

Impact of DES Design on the Duration of DAPT

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Disclosure

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

Employment in industry: No

Honorarium: Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

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Owner of a healthcare company: No









Stockholder of a healthcare company: No

Short-term DAPT: What Matters

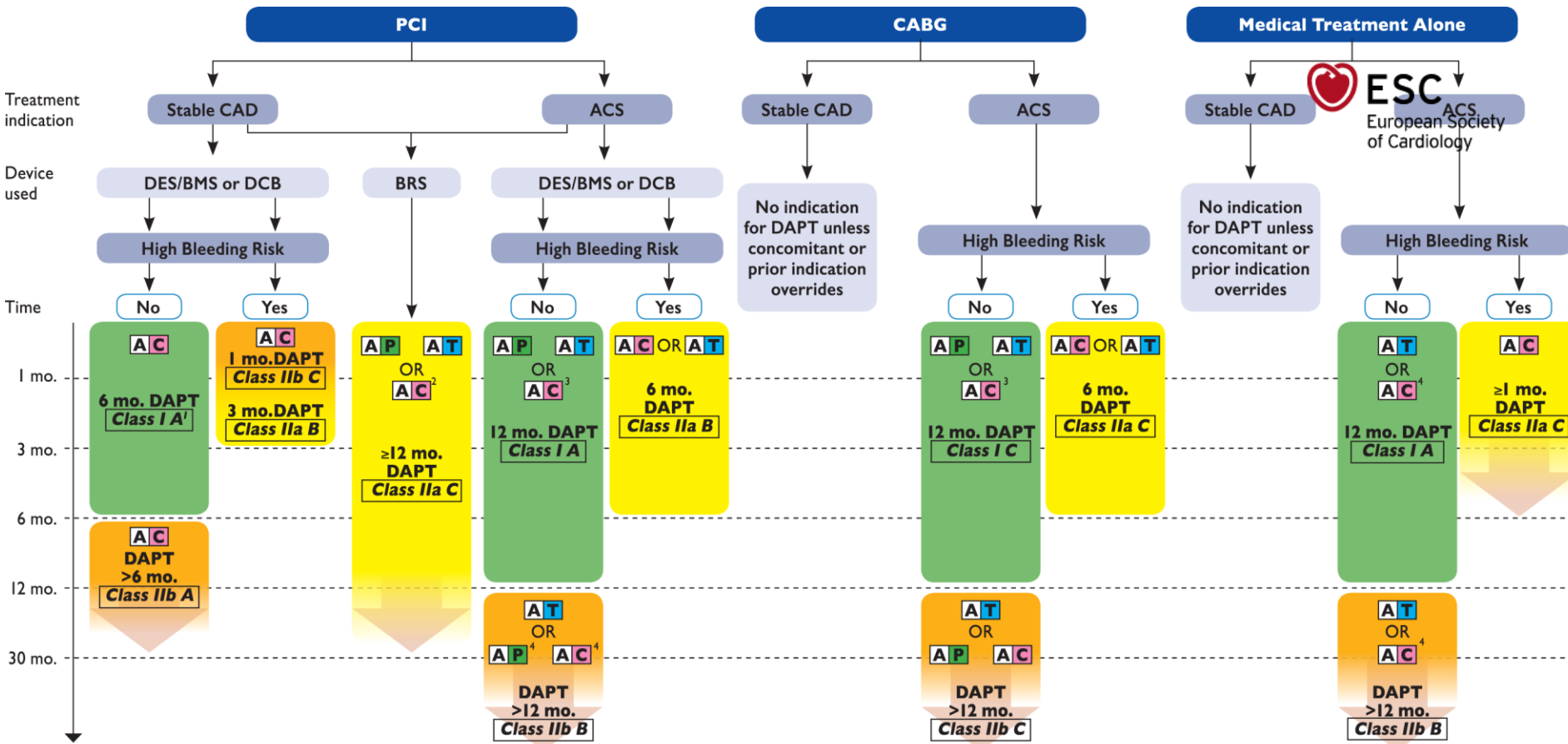
- Thromboresistance:
 - Thin strut design with minimal flow disturbance
 - Cell shape and size?
 - Polymer Coating
 - Permanent versus Bioabsorbable versus none
 - Permanent: FP (Xience and Promus), BioLinx (Onyx), and Elastomer (EluNIR)
 - Bioabsorbable: poly(α -hydroxy acid) family, including polylactic acid and polyglycolic acid and their co-polymer polylactic-co-glycolic acid
 - None
 - Conformal Versus Abluminal
- Healing Characteristics

Contemporary DES Platforms

Strut and Coating Thickness In Perspective

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute /Onyx	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"	89/81 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



[A] = Aspirin [C] = Clopidogrel [P] = Prasugrel [T] = Ticagrelor

Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

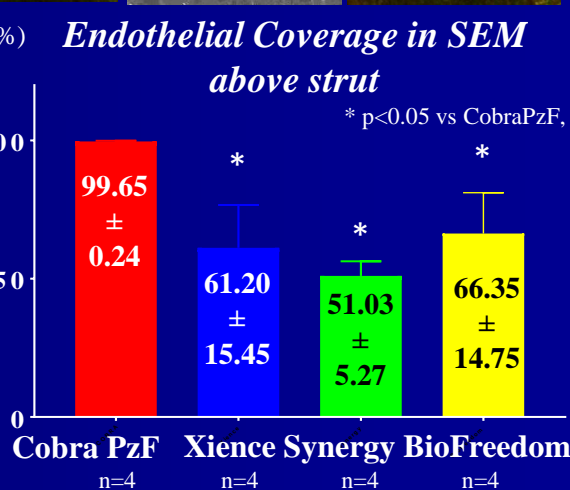
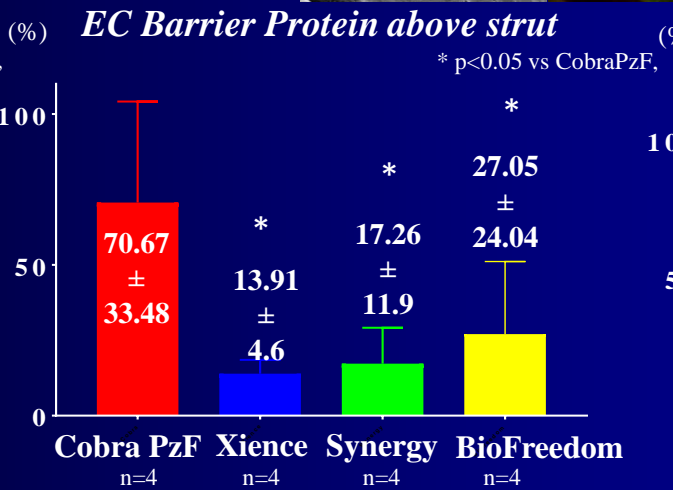
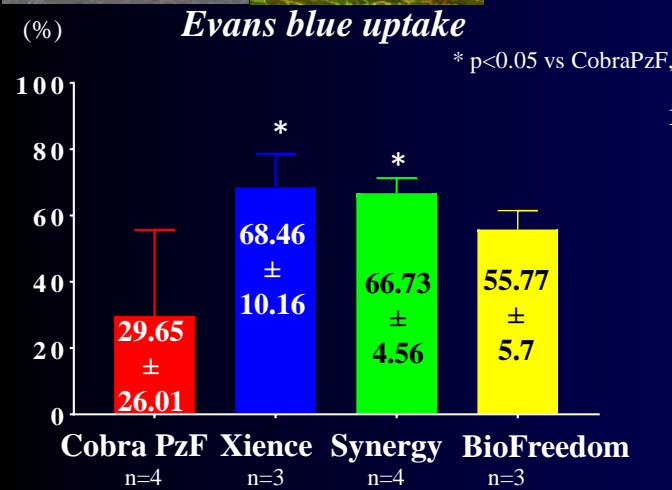
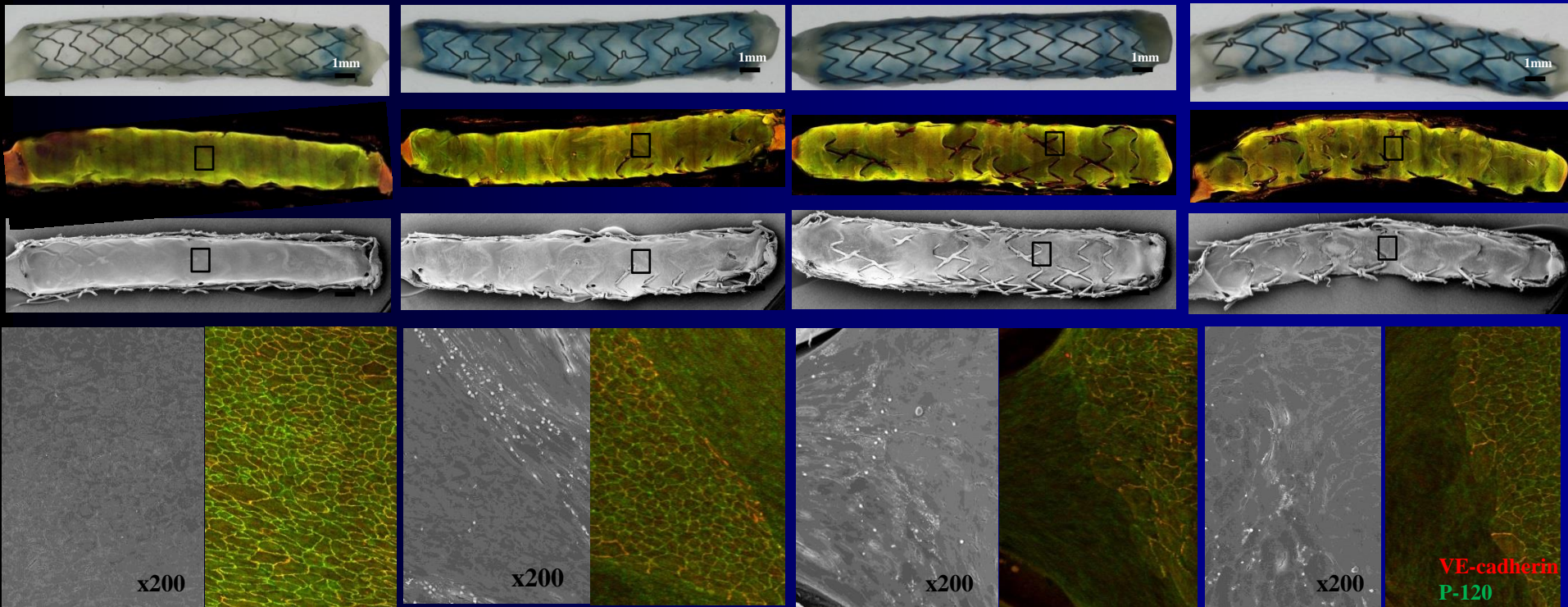
Healing Results of 28-Day In-Life

Cobra PzF

Xience

Synergy

BioFreedom



Presence of Polymer can contribute to reducing platelet adhesion and thrombogenicity

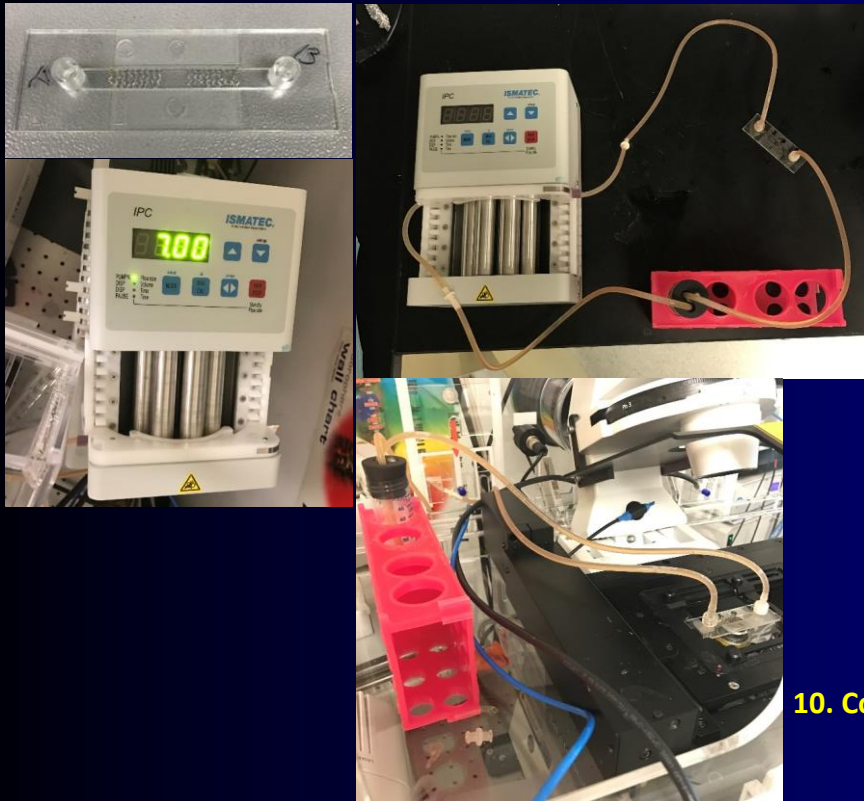
- ✓ Flow Model with Labeled Human Platelet
- ✓ Porcine AV Shunt Model
 - Low dose heparin

Understanding the Concept of Fluoropassivation with respect to thromboresistance of human platelet in a real-time system

Protocol

Stent Preparation

1. Put stents into fetal bovine serum for 24 hours.
2. Wash the stents using PBS with pumping
3. Confocal starts



10. Confocal

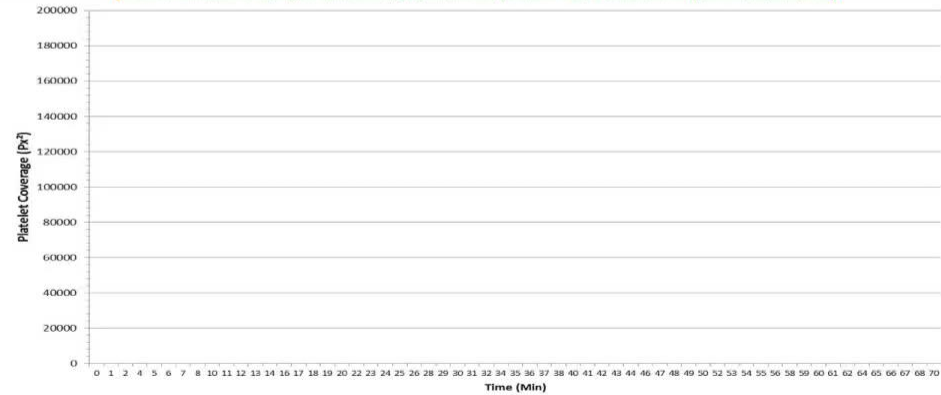
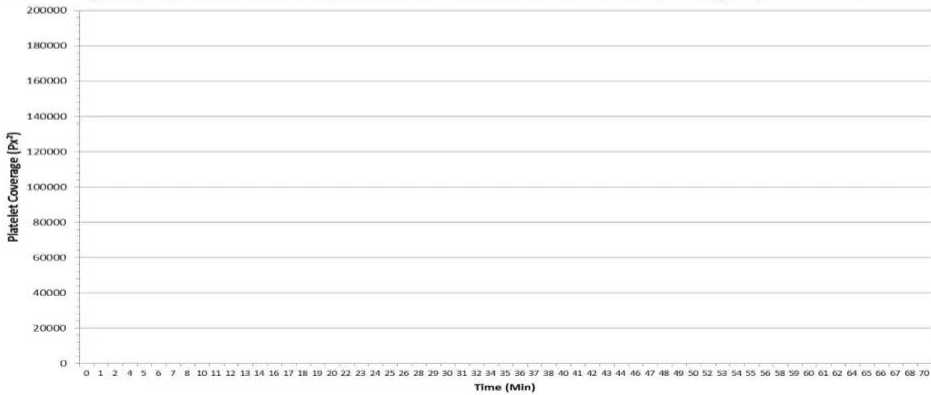
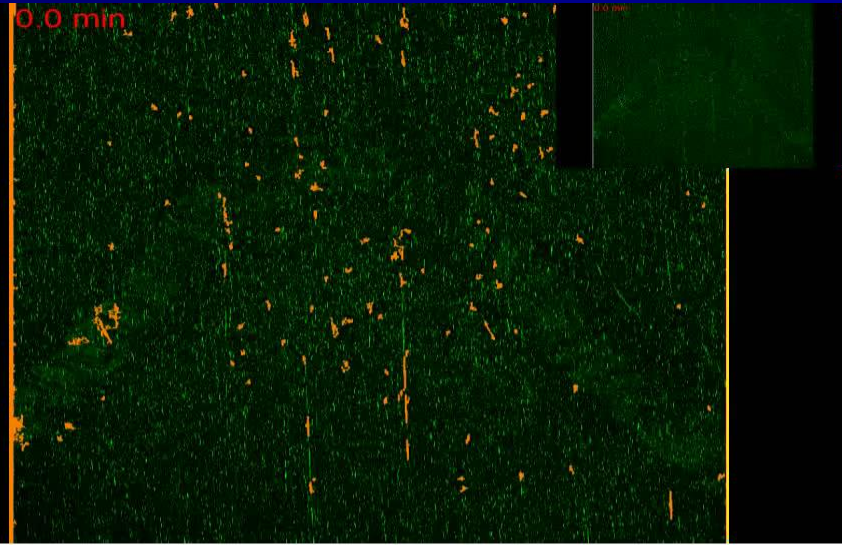
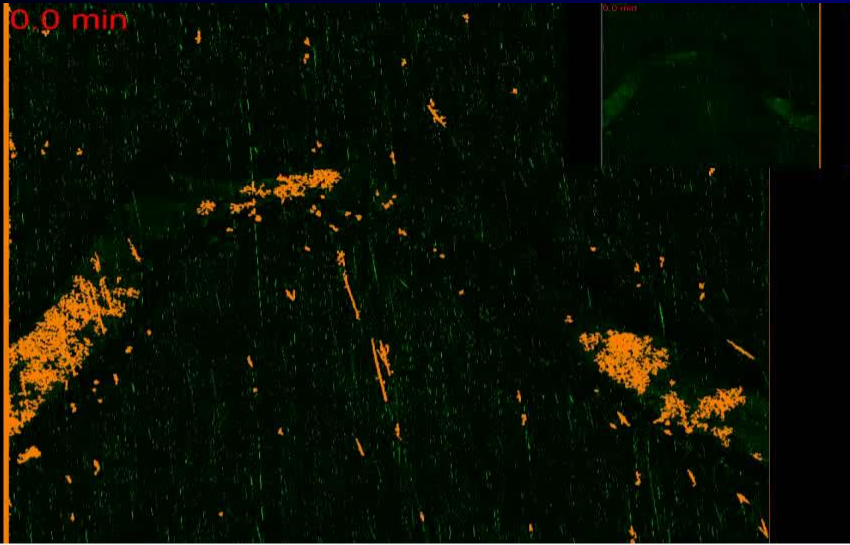
Platelet Preparation

1. Collect human blood (total 60ml, using citrate 0.32%)
2. 200g 10 min centrifuge (first spin)
3. Collect supernatant.
4. 700g 17min centrifuge (second spin)
5. Lower 1/3 PRP and upper 2/3 PPP. Collect PRP.
6. Resuspend PRP
7. Label platelet (using CMFDA) 45min
8. 1300g 10 min centrifuge (third spin)
9. Collect only pellet. And resuspend it using PPP (2-3ml)
Final volume is usually about 20-25ml

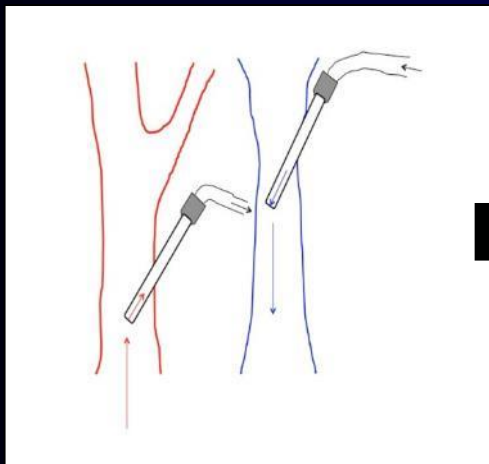


BMS

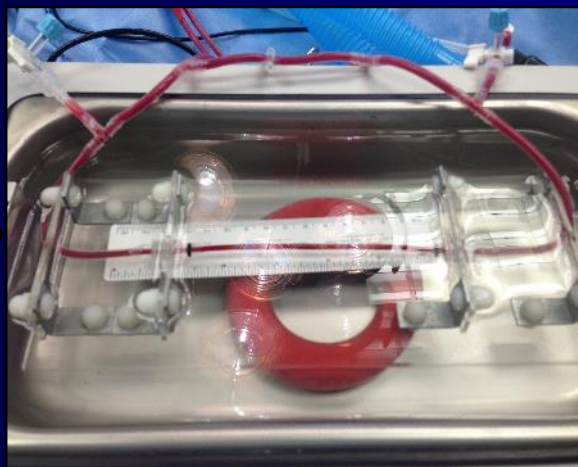
Fluoropolymer



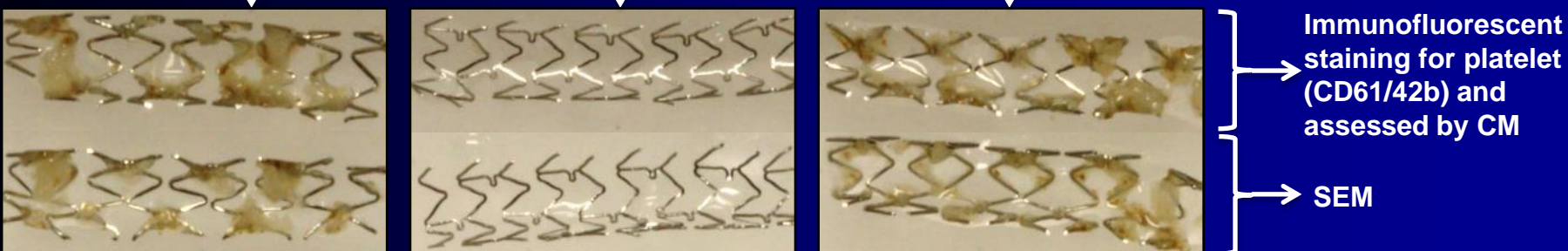
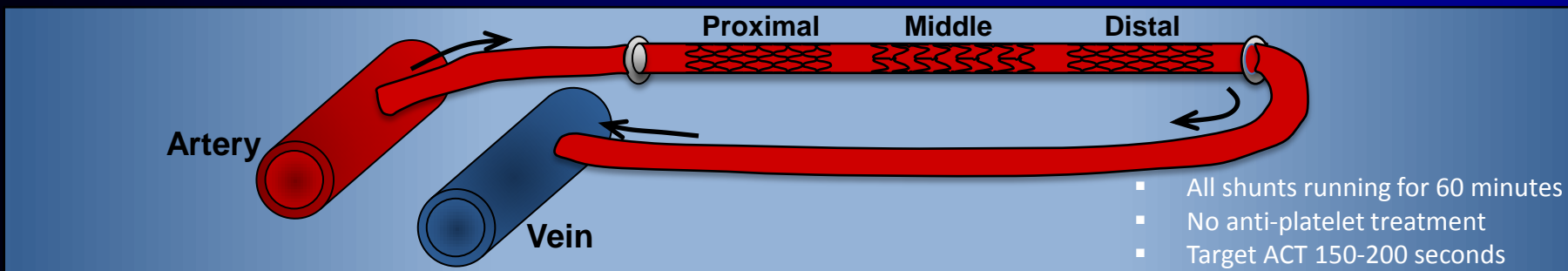
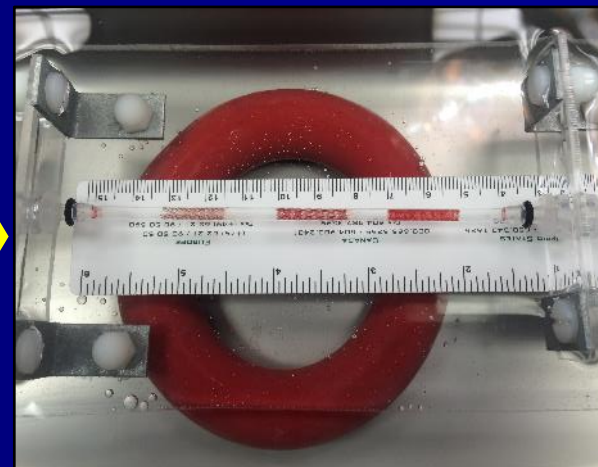
1. Porcine AV shunt: carotid-jugular using customized sheath



2. Arterialized flow using Sylgard tube

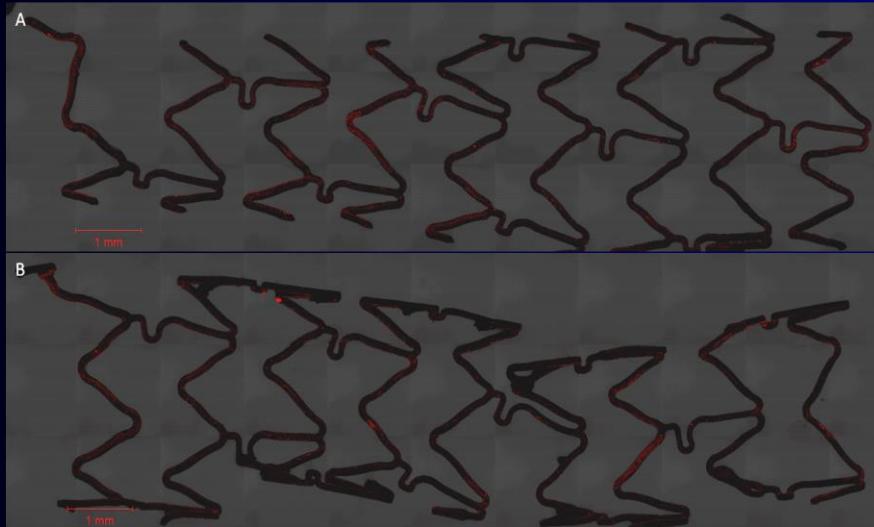


3. Thrombus formation after 1 hour

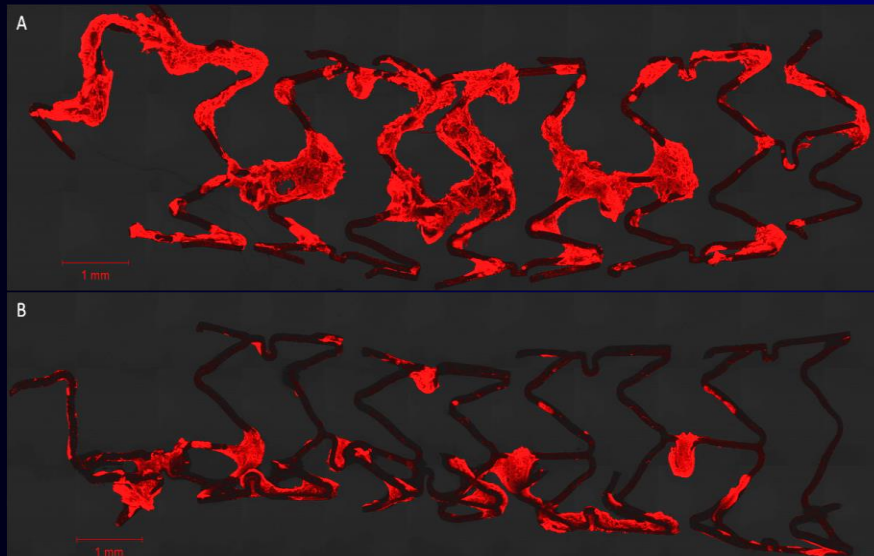


Confocal Microscopy of Shunt Model for Platelets

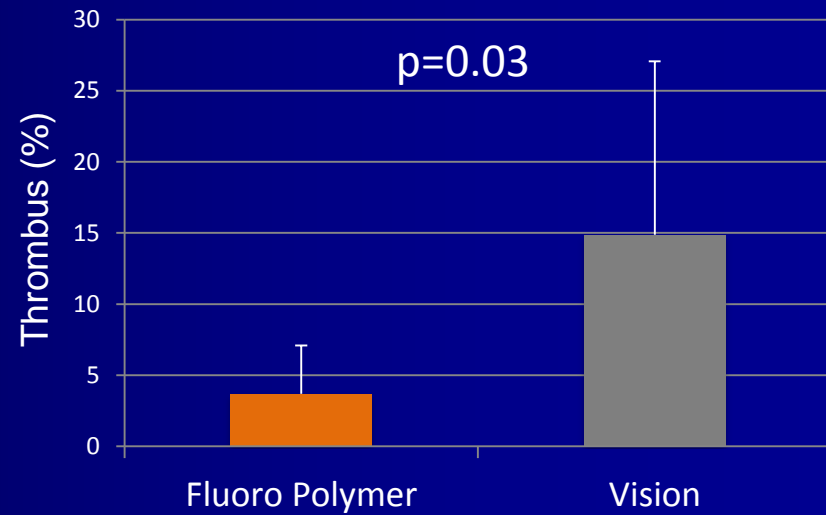
Fluoro Polymer coated



Vision (BMS)



CD42b/CD61 positive staining area

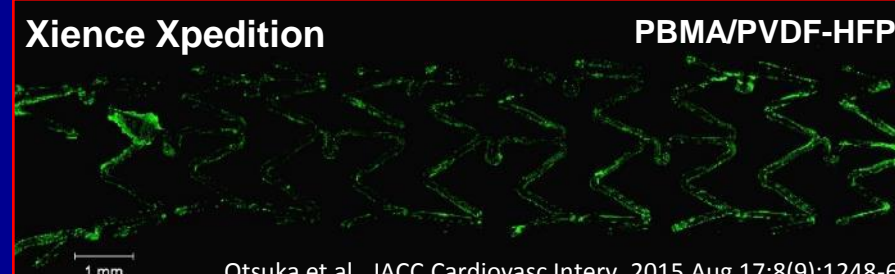
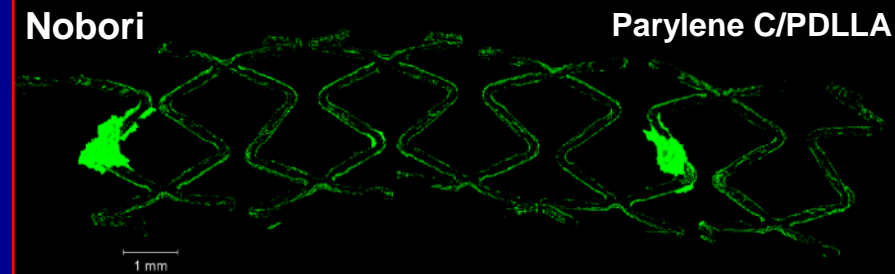
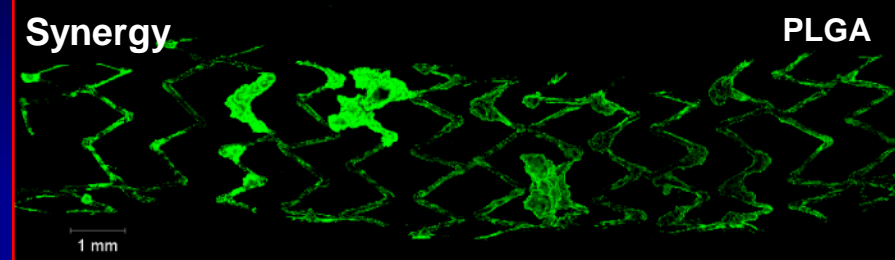
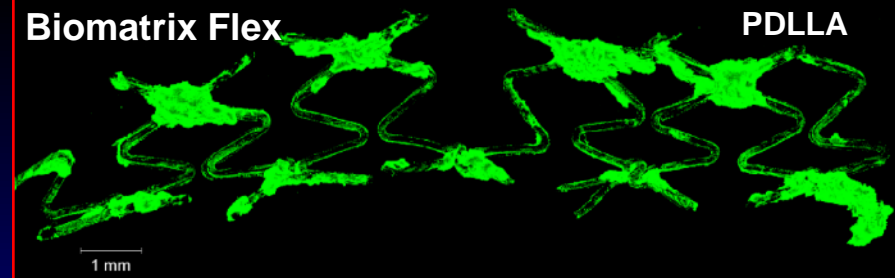
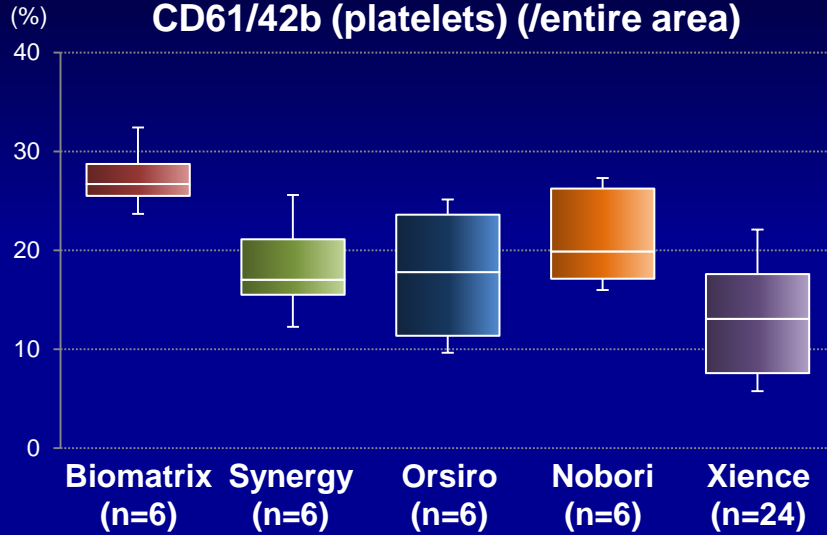


Comparison of different types of DES in thromboresistance using porcine shunt models

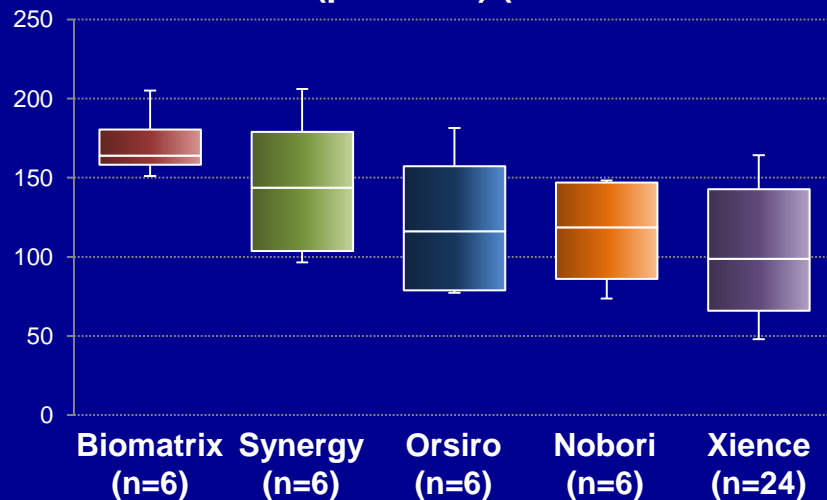
- ✓ Porcine AV Shunt Model
 - Low dose heparin
 - Aspirin Monotherapy

Significantly Reduced Platelet Aggregation in Xience than Comparator DES by Confocal Microscopy

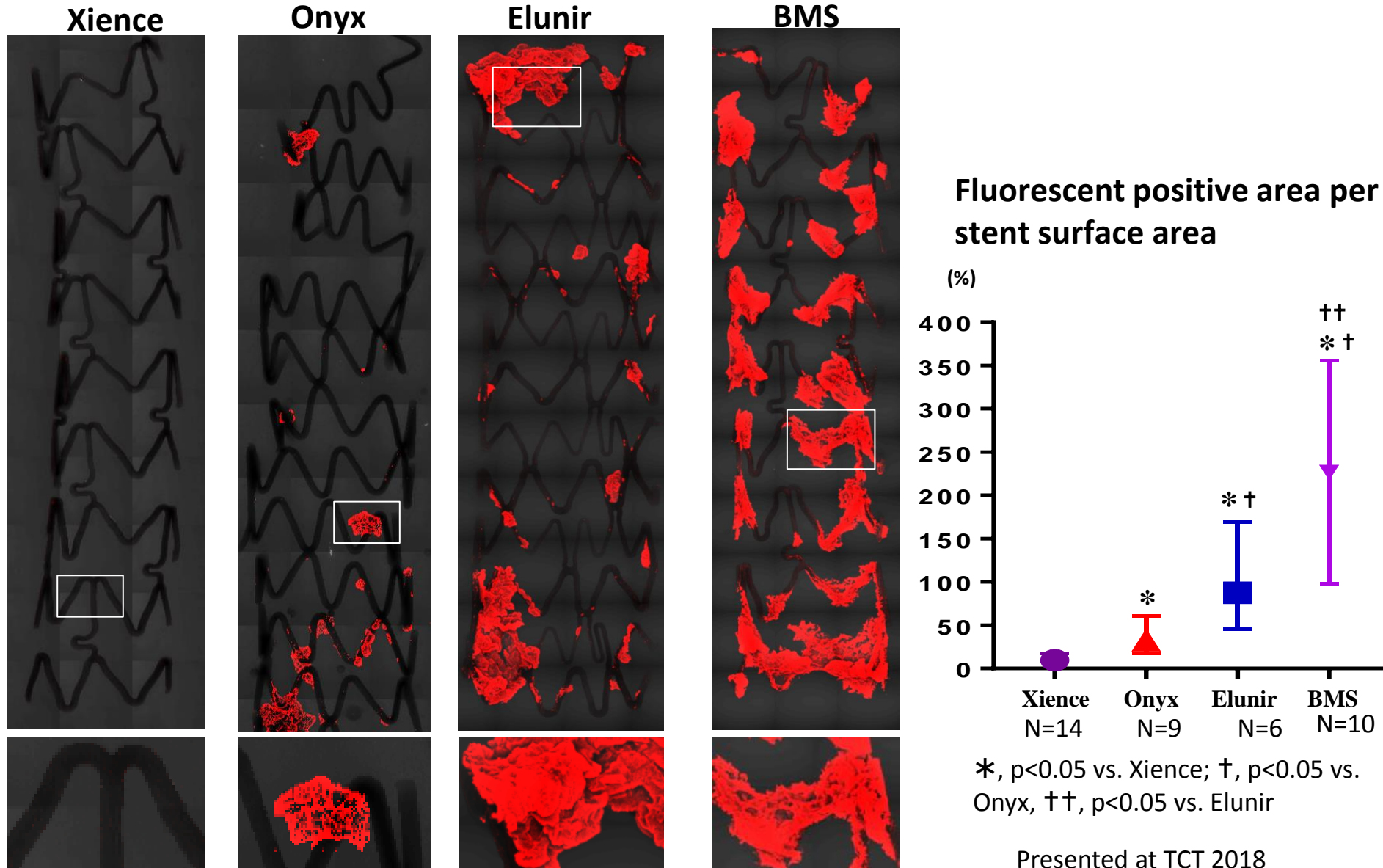
Percent fluorescent positive area for CD61/42b (platelets) (/entire area)



Adjusted percent fluorescent positive area for CD61/42b (platelets) (/stent surface area)



Comparison of Acute Thrombogenicity in Three Durable Polymer DES



AV Shunt Model Translatability to ASA monotherapy

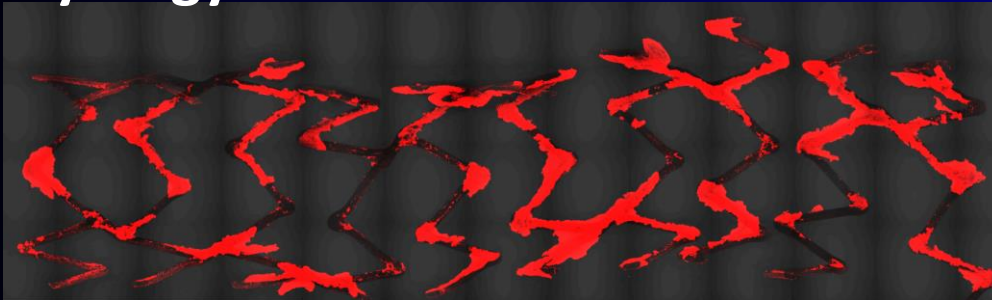
- AV shunt data in the setting of low dose heparin monotherapy
- Patients at time of DAPT discontinuation not on heparin but only ASA (with thienopyridine withdrawal)
- What is data like on ASA only?

Ex Vivo Swine Shunt models with Aspirin

Xience



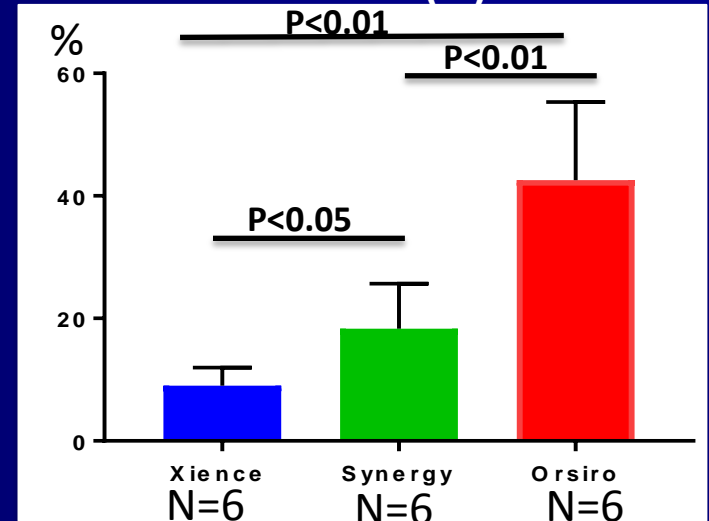
Synergy



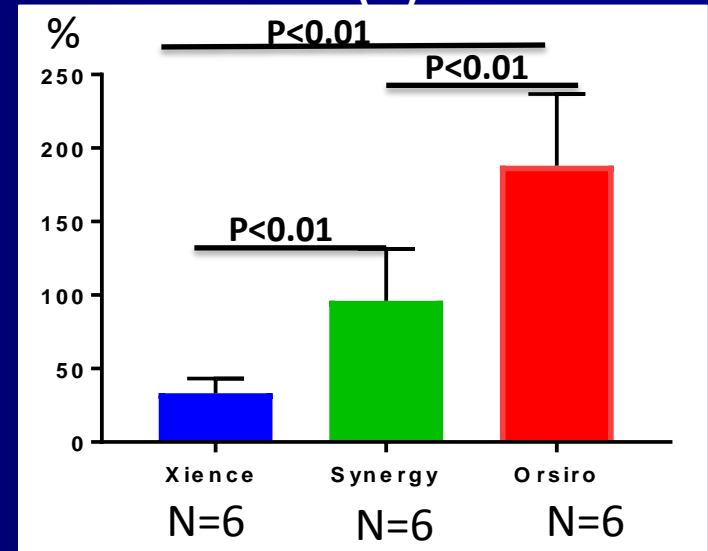
Orsiro



CD42b/CD61 immunofluorescence
Total Scanned Area (%)



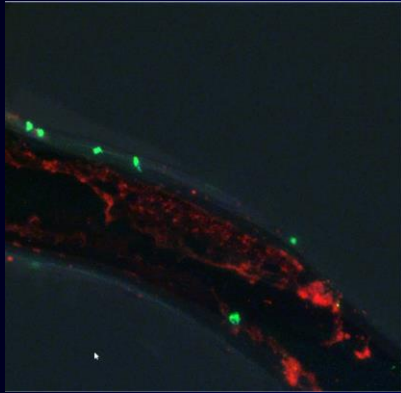
CD42b/CD61 immunofluorescence
Total Strut Area (%)



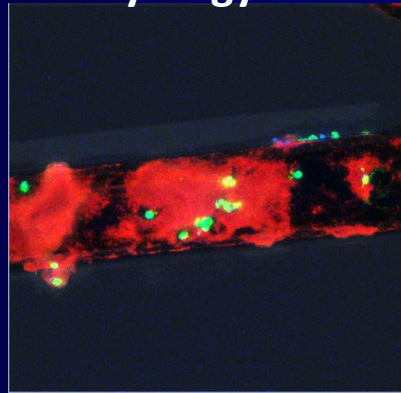
Ex Vivo Swine Shunt models with Aspirin

PM-1 (Neutrophils)

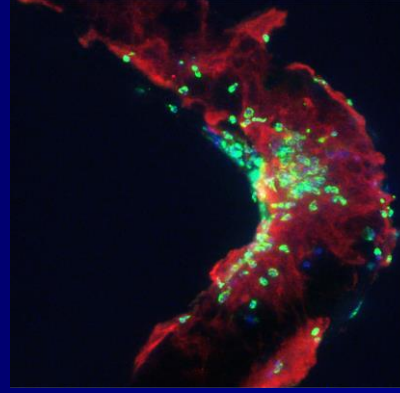
Xience



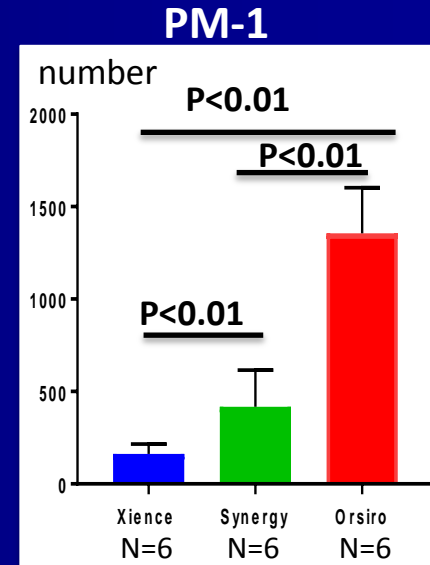
Synergy



Orsiro

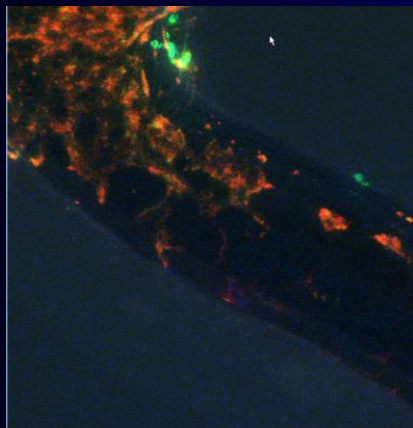


● PM-1
● DAPI
● CD61

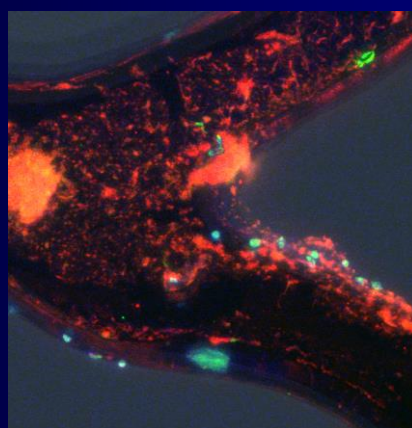


CD14 (Monocytes)

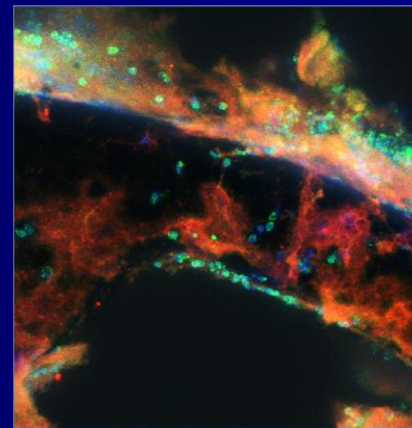
Xience



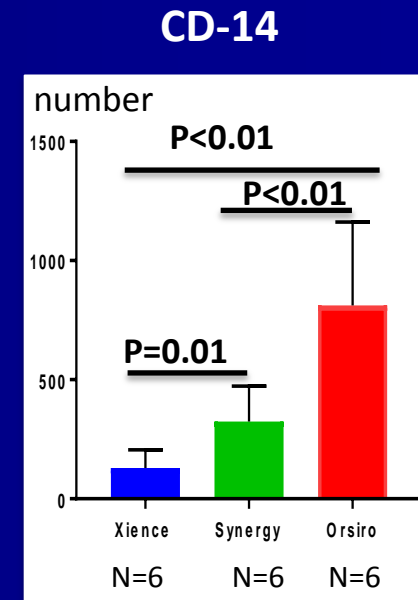
Synergy



Orsiro



● CD14
● DAPI
● CD61

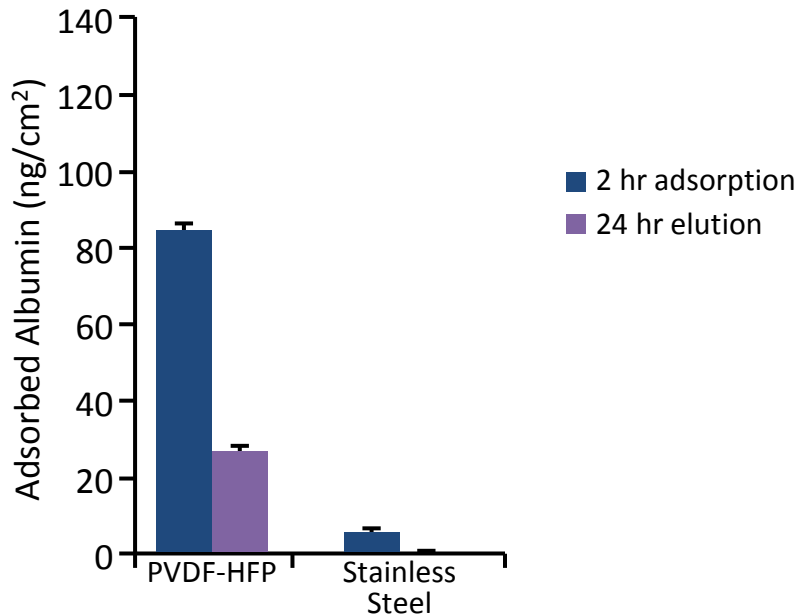


Permanent Polymers :Fluoropolymer Fluoropassivation

XIENCE Fluoropolymer has higher albumin adsorption/retention than bare metal

Preferential albumin adsorption of XIENCE Fluoropolymer offers the lower monocyte adhesion than bare metal

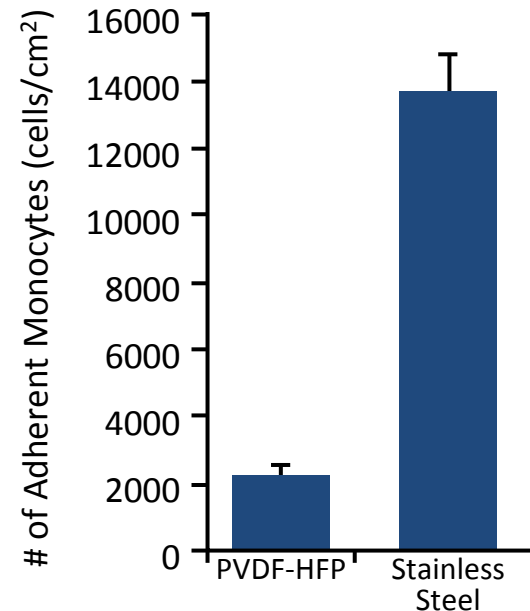
ALBUMIN ADSORPTION



Two-hour ALBUMIN adsorption from a pure Albumin solution (0.3 mg/mL)

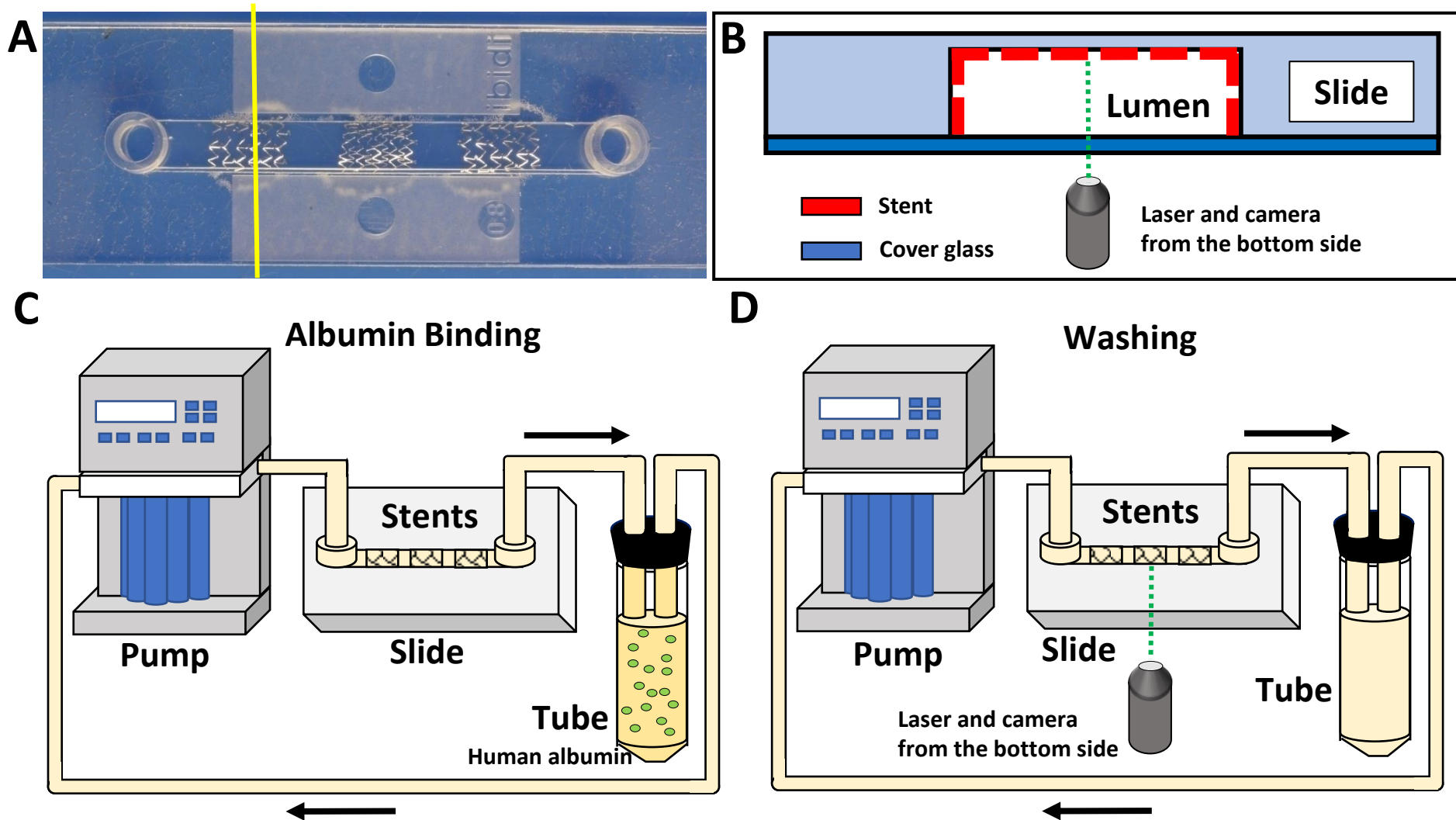
MONOCYTE ADHESION

To Surfaces
Pre-Adsorbed with
1% Human Plasma

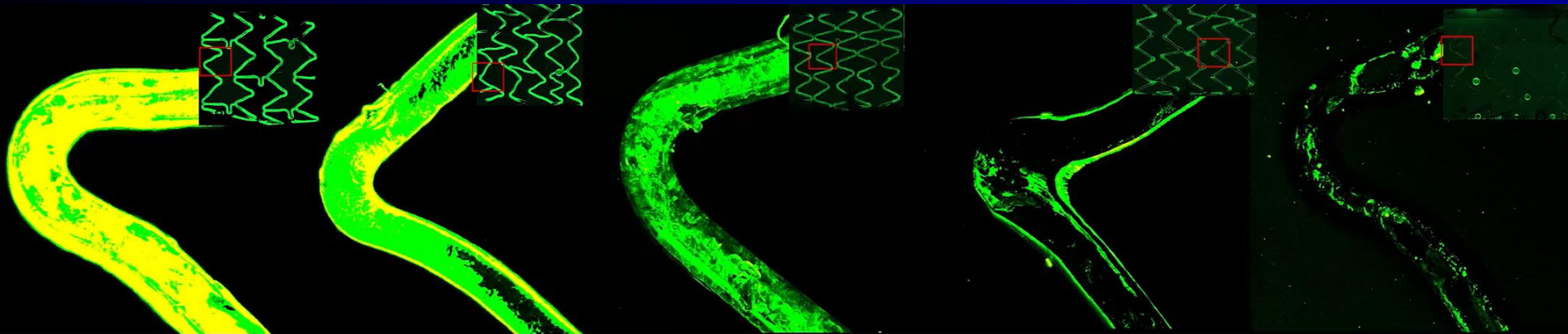


Albumin Retention in In Vitro Flow Models

Human fluorescent albumin



Albumin Retention in In Vitro Flow Models



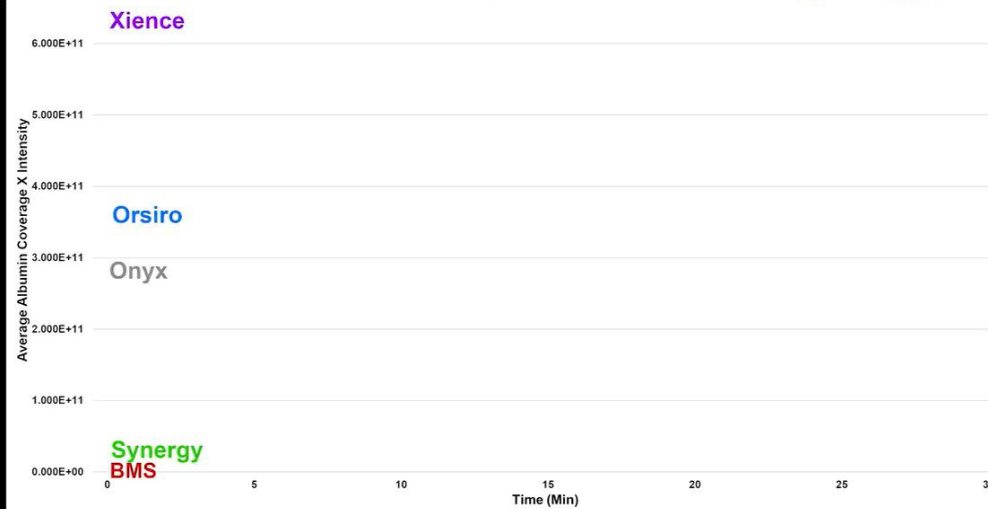
Xience

Orsiro

Onyx

Synergy

BMS



High Albumin Binding

Low Albumin Binding

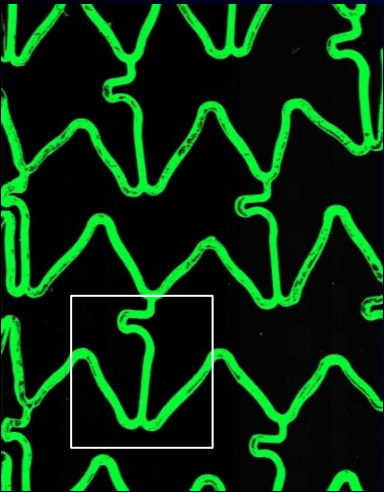


Albumin Retention in In Vitro Flow Models

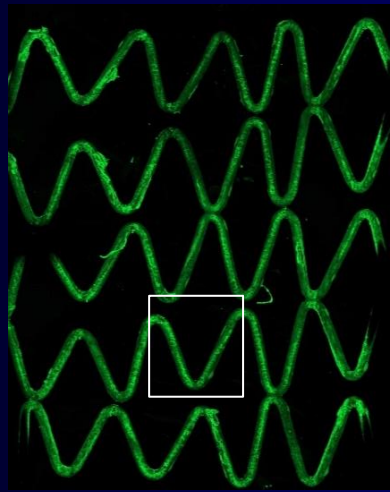
Xience shows greatest albumin coverage and strongest signal of albumin.

● Fluorescent Albumin

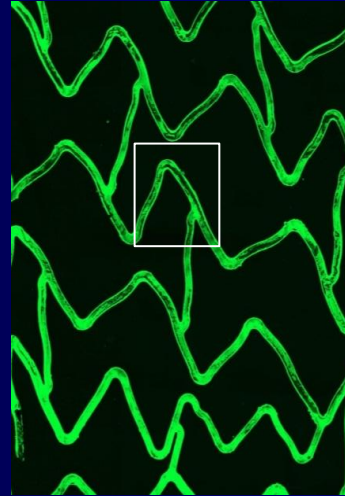
Xience



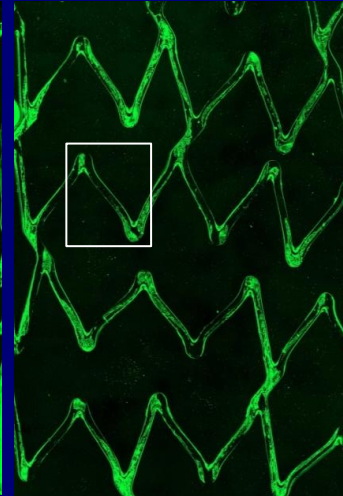
Onyx



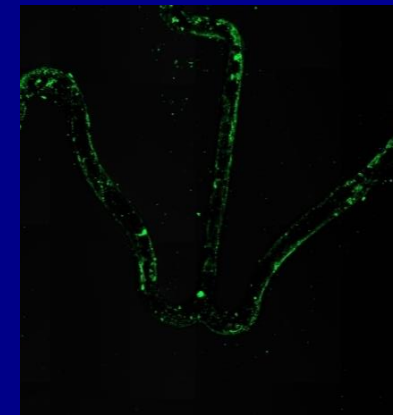
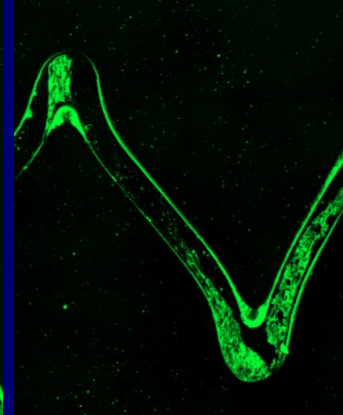
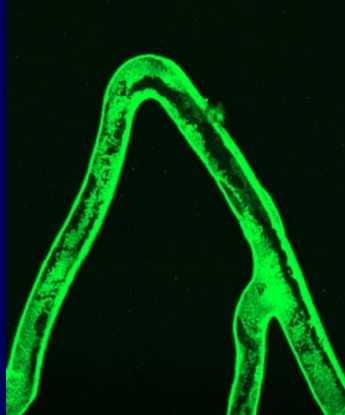
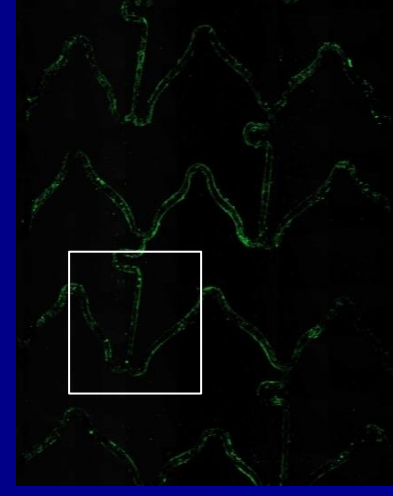
Orsiro



Synergy



BMS

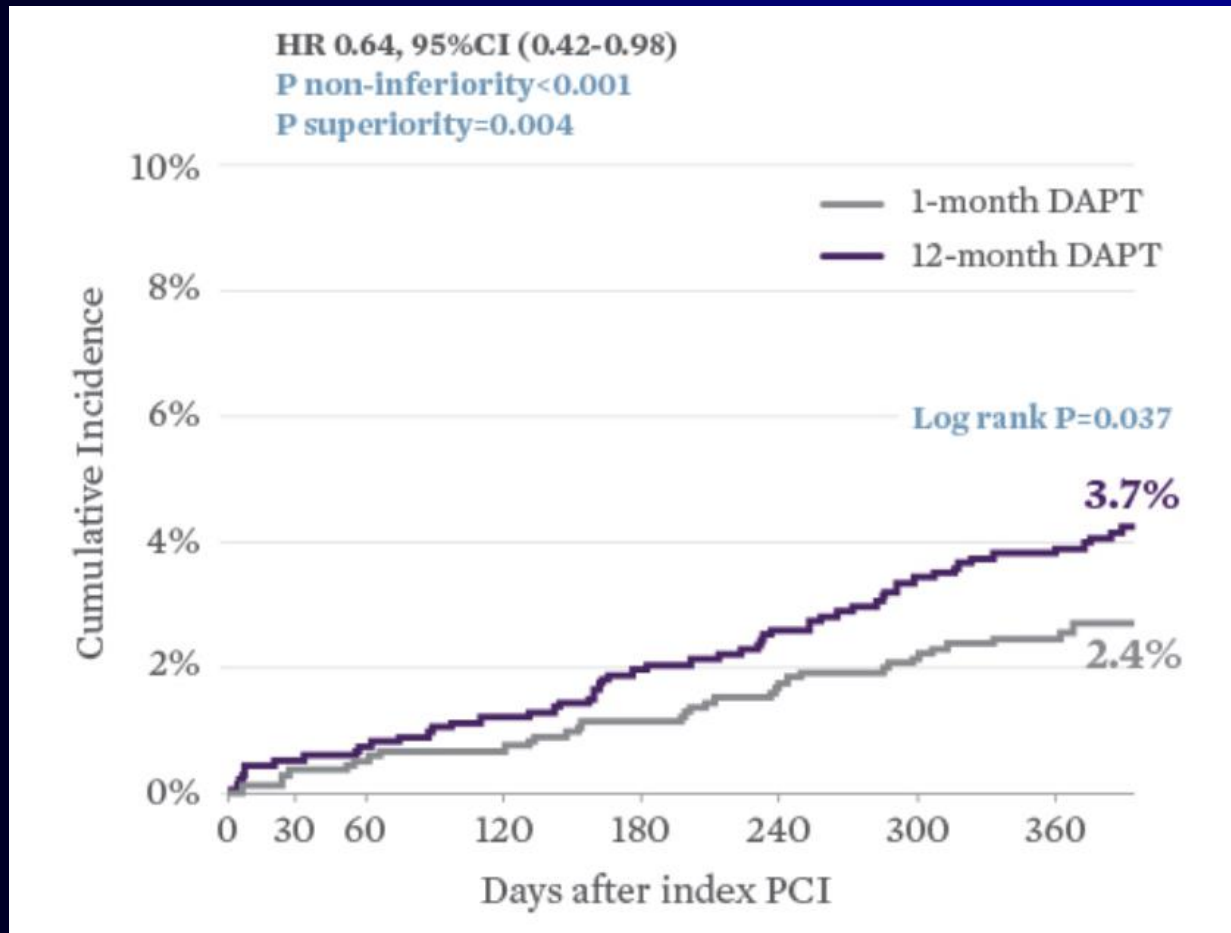


STOP DAPT 2 Trial

1-Month DAPT vs. 12-Month DAPT after Xience stents

Total 3000 patients were enrolled
Randomized controlled trial

Primary Endpoint:
Net Adverse Cardiovascular Events (NACE)
CV death/MI/ST/Stroke/TIMI major/minor bleeding



Not only stent design but also individual patient characteristics are important when considering short DAPT

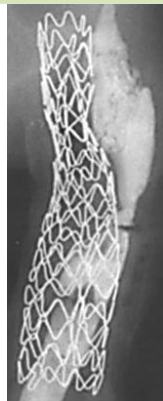
The optimal DAPT duration after DES placement should be tailored in individual patients after carefully balancing the risks of ischemic versus bleeding events.

Predictors of Events ^a	Predictors of Myocardial Infarction or Stent Thrombosis ^b		Predictors of Moderate or Severe Bleeding ^c	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Continued thienopyridine vs placebo	0.52 (0.42-0.65)	<.001	1.66 (1.26-2.19)	<.001
Myocardial infarction at presentation	1.65 (1.31-2.07)	<.001		
Prior PCI or prior myocardial infarction	1.79 (1.43-2.23)	<.001		
History of CHF or LVEF <30%	1.88 (1.35-2.62)	<.001		
Vein graft stent	1.75 (1.13-2.73)	.01		
Stent diameter <3 mm	1.61 (1.30-1.99)	<.001		
Paclitaxel-eluting stent	1.57 (1.26-1.97)	<.001		
Cigarette smoking	1.40 (1.11-1.76)	.01		
Diabetes mellitus	1.38 (1.10-1.72)	.01		
Age, per 10 y			1.54 (1.34-1.78)	<.001
Peripheral arterial disease	1.49 (1.05-2.13)	.03	2.16 (1.46-3.20)	<.001
Hypertension	1.37 (1.03-1.82)	.03	1.45 (1.00-2.11)	.05
Renal insufficiency/failure	1.55 (1.03-2.32)	.04	1.66 (1.04-2.66)	.03

Also, lesion characteristics maybe important

Impact of Calcification on strut coverage after current generation DES

Severe calcification



Severely calcified (SC) stented segment

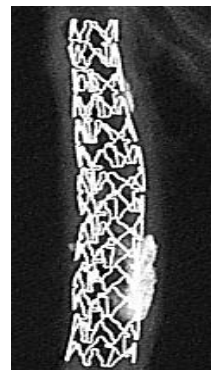
69 patients/ 88 lesions

Uncovered

No calcification



Mild calcification



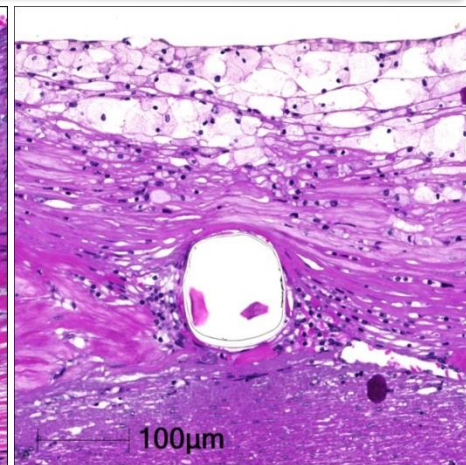
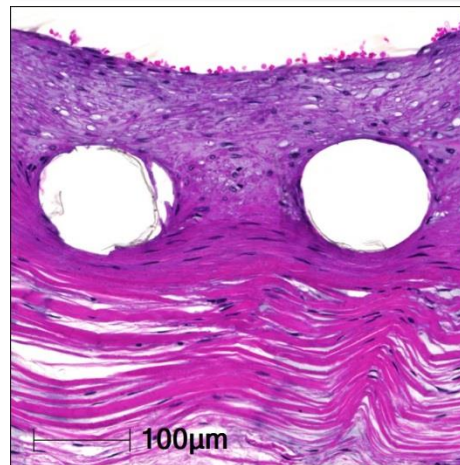
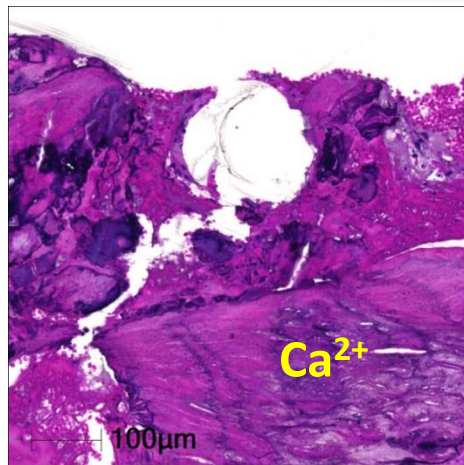
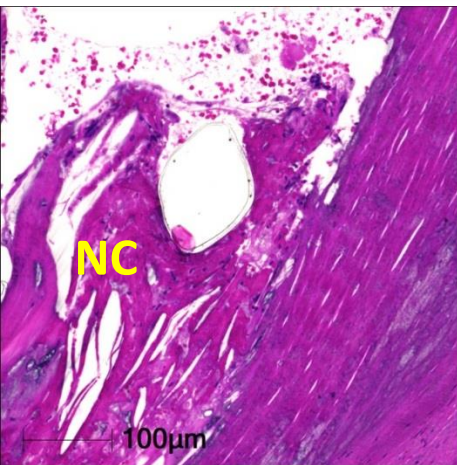
Moderate calcification



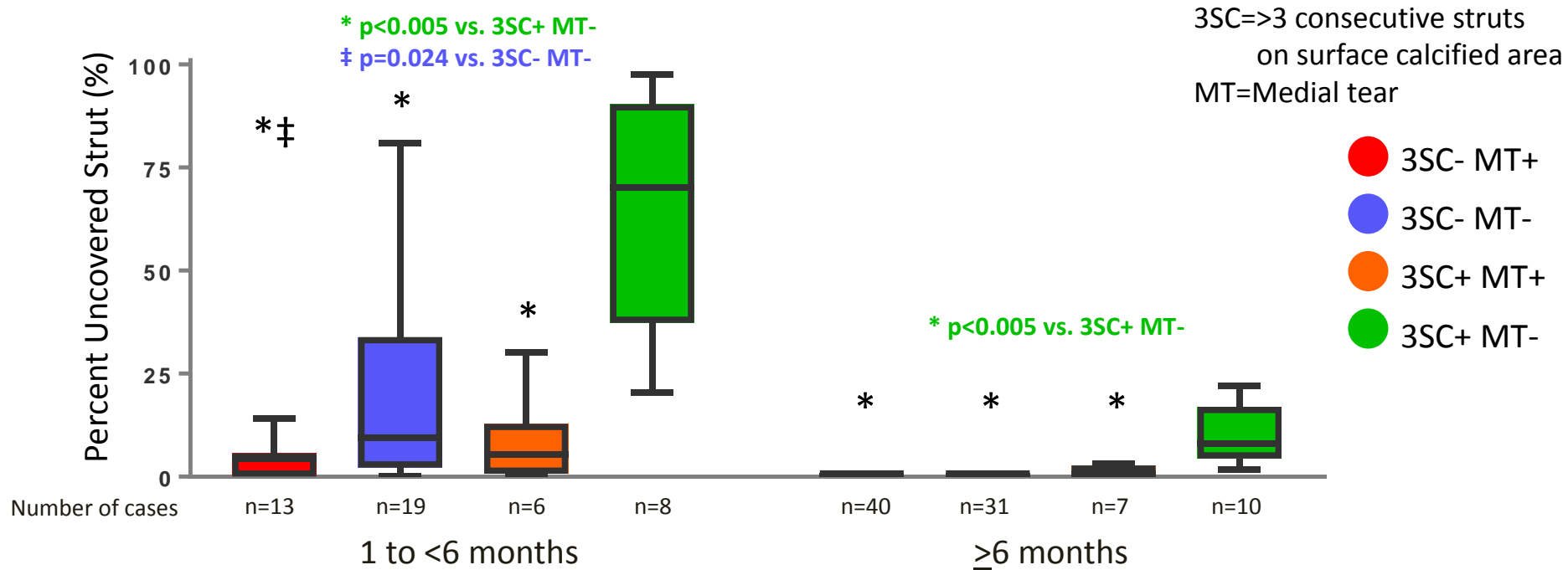
Non-severely calcified (NC) stented segment

35 patients/ 46 lesions

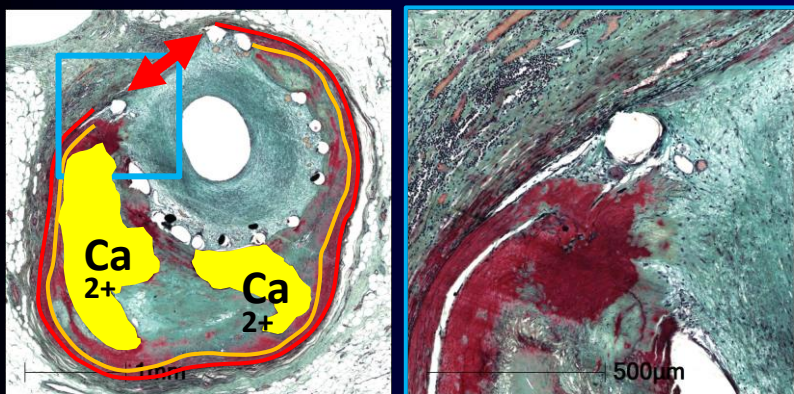
Covered



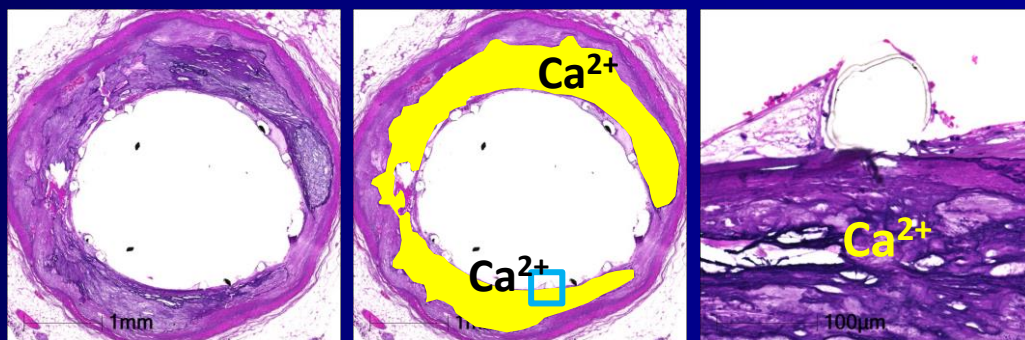
Impact of surface calcification and medial tear on uncovered struts



Severe medial tear



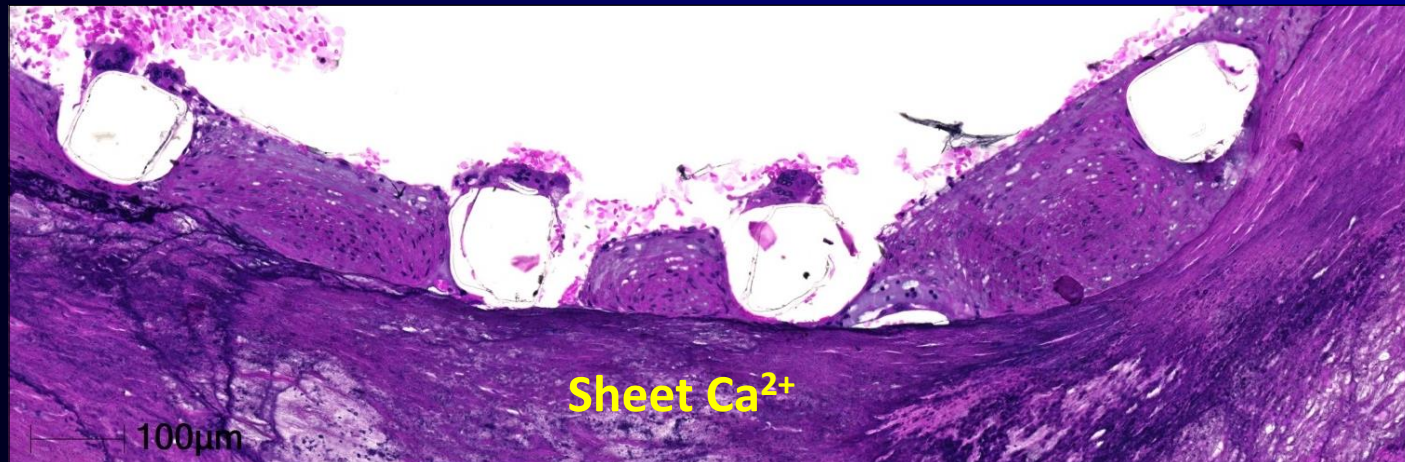
Surface calcified area



Surface calcification is a predictor for uncovered struts

Multivariate Analysis of Predictors for Delayed Strut Coverage in Newer-Generation DES

	OR	Lower 95% CI	Upper 95% CI	p value
Duration of implantation <6 months	7.7	5.18	11.50	<.0001
≥3 consecutive struts on surface calcified area	6.5	3.55	12.04	<.0001
Strut malapposition	5.0	3.34	7.57	<.0001
Lack of severe medial tear	2.5	1.53	4.34	0.0005



Summary:

Polymers are not same in terms of anti-thrombogenicity

- Ex vivo pig shunt models and in vitro flow models with labeled human platelet show different thromboresistance in different types of stents.
- Regarding albumin retention, durable polymer DESs were fully covered by albumin with strongest signal of albumin, as compared to bare and abluminally covered stents (i.e., BMS and Synergy). However, among durable polymer stents, albumin retention is higher in Xience >Onyx>Elunir.
- Overall permanent FP coated stent have advantage relative to bioabsorbable or no polymer DES
- Within 1-3 months, stent struts may not be fully covered by endothelium. When considering short DAPT, a capability of thromboresistance in individual stents is important. Those difference of thromboresistance in stents may require different duration of DAPT in each stent.
- Not only stent design but also individual patient and lesion characteristics are important.

Acknowledgments

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Qi Cheng, MD
Maria Romero, MD
Robert Kutz, MS
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Aloke V. Finn, MD



CVPath Institute, Inc.



Problems Encountered with Drug-Eluting Stents

Thick strut DES with durable polymer

- Thick struts
- Uneven polymer distribution with poor integrity, and thick coating of durable polymers
- High drug dose

Thin strut DES with durable polymer

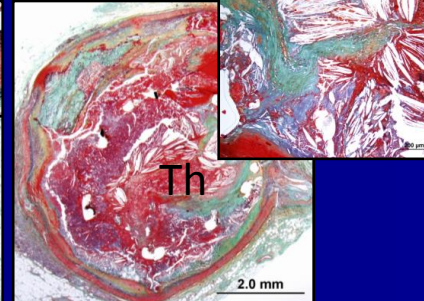
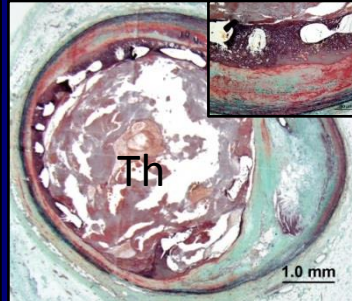
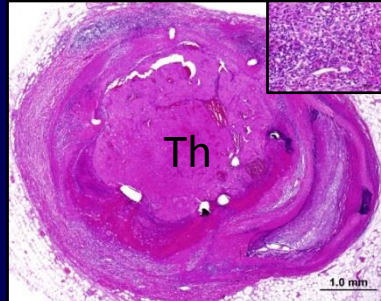
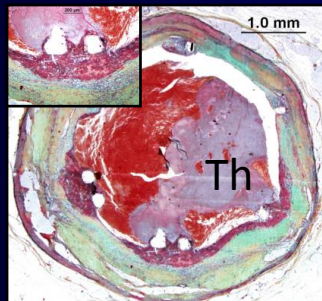
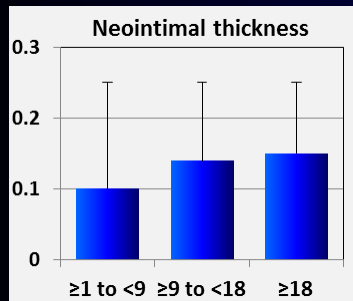
- Thinner struts
- More biocompatible polymer (Durable)
- Reduced drug dose

- ✓ Uncovered struts
- ✓ Hypersensitivity
- ✓ Malapposition from fibrin deposition
- ✓ Stent fracture
- ✓ Neointimal hyperplasia

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Late Stent Thrombosis / Restenosis

Clinical Late Catch-up



Late catch-up

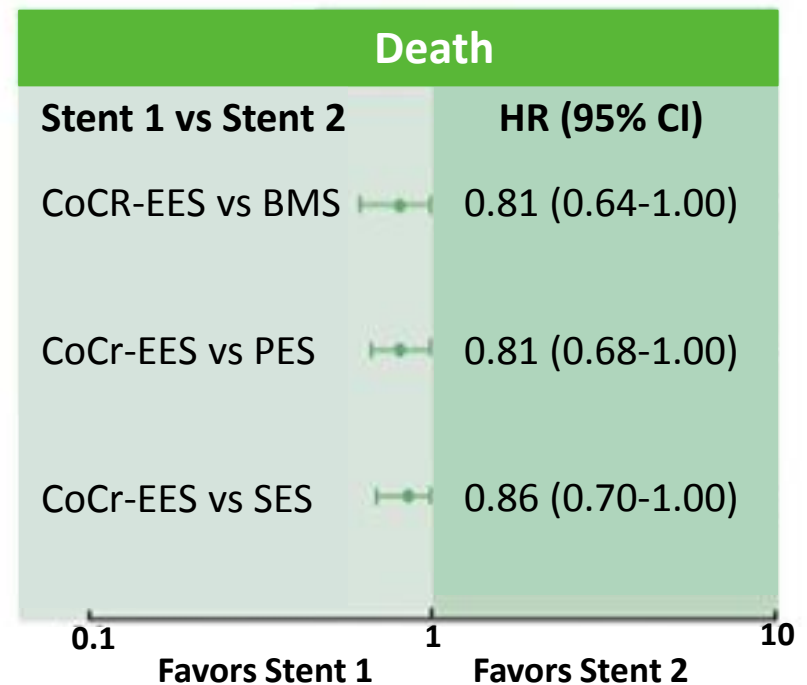
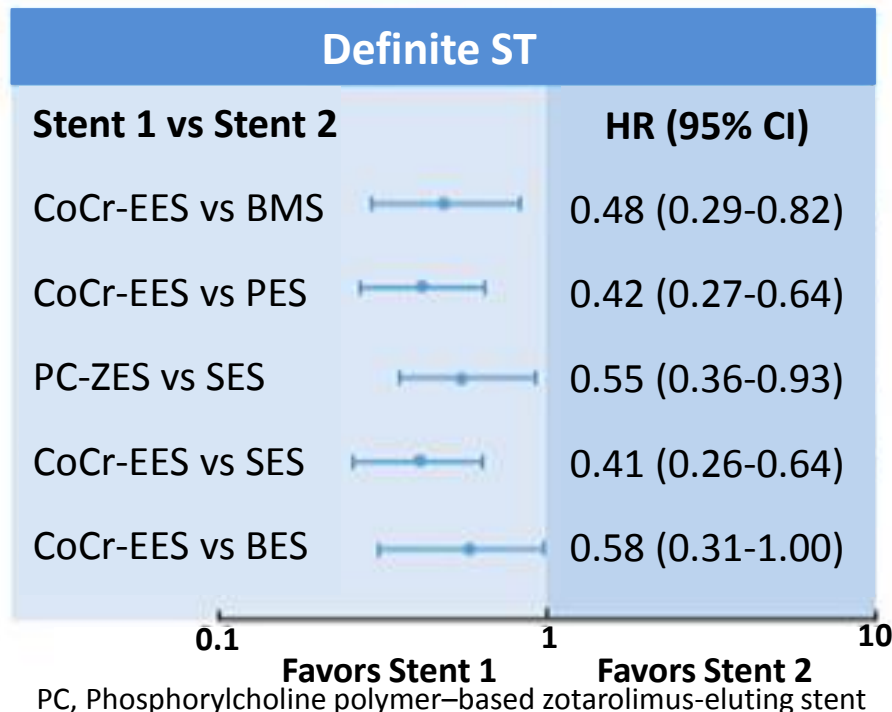
Uncovered struts

Hypersensitivity reaction

Malapposition from excessive fibrin deposition

Neointimal hyperplasia

2nd generation DES reduced stent thrombosis



51 trials that included a total of 52,158 randomized patients with follow up duration ≥ 3 years were analyzed.

Evolution of DES Technology

