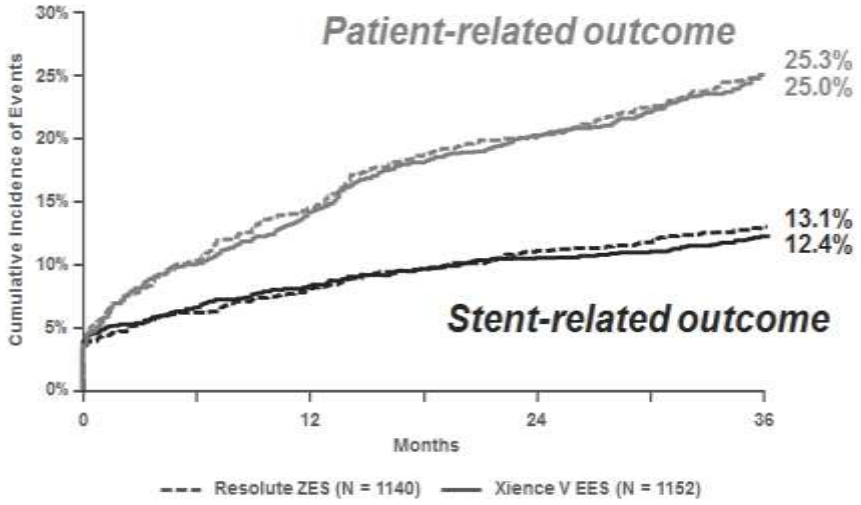
Diffused Multivessel CAD

Jolicoeur E et al. *CJC* 2012



CAD Progression

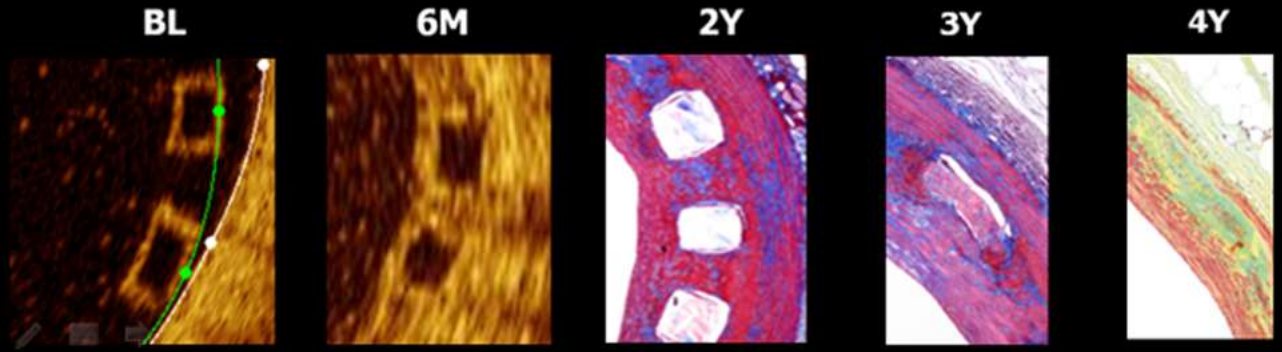
Silber S et al. *Lancet* 2011



BVS - Device Resorption; "They do their job and disappear"

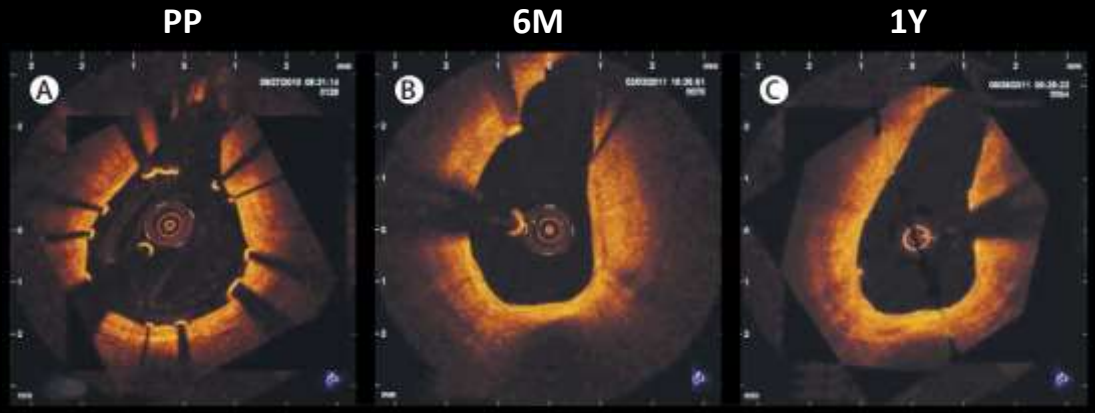
ABSORB BVS

Ormiston J et al. *Circ Cardiovasc Interv* 2012;5:620-32



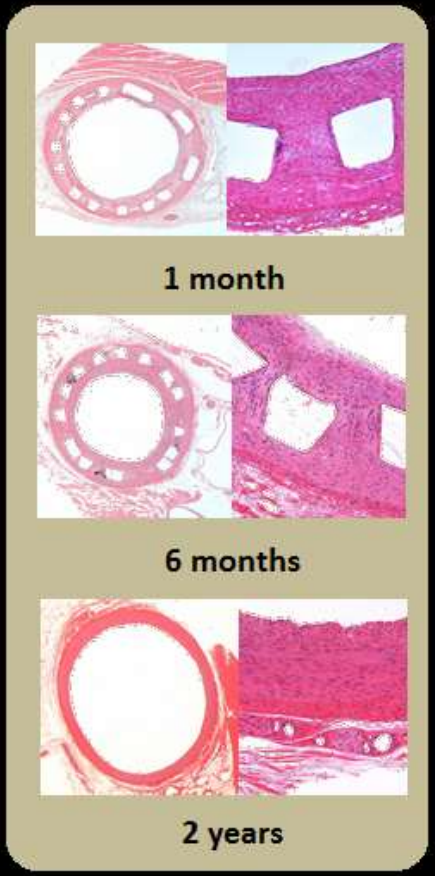
DREAMS

Haude M et al *Lancet* 2013; 381:836-44



DESolve

Preclinical Studies



Issues Briefs

BVS; Clinical Evidence

Existing data

- Registries and ABSORB II (first RCT)

Ongoing RCTs

- ABSORB III
- ABSORB IV

BVS: Concerns and Perspective

Stent thrombosis

Complex lesions; left main, bifurcation, long lesions

Preventive BVS for non-culprit lesions; BVS or medical DAPT durations

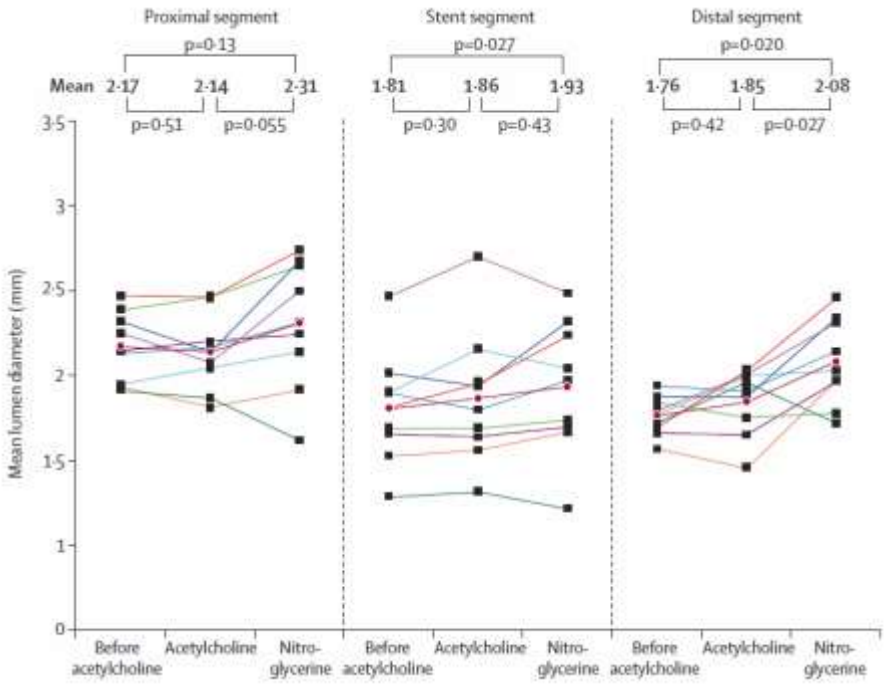
Potential Benefits of BVS

Potentials of Fully Bioresorbable Coronary Scaffolds

Serruys P et al. *Lancet* 2009;373:897-910

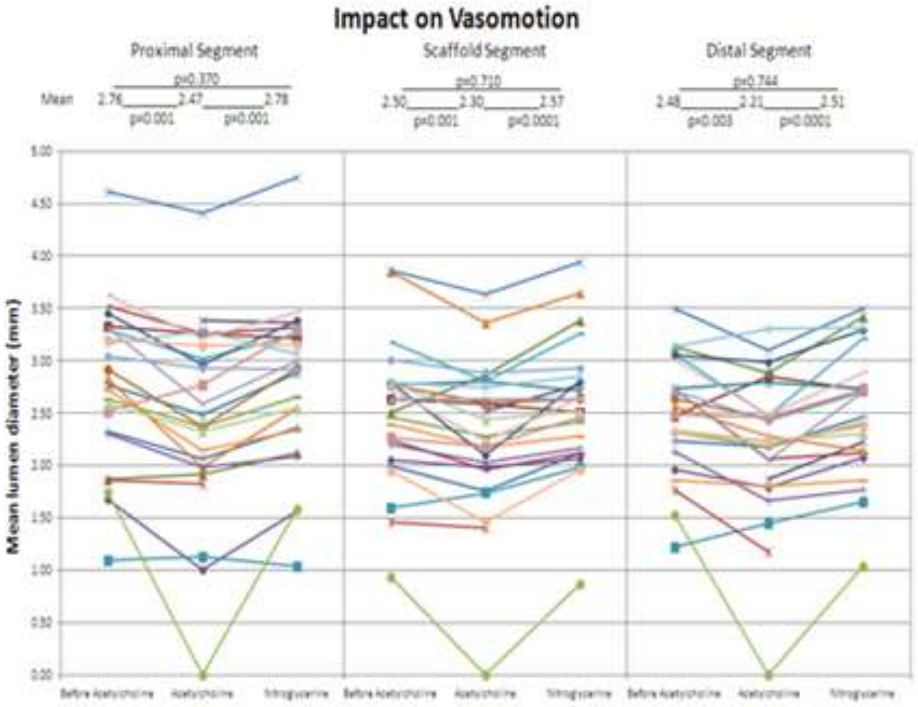
Vasomotion Restoration

ABSORB @ 2 years



Serruys P et al. *Lancet* 2009;373:897-910

BIOSOLVE-I

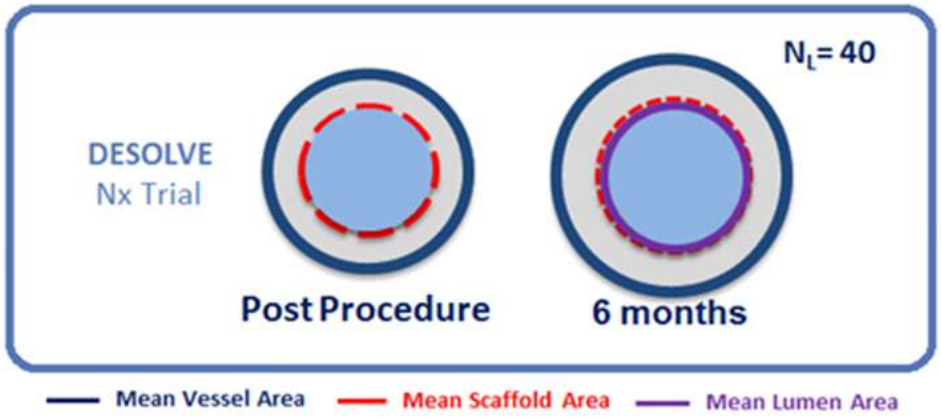


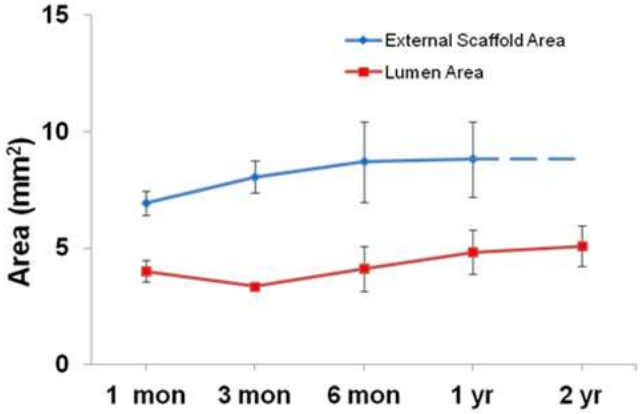
Haude M et al *Lancet* 2013; 381:836-44

Potentials of Fully Bioresorbable Coronary Scaffolds

Ormiston J et al. *Circ Cardiovasc Interv* 2012;5:620-32

Late Lumen Enlargement



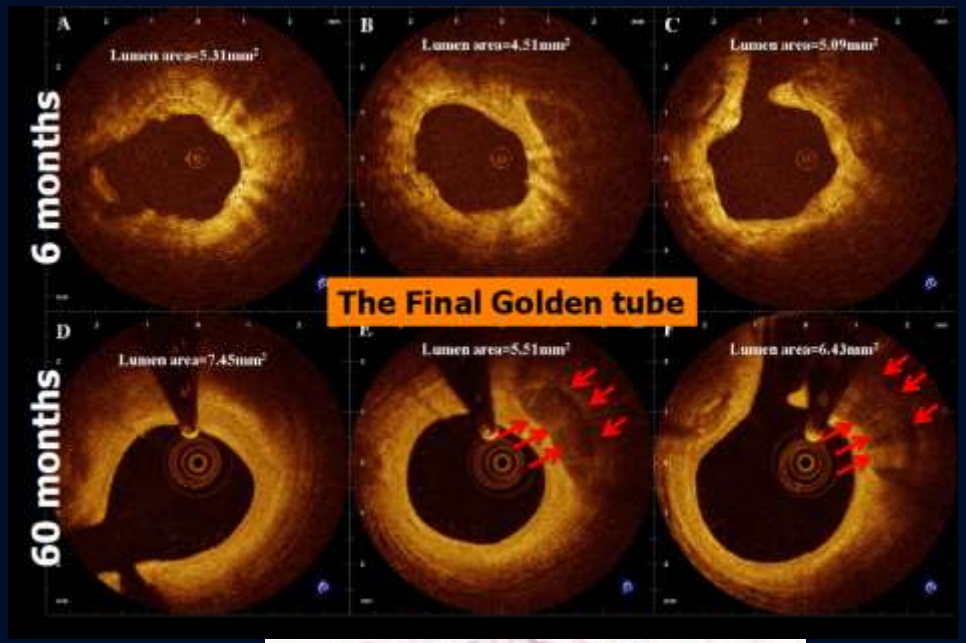


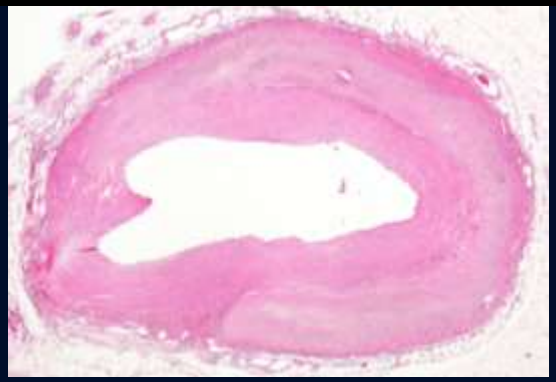
Potentials of Fully Bioresorbable Coronary Scaffolds

Brugaletta S et al. *Atherosclerosis* 2013

Neocap - Plaque Sealing

	BL	6 Ms (B1)	12 Ms (B2)	24 Ms (B1)	36 Ms (B2)
Neointimal Thick, µm	0	210	220	254	285
BVS area, mm^2	7.47 (B1) 7.73 (B2)	7.70	7.51	8.24	8.64
MLA, mm^2	7.23 (B1) 7.69 (B2)	6.07	6.01	5.99	6.09





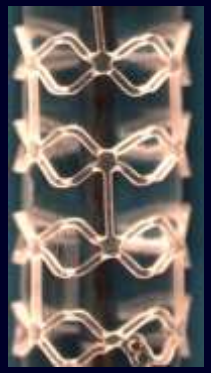
Potential Clinical Benefits of a Bioabsorbable DES…

- Provides *transient* vessel scaffolding when needed, "leaving nothing behind"
- Local drug release inhibits restenosis
- Restores vessel to natural state with normal function and healing responses
- Reduces need for long term DAPT
- Eliminates source of inflammation/ irritation
- Reduces late events (esp. SAT)
- Vessel free for future interventions; CABG

Current Technology of BVS

Bioresorbable Coronary Scaffolds




Van der Giessen *Circulation*

Tamai *Circulation*

Erbel *Lancet*

Ormiston *Lancet*

Jabara *PCR 2009*

Abizaid *PCR 2011*

Haude *Lancet*

1996 **2000** **2007** **2008** **2010** **2013**

Animal studies
polymeric scaffolds revealing excessive inflammatory reactions

Igaki Tamai
First fully biodegradable non drug eluting scaffold
N=15

AMS-1
first bioabsorbable metallic non drug-eluting scaffold
N=64

Bioresorbable vascular scaffold
first bioabsorbable drug eluting scaffold
N=31

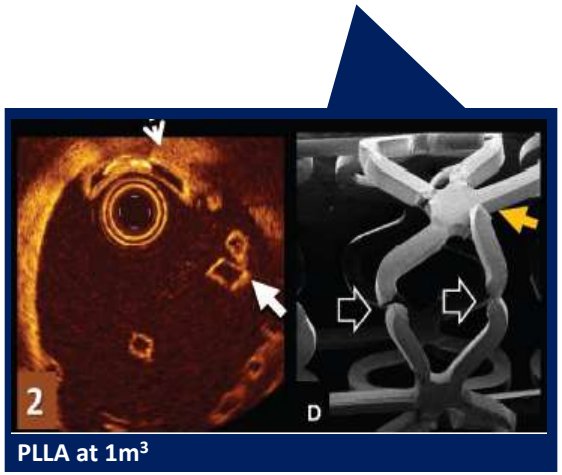
IDEAL BDS
Polyanhidride ester and salicylic acid, drug-eluting scaffold
N=11

REVA
Polycarbonate stent, radiopaque, non drug-eluting scaffold
N=31

DREAMS
first drug-eluting bioabsorbable metallic scaffold
N=22

Key characteristics of absorbable scaffold materials

	Polymeric		Metallic
Material	**PLLA[1]**	**Iron[2]**	**Magnesium Alloy[2]**
Tensile Strength (MPa)	~30-45	300	280
Elongation (%)	2 – 6	25	23
Total Degradation Time	2-3 Years	> 4 years	9-12 months



PLLA at 1m[3]

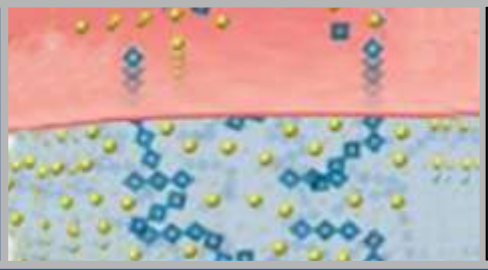

Iron at 28d


Magnesium at 180d

[1] Ratner DB, et al. Biomaterials Science: Introduction to Materials in Medicine, 2nd Edition. Elsevier Academic Press, 2004. [2] Hermanwan H, et al. Acta Biometerialia. 6 (2012):1693-1697. [3] Ormiston J et al. Circ Cardiovasc Interv 2011;4;535-538, Oct. 2011.

Clinical Data of Bioabsorbable Stent

Abbott Vascular Everolimus-Eluting Bioresorbable Vascular Scaffold

ML VISION Delivery System	Bioresorbable Device Platform	Bioresorbable Coating	Everolimus
• Seven generations of MULTI-LINK success • World-class deliverability	• Polylactide (PLLA) • Naturally resorbed, fully metabolized	• Polylactide (PDLLA) coating • Fully biodegradable	• Similar dose and release rate to XIENCE V
			

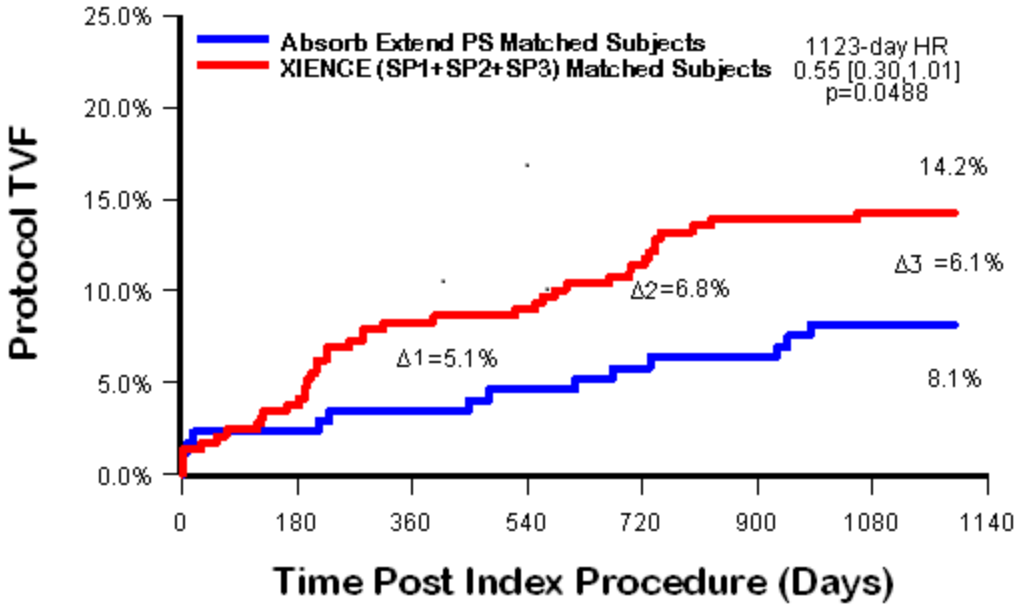
Investing in a Comprehensive ABSORB Clinical Trial Program

Total Patients Studied	**n=~599**	**n~930**	**n~5,674**	**n~13,453**	**n~13,453**	**n~13,453**

Note: Sample sizes reflect Absorb patients only.
* n= 10,000 f/u at 6 months. 1.000 patients f/u at 1 -3 years, 1.000 patients at 2-4 years

ABSORB Update: The EXTEND Real World Registry

Propensity Score Matched: TVF through 36 Months

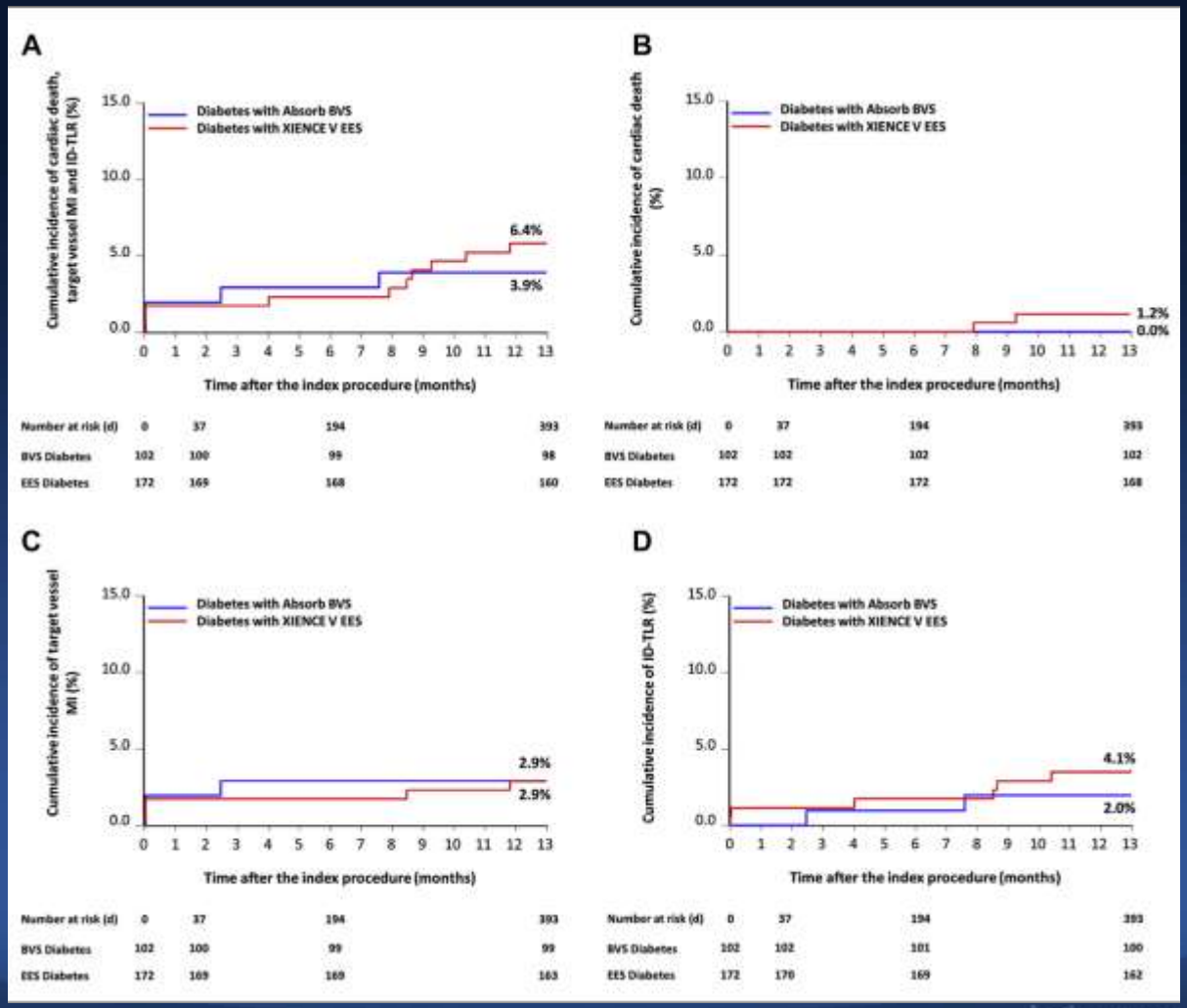


	0	37	194	393	758	1123
ABSORB EXTEND at Risk	174	169	169	166	160	156
XIENCE V (SPI,II,III) at Risk	290	285	276	264	246	241

Absorb vs. EES in DM Patients

A Pooled Analysis of the ABSORB and the SPIRIT Trials

Propensity-Matched

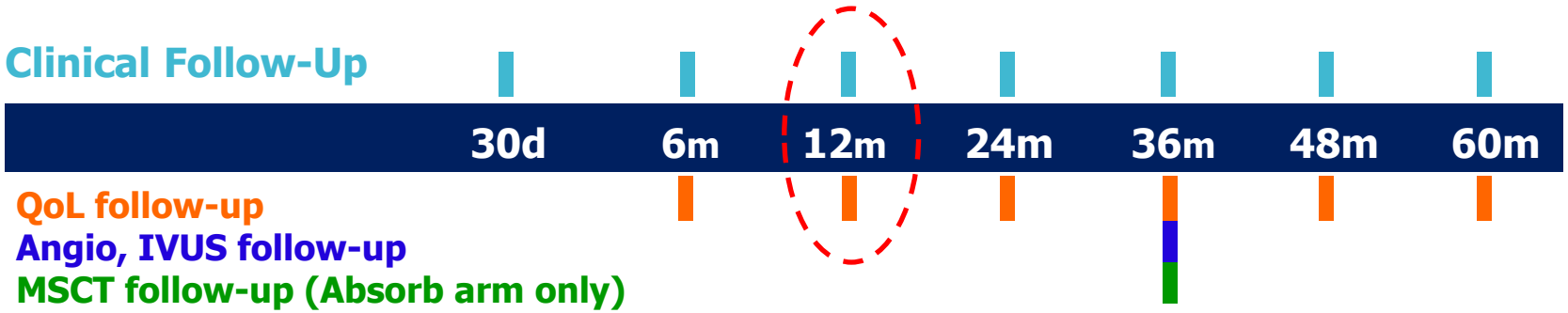


J Am Coll Cardiol Intv 2014;7:482–93

ABSORB II Study Design

501 subjects

Randomized 2:1 Absorb BVS:XIENCE / 46 sites (Europe and New Zealand)



Study Objective **Randomized against XIENCE control. First Patient In: 28-Nov-2011**

Lancet. 2015 Jan 3;385(9962):43-54

A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial

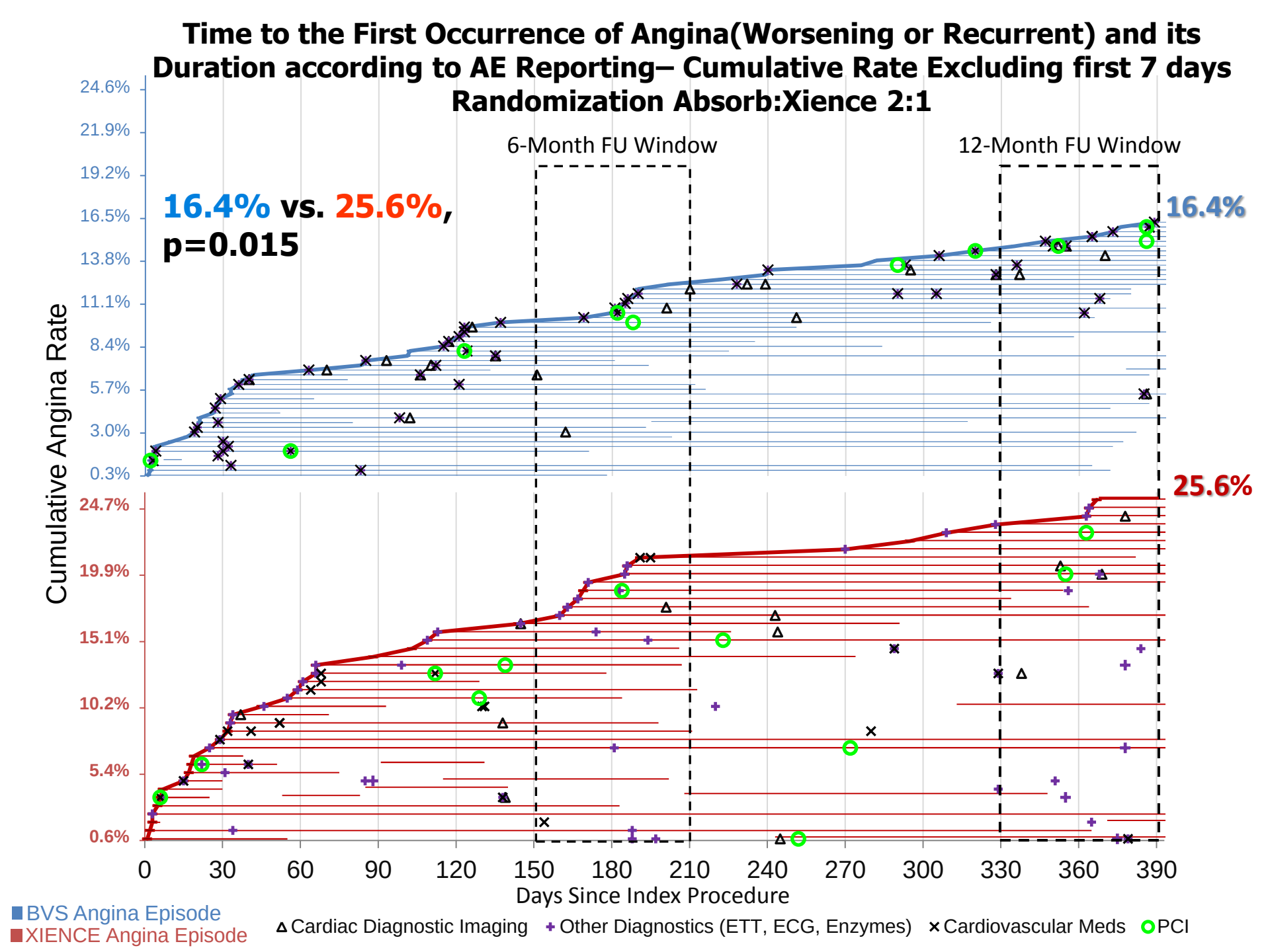
Patrick W Serruys, Bernard Chevalier, Dariusz Dudek, Angel Cequier, Didier Carrié, Andres Iniguez, Marcello Dominici, René J van der Schaaf, Michael Haude, Luc Wasungu, Susan Veldhof, Lei Peng, Peter Staehr, Maik J Grundeken, Yuki Ishibashi, Hector M Garcia-Garcia, Yoshinobu Onuma

ABSORB II - Clinical Outcomes

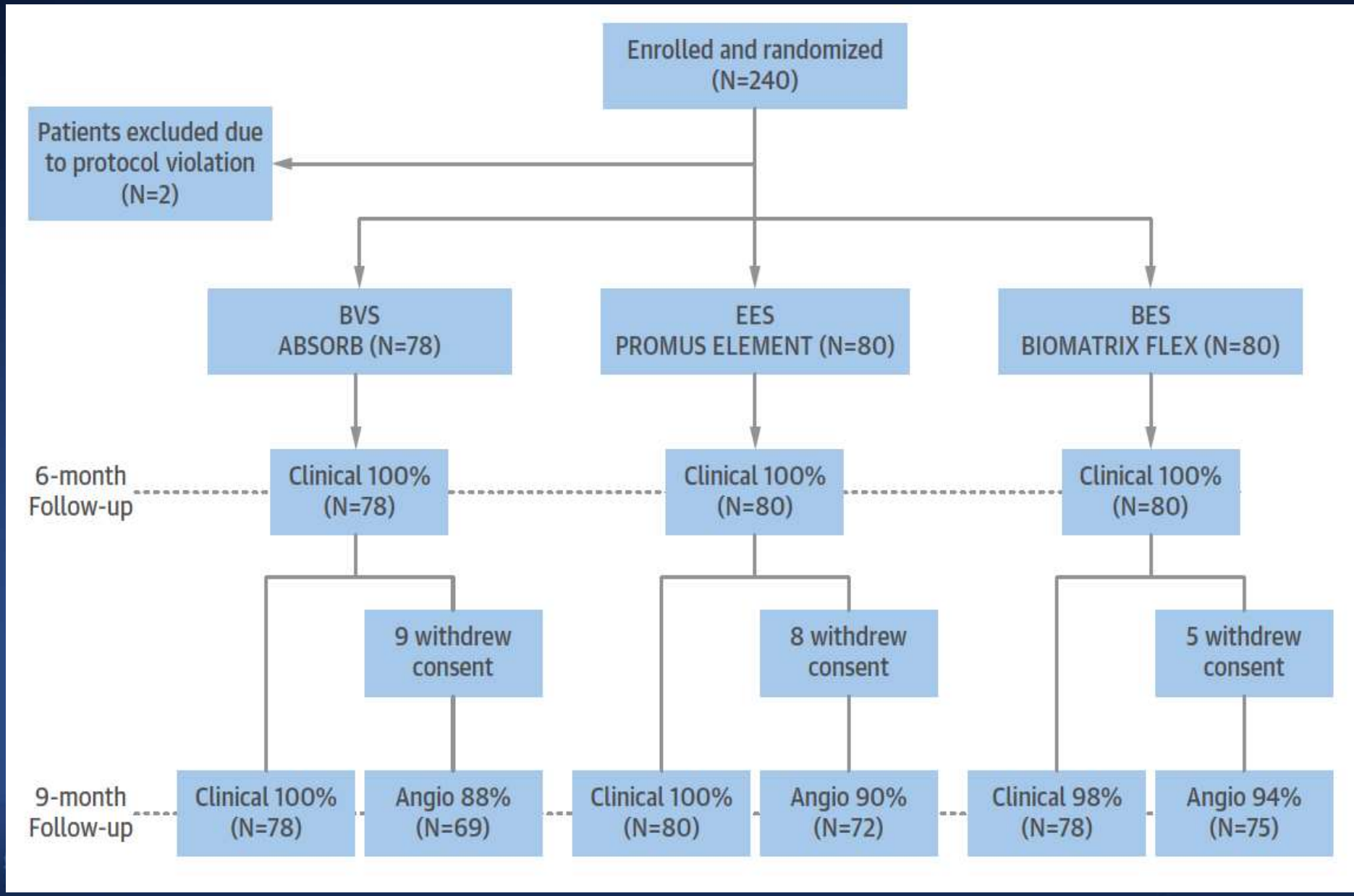
Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Composite of cardiac death, target vessel MI and clinically indicated target lesion revascularization (TLF, DoCE)	**4.8 %**	**3.0 %**	**0.35**
Cardiac death	0 %	0 %	1.00
Target vessel MI	4.2 %	1.2 %	0.07
Clinically indicated TLR	1.2 %	1.8 %	0.69
All TLR	1.2 %	1.8 %	0.69
Composite of all death, all MI and all revascularization (PoCE)	**7.3 %**	**9.1 %**	**0.47**
All death	0 %	0.6 %	0.33
All MI	4.5 %	1.2 %	0.06
All revascularization	3.6 %	7.3 %	0.08

Definite scaffold/stent thrombosis

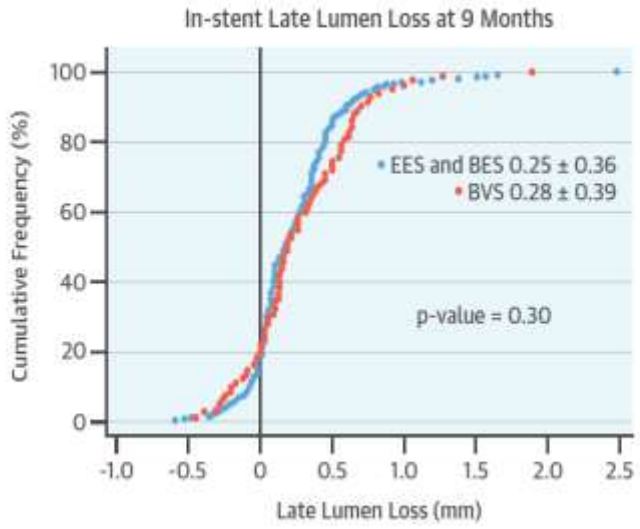
Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Definite scaffold/stent thrombosis			
Acute (0-1 day)	0.3 (1pt)	0.0	NS
Sub-acute (2–30 days)	0.3 (1pt)	0.0	NS
Late (31–365 days)	0.0	0.0	NS
Probable scaffold/stent thrombosis			
Acute (0-1 day)	0.0	0.0	NS
Sub-acute (2–30 days)	0.0	0.0	NS
Late (31–365 days)	0.3 (1pt)	0.0	NS

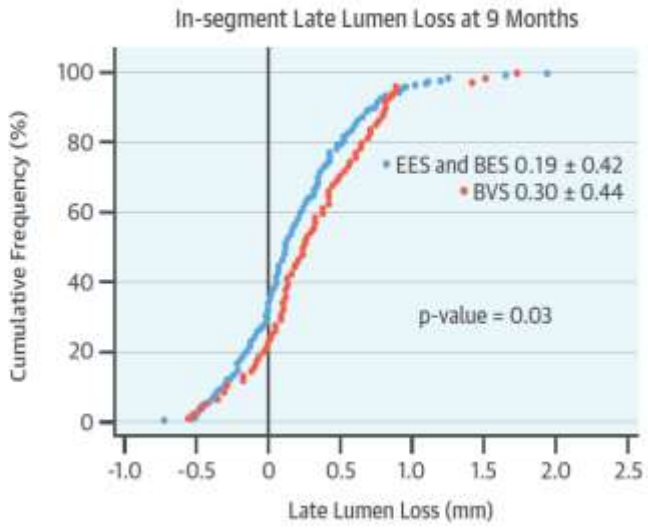

Time to the First Occurrence of Angina(Worsening or Recurrent) and its Duration according to AE Reporting– Cumulative Rate Excluding first 7 days
Randomization Absorb:Xience 2:1
6-Month FU Window
12-Month FU Window
16.4% vs. 25.6%,
p=0.015
16.4%
25.6%
Cumulative Angina Rate
24.6%
21.9%
19.2%
16.5%
13.8%
11.1%
8.4%
5.7%
3.0%
0.3%
24.7%
19.9%
15.1%
10.2%
5.4%
0.6%
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days Since Index Procedure
BVS Angina Episode
XIENCE Angina Episode
Cardiac Diagnostic Imaging
Other Diagnostics (ETT, ECG, Enzymes)
Cardiovascular Meds
PCI

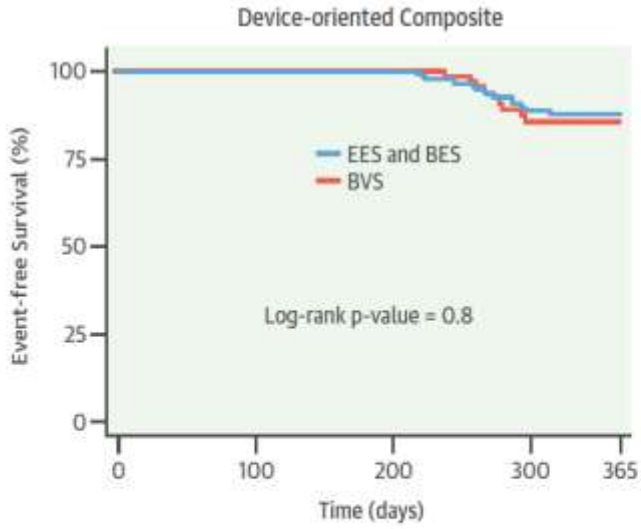
EVERBIO II RCT

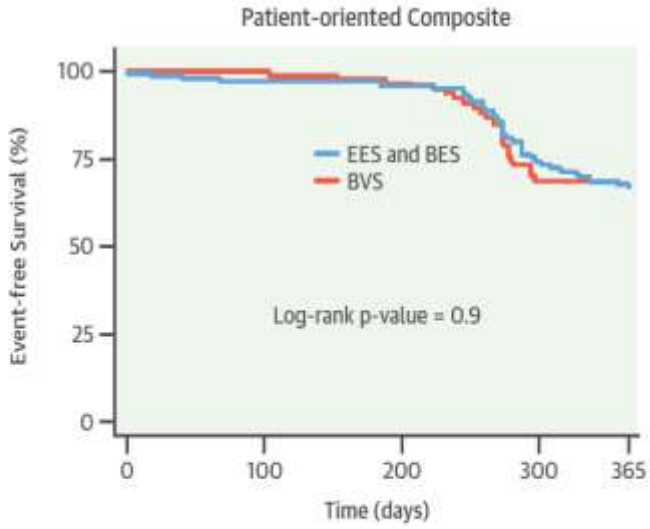


CENTRAL ILLUSTRATION **Comparison of Everolimus- and Biolimus-Eluting Coronary Stents With Everolimus-Eluting Bioresorbable Vascular Scaffolds: Clinical and Angiographic Endpoints**









Number at risk

BVS	78	78	78	49	48
EES and BES	160	158	158	91	87

Number at risk

BVS	78	78	75	39	39
EES and BES	160	154	153	79	70

Puricel, S. et al. J Am Coll Cardiol. 2015; 65(8):791-801.

US ABSORB Program and Trial Strategy

Protocol 10-392

ABSORB III
US Regulatory Approval Trial, n~2250

Lead-in Cohort (n <=50)	Training
Primary RCT Cohort (n~2000) **2:1 BVS vs XIENCE**	Approval
Imaging Cohort, RCT **RCT** (n~200)*	Vasomotion, & late lumen growth claims
PK Sub-study (n=12)	Pharmacokinetics

Achieve Regulatory Approval

Imaging Cohort of 200 subjects is separate from the 2000 primary endpoint subjects

ABSORB IV
Continued Access Trial, (n~3000)

Primary RCT Cohort (n~3000) **1:1 BVS vs XIENCE**	Angina Claim
RESOLVE Ischemia Sub-study (n~370) **1:1 BVS vs XIENCE**	Ischemia Assessment

ABSORB IV is ***currently enrolling***

Show superiority of Absorb to XIENCE

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

Michael Haude, Raimund Erbel, Paul Erne, Stefan Verheye, Hubertus Degen, Dirk Böse, Paul Vermeersch, Inge Wijnbergen, Neil Weissman, Francesco Prati, Ron Waksman, Jacques Koolen

Lancet 2013; 381: 836–44

Published Online January 15, 2013 http://dx.doi.org/10.1016/S0140-6736(12)61765-6

See Comment page 787

Medical Clinic I, Städtische Kliniken Neuss, Lukaskrankenhaus GmbH, Neuss, Germany (Prof M Haude MD, H Degen MD); Department of Cardiology, West German Heart Center Essen, Essen, Germany (Prof R Erbel MD, D Böse MD); Cardiology Department, Luzerner Kantonsspital, Luzern, Switzerland (Prof P Erne MD); Department of Cardiology, ZNA Middelheim, Antwerp, Belgium (S Verheye MD, P Vermeersch MD); Department of Cardiology, Catharina Hospital, Eindhoven, Netherlands (I Wijnbergen MD, J Koolen MD); MedStar Health Research Institute, Washington, DC, USA (N Weissman MD,

Summary

Background Bioabsorbable vascular scaffolds were developed to overcome limitations of permanent bare-metal or drug-eluting coronary stents—ie, stent thrombosis (despite prolonged dual antiplatelet therapy), the life-long presence of a caged vessel segment that does not allow vasomotion or remodelling, and chronic vessel wall inflammation. We assessed the safety and performance of a new magnesium-based paclitaxel-eluting absorbable metal scaffold in symptomatic patients with de-novo coronary lesions.

Methods We did a prospective, multicentre, first-in-man trial (BIOSOLVE-1) of the drug-eluting absorbable metal scaffold (DREAMS). 46 patients with 47 lesions were enrolled at five European centres. The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularisation, at 6 and 12 months. Clinical follow-up was scheduled at 1, 6, 12, 24, and 36 months. Patients were consecutively assigned to angiographic and intravascular ultrasonographic follow-up at 6 months or 12 months. Optical coherence tomography was done in some patients. All patients were recommended to take dual antiplatelet therapy for at least 12 months. This trial is registered with ClinicalTrials.gov, number NCT01168830.

Findings Overall device and procedural success was 100%. Two of 46 (4%) patients had target lesion failure at 6 months (both clinically driven target lesion revascularisations), which rose to three of 43 (7%) at 12 months (one periprocedural target vessel myocardial infarction occurred during angiography at the 12 month follow-up visit). We noted no cardiac death or scaffold thrombosis.

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.

Funding Biotronik.

BIOSOLVE-I study results

Six to 36-month clinical follow-up

BIOSOLVE-I

Device success	100% (47/47)
Procedure success	100% (46/46)

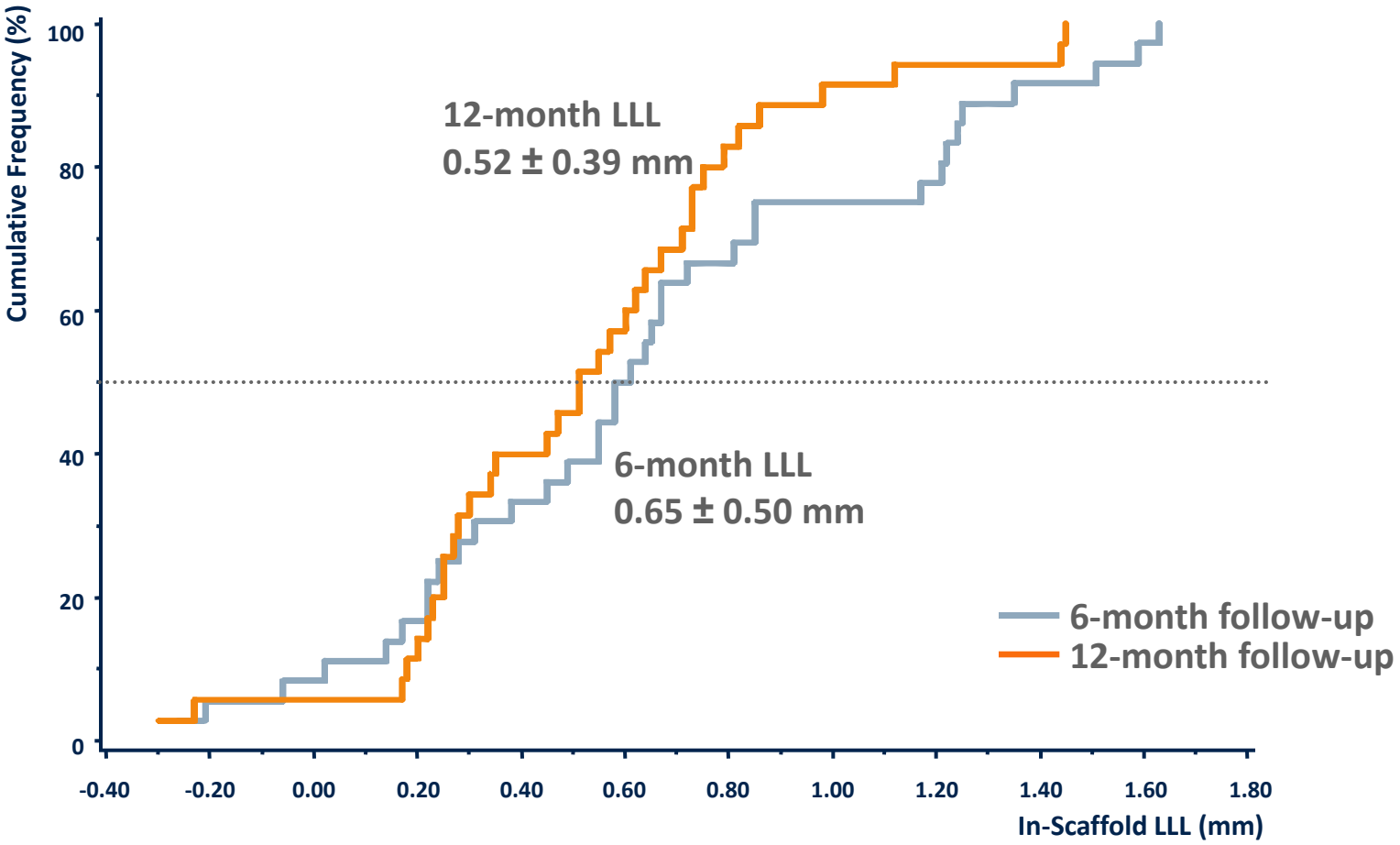
Clinical results	6-month[1]	12-month[1]	24-month[4]	36-month[4]
				Cohort 1
	N=46	N=44	N=44	N=20
TLF	2	3	3	2
Cardiac death	0	0	0	0
MI	0	1[2]	1[2]	0
Scaffold thrombosis	0	0	0	0
TLR[3]	2	2	2	2

M Haude. et al. Lancet 2013; 381:836-44.

BIOSOLVE-I study results

6-and 12-month late lumen loss (LLL)

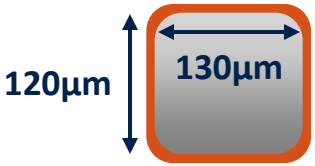
BIOSOLVE-I



M Haude. et al. Lancet 2013; 381:836-44.

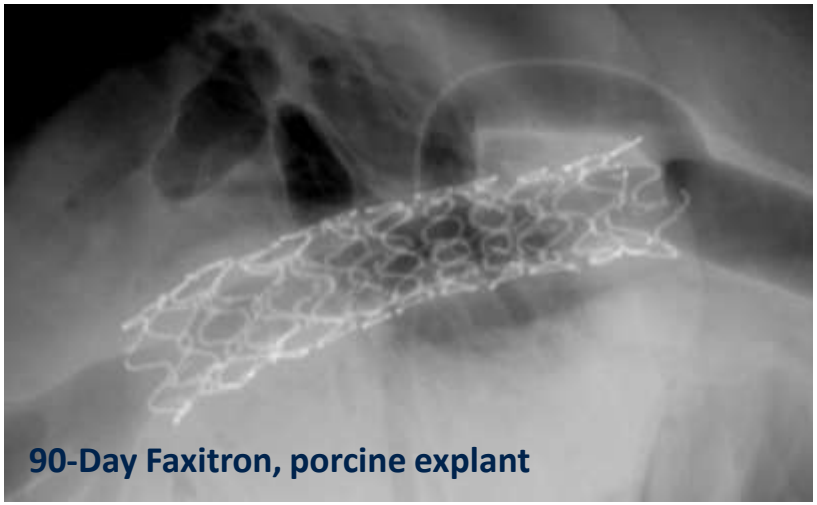
DREAMS Device Evolution (G1 → G2)

DREAMS G1

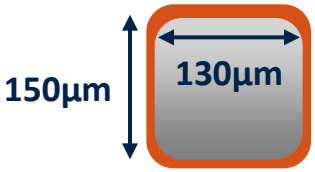


Drug: Paclitaxel

Polymer: PLGA

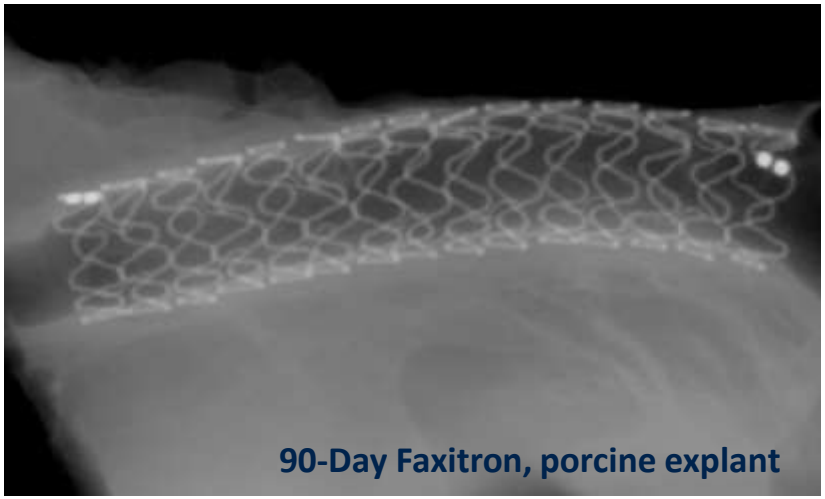


DREAMS G2



Drug: Sirolimus

Polymer: PLLA (BIOlute)



Source: BIOTROINK AG, data on file.

Issues Briefs

BVS; Clinical Evidence

Existing data

- ABSORB I and II, registries

Ongoing Trials

- ABSORB III
- ABSORB IV

BVS: Concerns and Practical Perspective

Stent thrombosis

Malapposition and aneurysm

Complex lesions; left main, bifurcation, long lesions

Preventive BVS for non-culprit lesions; BVS or medical DAPT durations

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Very late bioresorbable vascular scaffold thrombosis following discontinuation of antiplatelet therapy

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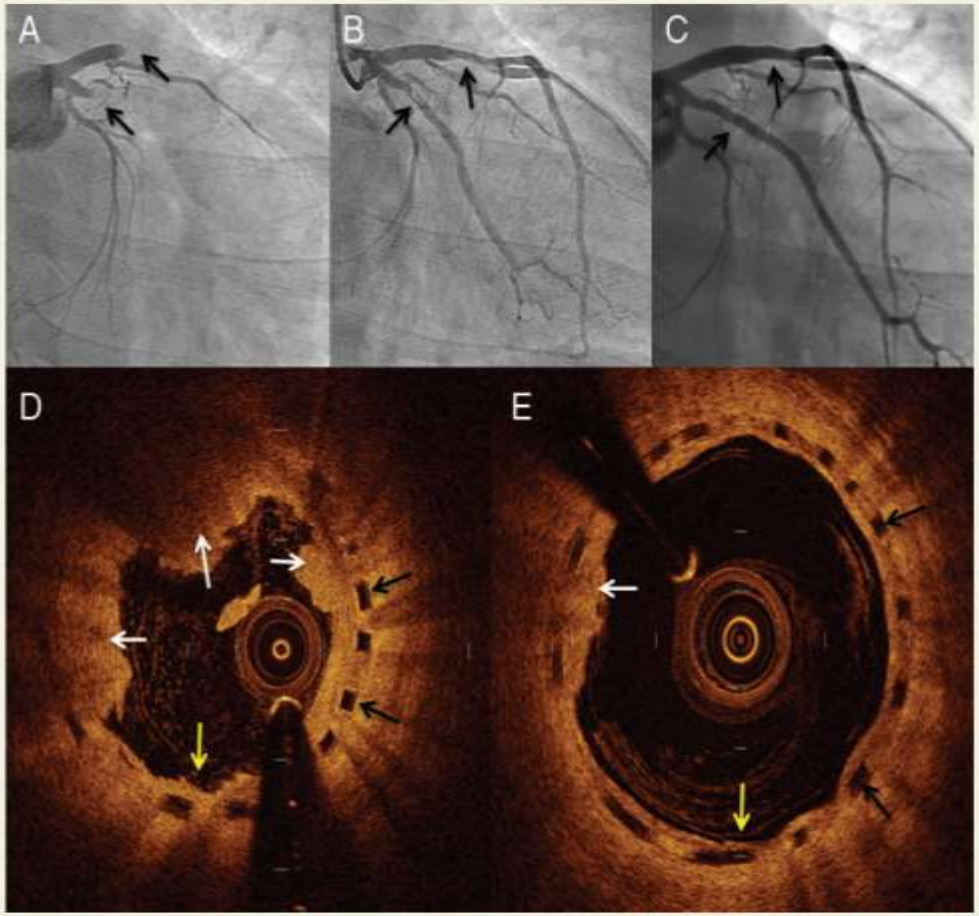
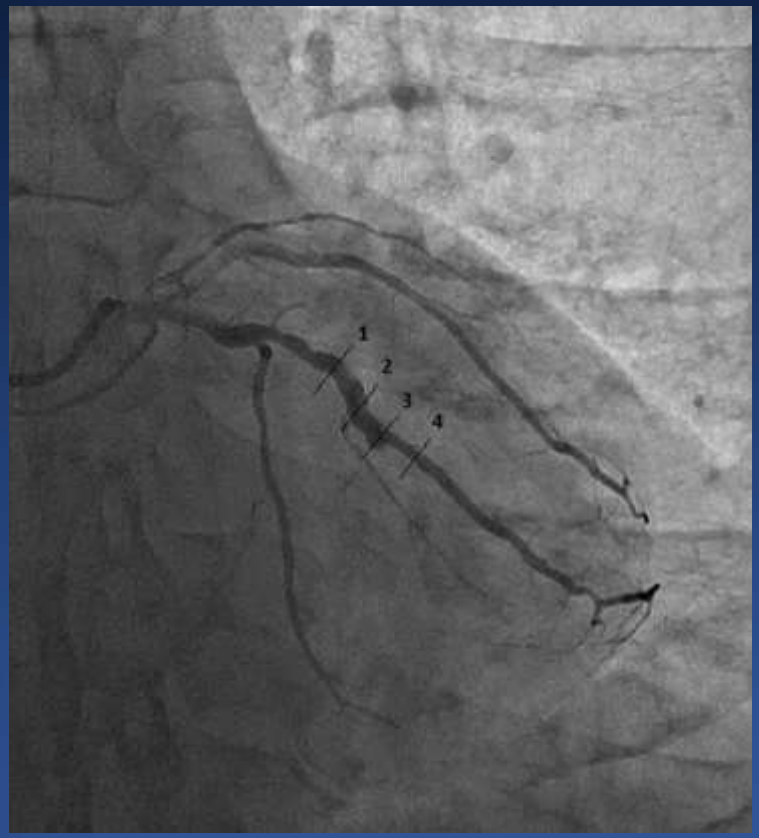
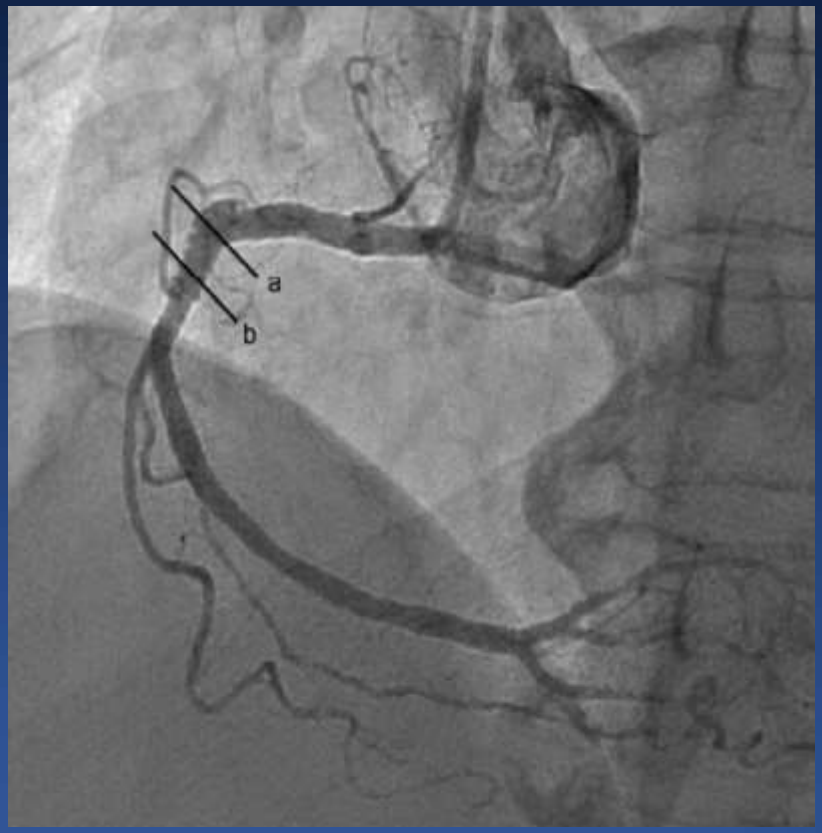
A 39-year-old Kuwaitian man was referred to our catheterization laboratory with an acute anterolateral myocardial infarction. Eighteen months before, he received bioresorbable vascular scaffolds (BVS) in the left anterior descending coronary artery (LAD) and obtuse marginal (OM) branch in Kuwait. After 12 months of treatment with aspirin and clopidogrel, both medications were discontinued as advised by the treating cardiologist. Coronary angiogram demonstrated occlusion of both BVS (*Panel A*, Supplementary material online, *Video S1*). After thrombosuction (*Panel B*, Supplementary material online, *Video S2*), optical coherence tomography revealed atherosclerotic plaque, BVS struts, still present 18 months after implantation (*Panel D*, black arrows, Supplementary material online, *Video S4*), inhomogeneous endothelialisation of the scaffold struts (yellow arrows) and the classical picture of intraluminal thrombus (white arrows). Three days later—after treatment with aspirin, ticagrelor and tirofiban—a marked reduction of thrombus burden in the BVS was observed (*Panel C* and *E*, Supplementary material online, *Videos S3* and *S5*).



Late coronary BVS malapposition and aneurysm: A time for appraisal



12 Mo after BVS



2 Mo after BVS

Catheter Cardiovasc Interv. 2014 Dec 13

Limitations of DES Platforms

Strut and Coating Thickness In Perspective

Durable Polymer Coated Stents		Bioabsorbable Polymer Coated Stents			Bioabsorbable Stent
Xience CoCr-EES Promus PtCr-EES	Resolute CoNi-ZES	Biomatrix 316L-BES	Nobori 316L-BES	SYNERGY PtCr-EES	BVS PLLA-EES

Strut Thickness					
81µm	89µm	120µm	125µm	74µm	150µm
Polymer Coating					
Conformable 7-8µm / side	Conformable 6µm / side	Abluminal 11µm	Abluminal 20µm	Abluminal 4µm	Conformable 3µm / side

BVS Practical Concerns

- Thick strut thickness; calcification or tortuosity.
- Prolonged, extensive, and time-consuming pre-dilation is mandatory for complex lesions.
- increased scaffold fracture risk with overdilation.
- The total cost and duration of PCI with a BRS may be higher than with a conventional DES?

Unresolved Limitations of Bioabsorbable Stent

- High profile; type A lesions
- Complex lesions; Calcified or tortuous, LM, long, bifurcation
- Stretchability and fracture
- Overlapping
- Side branch
- Relatively high late loss

Discussion

- **BVS benefit still hypothetical??**
  - ✓ Most data from SA and de novo lesions…
  - ✓ Future roles for complex anatomic or clinical setting?
  - ✓ How long DAPT?
  - ✓ Defective healing and late adverse reactions with BVS?
  - ✓ Preventive PCI role for non-culprit lesions?