Contemporary and Future Metallic DES:

What do we Expect More from Ongoing PCI Trials?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular, Medtronic
• Scientific Advisory Board	• Medtronic, Abbott Vascular
• Executive Physician Council	• Boston Scientific Corp

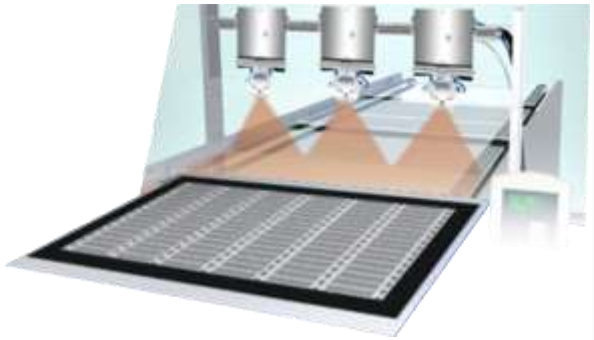
To Further Improve DES Outcomes

- Make the stent struts thinner
- Bioabsorbable polymers
- Eliminate the polymer
- Eliminate the stent ?
- Shorten DAPT need

Focus on New Stent Systems

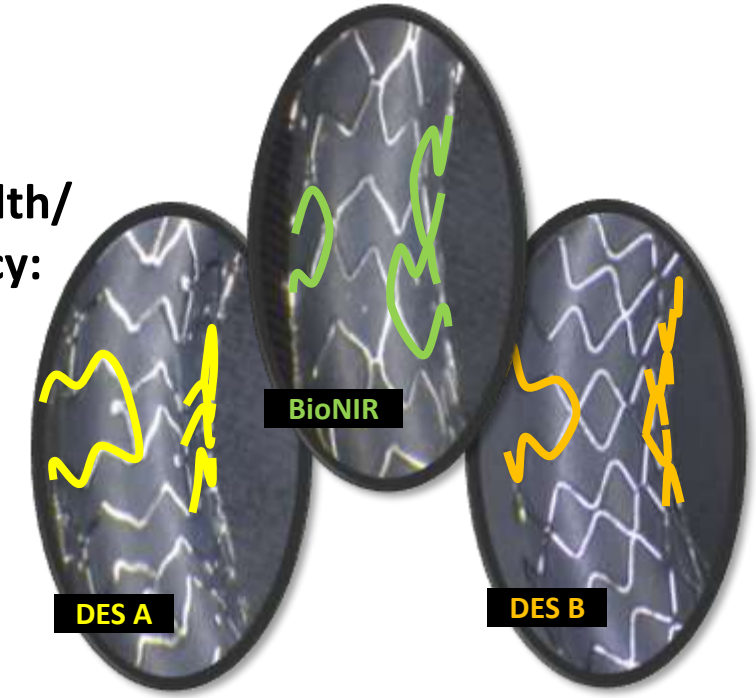
EluNIR (Cordis/Cardinal Health)

Flat manufacturing: Quality & cost efficiency

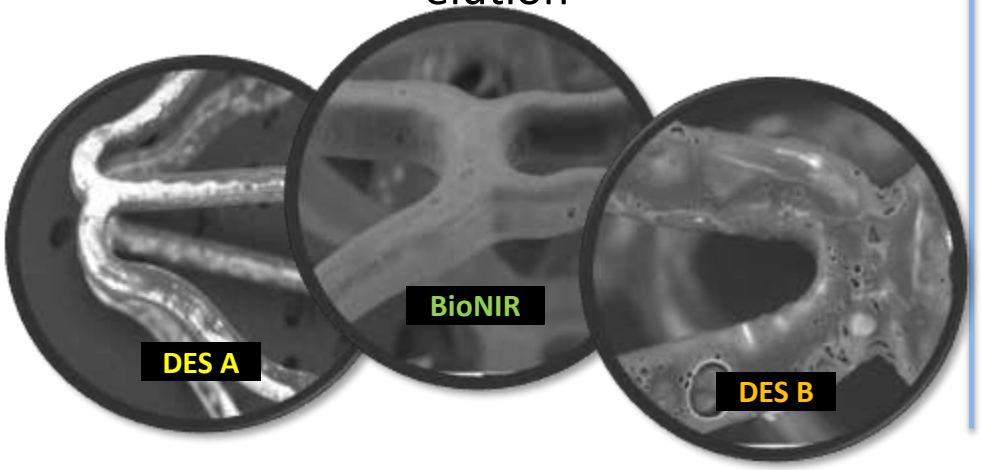


- *80µm CoCr Wizecell design*
- *Ridaforolimus high therapeutic index drug*

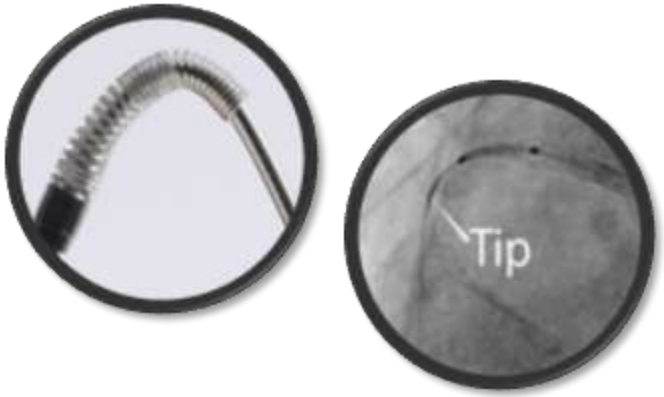
Variable strut width/ frequency: Uniform dosing



Elastomeric Polymer: Remains intact post elution

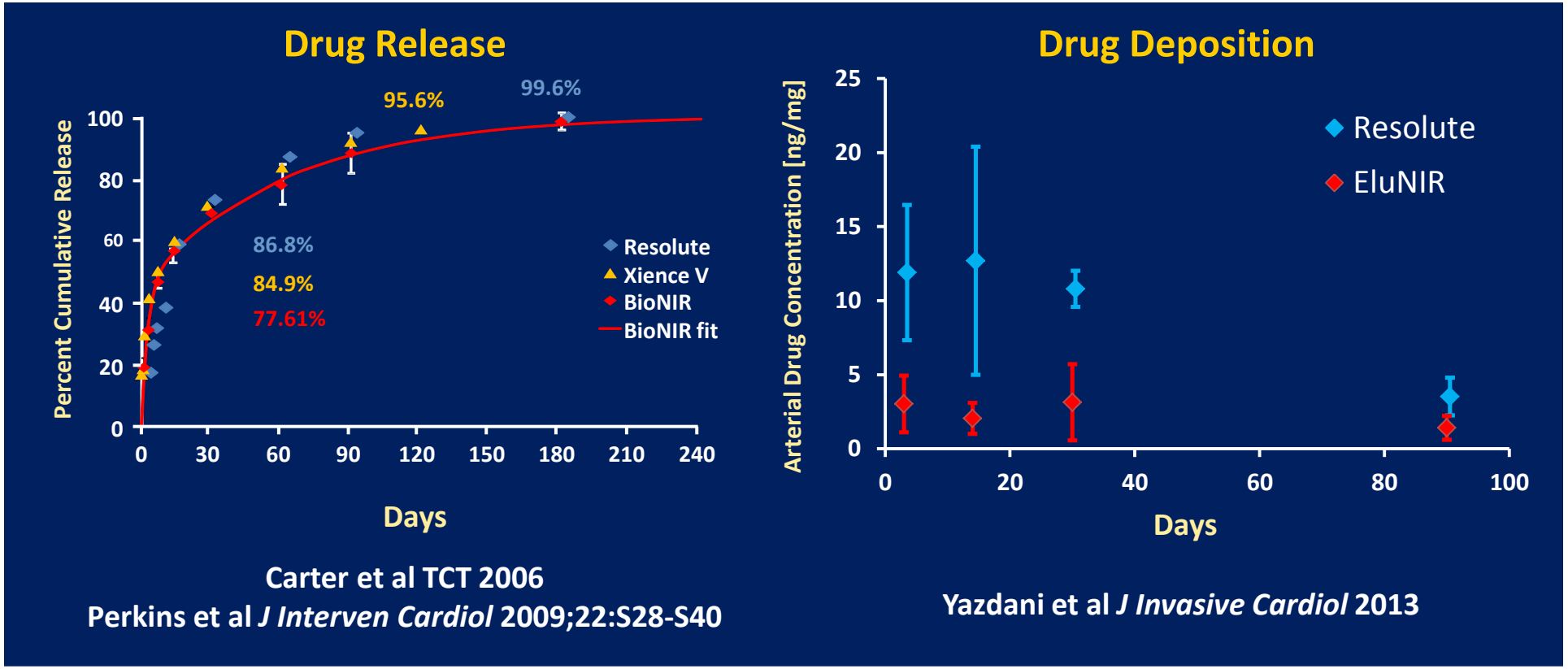


Spring tip: Pushable & visible



Medinol Ltd., Tel Aviv, Israel

EluNIR Pharmacokinetics



Kandzari et al. Circulation 2017

BIONICS Trial Design

"More Comers" Population with Symptomatic CAD (eg, NSTEMI, CTO, SVG, MVD)

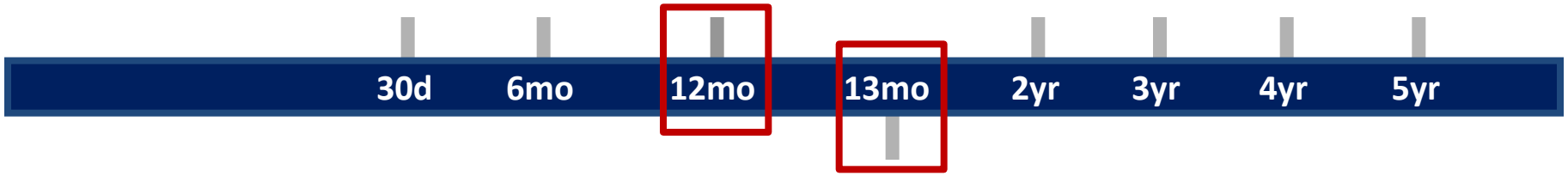
EluNIR Stent N=958

76 Centers in NA, Europe, Israel
FAS*:1919 patients randomized 1:1

Noninferiority Design
(Event rate 5.8%, Delta 3.3%, Power 90%)

Resolute Stent N=961

Primary Clinical Endpoint



QCA & Imaging Endpoints

Primary Endpoint:

- 12-month target lesion failure (TLF), composite of cardiac death, target vessel MI and ischemia driven TLR

Secondary Endpoints:

- 12-month MACE, TVF and individual component endpoints
- Definite/probable stent thrombosis
- Procedural success

*FAS= Full Analysis Set

Procedural Outcomes

	EluNIR N=958 patients, 1268 lesions	**Resolute** N=961 patients, 1268 lesions	***p* value**
Device Success	98.0%	99.4%	0.001
Lesion Success	99.9%	99.8%	0.99
Procedure Success	97.6%	97.3%	0.67

Device success: final in-stent residual QCA diameter stenosis of <50% using the assigned device only and without a device malfunction

Lesion success: final in-stent residual QCA diameter stenosis of <50% using any percutaneous method

Procedure success: final in-stent QCA diameter stenosis of <50% using the assigned device and/or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI, or repeat revascularization of the target lesion during the hospital stay

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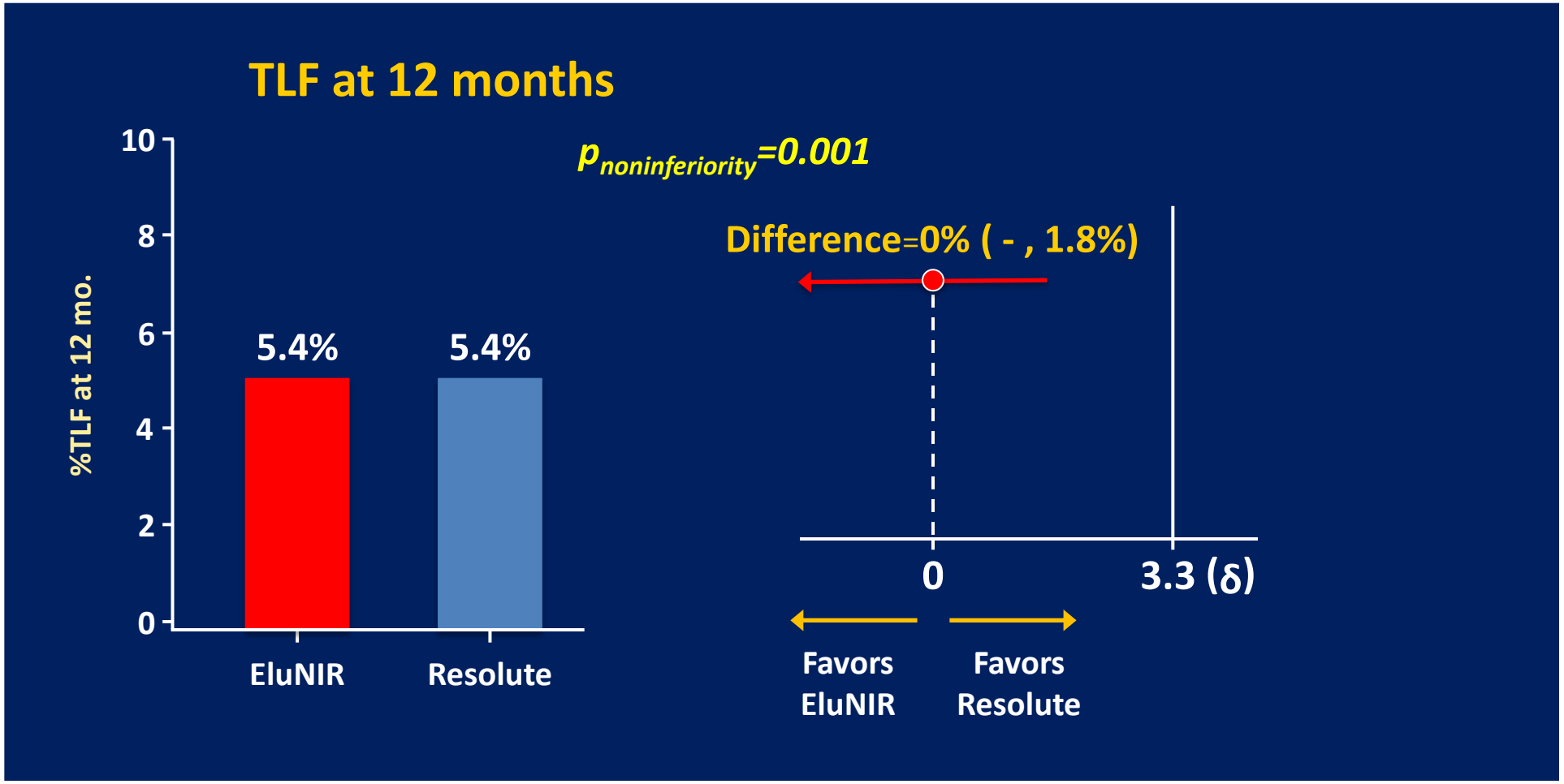
BIONICS
Primary Endpoint



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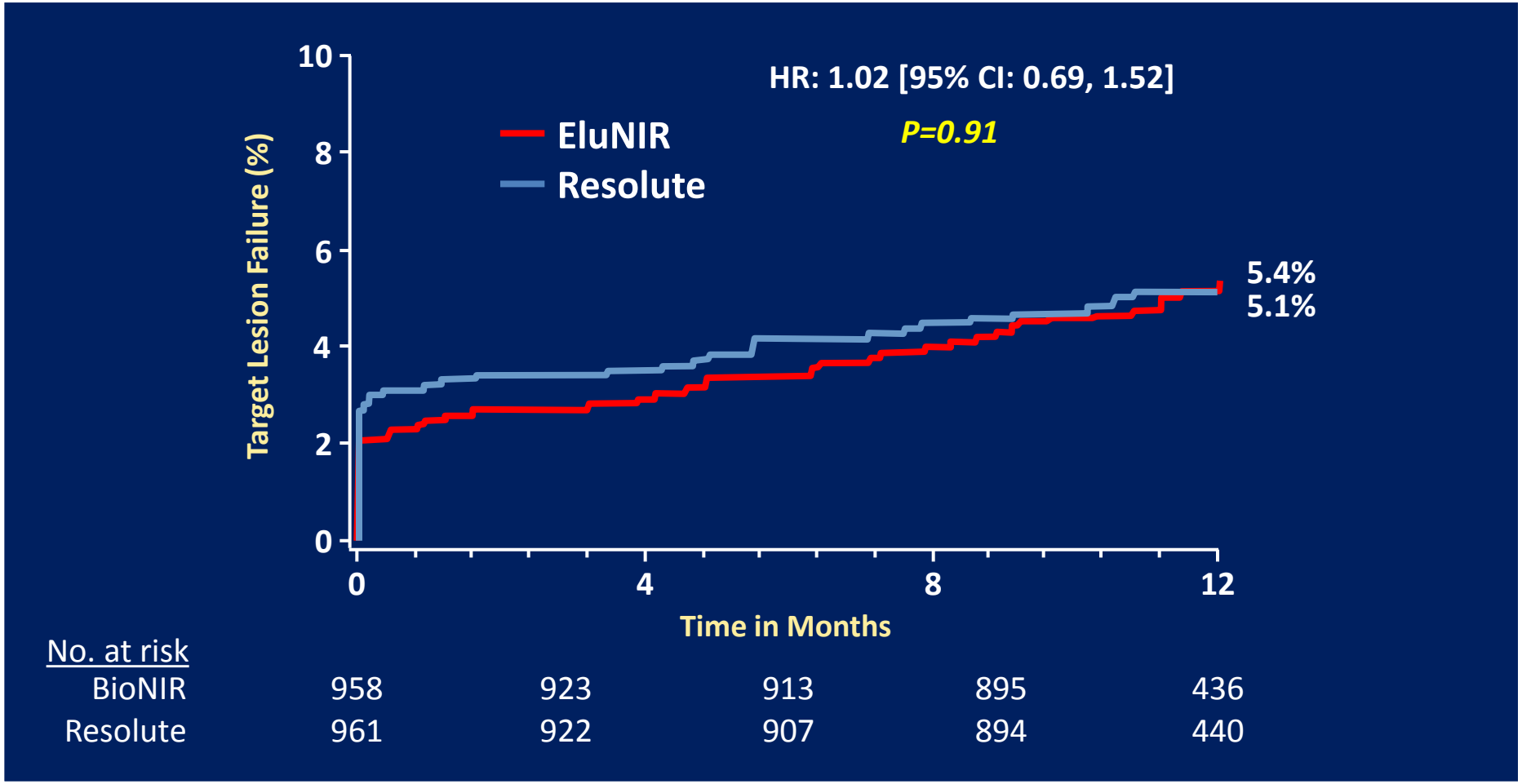
BIONICS
TLF to 12 Months: KM Curves



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BIONICS
Stent Thrombosis

	EluNIR (N=958)	Resolute (N=961)	*P* value
Stent Thrombosis			
Definite/Probable	0.4% (4/921)	0.6% (6/927)	0.53
Definite	0.4% (4/921)	0.5% (5/926)	0.74
Any Stent Thrombosis	0.4% (4/921)	0.8% (7/928)	0.37
Timing of Event			
Acute ST	0.1% (1/920)	0.1% (1/926)	0.99
Sub-Acute ST	0.3% (3/921)	0.3% (3/927)	0.99
Late	0.0% (0/920)	0.2% (2/927)	0.16

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12 Month DAPT Adherence: 75.1% BioNiR, 75.9% Resolute

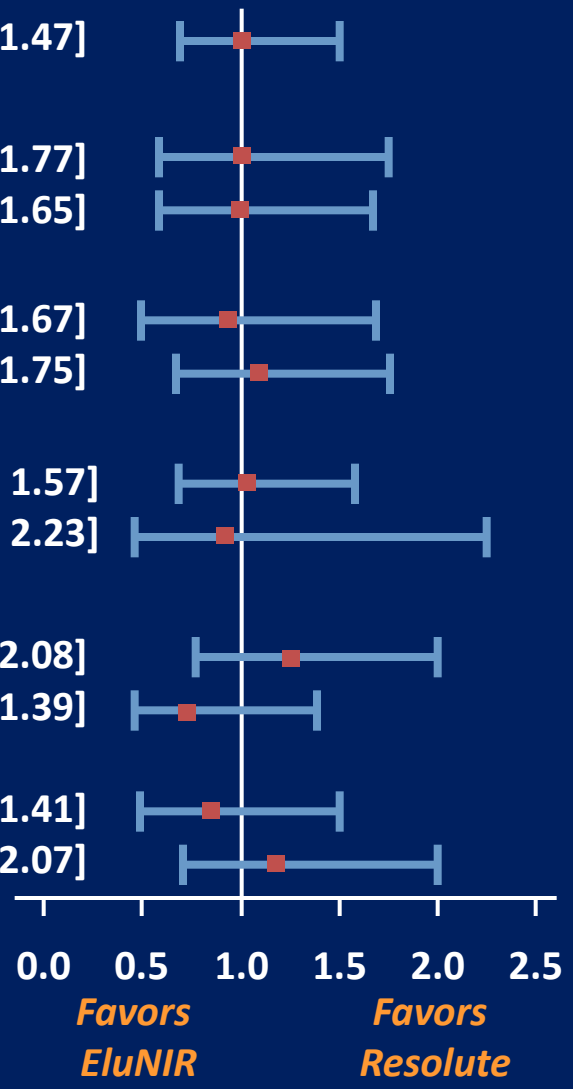
BIONICS
Angiographic and IVUS Outcomes

	Ridaforolimus-Eluting Stent (n=85 patients, 105 lesions)	Zotarolimus-Eluting Stent (n=73 patients, 96 lesions)	*P* value
Angiographic Results			
Late Lumen Loss (mm)			
In-Stent	0.22 ± 0.41	0.23 ± 0.39	0.85, 0.004 for noninferiority
In-Segment	0.17 ± 0.42	0.15 ± 0.38	0.58
Binary Restenosis			
In-Stent	8.9 (9/101)	7.5 (7/93)	0.73
In-Segment	10.7 (11/103)	7.5 (7/93)	0.43
IVUS Results			
Neointimal Hyperplasia (%)	8.1 ± 5.8	8.9 ± 7.8	0.95
Neointimal Volume (mm^3)	17.4 ± 21.8	17.2 ± 17.3	0.33
New Stent Malapposition (%)	3.7 (2/54)	0 (0/51)	0.50

IVUS was performed in 55 patients (61 lesions) in the Ridaforolimus group and in 56 patients (60 lesions) in the zotarolimus group
Kandzari et al. Circulation 2017

Target Lesion Failure at 1 Year by Subgroups

Subgroups	12-Month TLF Rate n/N (%)		Relative Risk [95% CI]	*P* value
	EluNIR	Resolute		
Overall	50/926 (5.4%)	50/930 (5.4%)	1.00 [0.69, 1.47]	
Medically Treated Diabetes				
Yes	22/277 (7.9%)	21/264 (7.9%)	1.00 [0.56, 1.77]	0.5
No	28/649 (4.3%)	29/666 (4.4%)	0.99 [0.60, 1.65]	
Acute Coronary Syndrome (ACS)				
ACS	19/380 (5.0%)	20/363 (5.5%)	0.91 [0.49, 1.67]	0.39
No ACS	31/546 (5.7%)	30/567 (5.3%)	1.07 [0.66, 1.75]	
Sex				
Male	40/725 (5.5%)	41/762 (5.4%)	1.03 [0.67, 1.57]	0.45
Female	10/201 (5.0%)	9/168 (5.4%)	0.93 [0.39, 2.23]	
Age				
>=65 Year	34/433 (7.9%)	27/441 (6.1%)	1.28 [0.79, 2.08]	0.16
<65 Year	16/493 (3.2%)	23/489 (4.7%)	0.69 [0.37, 1.39]	
Region				
North America	22/420 (5.2%)	26/402 (6.5%)	0.81 [0.47, 1.41]	0.23
Outside of N. Am.	28/506 (5.5%)	24/528 (4.5%)	1.22 [0.72, 2.07]	



Interaction p value: Gail-Simon test for qualitative interactions (interaction between the treatment and the subgroup variable)

November 28, 2017

Medinol, Ltd.
Marina Tikhonov-Demishtein
VP Regulatory Affairs
Kiryat Atidim, Bldg. 8
POB 58165
Tel Aviv 6158101, Israel

Re: P170008
Trade/Device Name: EluNIR™ Ridaforolimus Eluting Coronary Stent System
Filed: March 13, 2017
Amended: May 1, 2017; July 31, 2017; August 28, 2017; November 20, 2017
Product Code: NIQ

Dear Marina Tikhonov-Demishtein:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the EluNIR™ Ridaforolimus Eluting Coronary Stent System. This device is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo lesions ≤30mm in length in native coronary arteries with reference diameters of 2.50mm to 4.25mm. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

Disruption in US:

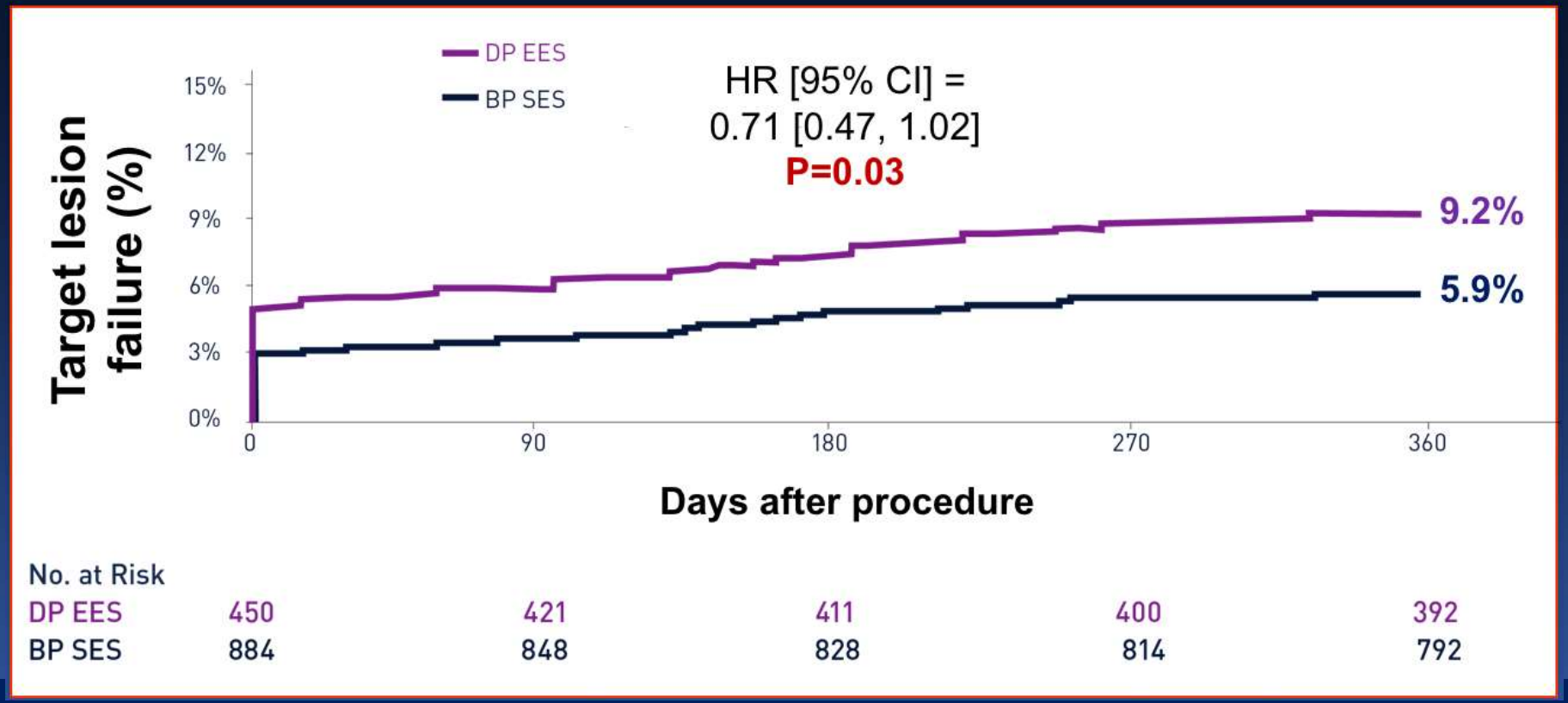
Same Clinical/Angiographic Outcomes at 1/2 or 1/3 of the Price !!

BIOFLOW V RCT (n=1334)

Orisiro 60 um CoCr bioabsorbable PLLA-based SES vs. Xience 82 um CoCr durable fluoropolymer-based EES

Primary Endpoint: Target Lesion Failure @ 1 Year

(2:1 randomization, powered for noninferiority)



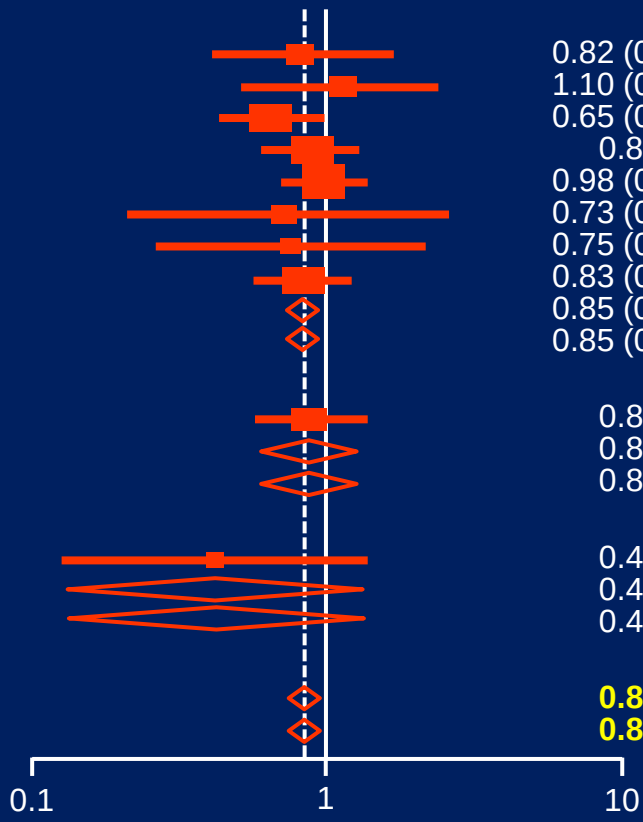
Kandzari DE et al. Lancet 2017;390:1843–52

Ultra-thin (<70 μm) vs. Thicker Strut 2nd Gen DES

10 RCTs, 11,658 pts, 3 ultra-thin strut DES:
Orsiro (60 μm), MiStent (64 μm) and BioMime (65 μm)

1-Year Target Lesion Failure

Study	Ultra-thin Events	Ultra-thin N	2nd Generation Events	2nd Generation N	RR (95% CI)	% Weight (D+L)
Orsiro						
BIOFLOW II	19	298	12	154	0.82 (0.40, 1.69)	4.83
BIOFLOW IV	20	354	9	176	1.10 (0.50, 2.43)	4.08
BIOFLOW V	52	884	41	450	0.65 (0.43, 0.97)	15.07
BIORESORT	47	1169	53	1173	0.89 (0.60, 1.32)	16.37
BIOSCIENCE	69	1063	70	1056	0.98 (0.70, 1.37)	22.84
ORIENT	6	250	4	122	0.73 (0.21, 2.59)	1.58
PRISON IV	6	165	8	165	0.75 (0.26, 2.16)	2.25
SORT OUT VII	48	1261	58	1264	0.83 (0.57, 1.22)	17.26
D+L Subtotal (I-squared = 0.0%, *p*=0.881)					0.85 (0.71, 1.01)	84.29
I-V Subtotal					0.85 (0.71, 1.01)	
MiStent						
DESSOLVE-III	40	703	45	695	0.88 (0.57, 1.35)	13.92
D+L Subtotal (I-squared = NA, *p* = NA)					0.88 (0.57, 1.35)	13.92
I-V Subtotal					0.88 (0.57, 1.35)	
BioMime						
Merit-V	5	170	6	86	0.42 (0.13, 1.38)	1.79
D+L Subtotal (I-squared = NA, p = NA)					0.42 (0.13, 1.38)	1.79
I-V Subtotal					0.42 (0.13, 1.38)	
All Stents						
D+L Subtotal (I^2 = 0.0%, *p* = 0.88)					**0.84 (0.72, 0.99)**	100.00
I-V Subtotal					**0.84 (0.72, 0.99)**	



Driven by less TV-MI with no differences in CD or ID-TLR

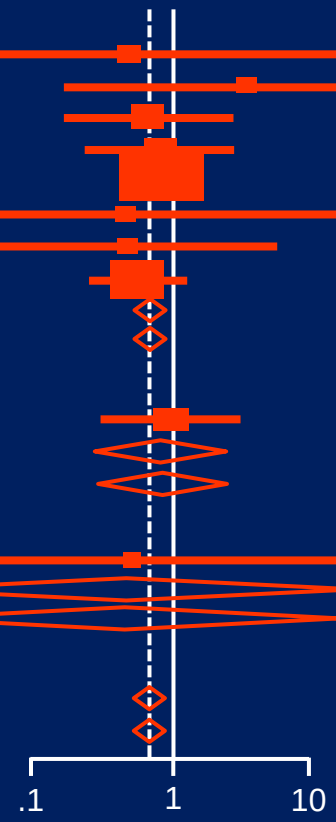
Bangalore S and Stone GW, submitted

Ultra-thin (<70 μm) vs. Thicker Strut 2nd Gen DES

10 RCTs, 11,658 pts, 3 ultra-thin strut DES:
Orsiro (60 μm), MiStent (64 μm) and BioMime (65 μm)

1-Year Stent Thrombosis (def/prob)

Study	Ultra-thin Events	Ultra-thin N	2nd Generation Events	2nd Generation N	RR (95% CI)	% Weight (D+L)
Orsiro						
BIOFLOW II	0	298	0	154	0.52 (0.01, 26.04)	0.78
BIOFLOW IV	3	354	0	176	3.48(0.18, 67.38)	1.37
BIOFLOW V	4	884	3	450	0.68 (0.15, 3.03)	5.36
BIORESORT	5	1169	6	1173	0.84 (0.26, 2.74)	8.53
BIOSCIENCE	29	1063	35	1056	0.82 (0.50, 1.35)	49.59
ORIENT	0	250	0	122	0.49 (0.01, 24.59)	0.78
PRISON IV	1	165	2	165	0.50 (0.05, 5.51)	2.08
SORT OUT VII	11	1261	20	1264	0.55 (0.26, 1.15)	22.19
D+L Subtotal (I-squared = 0.0%, *p*=0.956)					0.74 (0.51, 1.07)	90.69
I-V Subtotal					0.74 (0.51, 1.07)	
MiStent						
DESSOLVE-III	5	703	6	695	0.82 (0.25, 2.70)	8.53
D+L Subtotal (I-squared = NA, *p* = NA)					0.82 (0.25, 2.70)	8.53
I-V Subtotal					0.82 (0.25, 2.70)	
BioMime						
Merit-V	0	170	0	86	0.51 (0.01, 25.49)	1.79
D+L Subtotal (I-squared = NA, *p* = NA)					0.51 (0.01, 25.49)	1.79
I-V Subtotal					0.51 (0.01, 25.49)	
All Stents						
D+L Subtotal (I^2 = 0.0%, *p* = 0.99)					**0.74 (0.53, 1.05)**	100.00
I-V Subtotal					**0.74 (0.53, 1.05)**	

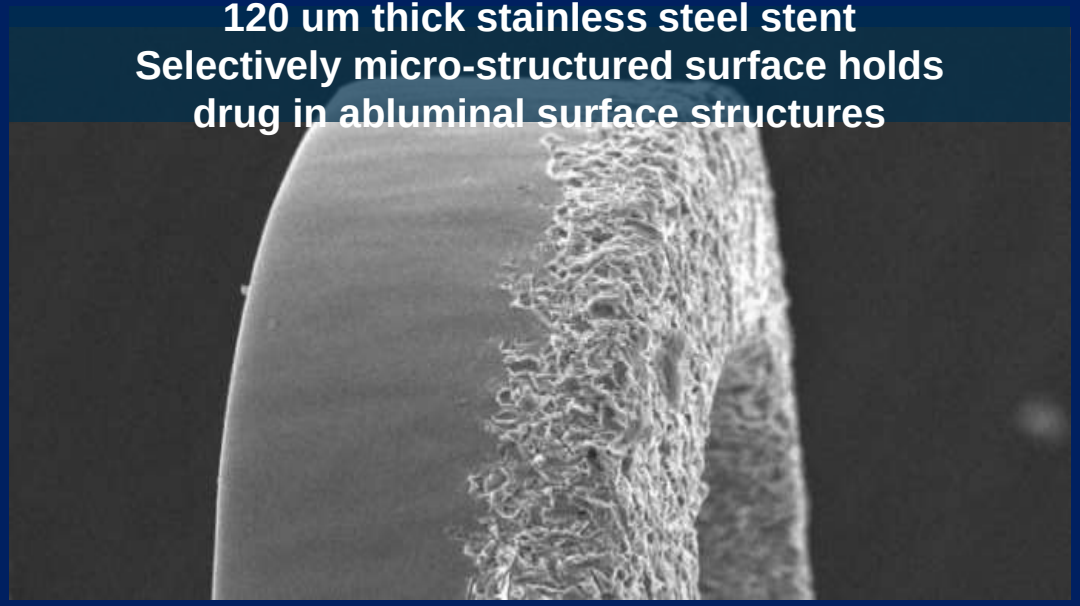


Bangalore S and Stone GW, submitted

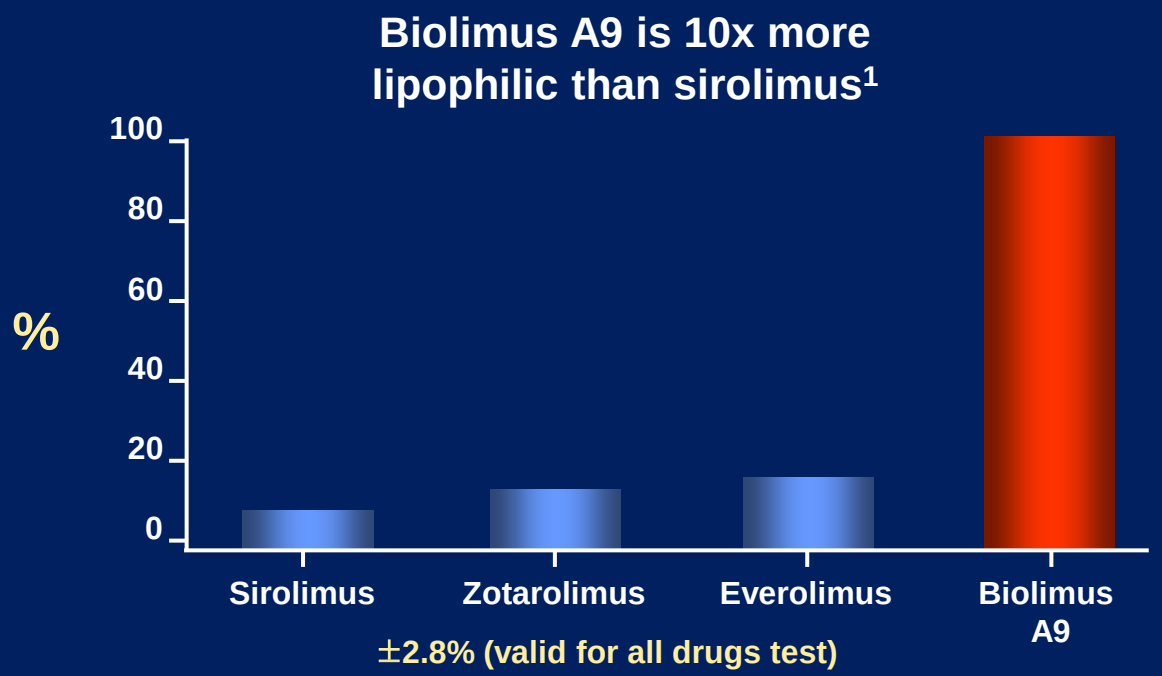
Disruption :

How thin can we go without losing radial strength and radio-opacity?

BioFreedom Drug Coated Stent (DCS)



12 mo in-stent LL ~0.17 mm (n=31)

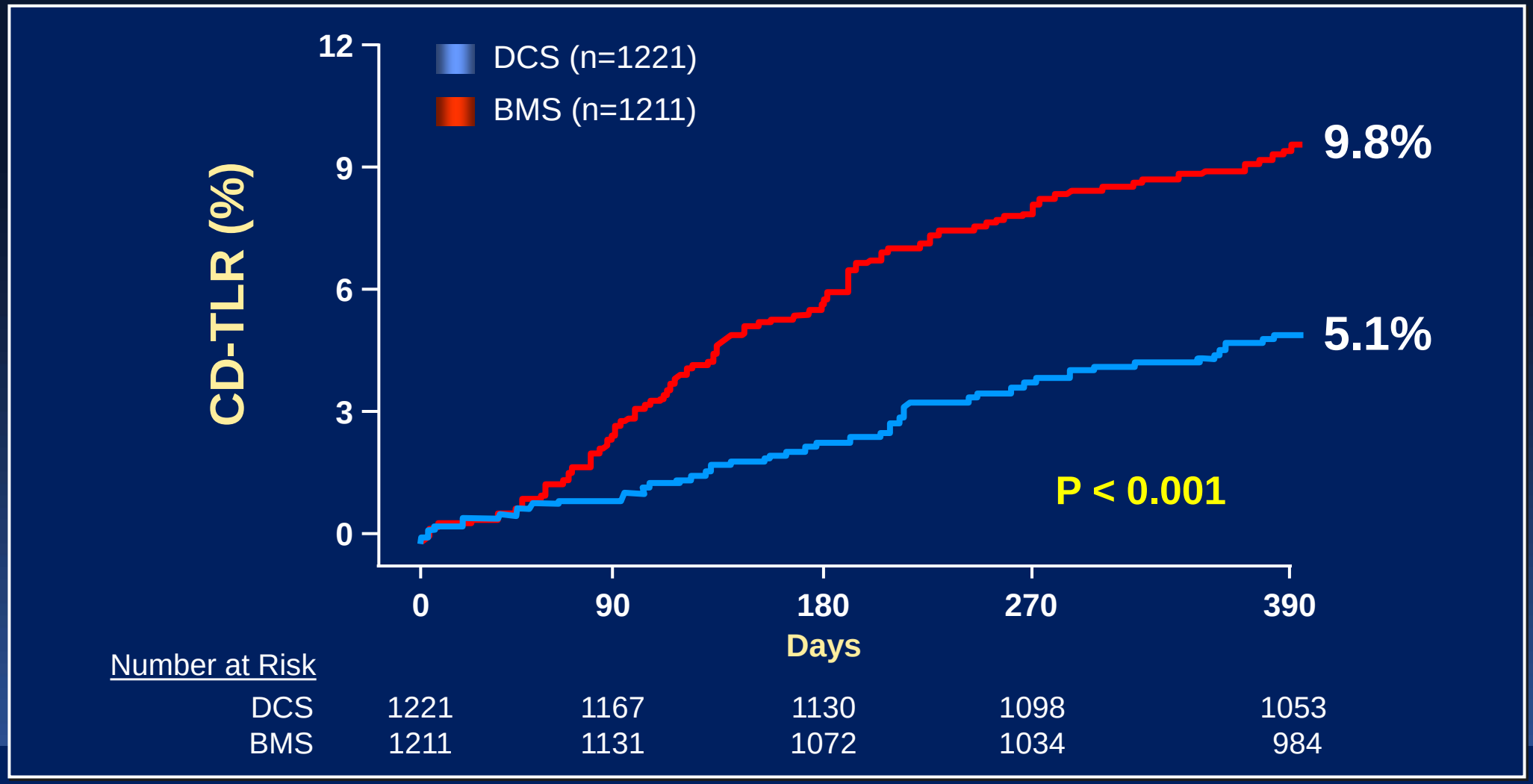


Potential Advantages:

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

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

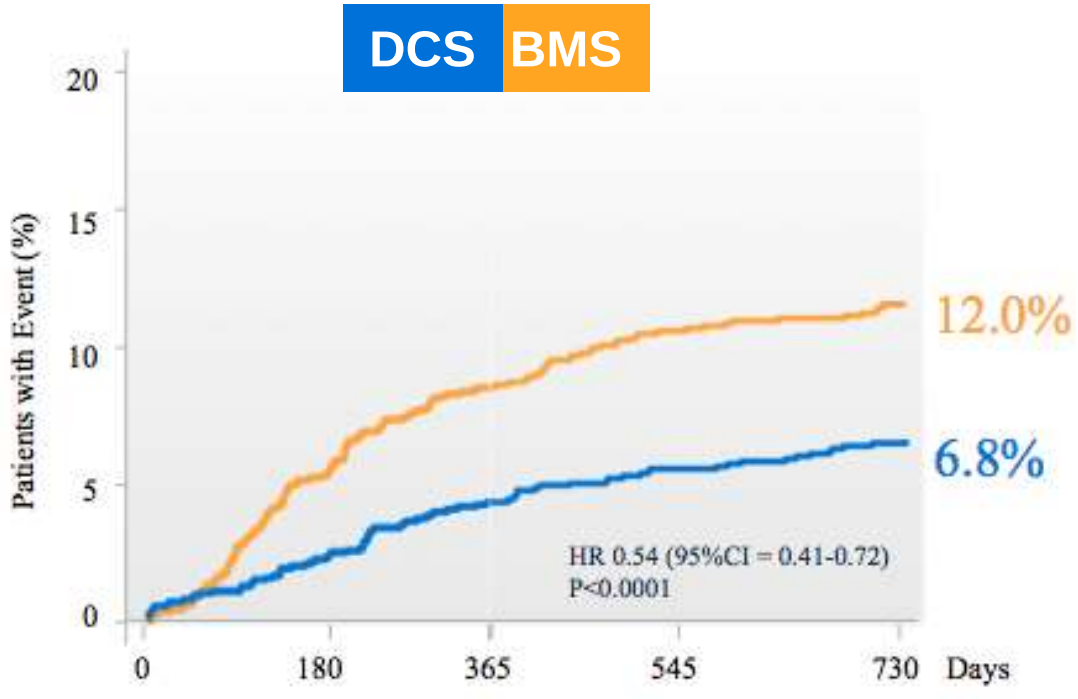
Leaders Free: Primary Efficacy Endpoint (Clinically-Driven TLR)



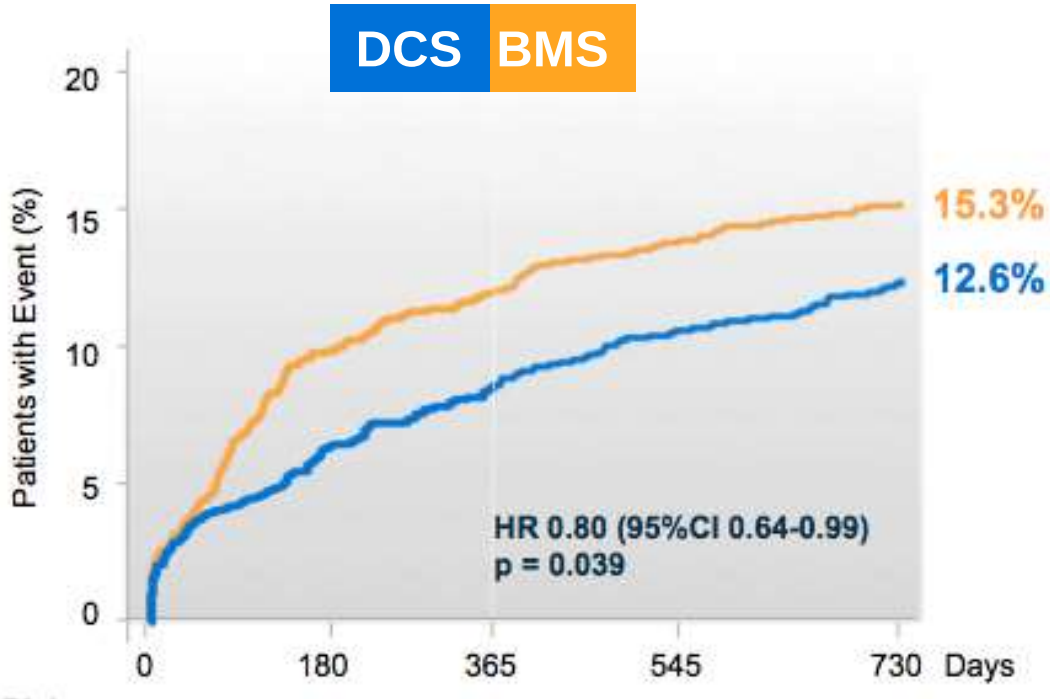
Urban P et al. *NEJM* 2015;373:2038-47

Efficacy and Safety Endpoints at 2 Year

Efficacy (cd-TLR)



Safety (cardiac death, MI, ST)



2 year FU was obtained at 730 days ± 60 days

Garot P et al. J Am Coll Cardiol 2017;69:162–71

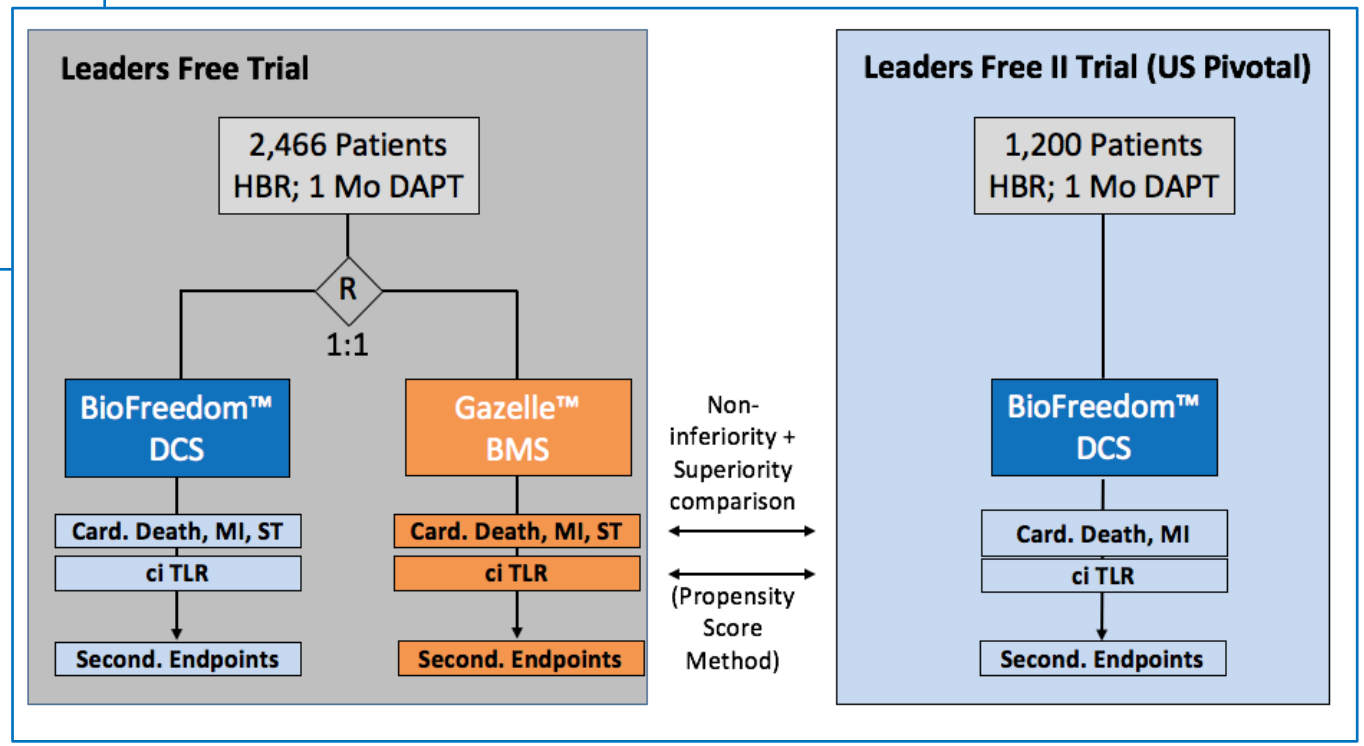
LEADERS FREE II US Pivotal Trial

LEADERS FREE II



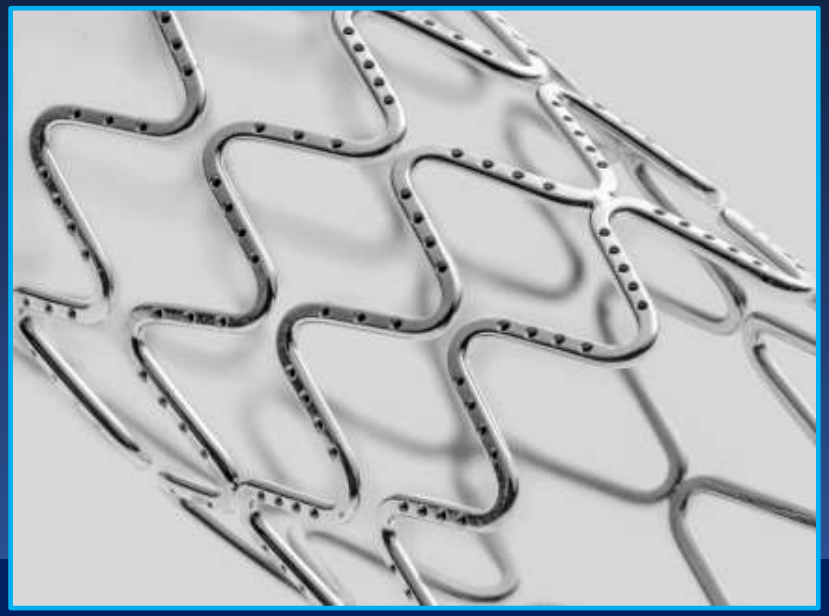
- Chairman: Dr. Marty Leon, CRF, NY
- PI: Dr. Mitch Krucoff, Duke, Durham, NC
- EU co-PI: Dr. Philip Urban, Geneva, Switzerland

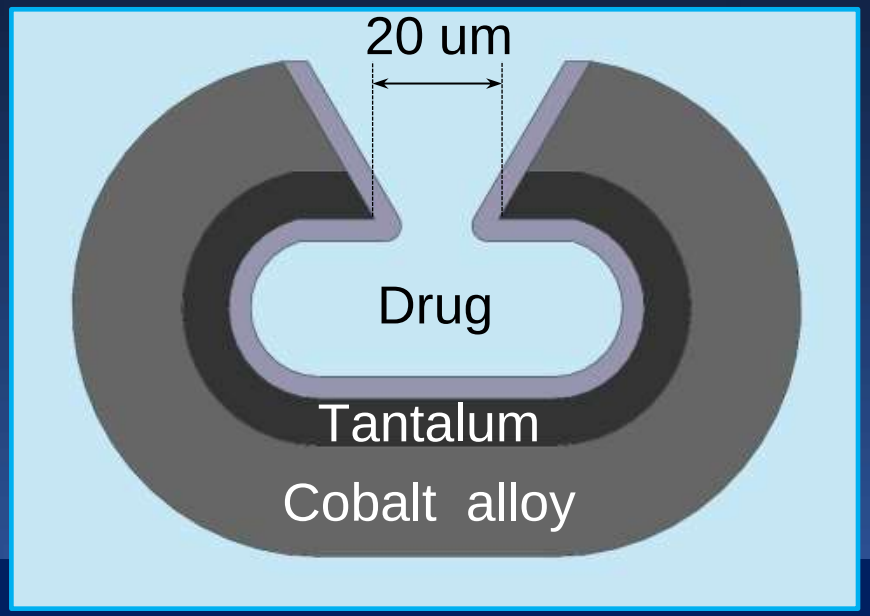
- Statistics: Stuart Pocock, School of Hygiene, London
- Project Management: Corie Diaz, Syntactx, NY
- Monitoring, CEC, Angio Corelab: CERC, Paris, Fr
- Data Management: Duke University, Durham, NC
- DSMB, Statistics: Cardiovascular Research Foundation, NY
- Sponsor: Biosensors Research, USA



Drug-Filled Stent: Concept

- DFS is made from a polymer-free tri-layer wire
  - Outer cobalt alloy layer for strength
  - Middle tantalum layer for radiopacity
  - Inner layer core material is removed and becomes a lumen that is filled with drug (sirolimus)





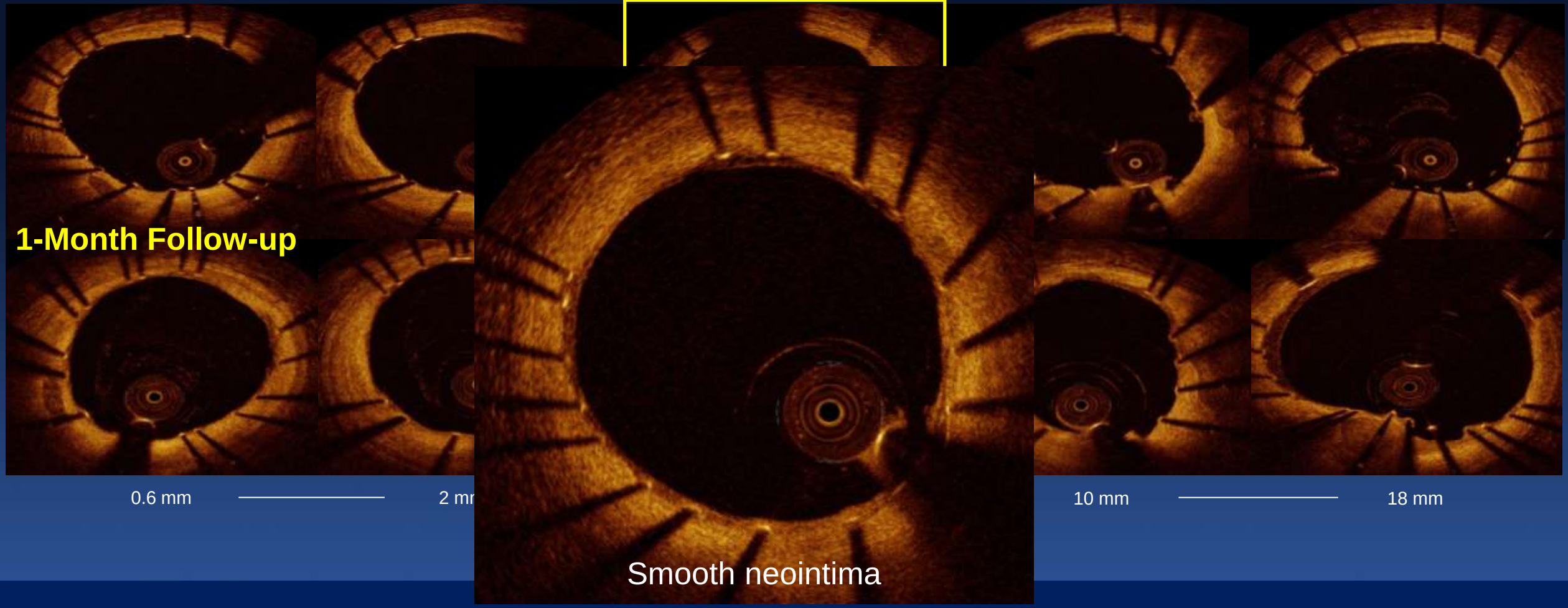
RevElution
Case 20001-002

Age (years)	65
Gender	M
Diabetes	Y
Hypertension	Y

Diameter stenosis (%)	75
RVD (mm)	3.5
Lesion length (mm)	10
Pre-dilatation performed	Y
Stents implanted (n)	1

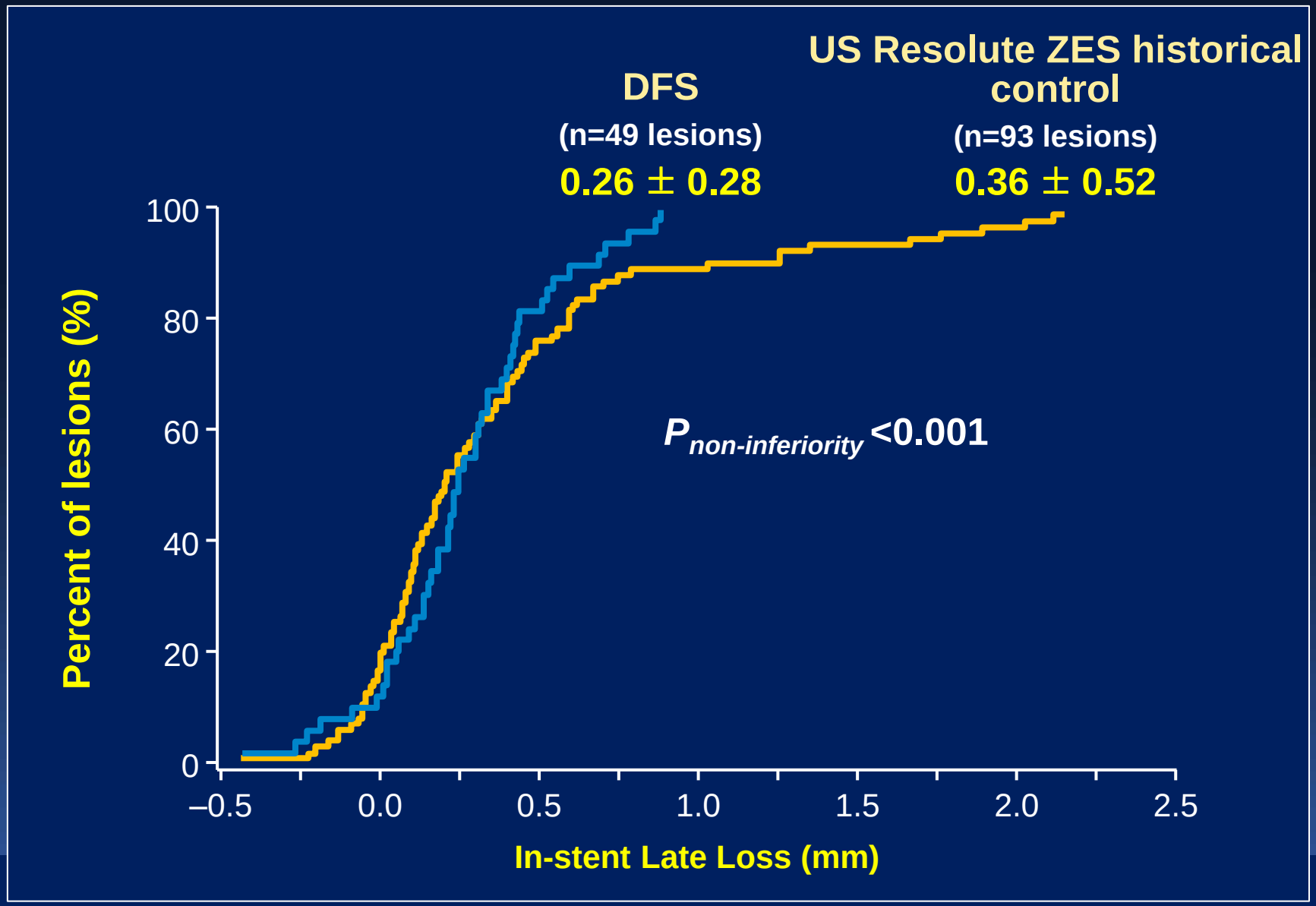
Post-Procedure

1-Month Follow-up



c/o Steve Worthley

RevElution: In-stent Late Loss at 9 Mo



Worthley S et al. JACC Int 2017:on-line

Potential Disruption :

BP or no polymer at all:
what is the clinical advantage beyond HBR?

Key Attributes of the DynamX BA-DES

Proven
Cobalt
Chromium Alloy
DESyne/
DESyne BD

Strut
Thickness
71µm

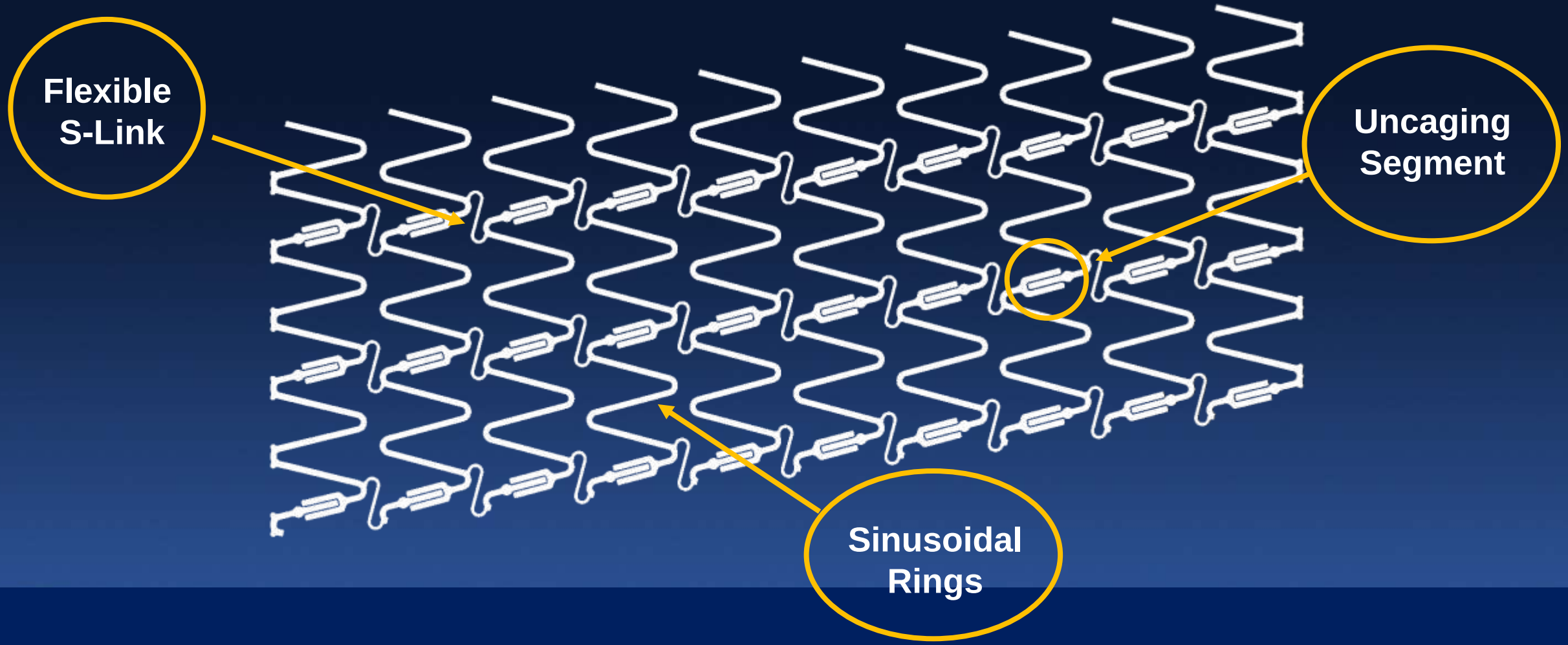
Proven
Conformal (3µm)
PLGA
Bioresorbable
Polymer Top coat
DESyne BD/
DESolve

Proven
Drug and Dose
Novolimus, 5µg/mm
DESyne/
DESyne BD/
DESolve

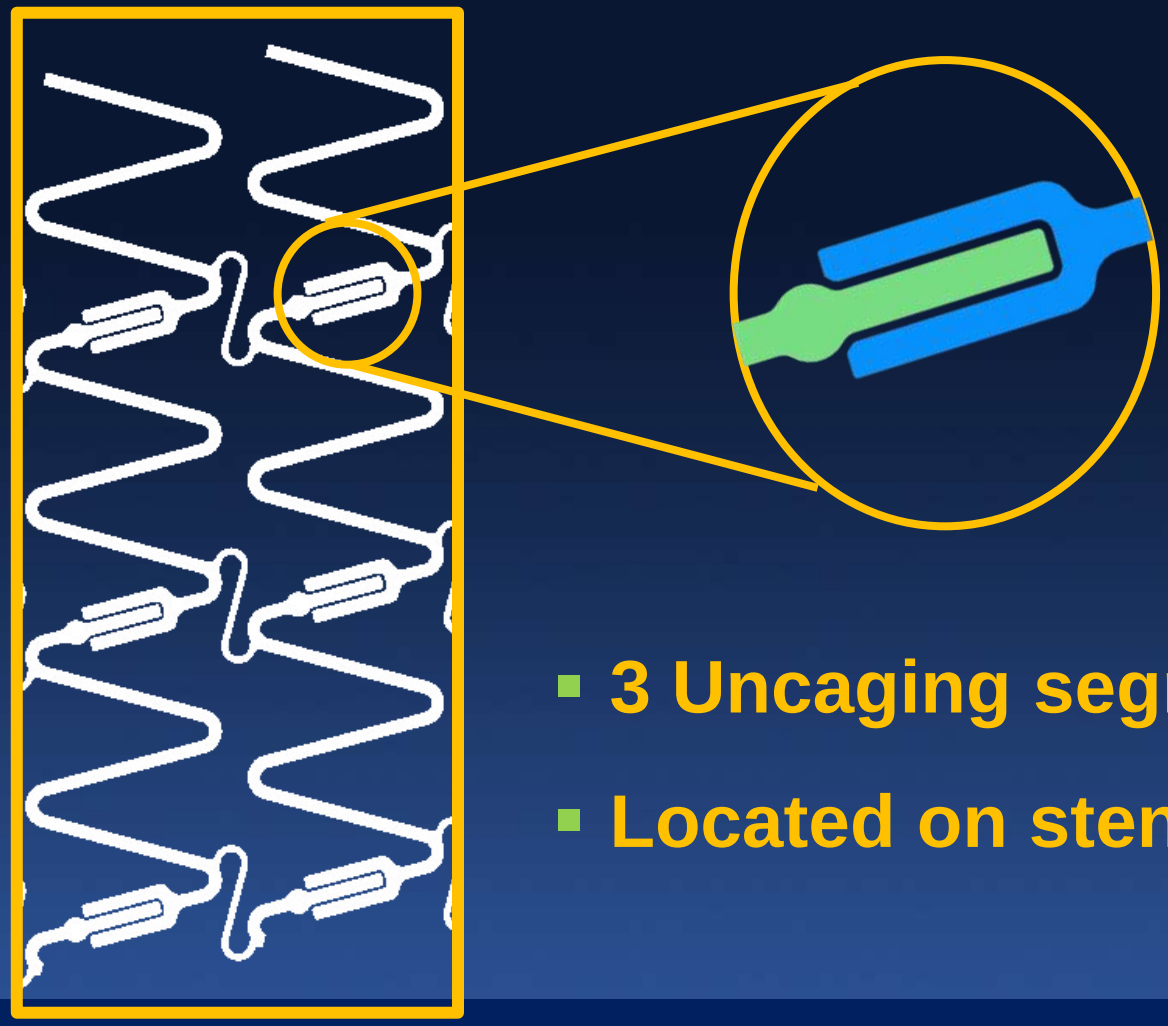
Drug elutes in 3M;
Polymer degrades
in 6M

Proven
Conformal (6µm)
PLLA-based
Bioresorbable
Polymer Base coat
DESolve

DynamX is designed to match DES acute performance

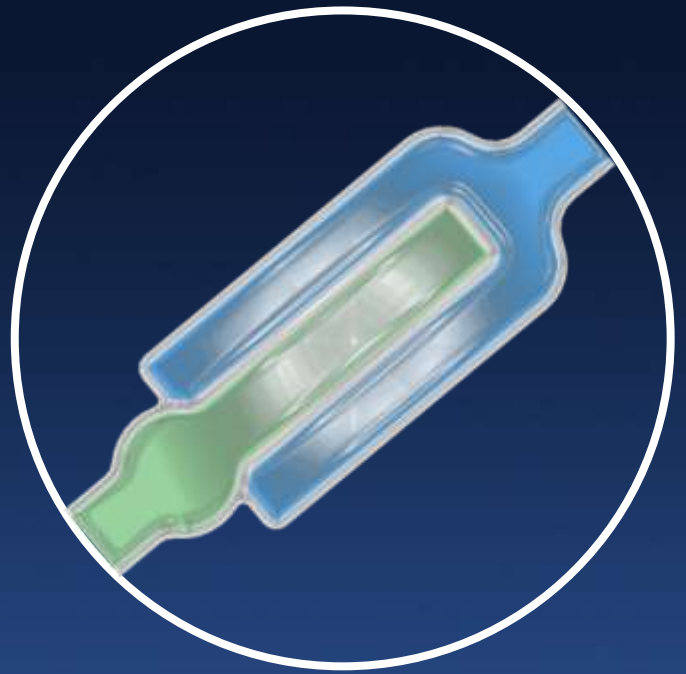


DynamX is uniquely designed with “uncaging” segments



- 3 Uncaging segments per ring
- Located on stent struts (low stress areas)

DynamX uncaging elements are bonded together with bioresorbable polymeric (BP) material



Bonded

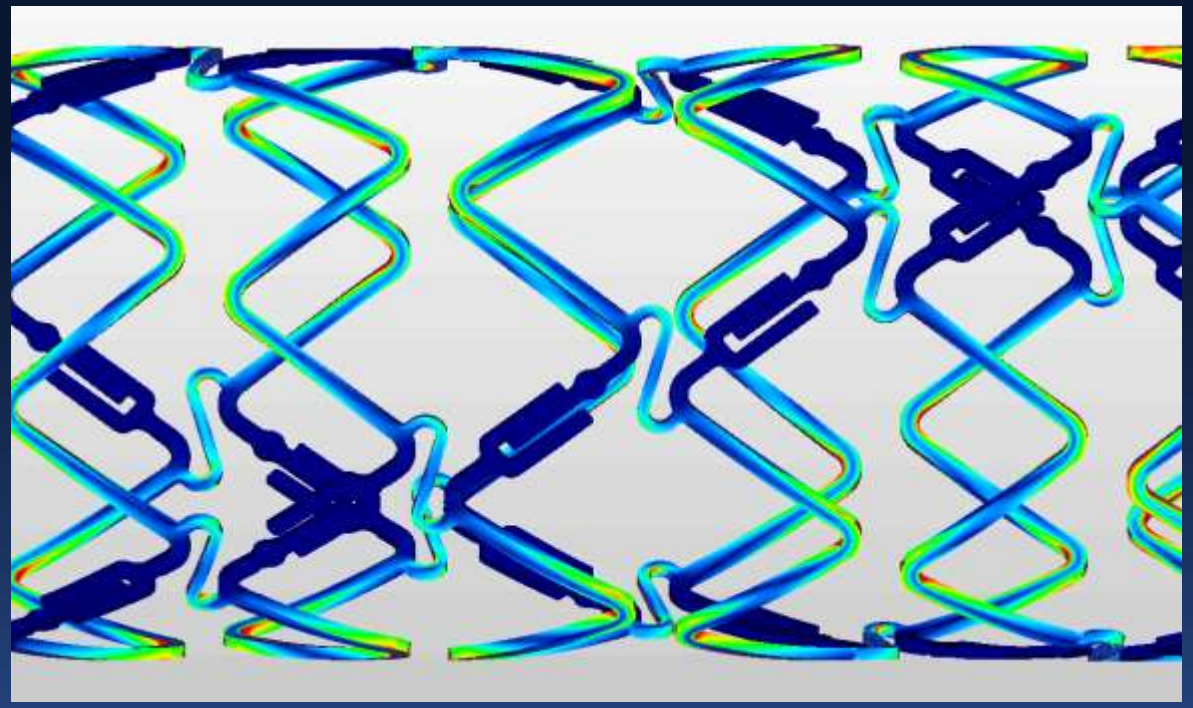
- *Uncaging elements are bonded by a conformal 6µ thick PLLA-based base coat and a conformal 3µ thick PLGA top coat*
- *The uncaging elements are designed to remain intact through expansion/over expansion for approximately 6 months until biopolymer resorption*
- *The stent design maintains radial strength and crush resistance for at least 6 months - similar to current generation DES*

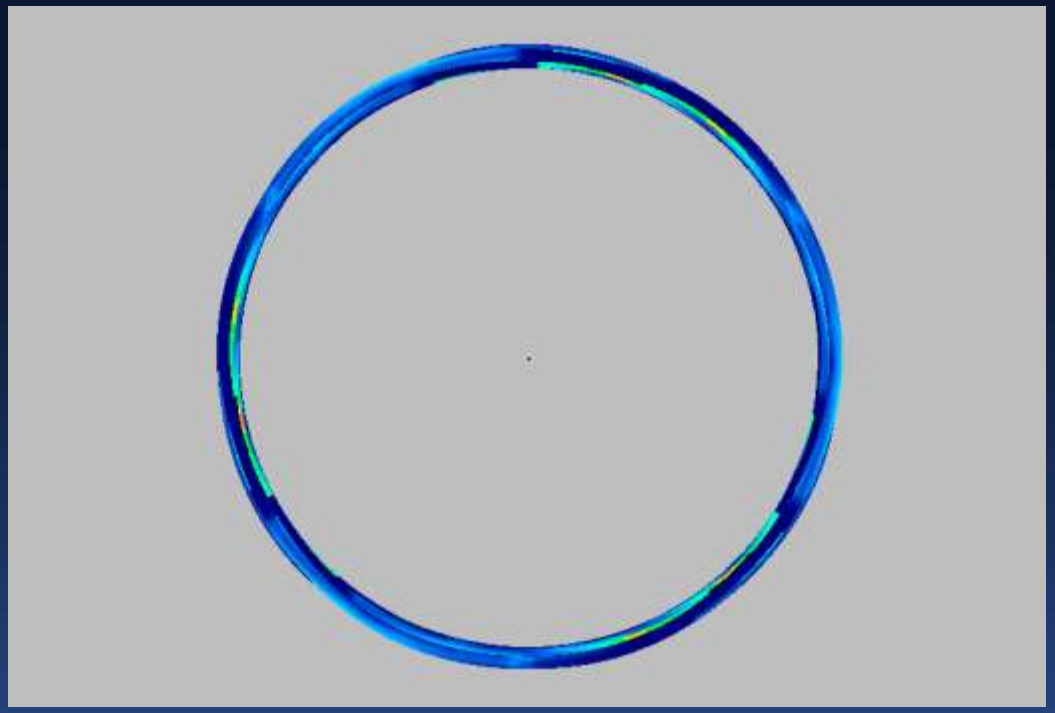
DynamX uncaging elements are bonded together with bioresorbable polymeric (BP) material

Uncaged

- *Uncaging elements are bonded by a conformal 6μ thick PLLA-based base coat and a conformal 3μ thick PLGA top coat*
- *The uncaging elements are designed to remain intact through expansion/over expansion for approximately 6 months until biopolymer resorption*
- *The stent design maintains radial strength and crush resistance for at least 6 months - similar to current generation DES*

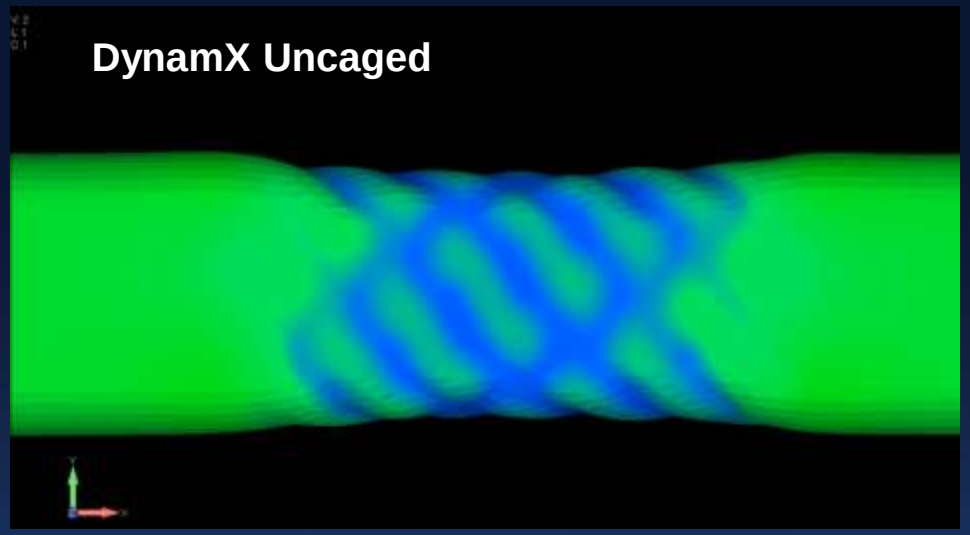
DynamX Allows the Vessel to Resume Normal Pulsatile Motion

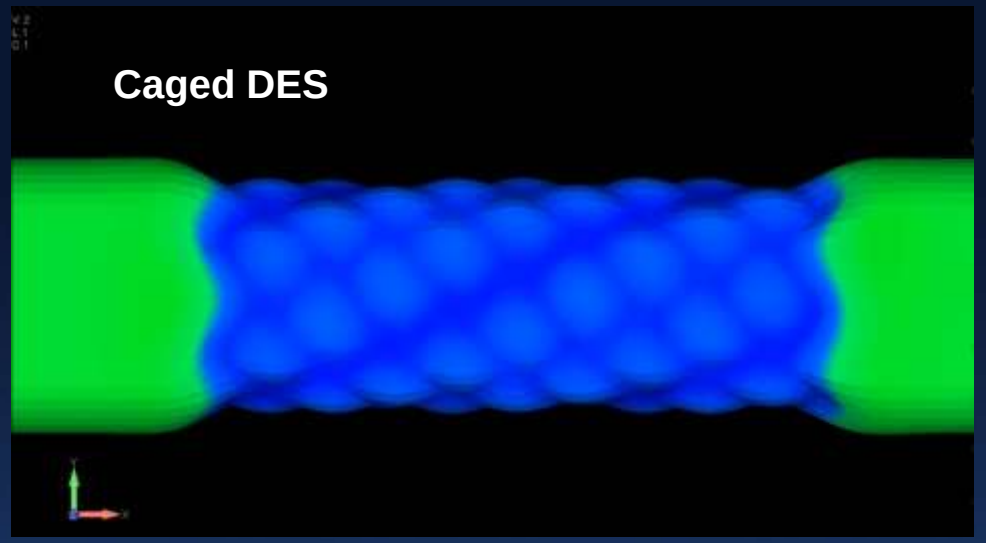




DynamX expands radially in synchrony with vessel pulsatility

DynamX Compliance > 2nd Gen DES

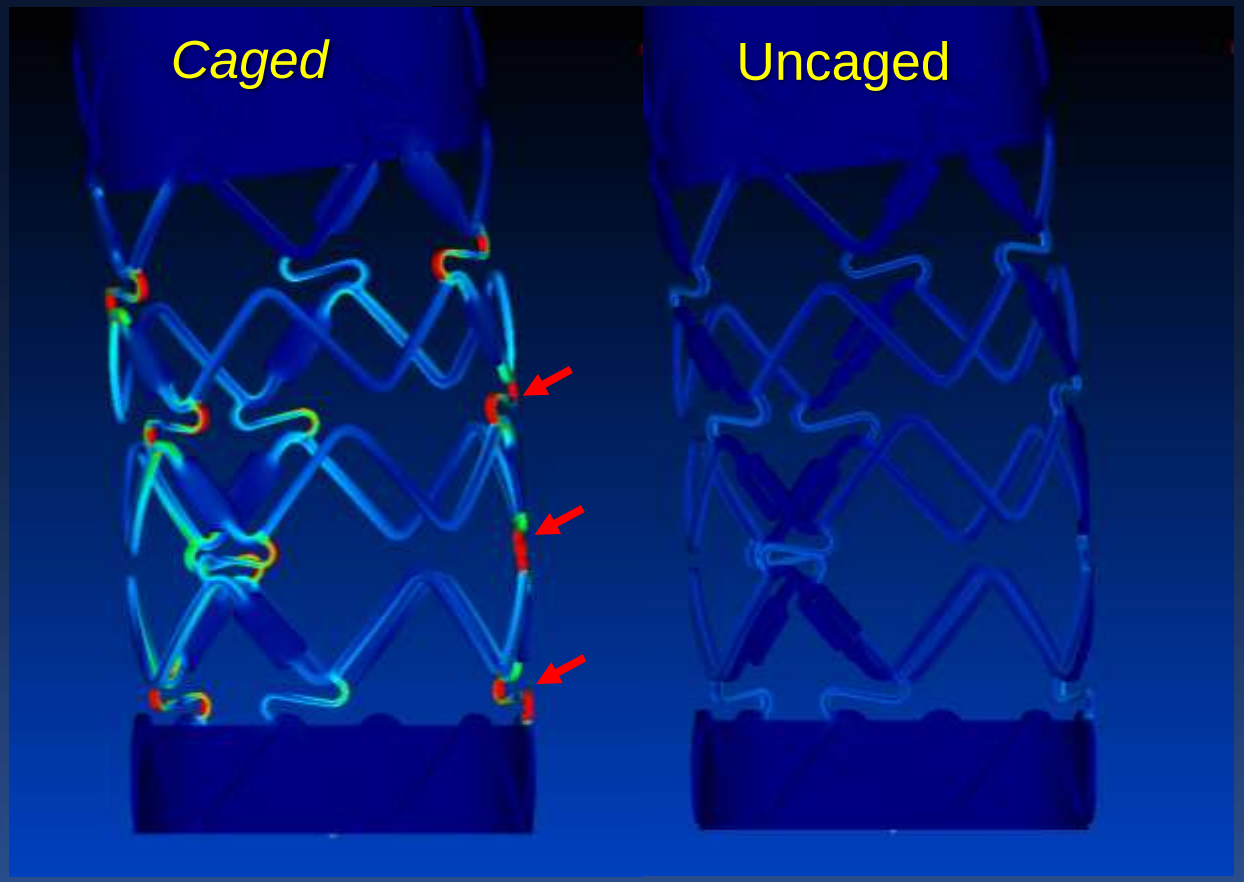




- More green = greater compliance
- DynamX stent has 10X the compliance of a caged DES

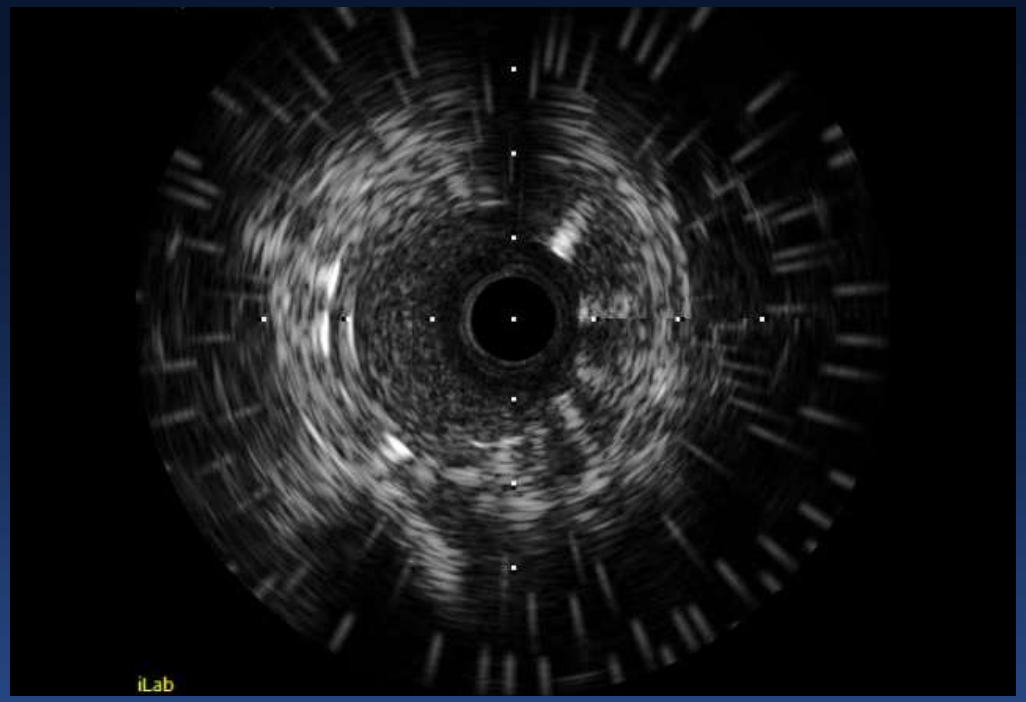
DynamX Improves Fracture Resistance

DynamX ***90% reduction in maximum tensile stress*** reduces probability of geometric distortion and/or fracture

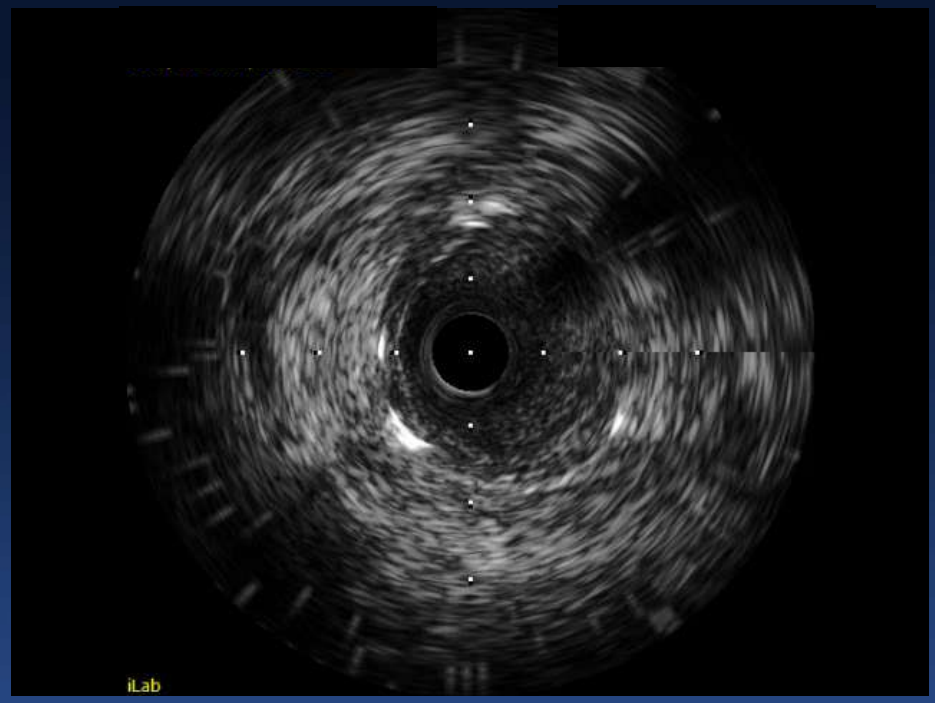


DynamX Restores Pulsatile Vessel Motion

DynamX stent in porcine coronary - IVUS imaging @ 60 days

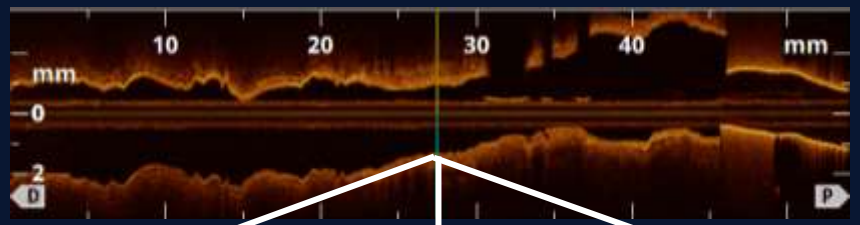


DES stented coronary

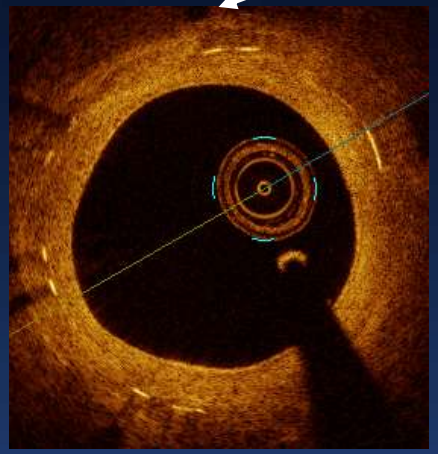


DynamX stented coronary

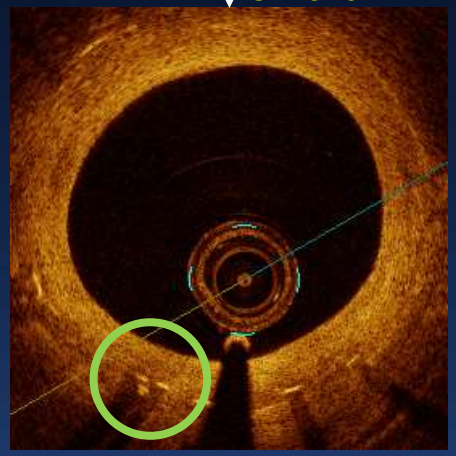
DynamX Shows Adaptive Remodeling



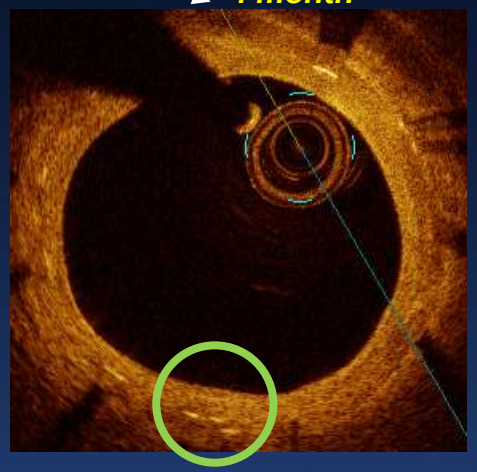
2 month



3 month



4 month



Parameter*	2 month	3 month	4 month
Stent Area (mm^2)	7.20	8.19	8.30
Lumen Area (mm^2)	4.60	5.73	5.95
NIH area (mm^2)	2.60	2.45	2.35

Preclinical Studies conducted at Accel LAB, Montreal, Canada

DynamX Stent Study

Single de novo Coronary Artery Lesions
Ref diam: 2.5-3.5mm, Lesion length: <14mm
3.0, 3.5mm diam; 14, 18mm lengths

10 Sites, Belgium and Italy
50 patients

Study Design: **Non-randomized, consecutive enrolment into two subsets : A and B with either 6 or 9 month clinical and imaging follow-up**

Principal Endpoints:

- **Clinical:** **Target lesion failure; stent thrombosis at 6 months and 9m (subset B), 1–3 yrs**
- **QCA:** **In-stent late lumen loss, MLD, % DS at baseline and follow-up**
- **IVUS:** **Mean and min lumen, stent and vessel areas (post –procedure to FU); pulsatile motion analysis; malapposition**

Potential Disruption :

DES with BRS benefits