Les outils et la performance en pratique

Comment choisir un stent actif ?

Didier CARRIE
CHU Toulouse

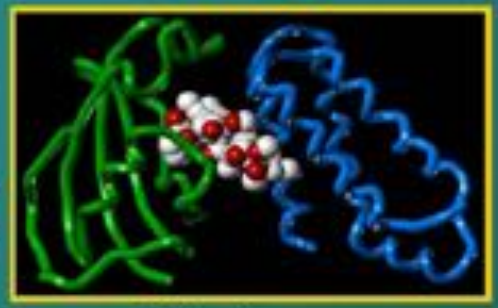
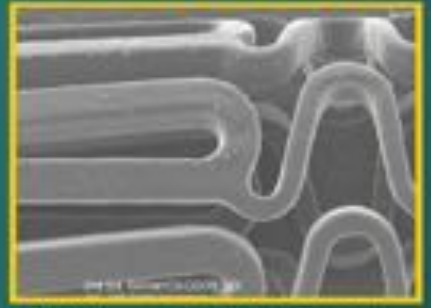
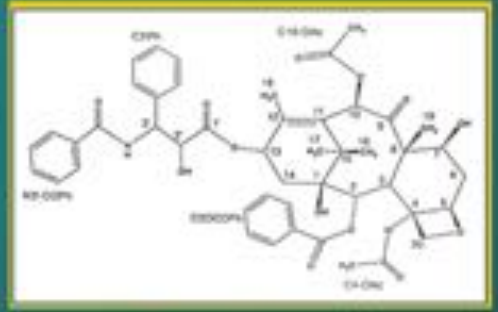
Symposium Boston
APPAC 08-06-2017

Déclaration de liens d'intérêts

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Astra Zeneca, Boston Scientific
• Consulting Fees/Honoraria	• Abbott, Astra Zeneca, BSC, Biotronik,
• Major Stock Shareholder/Equity	• None
• Royalty Income	• None
• Ownership/Founder	• None
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

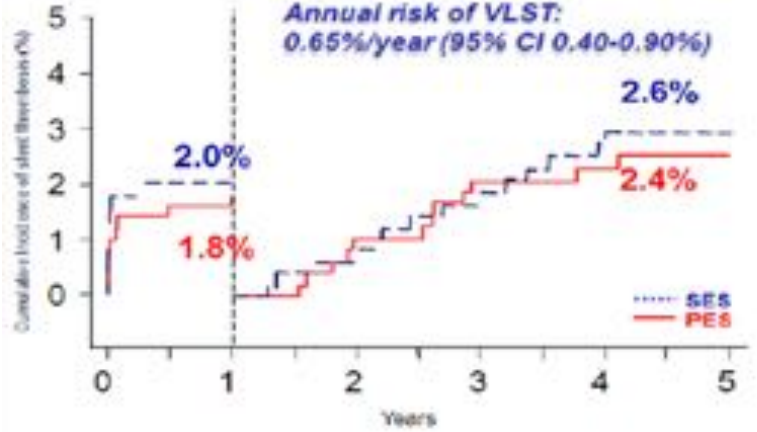
Drug-eluting Stents in 2004

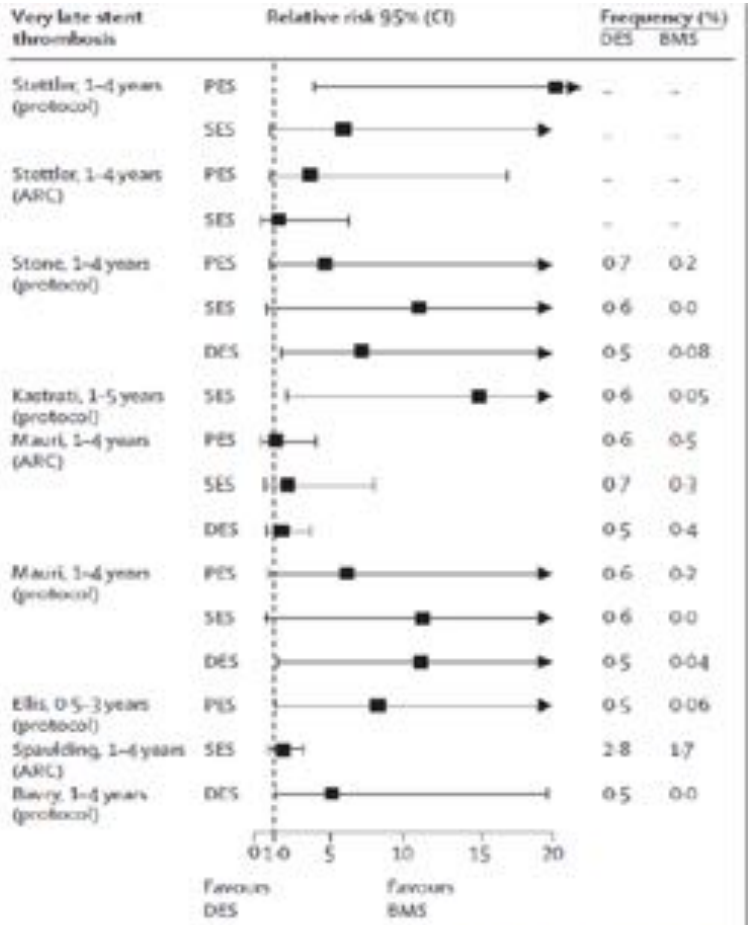
Safety and Efficacy Proven

	Drug	Polymer	Stent
Cypher			
	Sirolimus	PEVA + PBMA blend	BX Velocity
TAXUS			
	Paclitaxel	Polyolefin derivative	Express^2

Early DES and Very Late ST

SIRTAX LATE
Räber L et al. *Circulation* 2011





Bavry A et al. *Lancet* 2008

Stent fracture

- Incidence = 3 – 4%
- Strong association with MACE
- Can occur early (at implantation) or late (fatigue)
- Risk: long, overlap, RCA, bends, stent design, DES

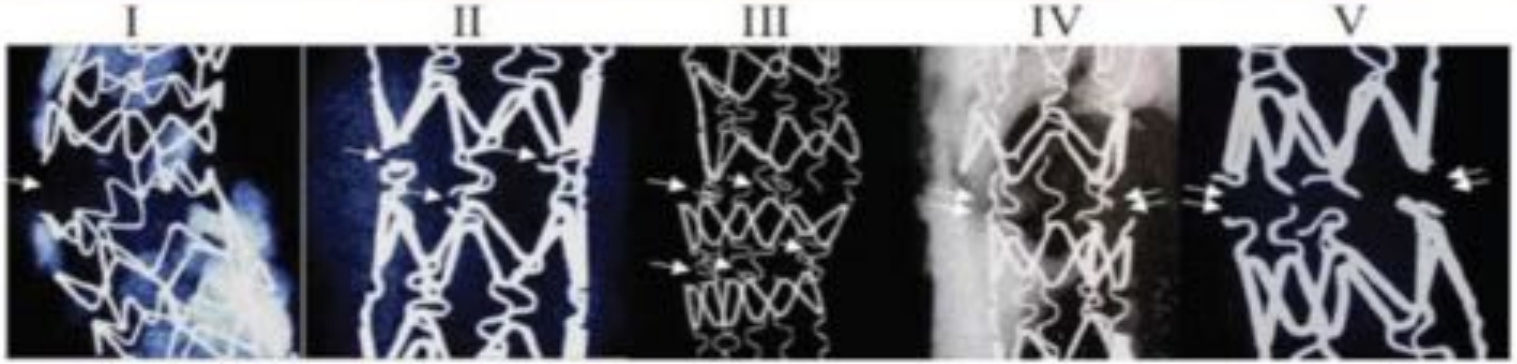
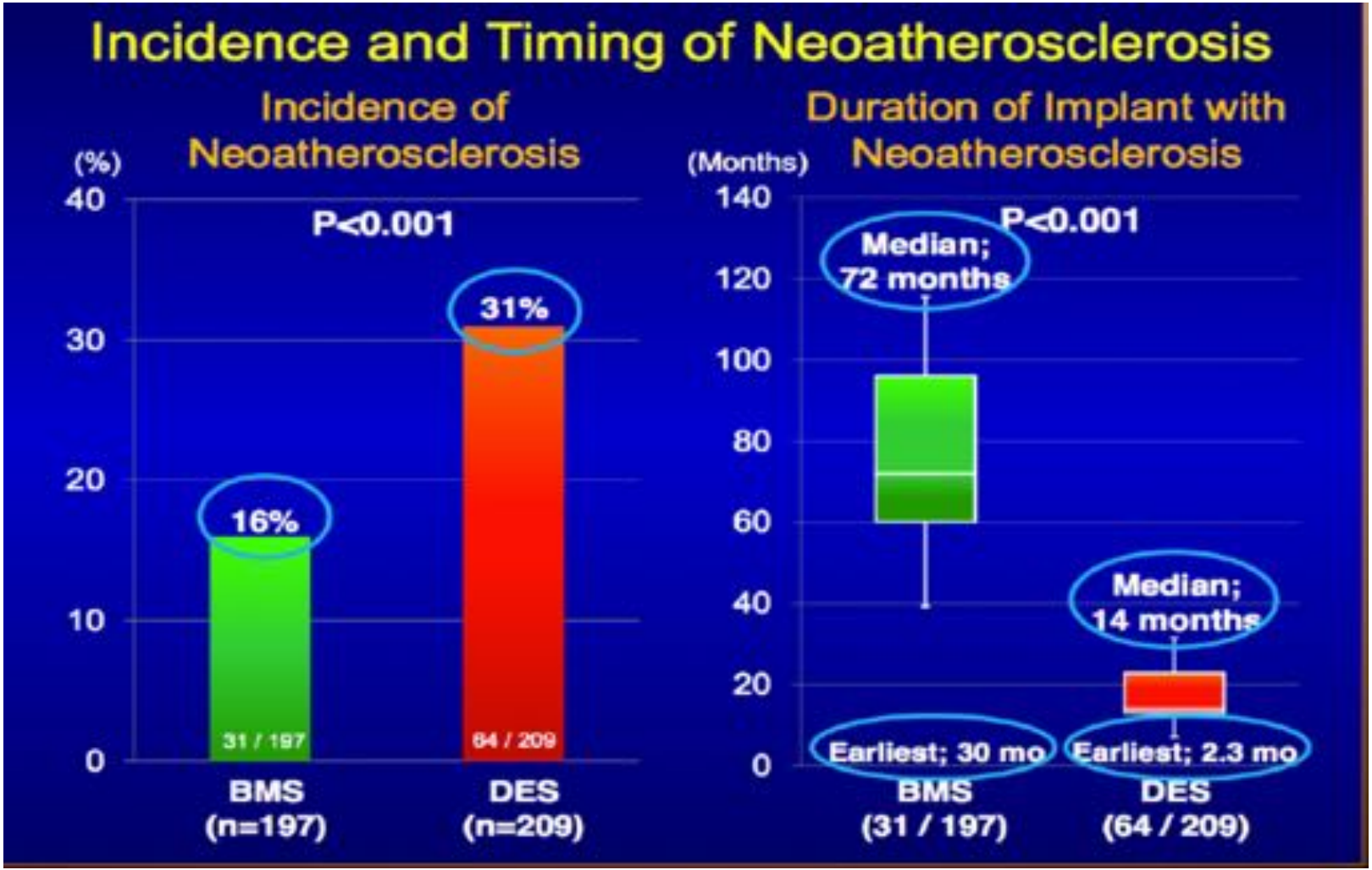


Illustration from Mohsen et al, Heart View 2013

From « plaque-sealing » to neoatherosclerosis


Incidence and Timing of Neoatherosclerosis
Incidence of Neoatherosclerosis
(%)
40
30
20
10
0
P<0.001
16%
31%
31 / 197
64 / 209
BMS (n=197)
DES (n=209)
Duration of Implant with Neoatherosclerosis
(Months)
140
120
100
80
60
40
20
0
P<0.001
Median; 72 months
Median; 14 months
Earliest; 30 mo
Earliest; 2.3 mo
BMS (31 / 197)
DES (64 / 209)

Next phase for the future of PCI: Optimal Healing

PCI EVOLUTION
Continuous improvement in platform design and acute performance

- **1977** • POBA: Getting Artery Open
- **1986** • BMS: Keeping Artery Open
- **2003** • DES Decrease Restenosis
- **2015+** • Future DES: Optimize Healing

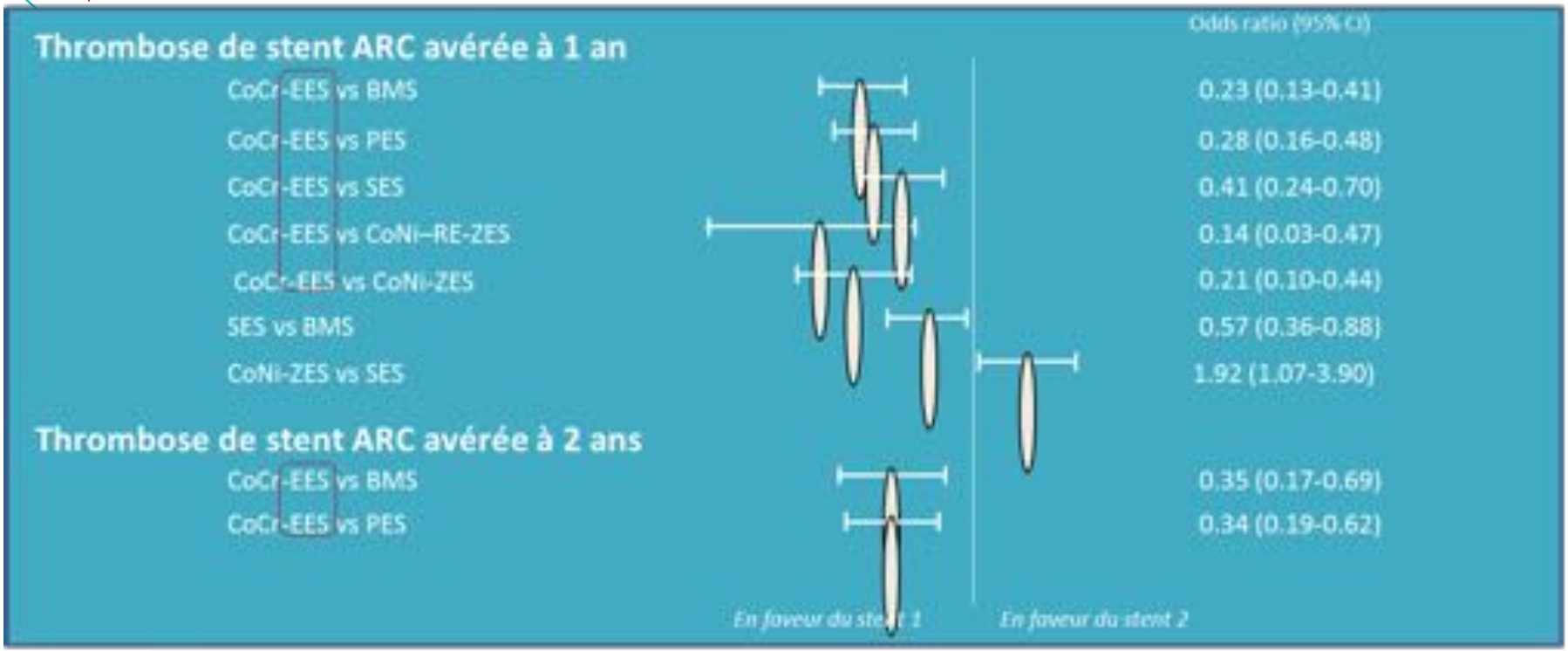
- **Lower late events rates – ST, TLR**
- **Reduced need for prolonged DAPT**
- **Reduced risk of neoatherosclerosis**

	Cypher	TAXUS Express	Biomatrix NOBORI	TAXUS Liberte	TAXUS Element	Endeavor	Resolute	PROMUS Xience V PRIME	PROMUS Element
Platform									
material	316L SS	316L SS	316L SS	316L SS	PtCr	MP35N	MP35N	CoCr L-605	PtCr
Strut (mm)	0.14	0.12	0.11	0.097	0.081	0.091	0.091	0.081	0.081
Polymer									
material	PEVA PBMA	SIBS	PLA	SIBS	SIBS	PC	C10 C19 PVP	PDVF-HFP	PDVF-HFP
microns	12.6	18	10	16	14	5.3	NA	7.6	7.6
Drug									
'limus	SIRO	(PTX)	BIO	(PTX)	(PTX)	ZOTA	ZOTA	EVERO	EVERO
Load * mcg	150	1mcg/mm3	280	1mcg/mm3	1mcg/mm3	180	180	88	88
Kinetics Time to ~70% release	28d	<10%	90d	<10%	<10%	2d	30d	30d	30d

*Load on a 3.0 x 18mm stent

Stent Thrombosis Network Meta-Analysis

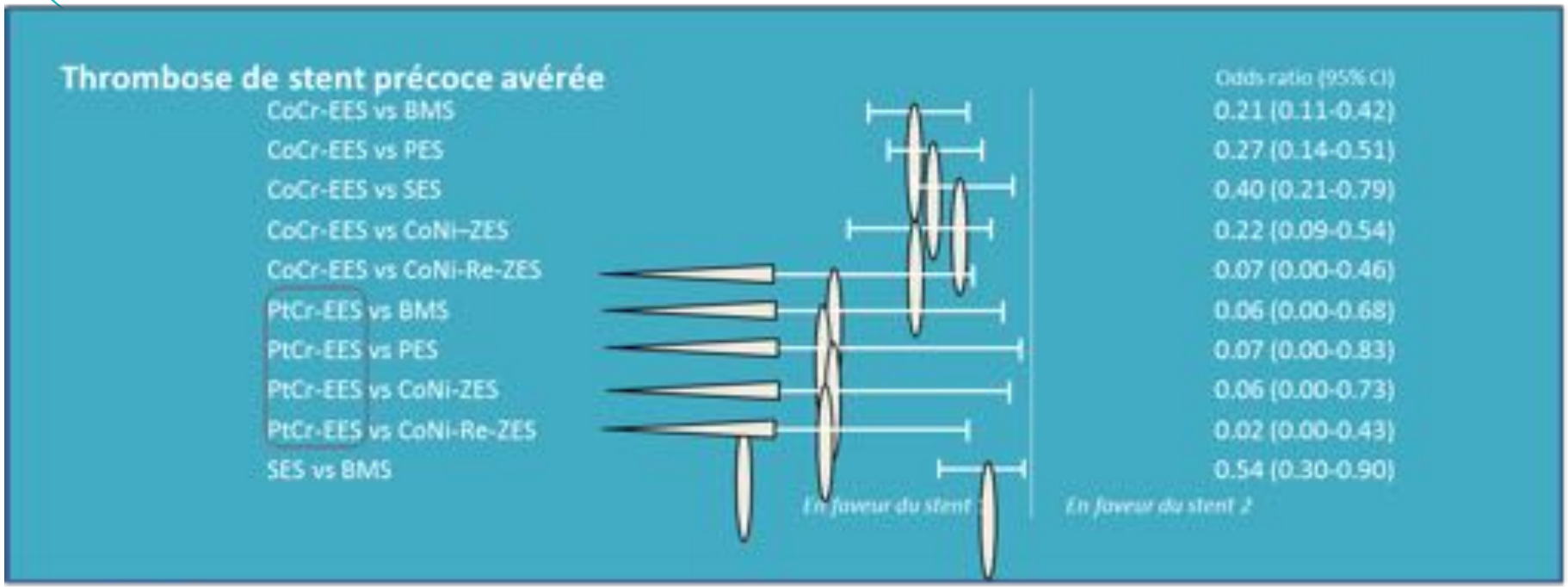
n = 50,844 pts



- **Significantly Lower ARC ST (Def) with CoCr-EES compared to other DES or BMS**
- **Reaffirms the safety profile of the everolimus-eluting stents**

Palmerini, et al. Lancet 2012; 7:84.

Stent Thrombosis Network Meta-Analysis



- **Significantly Lower Early and Late ARC ST (Def) with CoCr-EES compared to other DES or BMS**
- **Significantly Lower Early ARC ST (Def) with PtCr-EES**

Stent Thrombosis with Drug-Eluting Stents and Bare-Metal Stents: Evidence from a Comprehensive Network Meta-Analysis; Palmerini, et al. Lancet 2012;7:84.

	Postprocedure			6 months		
	CoCr-EES	PtCr-EES	CoCr vs. PtCr	CoCr-EES	PtCr-EES	CoCr vs. PtCr
	n = 19	n = 20	P	n = 19	n = 20	P
Strut level analysis (per patient)						
Analyzed struts, n	219.0 (125.0–253.0)	208.0 (94.0–275.0)	0.94	176.0 (126.0–297.0)	209.0 (132.5–285.5)	0.69
Analyzed struts/cross-sections, n	6.71 (5.21–7.90)	7.41 (6.06–8.34)	0.41	6.29 (5.65–8.93)	7.43 (6.68–7.97)	0.34
Embedded struts (%)	15.23 (13.89–24.00)	2.67 (1.38–6.19)	<0.001	–	–	–
Uncovered struts (%)	–	–	–	5.88 (1.35–13.27)	8.46 (3.05–17.26)	0.36
Uncovered, nonmalapposed struts (%)	–	–	–	5.04 (1.35–12.50)	6.23 (3.05–16.11)	0.28
Uncovered, malapposed struts (%)	1.80 (0.00–3.47)	1.15 (0.33–3.83)	0.92	0.48 (0.00–1.44)	0.00 (0.00–0.25)	0.10
Maximum length of uncovered segment (mm)	–	–	–	2.44 (0.64–3.85)	2.56 (1.25–5.13)	0.44
Maximum length of malapposed segment (mm)	0.64 (0.00–1.92)	0.64 (0.64–0.64)	0.38	0.64 (0.00–0.64)	0.00 (0.00–0.32)	0.10
Neointimal thickness (mm)	–	–	–	0.08 (0.05–0.12)	0.09 (0.06–0.14)	0.49
Stent eccentricity index	0.90 (0.89–0.91)	0.91 (0.89–0.92)	0.47	0.91 (0.90–0.93)	0.92 (0.91–0.93)	0.26
Pt with AIT related to uncovered struts (%)				2 (10)	2 (10)	1.00
Morphometric analysis						
Stent area (mm^2)	7.97 (6.60–8.80)	8.35 (6.91–9.41)	0.55	7.96 (6.92–9.50)	8.64 (6.96–9.62)	0.83
Lumen area (mm^2)	7.94 (6.60–8.73)	8.44 (6.90–9.34)	0.46	7.60 (6.21–8.19)	7.59 (6.28–8.52)	0.88
Protruding area (mm^2)	0.37 (0.30–0.45)	0.36 (0.27–0.51)	0.62	–	–	–
Neointimal area (mm^2)	–	–	–	0.83 (0.43–1.18)	0.88 (0.58–1.34)	0.38
Malapposition area (mm^2)	0.04 (0.02–0.06)	0.04 (0.01–0.06)	0.70	0.02 (0.00–0.07)	0.01 (0.00–0.05)	0.33
Percentage net volume obstruction (%)	–	–	–	9.67 (5.76–15.25)	11.03 (6.05–15.47)	0.55
Malapposition volume (mm^3)	0.70 (0.47–1.41)	0.75 (0.16–1.21)	0.97	0.43 (0.01–1.47)	0.11 (0.00–1.03)	0.30

Vascular response to different EES Alloy Platforms

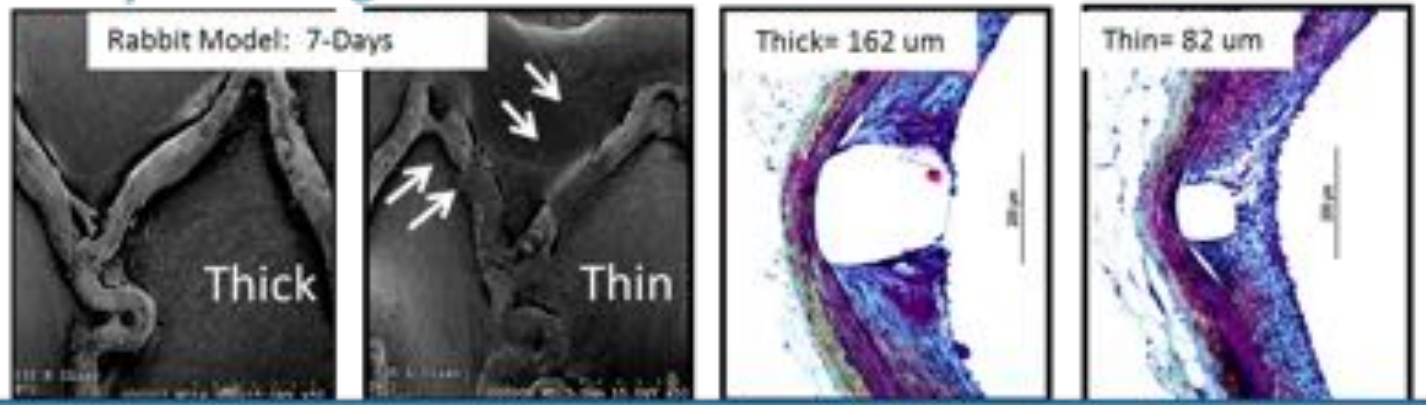
OCTEVEREST Study

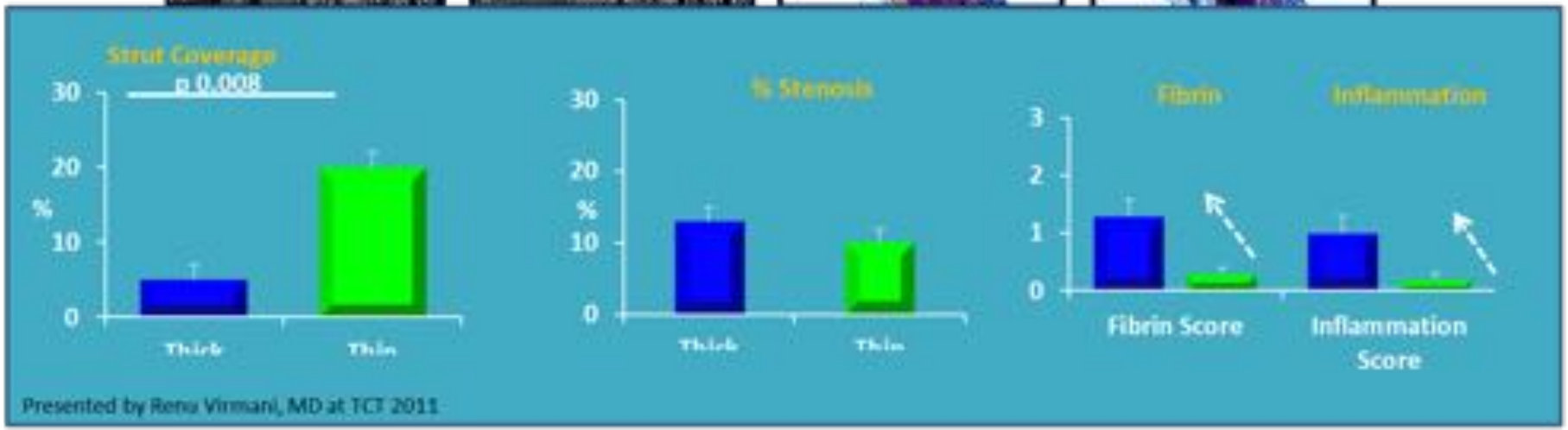
Guagliumi et al CCI 2013


S.S. FAT GUY

Impact of Strut Thickness on Healing

Delayed healing and increased inflammation with thicker struts

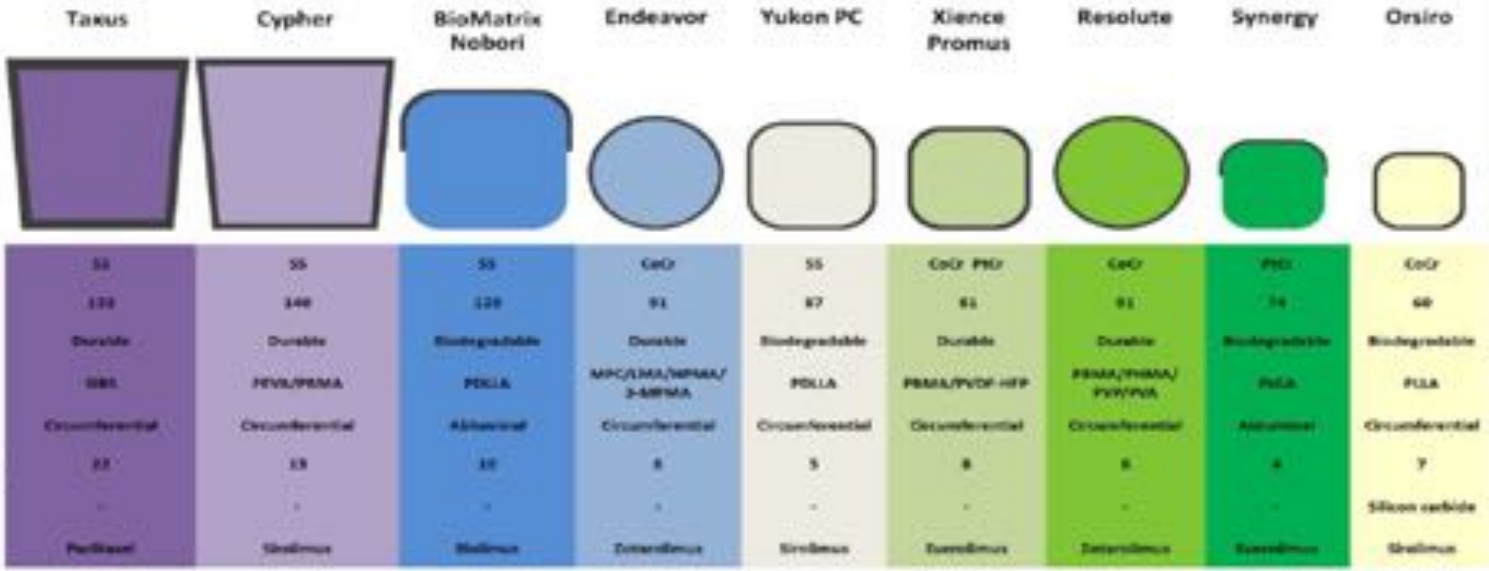




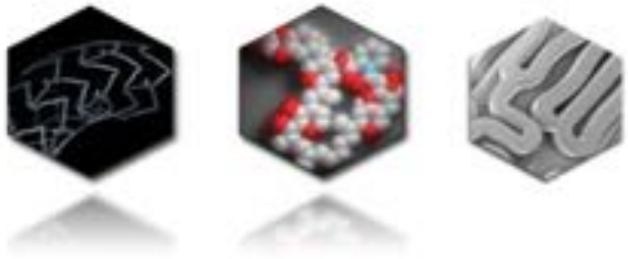
Presented by Renu Virmani, MD at TCT 2011

Progress in Metallic DES Technology

Stefanini, Taniwaki, Windecker. *Heart* 2013, ahead of print

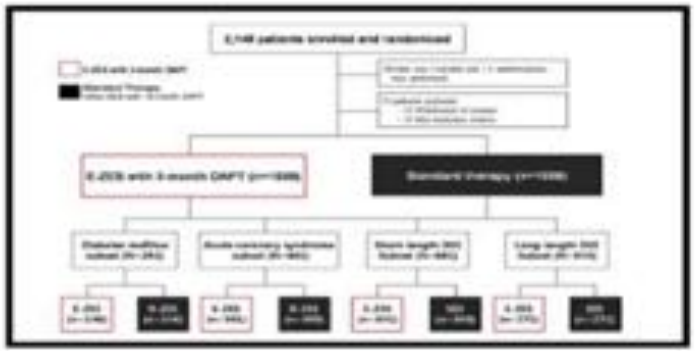


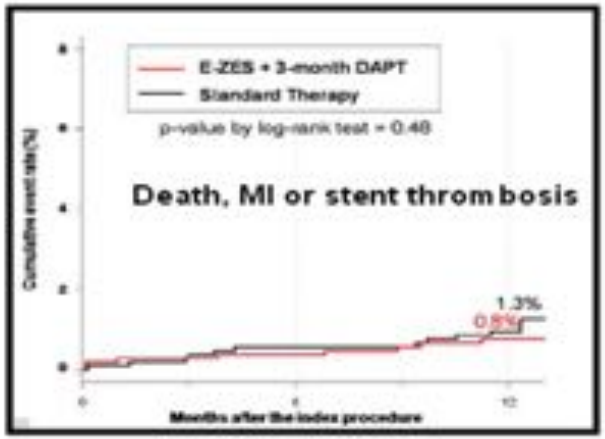
L'importance du type de stent



=> Stents de dernière génération
- Meilleure délivrabilité
- Mailles plus fines
- Polymères biocompatibles
- Délivrance de la molécule antiproliférative

The RESET trial

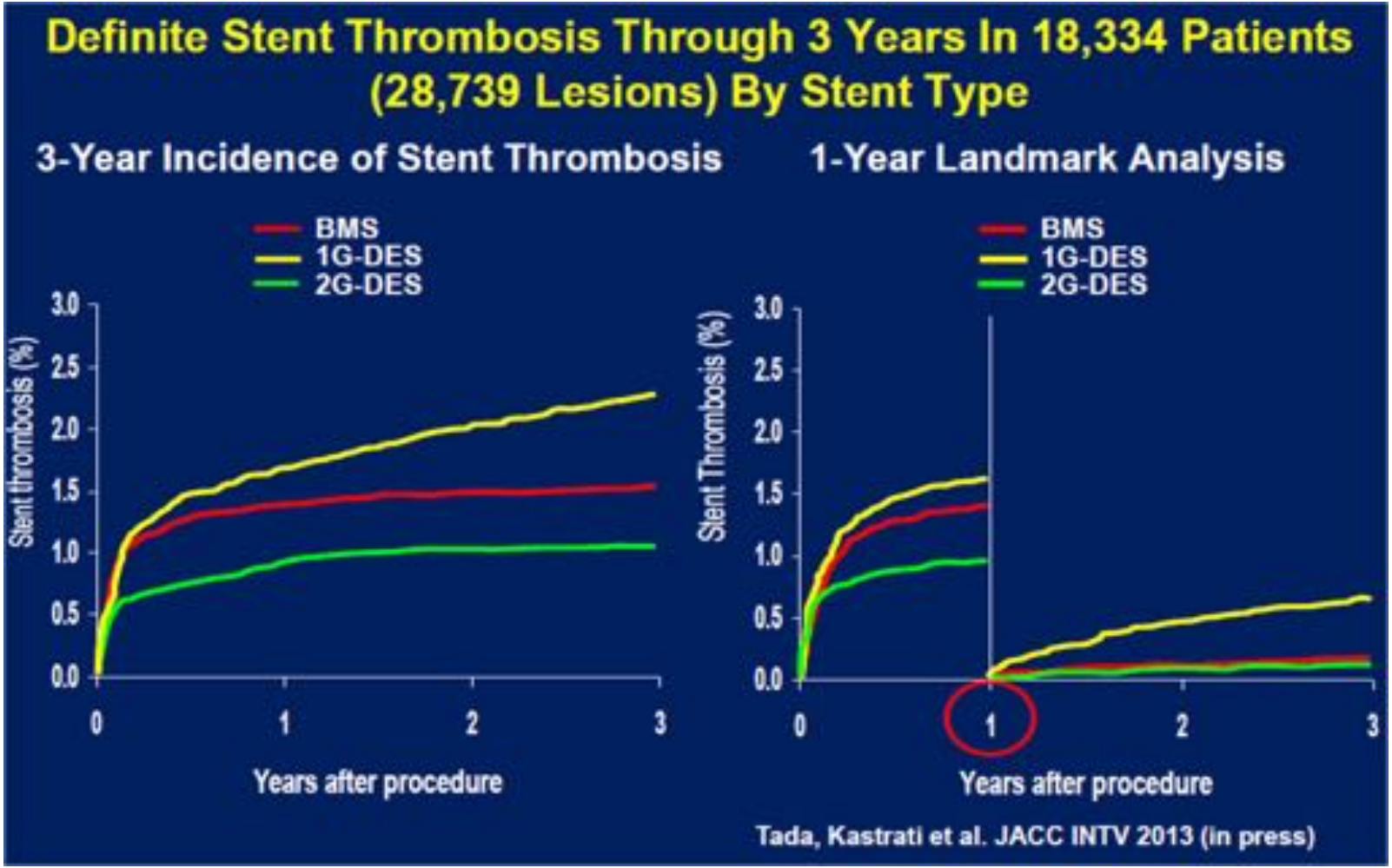




Hypothesis : Non inferiority of 3 months DAPT with ZES vs12 months with other DES

Kim et al – JACC 2012

Definite Stent Thrombosis Through 3 Years In 18,334 Patients (28,739 Lesions) By Stent Type



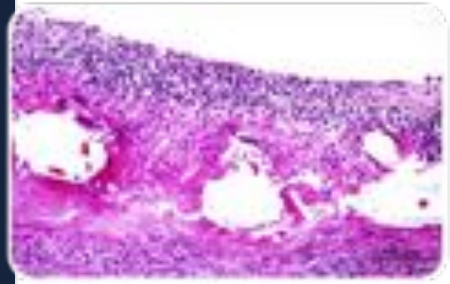
Vascular Response

to Durable Polymers

- Newer generation durable polymers are still a source of inflammation, neoatherosclerosis, and thrombosis risk

EES

Focal inflammation



Focal inflammation with eosinophils (4 months)

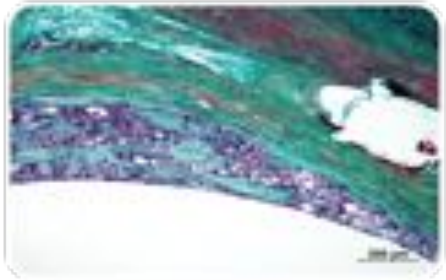
ZES

Chronic Inflammation

Chronic inflammation with giant cells secondary to polymer delamination (3 months)

EES

Neoatherosclerosis



Foamy macrophage accumulation (neoatherosclerosis)

EES

Late Stent Thrombosis

EES implanted within PES 6 months ante mortem

Current polymeric DES design

Persistence of durable polymer or breakdown products

- Delay in arterial healing
- Inflammation
- Aneurysm formation
- Mechanical disruption

Increased risk of:

- Mortality
- Myocardial infarction
- Very-late stent thrombosis

Contemporary DES Platforms

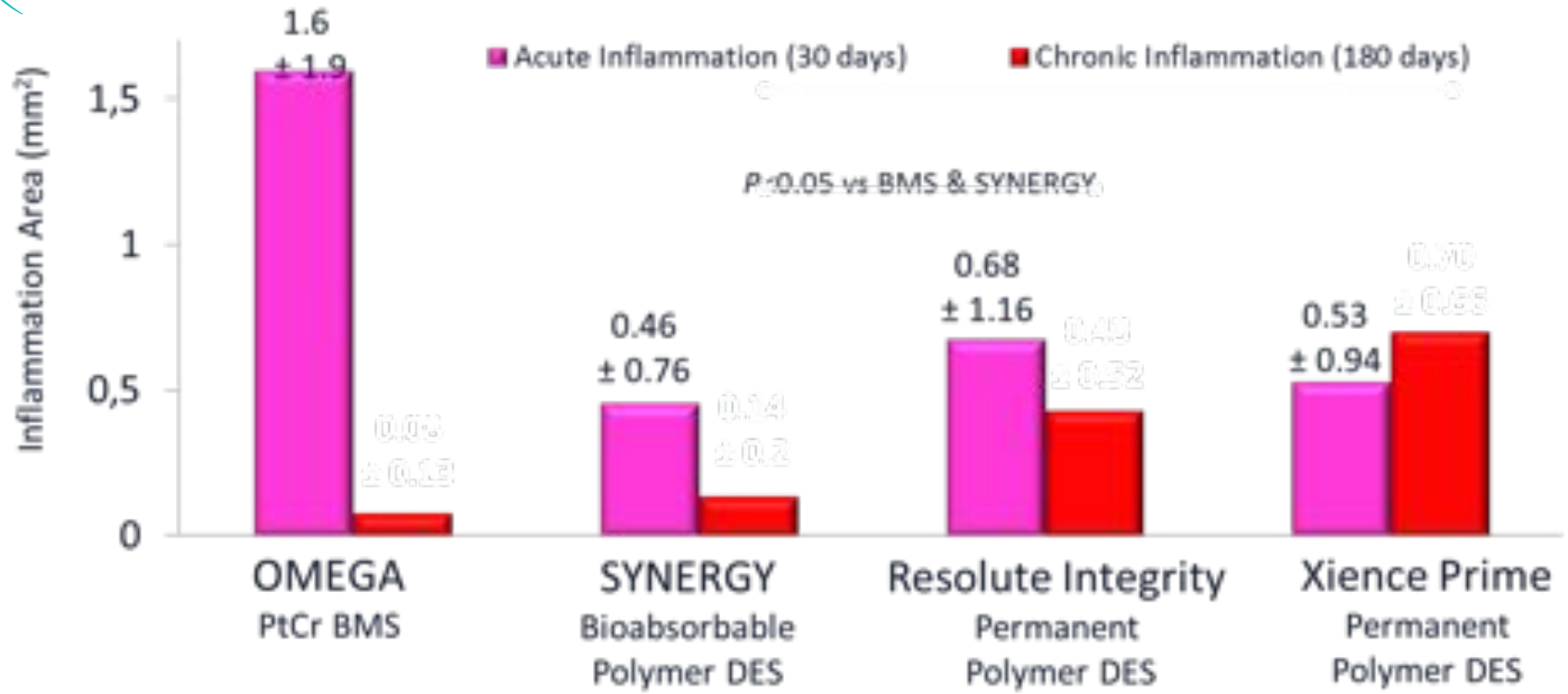
Strut and Coating Thickness In Perspective

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute	Biomatrix	Nobori	Ultimaster	SYNERGY	MiStent	Orsiro
	Promus PtCr-EES	CoNi-ZES	316L-BES	316L-BES	CoCr-SES	PtCr-EES	CoCr-SES	CoCr-SES
								
Strut thickness	81 µm 0.0032"	89 µm 0.0035"	120 µm 0.0046"	125 µm 0.0047"	80 µm 0.0031"	74 µm 0.0029"	64 µm 0.0025"	61 µm 0.0024"
Polymer	PVDF	BioLINX	PLA	PLA	PDLLA + PCL	PLGA	PLGA	PLLA Probio*
Distribution / thickness	Conformal 7-8µm / side	Conformal 6µm / side	Abluminal 10 µm	Abluminal 20 µm	Abluminal 15 µm	Abluminal 4 µm	Conformal 5 µm / 15 µm	Conformal 3.5 µm / 7.5 µm

*silicon carbide

Para-strut Inflammation with Current Generation Stents

Inflammation at 30 and 180 Days in Rapacz Hypercholesterolemic Swine Model

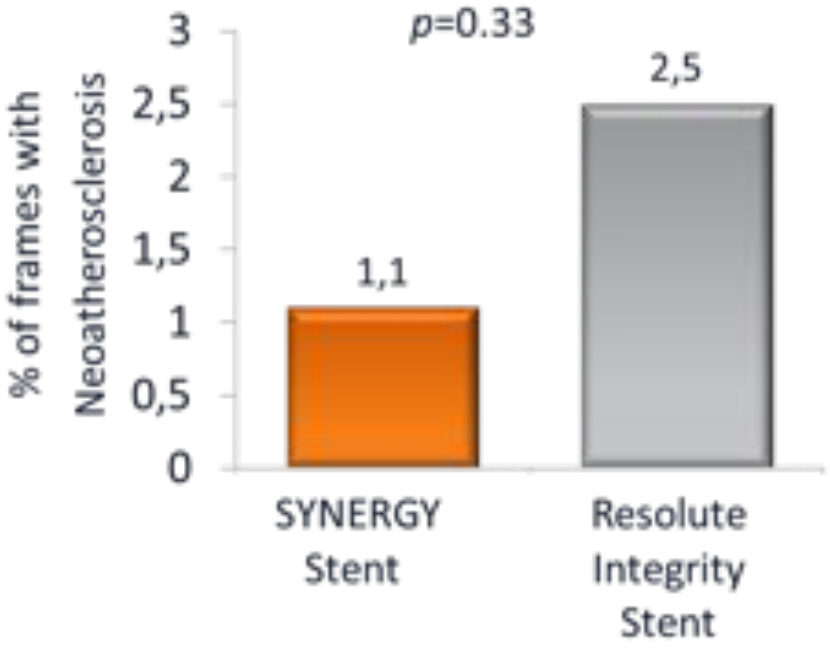


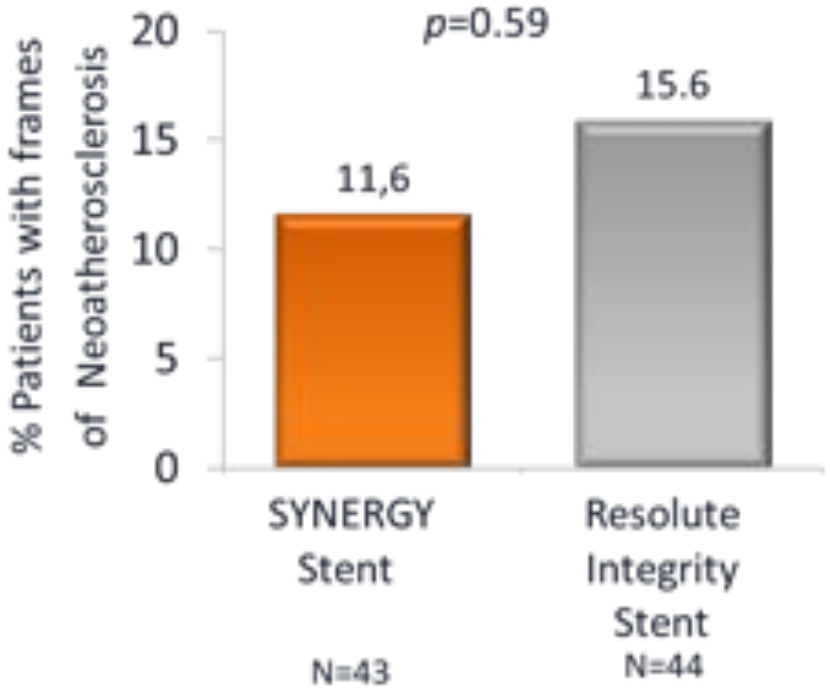
Low acute inflammation with SYNERGY similar to current gen DES
Low chronic inflammation with SYNERGY similar to current BMS

Adapted from Juan Granada, MD EuroPCR 2014/TCT 2014.

TRANSFORM OCT

Neoatherosclerosis at 18 months





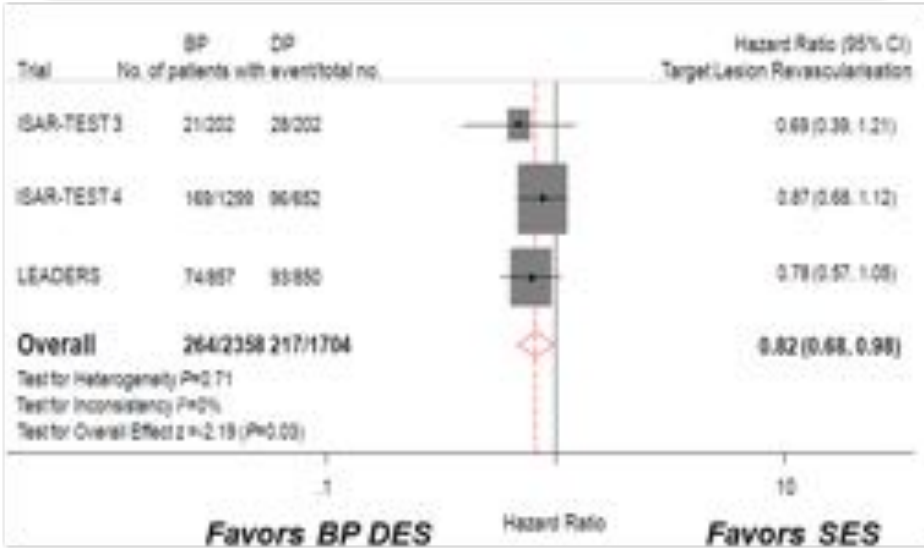
SYNERGY shows low levels of neoatherosclerosis at 18 months

Guagliumi, Presented at TCT 2016.

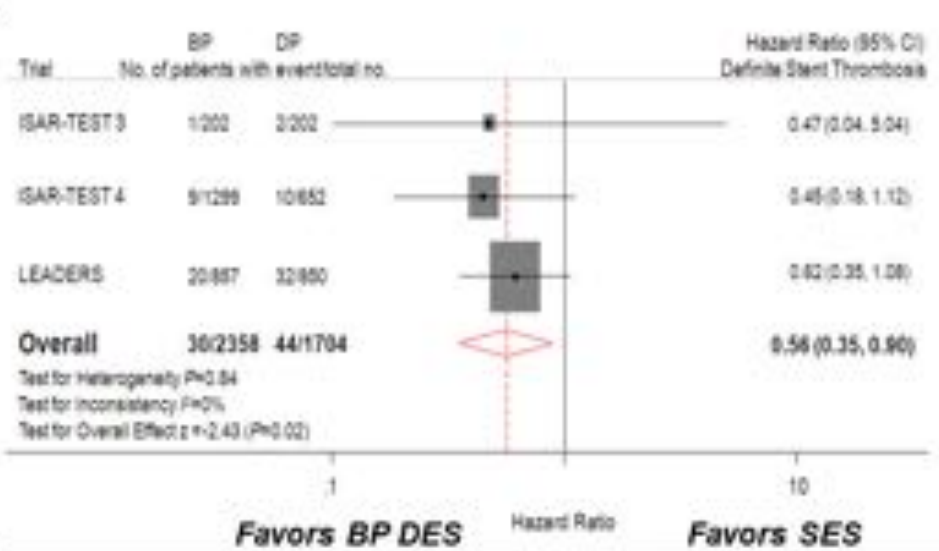
Biodegradable Polymer DES Versus Durable Polymer SES

Stefanini G et al. *Eur Heart J* 2012; 33, 1214–1222

Target-Lesion Revasc. at 4 Years



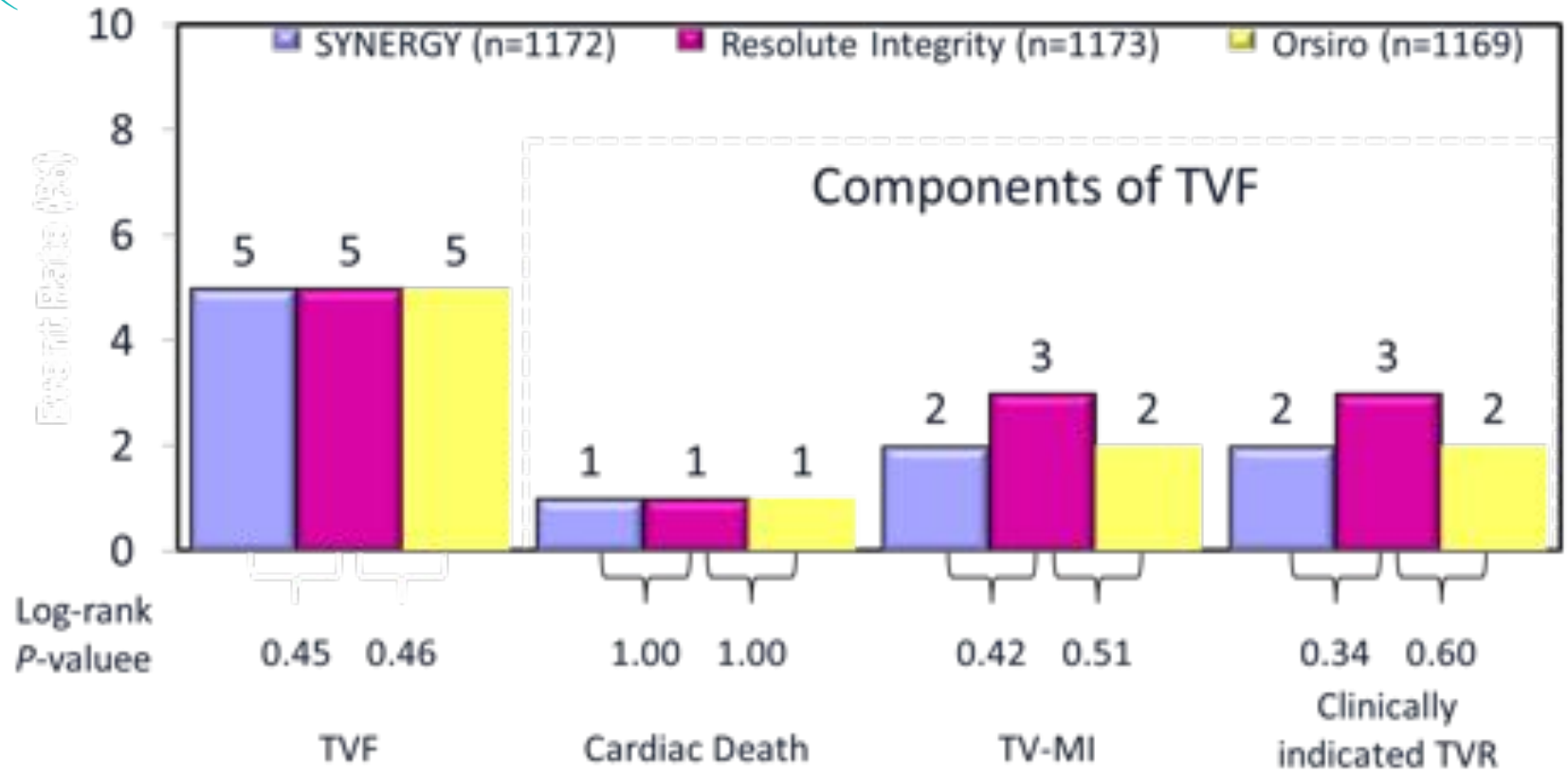
Definite ST at 4 Years



N = 4,062 – IPD Pooled Analysis of LEADERS, ISAR-TEST 3 and 4

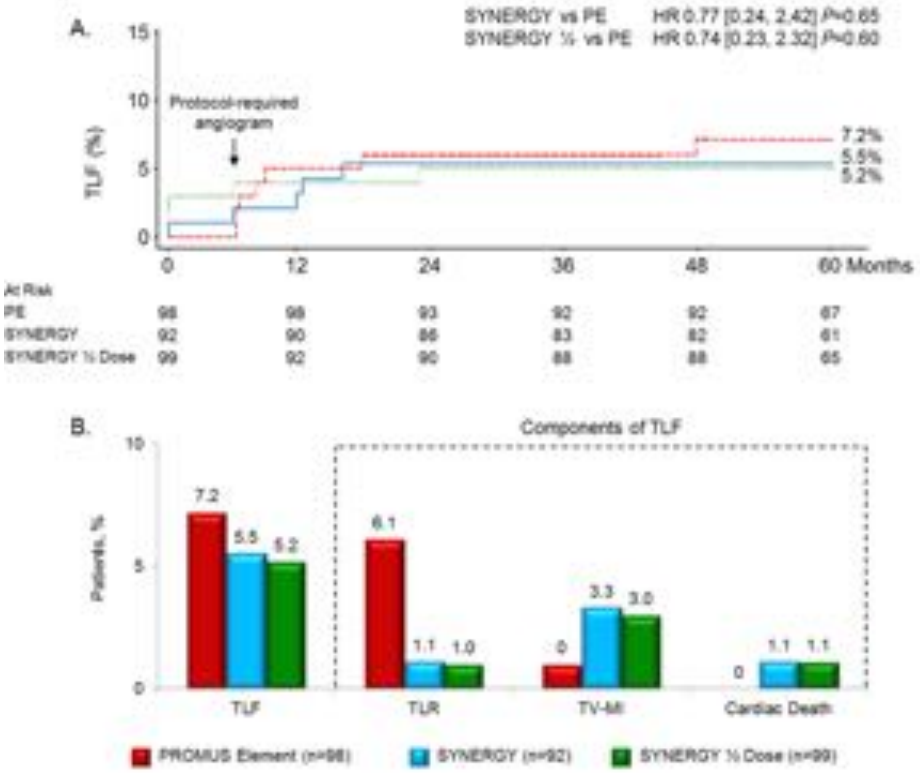
BIO-RESORT

Components of Primary Non-inferiority Endpoint: 1-Year TVF



Von Birgelen, C., et al. Lancet 2016

TLF and clinical outcomes at 5-years in EVOLVE trial



Submitted to EuroIntervention 2017

ARC ST (Def) Rates for the SYNERGY™ Stent *Consistently low sub-acute, late & very late ST in 18,000 patients across 9 studies*

	SWEET Registry	Fribourg Experience	Belfast Experience	EVOLVE II Trial	EVOLVE Trial	EVOLVE China	EVOLVE II QCA Study	SCAAR Registry	BIO-RESORT Trial
N:	820	671	185	846	94	205	100	14,979	1172
Acute	1.5%	0.3%	0%	0.2%	0%	0%	0%	0.08%*	0.1%
Sub-acute	0.1%	0.3%	0%	0%	0%	0%	0%	0.02%*	0.1%
Late	0.1%	0.1%	0%	0%	0%	0%	0%	0.2%*	0.2%
Very Late			0%	0.1%	0%			0.1%*	

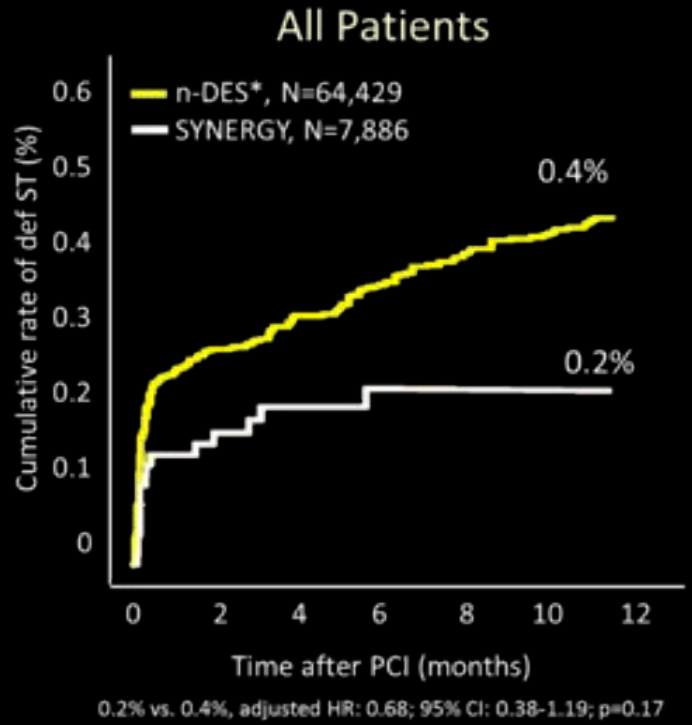
Acute: ≤ 1 day
Subacute: 2 – 30 days
Late: 30 days – 1 year
Very Late: Beyond 1 year

*Cumulative adjusted ARC def ST estimated from Kaplan Meier Curve

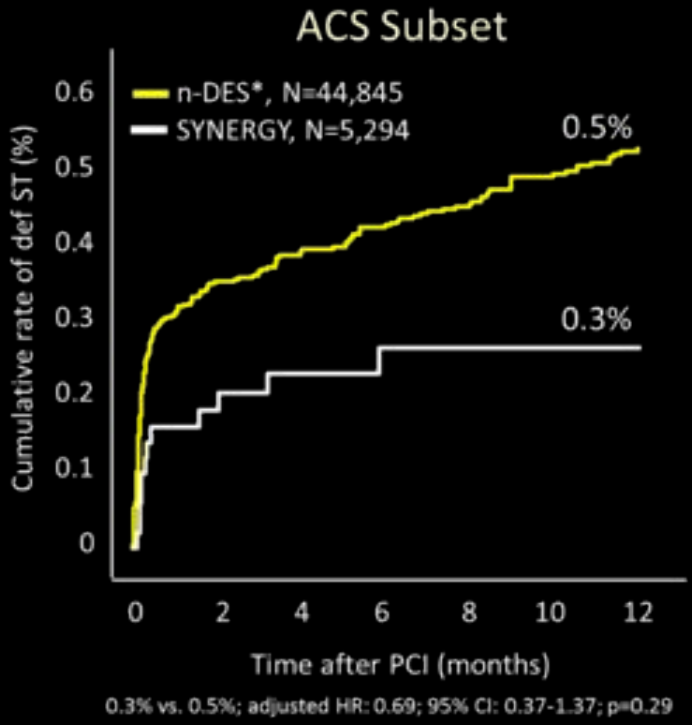
SWEET Registry: Cook TCT 2015., Fribourg Experience: Arroyo CRT 2016. Belfast Experience: Noad TCT 2015., EVOLVE II: Kereiakes, et al. Circ Cardiovasc Interv. 2015;8:e002372.DOI:10.1161/CIRCINTERVENTIONS.114.002372.EVOLVE FIH: Meredith et al. *J Am Coll Cardiol.* 2012; 59 (15):1362., EVOLVE II QCA: Meredith ACC 2015., SCAAR Registry: James TCT 2016 BIO-RESORT presented by Clemens von Birgelen, MD PhD, TCT 2015

SCAAR Registry Definite ST Rates

SYNERGY vs Other Current Generation DES



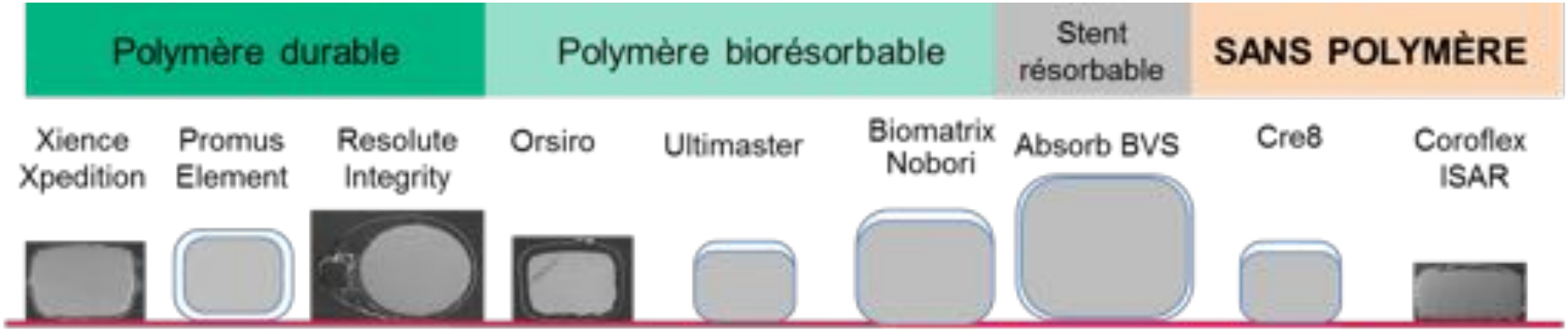
0.2% vs. 0.4%, adjusted HR: 0.68; 95% CI: 0.38-1.19; p=0.17



0.3% vs. 0.5%; adjusted HR: 0.69; 95% CI: 0.37-1.37; p=0.29

No additional def ST past 6 months with SYNERGY in both groups

*Other current gen DES includes: BioMatrix, Orsiro, Promus Element Plus, Promus PREMIER, Xience Xpedition, Resolute/Resolute Integrity, Ultimaster, & Resolute Onyx.
Presented by Sarno CRT 2016.



Epaisseur des mailles

81 µm	81 µm	91 µm	60-80 µm	80 µm	120 µm	150 µm	70-80 µm	50-60 µm

Revêtement

Circulaire	Circulaire	Circulaire	Circulaire	Abluminal	Circulaire	Circulaire	Abluminal	Abluminal

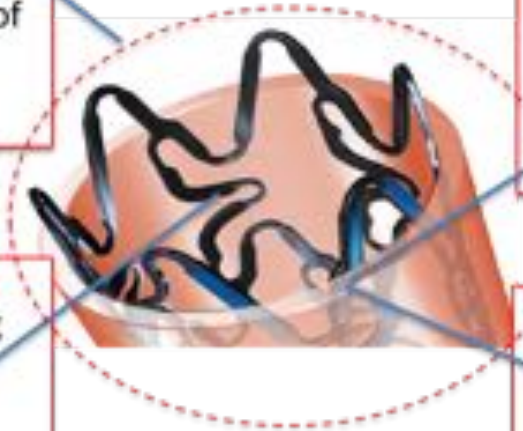
Cre8™: Distinctive Features

Polymer-Free platform

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall

Abluminal Reservoir Technology (ART)

Controlled and directed elution to the vessel wall



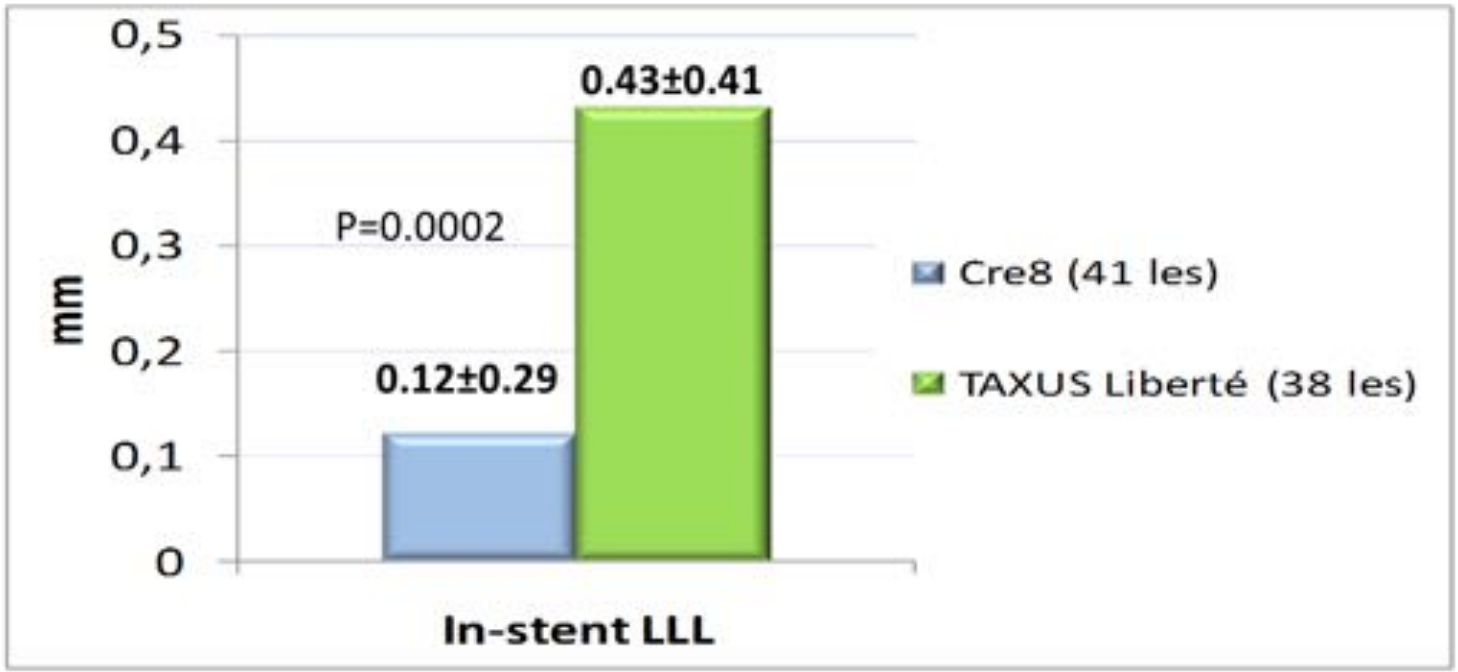
Bio Inducer Surface (BIS) = 2nd generation pure carbon coating

Optimal haemo-compatibility vs. lumen blood flow

Amphilimus Formulation = Formulated Sirolimus with an organic acid

Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy

Diabetic Subgroup:
6-month Late Lumen Loss



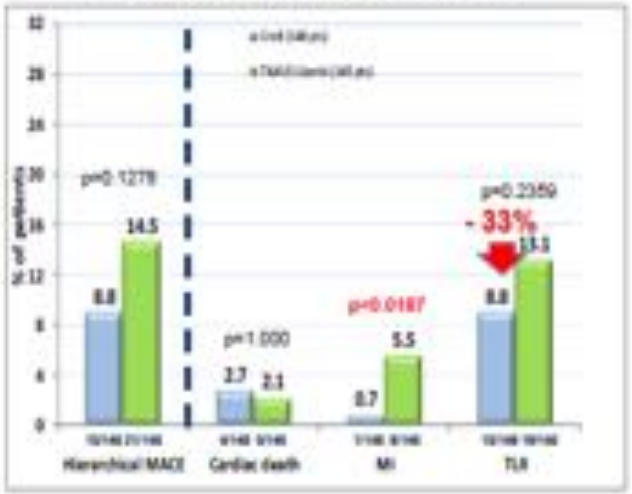
The NEXT randomized study

Alvimedica

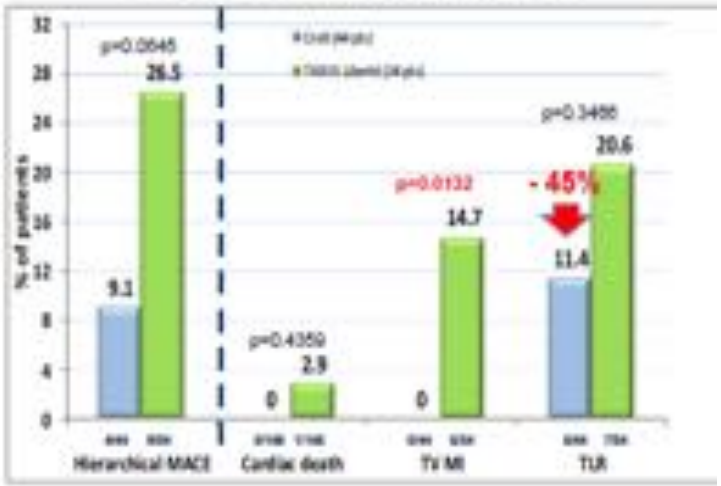
60-month cumulative TLF

(Cardiac death, TV MI, all TLR)

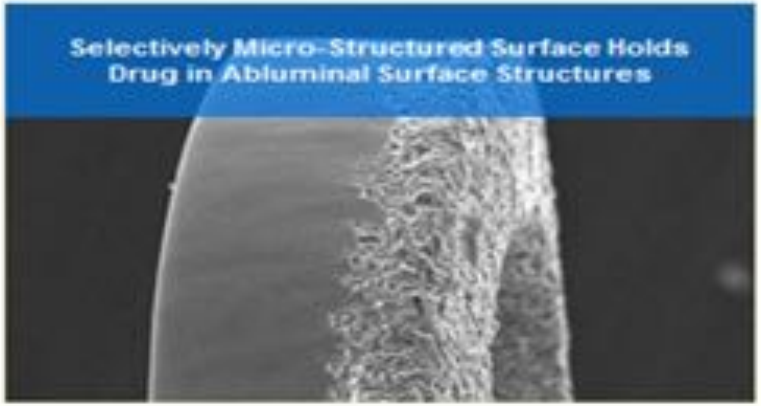
Overall population

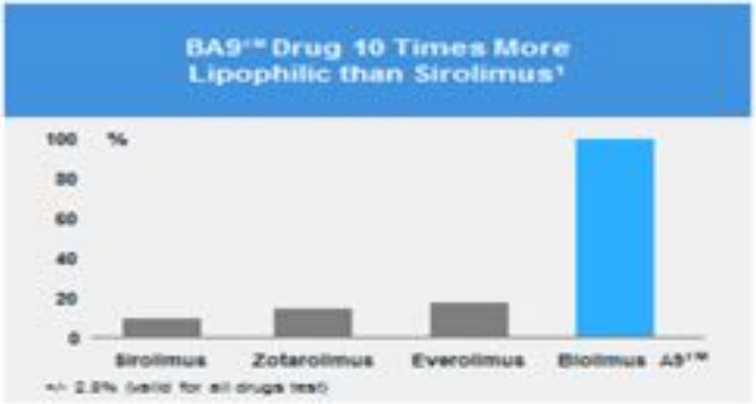


Diabetic population



BioFreedom™ Drug Coated Stent (DCS)



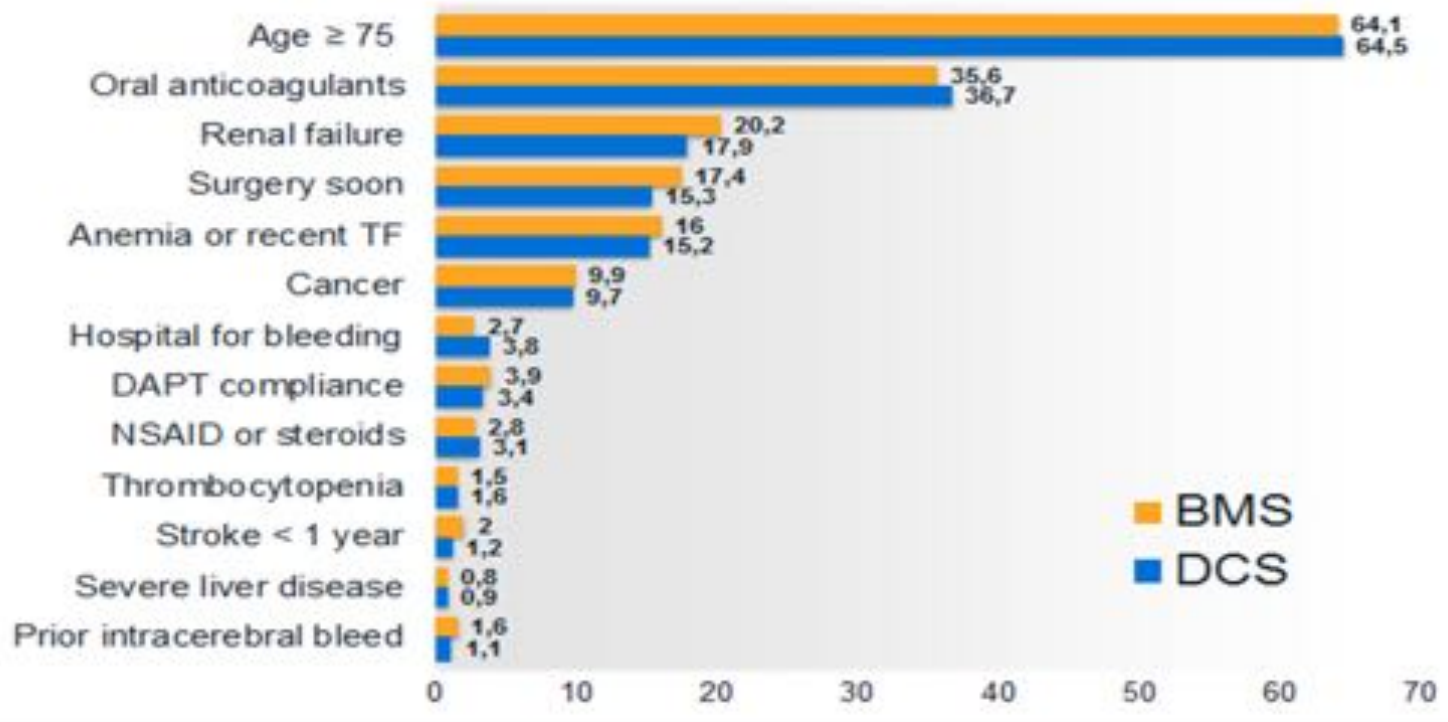


Potential Advantages:

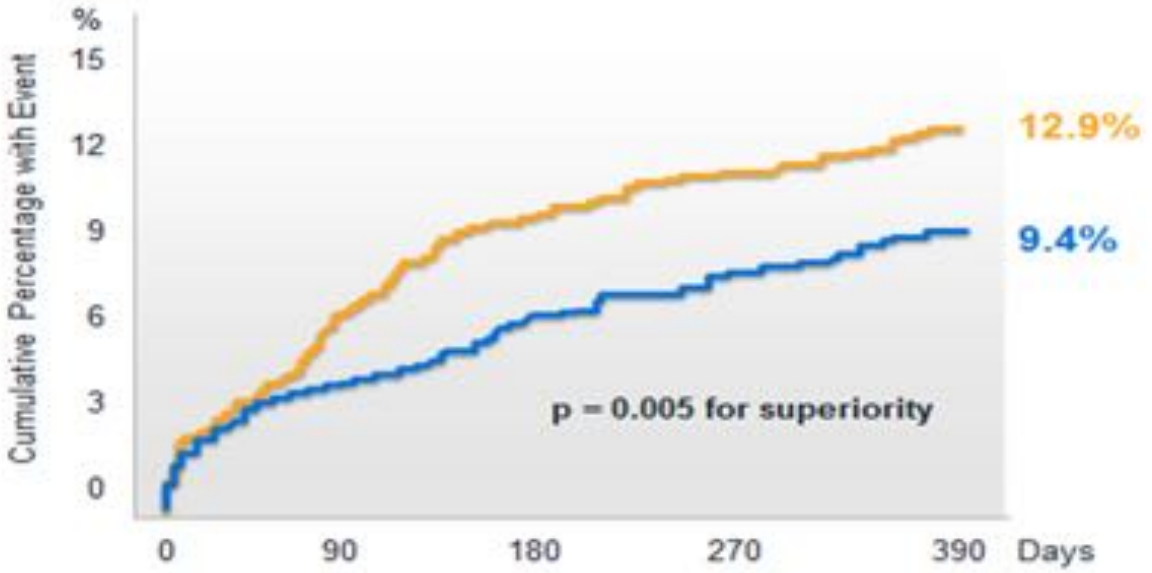
- ✓ Avoid any possible polymer-related adverse effects
- ✓ Rapid drug transfer to vessel wall (98% within one month[2])
- ✓ Safe to shorten DAPT?

1. Data on file at Biosensors Intl; 2. Tada et al., Circ Cardiovasc Interv 2010;3:174-183

Inclusion Criteria Applied (1.7 criteria / patient)



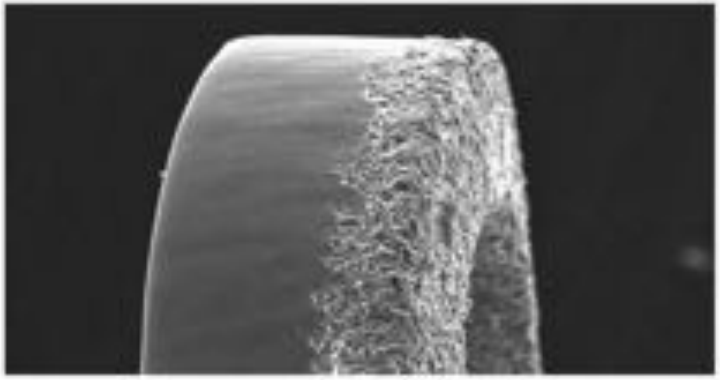
Primary Safety Endpoint (Cardiac Death, MI, ST)



Number at Risk

DCS	1221	1146	1105	1081	1045
BMS	1211	1115	1066	1037	1000

COROFLEX ISAR : Elution du Sirolimus sans polymère



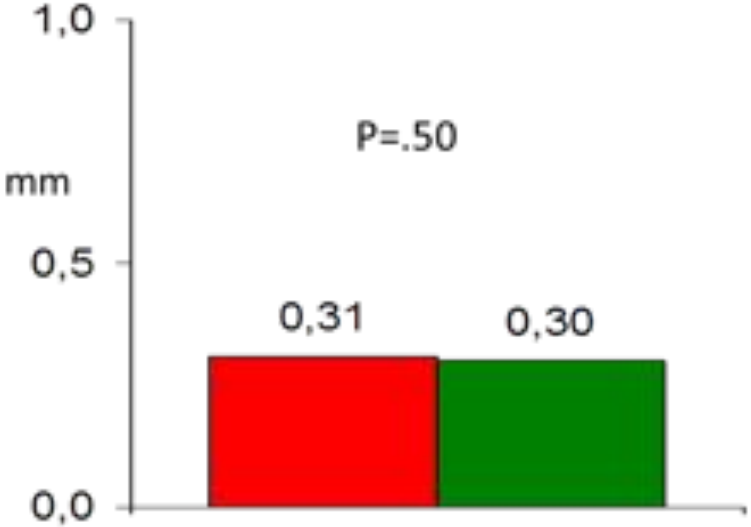
• Surface microporeuse permettant l'adhésion du mélange Probucol/Sirolimus sans l'utilisation de polymère

• Le Probucol associé à la surface microporeuse de la plateforme permet de retarder l'élution du Sirolimus

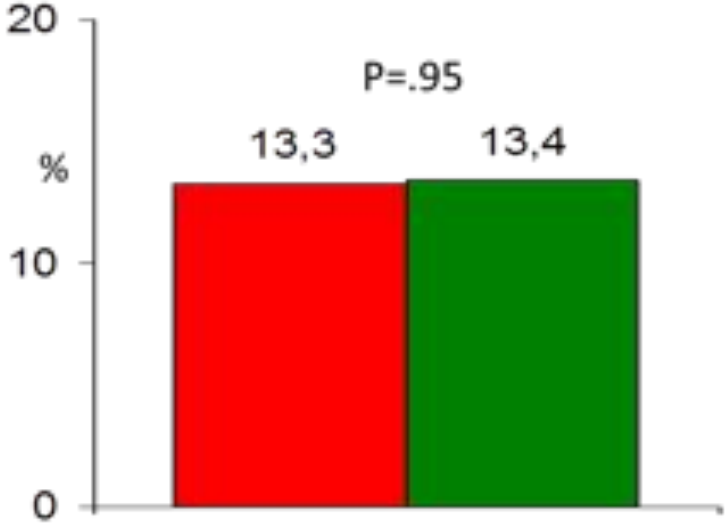
• Revêtement uniquement sur la face abluminale du stent, pour une action ciblée du principe actif sur la paroi vasculaire

Angiographic results

In-stent late lumen loss



In-segment binary restenosis

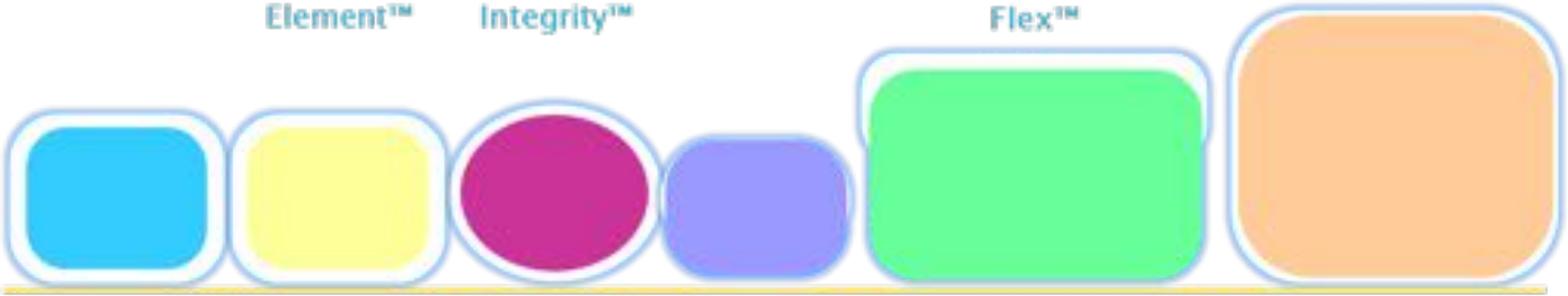


Sirolimus and probucol eluting stent (ISAR)
(Plateforme en acier 90µm, ancienne génération)

Zotarolimus-eluting stent

DES Strut and Coating Thickness In Perspective

Durable Polymer Coated Stents			Bioabsorbable Polymer Coated Stents		Bioabsorbable Stent
Xience V™	PROMUS Element™	Resolute Integrity™	SYNERGY™	BioMatrix Flex™	BVS



Strut Thickness					
81 µm (0.0032")	81 µm (0.0032")	89 µm (0.0035")	74 µm (0.0029")	120 µm (0.0047")	150 µm (0.0059")
Coating Thickness					
Conformal 8µm / side	Conformal 8µm / side	Conformal 6µm / side	Abluminal 4µm	Abluminal 10µm	Conformal 3µm / side

Available and upcoming BRS

BIOTRONIK excellence for life | Abbott A Promise for Life | Elixir MEDICAL CORPORATION | REVA

Product	Magmaris	Absorb (GT1)	DESolve	Fantom
Availability	CE June 2016	2012;(2015): CE Planned: Japan, China, US	2013: CE	Expected CE Q4 2016
Material	**Magnesium**	PLLA	PLLA	Desaminotyrosine-derived polycarbonate
Scaffolding time	**Up to 3m**	6-12m	1-3m	Up to 3m
Resorption time	**1y**	3-4y	~2y	3-4y
Number of sizes	6	14	12	4
Diameter [mm]	3.0; 3.5	2.5; 3.0; 3.5	2.5; 3.0; 3.25; 4.0	2.5; 3.0
Length [mm]	15; 20; 25	8; 12; 18; 23; 28	14; 18; 28	18; 24
Marker	Tantalum	Platinum	Pt/Ir	Not needed
Struts thickness/width [µm]	150/150	150/**180**	150 DESolve CX will have a strut thickness of 120 µm	**125**
Crossing profile [mm]	1.5	1.45	1.4	1.27
Drug	Sirolimus	Everolimus	Novolimus	Sirolimus

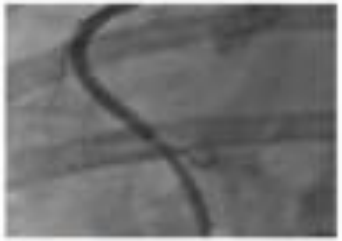
Fantom Bioresorbable Scaffold

***Fantom*® (REVA Medical)**
Sirolimus-Eluting Bioresorbable Scaffold
Desaminotyrosine Polycarbonate

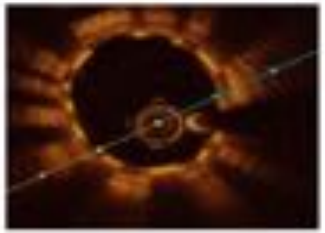
Key Scaffold Features

- Complete scaffold visibility under x-ray
- Single-step continuous inflation
- Clinically significant expansion range
- Optimal radial strength at 125 µm thickness
- Vasomotion restoration ~1 year
- No special storage or handling

Visibility



Deliverability



Vessel Patency

FANTOM II – Cohort A

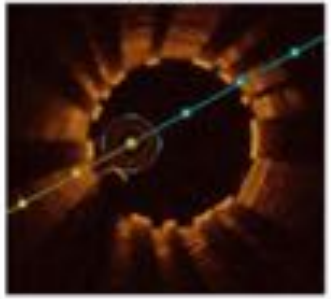
Angiographic – QCA Results*

In-Scaffold Analysis	Baseline (n=115)	Post Procedure (n=112)	6 Months (n=100)
RVD (mm)	2.68 ± 0.37	2.75 ± 0.40	2.69 ± 0.35 (n=93)
MLD (mm)	0.79 ± 0.29	2.47 ± 0.37	2.20 ± 0.39
Diameter Stenosis (%)	70.3 ± 10.4	10.7 ± 7.6	18.8 ± 11.5 (n=93)
Acute Gain (mm)		1.67 ± 0.41	
Acute Recoil (%)		2.9 ± 8.8	
Mean LLL (mm)			0.29 ± 0.38
Median LLL (mm)			0.22 (-0.41, 1.19)
In-Segment Analysis			
Mean LLL (mm)			0.21 ± 0.32
Median LLL (mm)			0.18 (-0.41, 1.63)

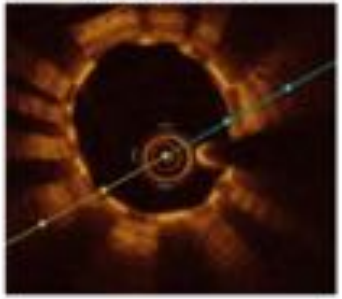
FANTOM II Case Sample

OCT Assessment

Post-Implant



6-Month Follow-up



FANTOM II – Cohort A

MACE Results

6 Month MACE Results Timeframe	Event
In-Hospital	1 (Post Procedure MI)
30-Day Follow-up	1 (MI/TLR/TVF)
90-Day Follow-up	0
6-Month Follow-up	0

Components of the Primary Endpoint (ITT): Hierarchical	N=117
MACE[1]	1.71%
Cardiac Death	0.0%
Target vessel MI	1.71%
Clinically Driven TLR	0.0%

Magmaris components

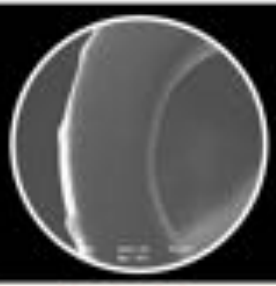
Backbone

Mg alloy

Tantalum markers

6-crown & 2-link design

150µm strut thickness

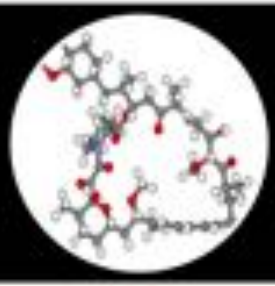


Coating

PLLA

Proven resorption profile

Proven technology identical to Orsiro



BIOlute

Drug

Limus

1.4 µg/mm² same as for Orsiro

Release kinetics

Delivery system

RX, 0.014"

6F compatible

Adapted from Orsiro system

- A combination of proven Orsiro elements and the benefits of a resorbable Magnesium scaffold

BIOSOLVE II – 12 mo QCA

Serial QCA data in 42 patients at post-procedure, 6 and 12-month follow-up

	Baseline	Post-Procedure	6-Month	12-Month
Lesion length (mm)	12.84 ± 4.71	NA	NA	NA
In-segment RVD (mm)	2.74 ± 0.35	2.75 ± 0.35	2.60 ± 0.38	2.60 ± 0.44
In-scaffold RVD (mm)	NA	2.84 ± 0.37	2.66 ± 0.34	2.64 ± 0.41
In-segment MLD (mm)	1.22 ± 0.33	2.25 ± 0.41	2.01 ± 0.38	1.96 ± 0.41
In-scaffold MLD (mm)	NA	2.54 ± 0.33	2.14 ± 0.38	2.10 ± 0.41
In-segment acute gain (mm)	NA	1.00 ± 0.38	NA	NA
In-scaffold acute gain (mm)	NA	1.29 ± 0.34	NA	NA
In-segment DS (%)	55.2 ± 10.9	18.7 ± 6.8	22.6 ± 9.2	24.7 ± 10.6
In-scaffold DS (%)	NA	10.4 ± 6.0	19.6 ± 8.4	20.4 ± 8.6
In-segment LLL (mm)	NA	NA	0.20 ± 0.21	0.25 ± 0.22
In-scaffold LLL (mm)	NA	NA	0.37 ± 0.25	0.39 ± 0.27
In-segment binary restenosis (%)	NA	NA	0.0	2 (4.8)
In-scaffold binary restenosis (%)	NA	NA	0.0	0 (0.0)

M Haude – EuroPCR 2016

Data are mean SD or n (%)

COMMENT CHOISIR UN STENT ACTIF ?

AMELIORER LA SECURITE

Minimiser les thromboses de stent

Réduire la durée de la double AAP (1 à 6 mois)

MAINTENIR L'EFFICACITE

Faible % late loss et resténose binaire

Faible taux de réintervention et de symptôme clinique

NE RIEN LAISSER DERRIERE

Réduire la quantité de principe actif et de polymère

Dissolution du polymère

Résorption du stent