TCT@SOLACI/SOCIME, Wednesday, August 5th, 2015

Fully Bioresorbable Scaffolds

Technical and Biological Requirements for Clinical Adoption

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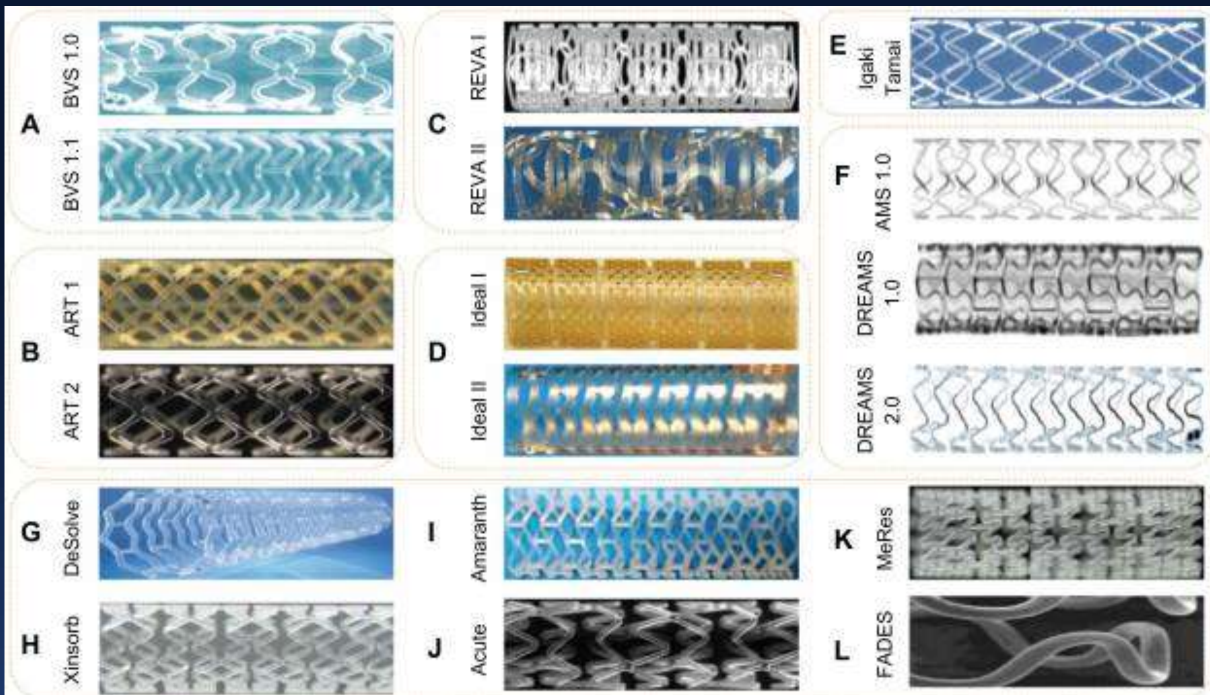
Disclosure Statement of Financial Interest

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

- Grant/Research Support: Abbott Vascular, Amaranth Medical, Angiometrix, AstraZeneca, Bioventrix, Boston Scientific, Caliber Therapeutics, Cardia, Cardiac Implants, Cardiovascular Systems Inc., Cardiosolutions, Celladon, Cephea, Circulite/Heartware, ControlRad, Corindus Vascular Robotics, CR Bard/Lutonix, DC Devices, Direct Flow Medical, Intact Vascular, MedAlliance, Meril Life Sciences, Mitralign, Neovasc, Nitiloop, Orbus Neich Medical, REVA Medical, Siemens, Stentys, Surmodics, Thoratec, Volcano, WL Gore
- SAB/Advisory Role: Boston Scientific, Amaranth, Covidien

BRS Architecture and Clinical Success

Contributing Technical Factors



- **Polymer Biocompatibility**
- **Chemical Properties**
  - **Polymer Crystallinity**
- **Polymeric Mass**
  - **Scaffold Design**
  - **Strut Thickness-Width**
- **Scaffold Absorption Time**
  - **Vessel Scaffold Capacity**
- **Polymer-Drug Interaction**
  - **Tissue Pharmacokinetics**
  - **Restenosis Prevention**

Figure (Left) Med Devices (Auckl). 2013;6:37–48

The resulting vascular healing profile of each individual BRS depends on the interaction of all scaffold components (i.e. polymeric material) with the vessel wall at different stages of the healing process

BRS and Short Term Vessel Patency

Multifactorial and Time-Dependent Process

ACUTE PHASE

(1) Scaffold Biomechanics: Dilatation and Recoil

↓

(2) Mechanical Impact on Vessel Injury

↓

(3) Scaffold Material Exposure

Acute Vessel Wall Inflammation

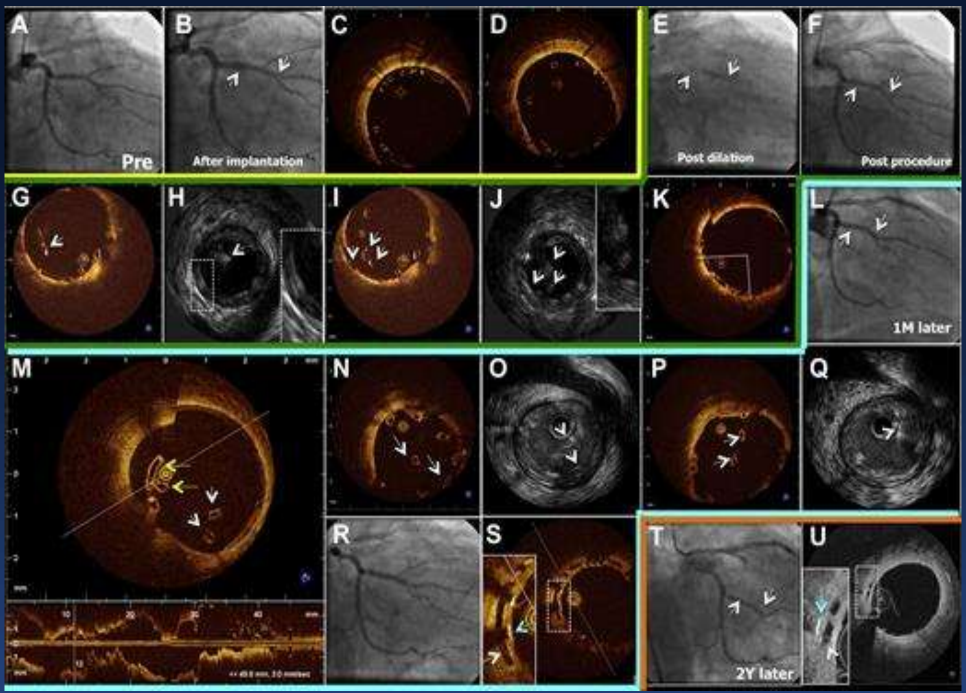
Scaffold Surface Cell Coverage

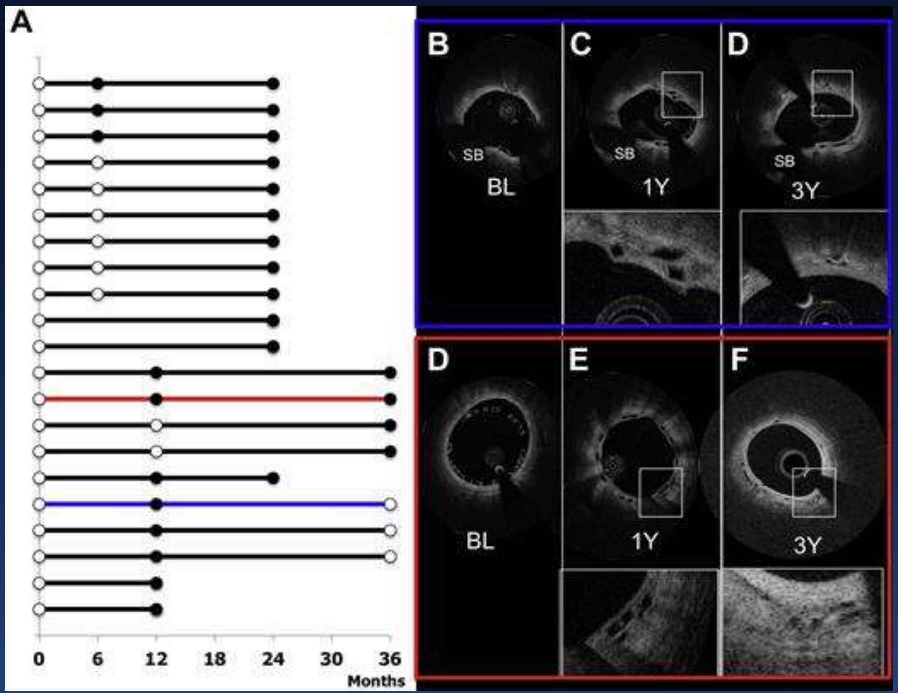
ACUTE VESSEL PATENCY:
SCAFFOLD BIOMECHANICS
MATERIAL THROMBOGENICITY

In the acute setting; is the biomechanical behavior and thrombogenicity profile of BRS comparable to conventional metallic Drug Eluting Stents?

Acute Scaffold Disruption and Late Structural Discontinuity in BVS

Implications for Clinical Outcomes





Acute Scaffold Disruption= 2/51 (3.9%)

One TLR Event

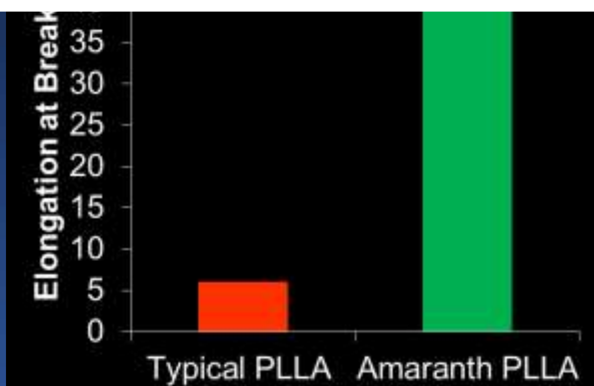
Late Discontinuities= 21/49 (42%)

One-Non-Ischemia Driven TLR

Onuma Y. JACC Cardiovasc Interv. 2014 Dec;7(12):1400-11

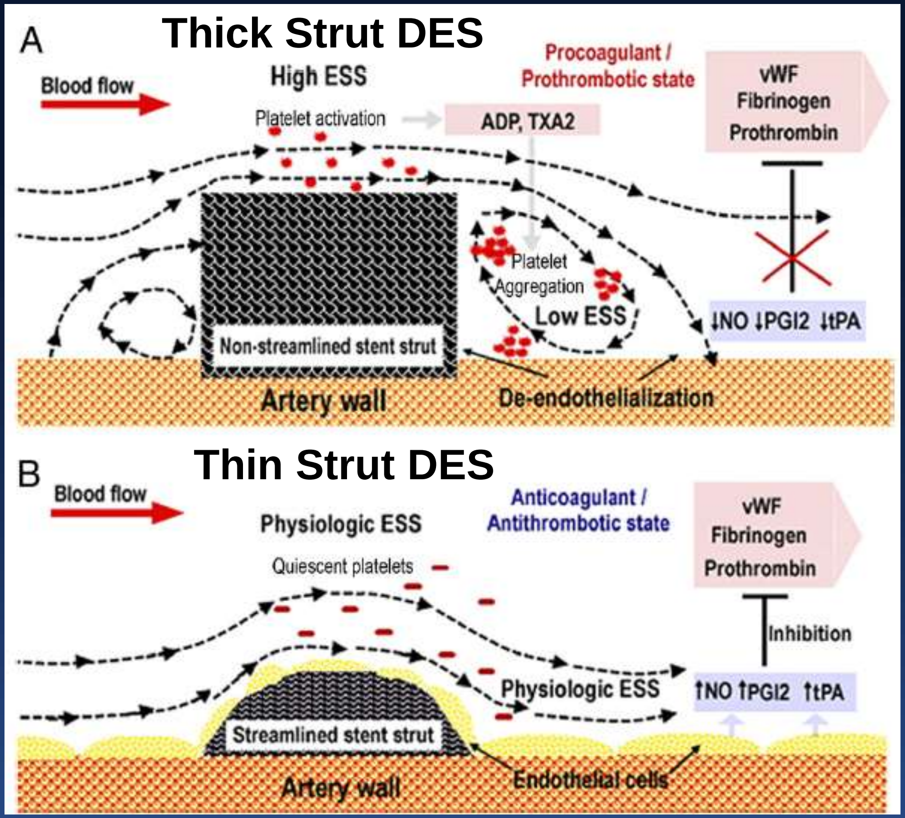
BRS Biomechanics in Second Generation BRS (Amaranth)

For all BRS, biomechanical properties below 100 microns need further clinical evaluation (vs. conventional DES)!



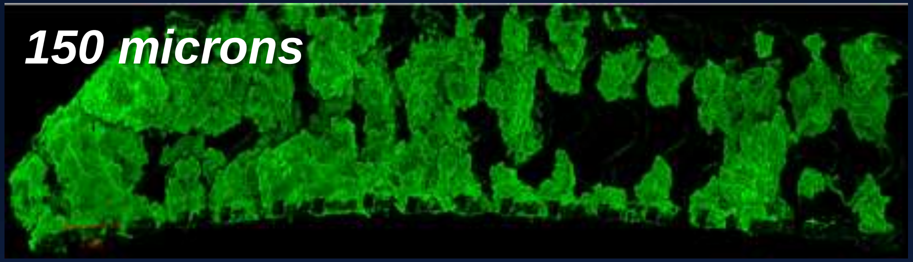
In Vivo BVS Thrombogenicity

Absorbable Polymer DES vs. BVS

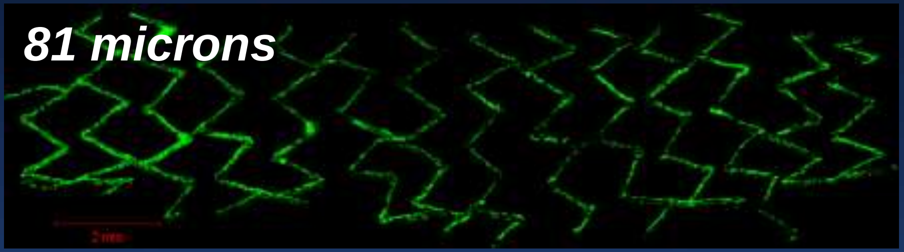


Koskinas et al. JACC 2012;59:1337-49

BVS



SYNERGY



- Ex vivo AV shunt in pigs (carotid artery-JV)
- 3 Stents deployed in series in a silicone tube
- Order of devices was varied in different shunts
- Stents exposed to flowing blood for ~60 min
- Staining for platelets (CD61) was performed

Michael Joner, EuroPCR 2014

GHOST-EU Registry: PCI With BVS in Routine Clinical Practice

1,189 Patients received BVS at 10 European centers, Nov 2011-Jan 2014

- Target lesion failure (cardiac death, target vessel MI, or clinically driven TLR) occurred in 4.4% of patients at 6 months

Compared to DES: (1) strut thickness (polymeric mass), (2) biomechanical behavior and (3) thrombogenic profile of BRS are different, then proper patient and lesion selection are key to obtain optimal clinical outcomes

Capodanno D, et al. EuroIntervention, 2014

BRS and Vessel Healing

Multifactorial and Time-Dependent Process

ACUTE PHASE

(1) Scaffold Biomechanics: Dilatation and Recoil

(2) Mechanical Impact on Vessel Injury

(3) Scaffold Material Exposure

Acute Vessel Wall Inflammation

Scaffold Surface Cell Coverage

ACUTE VESSEL PATENCY:
SCAFFOLD BIOMECHANICS
MATERIAL THROMBOGENICITY

CHRONIC PHASE

(1) Polymer Biocompatibility
(2) Polymer Absorption Rate
(3) Drug PK Profile

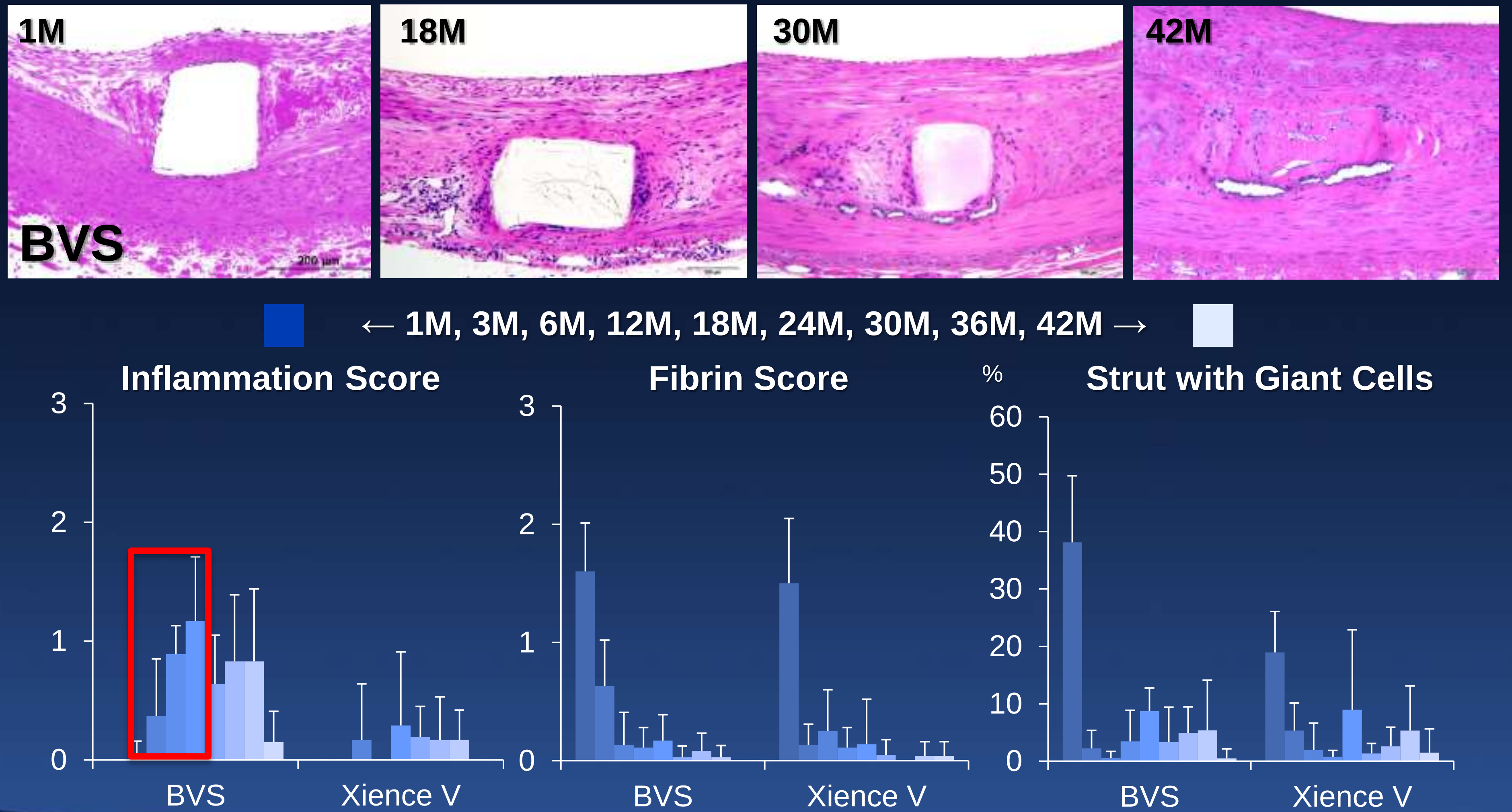
Chronic Vessel Injury & Healing (Inflammatory)

Vessel Wall Healing

Neointimal Proliferation

Do BRS induce higher levels of inflammation and neointimal formation compared to metallic DES?

Progression of Para-Strut Inflammation: BVS vs. Xience V



Courtesy of Renu Virmani

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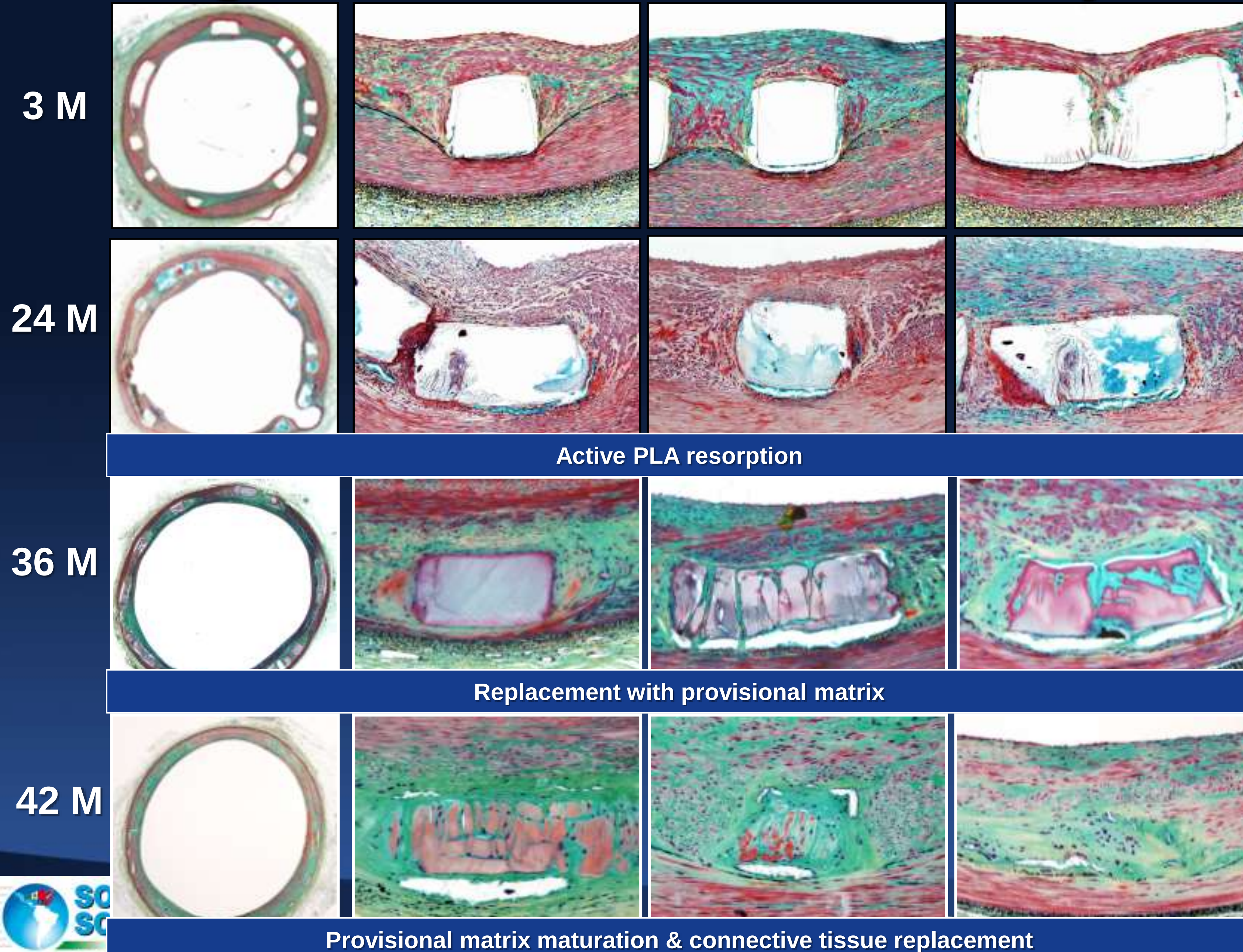
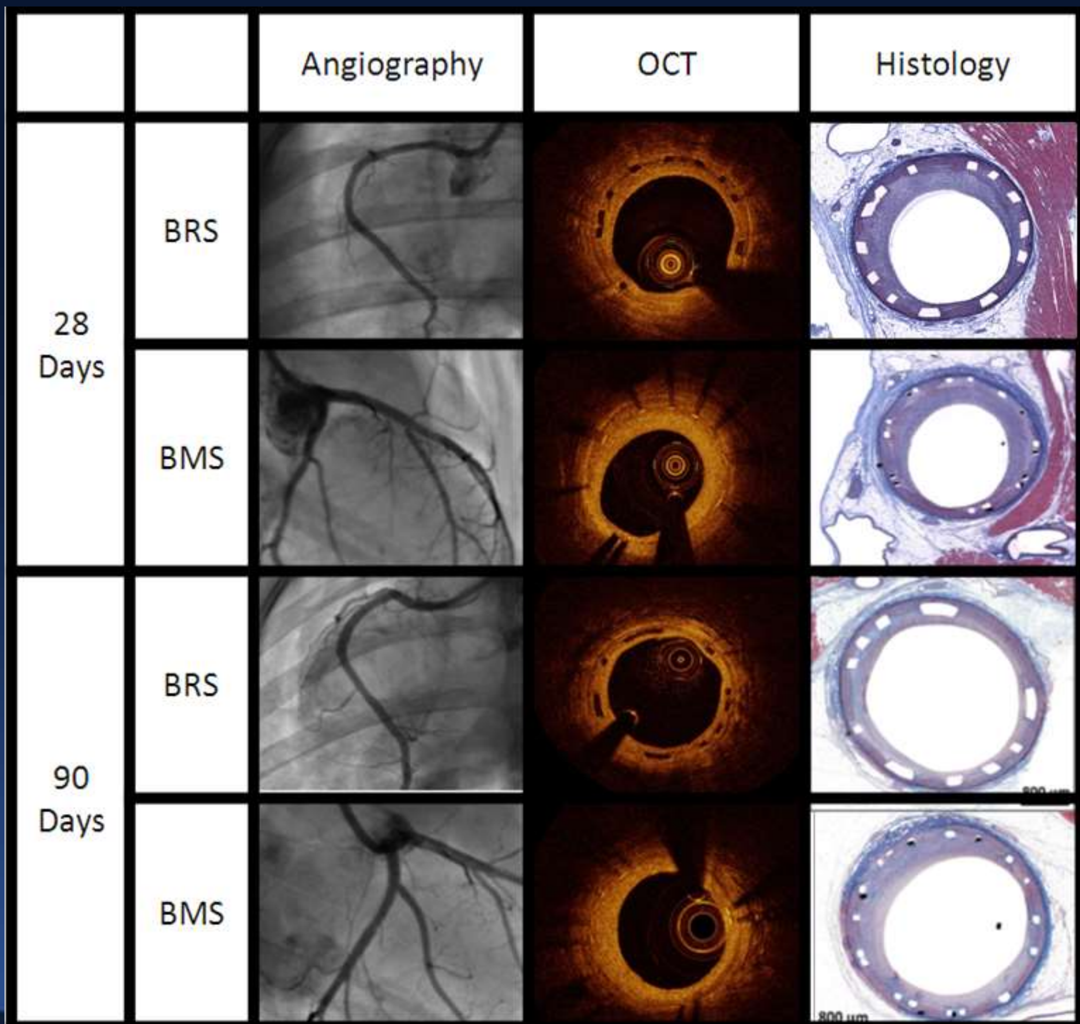
BVS Degradation in Porcine Coronary Arteries



Bare 2nd Generation BRS (Amaranth)

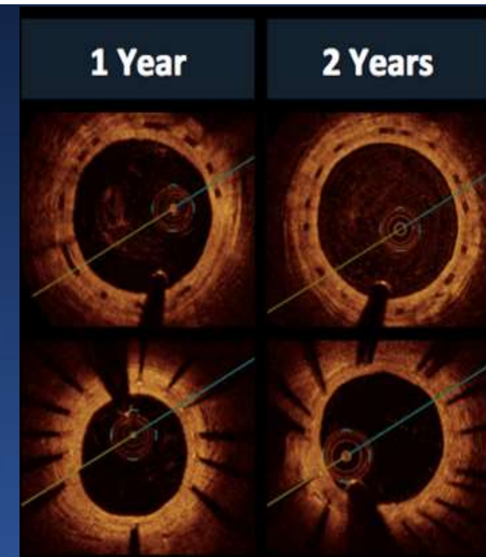
Biocompatibility vs. Thin Strut BMS at 2 Years



Comparable long-term polymer biocompatibility compared to thin-strut BMS

Amaranth BRS

Xience V BMS



BRS and Vessel Healing

Multifactorial and Time-Dependent Process

ACUTE PHASE

(1) Scaffold Biomechanics: Dilatation and Recoil

↓

(2) Mechanical Impact on Vessel Injury

↓

(3) Scaffold Material Exposure

↙ Acute Vessel Wall Inflammation

↓

↘ Scaffold Surface Cell Coverage

ACUTE VESSEL PATENCY:
SCAFFOLD BIOMECHANICS
MATERIAL THROMBOGENICITY

CHRONIC PHASE

(1) Polymer Biocompatibility
(2) Polymer Absorption Rate
(3) Drug PK Profile

↓

Chronic Vessel Injury & Healing (Inflammatory)

↓

Vessel Wall Healing

↓ Neointimal Proliferation

↓ Vessel Remodeling

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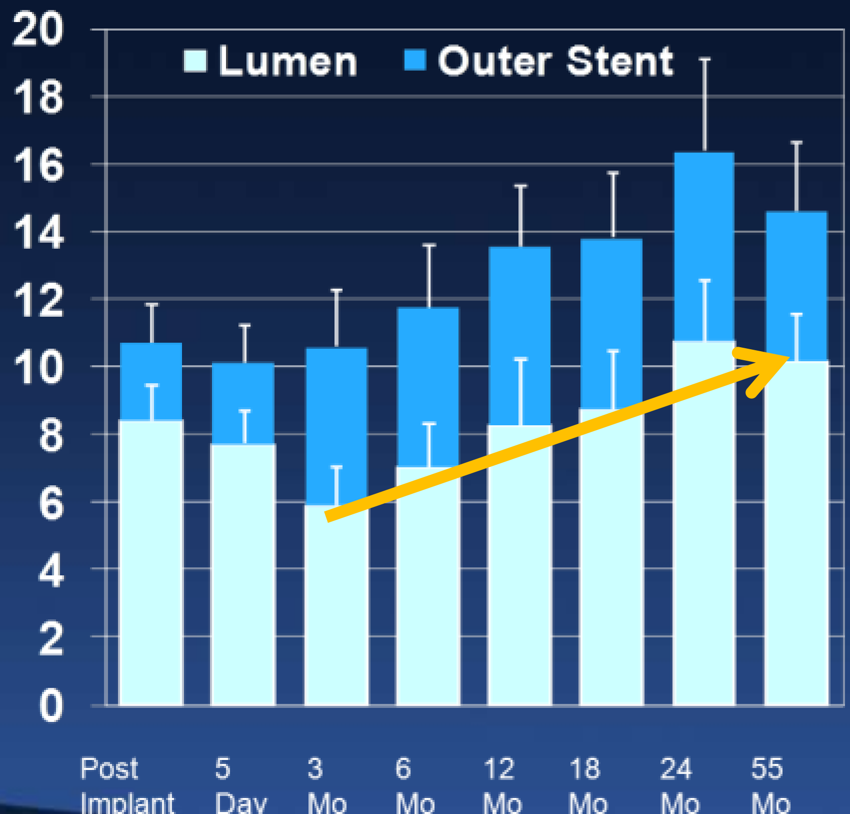
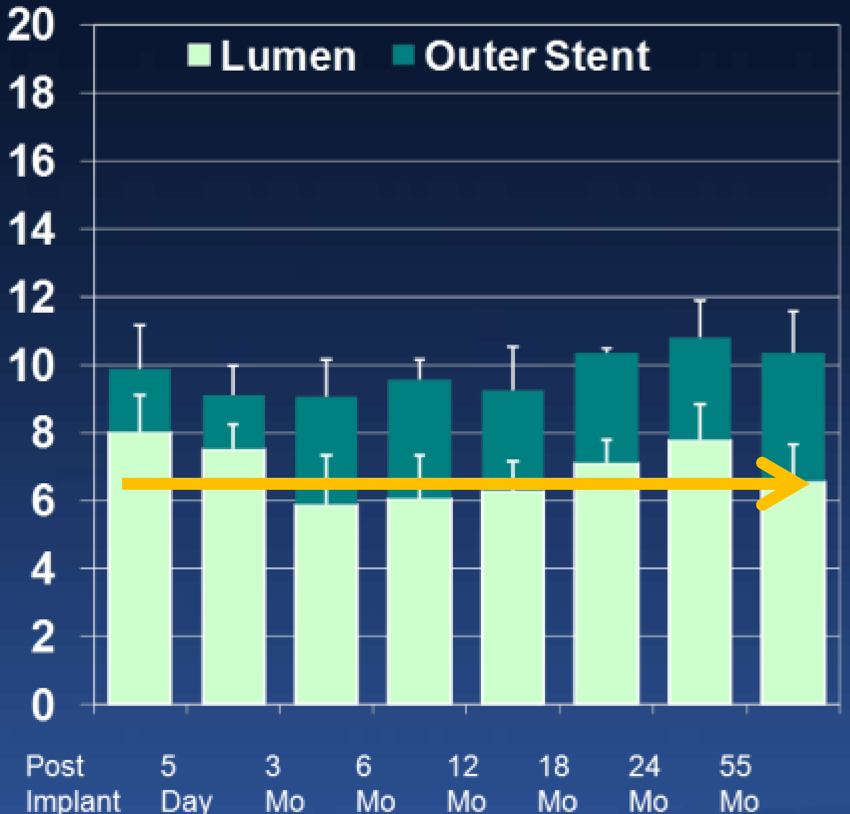
Positive Vascular Remodeling in Non-Drug Eluting BRS

IVUS-Based Lumen and Stent Areas (mm^2)

Bioresorbable (No Drug)



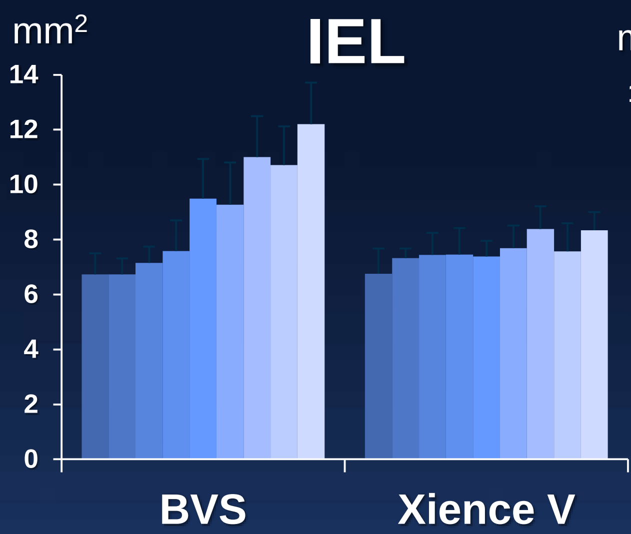
Bare Metal

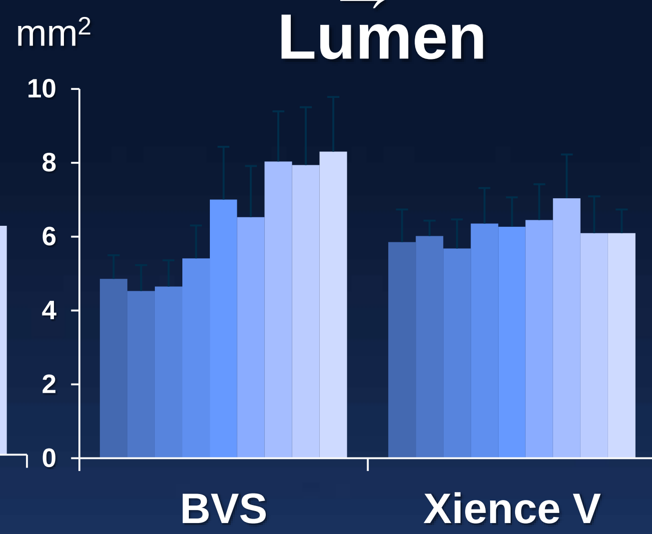


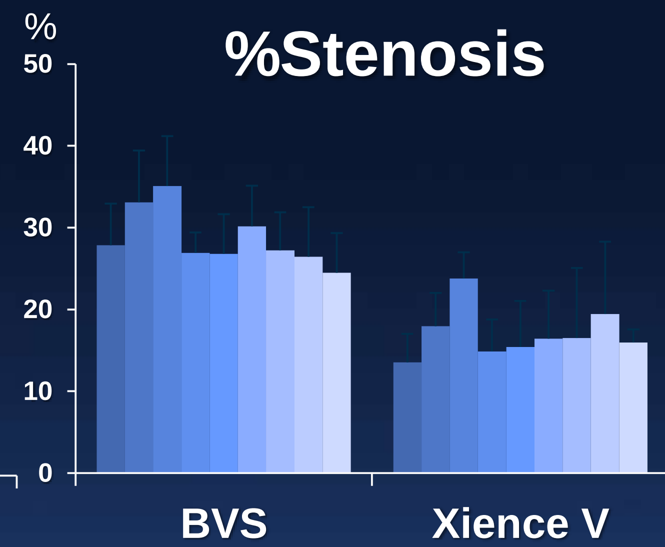
Strandberg E. Circ Cardiovasc Interv, 2012; 5(1):39-46

Morphometric Analysis of BVS and Xience V in Porcine Coronary Model

← 1M, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M →

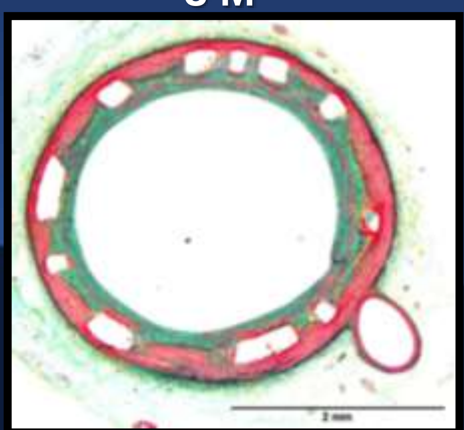




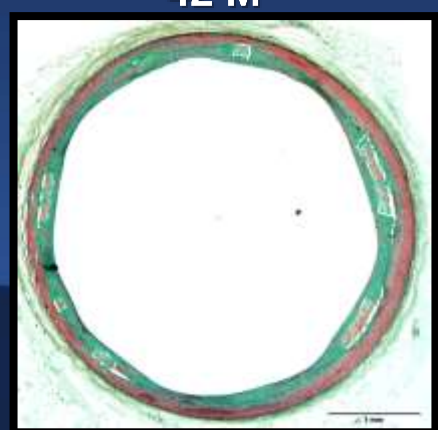


BVS

3 M

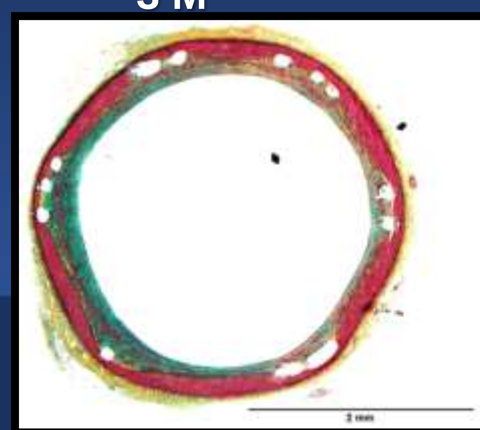


42 M



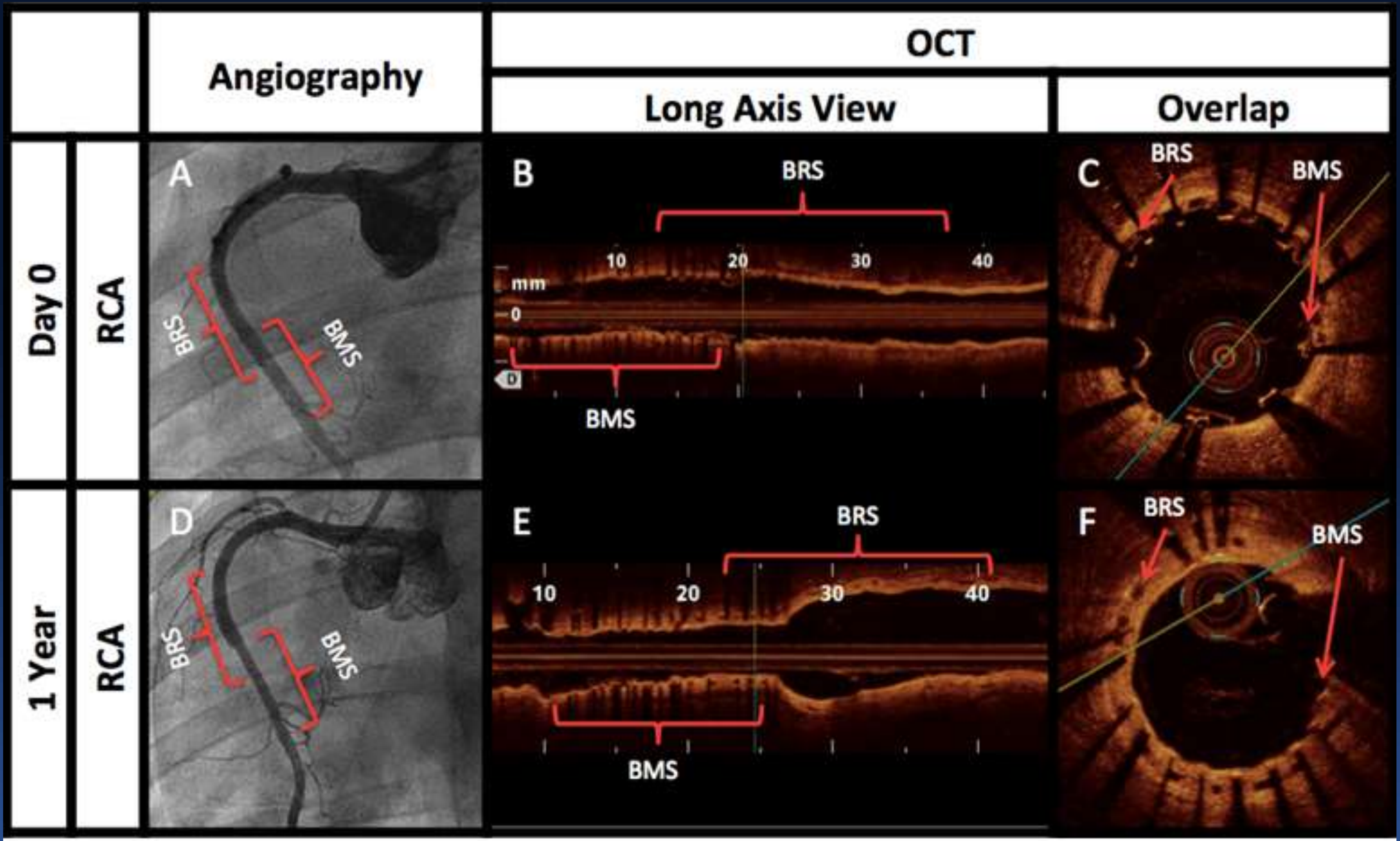
Xience V

3 M



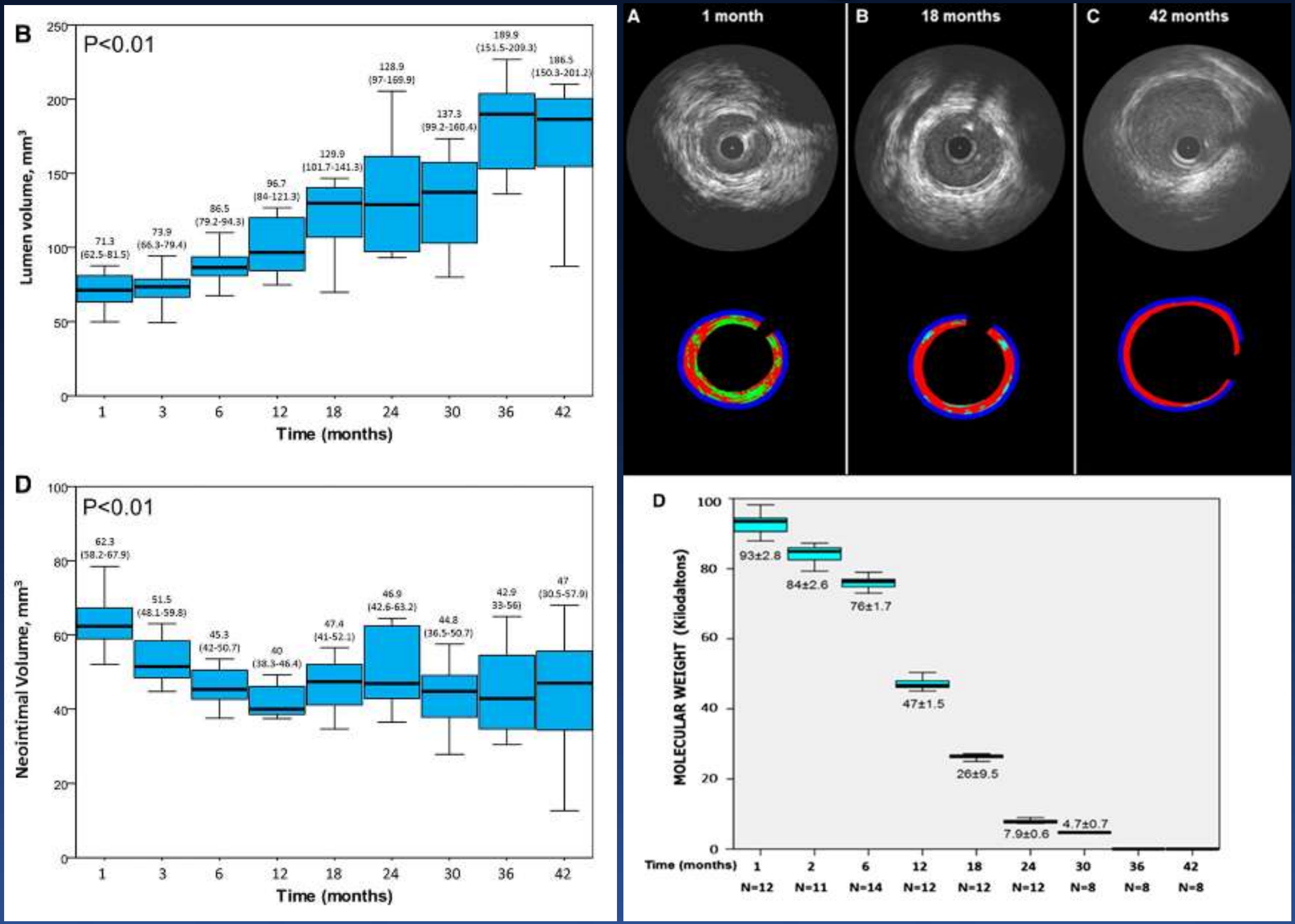
42 M

Overlapping ABRS and BMS at 1-Year



Gongora C, Kaluza G. JACC Interv. July 2015

Impact of BVS Degradation in Vascular Remodeling in Porcine



Campos CM. Int J Cardiovasc Imaging. 2015 Jan 28

BRS and Vessel Healing

Multifactorial and Time-Dependent Process

ACUTE PHASE

(1) Scaffold Biomechanics: Dilatation and Recoil

(2) Mechanical Impact on Vessel Injury

(3) Scaffold Material Exposure

Acute Vessel Wall Inflammation

Scaffold Surface Cell Coverage

ACUTE VESSEL PATENCY:
SCAFFOLD BIOMECHANICS
MATERIAL THROMBOGENICITY

CHRONIC PHASE

(1) Polymer Biocompatibility
(2) Polymer Absorption Rate
(3) Drug PK Profile

Chronic Vessel Injury & Healing (Inflammatory)

Vessel Wall Healing

Scaffold Surface Coverage

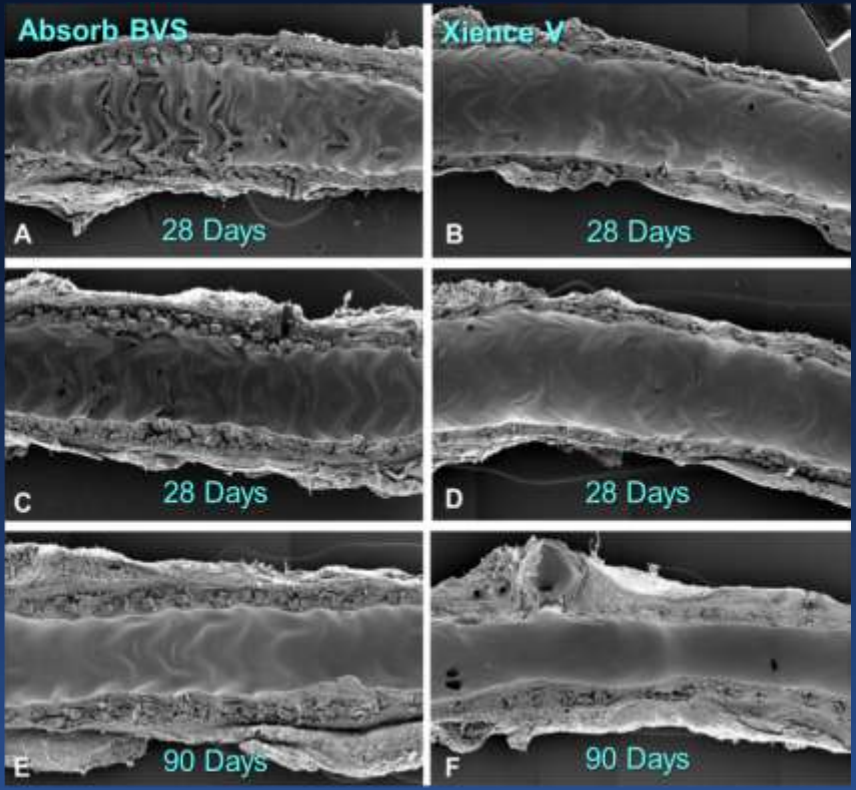
Neointimal Proliferation

Vessel Remodeling

Surface Endothelialization

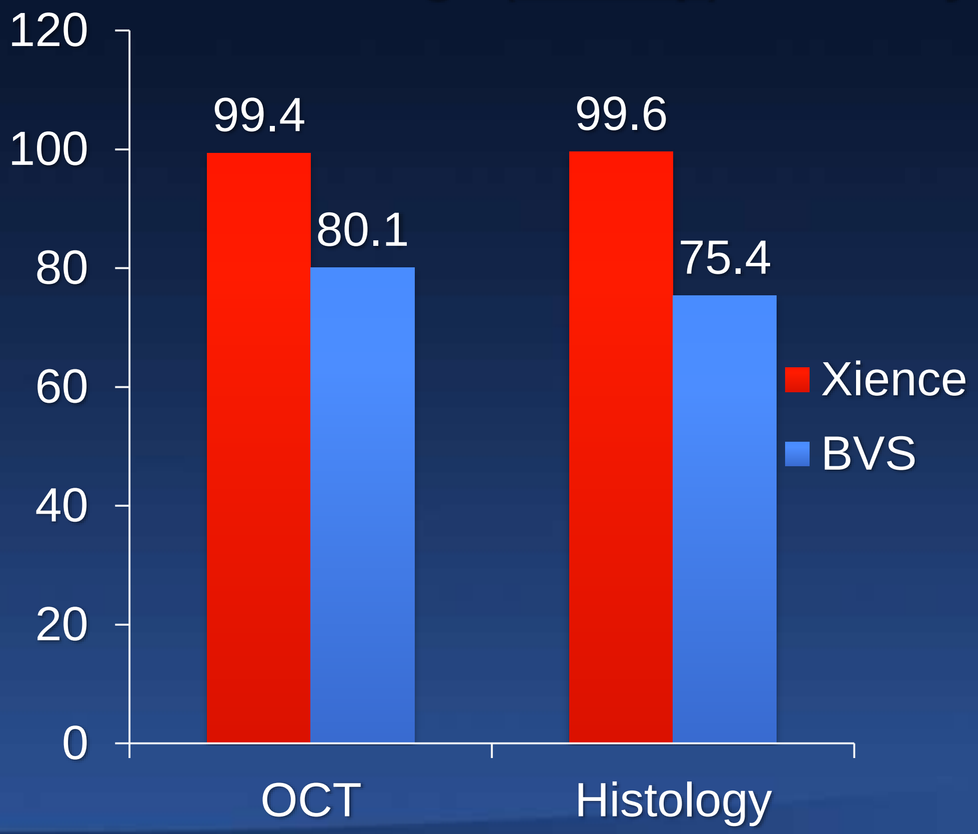
Intracoronary Optical Coherence Tomography and Histology of Overlapping Everolimus-Eluting Bioresorbable Vascular Scaffolds in a Porcine Coronary Artery Model

The Potential Implications for Clinical Practice



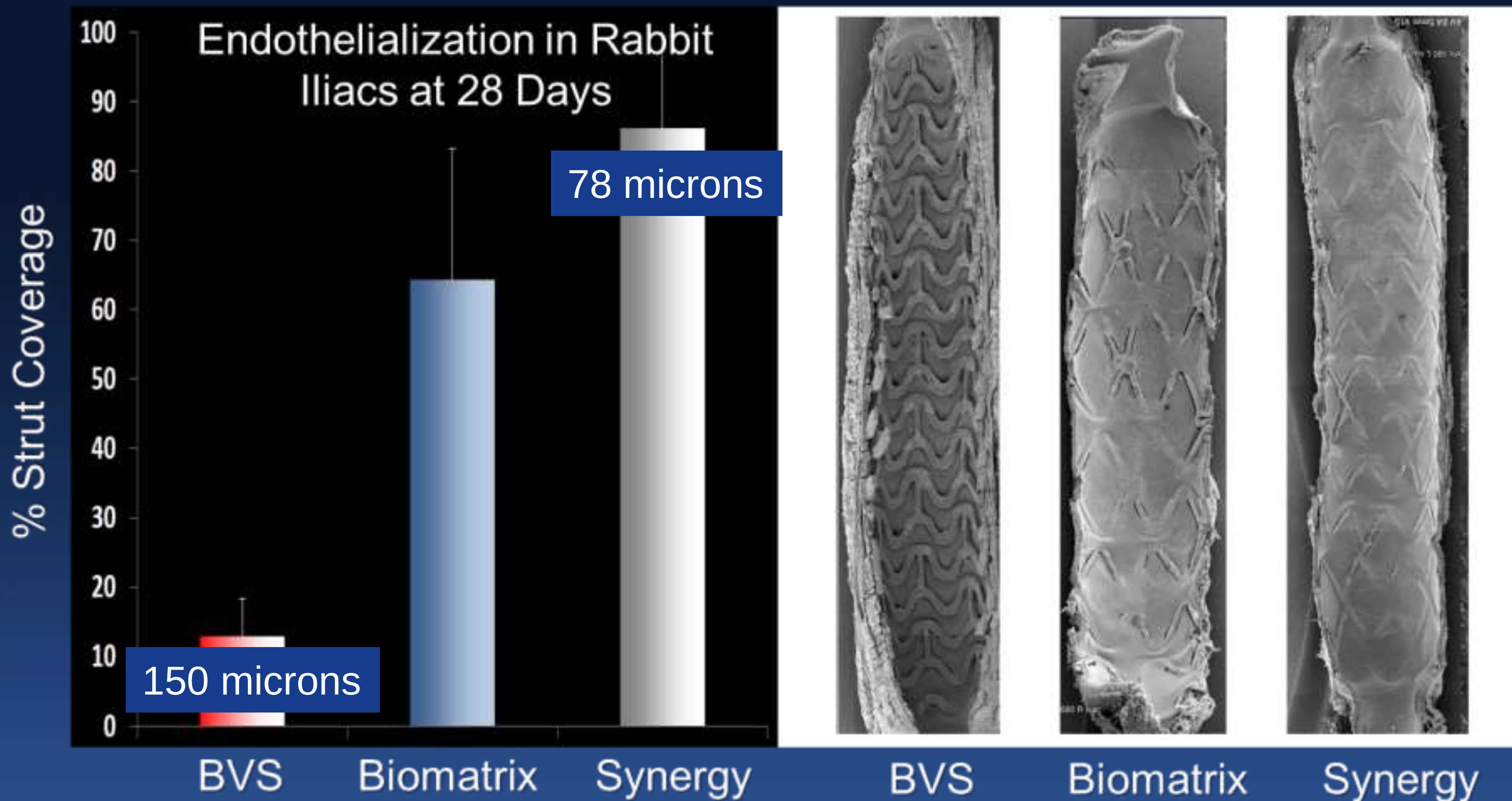
Both devices fully covered by 90 days

% Strut Coverage (overlap) at 28 Days



Farooq V. JACC Interv 2013;6:523-32

Impact of Strut Thickness on EC Coverage: BVS vs. Metallic DES



Presented by Renu Virmani, TCTAP2014

BRS and Vessel Healing

Multifactorial and Time-Dependent Process

ACUTE PHASE

(1) Scaffold Biomechanics: Dilatation and Recoil

↓

(2) Mechanical Impact on Vessel Injury

↓

(3) Scaffold Material Exposure

↓

- Acute Vessel Wall Inflammation
- Scaffold Surface Cell Coverage

↓

ACUTE VESSEL PATENCY:
SCAFFOLD BIOMECHANICS
MATERIAL THROMBOGENICITY

CHRONIC PHASE

(1) Polymer Biocompatibility
(2) Polymer Absorption Rate
(3) Drug PK Profile

↓

Chronic Vessel Injury & Healing (Inflammatory)

↓

- Vessel Wall Healing → Neointimal Proliferation; Vessel Remodeling
- Scaffold Surface Coverage → Surface Endothelialization

↓

RESTENOSIS
NEOATHEROSCLEROSIS

↓

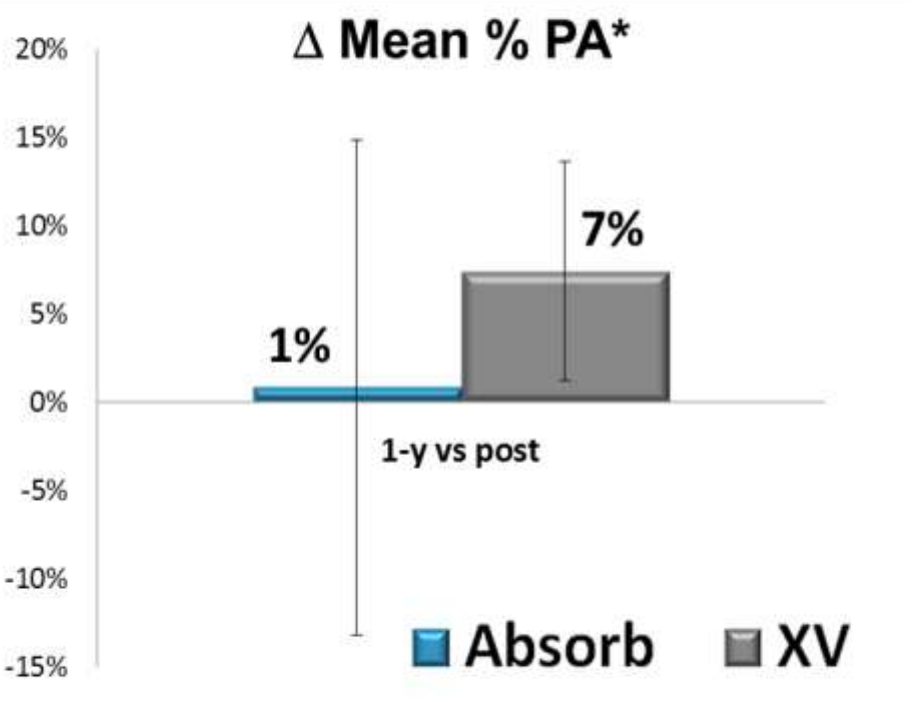
VESSEL PATENCY
VESSEL HEALING & REMODELING

Absorb BVS in FHS Lesion Model

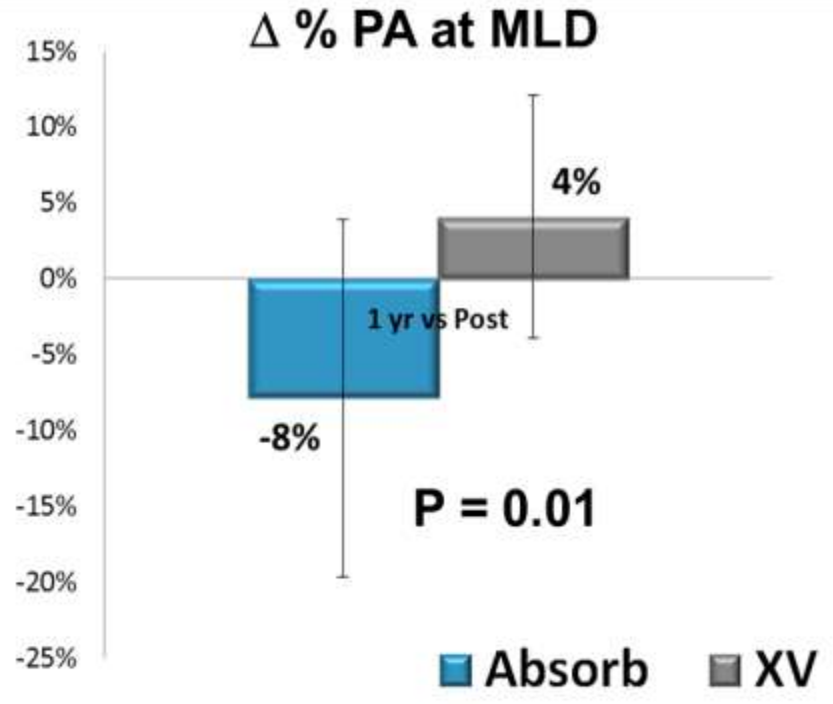
Mean Plaque Progression in Device Segment

Baseline to 1 year Δ % Plaque Area (PA) by IVUS

Vessel Segment*



At MLD Segment



*Values represent the mean of proximal, mid and distal segments

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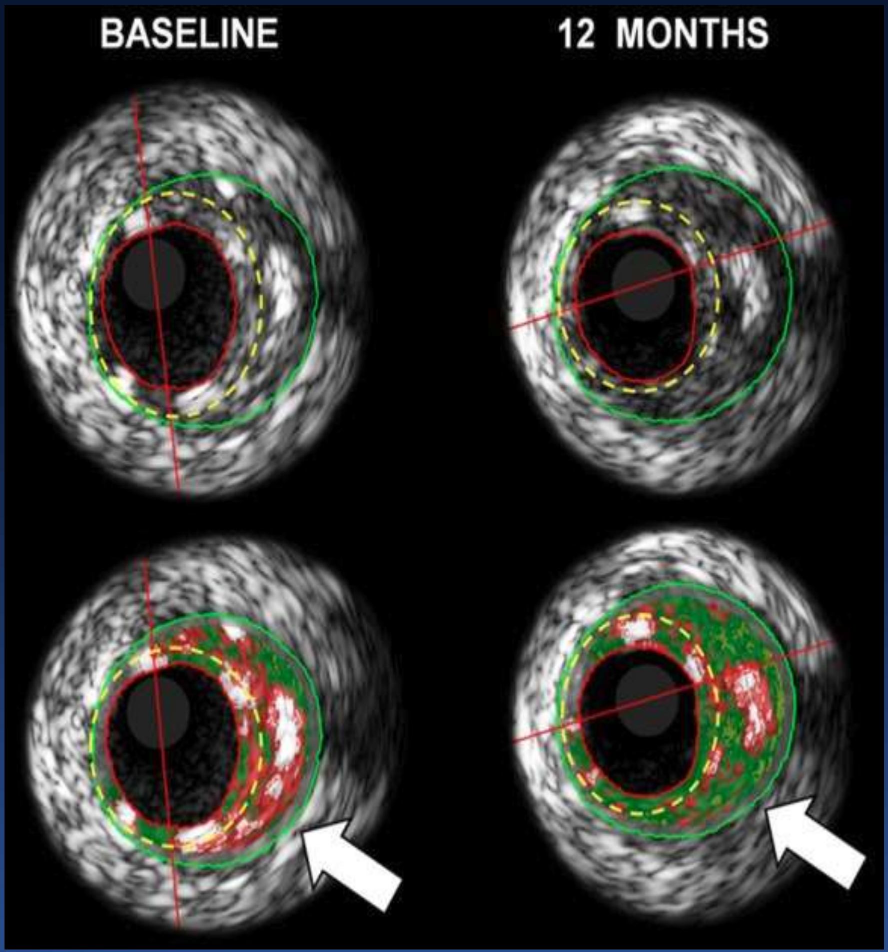
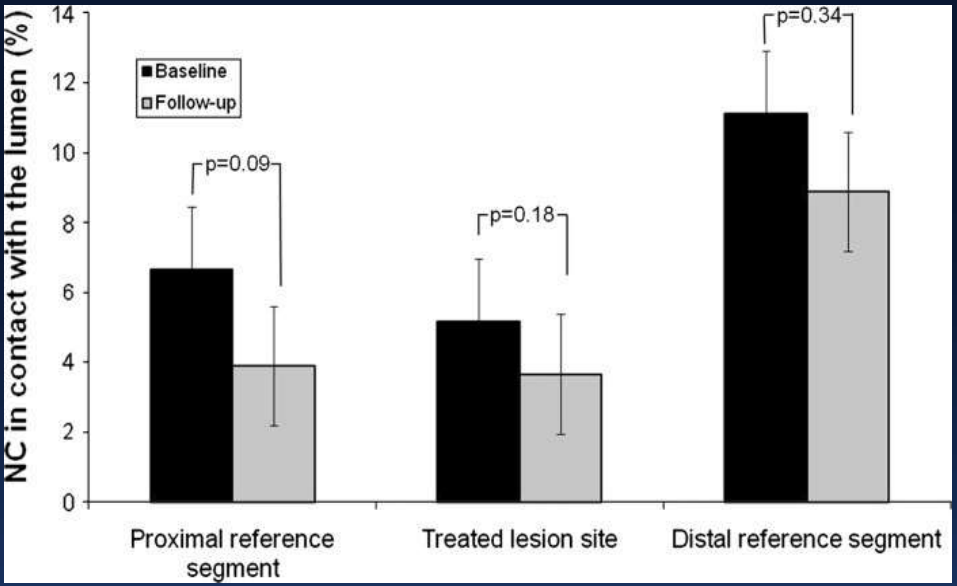
Atherosclerotic Plaque Component Change at 12 Months Following BVS

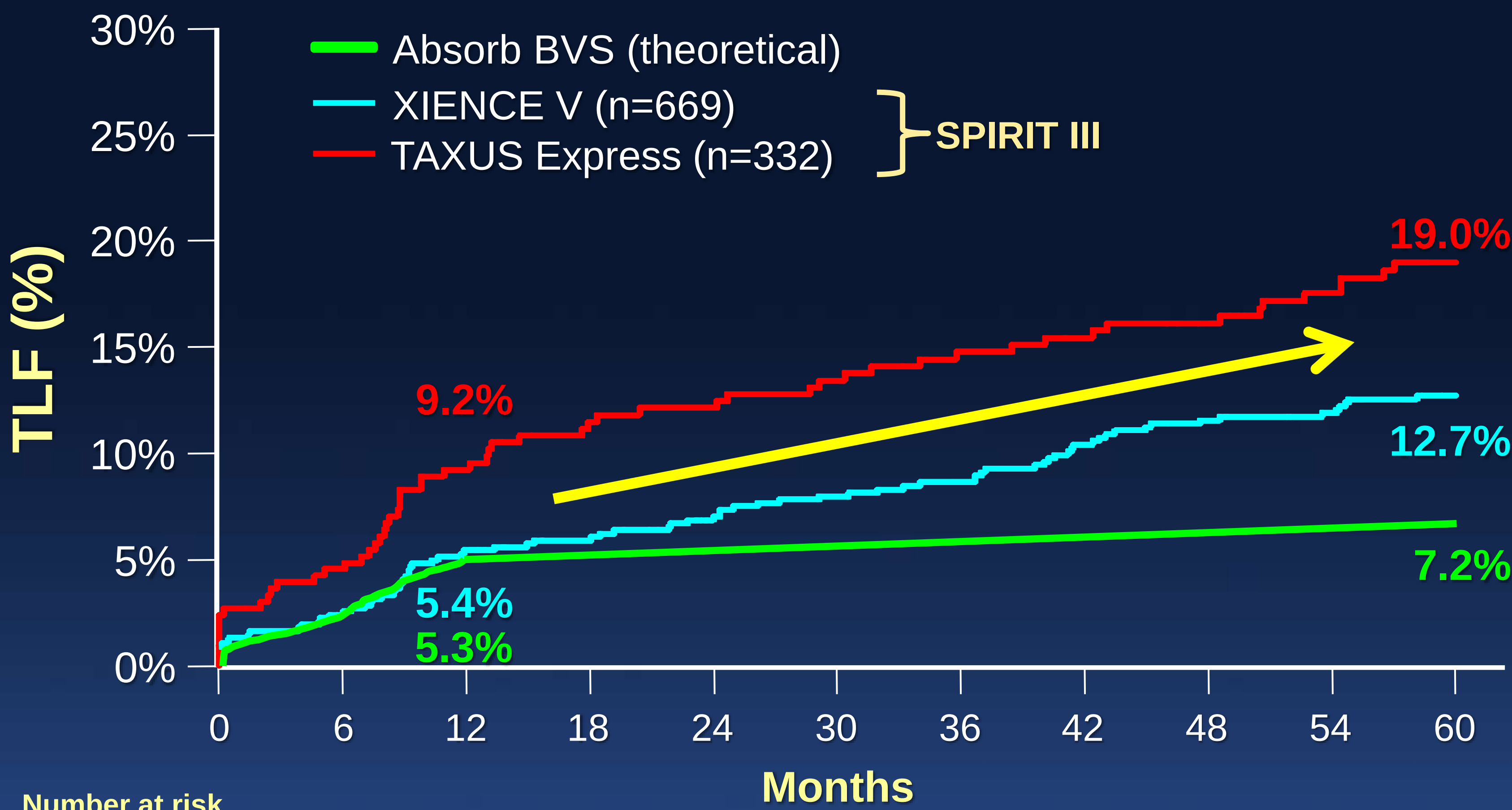




Increase in mean PBS area (2.39 ± 1.85 mm^2 vs. 2.76 ± 1.79 mm^2, P = 0.078). Significant decrease of 16% and 30% in necrotic core (NC) and dense calcium (DC) content

Brugaletta S. Int J Cardiovasc Imaging. 2012 Aug; 28(6): 1307–1314

The Promise of BRS…



Number at risk											
XIENCE V	669	646	616	601	582	571	565	548	537	529	521
TAXUS	332	310	288	274	269	262	255	248	243	231	223

TLF = cardiac death, target vessel MI, or ischemic-driven TLR

Spirit III: Gada H et al. J Am Coll Cardiol Intv 2013;6:1263–6

ABSORB II: 1-Year Clinical Outcomes

501 randomized pts (non-complex)	Absorb 335 pts	Xience 166 pts	*P* value
Composite of cardiac death, TV-MI, clinically indicated TLR (TLF; DoCE)	4.8%	3.0%	0.35
- Cardiac death	0%	0%	1.00
- Target vessel MI	**4.2%**	1.2%	0.07
- Clinically indicated TLR	1.2%	1.8%	0.69
- All TLR	1.2%	1.8%	0.69
Composite all death, all MI, all revasc (PoCE)	7.3%	9.1%	0.47
- All death	0%	0.6%	0.33
- All MI	**4.5%**	1.2%	0.06
- All revascularization	3.6%	**7.3%**	0.08

Serruys PW et al. *Lancet* 2014

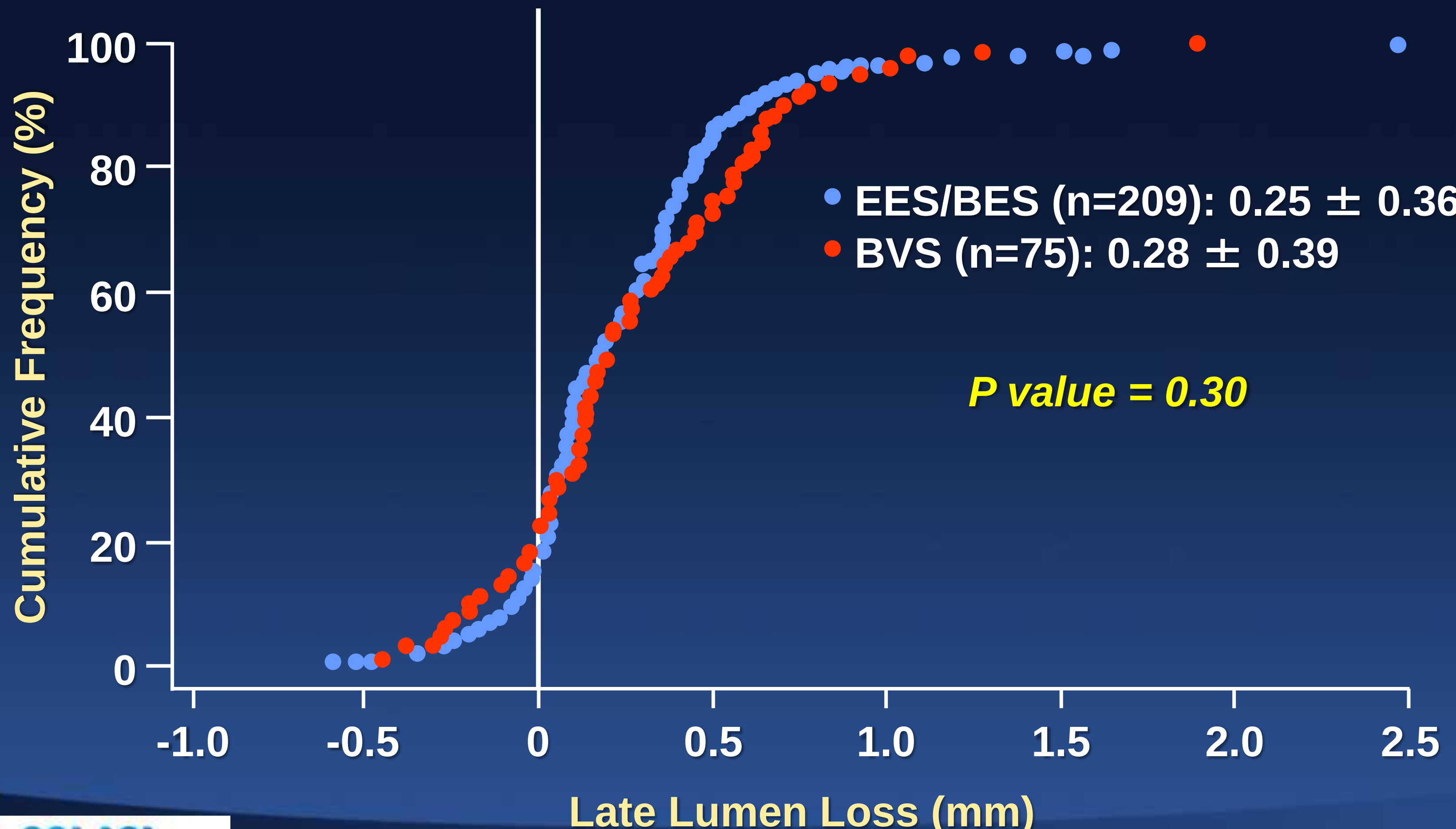
ABSORB II: Scaffold Thrombosis

501 randomized pts (non-complex)	Absorb 335 pts	Xience 166 pts	*P* value
Definite scaffold/stent thrombosis			
- Acute (0-1 day)	0.3% (1 pt)	0.0	1.0
- Sub-acute (2–30 days)	0.3% (1 pt)	0.0	1.0
- Late (31–365 days)	0.0	0.0	-
Probable scaffold/stent thrombosis			
- Acute (0-1 day)	0.0	0.0	-
- Sub-acute (2–30 days)	0.0	0.0	-
- Late (31–365 days)	0.3% (1 pt)	0.0	1.0
Definite or probable scaffold/stent thrombosis	0.9% (3 pts)	0.0	0.55

Serruys PW et al. *Lancet* 2014

EVERBIO II: 240 Pts Ranromized 1:1:1 at a Single Center to EES, BES or BVS

1° EP: 9-Month In-Stent Late Lumen Loss (mm)



Puricel S et al. *JACC* 2015;65:791–801

The Reality Today: Issues that 2nd Gen. BRS Will Have to Overcome

Technical-Procedural

1. Profile, deliverability, visibility, overlap, retention
2. Efficient pre and post-dilatation
3. Avoid complex peri-procedural imaging
4. Use in all type of lesions (i.e., calcified)

Clinical Outcomes

1. Comparable short term TVF-ST rates
2. Superior long-term TLR rates?

ABSORB III (TCT2015) + IV

A clinical program consisting of 2 integrated randomized trials designed to:

1) Achieve approval of ABSORB in the US

and

2) Demonstrate superiority of ABSORB compared to best in class DES

ABSORB III: 2,000 randomized patients
ABSORB IV: 3,000 randomized patients (enrolling)

Comparative Vascular Compatibility

BRS versus Metallic DES

BIOLOGICAL VARIABLE	Metallic DES	CURRENT BRS

- In general, BRS display a vascular healing profile comparable to metallic DES, although current structural properties sustain some concerns about higher thrombogenic potential. As with DES, however, prompt improvements are expected as technology advances rapidly (thinner struts etc.)
- Outside this issue, compared to metallic DES:
  - BRS have the potential to achieve higher long term lumen patency rates and lower degrees of plaque progression
  - BRS offer additional biological advantages and have the potential to improve long-term clinical outcomes compared to metallic DES