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Taking DES technology from concept to clinical proof

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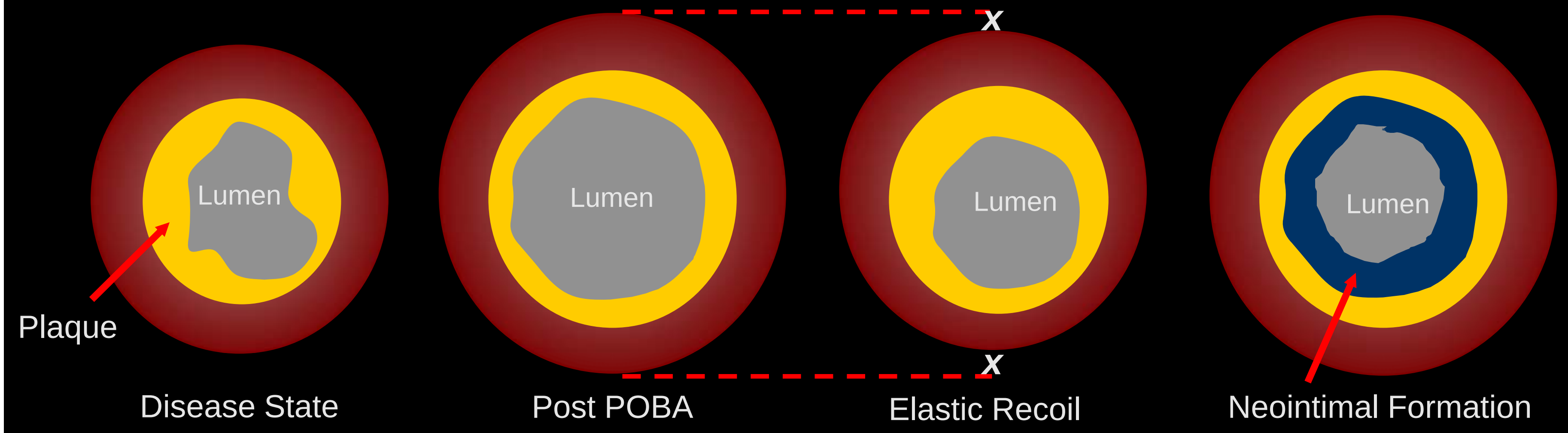
Acute vessel closure and restenosis are major limitations of balloon angioplasty

Complications with Balloon Angioplasty

Abrupt Closure	Restenosis
4-8% of patients	30-50% of patients
20% require emergency CABG	20-30% revascularization rate



Stents evolved from studies in 1912 to maintain arterial lumen with foreign bodies

1912 – Alexis Carrel
First implants in canine aortae

En.wikipedia.org

1985 – Julio Palmaz
First peripheral stent in human

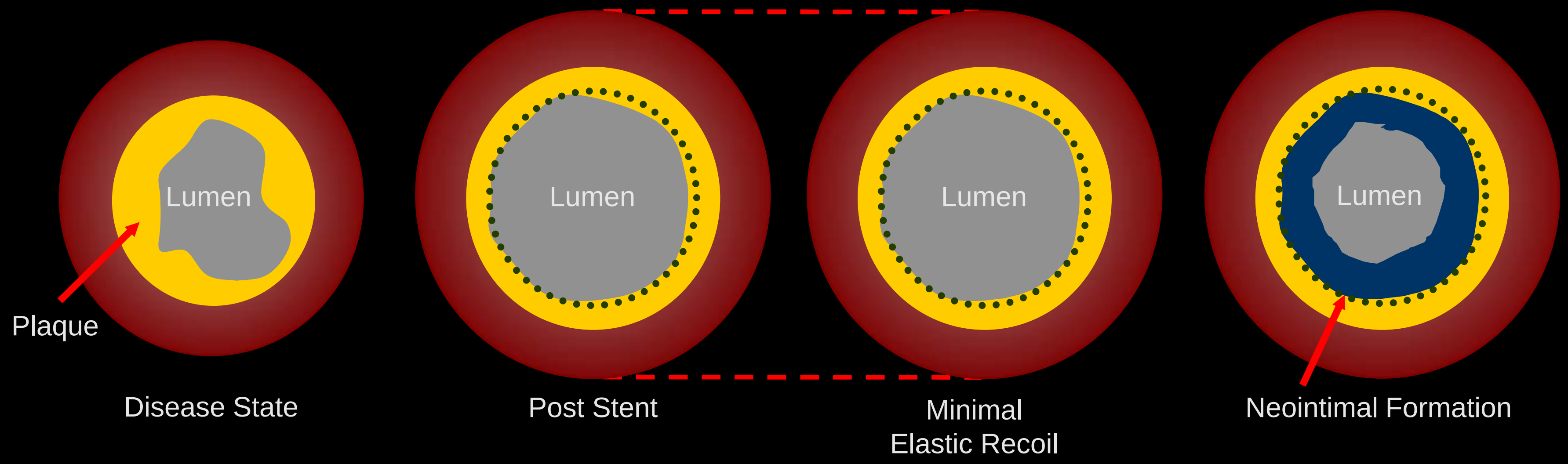
theheart.org

1986 – Jacques Puel and Ulrich Sigwart
First coronary stents in humans

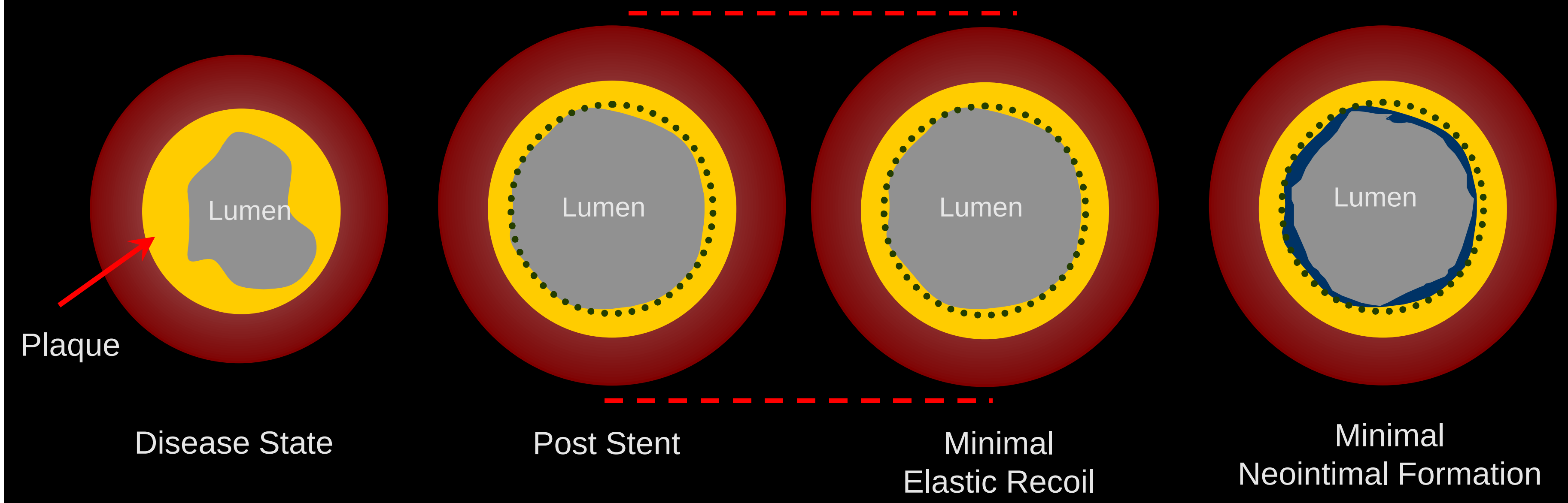
Sfcardio.fr

Cxvascular.com

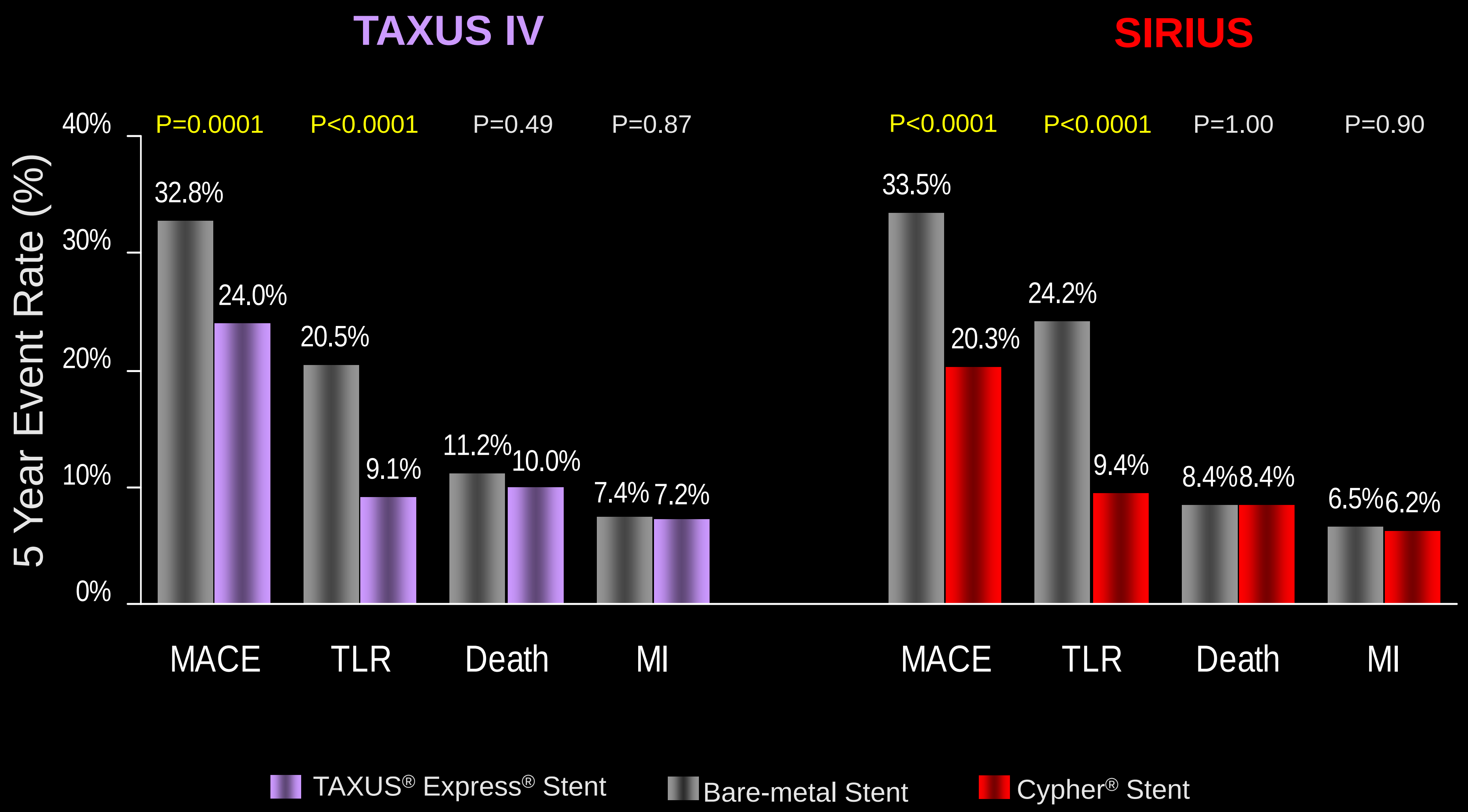
BMS associated with 20-25% restenosis rates



DES developed to prevent cellular response leading to restenosis



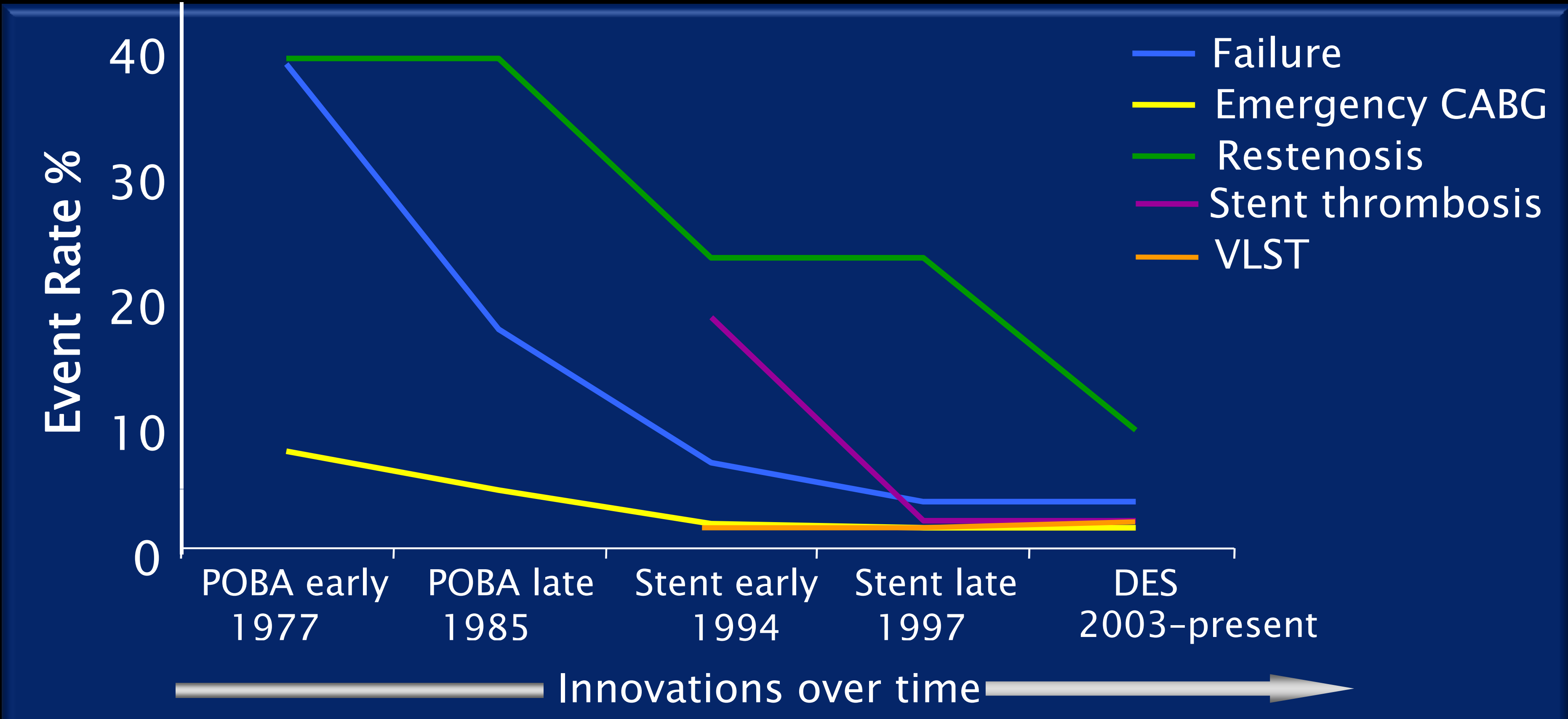
First generation DES demonstrated superiority in efficacy over BMS



Presented by Giora Weisz, ACC 2007.

Progress in Interventional Cardiology

1977	1994	2003
POBA "Getting Artery Open"	**BMS** "Keeping Artery Open"	**DES** "Decrease Restenosis"

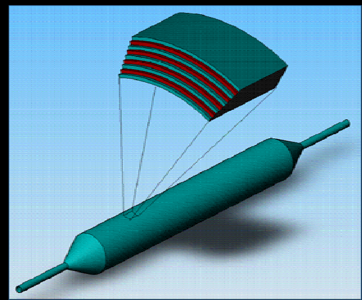
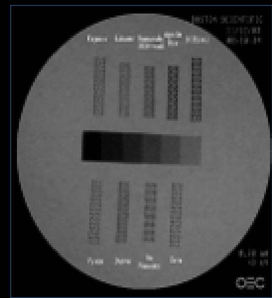
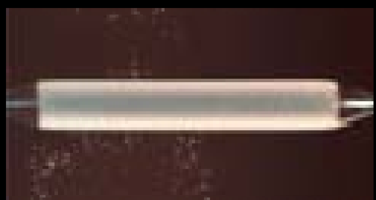
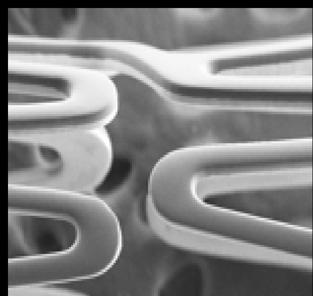
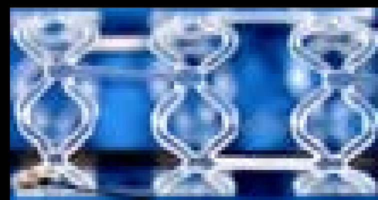


Dr. Don Baim, FDA Panel Meeting, December 2006

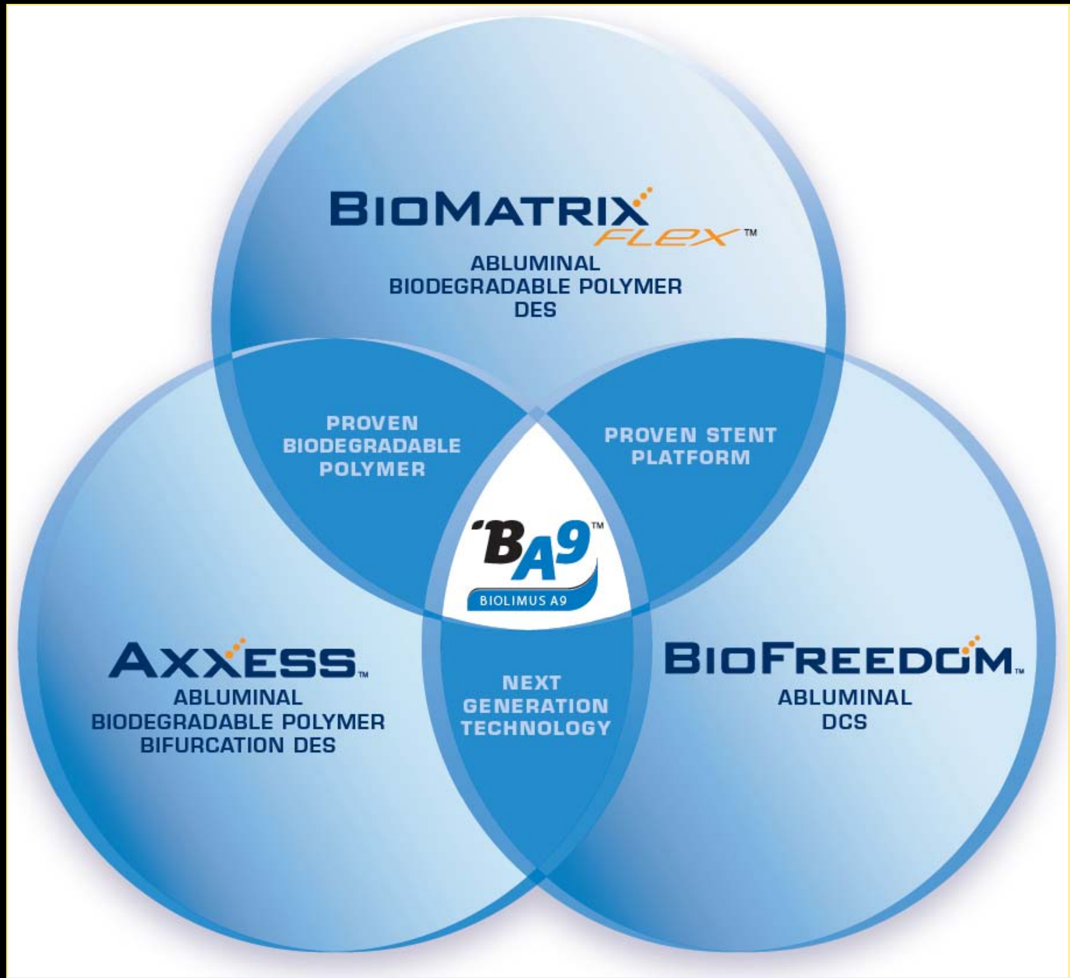
Stent Technology Continues to Advance

- Stent material
- Strut design
- Delivery improvements
- Abluminal coatings
- Bioabsorbable coatings
- Bioabsorbable stents
- Drug optimization
- Stent Alternatives

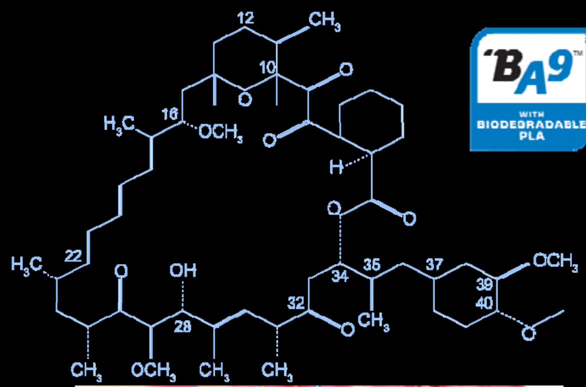


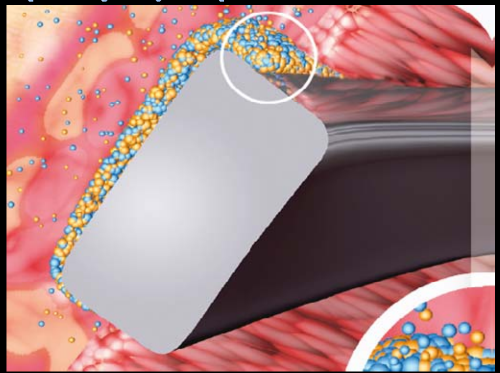






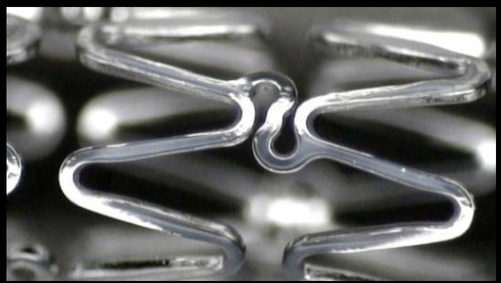
Biosensors' DES program
Biodegradable DES & Polymer-Free DCS



BioMatrix Flex™







- Biolimus is a semi-synthetic sirolimus analogue with **10x higher lipophilicity** and similar potency as sirolimus.

- Biolimus is immersed at a concentration of 15.6 μg/mm into a biodegradable polymer, polylactic acid, and applied solely to **the abluminal stent surface** by a fully automated process.

- Biolimus is co-released with polylactic acid and completely desolves into carbon dioxide and water after **a 6-9 months period.**

- The stainless steel stent platform has a strut thickness of 120 μm with a quadrature link design.

LEADERS ‘all-comers’ Trial Design

Stable and ACS Patients Undergoing PCI

Assessor-blind
1:1 Randomisation

N=1700 Patients
10 European centers

BioMatrix Flex™ (BES)*
N=850

Cypher® Select™ (SES)
N=850

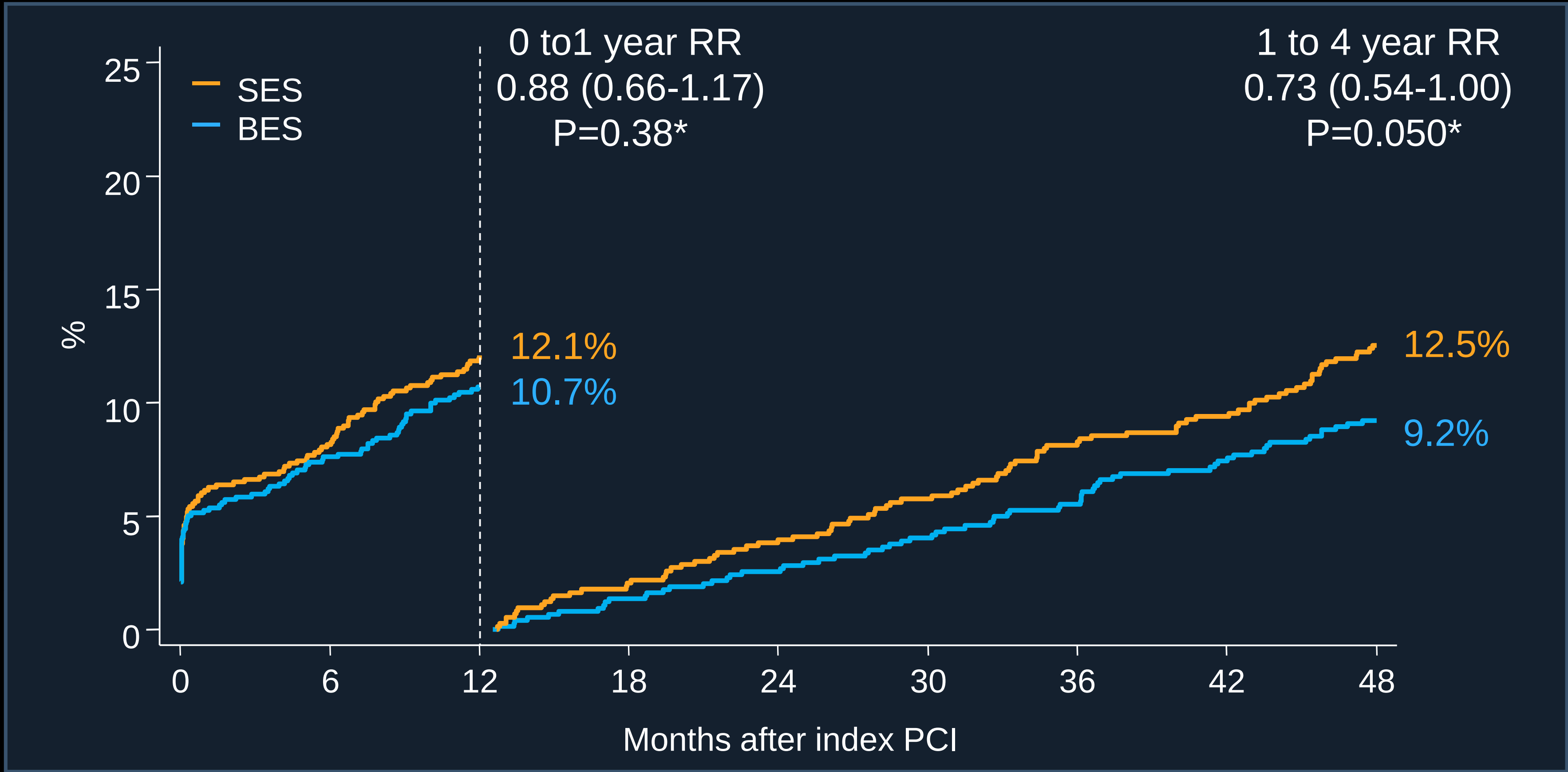
1:3 Randomisation

BioMatrix Flex™ (BES)*		Cypher® Select™ (SES)	
Clinical F/U N=640	Angio F/U N=210	Clinical F/U N=640	Angio F/U N=210

1º endpoint:	MACE: Cardiac death, MI, clinically-indicated TVR (9 mo)
2º endpoints:	Death, CV death, MI, TLR, TVR
	Stent thrombosis according to ARC
Angiographic study:	In-stent % diameter stenosis (9 mo)
	Late loss, binary restenosis
DAPT recommended for 12 months	

LEADERS

MACE : Landmark Analysis @ 1 Year



No. at risk

SES	850	775	738	718	702	676	656	639	614
BES	857	781	749	733	723	710	697	677	659

P for interaction=0.39
* P values for superiority

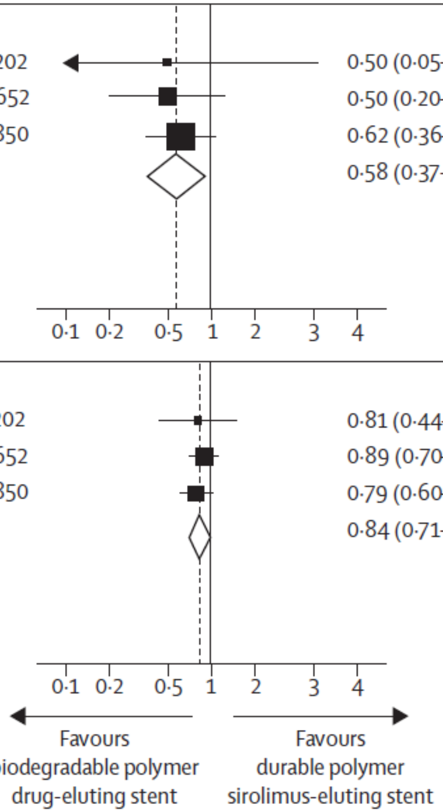
Thomas Ischinger, TCT 2011

Biodegradable vs. durable Polymer

Definite ST & TLR

	Biodegradable polymer drug-eluting stent	Durable polymer sirolimus-eluting stent	Relative risk (95% CI)
Definite stent thrombosis			
ISAR-TEST 3[25]	1/202	2/202	0·50 (0·05–5·47)
ISAR-TEST 4[24]	9/1299	9/652	0·50 (0·20–1·26)
LEADERS	20/857	32/850	0·62 (0·36–1·08)
Overall			0·58 (0·37–0·93)
Test for inconsistency I^2=0			
Test for heterogeneity p=0·92			
Test for overall effect p=0·022			

	Biodegradable polymer drug-eluting stent	Durable polymer sirolimus-eluting stent	Relative risk (95% CI)
Target lesion revascularisation			
ISAR-TEST 3[25]	17/202	21/202	0·81 (0·44–1·49)
ISAR-TEST 4[24]	168/1299	95/652	0·89 (0·70–1·12)
LEADERS	88/857	111/850	0·79 (0·60–1·02)
Overall			0·84 (0·71–0·99)
Test for inconsistency I^2=0			
Test for heterogeneity p=0·79			
Test for overall effect p=0·040			



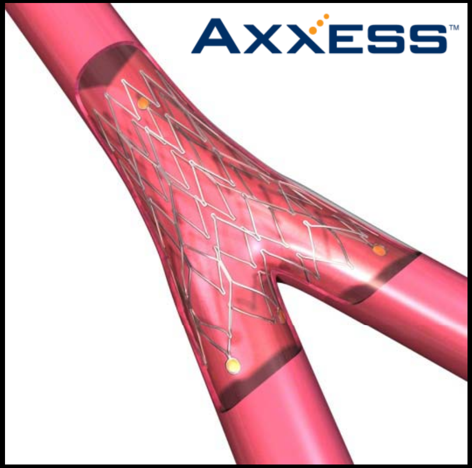
‘ The use of biodegradable polymer drug-eluting stents is associated with a statistically significant risk reduction with respect to definite stent thrombosis and target lesion revascularization compared with use of durable polymer SES’[1]

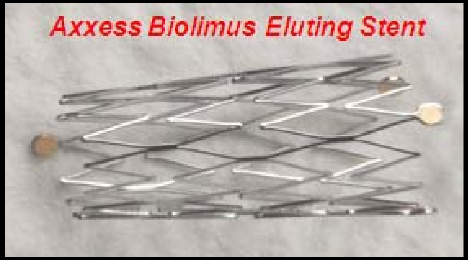
1. Stefanini G. et al., The Lancet, 2011

The Axxess™ Bifurcation DES

Dedicated bifurcation DES

- Nitinol self expanding stent
- Abluminal biodegradable PLA/BA9™ coating technology
- Available sizes:
  - 3.0 and 3.5 mm in diameter
  - 11 and 14 mm in length





Clinical programs

- AXXESS Plus – 5 year FU available[1]
- DIVERGE – 3 year FU available[2]

Axxess™ bifurcation DES is CE approved

1. Grube E., oral presentation, TCT 2011
2. Agostoni F., oral presentation, EuroPCR 2011

Axxess™ Clinical Program

AXXESS N=43	• *France & Germany* • *Pilot study using bare metal stent Axxess™ Platform* • *In-segment restenosis at 6 months* • *6 month follow-up available, study completed*
AXXESS PLUS N=139	• *Europe, Brazil and New Zealand* • *FIM Safety and performance evaluation of Axxess™ DES* • *Main vessel in-stent late loss at 6 months* • *5 year follow-up available, study completed*
DIVERGE N=302	• *Europe, Australia and New Zealand* • *Evaluated best practices from AXXESS Plus* • *MACE[1] at 9 months* • *3 year follow-up available, follow-up planned up to 5 years*

BA9™ WITH BIODEGRADABLE PLA

1. MACE: Composite of Death, MI and ischemia-driven TLR

AXXESS PLUS Primary Endpoint
In-Stent Late Lumen Loss @ 6 Months

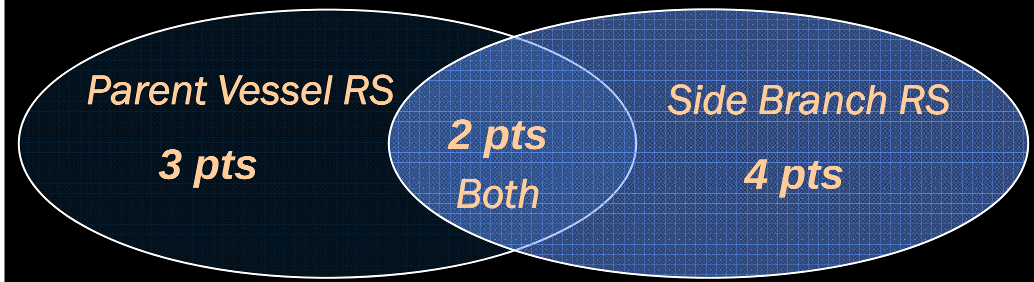
	Axxess BA9 Stent	Axxess Bare Metal Stent[1]	*p*
N (%)	**126 (93%)**	37 (90%)	
Late Lumen Loss - Axxess Stent	**0.09 ± 0.56 mm**	0.46 ± 0.51 mm	<0.001

Grube et al., Am J Cardiol 2007;99:1691-1697

[1]Historical data on file at Biosensors International

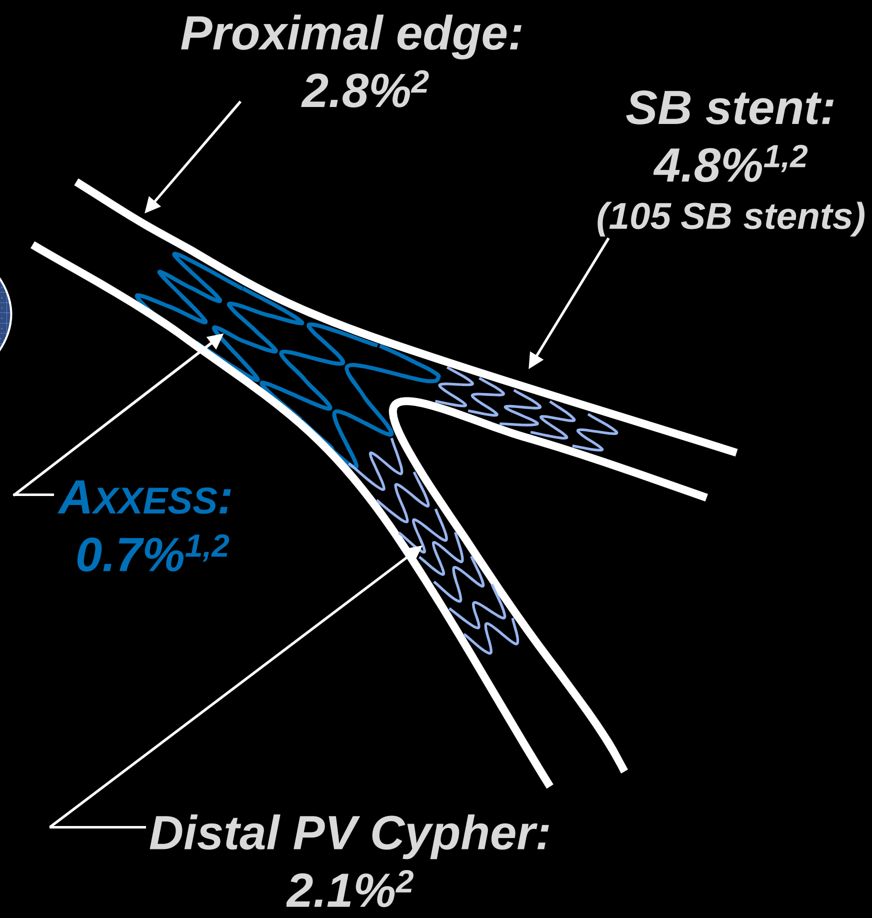
9 Month Restenosis in DIVERGE

Any In-segment bifurcation restenosis:
6.4% (9/140 at 9 months)[1,2]



Very low restenosis rate in bifurcation lesions.

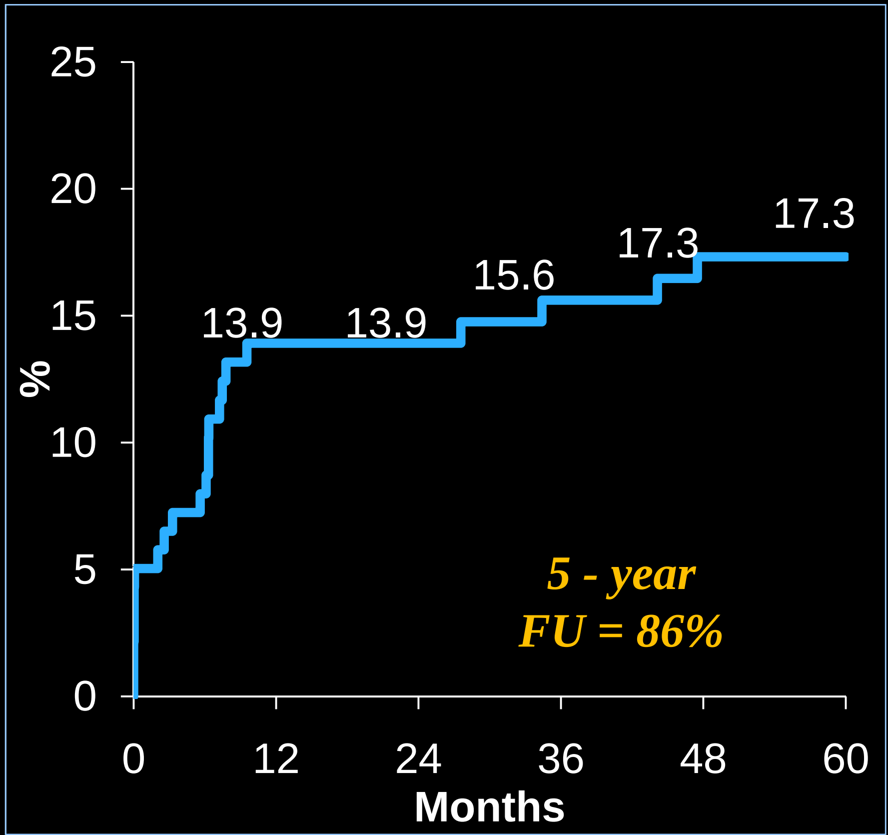
Location Analysis:



1. Verheye S. et al, J Am Coll Cardiol, 2009
2. Verheye S. et al, oral presentation, TCT 2009

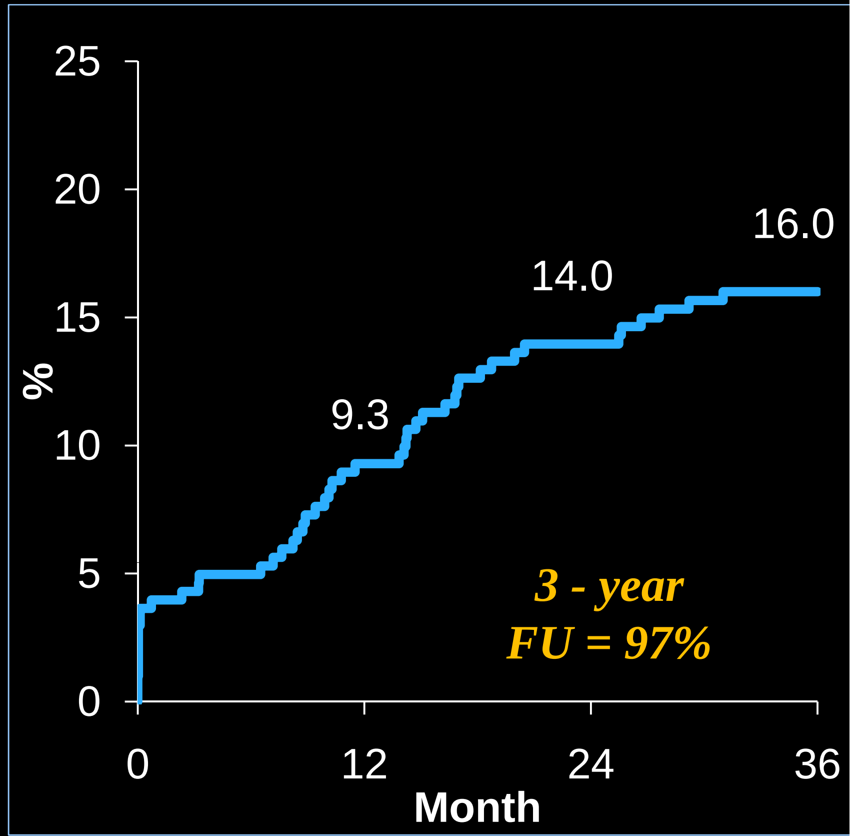
MACE*

AXXESS PLUS – 5 Years



*(Cardiac death, MI, bypass, ci-TLR)
Grube, oral presentation, TCT 2011

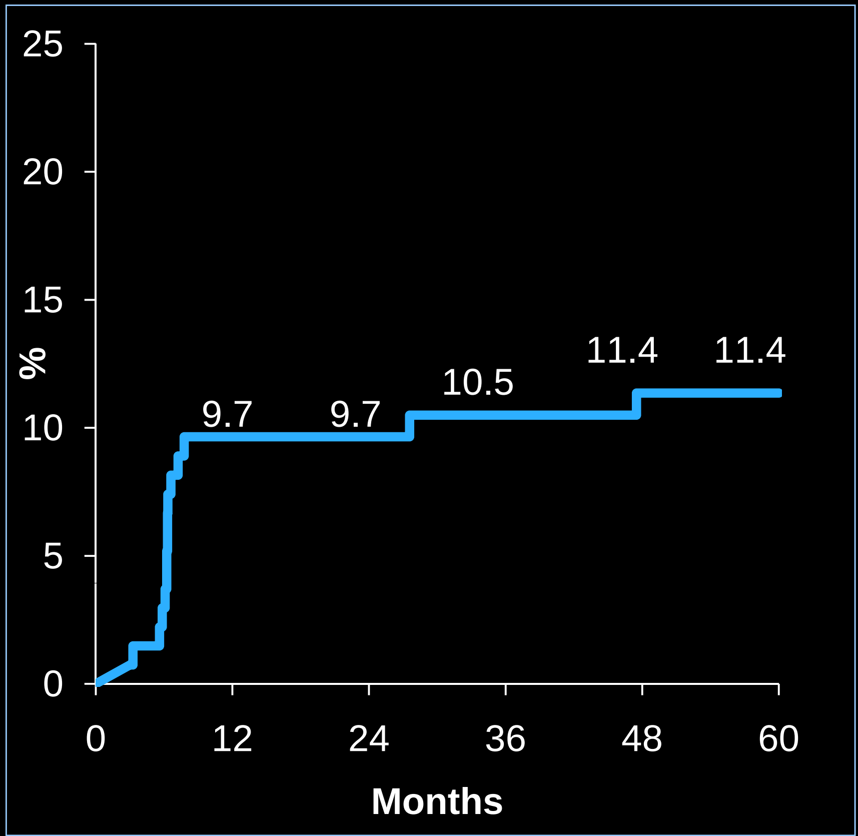
DIVERGE – 3 Years



*(all death, MI, ci-TLR)
Agostoni, oral presentation, EuroPCR 2011

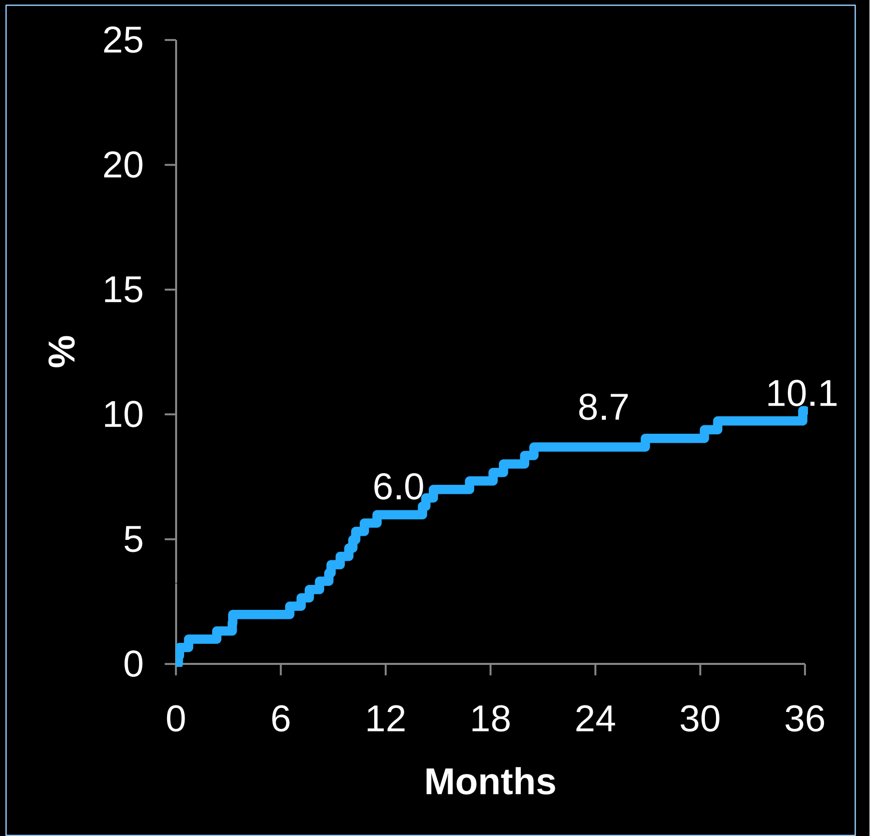
Ischemia-driven TLR

AXXESS PLUS – 5 Years



Grube, oral presentation, TCT 2011

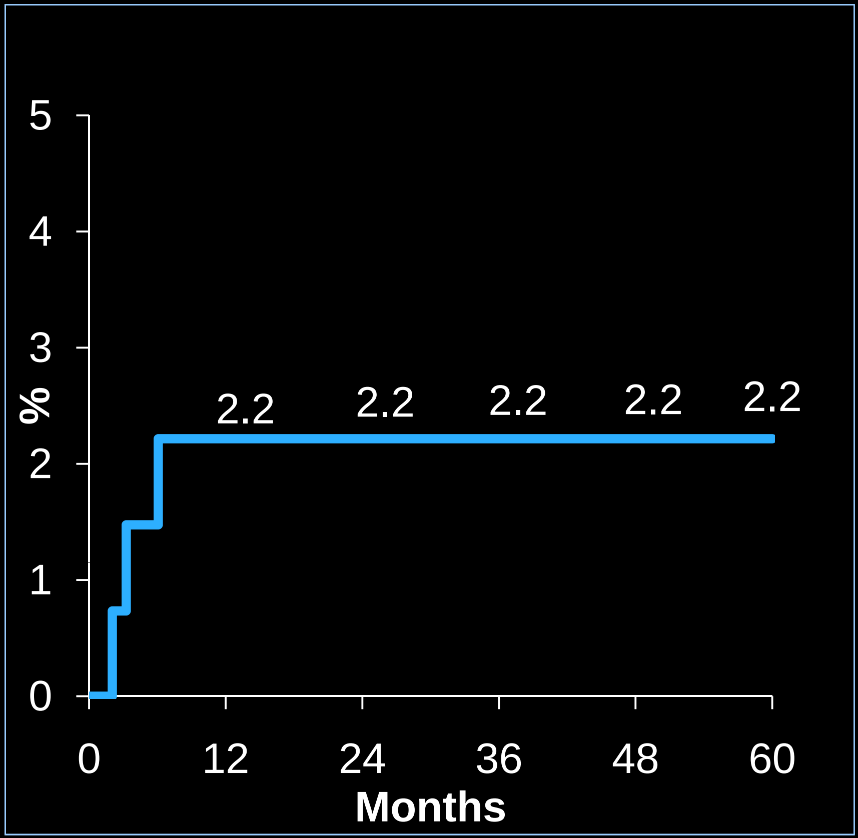
DIVERGE – 3 Years



Agostoni, oral presentation, EuroPCR 2011

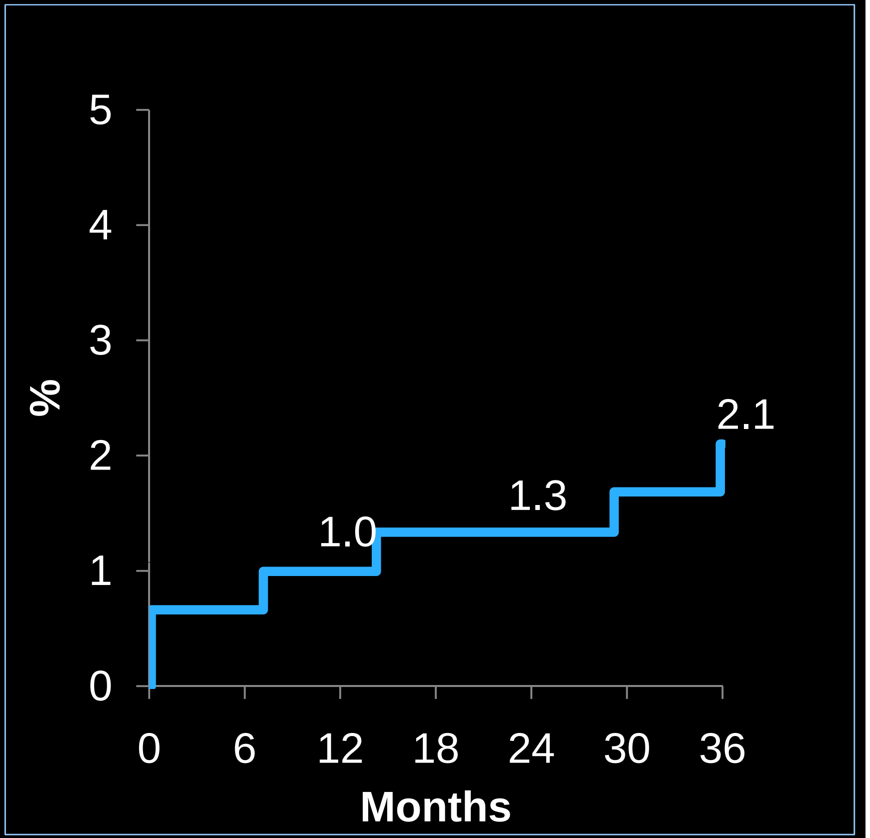
Definite & Probable ST (ARC)

AXXESS PLUS – 5 Years



Grube, oral *presentation, TCT 2011*

DIVERGE – 3 Years

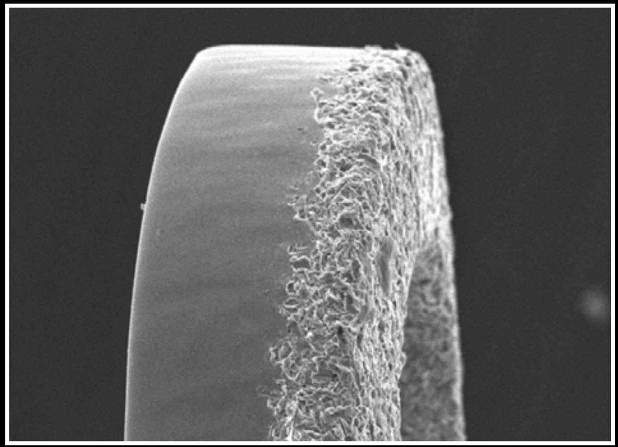


Agostoni, oral presentation, EuroPCR 2011

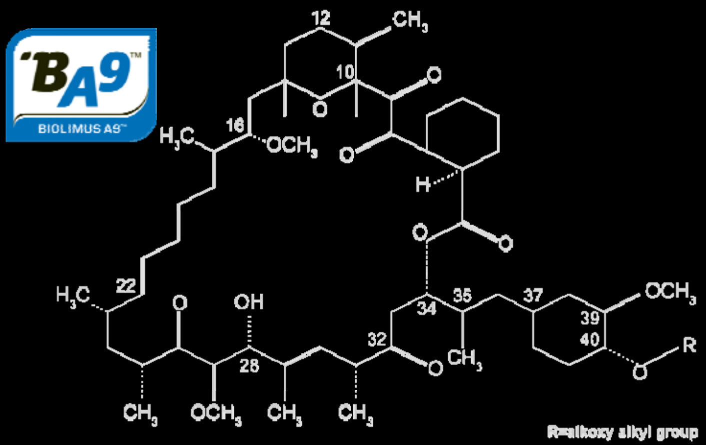
Only one definite VLST attributed to the Axxess stent whereas all events were present in the Cypher stent

BioFreedom™ Polymer-free stent

Selectively micro-structured surface holds drug in abluminal surface structures



Proprietary Highly Lipophilic Limus drug



Hypothesis: **Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings.**

Potential advantage

- **Avoid long term late adverse effects that might be attributable to the polymer**
- **Improved surface integrity since there is no polymer to be sheared or peeled away from the stent struts**
- **Possible shorter need of dual antiplatelet therapy**

BioFreedom FIM Design

BioFreedom FIM
182 patients

12 Month Clinical FU 99%

First Cohort

4 Month Angio FU
75 patients

Angio FU 92%

- *BioFreedom standard dose (BFD SD) N=25*
- *BioFreedom low dose (BFD LD) N=26*
- *TAXUS® Liberté ® N=24*

Enrollment Period
Sept 2008 – Jan 2009

Second Cohort

12 Month Angio FU
107 patients

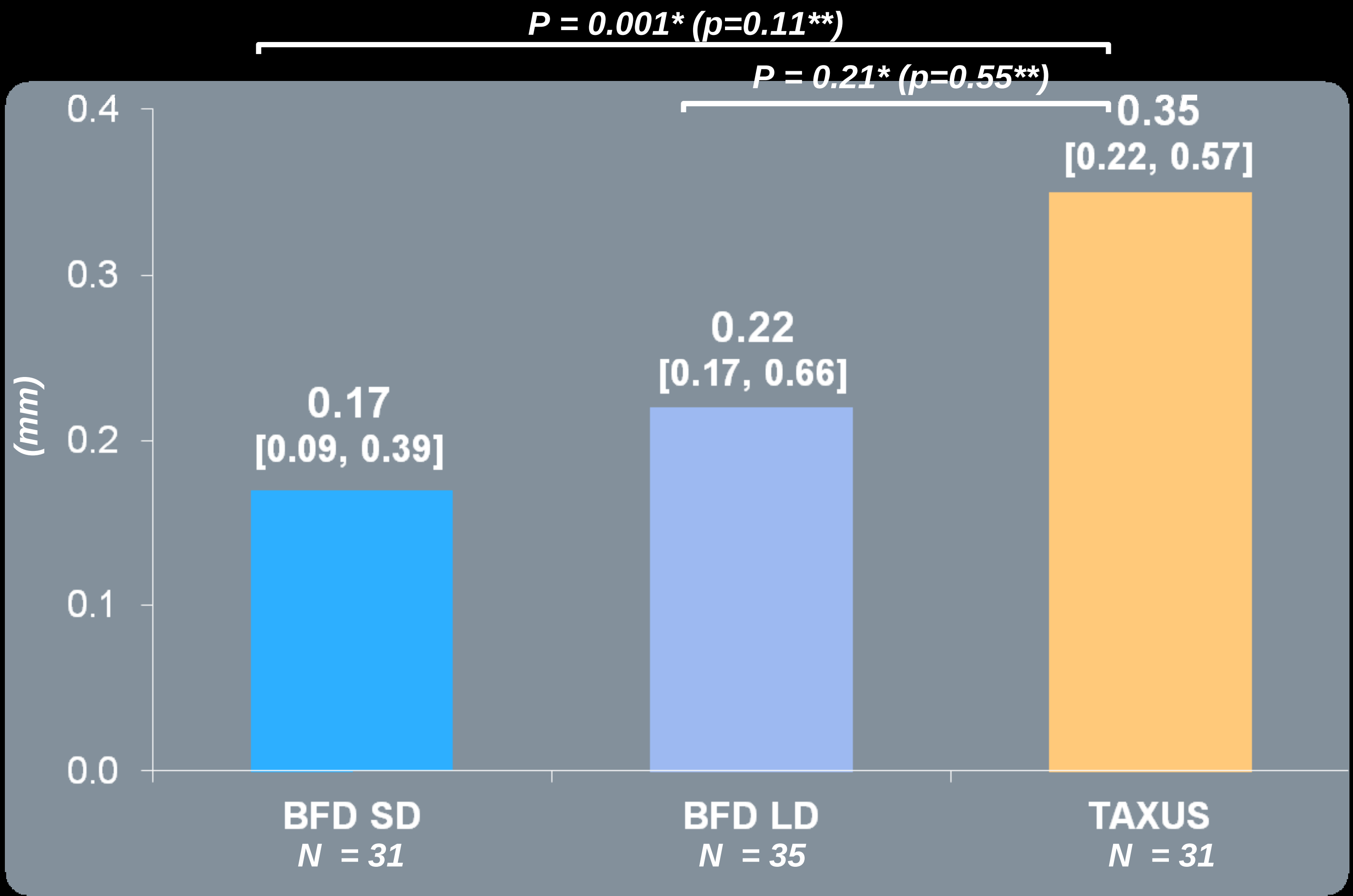
Angio FU 92%

- *BioFreedom standard dose (BFD SD) N=35*
- *BioFreedom low dose (BFD LD) N=36*
- *TAXUS® Liberté ® N=36*

Enrollment Period
Jan 2009 – Jun 2009

In-Stent LLL at 12 Months FU

2nd Cohort – PRIMARY ENDPOINT



*Non-inferiority tests. **Superiority tests.
Grube E., oral presentation, TCT 2010

24-Month Outcomes

All patients – 1st and 2nd Cohorts (98.9%)

EVENT	BFD SD N = 60	BFD LD N = 61	TAXUS N = 59
MACE (All Death, MI, Emergent Bypass or TLR)	4 (6.8%)	9 (14.7%)	6 (10.0%)
All Death	1 (1.7%)	1 (1.6%)	1 (1.7%)
MI	1 (1.7%)	1 (1.6%)	1 (1.7%)
Q Wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Q Wave MI	1 (1.7%)	1 (1.6%)	1 (1.7%)
Emergent Bypass	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	2 (3.4%)	7 (11.5%)	4 (6.7%)
Stent thrombosis (ARC)	0 (0.0%)	0 (0.0%)	0 (0.0%)

All P values are non-significant.
Tests were performed for BFD SD vs. TAXUS and BFD LD vs. TAXUS.
Grube E., oral presentation, TCT 2010

Conclusions

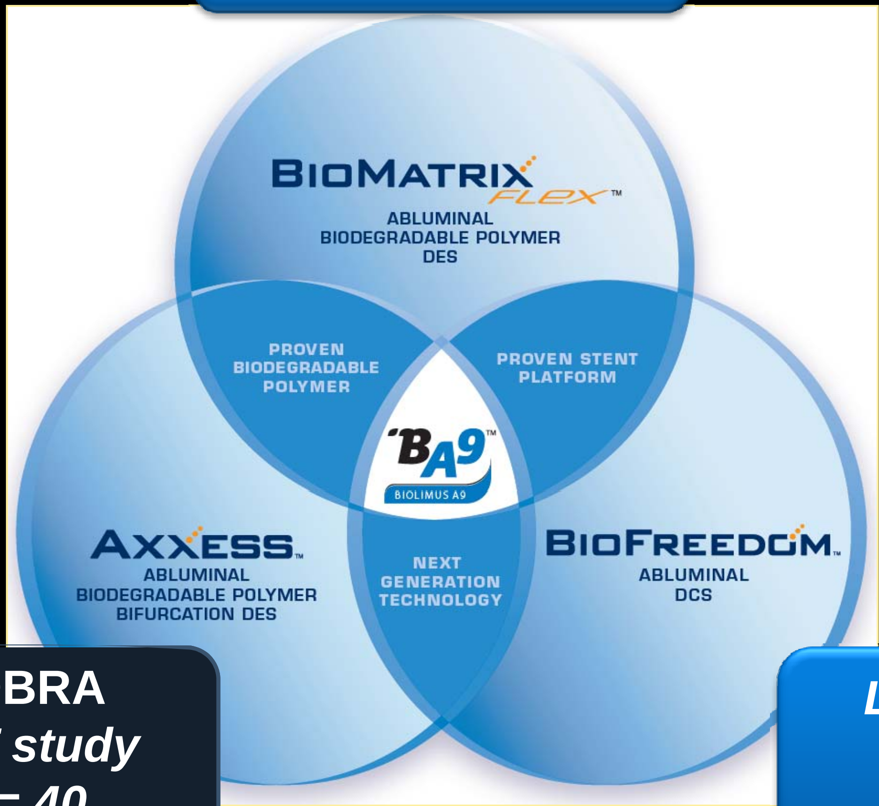
Technology has helped advance the field of Interventional Cardiology, particularly with the introduction of drug-eluting stents

Drug eluting stent technology advancements can have a significant clinical benefit from previous generations, particularly in more challenging patient subsets (small vessels and long lesions)

Despite good results with current technology, the future of drug-eluting stent technology is promising

NEXT steps
Future Randomized Trials

Global LEADERS
n ~ 15 000



COBRA
OCT study
n = 40

LEADERS
Free
n ~ 2600

Details of trial designs will be presented during EuroPCR 12