The BIO revolution: bioadsorbable stents

Federico Conrotto

Cardiologia 2

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BVS stent (Abbot Vascular)

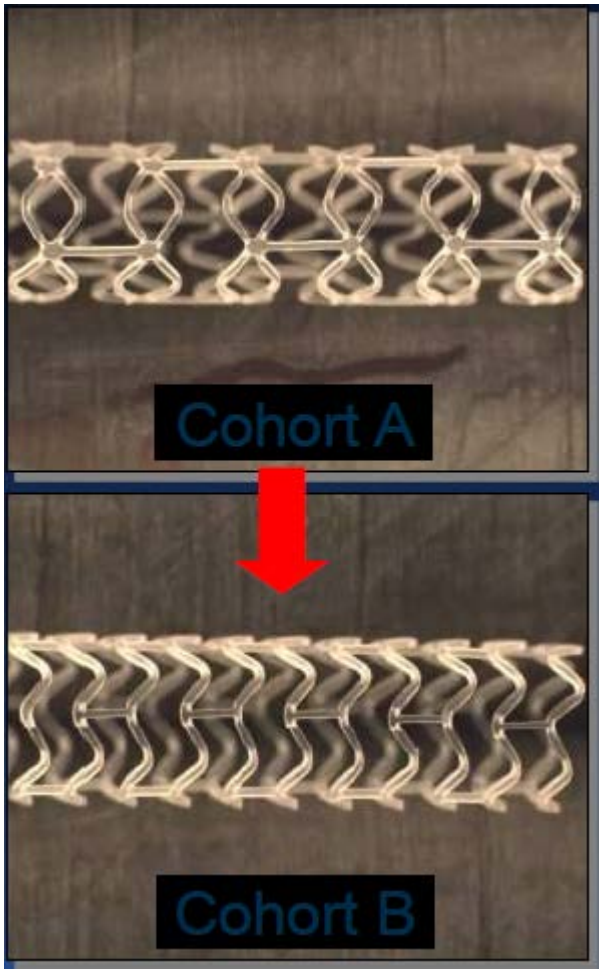
Strut Material: Poly-L-Lactic acid

Coating Material: Poly-D,L-lactide

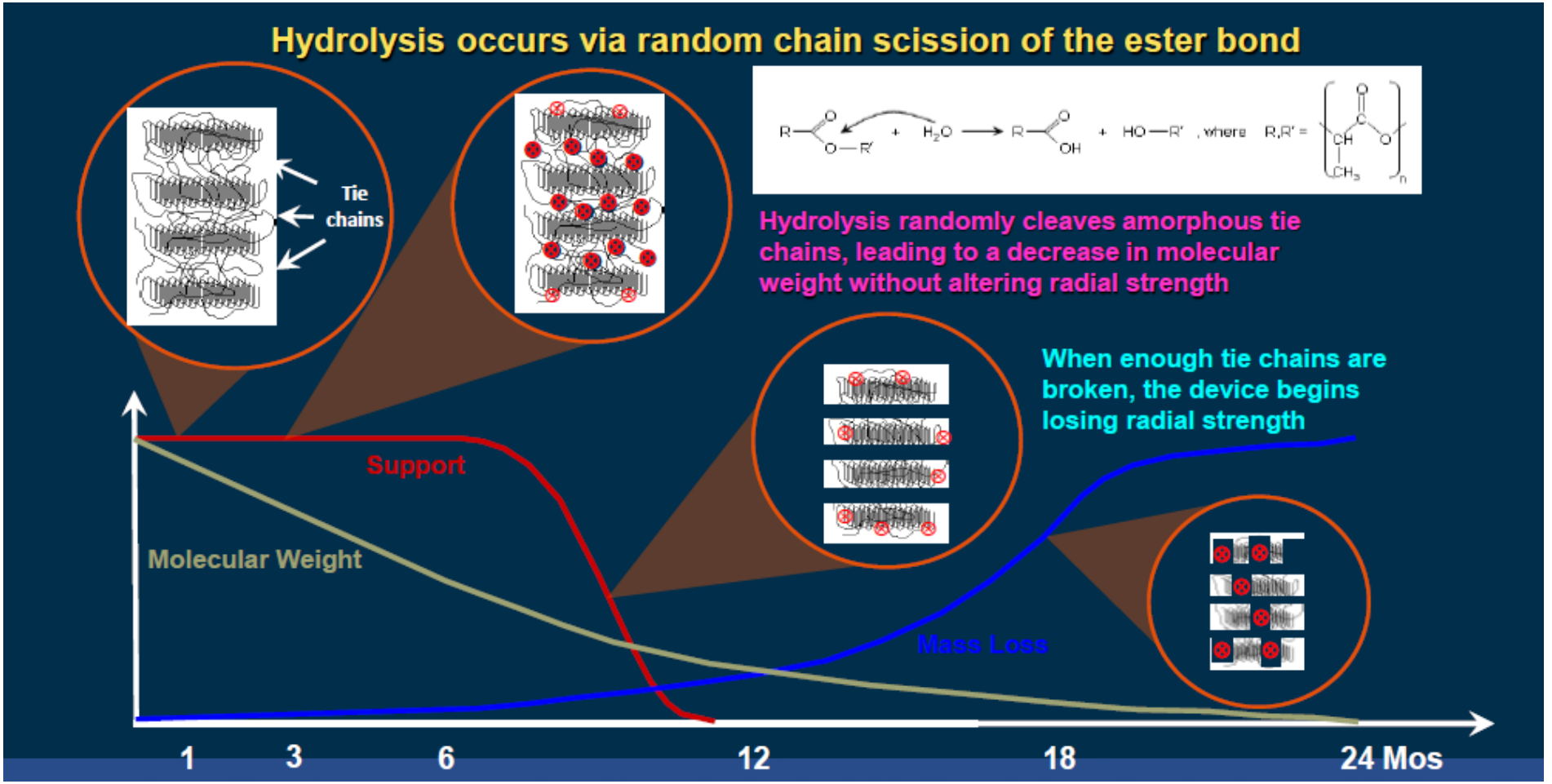
Design: out of phase sinusoidal hoops with straight and direct links in cohort A and in-phase hoops with straight links in cohort-B

Absorption products: Lactic acid, CO2 and H2o

Drug: Everolimus



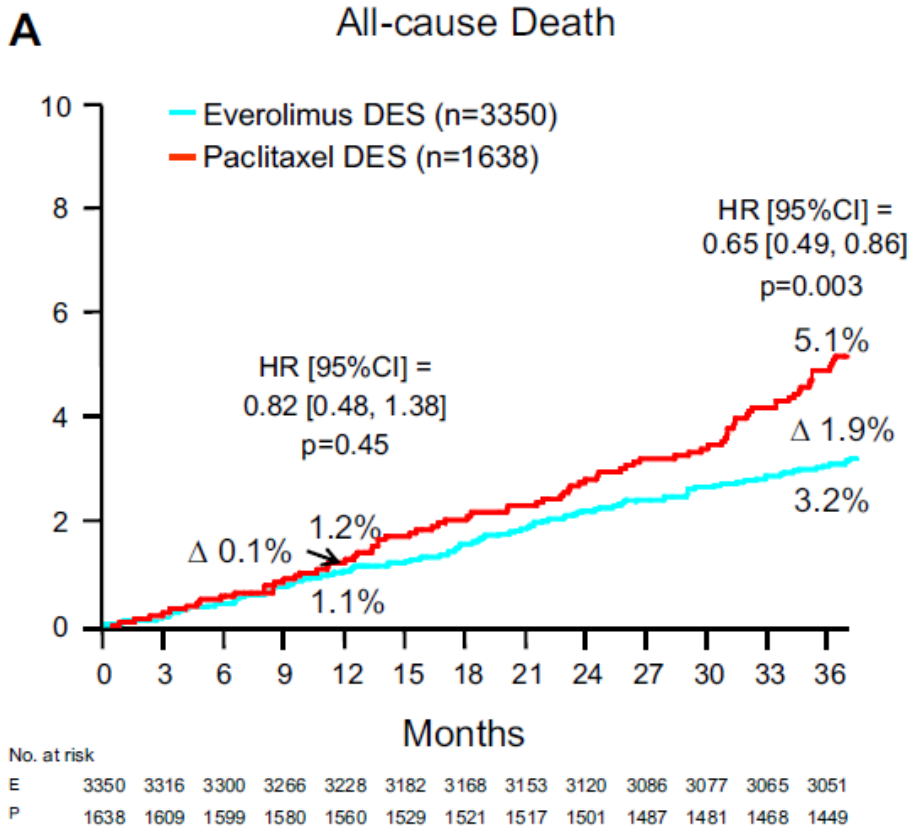
Bioresorbable Scaffolds Polylactide Resorption vs. Radial Support

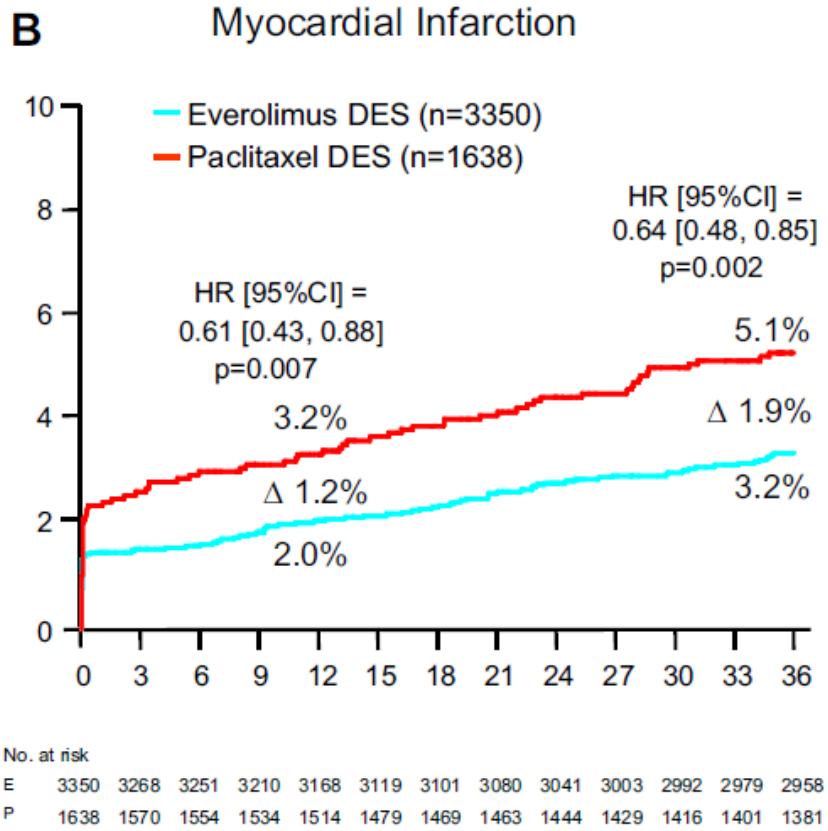


"In a BRS era, the goal is to provide temporary vessel support and then allow the physiology to evolve naturally"

Meta-Analysis of Everolimus-Eluting Versus Paclitaxel-Eluting Stents in Coronary Artery Disease.

Final 3-Year Results of the SPIRIT Clinical Trials Program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions)





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J Am Coll Cardiol Intv 2013;6:914–22

Meta-Analysis of Everolimus-Eluting Versus Paclitaxel-Eluting Stents in Coronary Artery Disease.

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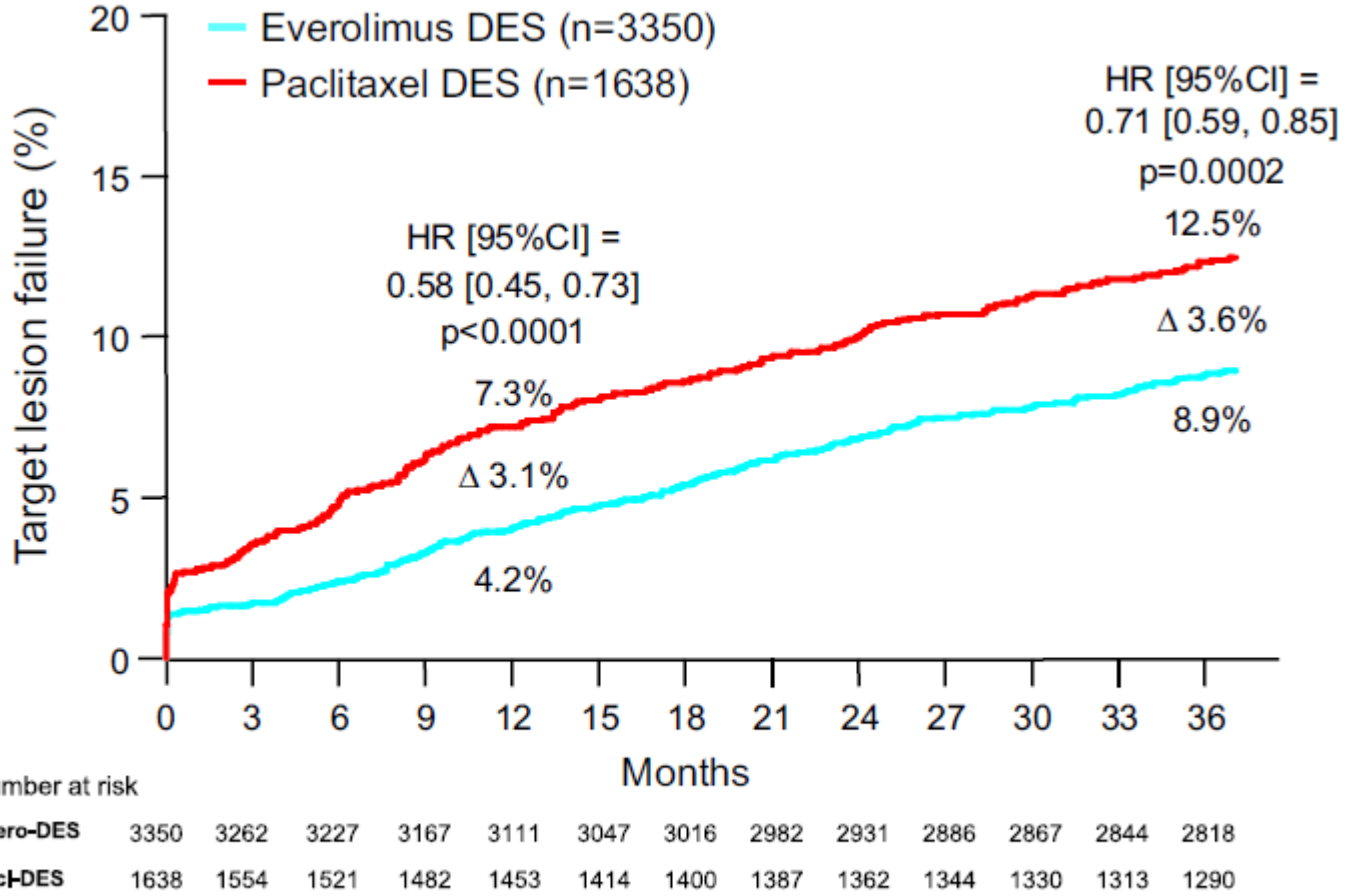
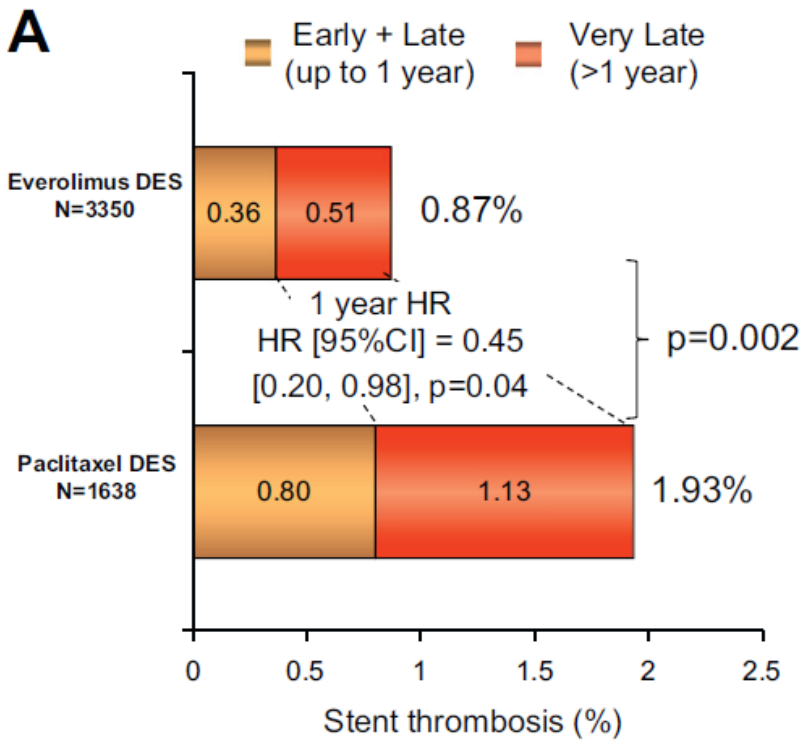
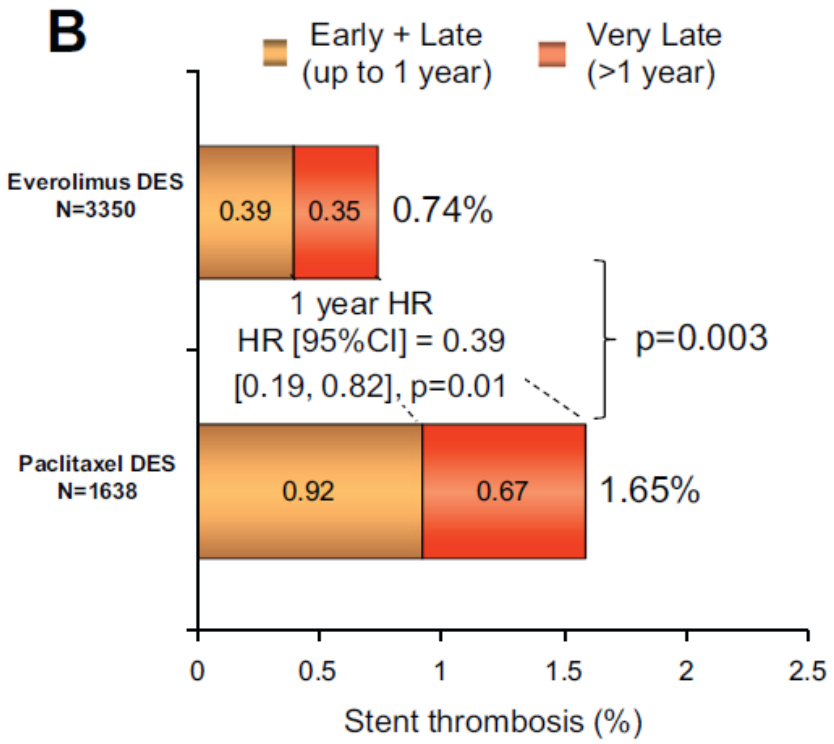


Figure 1. Three-Year Differences in TLF

Meta-Analysis of Everolimus-Eluting Versus Paclitaxel-Eluting Stents in Coronary Artery Disease.

Final 3-Year Results of the SPIRIT Clinical Trials Program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions)





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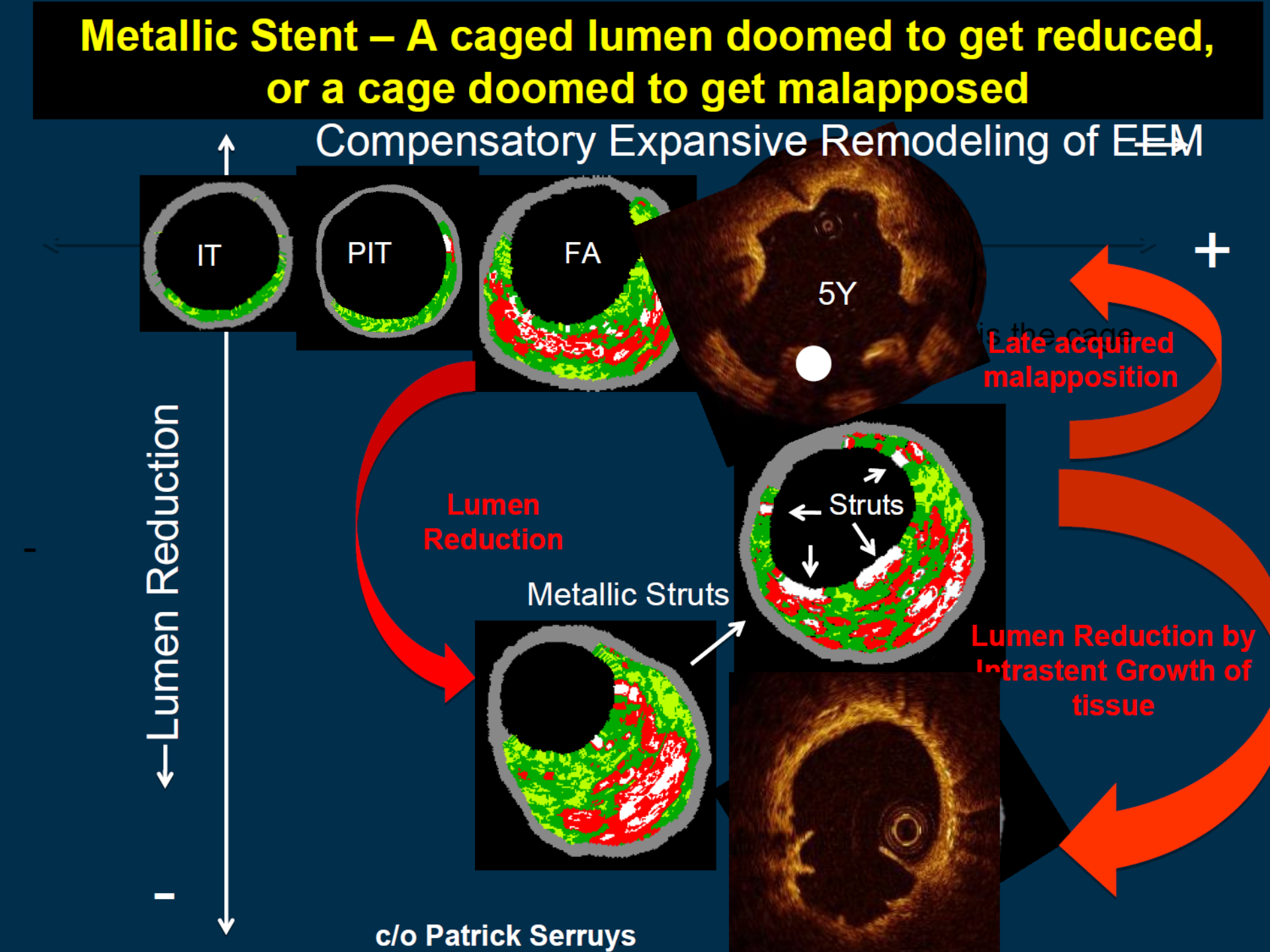
J Am Coll Cardiol Intv 2013;6:914–22

Etiology of DES events beyond 1 year

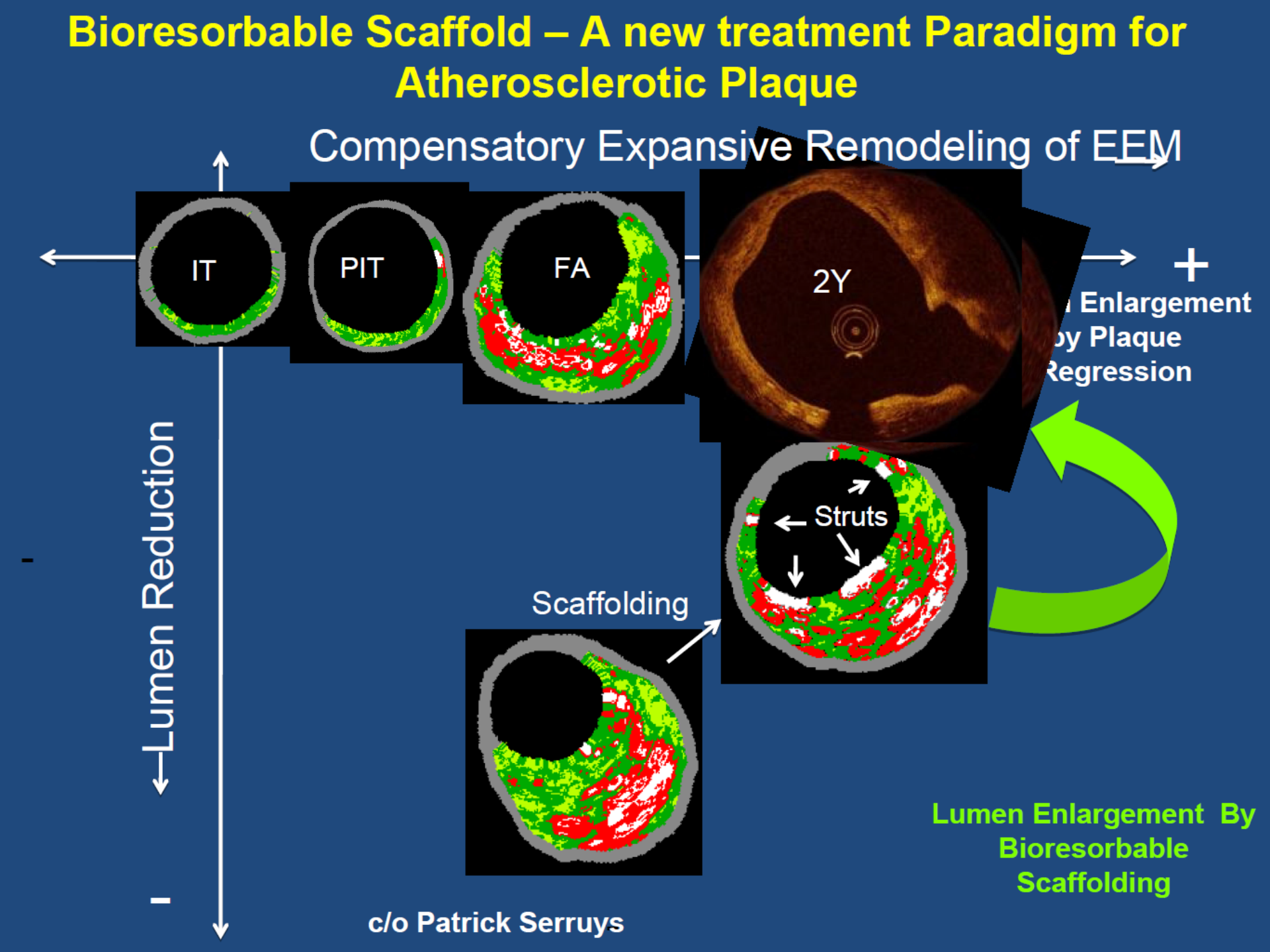
Very Late Thrombosis and restenosis

1. Uncovered stent struts (thrombosis)
2. Persistent stimulation of SMCs, from adherent fibrin and/or loss of normal vessel curvature
3. Abnormal shear stress form protruding struts and/or loss of cyclic strain relief (compliance mismatch)
4. Chronic inflammation due to late foreign body reactions and polymer hypersensivity
5. Positive remodeling with strut malapposition
6. Strut fracture
7. Neoatherosclerosis

Metallic Stent – A caged lumen doomed to get reduced, or a cage doomed to get malapposed



Bioresorbable Scaffold – A new treatment Paradigm for Atherosclerotic Plaque



Incremental benefit of BRS over Xience

	One year	Five year
Mortality	-	?
MI	-	?
TLR	-	?

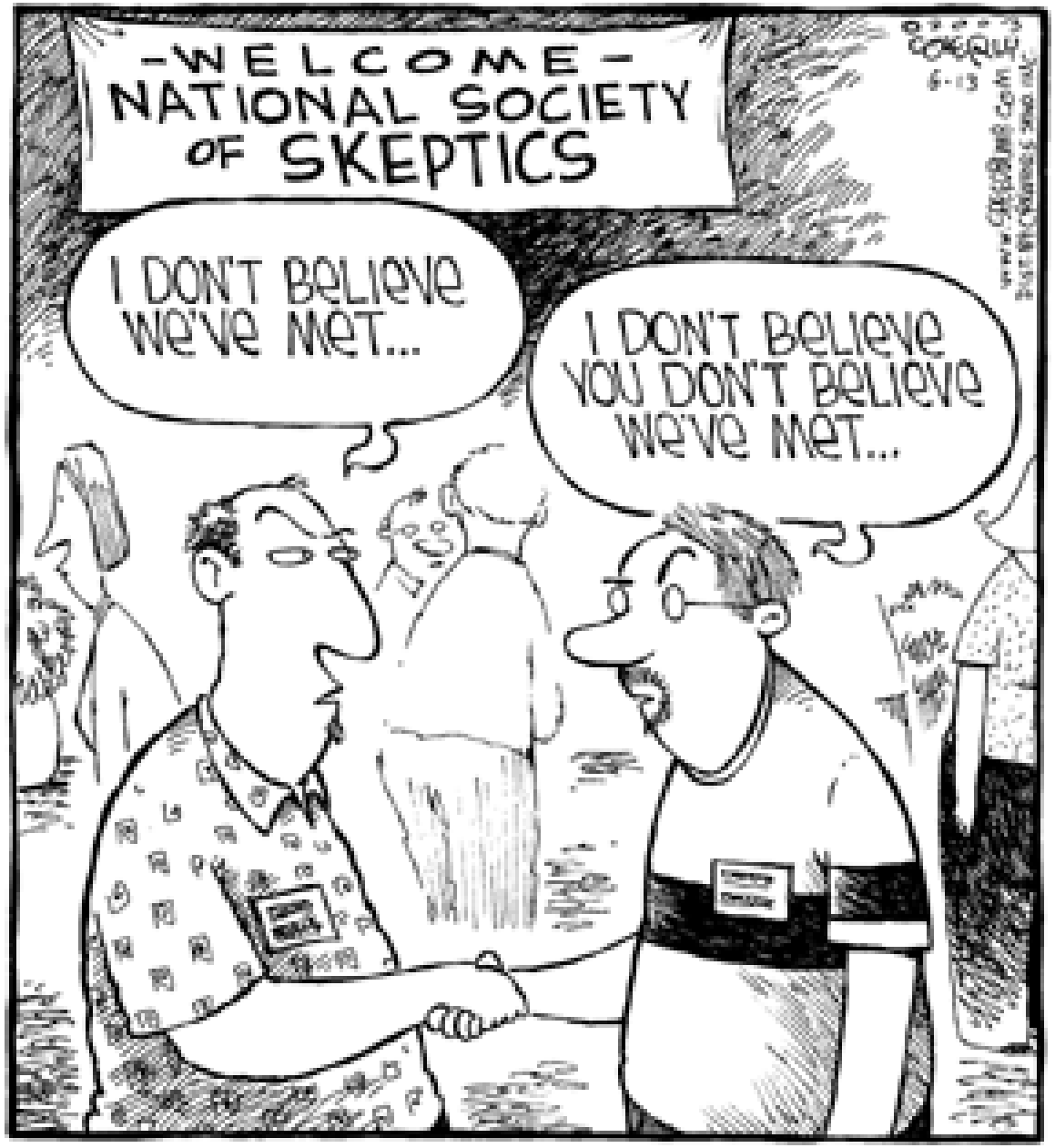
Conclusion: No benefit at one year

	One year	Five year
Scaffold thrombosis	-	+?
Vasomotion/ Pulsatility	+	+
Pharmaco-access	+	+

Acetylcholine positive have better outcomes

	One year	Five year
Late lumen enlargement	-	+
Wall thinning	-	+
Adaptive remodelling	-	+

Late benefit of VRT



A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods

Patrick W Serruys, John A Ormiston, Yoshinobu Onuma, Evelyn Regar, Nieves Gonzalo, Hector M Garcia-Garcia, Koen Nieman, Nico Bruining, Cécile Dorange, KarineMiquel-Hébert, Susan Veldhof, Mark Webster, Leif Thuesen, Dariusz Dudek

Summary

Background Drug-eluting metallic coronary stents predispose to late stent thrombosis, prevent late lumen vessel enlargement, hinder surgical revascularisation, and impair imaging with multislice CT. We assessed the safety of the bioabsorbable everolimus-eluting stent (BVS).

Methods 30 patients with a single de-novo coronary artery lesion were followed up for 2 years clinically and with multiple imaging methods: multislice CT, angiography, intravascular ultrasound, derived morphology parameters (virtual histology, palpography, and echogenicity), and optical coherence tomography (OCT).

Findings Clinical data were obtained from 29 of 30 patients. At 2 years, the device was safe with no cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses recorded, and only one myocardial infarction (non-Q wave). 18-month multislice CT (assessed in 25 patients) showed a mean diameter stenosis of 19% (SD 9). At 2-year angiography, the in-stent late loss of 0·48 mm (SD 0·28) and the diameter stenosis of 27% (11) did not differ from the findings at 6 months. The luminal area enlargement on OCT and intravascular ultrasound between 6 months and 2 years was due to a decrease in plaque size without change in vessel size. At 2 years, 34·5% of strut locations presented no discernible features by OCT, confirming decreases in echogenicity and in radiofrequency backscattering; the remaining apparent struts were fully apposed. Additionally, vasomotion occurred at the stented site and adjacent coronary artery in response to vasoactive agents.

Interpretation At 2 years after implantation the stent was bioabsorbed, had vasomotion restored and restenosis prevented, and was clinically safe, suggesting freedom from late thrombosis. Late luminal enlargement due to plaque reduction without vessel remodelling needs confirmation.

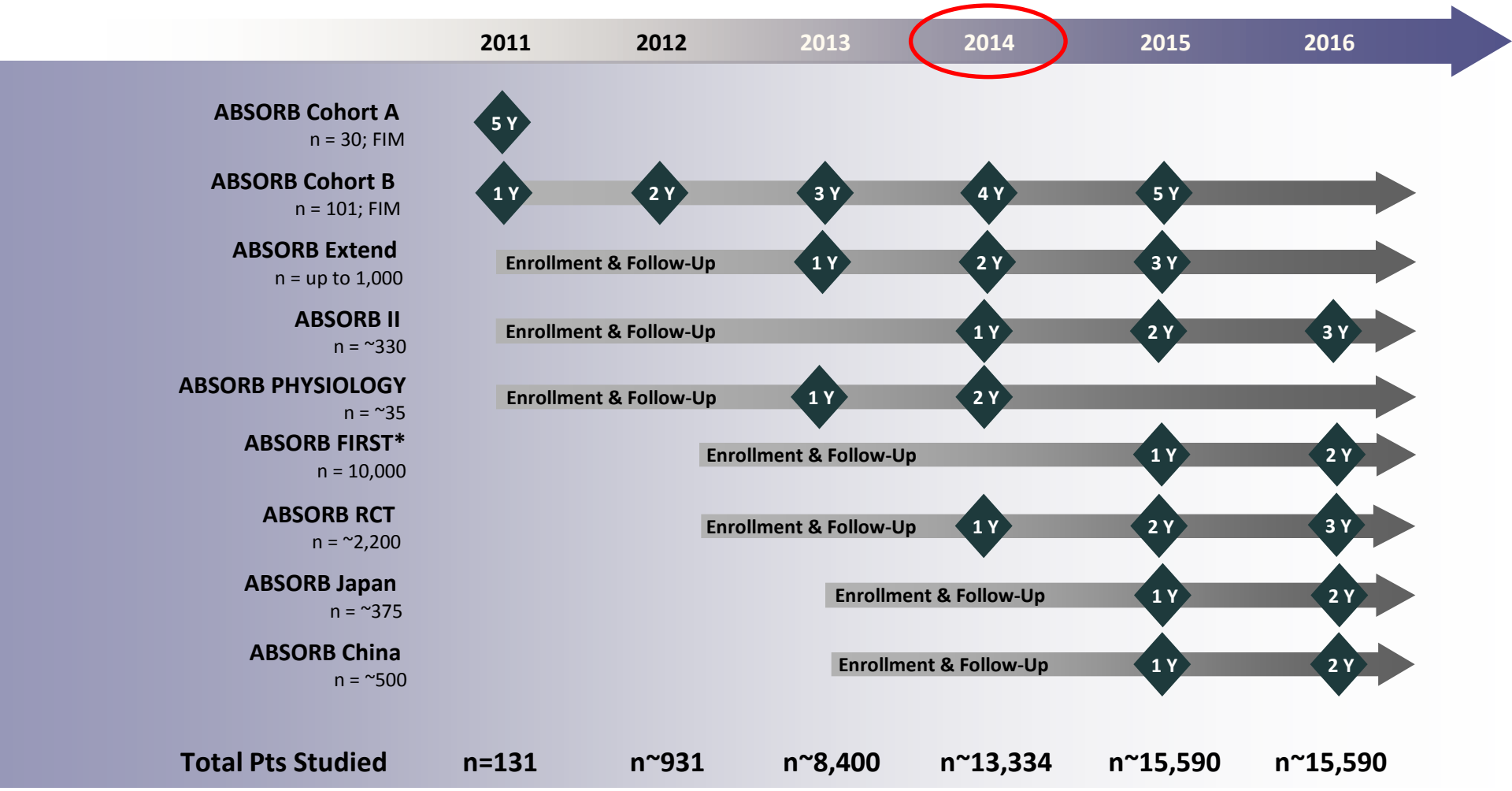
Lancet 2009; 373: 897–910

See Comment page 869

See Perspectives page 887

Thorax Center (Prof P W Serruys MD, Y Onuma MD, E Regar MD, N Gonzalo MD, K Nieman MD, N Bruining PhD) **and Department of Radiology** (K Nieman MD), **Erasmus Medical Center, Rotterdam, Netherlands; Auckland City Hospital, Auckland, New Zealand** (Prof J A Ormiston MB, M Webster MB); **Cardialysis BV, Rotterdam, Netherlands** (H M Garcia-Garcia MD); **Abbott Vascular, Diegem, Belgium** (C Dorange MSc, K Miquel-Hébert PhD, S Veldhof RN); **Skejby Sygehus, Aarhus University Hospital, Skejby, Denmark** (L Thuesen MD); **and Jagiellonian University, Krakow, Poland** (D Dudek MD)

The ABSORB Clinical Trial Program



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Five Year Angiographic Results of the ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold

B De Bruyne1, MD, PhD; G.G Toth1, MD; Y Onuma2,3, MD, PhD; HM Garcia Garcia3, MD, PhD; PW Serruys2, MD, PhD

1OLV Hospital, Aalst, Belgium; 2Thorax Centre, Erasmus MC, Rotterdam, The Netherlands; 3 CardialysisBV, Rotterdam, The Netherlands

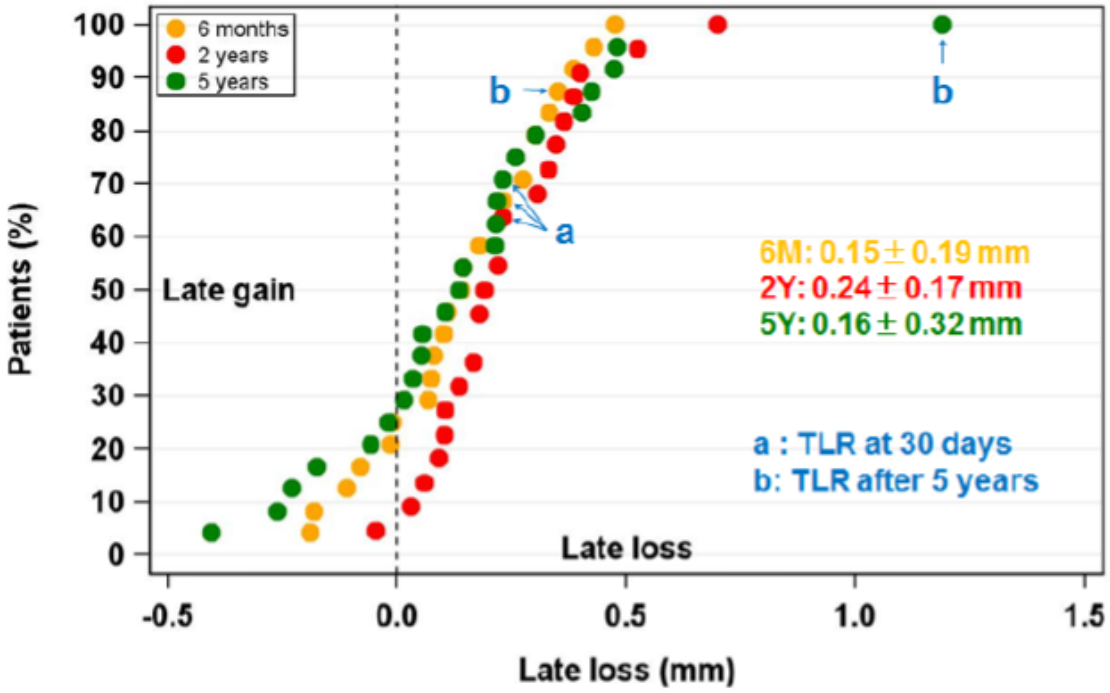
- The ABSORB Cohort A trial results demonstrated the safety of Absorb BVS in 30 patients with single de novo native coronary artery lesions.
- The ABSORB Cohort B trial, a continuation of that assessment, enrolled 101 patients at 12 sites in Europe and Asia Pacific

Methods

- The patients of the ABSORB Cohort B Trial were divided into 2 groups, Cohort B1 (n=45) with imaging follow-up at 180 days & 2 years and Cohort B2 (n=56) with imaging follow-up at 1& 3 years.
- A protocol amendment was implemented for a 5 year imaging follow up in all 101 patients.
- The results of the 24/45 patients in B1 who agreed to return for 5 year imaging are presented

Results 1

- Summary of Late Loss at 5-years

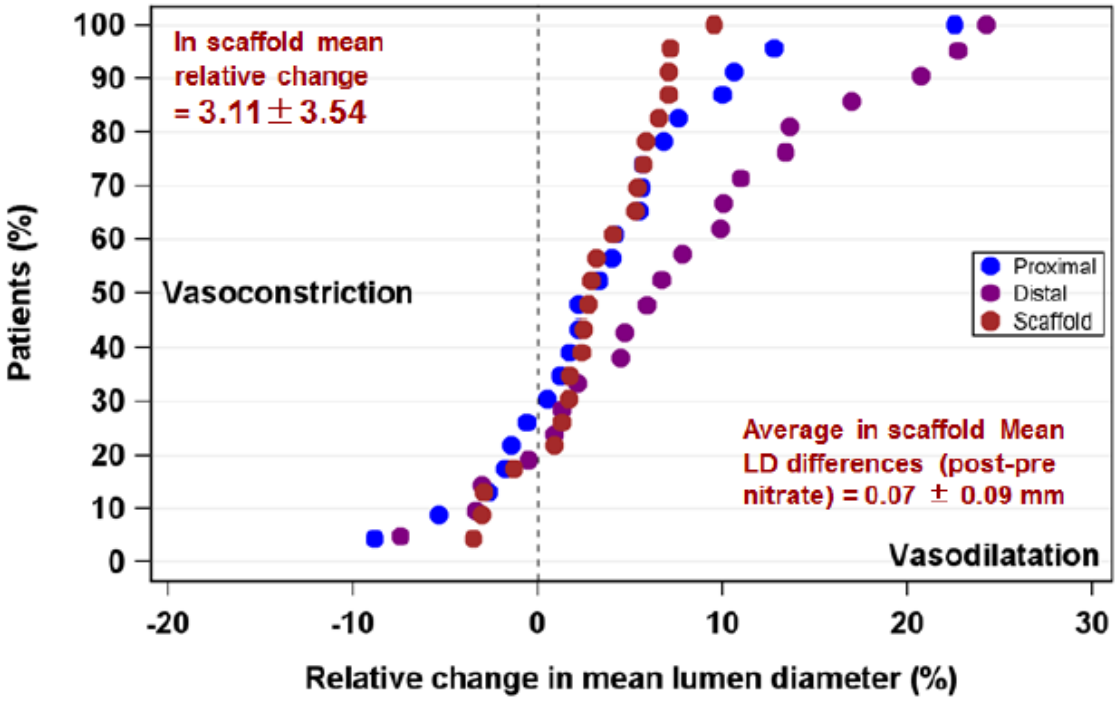


	6 months n=24	2 years n=22	5 years n=24	Diff 6m vs. 2yrs n=22	Diff 6m vs. 5yrs n=24	Diff 2yrs vs. 5yrs n=22
In scaffold mean late loss	0.15±0.19	0.24±0.17	0.16±0.32	0.10±0.17	0.01±0.29	-0.11±0.18
P-values				0.0133	0.8368	0.0035

Absorb Cohort B1 5 Year Results; B de Bruyne, TCT 2014

Results 2

- Results of nitrate induced vasomotor function at 5-years, n-23. The in-scaffold segment shows either vasodilation (in 83% of the patients) or vasoconstriction, unlike metallic DES in a previous report.[1]



Relative change = 100 x (mean LD post Nit-mean LD pre Nit) / mean LD pre Nit

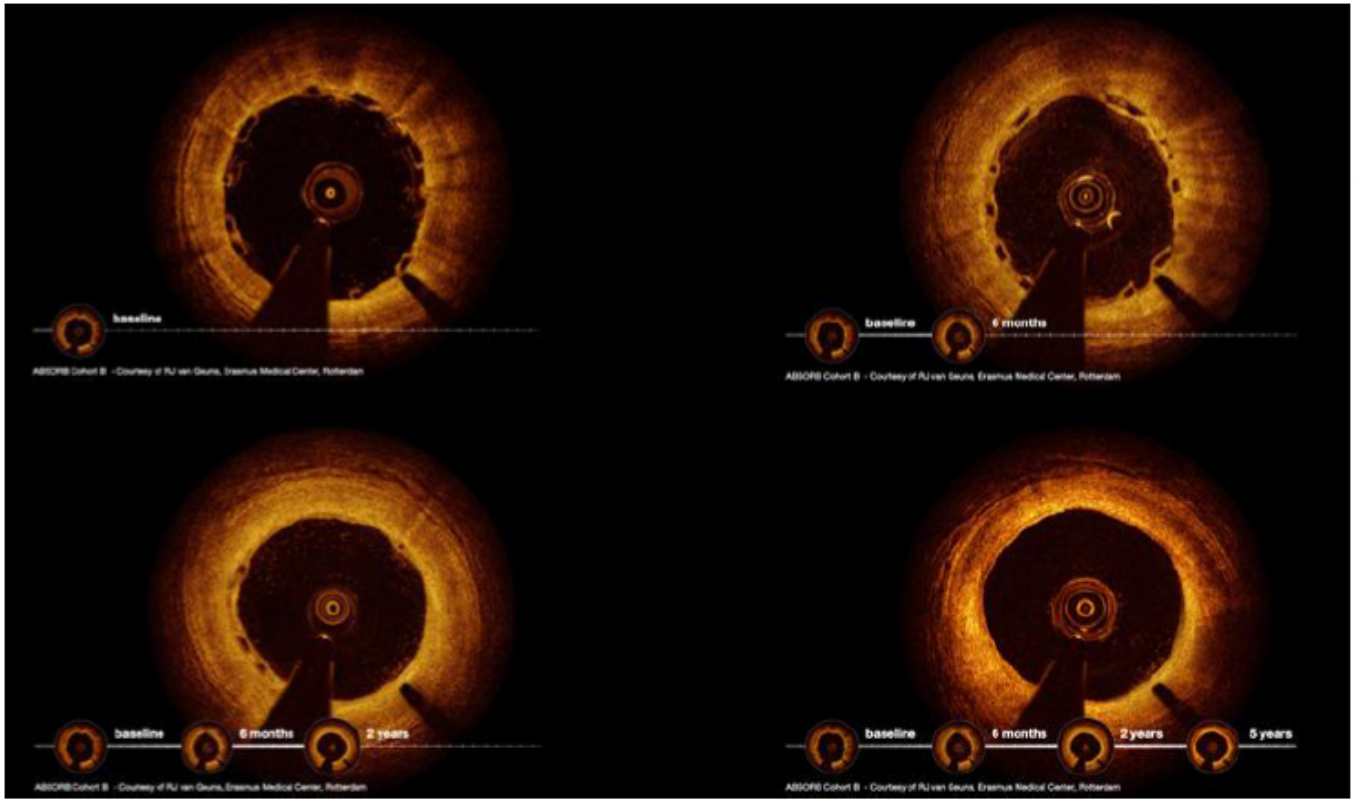
[1]*DES implantation associated with long term coronary endothelial dysfunction. Shin et al. Int Heart J 2007;48:553-567*

Absorb Cohort B1 5 Year Results; B de Bruyne, TCT 2014

Results 3

OCT Images Over Time Showing Complete Resorbtion of the Scaffold Struts

Baseline



6 Months

2 Years

5 Years

Courtesy of Dr RJ v Geuns, Rotterdam, The Netherlands

Absorb Cohort B1 5 Year Results; B de Bruyne, TCT 2014

Which factors drive implementation in my clinical practice ?

1. Evidence from controlled randomized trials
2. Hard endpoints
3. Generalizability
4. Ease of use
5. Costs (positive cost-effectiveness ratio)
6. Soft endpoints

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

Single-blind, multicentre, randomised trial,
2:1 ratio: everolimus-eluting bioresorbable scaffold (Absorb) or everolimus-eluting metallic stent (Xience)
501 patients

The co-primary endpoints

1) Vasomotion (change in mean lumen diameter before and after nitrate administration at 3 years)
2) Difference between minimum lumen diameter (after nitrate administration) after the index procedure and at 3 years.

….but recognizing the scaffold's widespread use – 70,000-100,000 implants in use - the ABSORB II investigators decided to "report the secondary clinical endpoints at 1 year in order to provide the medical community with the first randomized data on the device."

1) Despite a larger profile (ABSORB: 1.4mm, vs. Xience1.1mm), device success was similar

	Bioresorbable scaffold group	Metallic stent group	Difference (95% CI)	p value
Procedural details				
Number of lesions	364	182	..	..
Balloon dilatation prior to device implantation	364 (100%)	180 (99%)	1·10% (–0·21, 3·92)	0·11
Planned overlap with the same type of device	56 (15%)	20 (11%)	4·40% (–1·93, 9·94)	0·16
Unforeseen additional implantation with the same device	14 (4%)	11 (6·0)	–2·20% (–6·91, 1·44)	0·25
More than one study device implanted	70 (19%)	27 (15%)	4·40% (–2·57, 10·62)	0·21
Nominal size of study device (mm)	3·01 (0·31)	3·05 (0·28)	–0·04 (–0·10, 0·01)	0·10
Balloon dilatation after device implantation	221 (61%)	107 (59%)	1·92% (–6·66, 10·67)	0·67
Nominal diameter of balloon used (implantation or post–dilatation; mm)	3·08 (0·34)	3·16 (0·36)	–0·08 (–0·14, 0·01)	0·02
Maximum balloon pressure used (implantation or post-dilatation; atm)	14·23 (3·43)	15·03 (3·33)	–0·80 (–1·4, –0·2)	0·01
Expected diameter of balloon used (implantation or post-dilatation; mm)	3·29 (0·35)	3·35 (0·37)	–0·06 (–0·14, 0·02)	0·15
Angiographic acute recoil of device following implantation per device (mm)	0·19 (0·19)	0·19 (0·18)	–0·00 (–0·04, 0·03)	0·85
Device success				
Clinical device success	361 (99%)	182 (100%)	–0·82% (–2·39, 1·31)	0·55
Clinical procedural success	322 (96%)*	164 (99%)*	–2·68% (–5·46, 0·80)	0·16

99% Vs 100%

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2) Acute gain was reduced
QCA (ABSORB: 1.15mm vs. Xience: 1.46mm)
Q-IVUS (ABSORB 2.9mm2vs. Xience: 3.6mm2).

Operator's behavior
•Limited expansion of device
•Fear of scaffold disruption
•Use of a smaller postdilatationballoon at a lower pressure

Preparation strategy
•Protocol did not allow use of adjunctive device

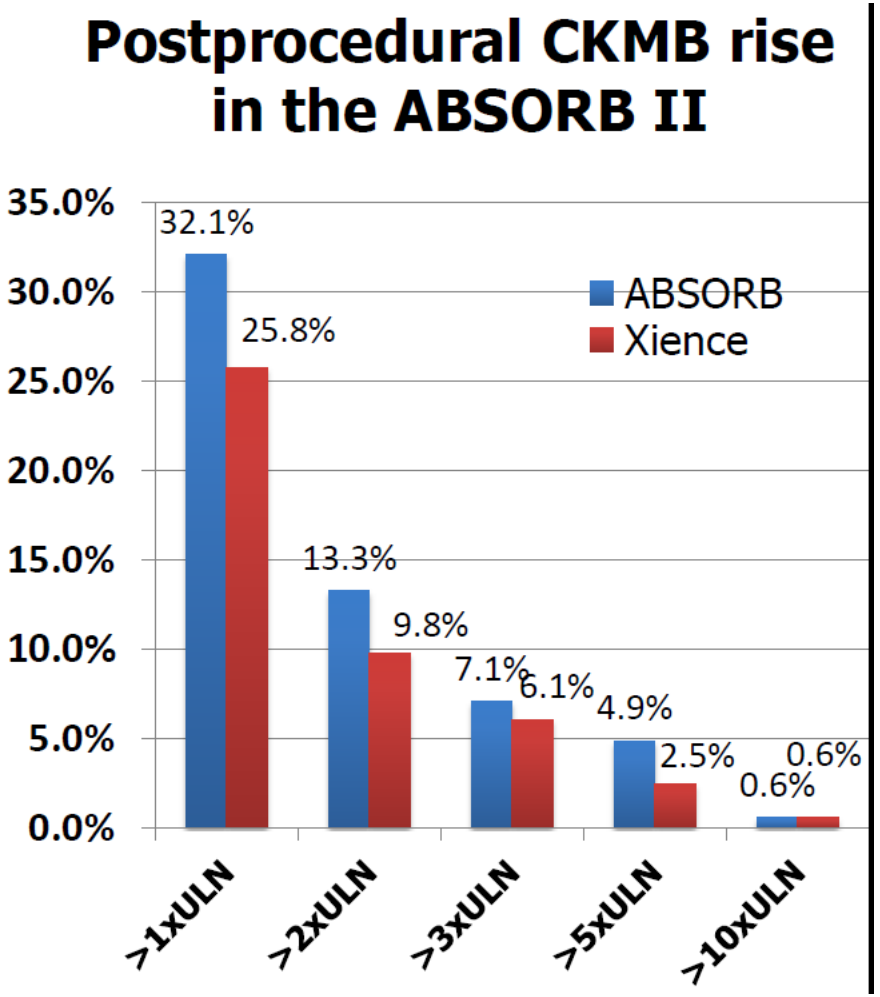
Reduced acute gain

Acute recoil
•Not an issue

3) The definite scaffold/stent thrombosis 0.6% (1 acute and 1 subsacute) in the ABSORB arm vs. 0% in the Xience arm.

	Bioresorbable scaffold group (n=335)	Metallic stent group (n=166)	Difference (95% CI)†	p value
Outcomes				
All deaths	0	1 (1%)	−0·61% (−3·35 to 0·65)	0·33
Cardiac deaths	0	0	0·00% (NA)	1·00
Myocardial infarction per protocol	15 (4%)	2 (1%)	3·32% (−0·25 to 6·26)	0·06
Q-wave	2 (1%)	0	0·60% (−1·71 to 2·18)	1·00
Non-Q-wave	13 (4%)	2 (1%)	2·72% (−0·78 to 5·53)	0·16
All target-lesion revascularisation	4 (1%)	3 (2%)	−0·61% (−4·08 to 1·60)	0·69
Clinically indicated target-lesion revascularisation	4 (1%)	3 (2%)	−0·61% (−4·08 to 1·60)	0·69
All target-vessel revascularisation	8 (2%)	8 (5%)	−2·43% (−7·01 to 0·86)	0·15
Clinically indicated target-vessel revascularisation	6 (2%)	6 (4%)	−1·82% (−6·01 to 1·04)	0·23
Non-clinically indicated target-vessel revascularisation	3 (1%)	3 (2%)	−0·91% (−4·35 to 1·19)	0·40
Non-target-vessel revascularisation	6 (2%)	6 (4%)	−1·82% (−6·01 to 1·04)	0·23
Clinically indicated non-target-vessel revascularisation	5 (1%)	4 (2%)	−0·91% (−4·66 to 1·55)	0·49
Non-clinically indicated non-target-vessel revascularisation	3 (1%)	2 (1%)	−0·31% (−3·46 to 1·63)	1·00
All revascularisation	12 (4%)	12 (7%)	−3·65% (−8·89 to 0·37)	0·08
Clinically indicated revascularisation	9 (3%)	9 (5%)	−2·74% (−7·50 to 0·75)	0·12
Non-clinically indicated revascularisation	6 (2%)	5 (3%)	−1·22% (−5·21 to 1·49)	0·52

4) Cardiac biomarker rise < 48 hours after the index procedure and per-protocol peri-procedural MI did not differ between the two arms.



5) Exercise performance and angina status as assessed by SAQ were comparable, however a difference in nitrate use was observed at 6 months (17.8% vs26.7%, p=0.02)and 12 months (19.5% vs26.2%, p=0.09)in favor of the Absorb arm.

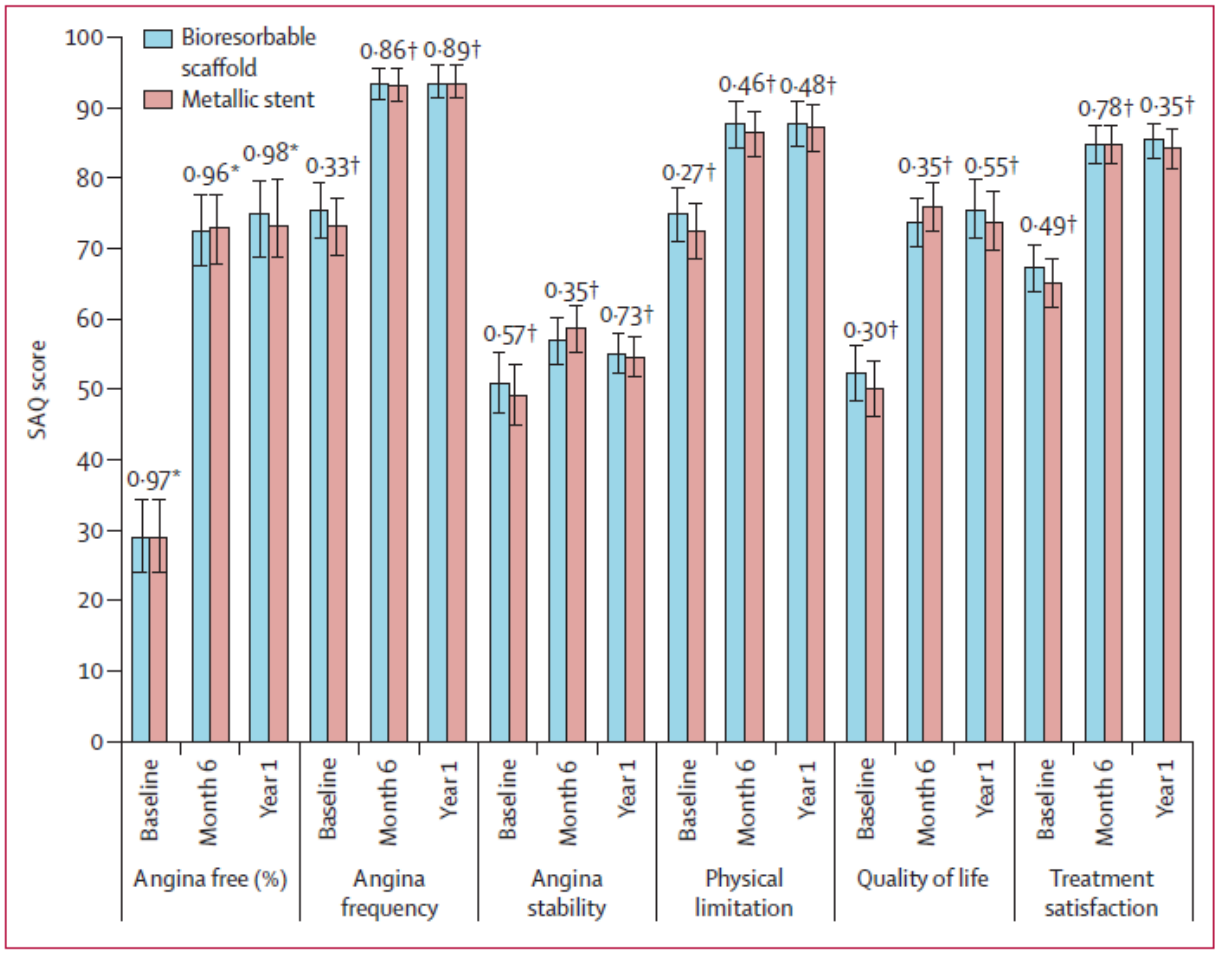


Figure 2: Seattle Angina Questionnaire responses
Figure shows five domains of the Seattle Angina Questionnaire related to angina stability, frequency, physical limitation, disease perception, and treatment satisfaction in addition to number of patients with no angina. The bars show 95% CIs. SAQ=Seattle Angina Questionnaire. *p value from post-hoc test. †p value from χ^2 test.

6)

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

Registry data

1) Absorb EXPAND Real-World Registry (TCT 2014)

2) EXTEND Real World Registry (Eurointervention 2014)

3) ASSURE Registry (TCT 2014)

4) Ghost-EU Registry (Eurointervention 2014)

5) AMC Single Centre Real World PCI Registry (Eurointervention 2014)

Results from 5 studies and 2206 Patients

Study (n)	Expand (187)	GHOST (1189)	AMC (135)	Extend (512)	Assure (183)
FU Lenght months	6	6	6	12	12
Multicenter	No	Yes	No	Yes	Yes

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Patient characteristics

Study (n)	Expand (187)	GHOST (1189)	AMC (135)	Extend (512)	Assure (183)
Age	60.2±11.1	62±11	59±11	62±11	63.5
Female	24.5%	21%	27%	26%	
Diabetes	17.9%	25%	20%	25%	25.7
Hypertension	60.8%	74%	50%	65%	82%
Renal impairment	5.4%	14.9%	8%		
Previous MI	18.8%		25%	29%	27%
Previous PCI	9.9%	34%	26%	6	
Previous CABG	0	4.6%	2%		
ACS	59.1%	47.4%	53%	35% (UA)	

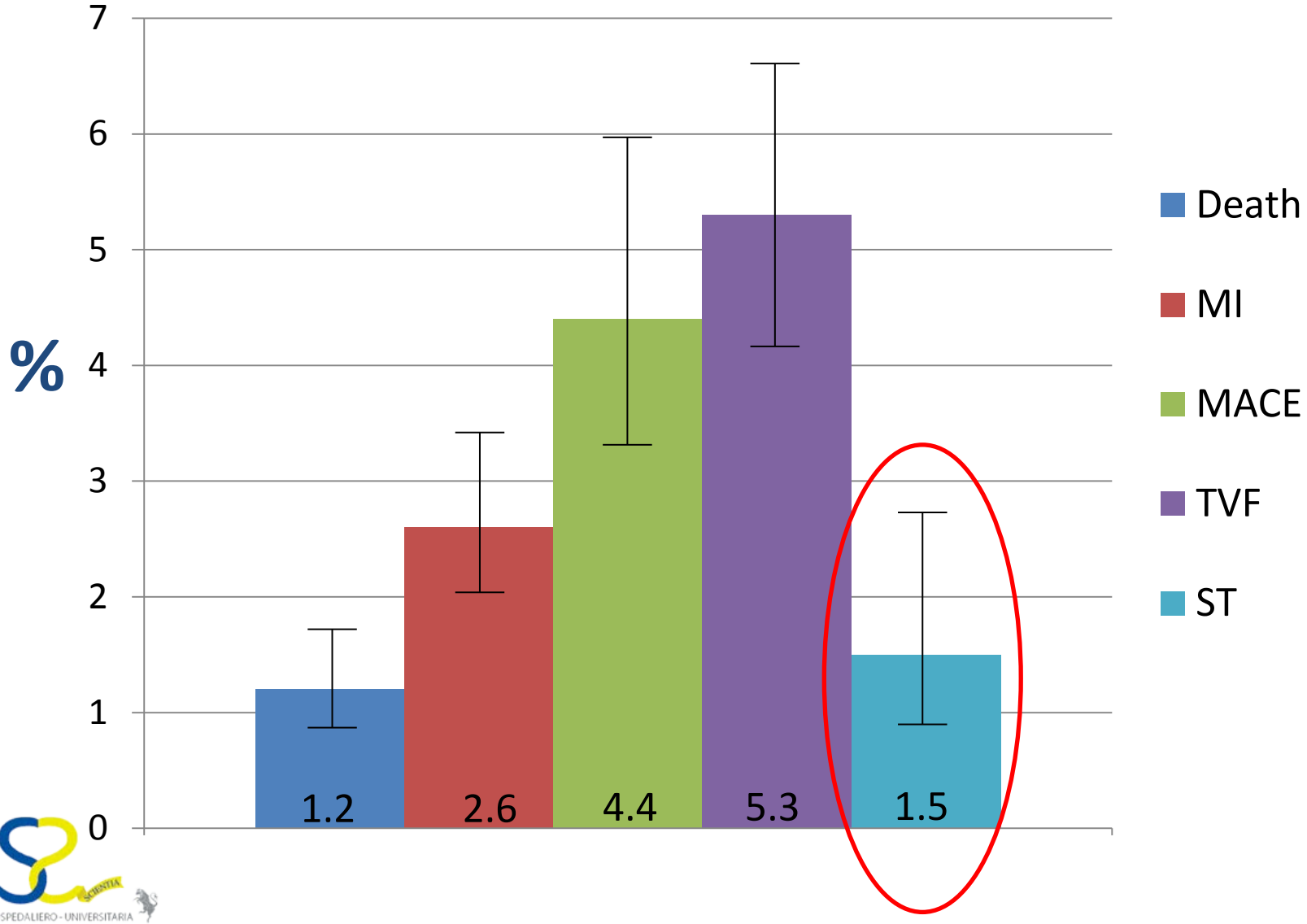
Procedural characteristics

Study (n)	Expand (187)	GHOST (1189)	AMC (135)	Extend (512)	Assure (183)
AHA/ACC A/B1/B2/C type	100 (B2 + C)	22/26.8/23.6/27.6	17/16/42/25	41 (B2+C)	13.1/22.2/43.4/25.2
Number of stents	2.16±1.32	1.4			
Stent diameter	3.00±0.44	3.0±0.5			2.7±0.4
Total stent length, mm	42.8±30.0	32.6±23.0			

Clinical outcomes

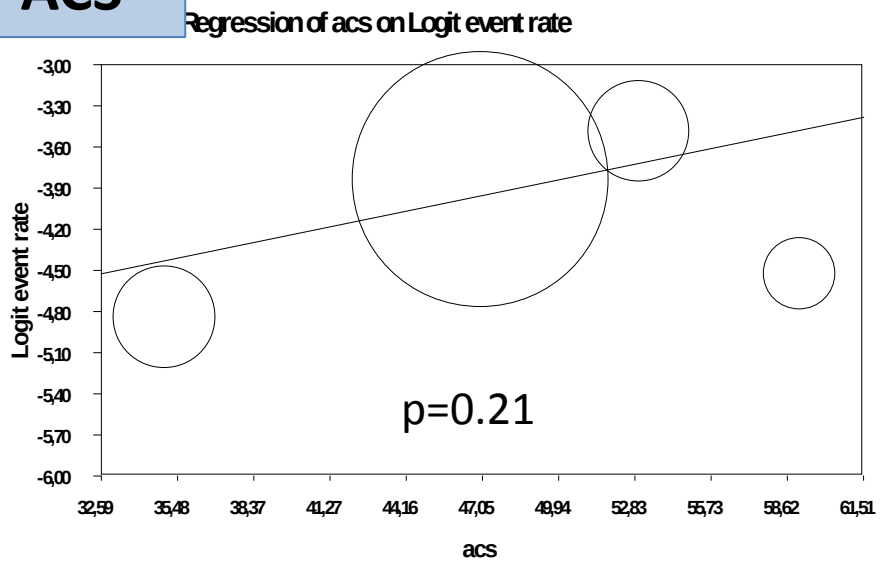
Study (n)	Expand (187)	GHOST (1189)	AMC (135)	Extend (512)	Assure (183)
Death	4(2.2%)	15 (1.3%)	1 (0.8%)	2 (0.4%)	1(0.5%)
MI	3 (1.7%)	32 (2.7%)	4 (3%)	15 (2.9%)	3 (1.6%)
MACE	8 (4.3%)			22 (4.3%)	9 (5%)
TVF		58 (4.9%)	11 (8.5%)	25 (4.9%)	
ST	2 (2.2%)	25 (2.1%)	4 (3%)	4 (0.8%)	0

Random-effect pooled estimates of clinical outcomes

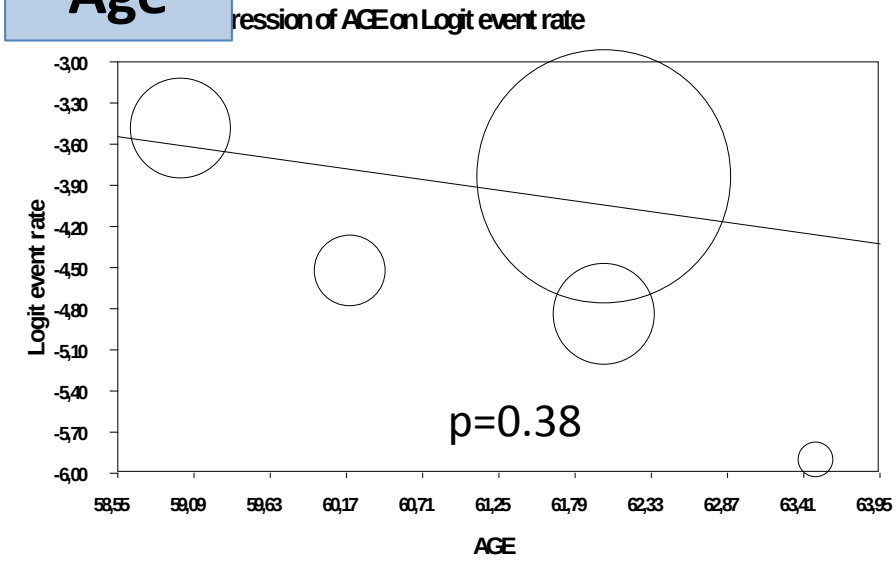


Meta regression analysis

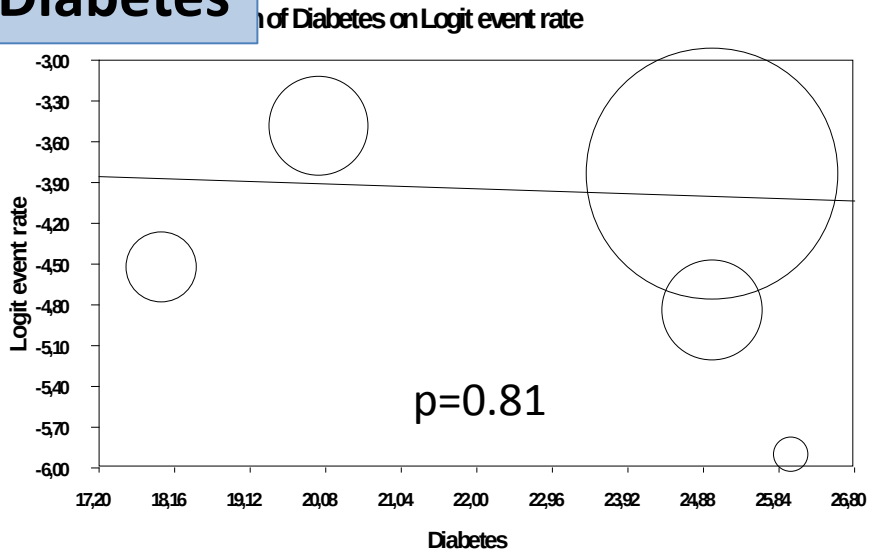
ACS



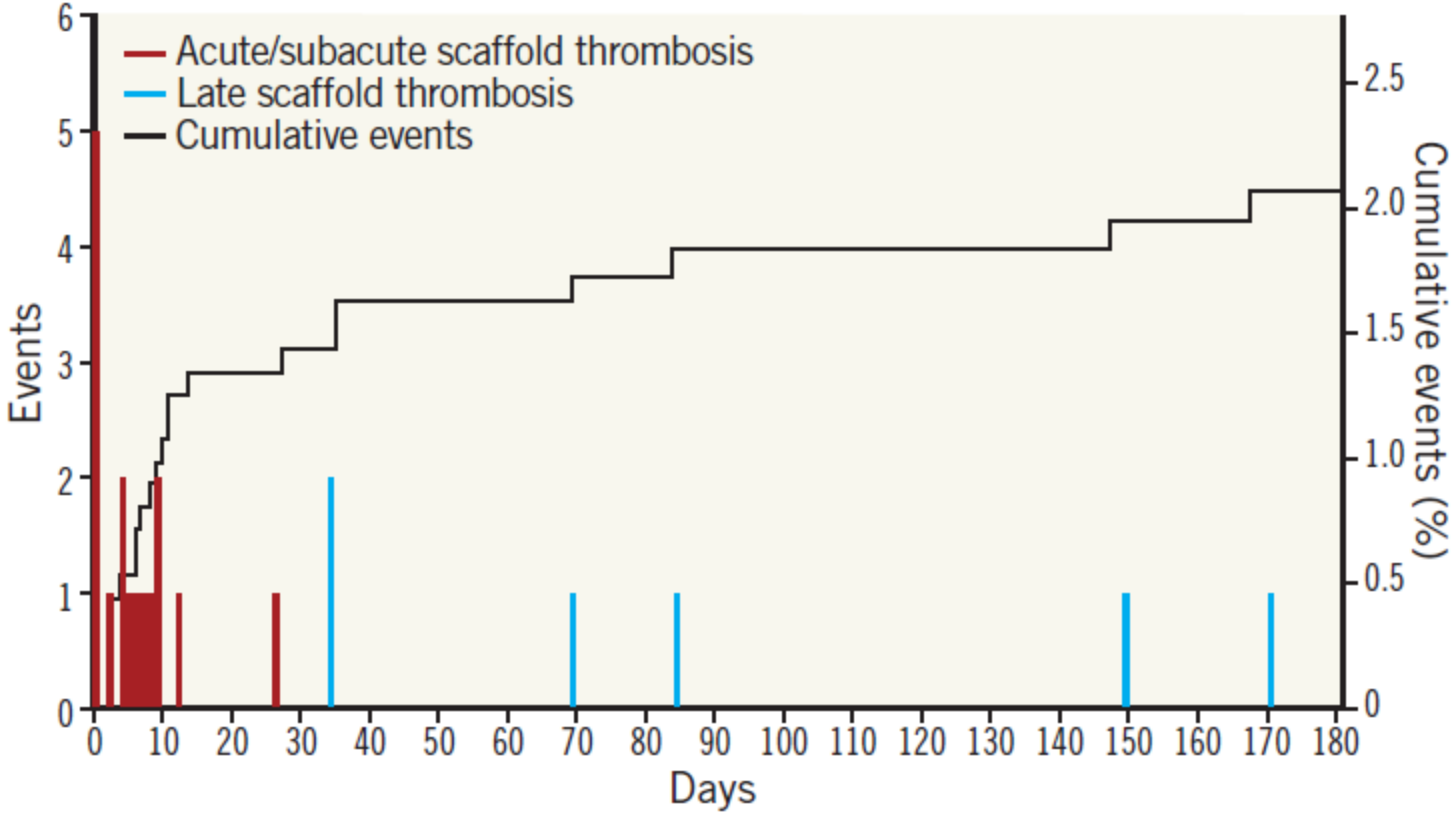
Age



Diabetes



Def/ProbST Ghost-EU registry (1.189 patients)



Capodanno et al.

EuroIntervention 2014;10-online publish-ahead-of-print July 2014

Possible causes of BVS thrombosis

- Underexpansion
- Multiple Overlap
- Possible scaffold disruption
- Malapposition
- Microenviromental flow turbulence potentially caused by the BVS thick struts (~ 150 µm)

Update: The Absorb EXPAND Real-World Registry

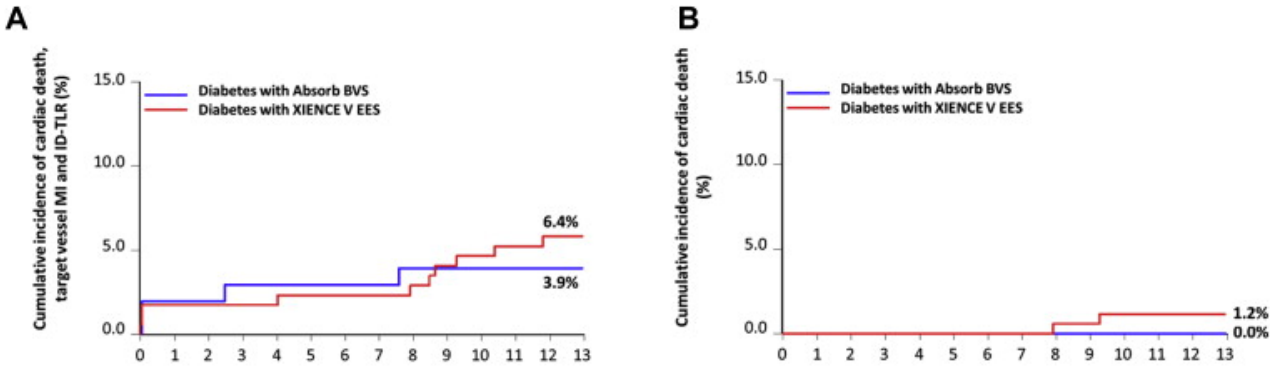
A propensity matched comparison of complete 6 months FU

Diameter up to 4.0 mm, length: > 32 mm, Bifurcations, Calcified lesions, ACS patients (non-STEMI), No previous CABG or metallic stent in target vessel

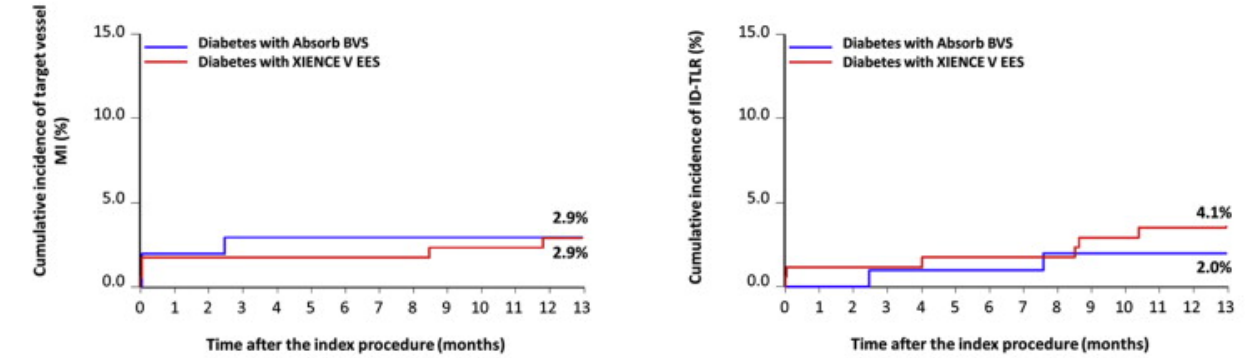
	Absorb	Drug-eluting metallic stents	
	(n=187)	(n=365)	p-value
Mortality	2.2%	1.9%	0.76
Myocardial infarction	1.7%	0.0%	0.04
Target-lesion revascularization	2.2%	1.1%	0.26
Composite of death, MI and TLR	4.3%	3.0%	0.44
Definite stent/scaffold thrombosis	2.2%	0.0%	0.01
Acute/subacute	0.0%/0.0%	0.0%/0.0%	-
Late	2.2%	0.0%	0.01

TCT 2014

1-Year Clinical Outcomes of Diabetic Patients Treated With Everolimus-Eluting Bioresorbable Vascular Scaffolds : A Pooled Analysis of the ABSORB and the SPIRIT Trials



no differences in the incidence of definite or probable scaffold/stent thrombosis



Number at risk (d)	0	37	194	393
BVS Diabetes	102	100	99	99
EES Diabetes	172	169	169	163

Number at risk (d)	0	37	194	393
BVS Diabetes	102	102	101	100
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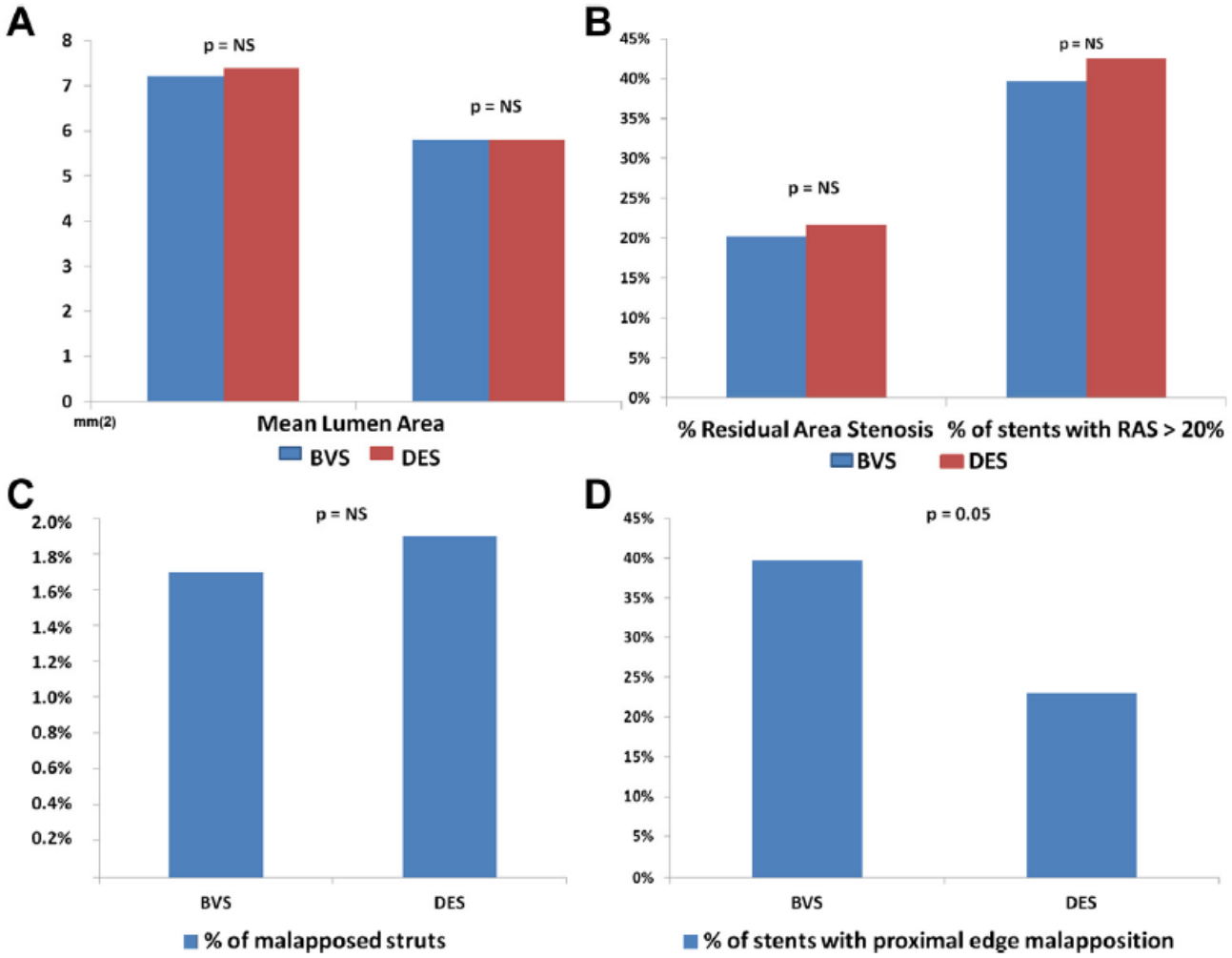
Città della Salute e della Scienza di Torino

JACC Cardiovasc Interv. 2014;7:482-93

ABSORB Biodegradable Stents Versus Second-Generation Metal Stents : A Comparison Study of 100 Complex Lesions Treated Under OCT Guidance



JACC Cardiovasc Interv. 2014;7:741-5

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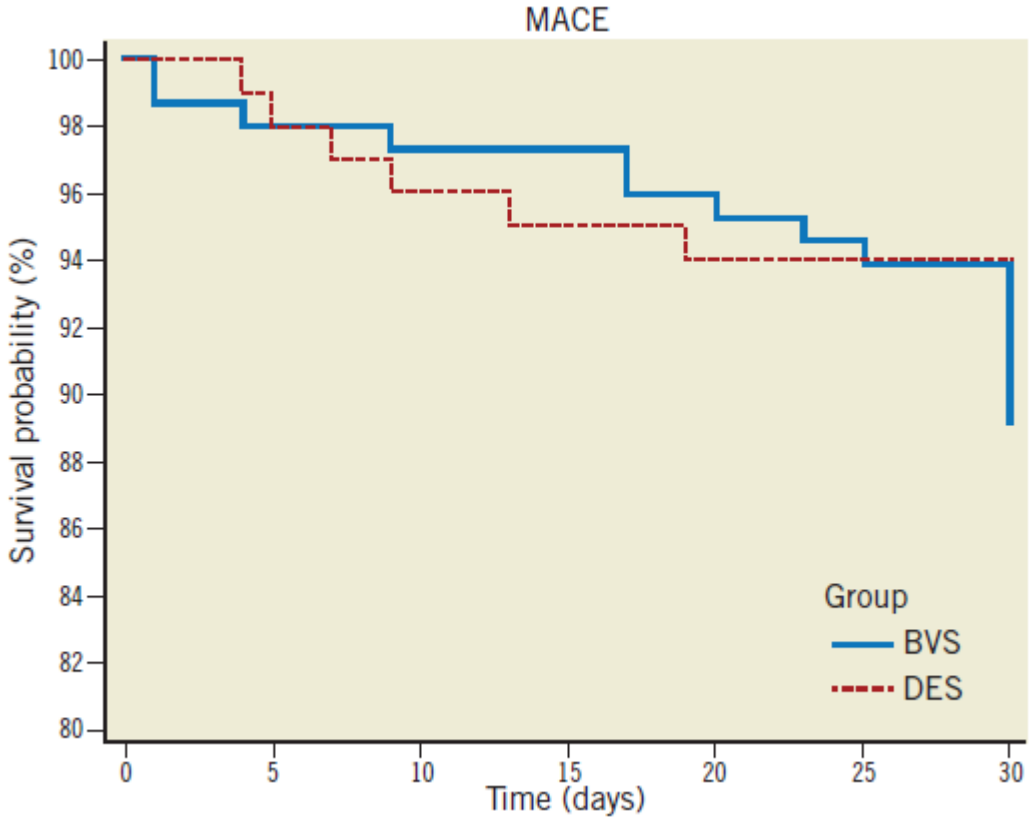
Early outcome after implantation of Absorb bioresorbable drug-eluting scaffolds in patients with acute coronary syndromes

150 patients with ACS treated with BVS

Vs

103 consecutive patients treated with everolimus drug-eluting stent



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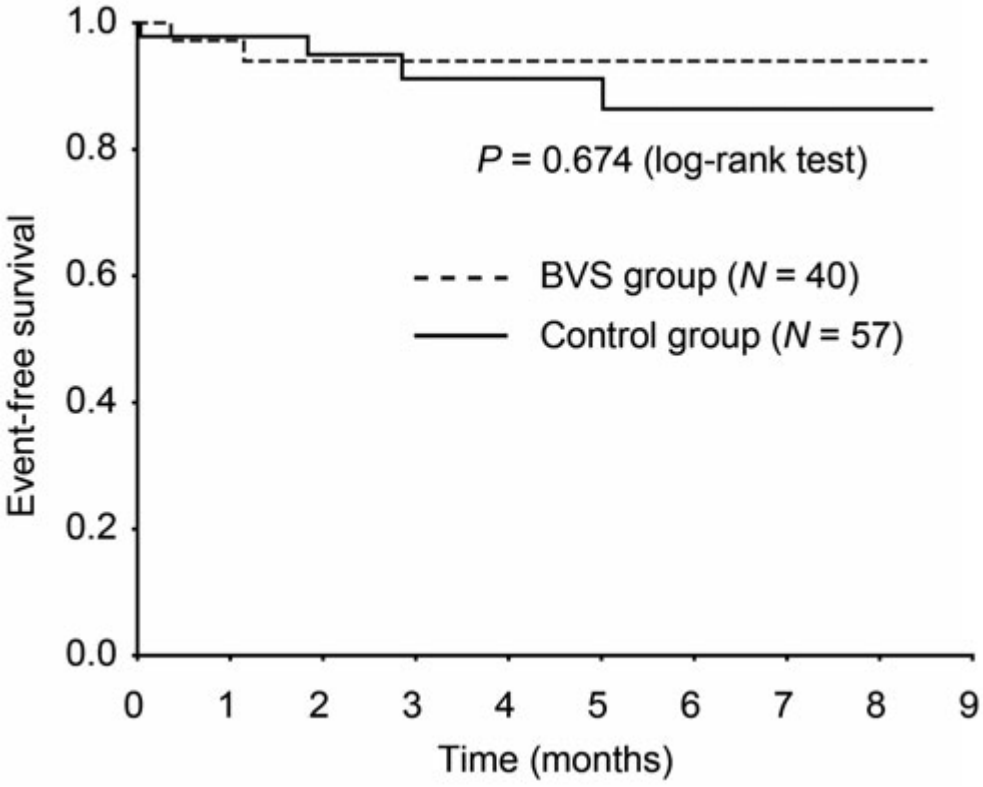
EuroIntervention 2013; 9-online publish-ahead-of-print September 2013

European Heart Journal
doi:10.1093/eurheartj/eht545

Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'

40 patients with STEMI



European Heart Journal (2014) **35**, 777–788
doi:10.1093/eurheartj/eht546

Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study

Roberto Diletti, Antonios Karanasos, Takashi Muramatsu, Shimpei Nakatani, Nicolas M. Van Mieghem, Yoshinobu Onuma, Sjoerd T. Nauta, Yuki Ishibashi, Mattie J. Lenzen, Jurgen Ligthart, Carl Schultz, Evelyn Regar, Peter P. de Jaegere, Patrick W. Serruys, Felix Zijlstra, and Robert Jan van Geuns*

Table 6 Clinical outcomes at the 30-day follow-up intent-to-treat population

Clinical events	*N* = 49	95% CI
Target-lesion failure	(0/49) 0%	(0–7.41)
TVF	(0/49) 0%	(0–7.41)
Cardiac death	(0/49) 0%	(0–7.41)
Target-vessel MI	(0/49) 0%	(0–7.41)
Q-wave MI	(0/49) 0%	(0–7.41)
Non Q-wave MI	(0/49) 0%	(0–7.41)
Clinically driven target-vessel revascularization	(0/49) 0%	(0–7.41)
Any MI	(1/49) 2.6%	(0–10.69)
Q-wave MI	(0/49) 0%	(0–7.41)
Non Q-wave MI	(1/49) 2.6%	(0–10.69)
Major adverse cardiac events	(1/49) 2.6%	(0–10.69)
Non-target-vessel revascularization	(1/49) 2.6%	(0–10.69)
Definite or probable scaffold thrombosis	(0/49) 0%	(0–7.41)

Data are expressed number and proportion, *n* (%). 95% CI, 95% confidence interval.

Conclusions

1. Solid physiopathological bases
2. Limited outcome data (long term?)
3. ST: an issue?
4. Safe in ACS
5. Optimal deployment