Focusing on the Clinical Importance of Conformability

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Disclosure Statement of Financial Interest

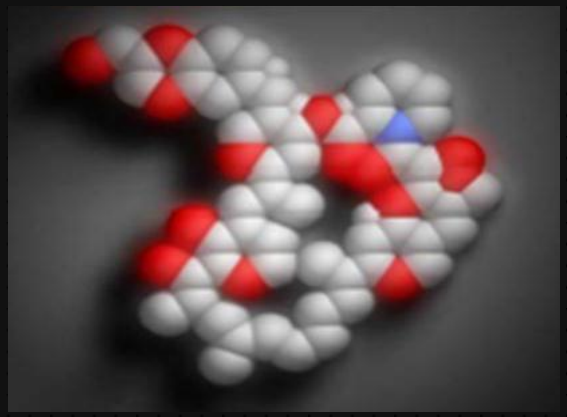
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Volcano • Medtronic Vascular • Abbott Vascular • Boston Scientific
• Consulting Fees/Honoraria	• Biotronik • Medtronic • Abbott Vascular • Boston Scientific • Lilly Daiichi • Astra Zeneca

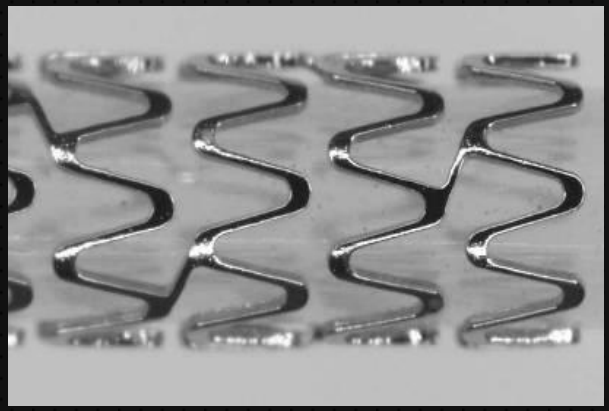
DES design affects procedural success and clinical outcomes

Elements of DES Design

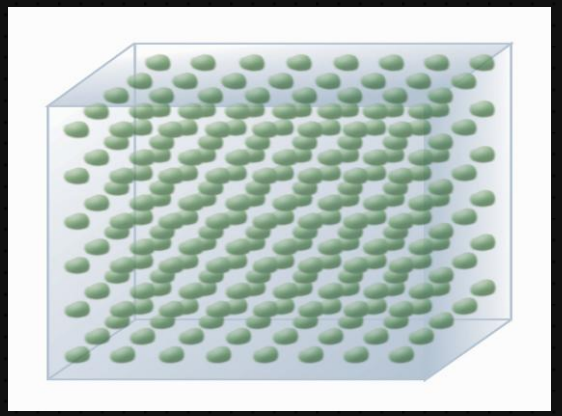
Drug



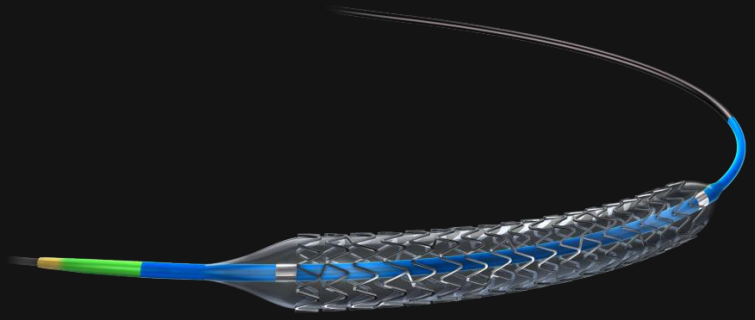
Scaffold



Polymer

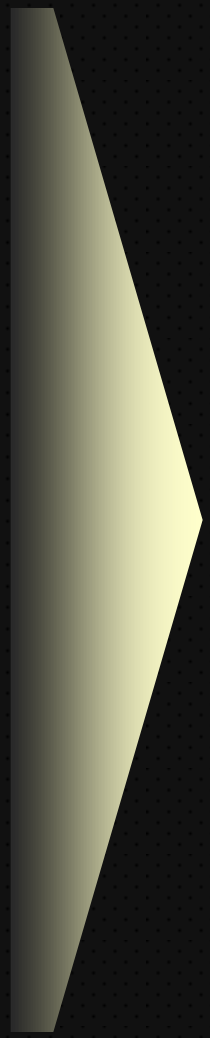


Delivery System



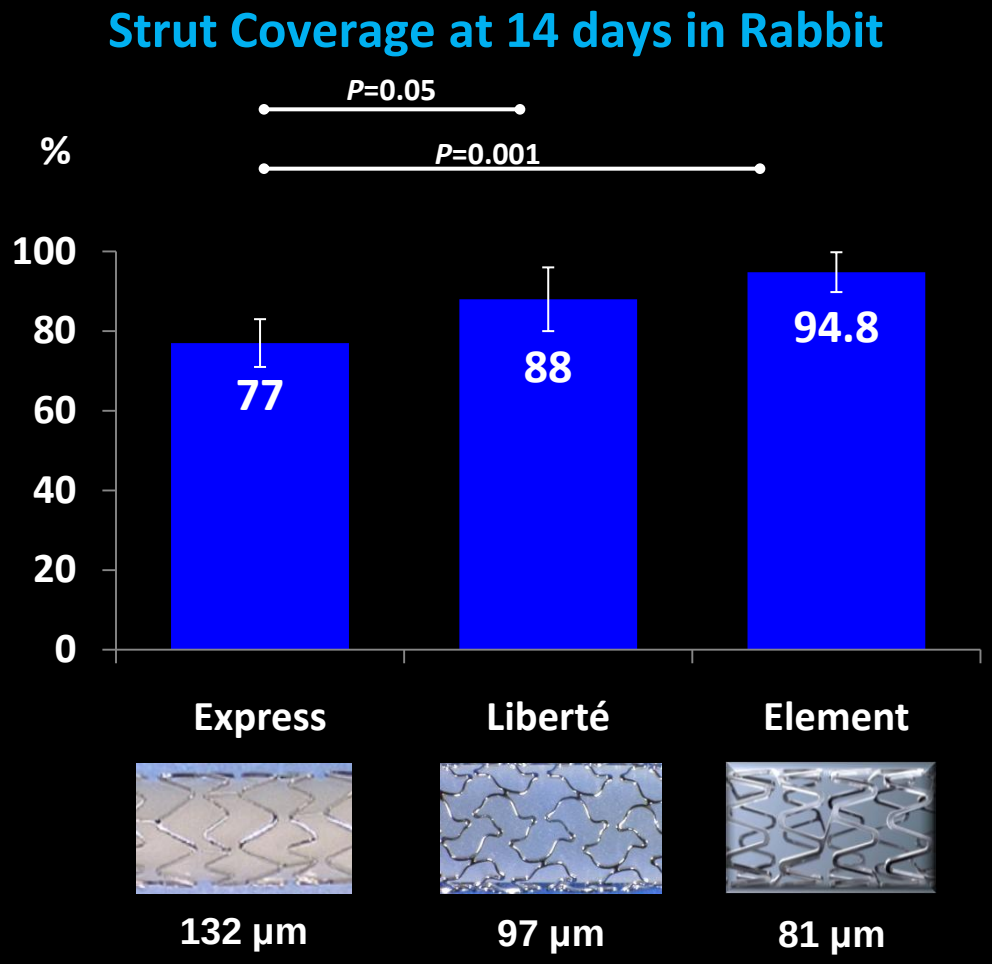
The Value of Thin Stent Struts

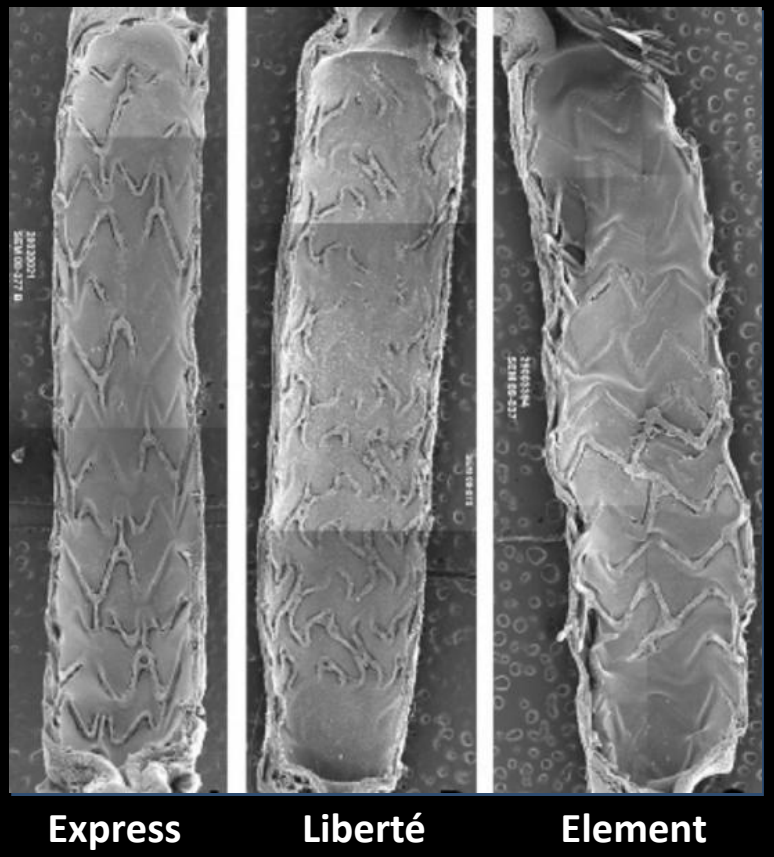
- PreClinical Models have demonstrated



- Reduced acute injury
- Reduced inflammation
- Rapid incorporation of struts within neointima
- Rapid re-endothelialization

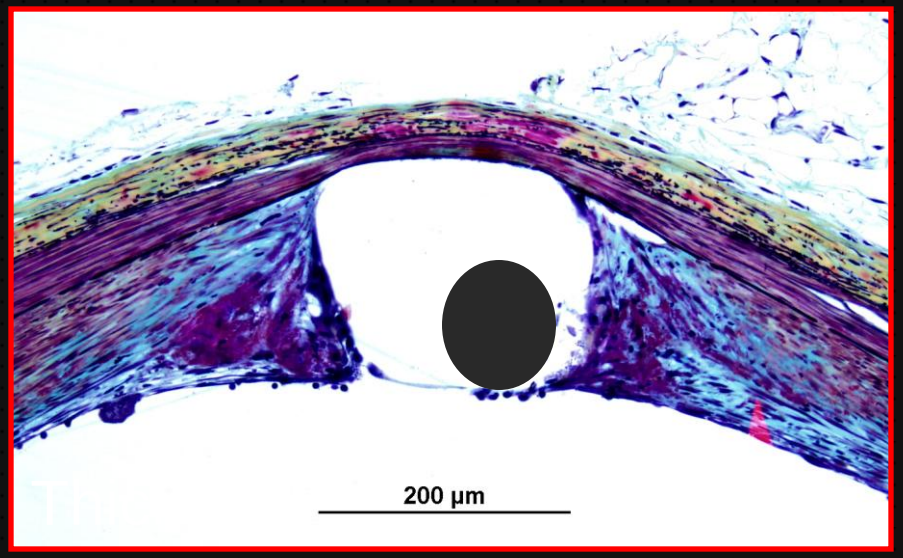
Impact of Strut Thickness on Vascular Healing and Neointimal Formation in BMS

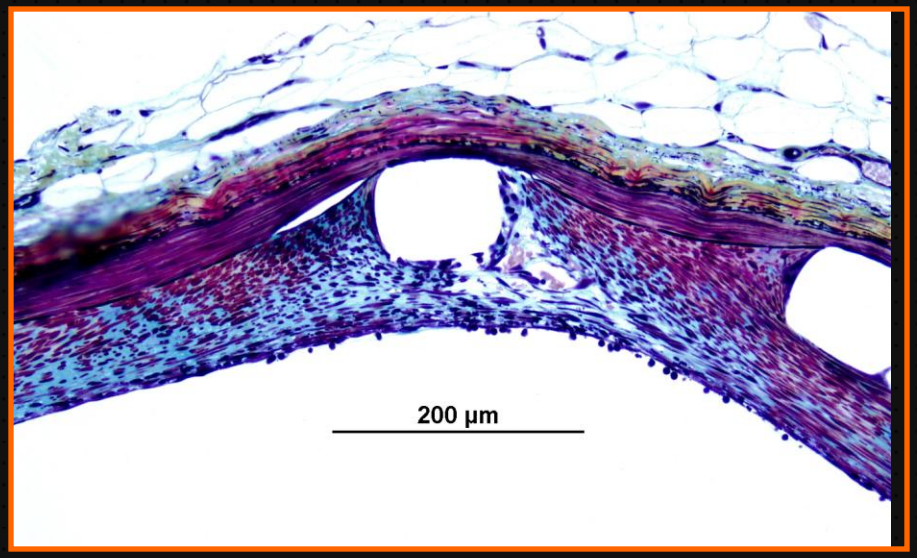


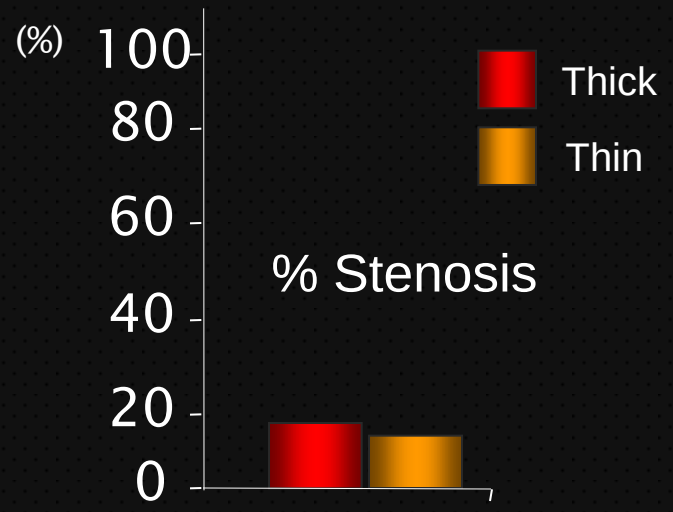


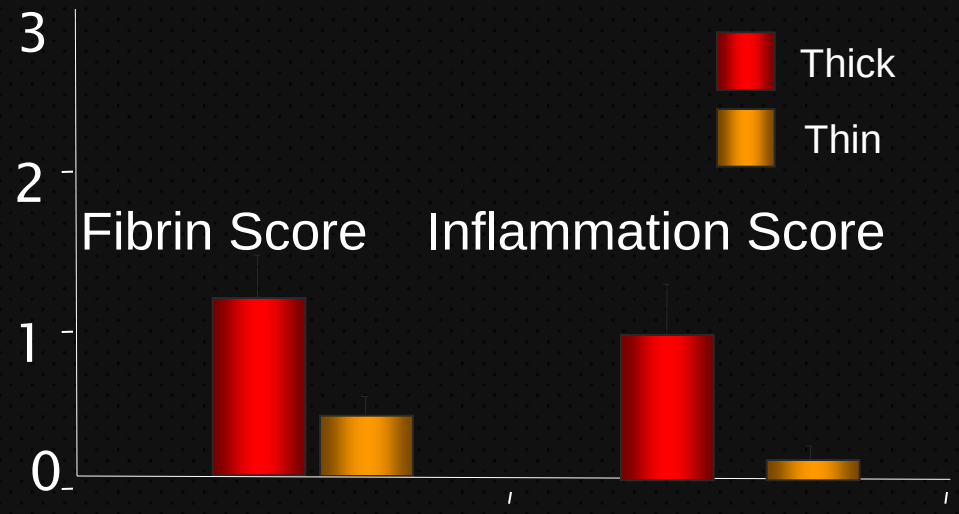
Soucy N, Feygin J et al, EuroIntervention. 2010 Nov;6(5):630-7

Optimization of Strut Thickness Leads to Reduction of Inflammation





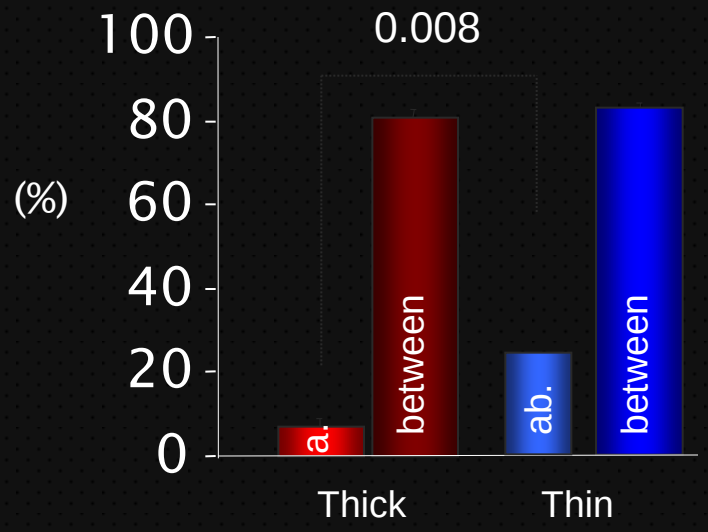




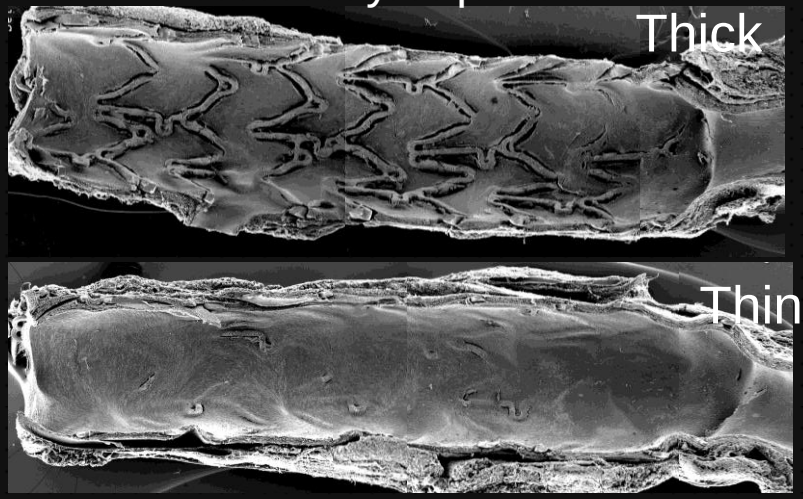
Tests performed by and data on file at Abbott Vascular

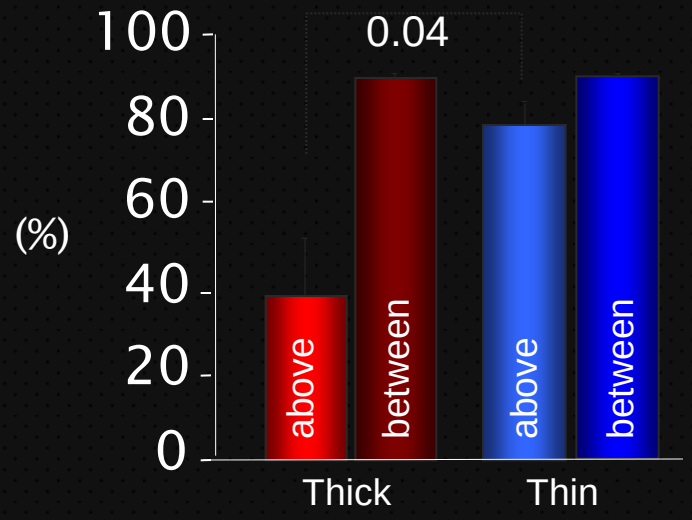
Optimization of Strut Thickness Leads to Rapid Re-Endothelialization

7-Day Implants



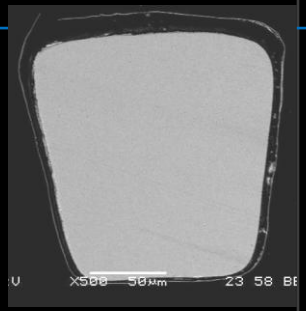
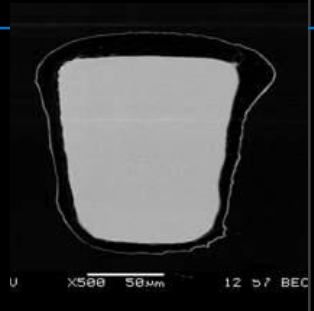
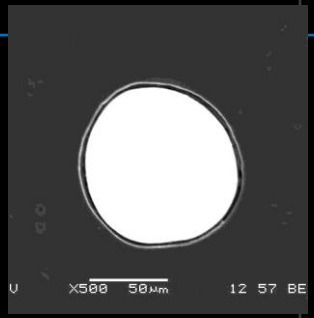
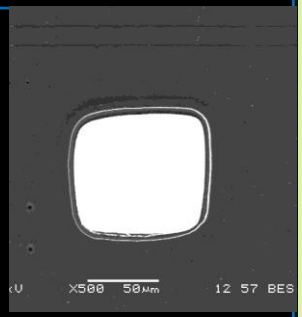
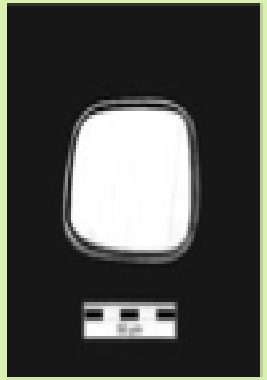
14-Day Implants





Tests performed by and data on file at Abbott Vascular

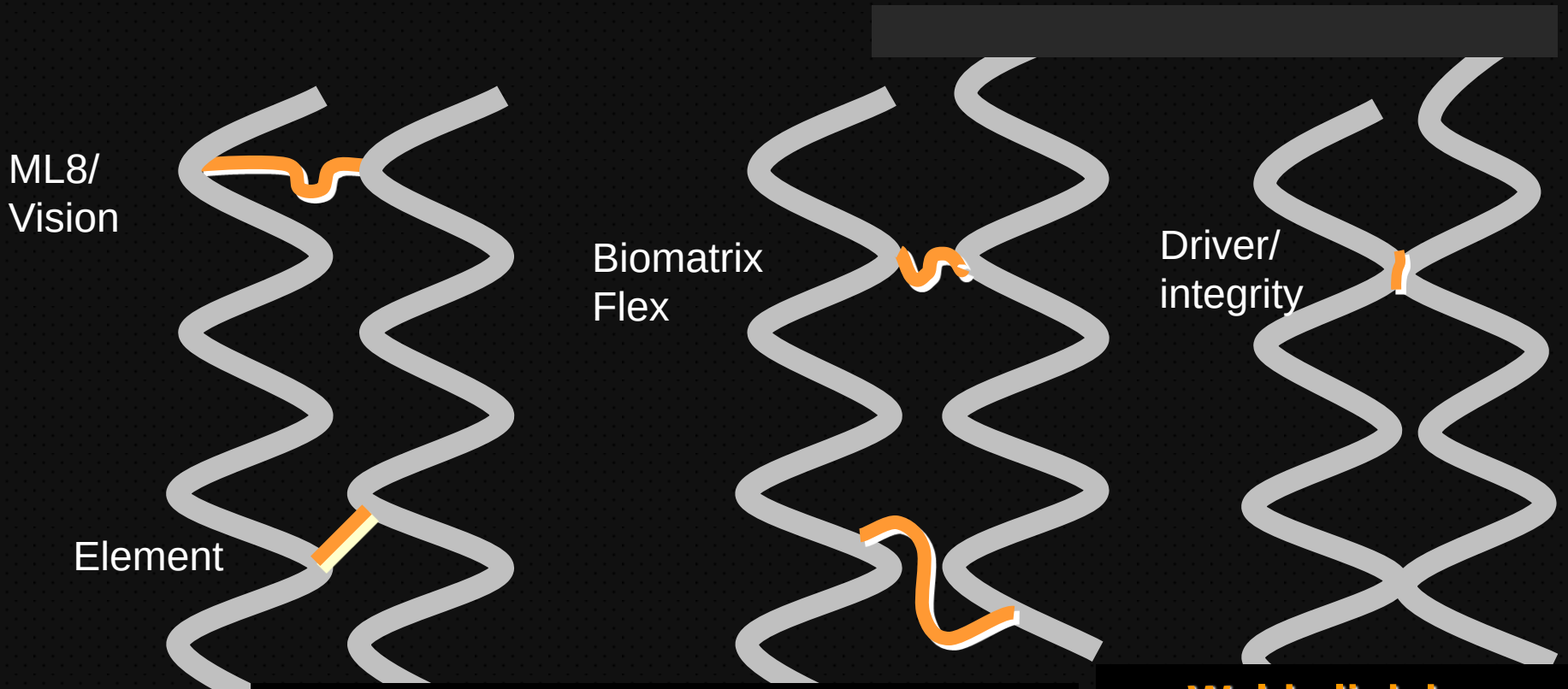
Stent Platforms: Strut & Polymer Thickness*

	CYPHER	TAXUS	ENDEAVOR	XIENCE PROMUS	Orsiro Hybrid DES
Stent					
Strut Thickness	140.0µm	132.0µm	91.0µm	81.0µm	
Polymer Thickness	12.6µm	16.0µm	5.3µm	7.6µm	60 µm
Total	152.6µm	148.0µm	96.3µm	88.6µm	7.4 µm 71 µm

*3.0 mm diameter stents, 500x magnification

All stents have the following design features

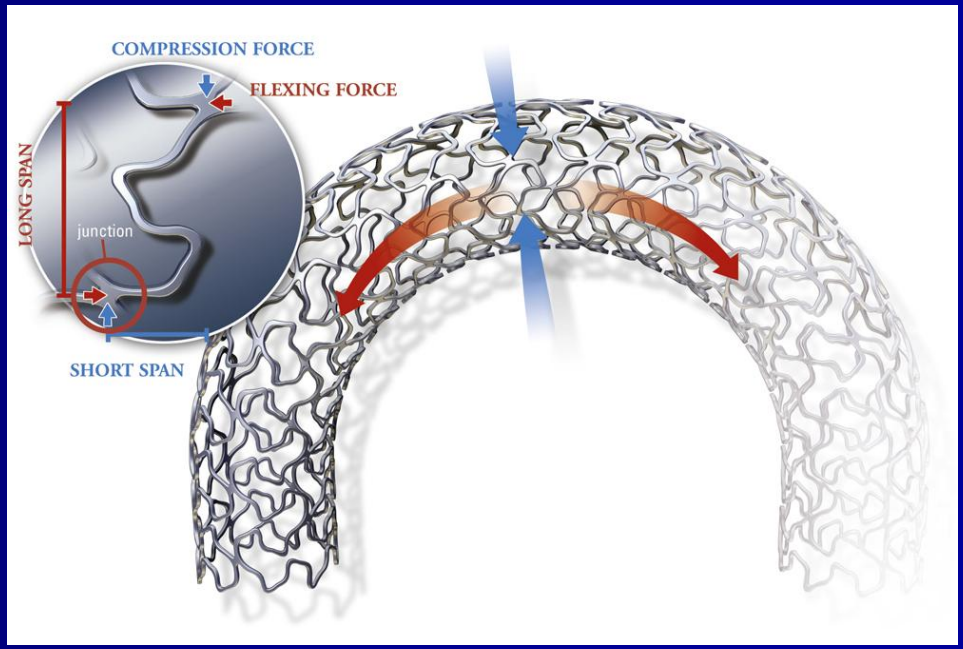
- Hoops provide radial strength
- Connectors hold hoops together and provide longitudinal strength
- Connectors play major role in flexibility



Ormiston JACC Int 2011

Design Considerations

- Uniform cell distribution
- Strut dimensions designed to provide radial strength and flexibility
- Continuous cell design and small open cell area provide uniform vessel coverage
- Thin struts for flexibility



Everolimus-Eluting Stents
Xience V™ and PROMUS Element™

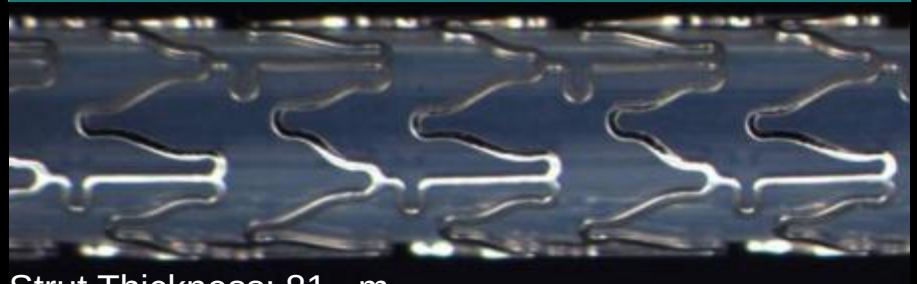
<u>Same Drug and Polymer</u>

Everolimus concentration: 100 ug/cm2

Polymer: PVDF

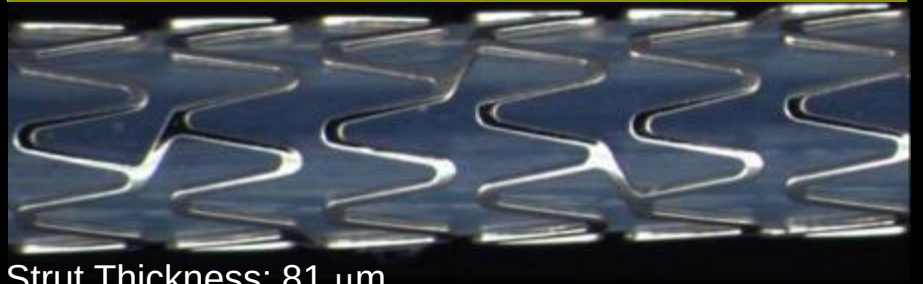
Polymer Thickness: 8 μm

Xience V™ Stent

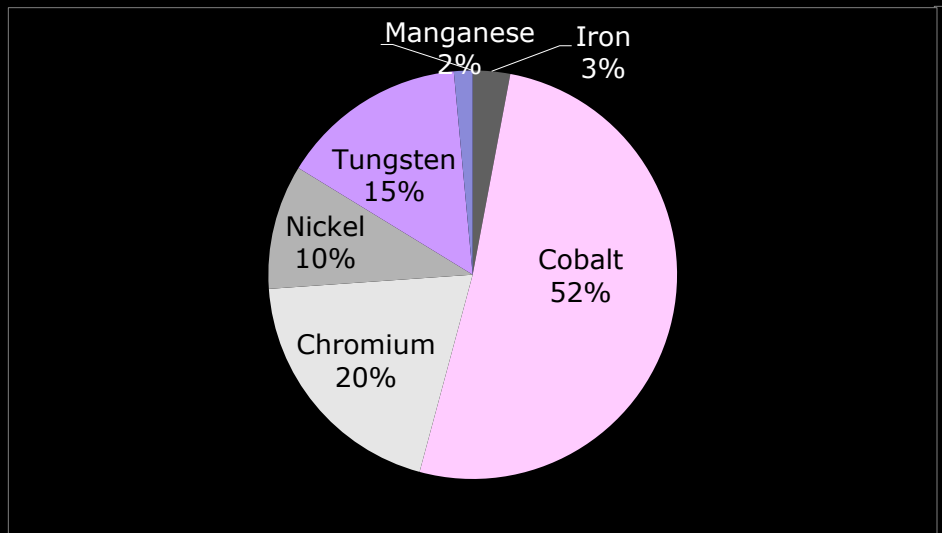


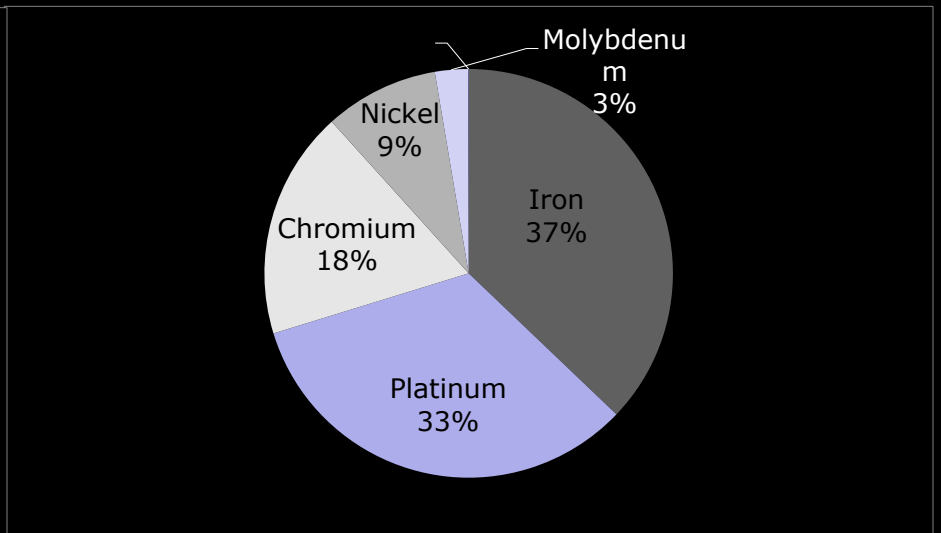
Strut Thickness: 81 μm

PROMUS Element™ Stent



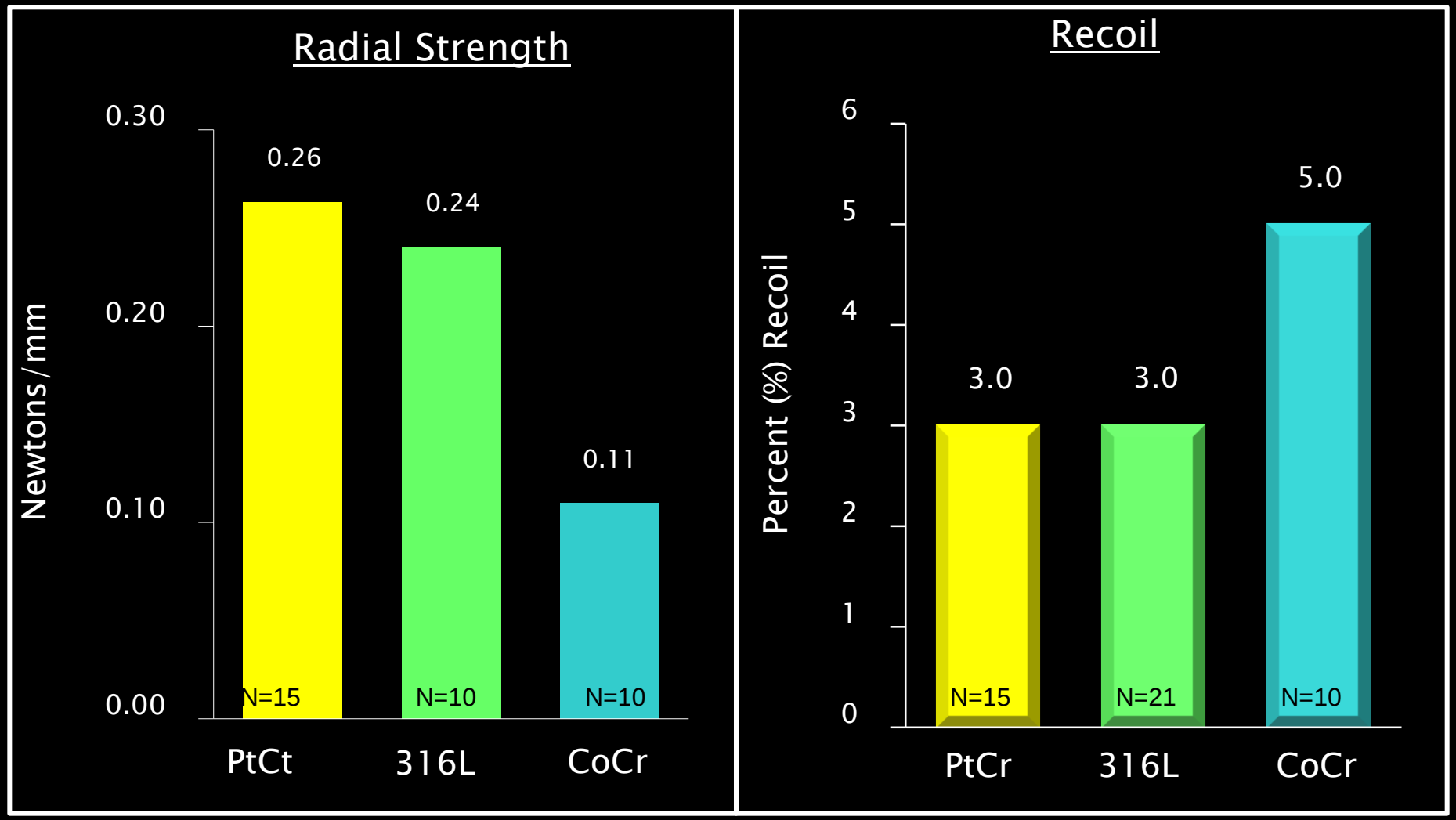
Strut Thickness: 81 μm





Radial Strength and Recoil

Bench Test Data

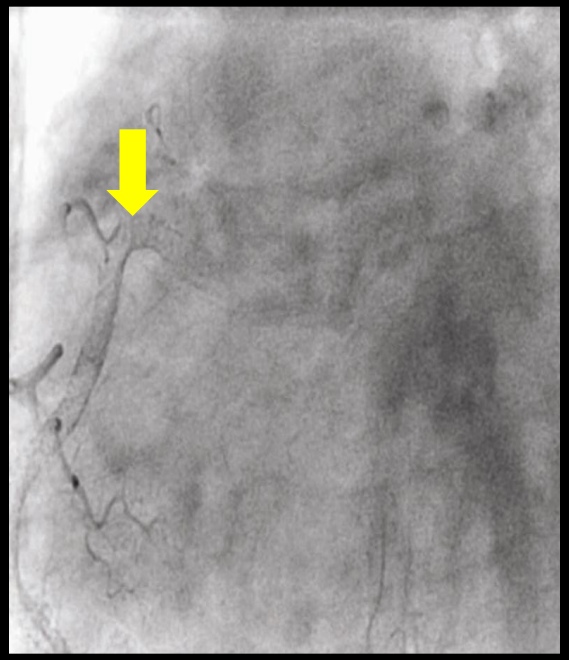


PROMUS Element™ Stent TAXUS Liberte™ Stent Xience V™ Stent

Data on file at Boston Scientific. 2.5mm diameter stents. Bench test results may not be indicative of clinical performance.

PROMUS Element™ Stent

Conformable platform allows artery to retain natural curvature

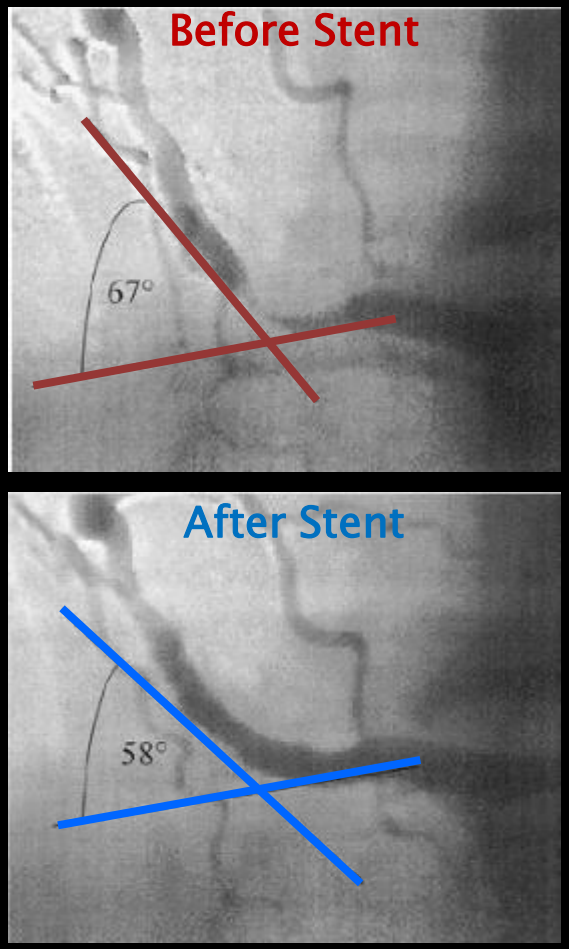


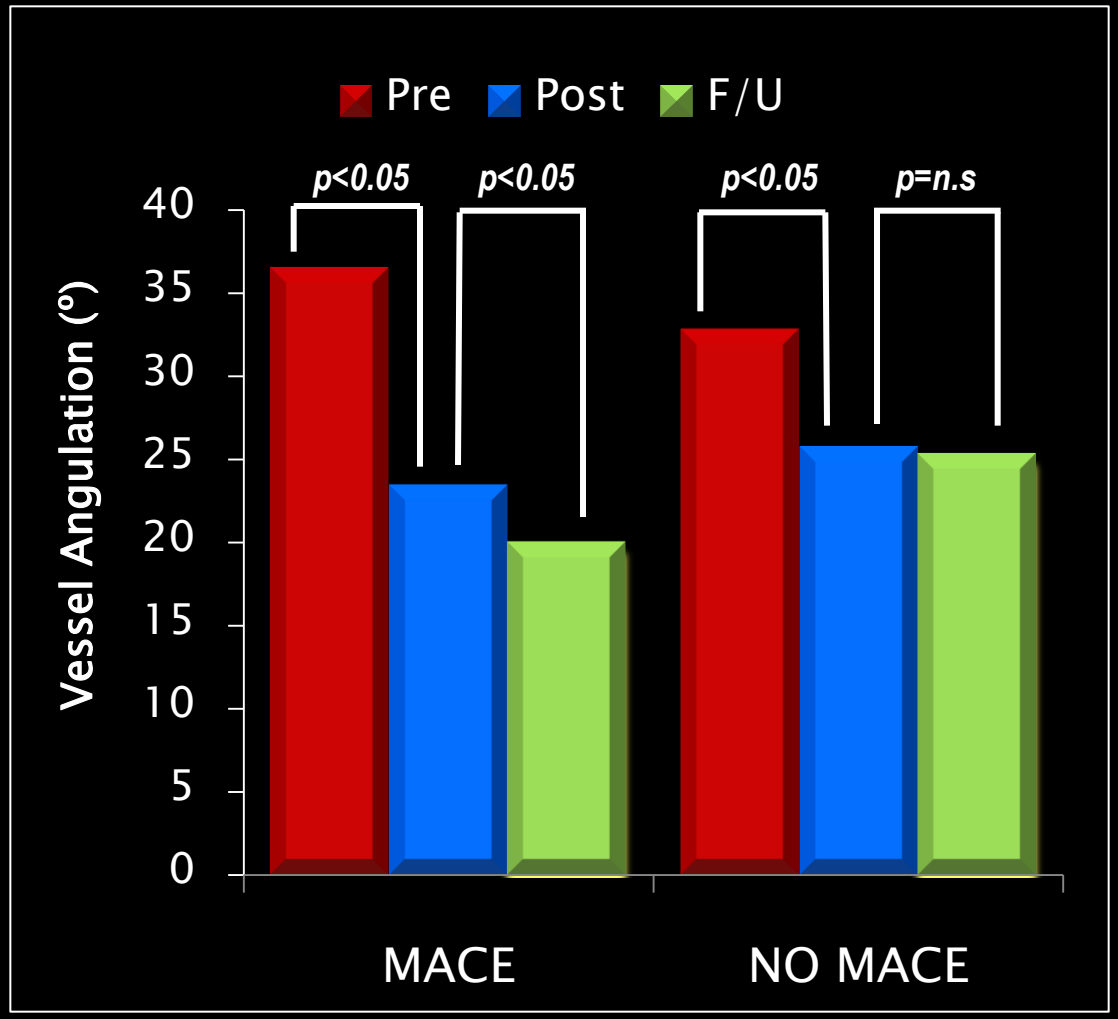
Results from case studies are not predictive of results in other cases.

Vessel Angulation and Straightening

Pronounced straightening of stented artery associated with MACE

Measurement Methodology





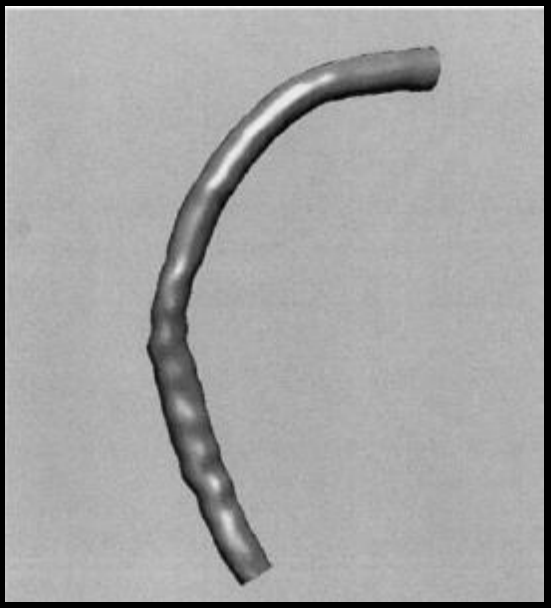
Pre-stent vessel angulation ≥33.5° and change in vessel angulation post-stent ≥9.1° found to be significant predictors of MACE

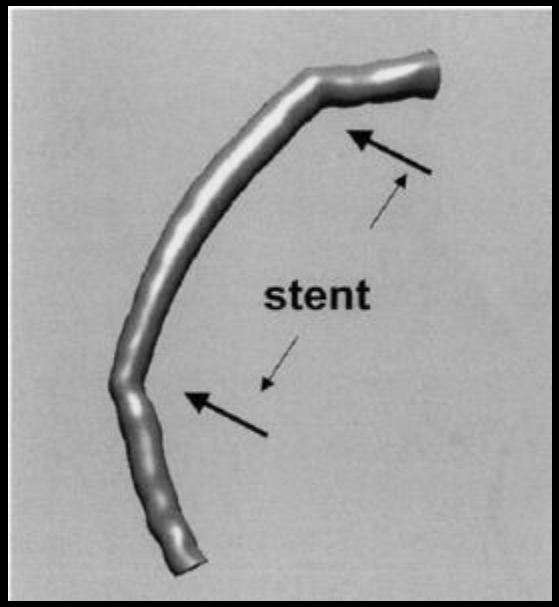
MACE includes death,nonfatal MI, and revascularization

Gyongyosi et al, JACC 2000;35:1580-9

Edge Effects, Shear Stress, and Restenosis

Shear stress changes may affect restenosis

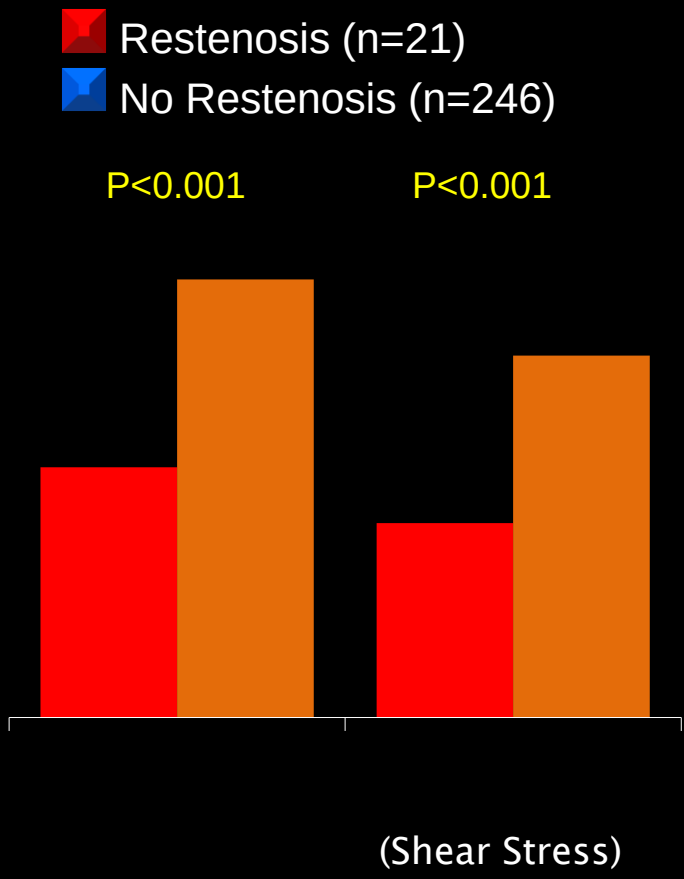




Stent implantation changes 3D vessel geometry

Changes in shear stress occur near stent edges and may result in restenosis

Changes in shear stress and flow velocity associated with restenosis

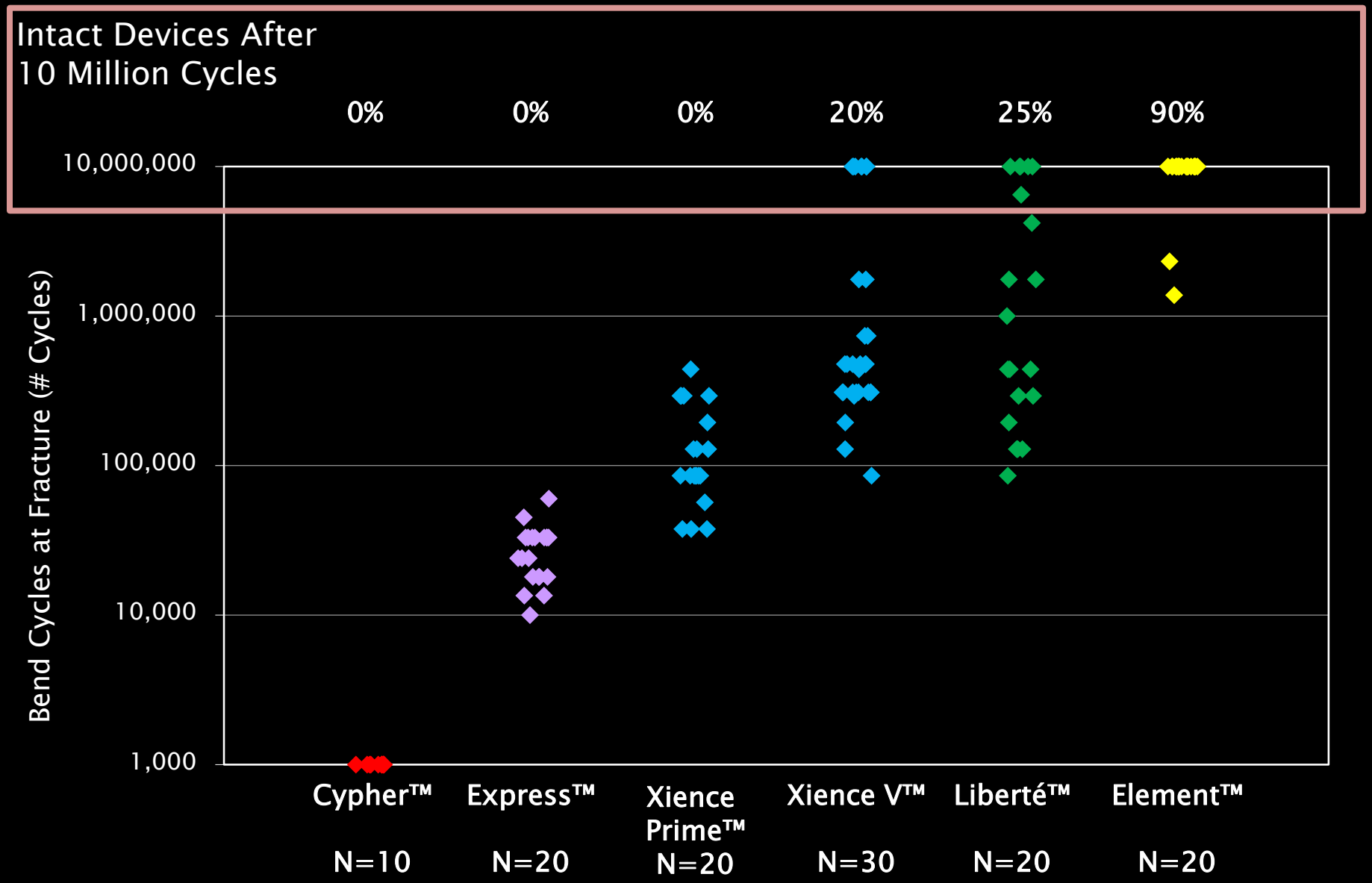


Wentzel et al. Jour Biomechanics 2000;33:1287-1295

Hikita et al. Scandinav Cardiovasc Jour 2009;43:298-303

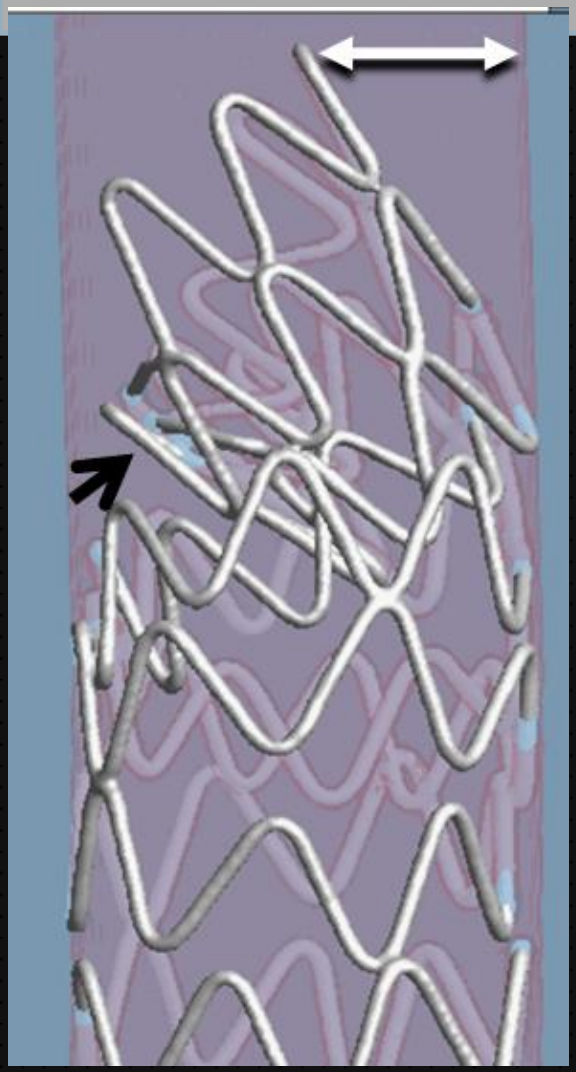
Increased Fracture Resistance with Flexibility

Bend Fatigue Bench Test



Data on file at Boston Scientific. 3.0mm diameter stents, 5mm test length. Bench test results not necessarily indicative of clinical performance.

Longitudinal strength/distortion

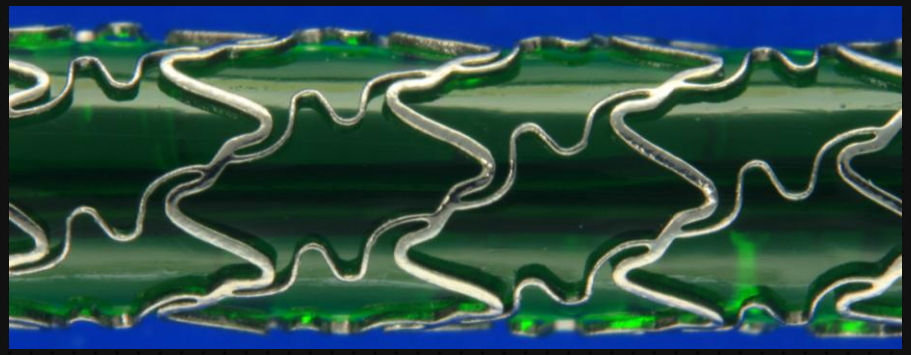


- This stent has 2 connectors
- It was distorted by a post-dilating balloon catching a point on the proximal hoop
- Hoops have been pushed together, overlap and obstruct. The proximal hoops are tilted

Longitudinal strength/distortion

- Stent design is a trade-off and improving one property may be at the expense of a desirable property

- Reducing connectors improves flexibility, SB access and stent fracture potential, it also reduces longitudinal strength



- The Cypher Select stent has 6 connectors linking hoops has high longitudinal stength and low flexibility. Reducing connectors may improve flexibility but at the expense of longitudinal strength

First Generation Test for Stent Longitudinal Strength-

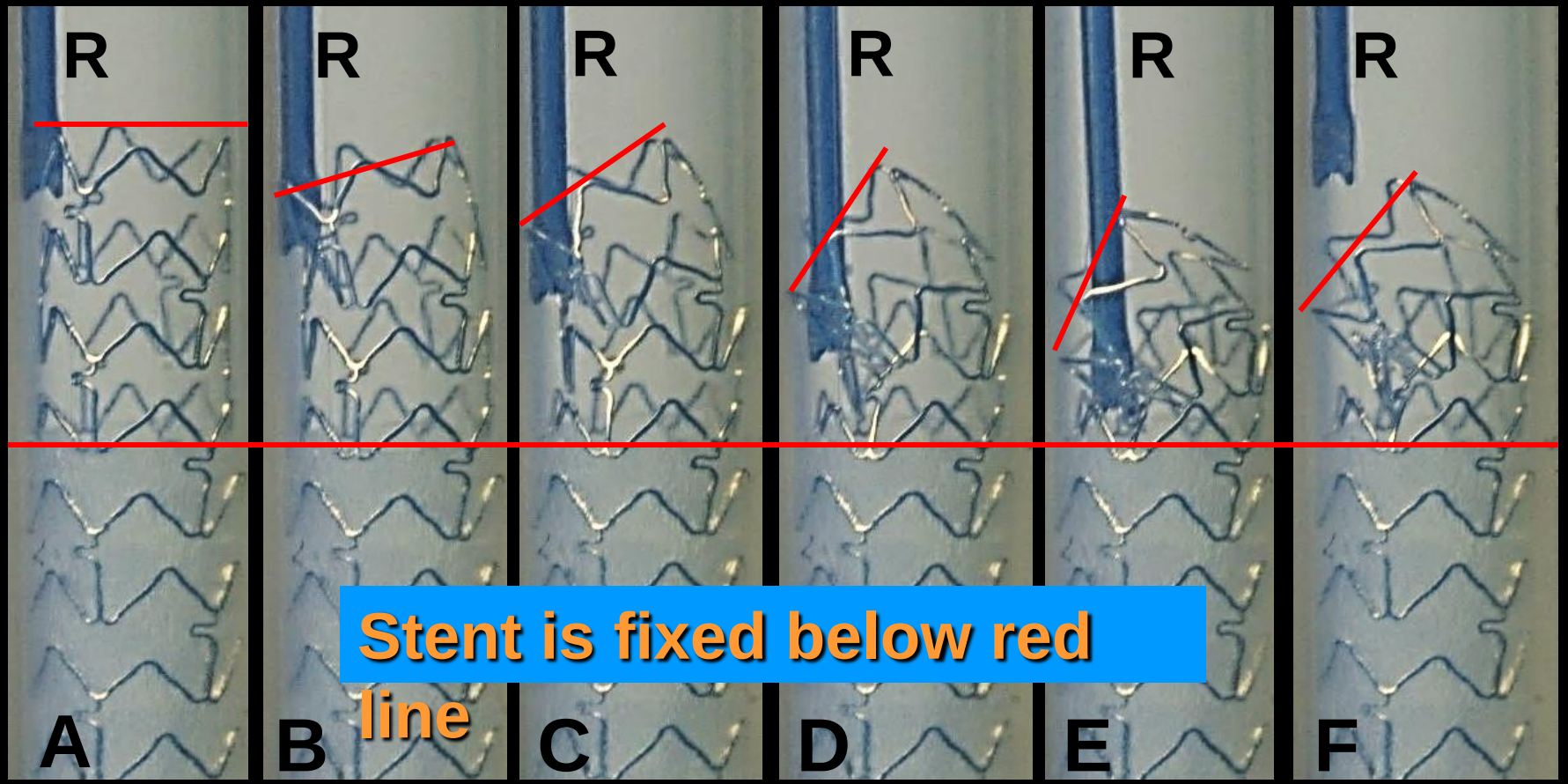
- An instron universal testing machine applied force to the circumference of the proximal hoop

- The force was plotted against distance compressed

Ormiston JACC Interv 2011

2nd Generation point force compression of a stent

- Stent is fixed distally
- Force from the Instron pushes hoops together and tilts proximal hoop
- Hoops are displaced into and obstruct the lumen
- Struts pulled away from the opposite side are malapposed and obstruct
- Instron measures force and distance



Reported Longitudinal Stent Deformation

Described with at least 12 stents

BioMATRIX™ Stent Hanratty EuroIntervention, 2011 Williams, EuroIntervention, 2011	**Micro Driver™ Stent** Pitney, EuroIntervention, 2011 Mammas, EuroIntervention, 2012	**Resolute Integrity™ Stent** Hanratty EuroIntervention, 2011	**TAXUS™ Liberté™ Stent** Williams, EuroIntervention, 2011 Mammas, EuroIntervention, 2012
Endeavor™ Stent Pitney, EuroIntervention, 2011 Mammas, EuroIntervention, 2012	**PROMUS Element™ Stent** Hanratty EuroIntervention, 2011 Williams, EuroIntervention, 2011 Mammas, EuroIntervention, 2012	**ION™ / TAXUS Element™ Stent** Robinson, J Interv Cardiol, 2011 Mammas, EuroIntervention, 2012	**Xience V™** Olcay, TCT 2011 Mammas, EuroIntervention, 2012 Yamaguchi, JACC, 2012
OMEGA™ Stent Mammas, EuroIntervention, 2012	**Driver™ Stent** Mammas, EuroIntervention, 2012	**Cypher™ Stent** Mammas, EuroIntervention, 2012	**Nobori™ Stent** Mammas, EuroIntervention, 2012

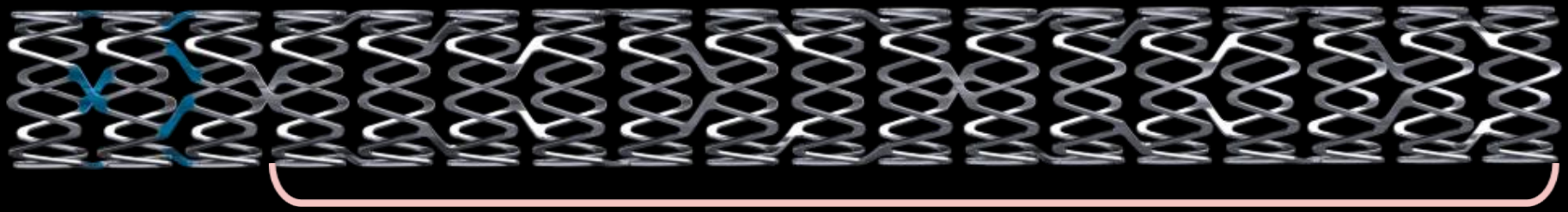
Most reports have been restricted to anecdotal case reports

*ION is commercialized as TAXUS Element™ outside the US.

Promus PREMIER™ Everolimus-Eluting Stent
Design Goals

Customized Platinum Chromium (PtCr) Stent Architecture

Additional connectors on proximal end → Proximal end more robust to provide increased axial strength

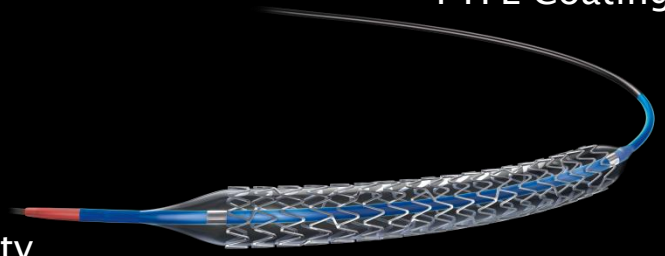


2 connectors throughout body → Design maintains flexibility, conformability, and fracture resistance

Enhanced Stent Delivery System

PTFE Coating on hypotube to reduce friction

Bi-segment inner lumen catheter for pushability and flexibility



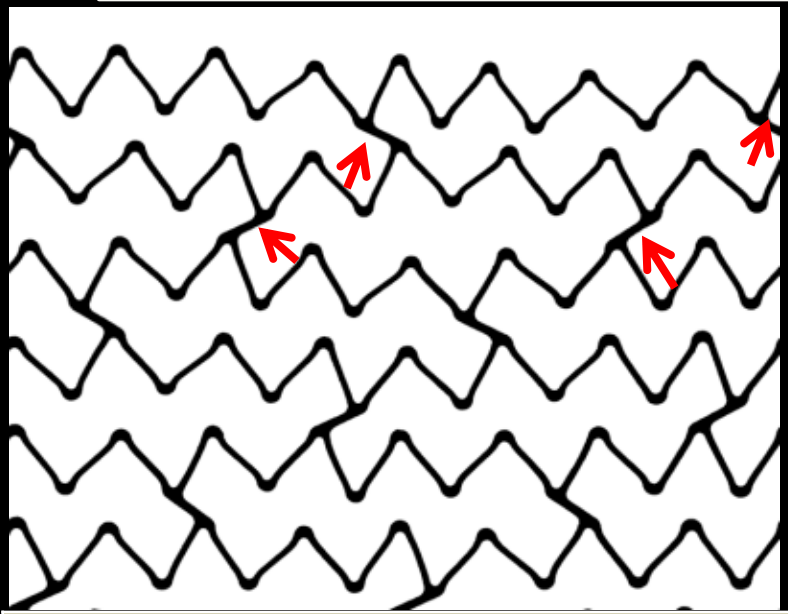
Shorter tip to improve flexibility

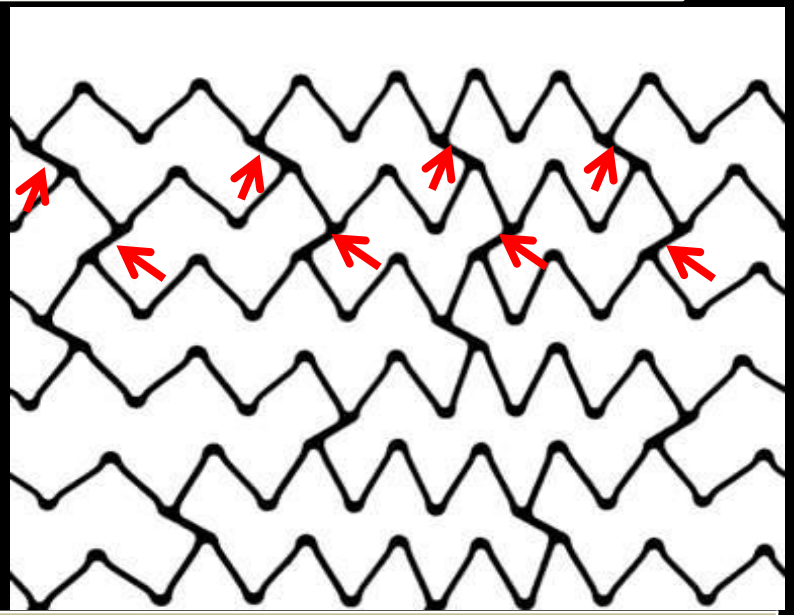
Dual-layer balloon for optimal compliance and minimal balloon growth

*Data on file-Boston Scientific. In the US and Japan, the Promus PREMIER stent system is an investigational device and not for sale.

Promus PREMIER™ Stent

- Promus PREMIER design improves longitudinal strength by supporting proximal end with additional connectors where distortion most commonly occurs
- Delivery system improved
- Retains the desirable features of the Element design (flexibility, conformability, radiopacity)
- No change to drug or polymer



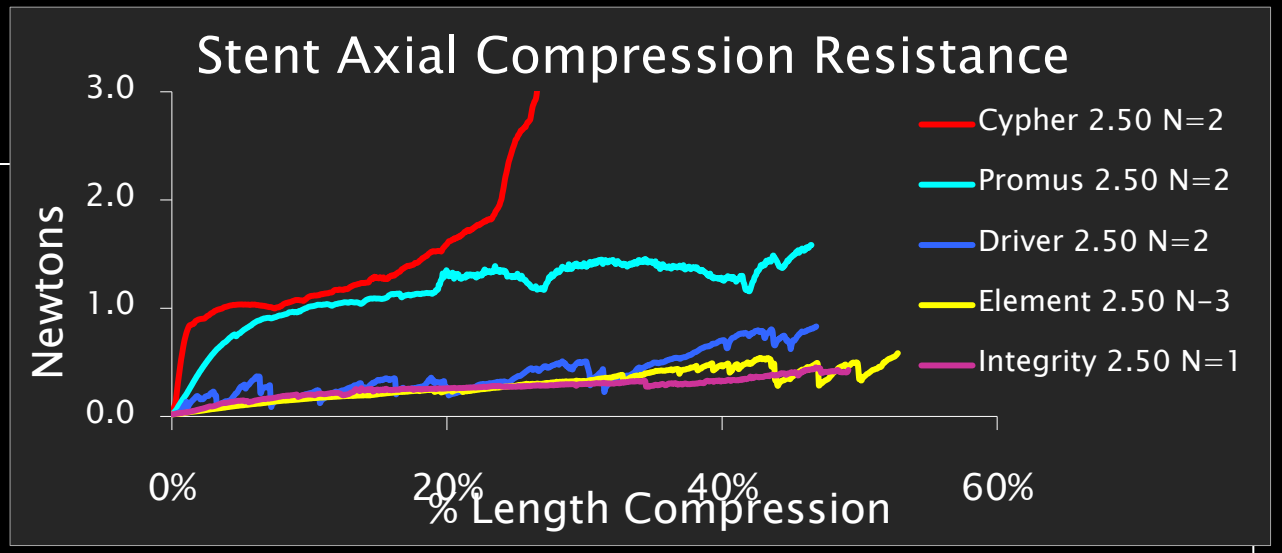


Element Design	Promus Premier design
• 2 connectors between hoops	• 4 connectors between proximal 3 hoops. • 2 connectors between remaining hoops.

John Ormiston, MD at CRT 2013

Flexibility and Conformability

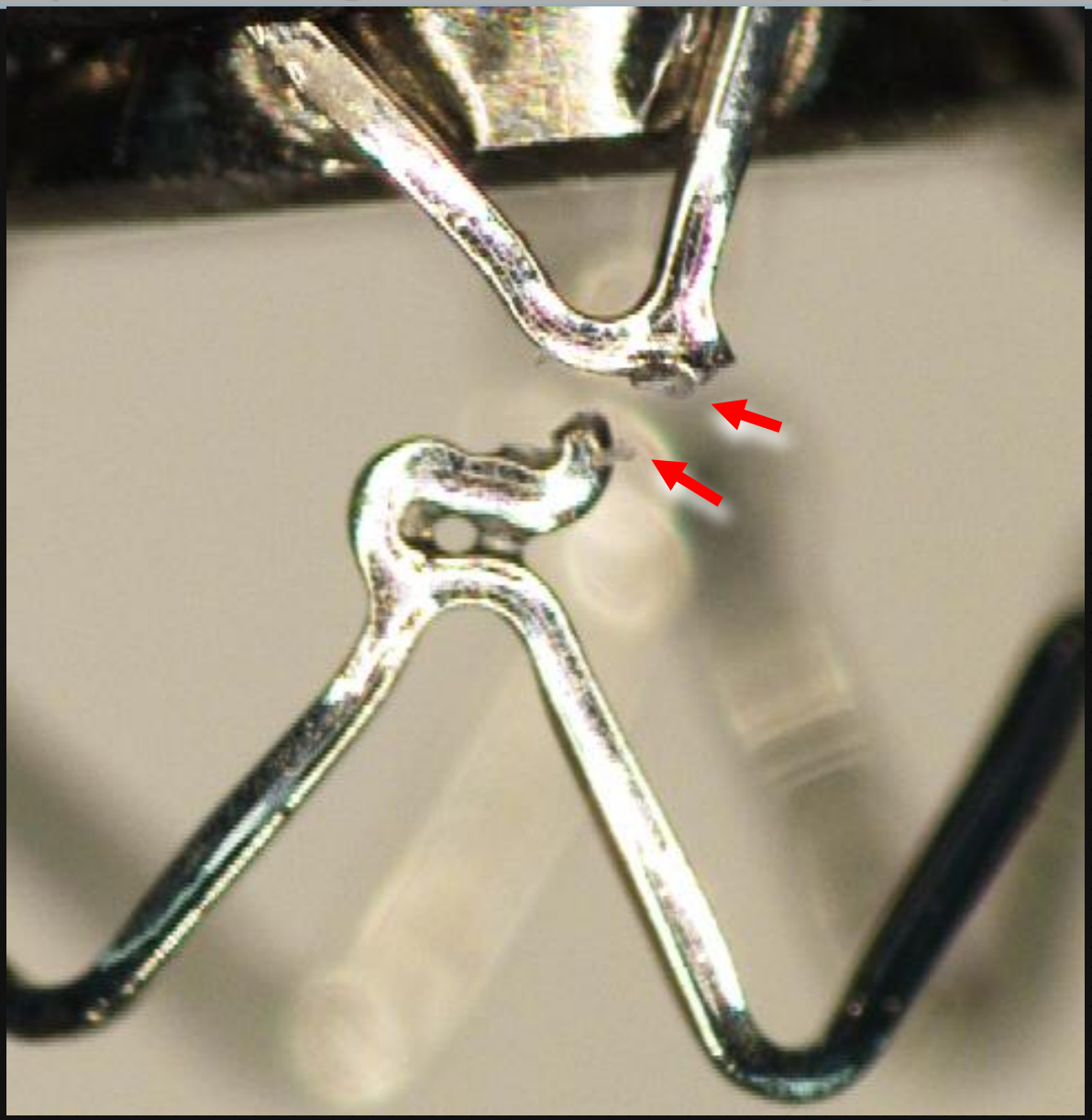
Flexibility & conformability inversely related to axial strength



Stent diameter: 2.5mm , Similar Stent lengths. Cypher n=6, Xience Prime n=5, Xience V n=10, Resolute Integrity n=3, Endeavor n=7, Promus Element n=15. Bench test results may not necessarily be indicative of clinical performance. Data on file at BSC.

Stent strut fracture

(and damaged resorbable polymer)

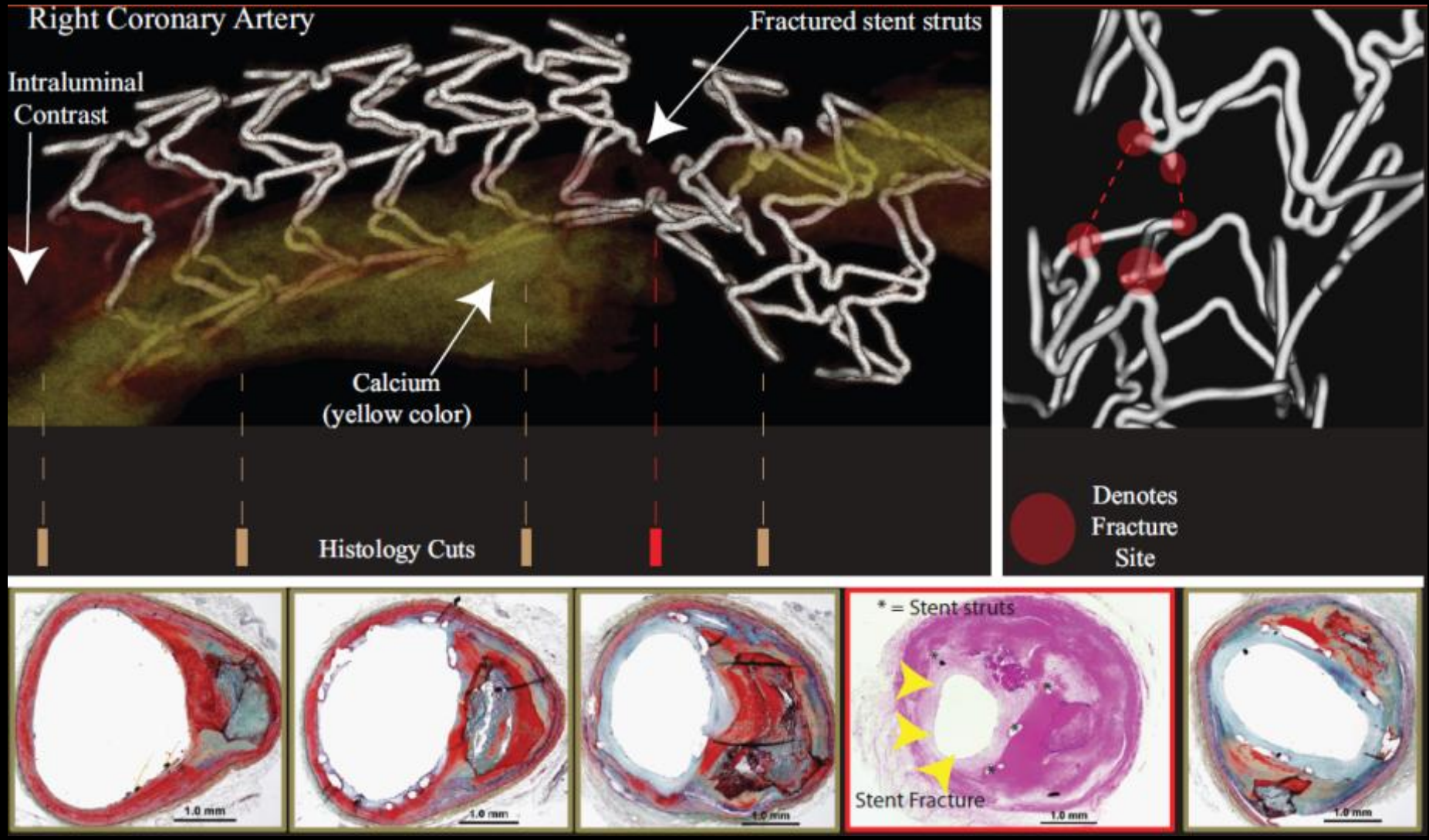


Stent fracture

- Recognized for at least 10 years (Chowdhry, NEJM 2002)
- Associated with MACE (may cause of ST, restenosis, late “catch up”)
- Meta-analysis of 8 studies with 5321 patients and 108 stent fractures
  incidence of fracture was 4% (All but one were in Cypher)
  (Charkravarty, AJC 2010)
- The probability of fracture is increased with long stents, overlapping stents, RCA, bend points, DES, stent design
- Recent single center report
  Xience V implanted in 1339 lesions
  Fracture at 6-9 months in 2.9% lesions, 3.8% patients
  MACE higher in fracture group vs no-fracture (25.6% vs 2.3%; $P<0.001$)
  (Kuramitsu, Circ Int 2012)

Stent Fracture Associated with DES Restenosis

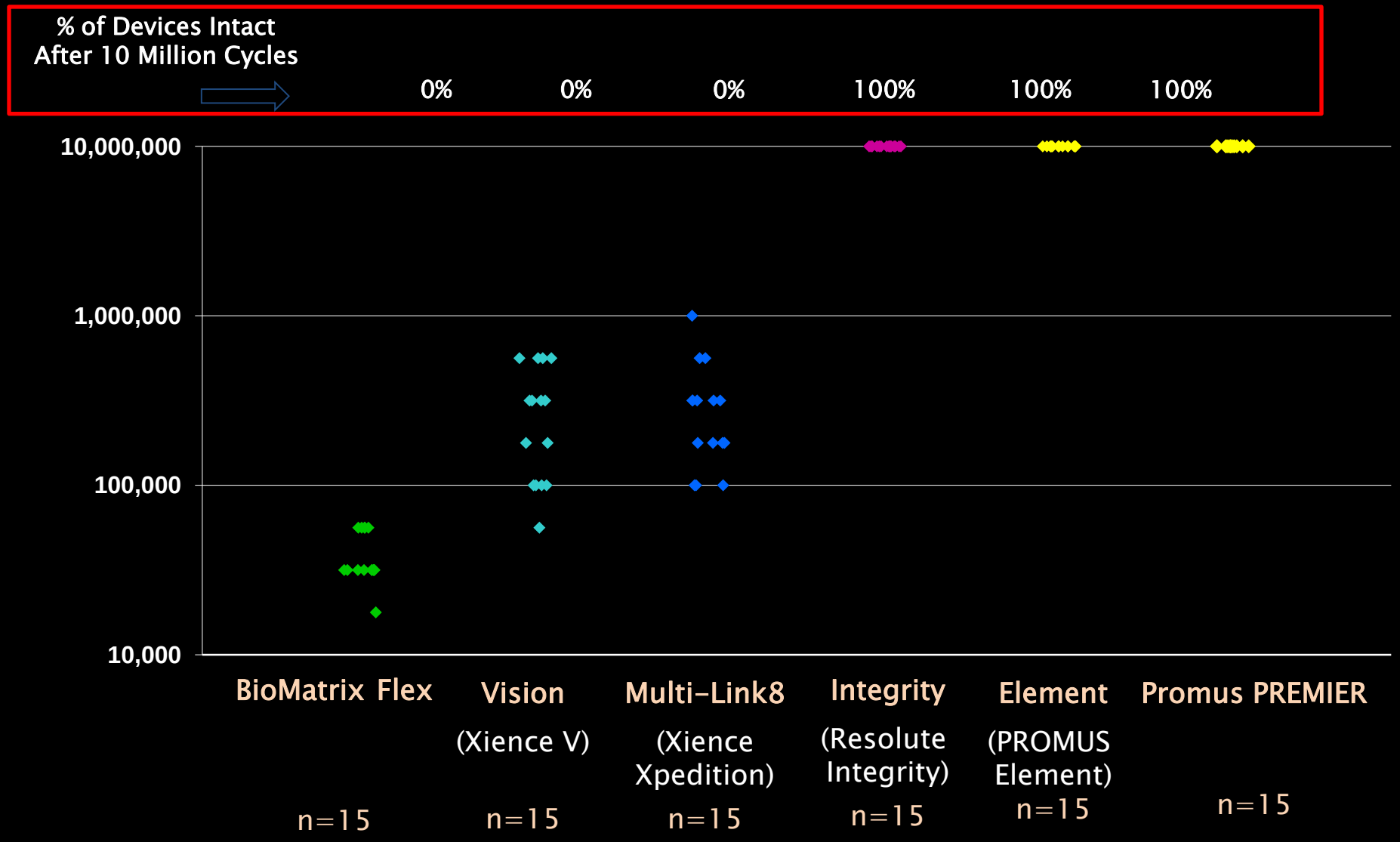
Human autopsy analysis



Foerst et al. *JACC* 2012;5(3): 239–242.

Stent Fracture

Bend cycles to fracture for 6 contemporary platforms

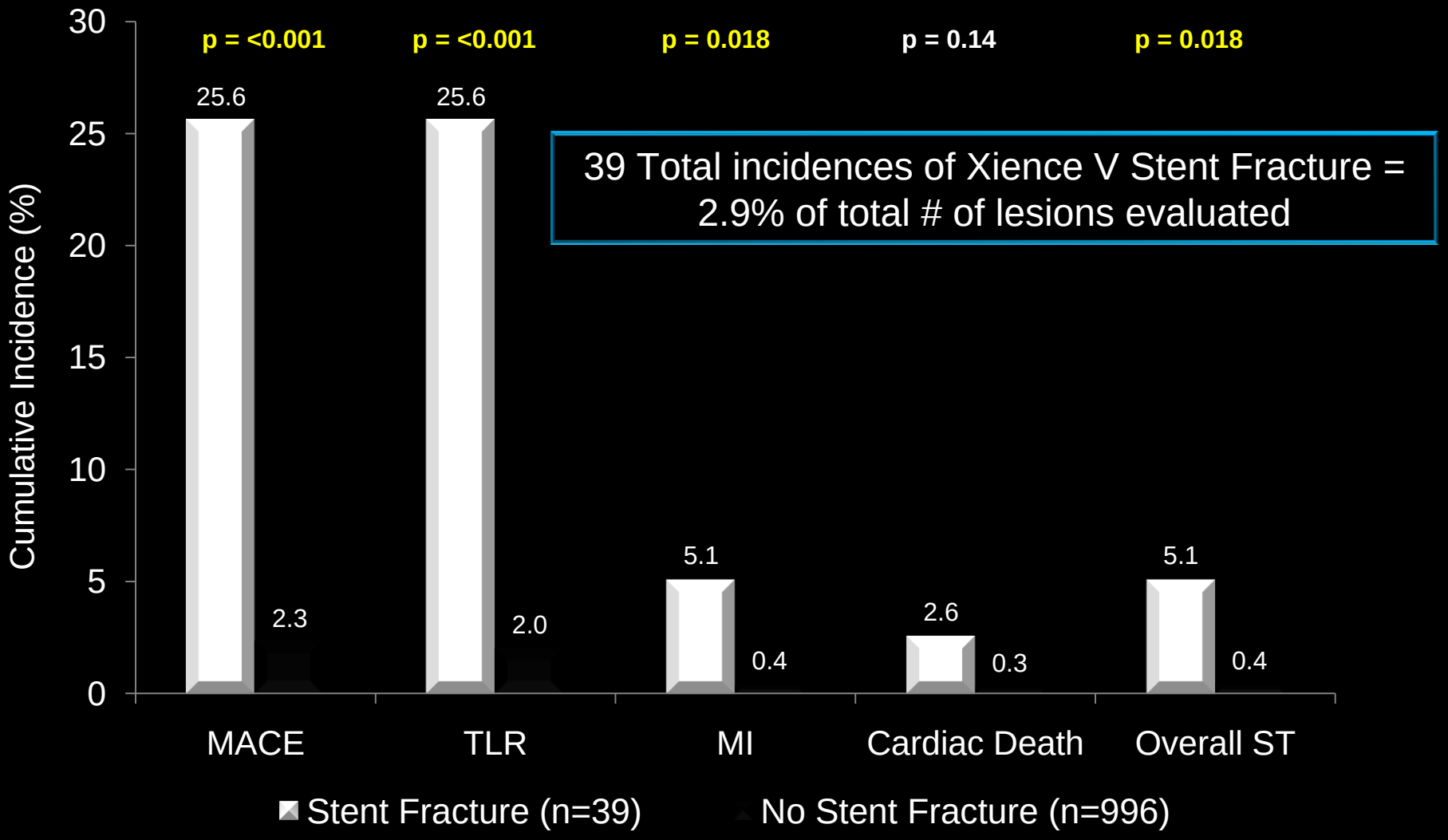


Presented by John Ormiston, MD at CRT 2013

In the United States, Promus PREMIER is an investigational device and not for sale.

Stent Fracture following Xience V™ Deployment

Major Adverse Cardiac Events within 9-months



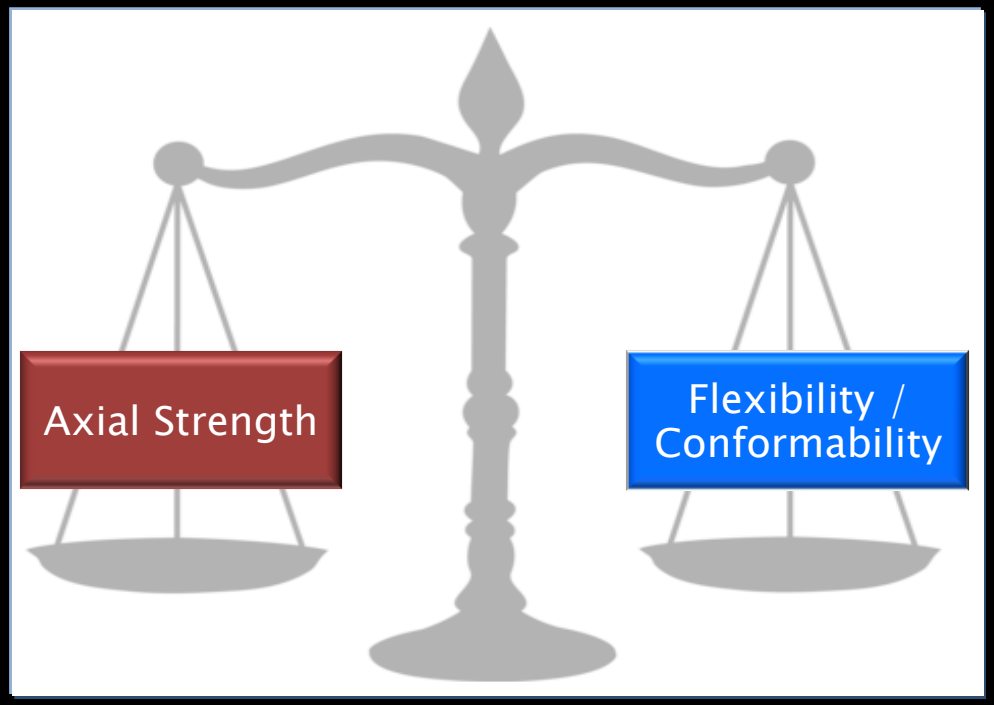
Kuramitsu et al. Circ Cardiovasc Int 2012 (epub)

Flexibility and Axial Strength

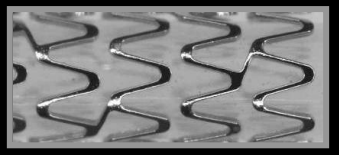
A Balancing Act

SSTL

Closed Cell



PtCr



Open Cell

Greater Axial Strength

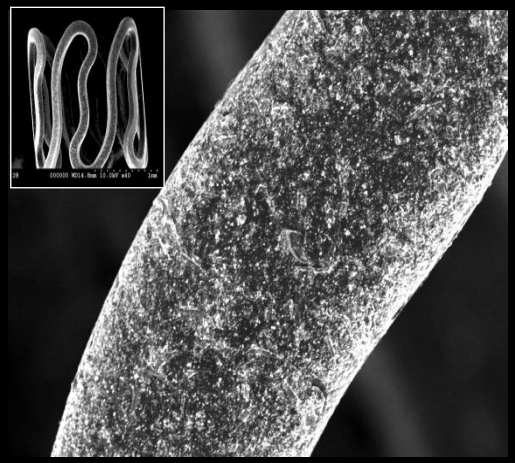
- Decreased risk of longitudinal compression

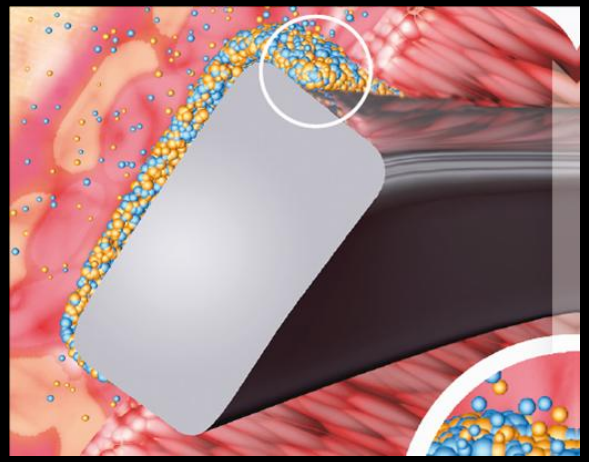
Greater Flexibility / Conformability

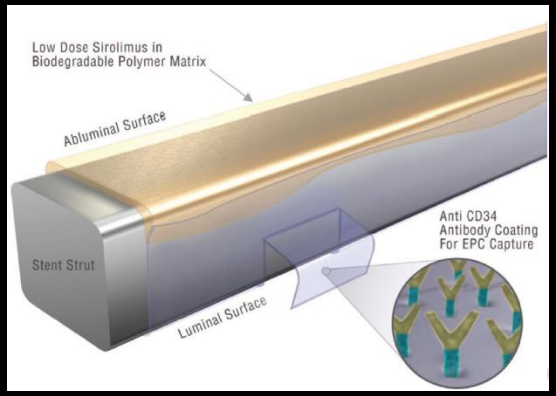
- Improved deliverability
- Lower rates of incomplete apposition
- Less distortion of vessel architecture
- Increased fracture resistance

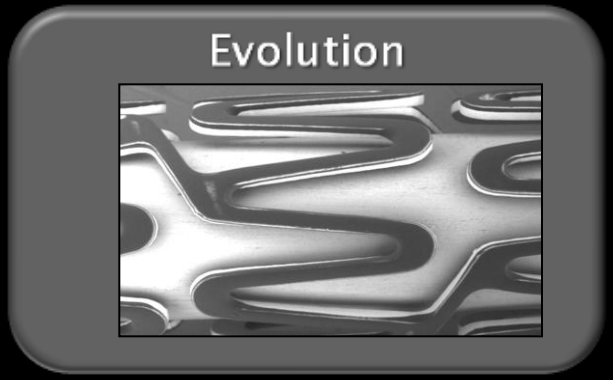
Data on file at Boston Scientific. Meredith et al. *EuroIntervention* 2011;7:84-90. Wentzel et al. Jour Biomechanics 2000;33:1287-1295

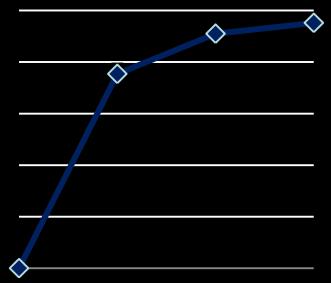
Biodegradable Polymer Based DES Platforms



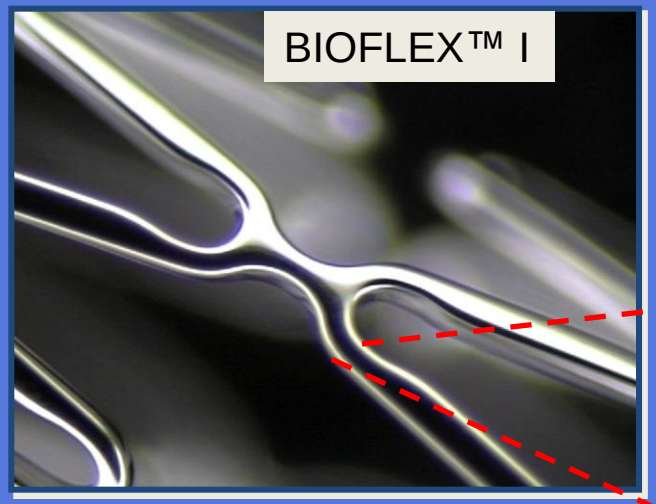






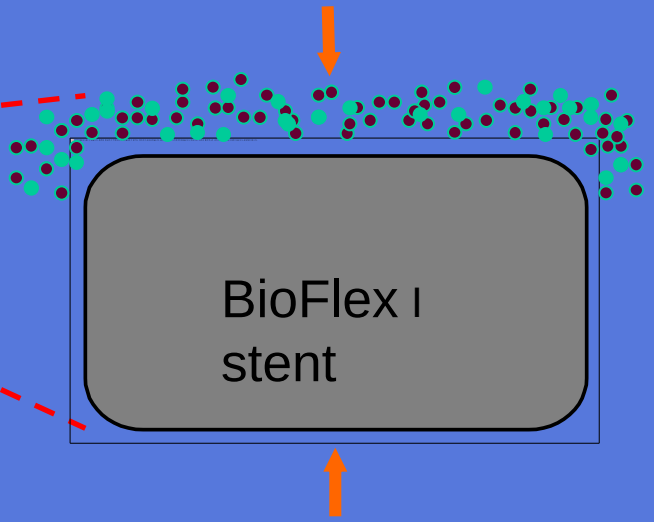


BioMatrix® II Stent Platform Design



Biodegradable Drug/Carrier:

- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 15 µmeter coating thickness
- degrades in 9 months releasing CO_2+ water



Stent Platform:

- stainless steel (112 µm)
- corrugated ring, quadrature-link™ design
- radius link enhances axial fatigue life

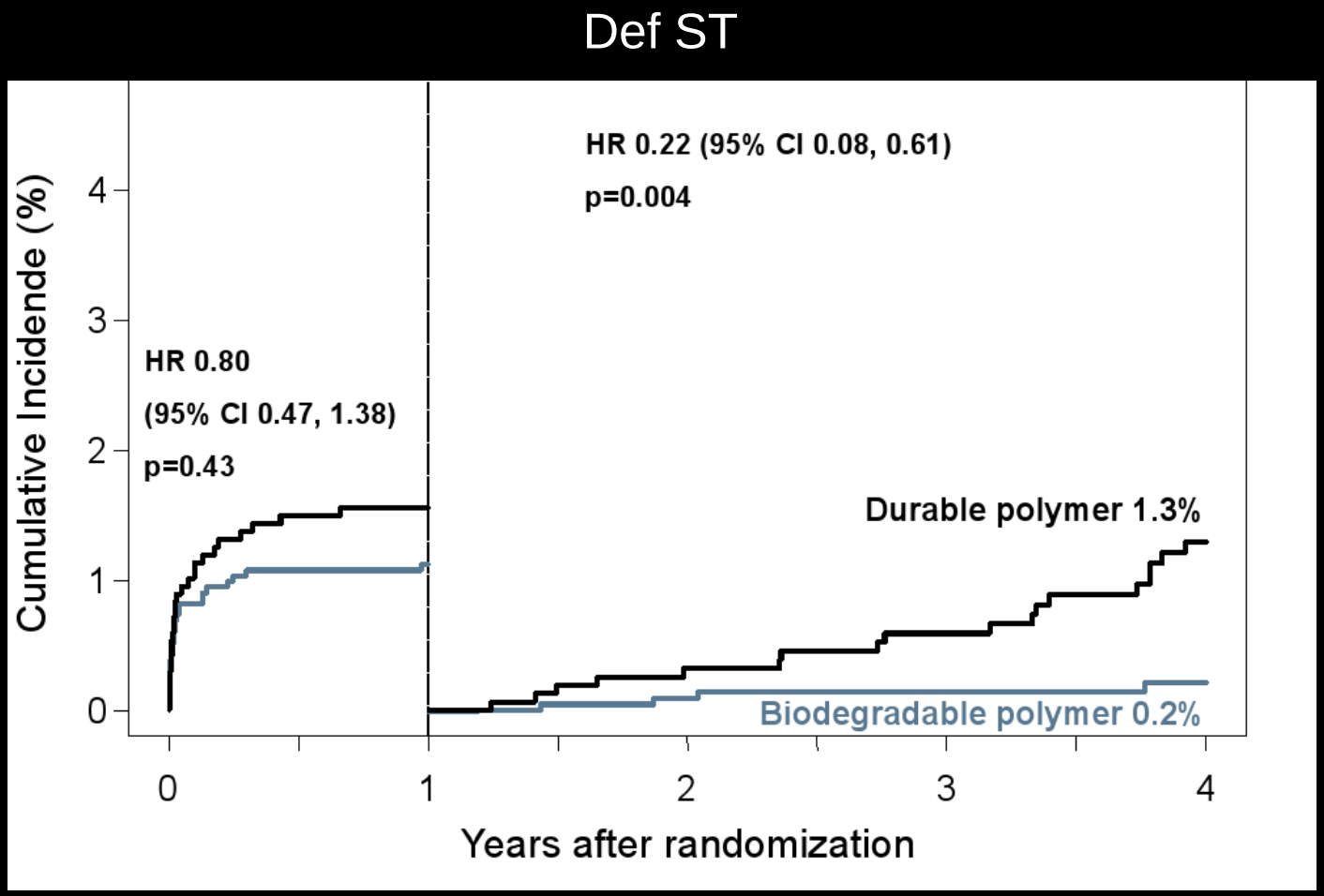
Parylene Durable Primer Coating:

- 5 µmeter thick, encapsulates stent
- prevents surface metal ion migration
- biostable + athrombogenic*

* Data per NHLBI sponsored study, available from BSI

Bioabsorbable vs. Durable Polymer DES

Meta Analysis: ISAR Test-3, ISAR Test-4, & LEADERS



Presented by Robert Byrne, MD at ACC 2012

SYNERGY™ Everolimus-Eluting Stent with Synchrony™ Bioabsorbable Coating

Polymer and drug applied as ultra-thin abluminal coating

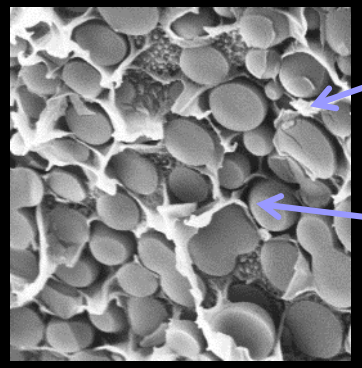
Synchronized drug release and polymer absorption

Polymer gone shortly after completion of drug elution at 3 months

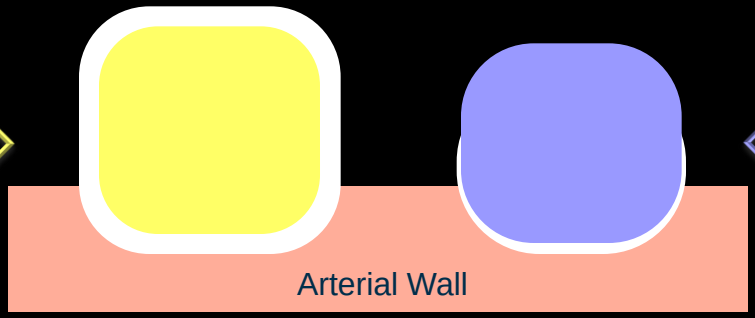
SYNERGY Stent

Abluminal Coating

Coating Microstructure



Stent Strut Cross Sections



PROMUS Element

PVDF durable polymer 360° around stent strut

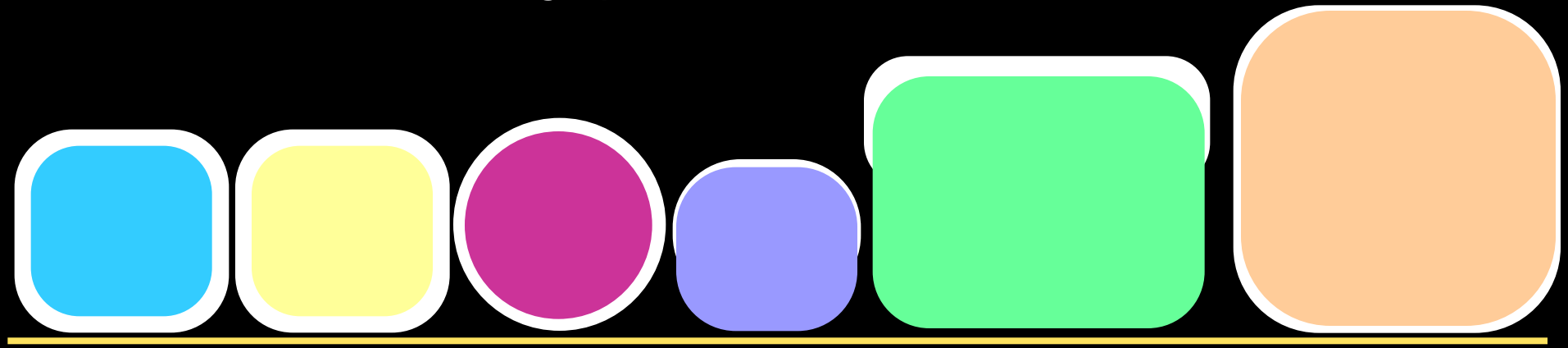
SYNERGY

PLGA bioabsorbable polymer only on abluminal surface

SYNERGY™ Stent Platform

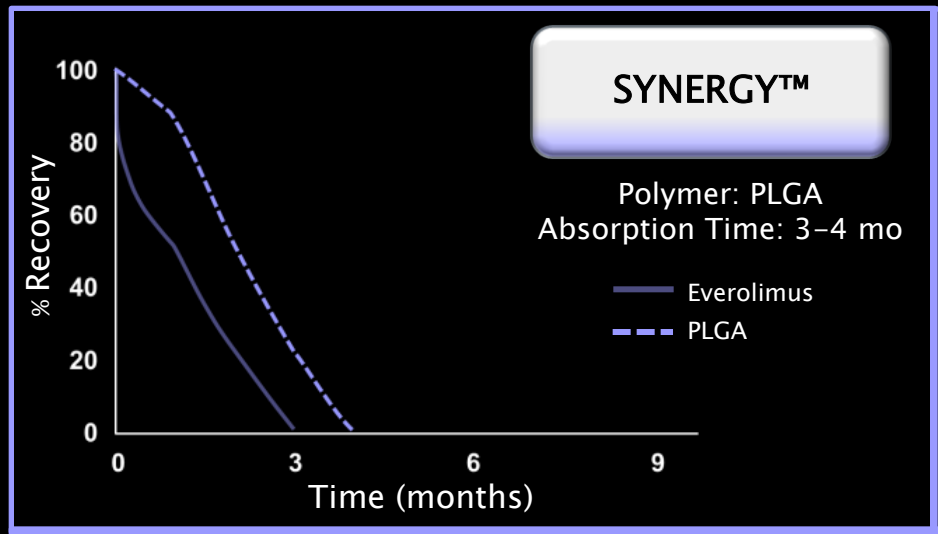
Strut and Coating Thickness In Perspective

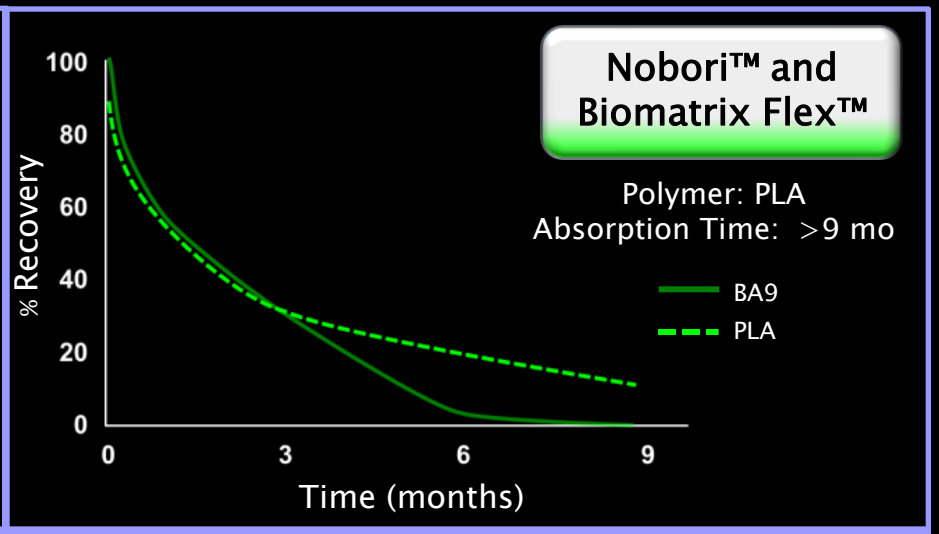
Durable Polymer Coated Stents			Bioabsorbable Polymer Coated Stents		Bioabsorbable Stent
Xience V™	PROMUS Element™	Resolute Integrity™	SYNERGY™	BioMatrix Flex™	BVS

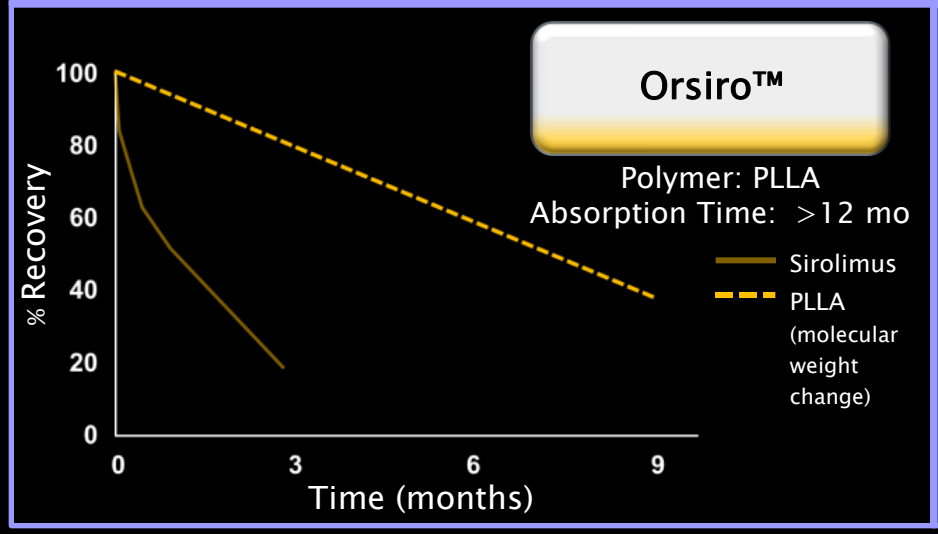


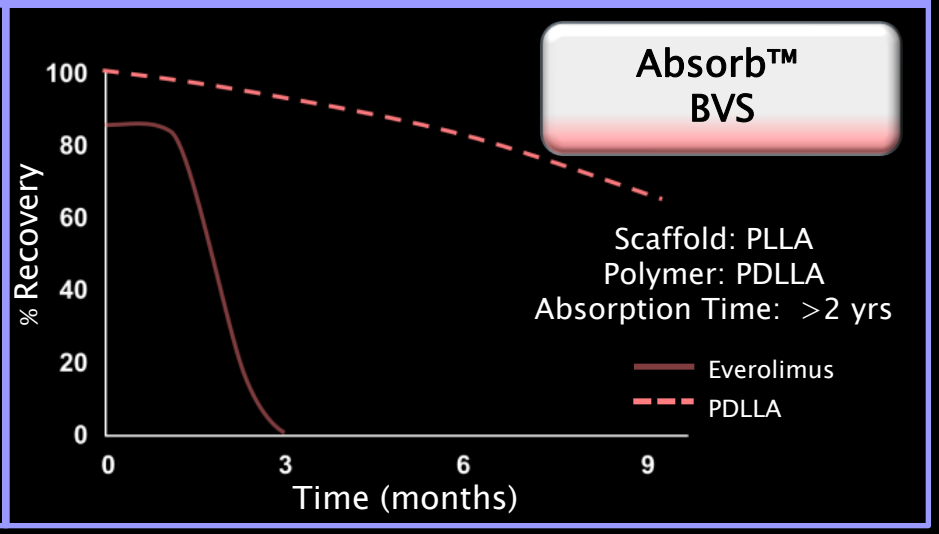
Strut Thickness					
81 µm (0.0032”)	81 µm (0.0032”)	89 µm (0.0035”)	74 µm (0.0029”)	120 µm (0.0047”)	150 µm (0.0059”)
Coating Thickness					
Conformal 8µm / side	Conformal 8µm / side	Conformal 6µm / side	Abluminal 4µm	Abluminal 10µm	Conformal 3µm / side

Drug Release and Polymer Degradation Profiles









Boston Scientific data on file; *World J Cardiol* 2011 March 26; 3(3): 84-92;
Garg, S, *J Am Coll Cardiol*. 2010;56(10s1):S43-S78. doi:10.1016. Presented by Stephen Windecker, MD, TCT2012.

Summary

- Architecture design have impact on deliverability, flexibility, conformability and deformation
- Two connectors design can easily deformed and require extra care
- Stent fractures occur more in less flexible stents with more connectors & associated with clinical events
- Strut thickness has impact on outcome. The thinner the Better. radial strength may be a limitation
- Polymers has a temporary function for drug elution beyond that they pose hazard to late events
- Thinner biodegradable polymers or no polymers are desire for the next generation DES