Functional Healing with Synergy BP-DES

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PCI EVOLUTION
Continuous improvement in platform design and acute performance

1977
- POBA: Getting Artery Open

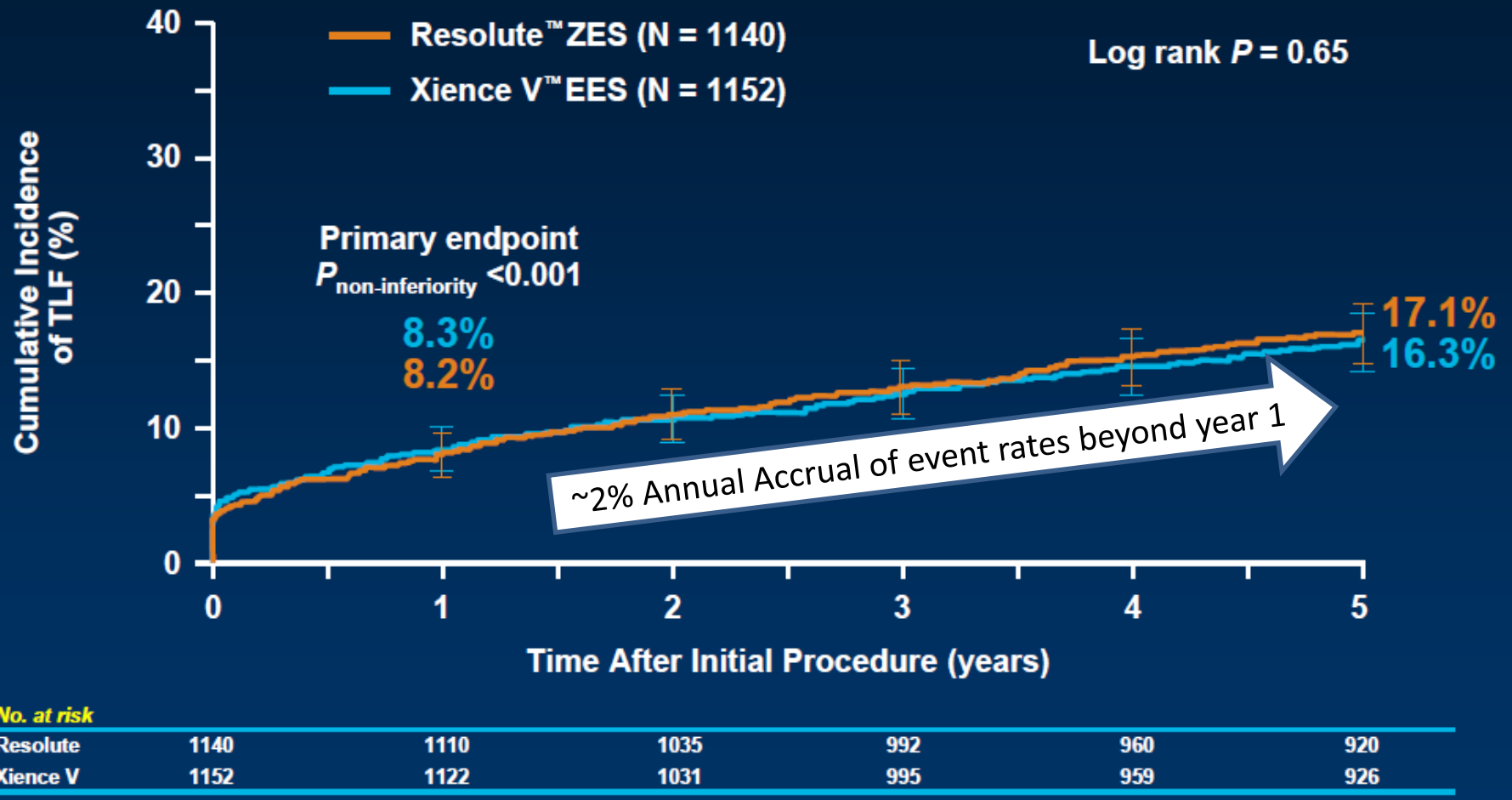
1986
- BMS: Keeping Artery Open

2003
- DES Decrease Restenosis

2015+
- Future DES: Optimize Healing
  - Lower late events rates – ST, TLR
  - Reduced need for prolonged DAPT
  - Reduced risk of neoatherosclerosis

Event rates persist beyond 1 year with current PERMANENT Polymer DES-Why?

Resolute All Comers 5-year TLF

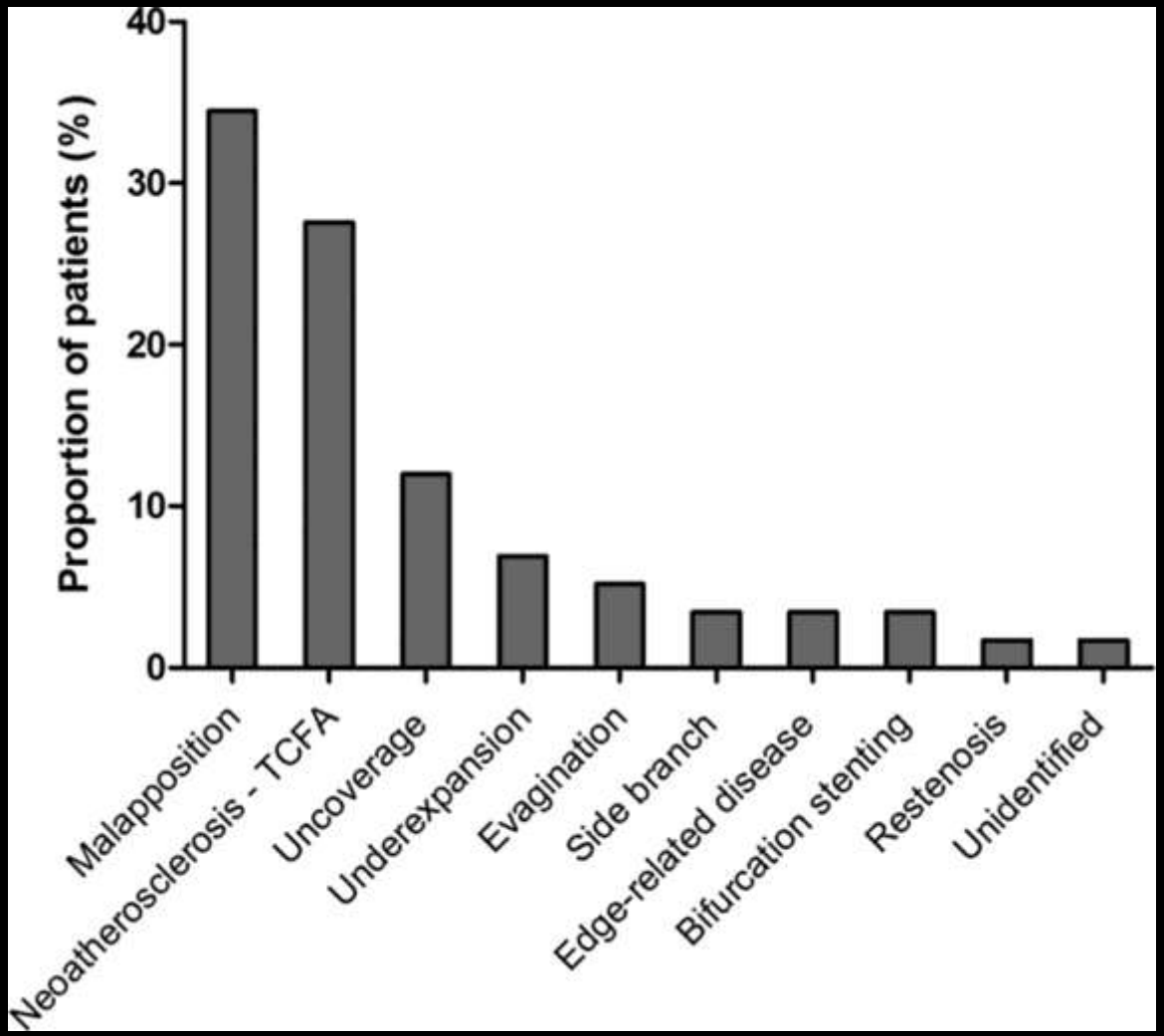


No. at risk						
Resolute	1140	1110	1035	992	960	920
Xience V	1152	1122	1031	995	959	926

TLF (target Lesion Failure) is defined as cardiac death, TVMI, of clinically driven TLR.

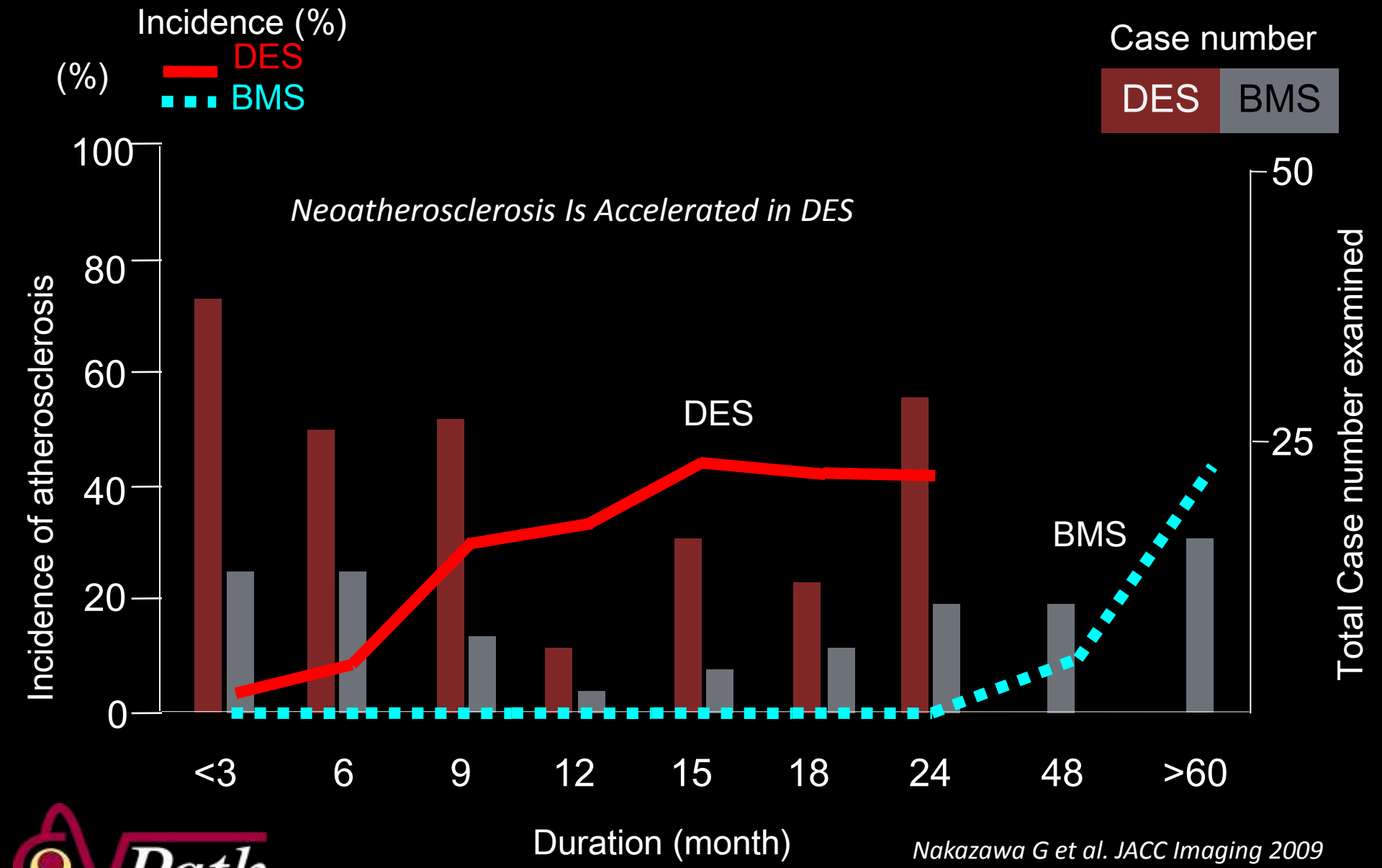
Presented by Stephan Windecker, MD PCR 2014.

Frequency of the single or highest-ranked (most plausible) mechanism of very late stent thrombosis in the 58 analyzed stents



Masanori Taniwaki et al. Circulation. 2016;133:650-660

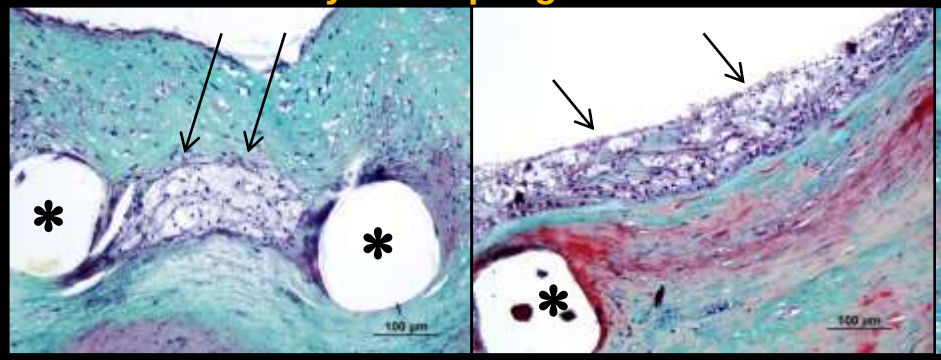
Incidence and Timing of Atherosclerotic Change



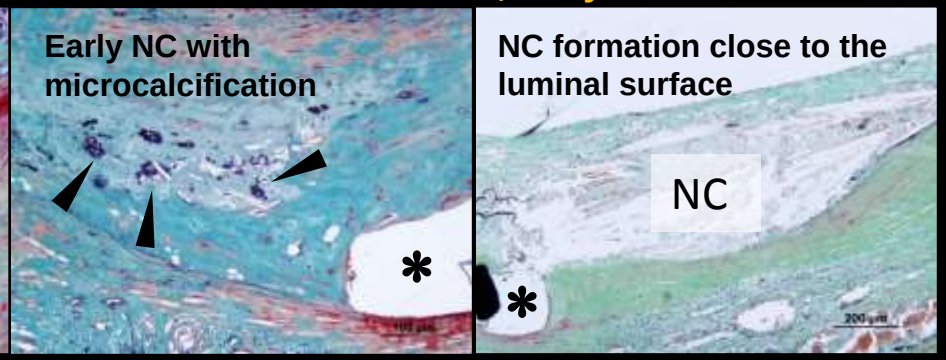
Nakazawa G et al. JACC Imaging 2009

Progression of Neoatherosclerosis

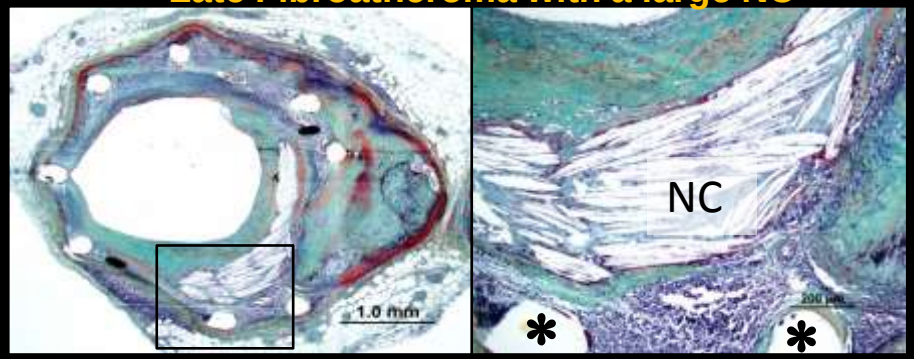
Foamy macrophage clusters



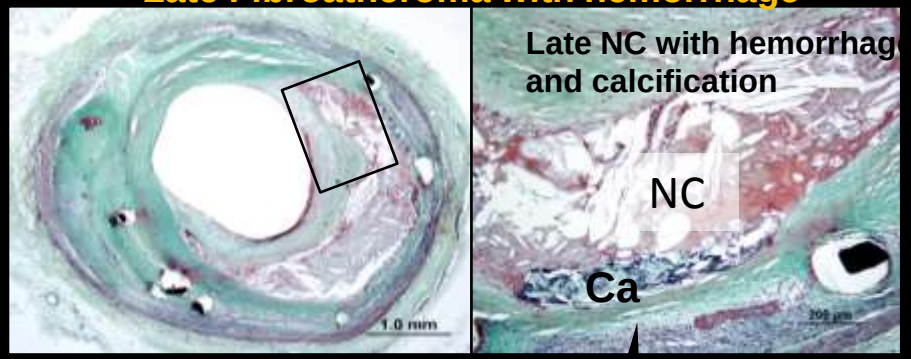
Fibroatheroma, early and late



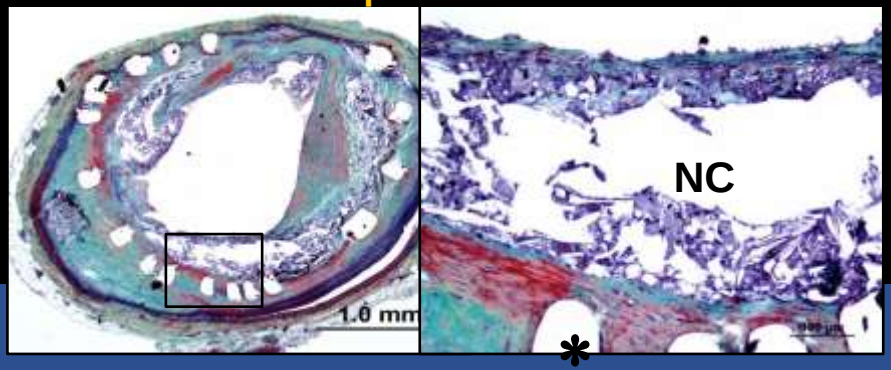
Late Fibroatheroma with a large NC



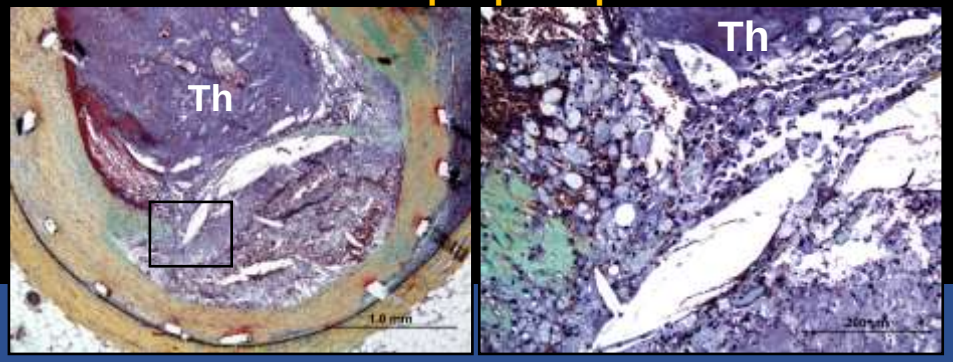
Late Fibroatheroma with hemorrhage



Thin-cap Fibroatheroma

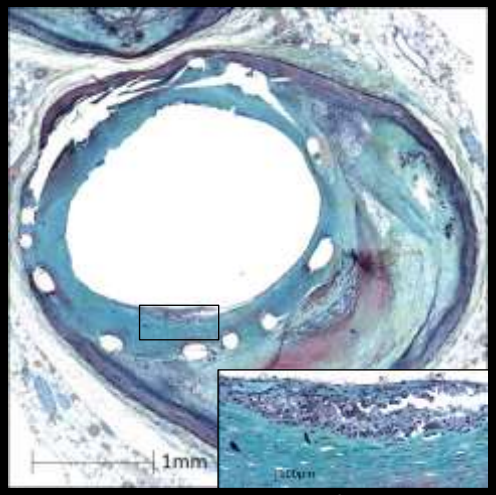


In-stent plaque rupture

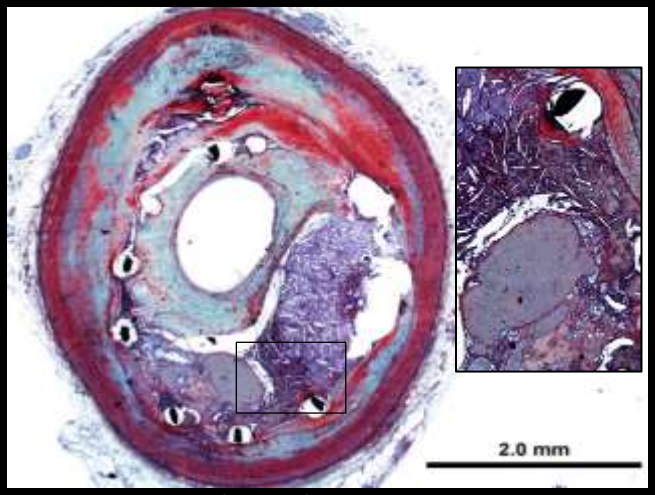


Neoatherosclerosis was defined as the presence of foamy macrophages within the neointima with or without necrotic core and/or calcification.

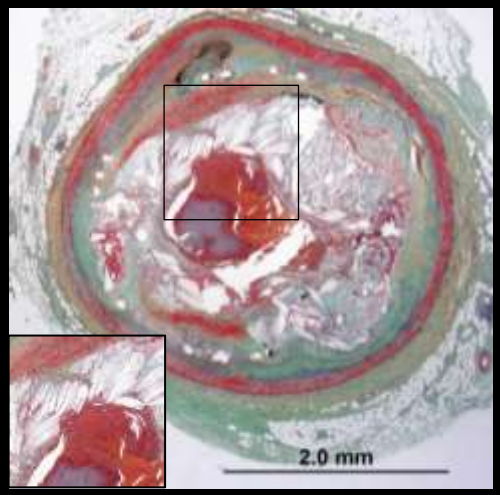
Cumulative incidence of Neoatherosclerosis(%)



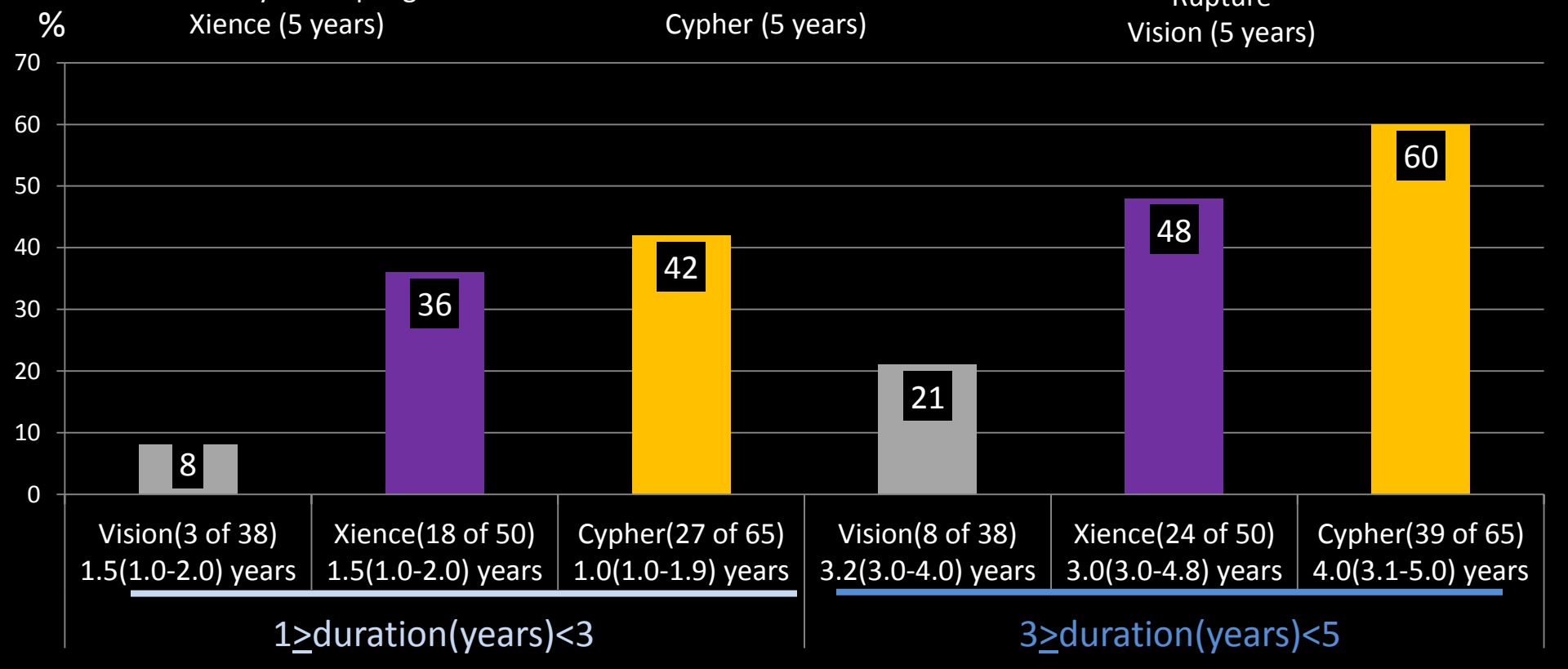
Foamy macrophage
Xience (5 years)



Fibroatheroma
Cypher (5 years)



Rupture
Vision (5 years)



Causes of Neoatherosclerosis: Impact of Vascular Healing

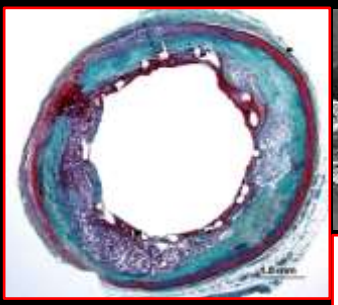
What is Complete Vessel healing?

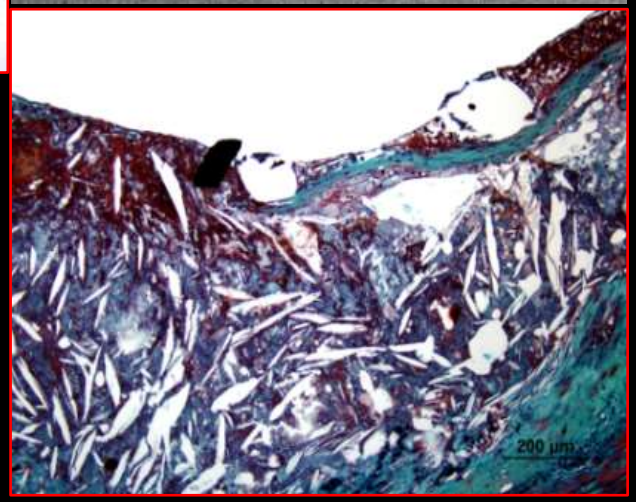
Delayed Healing

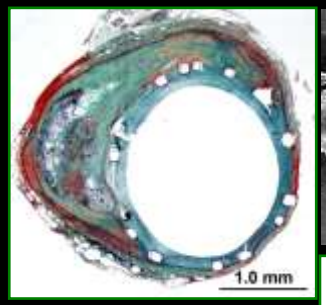
- Peristrut fibrin deposition
- Few Smooth muscle cells – peristrut and above the strut
- Incomplete endothelialization

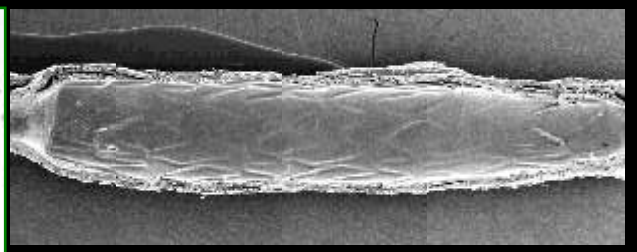
Complete Healing

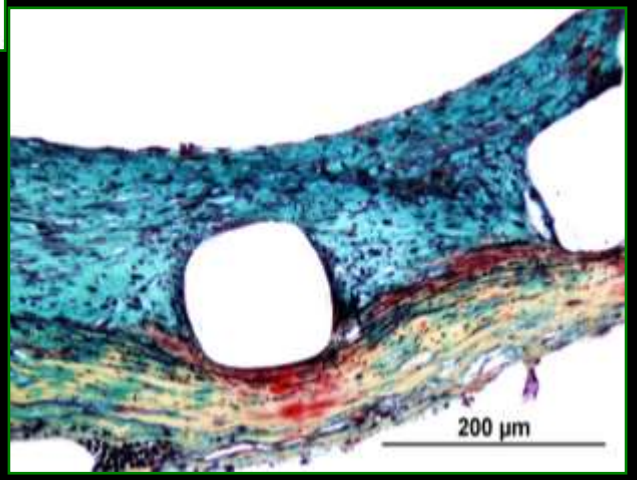
- No fibrin deposition
- Smooth muscle cells, proteoglycans & collagen – above the strut
- Complete and functional endothelium



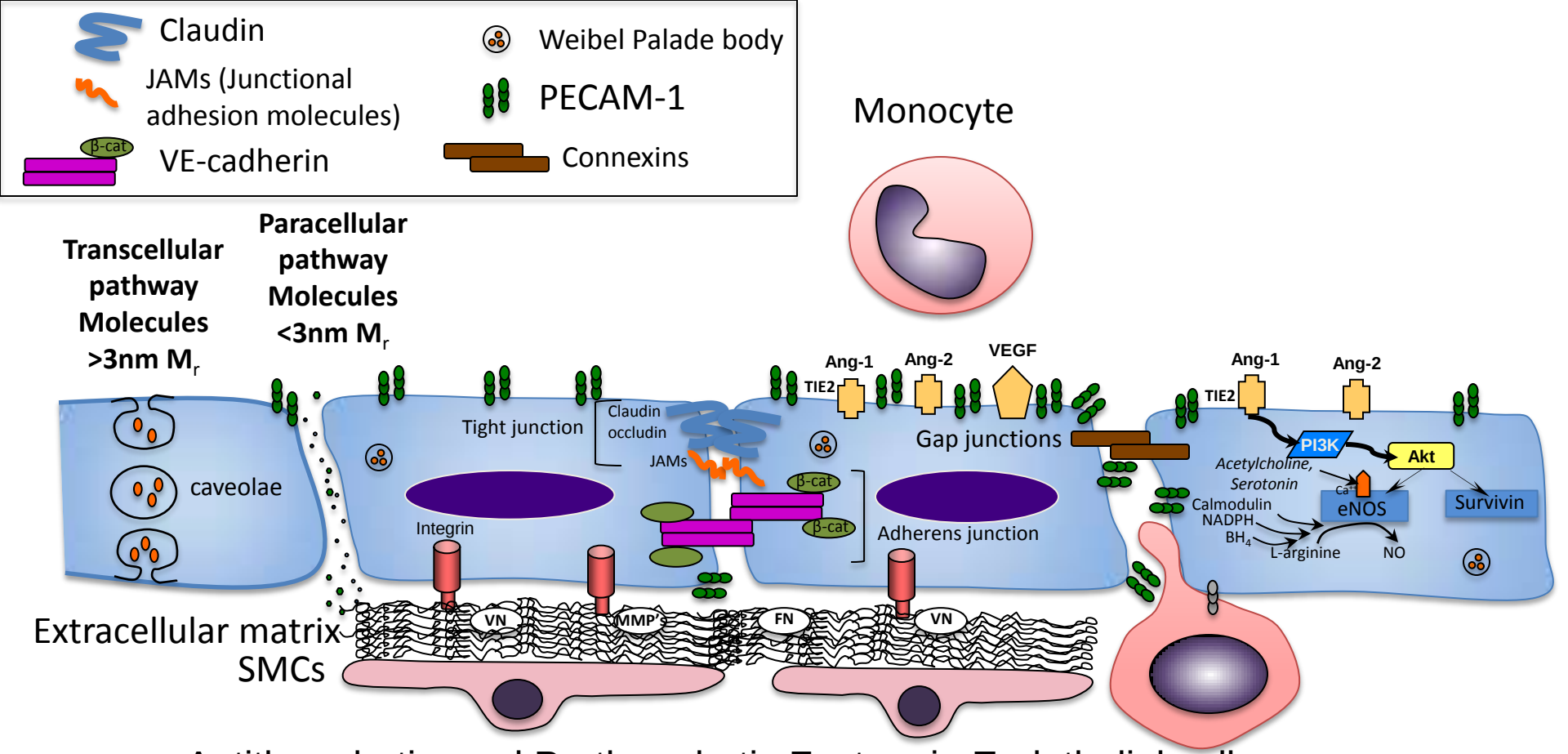








eVPath



Antithrombotic and Prothrombotic Factors in Endothelial cells

Antithrombotic

- Prostacyclin (PGI_2)
- Nitric oxide (NO)
- Thrombin/thrombomodulin → PC → aPC → Protein S → VIIIa Va
- Antithrombin
- Heparin sulphate proteoglycan → IIa, Xa, XIa IXa
- Tissue Factor Pathway Inhibitor → VIIa/TF/Xa
- Tissue Plasminogen activator → Fibrinolysis

Prothrombotic

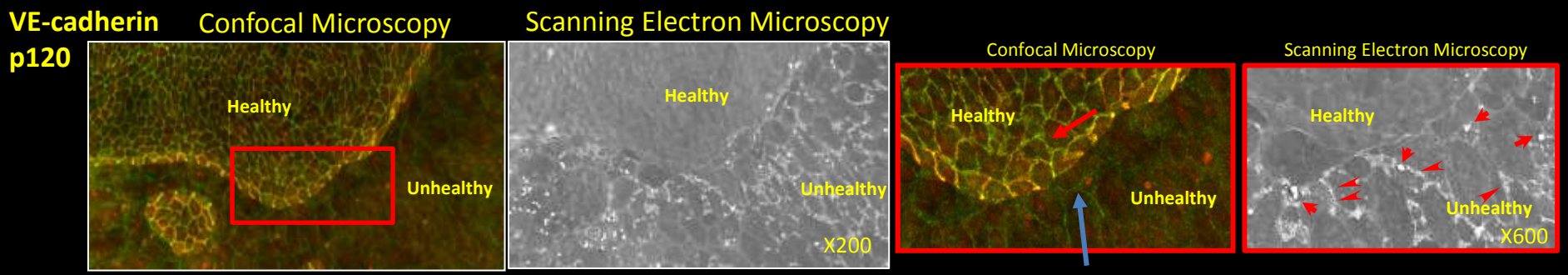
- Von Willebrand factor → Platelets
- Thrombin → Coagulation
- Xa ← X ← VIIa / TF
- IXa ← IX ← VIIa / TF
- Prothrombin
- PAI-1 → Fibrinolysis

Endothelial cell

Endothelial cell

Importance of the Endothelial Function in Health and Disease

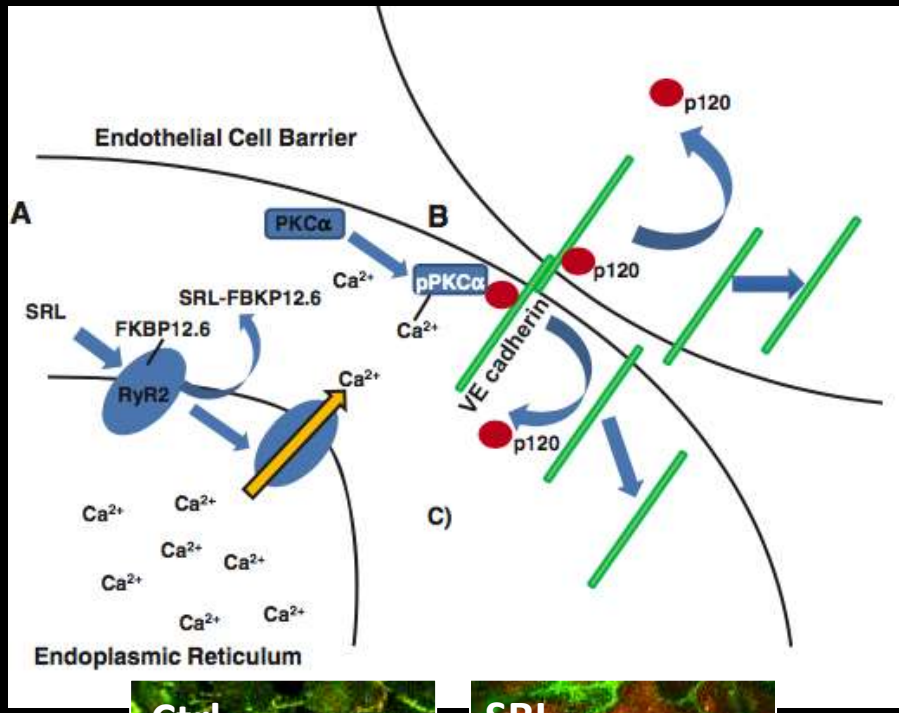
- The endothelium plays a critical role in vascular homeostasis by providing a solid barrier between blood and vessel wall, secreting substances that not only acutely regulate vascular tone, platelet activity, and coagulation factors but also influence vascular inflammation, cell migration, and proliferation over the longer term
- Dysfunction of the endothelium is the initial inciting event in atherogenesis
- VE-cadherin regulates endothelial barrier function via binding to p120 (red arrow). Impaired endothelial barrier function because of dissociation of VE-cadherin and p120 interaction (blue arrow)
- Unhealthy endothelium has dysregulation of these two molecules which normally should be expressed together at endothelial cell borders

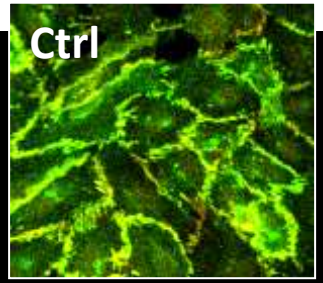


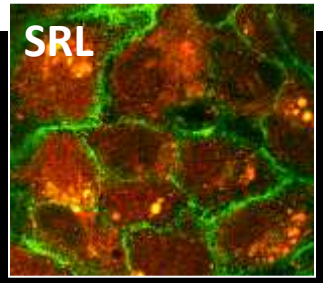
VPath

mTOR inhibitors and the endothelium

- Sirolimus inhibits mTOR complex by binding FKBP12.6 and displaces it from intracellular calcium release channels
- Sirolimus/FKBP12.6 increases intracellular calcium levels and endothelial dysfunction by PKC activation
- VE-cadherin regulates endothelial barrier function via binding to p120. PKCα activation causes impaired endothelial barrier function via disruption of the VE-cadherin and p120 interaction
- Limiting exposure to sirolimus through biodegradable polymers may improve endothelial function more quickly

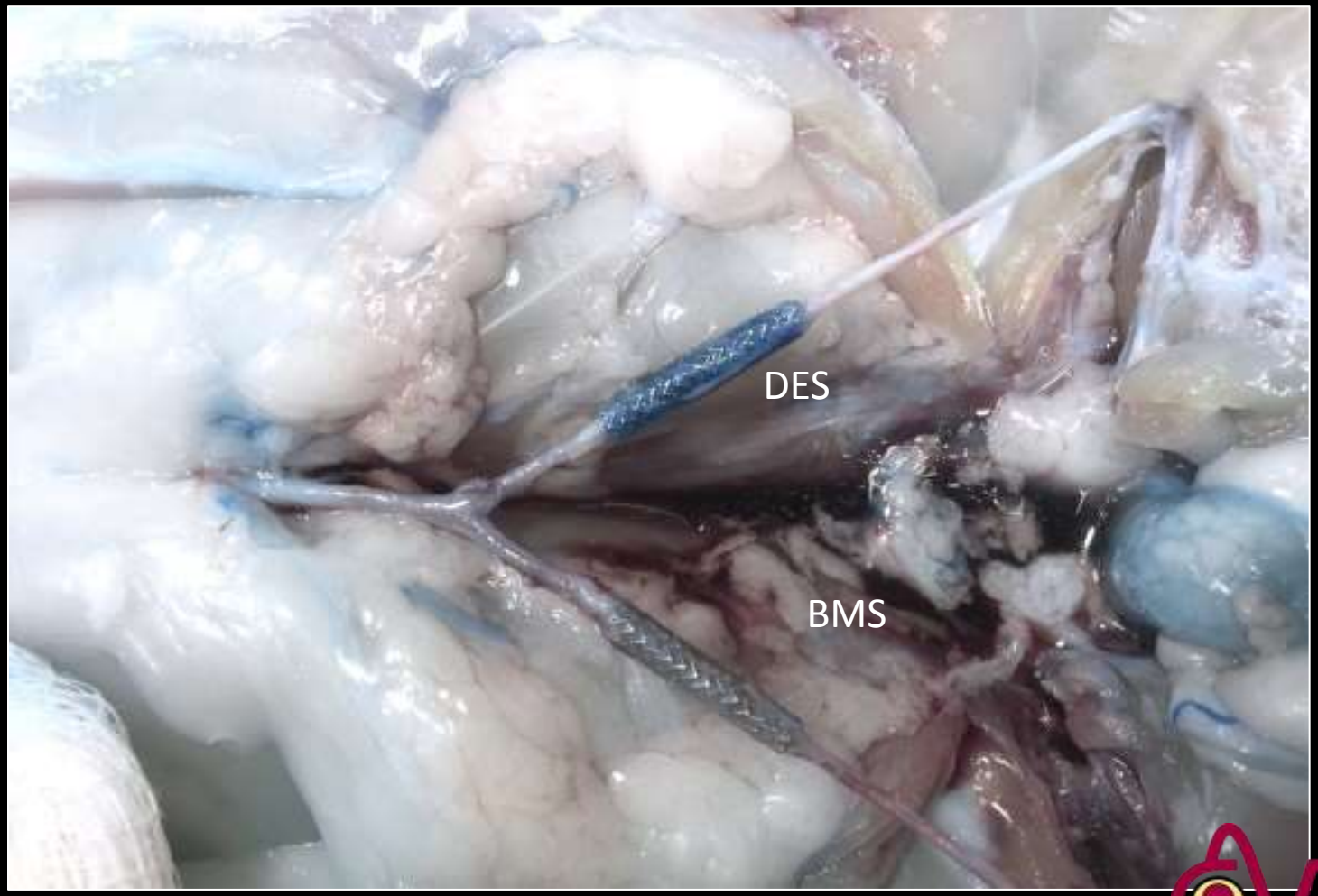




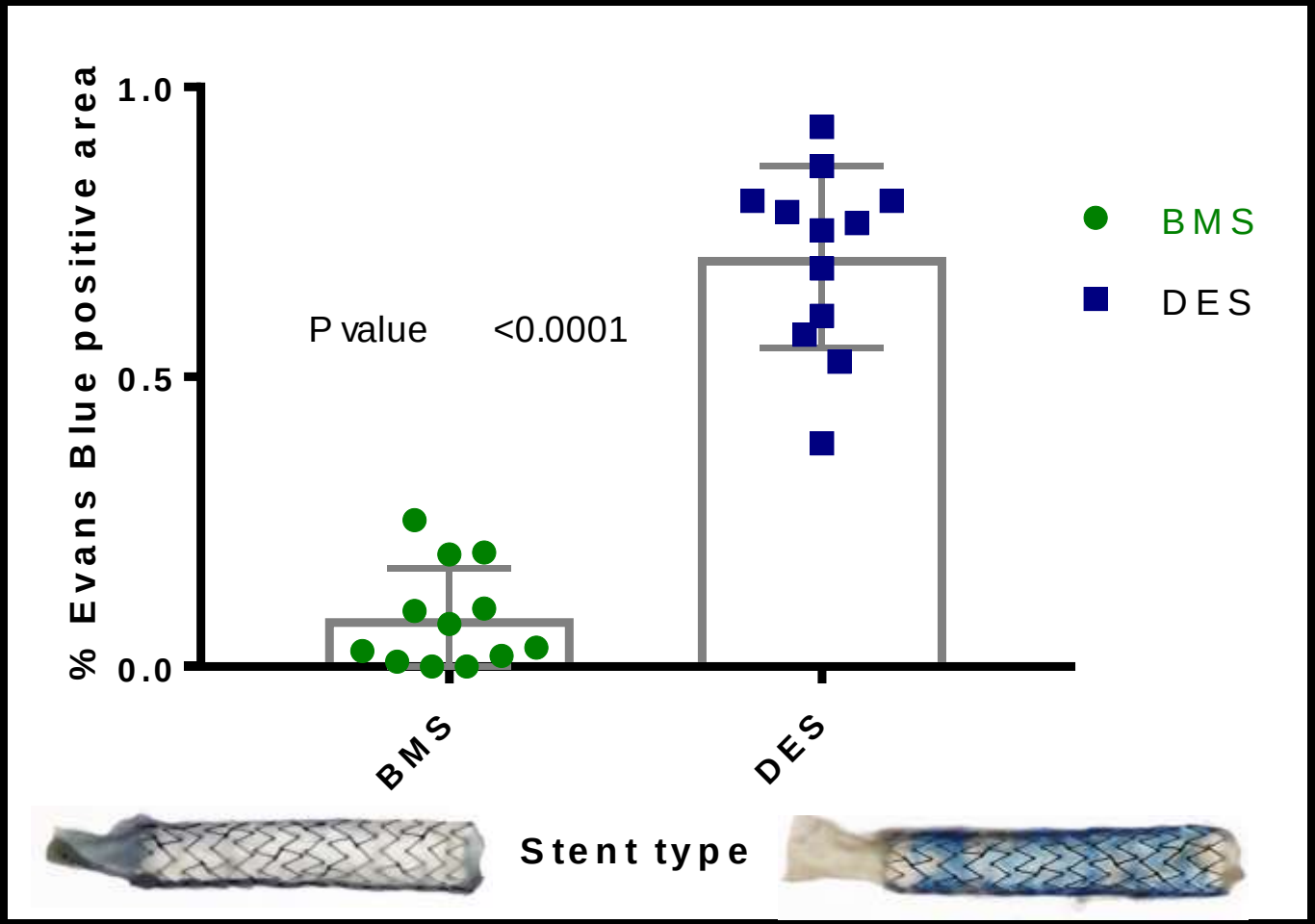


Endothelial permeability can be measured using Evans Blue, a dye which binds highly to albumin and stains areas of vascular permeability blue when infused intravenously

BMS vs Durable Polymer DES at 60 Days Following Evans Blue Dye



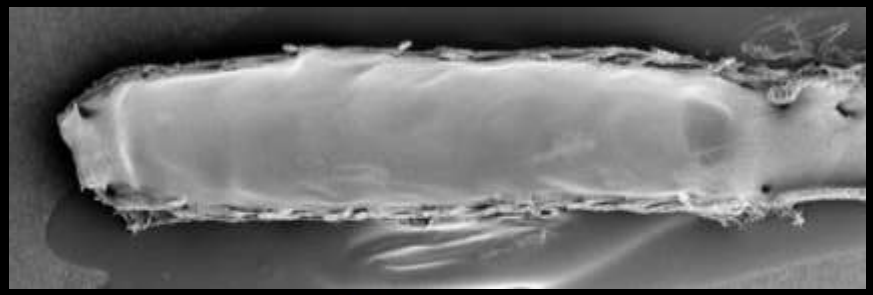
Evans Blue Analysis of Endothelial permeability

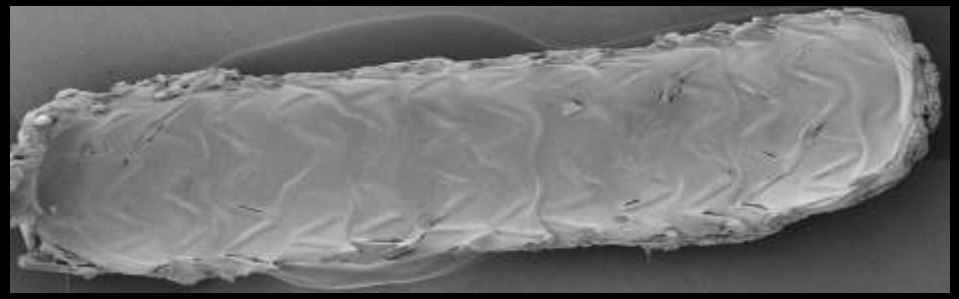


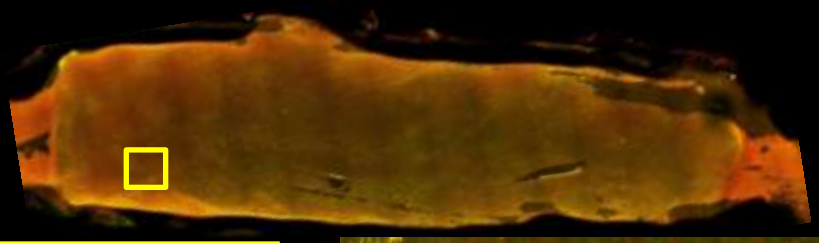
VE-CAD / p120 Co-localization – at 60 days

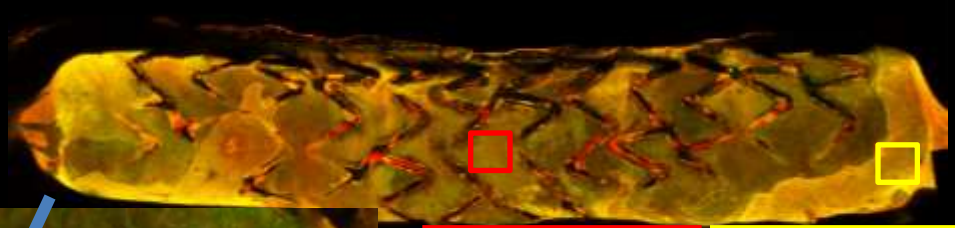
BMS

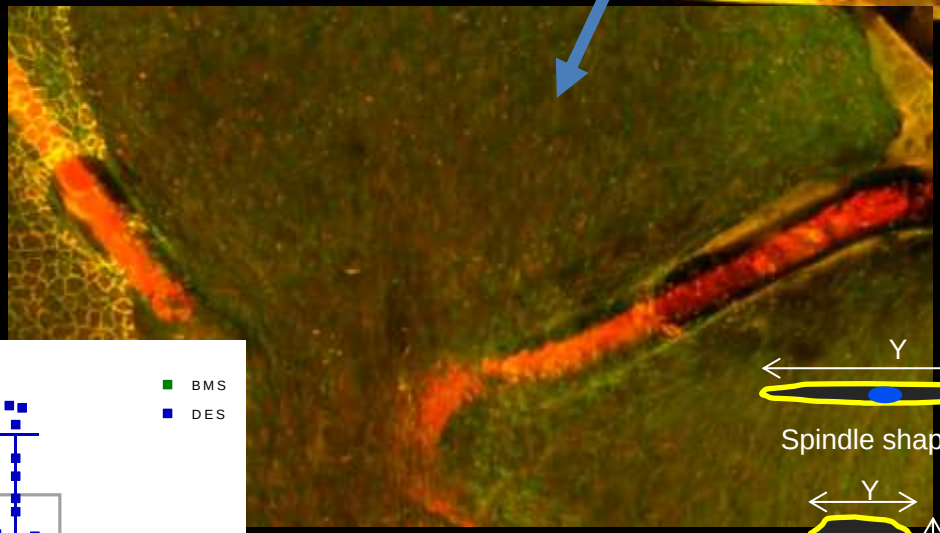
DP-DES

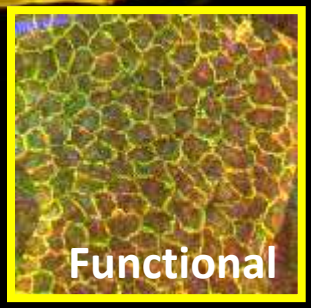


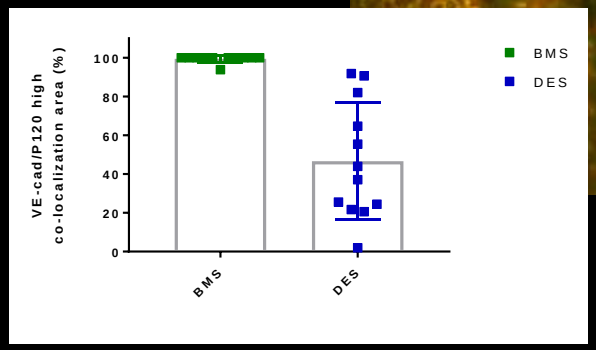




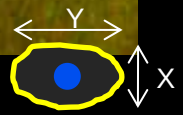




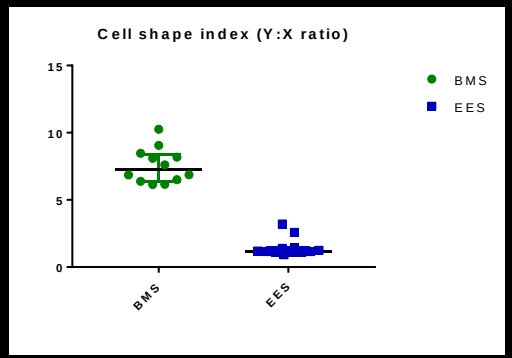




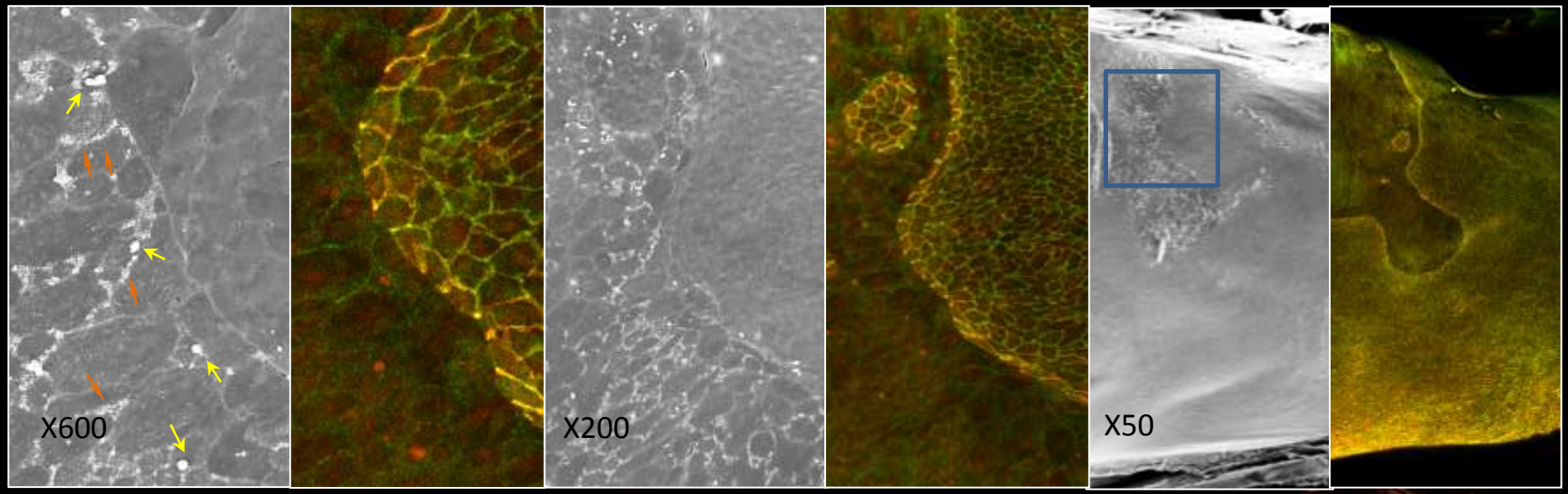
Spindle shape

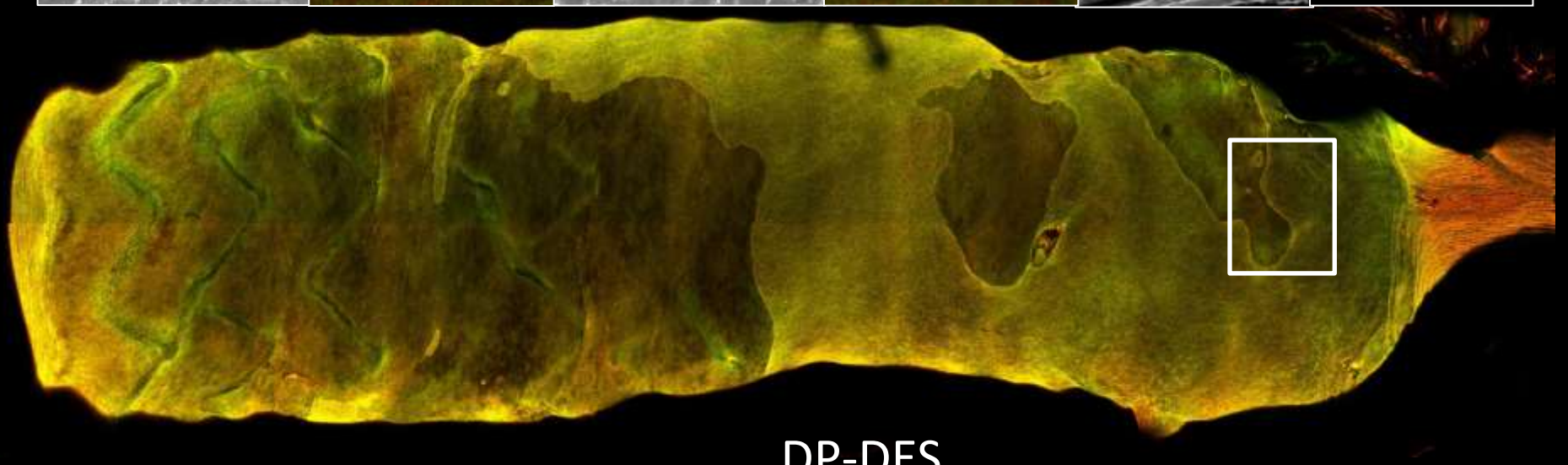


Cobble-stone shape



VE-CAD Pattern and Monocyte Adhesion





DP-DES

Atherosclerosis Rabbit Model

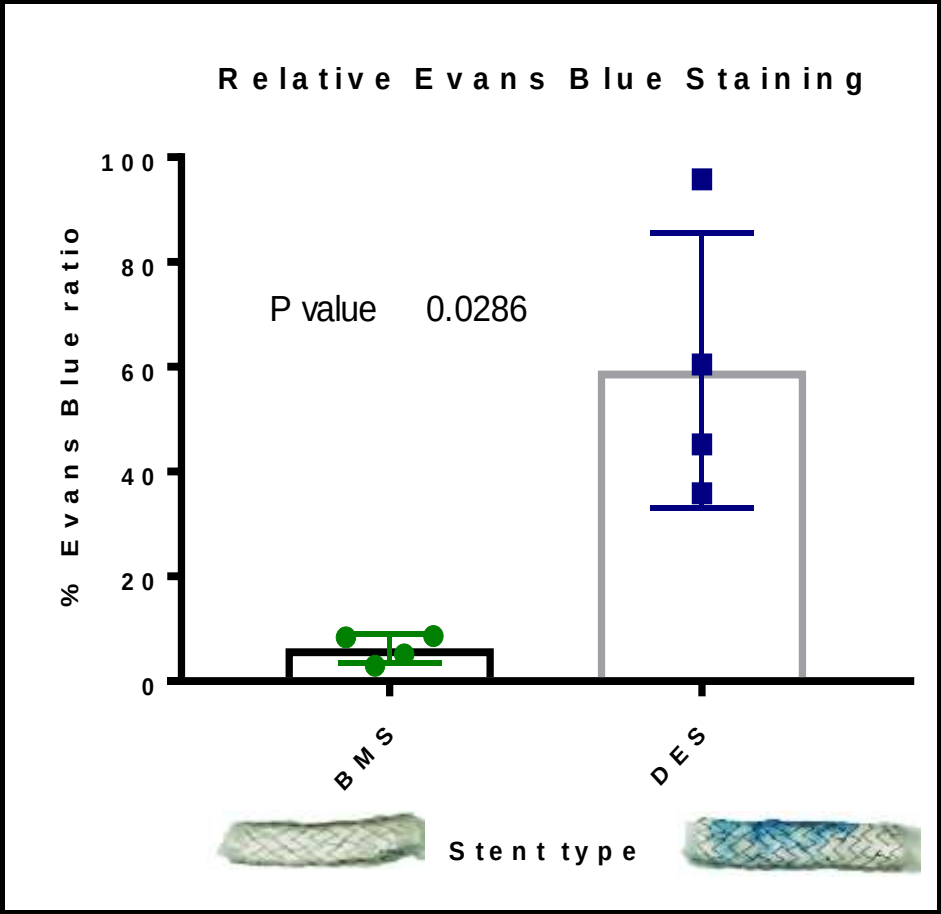
Stent Implantation
Ileofemoral Artery

Explantation

Evans Blue
Injection

100 Days Normal Diet | 30d Pulse

N=6



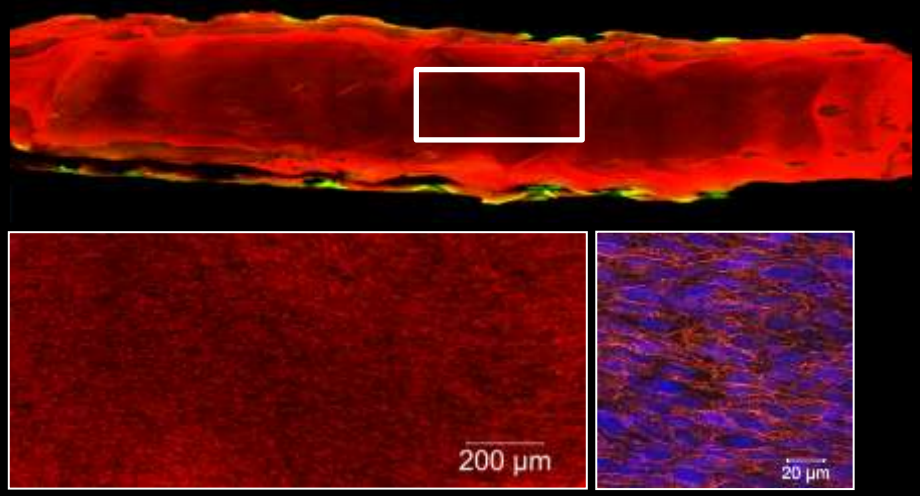
Baseline cholesterol level 29 ± 18
Final cholesterol level 273 ± 98

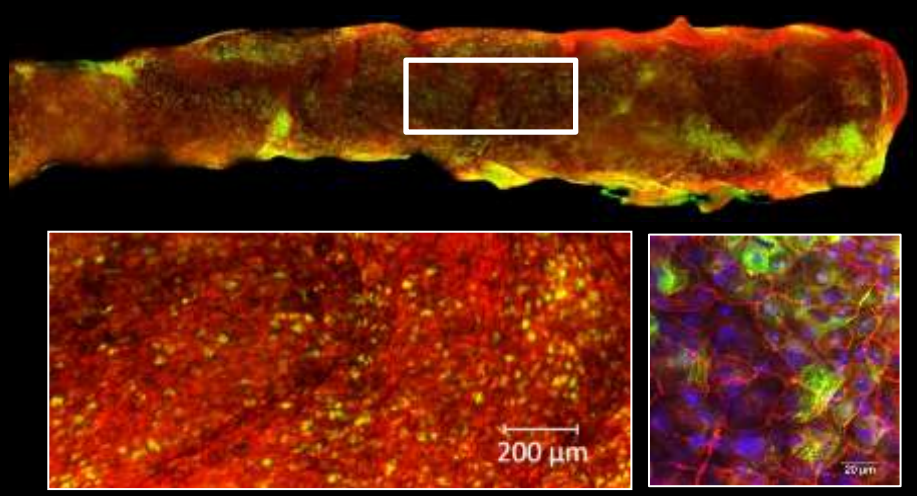
High Cholesterol

Neoatherosclerosis model at 130 days

BMS

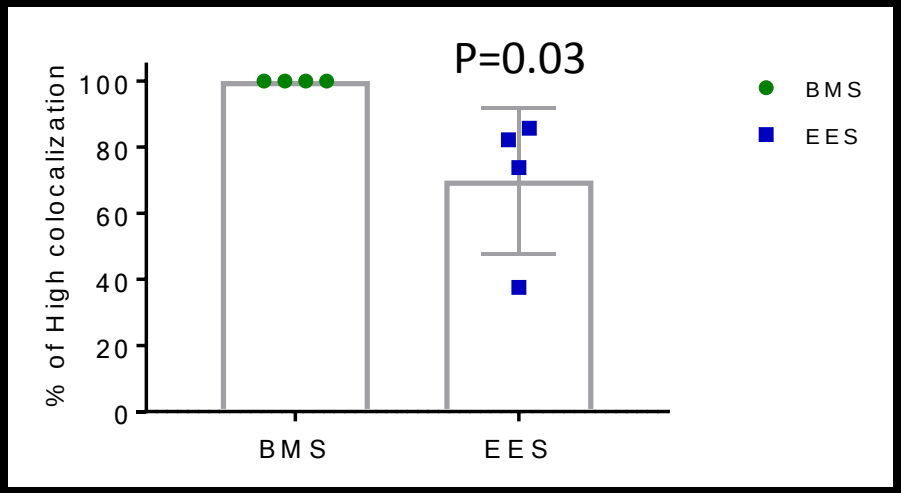
DP-EES



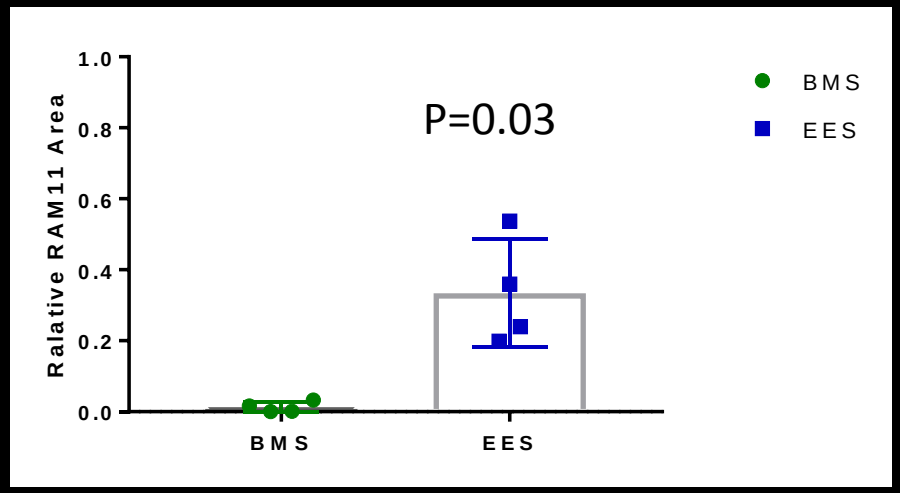


VECAD RAM11 DAPI

VE-Cad/P120



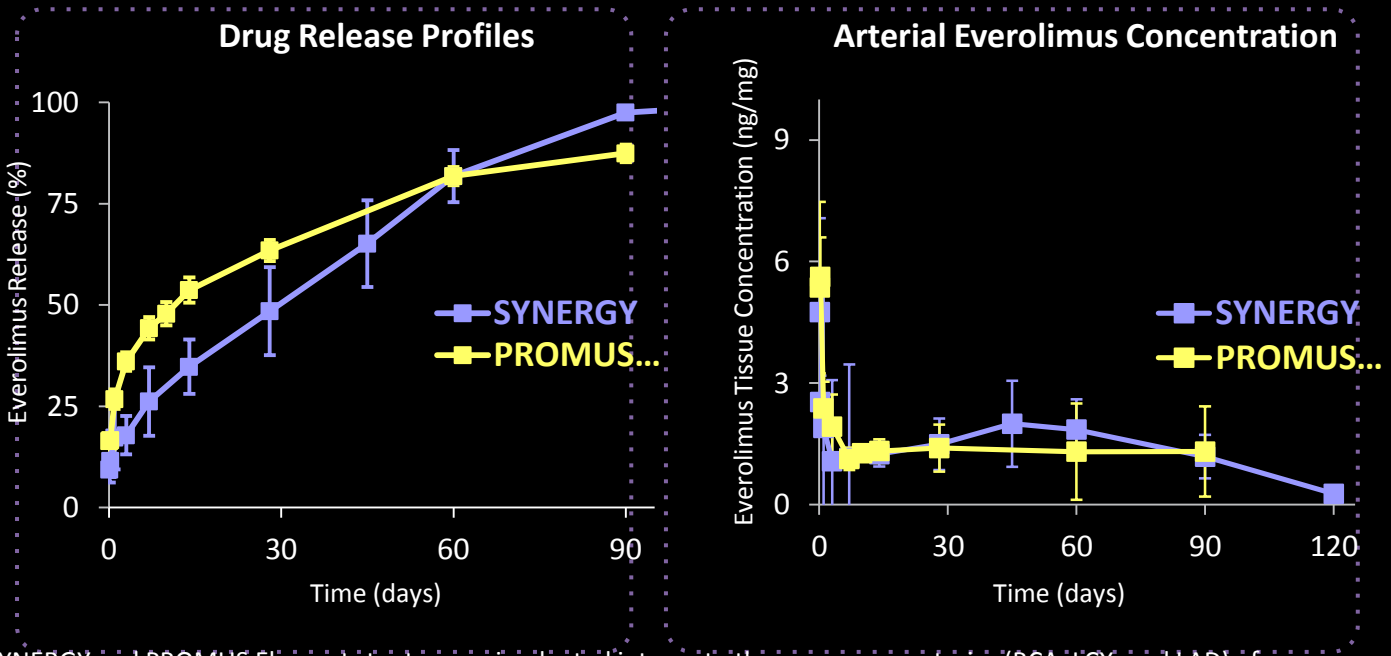
RAM11 area



Endothelial Function in biodegradable polymer Synergy DES

SYNERGY vs PROMUS Element

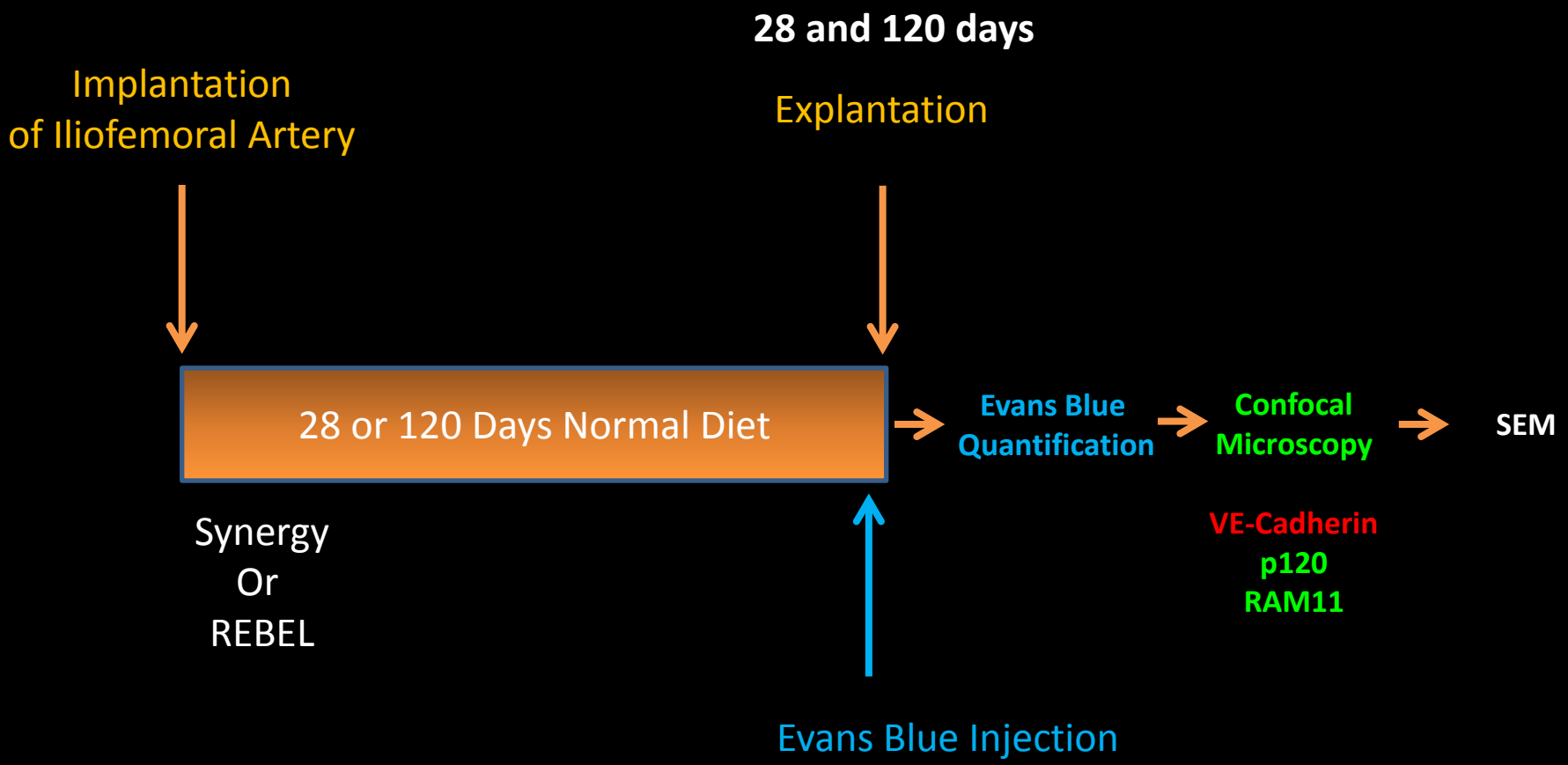
In Vivo Release and Pharmacokinetic Analysis



SYNERGY and PROMUS Element stents were implanted into up to three coronary arteries (RCA, LCX, and LAD) of un-injured, domestic, Yorkshire cross swine (N=134 swine). Stents were explanted at pre-determined time points up to 120 days. Everolimus remaining on the explanted stents was extracted and arterial everolimus concentration was analyzed using HPLC/MS.

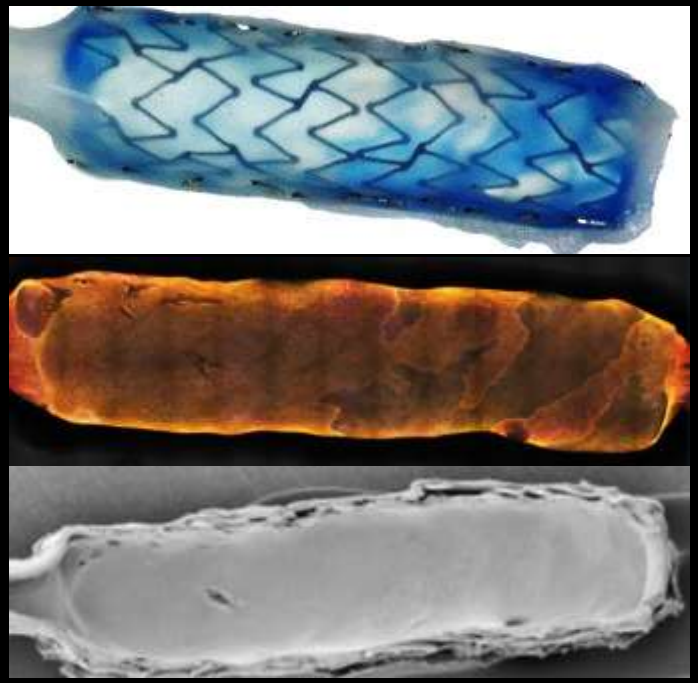
Wilson, G.J., et al. Cathet Cardiovasc Interv 2015. PROMUS Element data on file at BSC.

Experiment design
Rabbit Model

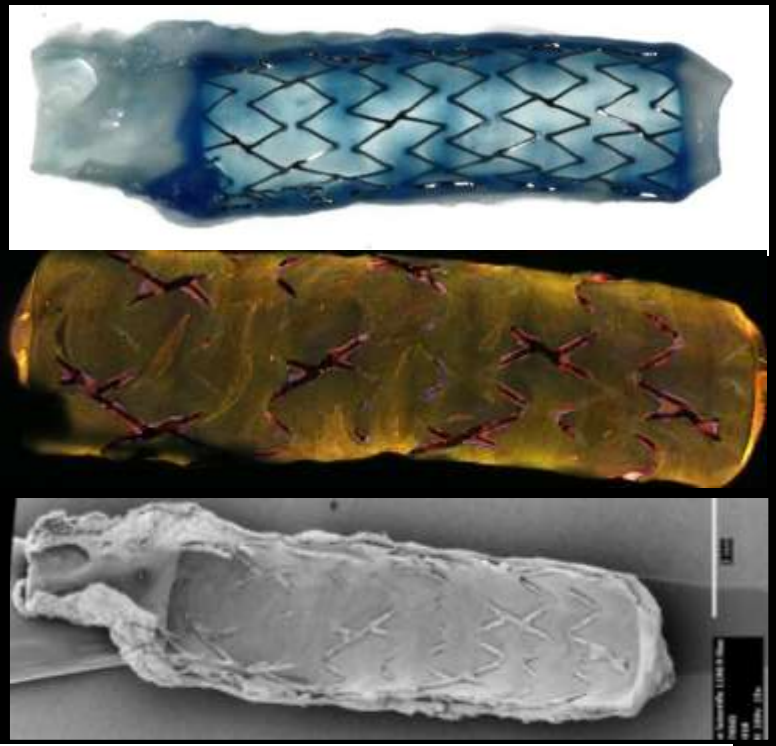


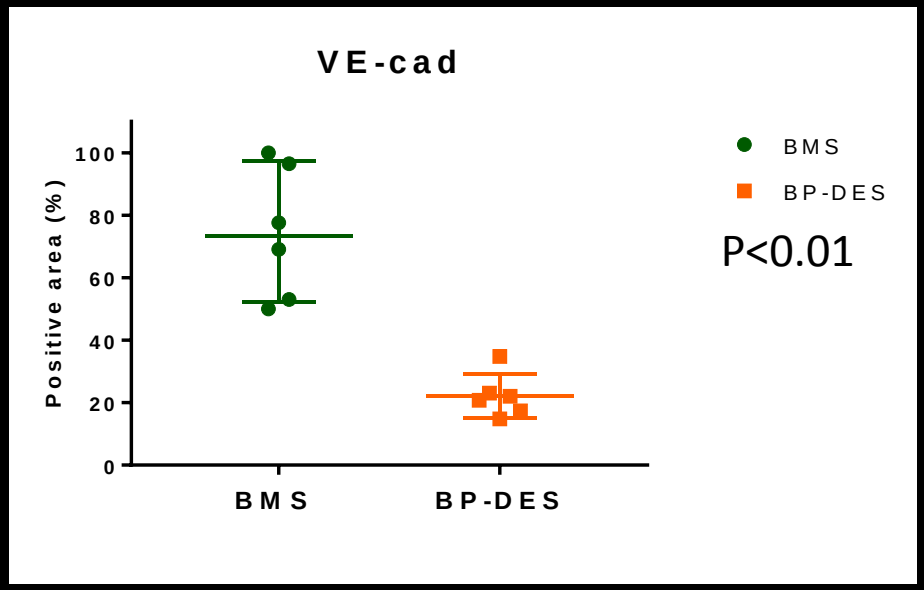
BMS vs. BP-DES at 28-days in rabbit model

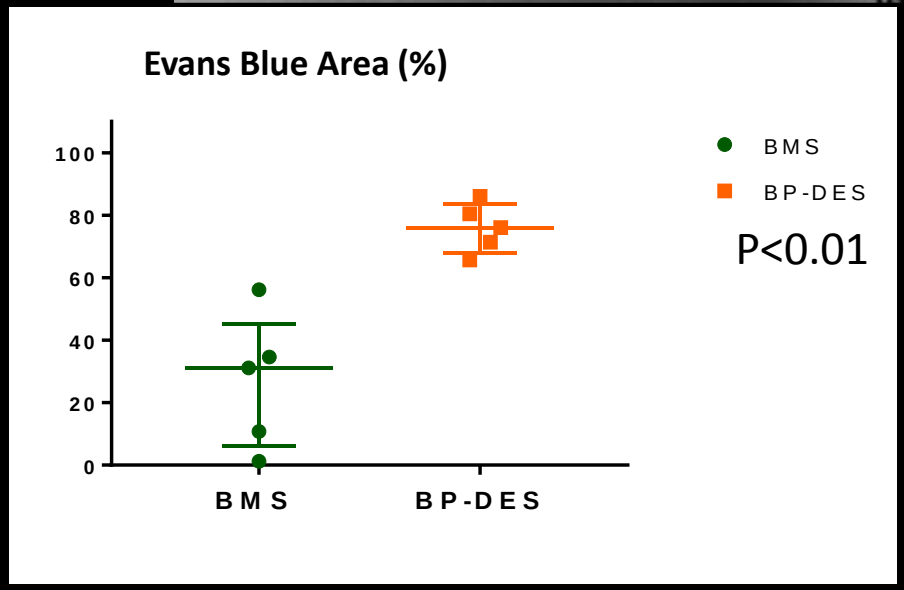
BMS



Synergy

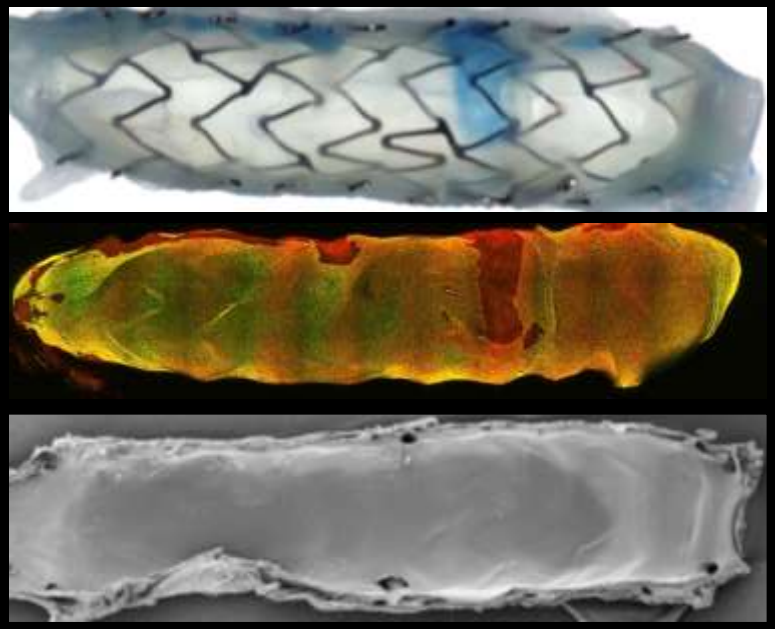




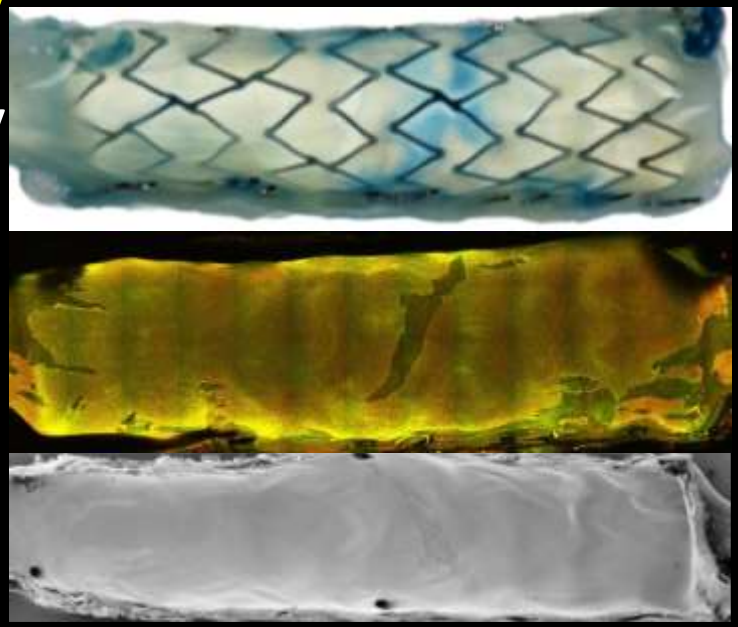


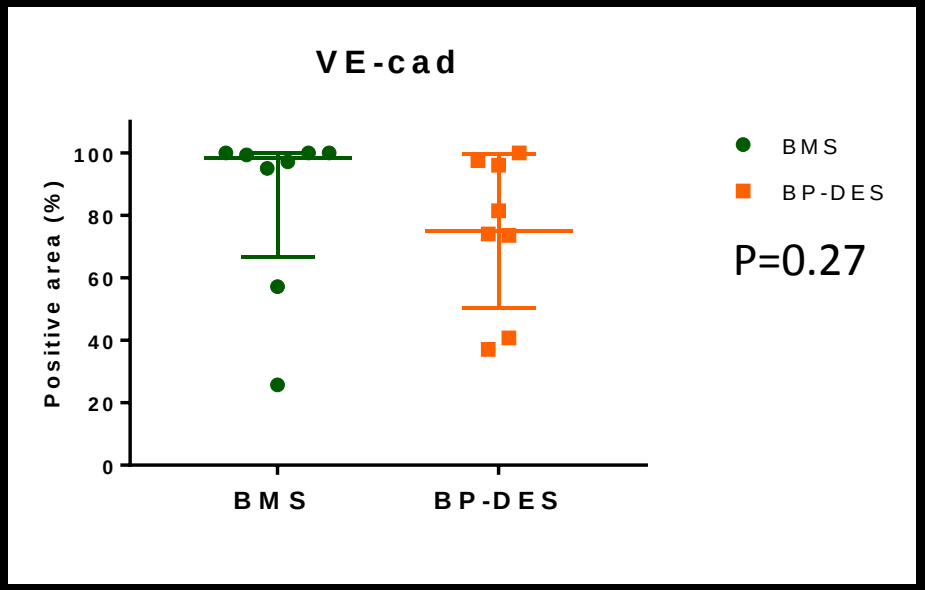
BMS vs. BP-DES at 120-days in rabbit model

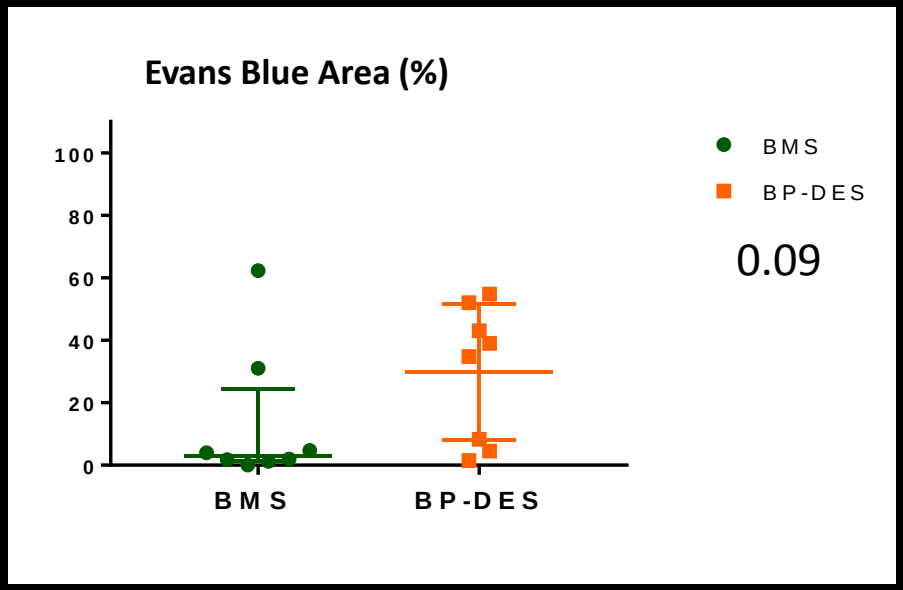
BMS



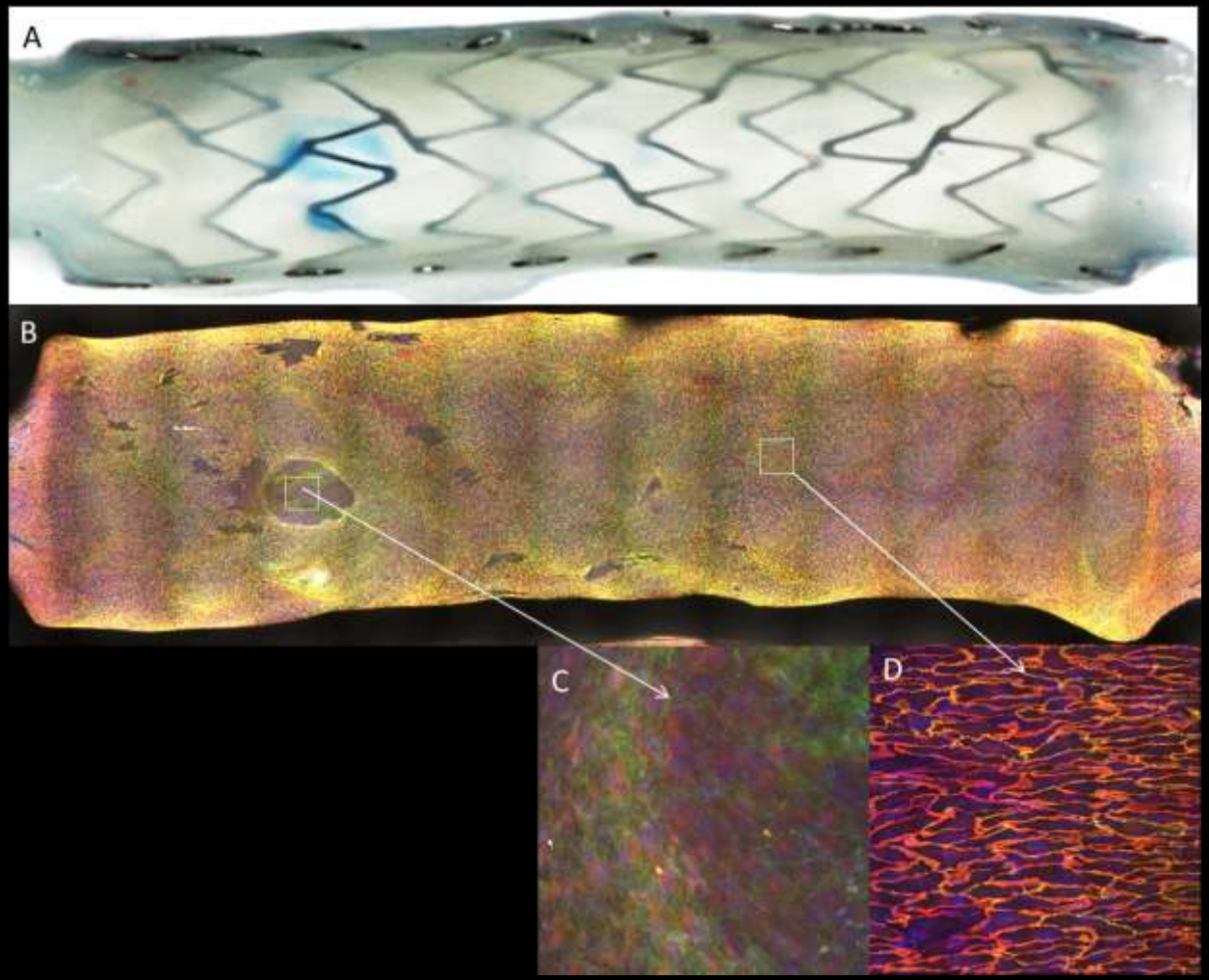
Synergy



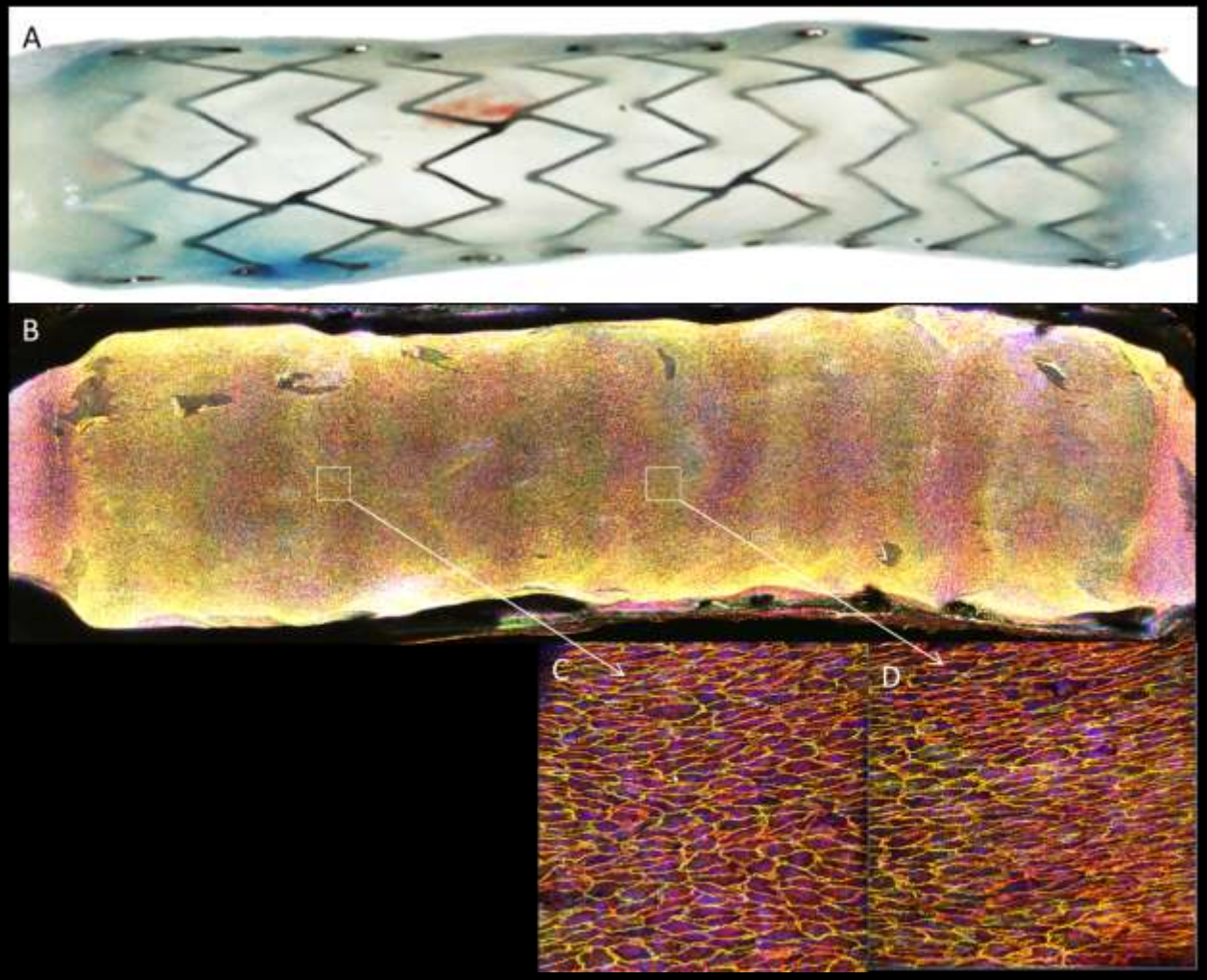




120 Days REBEL



120 Days Synergy



Do Bioabsorable Polymer Synergy offer an advantage over durable polymers?

Conclusions:

- Bioabsorable polymers have an important advantage over durable polymers.
- Endothelial barrier function is impaired in durable polymer DES for long period of time (?how long) as compared to BMS. These cells are more prone to neoatherosclerosis as shown in our enriched cholesterol fed rabbit model.
- In biodegradable polymer Synergy, endothelium function was comparable to BMS at 120 days, a timepoint by which polymer had degraded.
- Further studies are needed to demonstrate a definite advantage for Synergy over durable polymer DES
  - Neoatherosclerosis model
  - Profiling of dysfunctional endothelial cells
- Such findings are impossible to show in humans at the current time but should result in lower long-term events

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