The Mechanisms of ISR:

Insights from Pathologic Studies

Aloke V Finn, MD.

CVPath Institute, Inc.

Gaithersburg, MD, USA.

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.

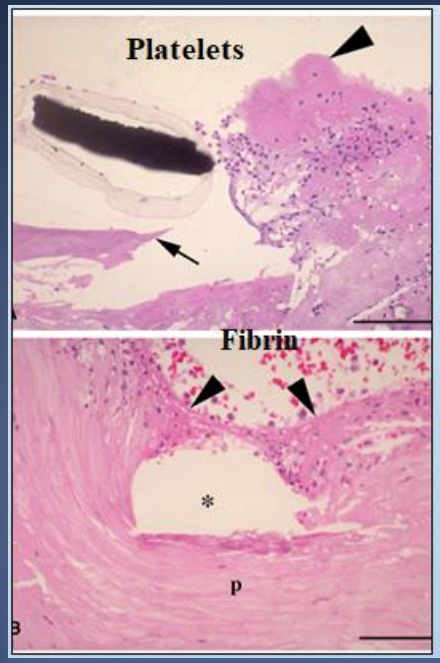
Institutional grant/research support: R01 HL141425 Leducq Foundation Grant; 480 Biomedical; 4C Medical; 4Tech; Abbott; Accumedical; Amgen; Biosensors; Boston Scientific; Cardiac Implants; Celonova; Claret; Concept Medical; Cook; CSI; DuNing; Edwards; Emboline; Endotronix; Envision Scientific; Lutonix/Bard; Gateway; Lifetech; Limflo; MedAlliance; Medtronic; Mercator; Merill; Microport; Microvention; Mitraalign; Mitra assist; NAMSA; Nanova; Neovasc; NIPRO; Novogate; Occulotech; Orbus Neich; Phenox; Profusa; Protembis; Qool; Recor; Senseonics; Shockwave; Sinomed; Spectranetics; Surmodics; Symic; Vesper; W.L. Gore; Xeltis.

Owner of a healthcare company: No

Stockholder of a healthcare company: No

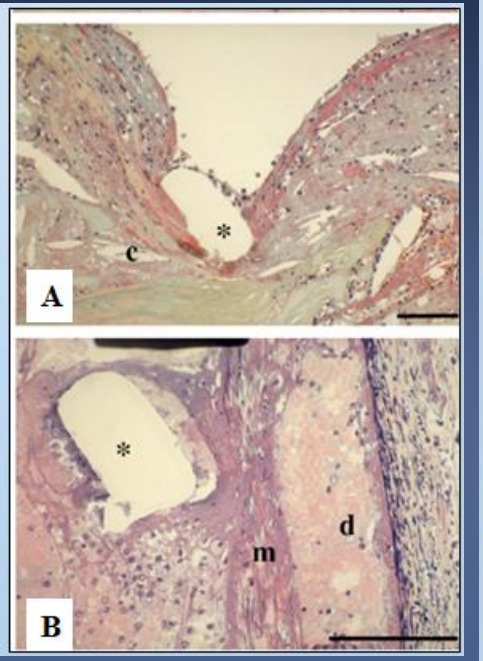
Bare Metal Stent Healing in Human

Thrombus



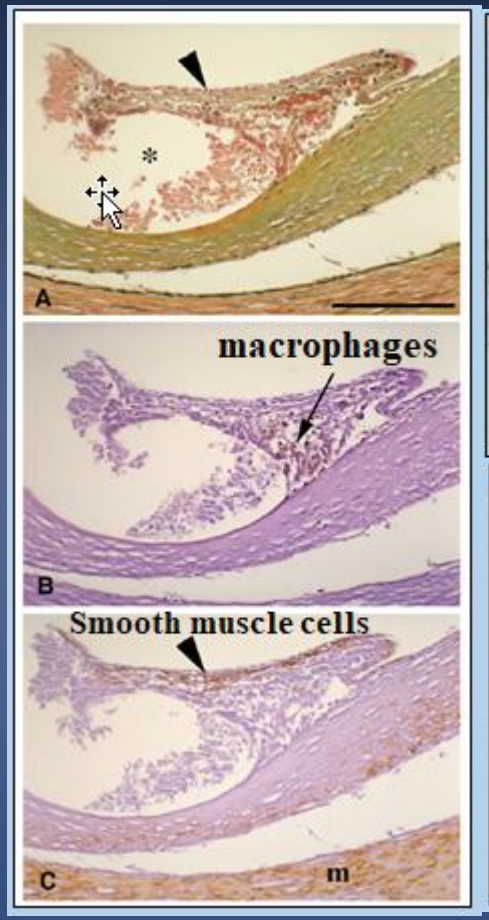
1-30 days

Acute Inflammation



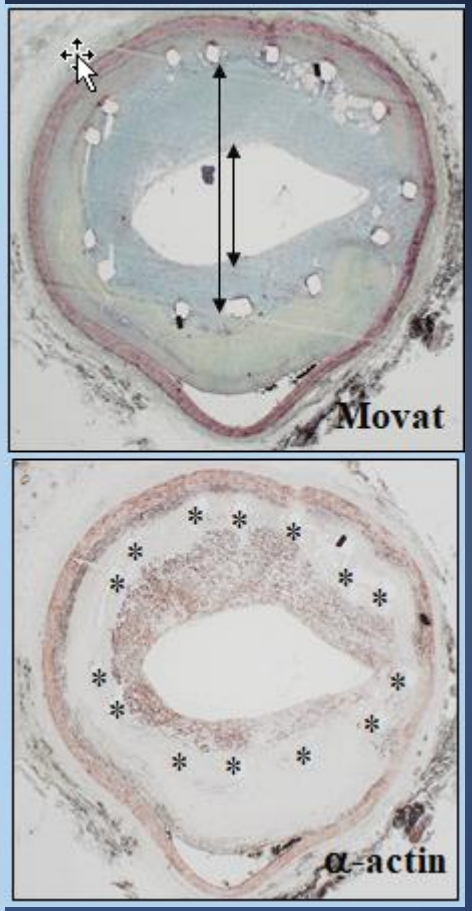
1-30 days

Granulation tissue



14 – 90 days

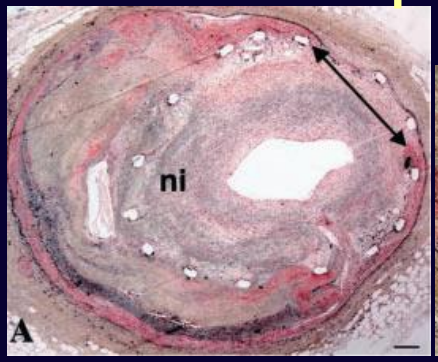
Smooth muscle cells and matrix

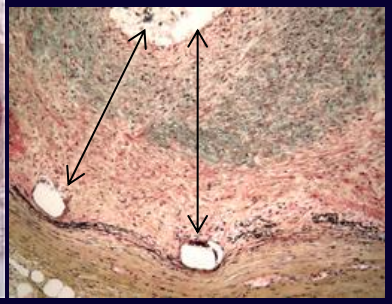


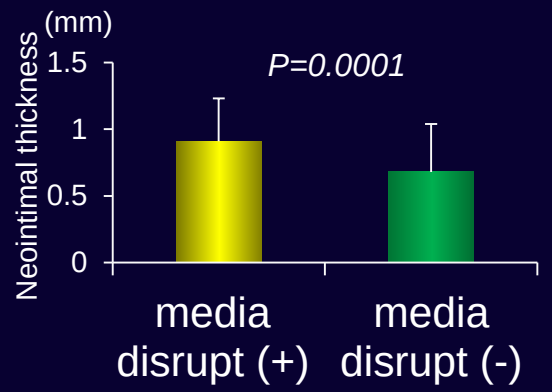
≥ 6 months

Predictors of BMS Restenosis

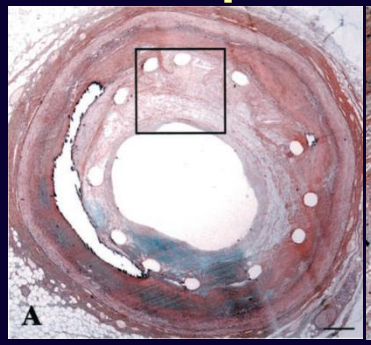
Media disruption

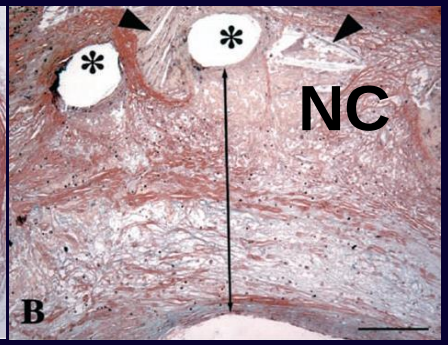


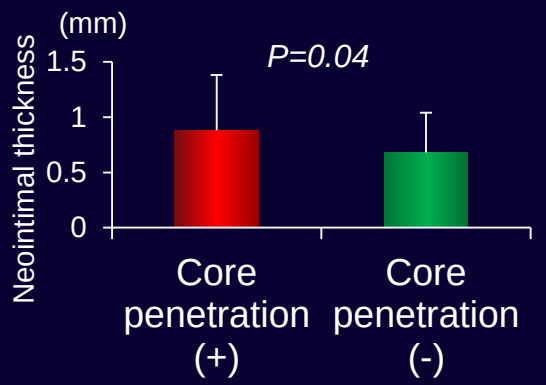




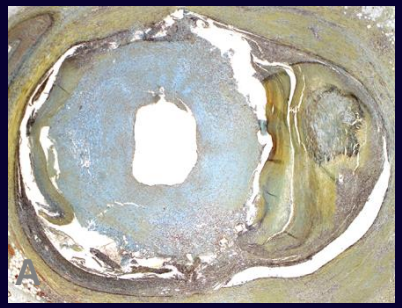
Strut penetration into NC

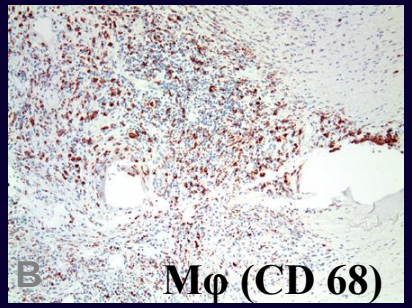


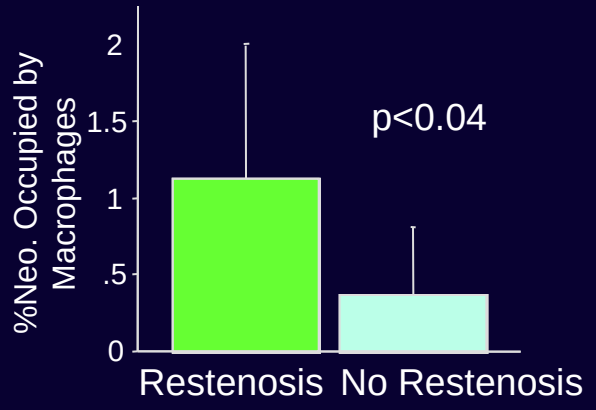




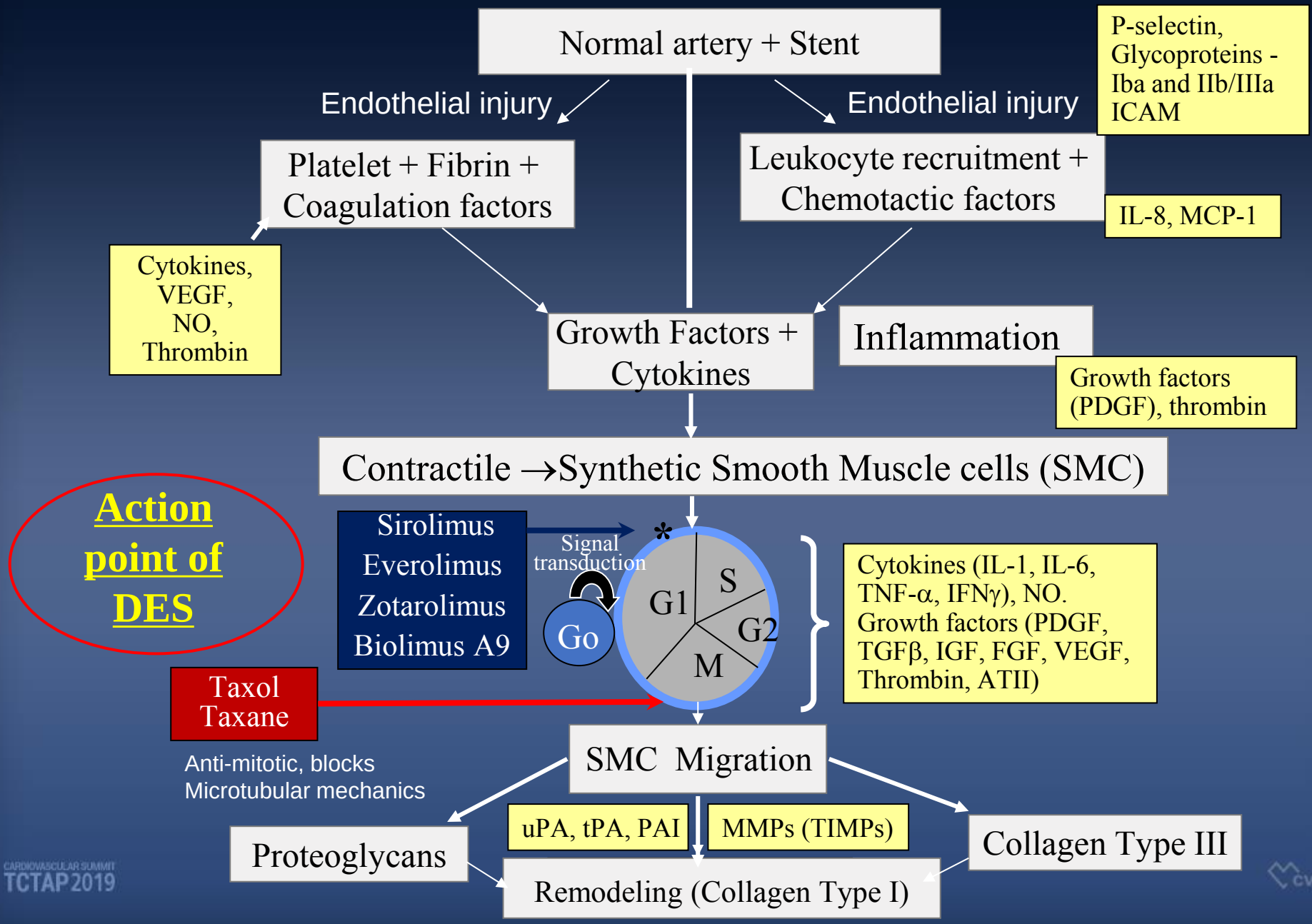
Inflammation





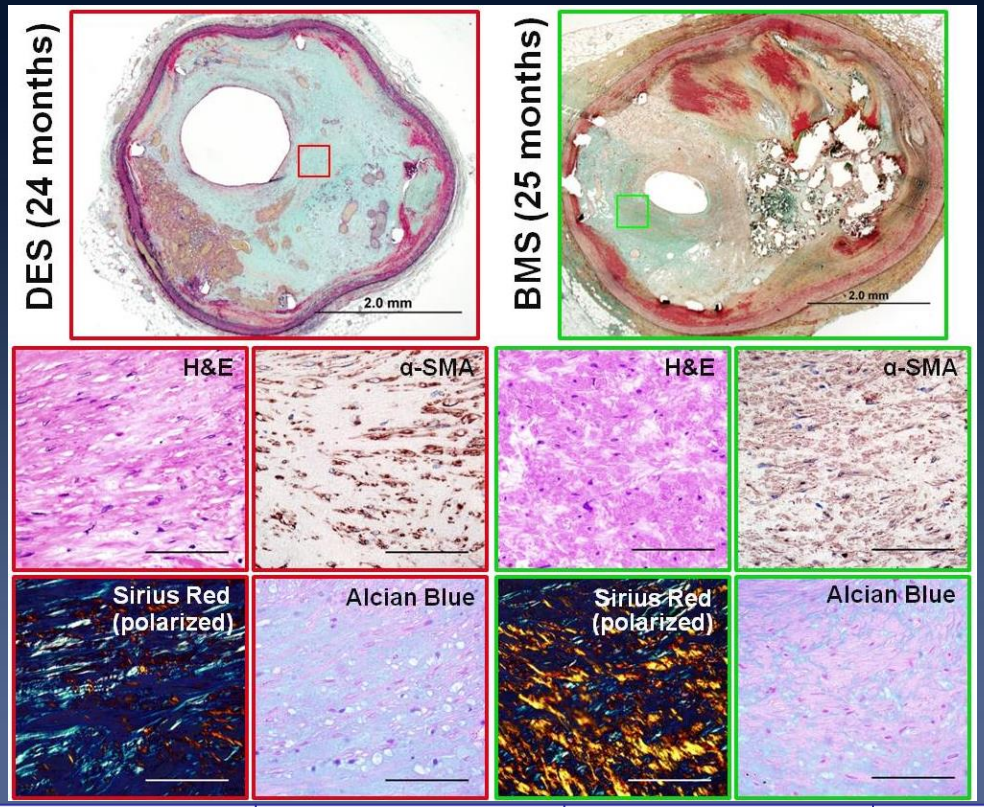


Processes of BMS Restenosis

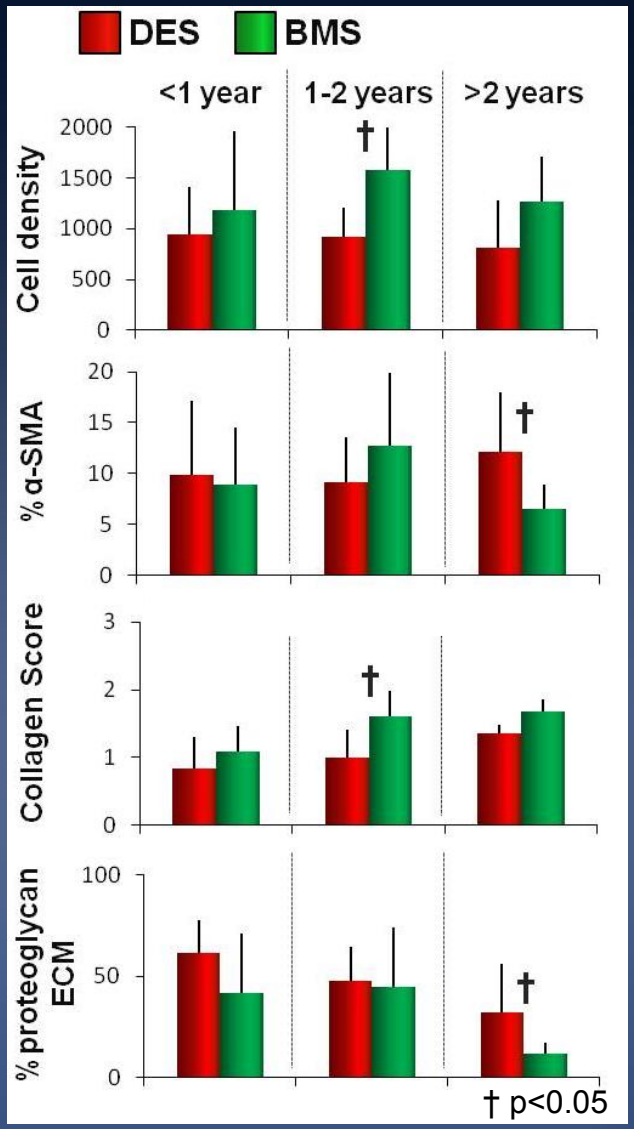


Restenosis in DES

Neointimal Characteristics in DES and BMS



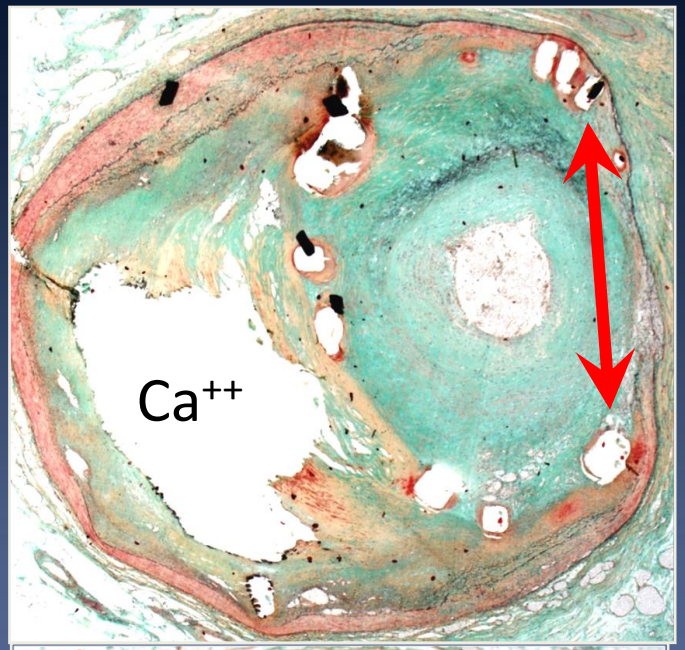
	DES (N=15)	BMS (N=15)	P value
Total cell count, /mm^2	906±404	1409±549	0.014
% α-SMA area	9.5±6.2	10.5±6.3	0.66
Collagen score (0-3)	1.0±0.4	1.4±0.4	0.022
% Proteoglycan area	69.3±22.4	48.0±28.4	0.032



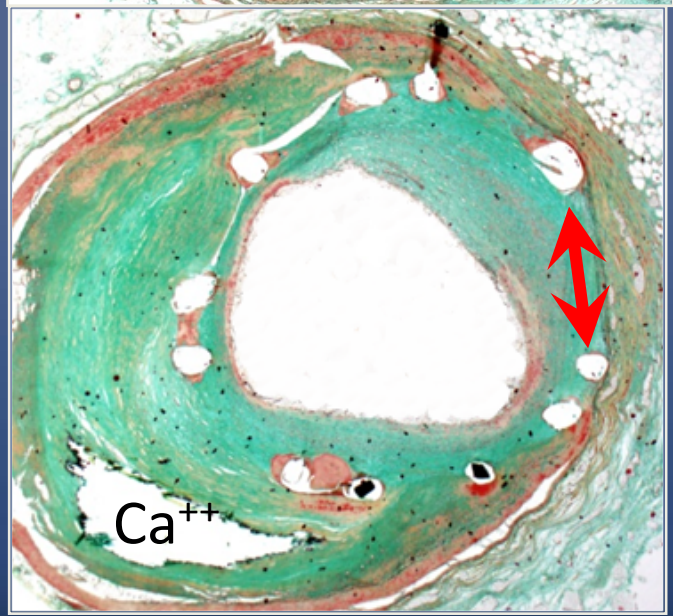
- α-SMA positive SMC activity peaks at 1-2 years and then decreases in BMS whereas in DES there is no change over time, suggesting a persisting neointimal activity .
- DES neointima demonstrates greater proteoglycan deposition and less collagen production.

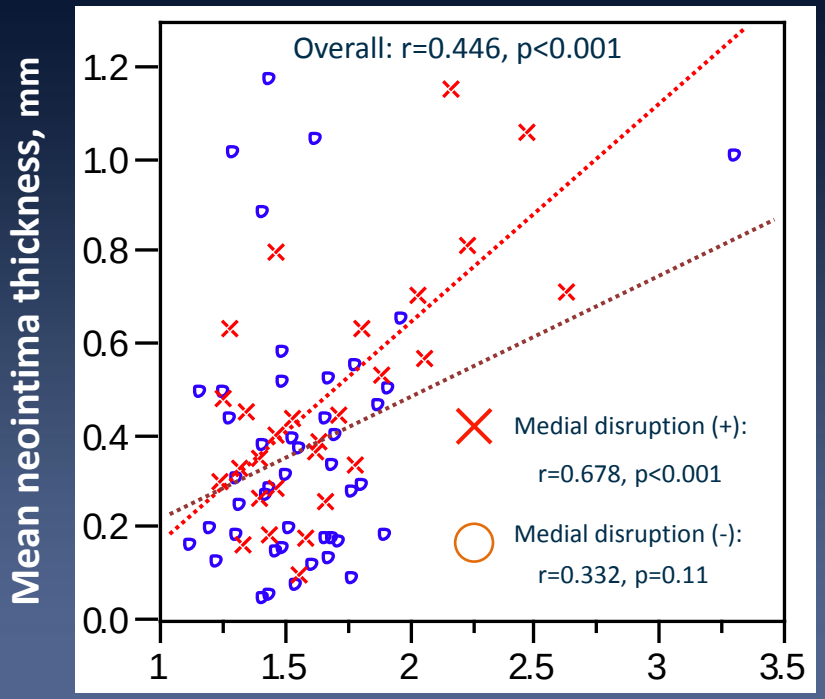
The efficacy of DES wanes if the distribution of anti-proliferative drug is uneven

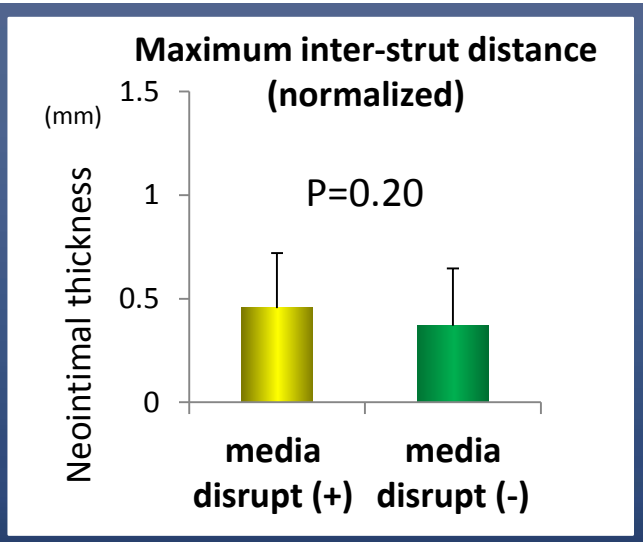
Longer inter-strut distance



Shorter inter-strut distance



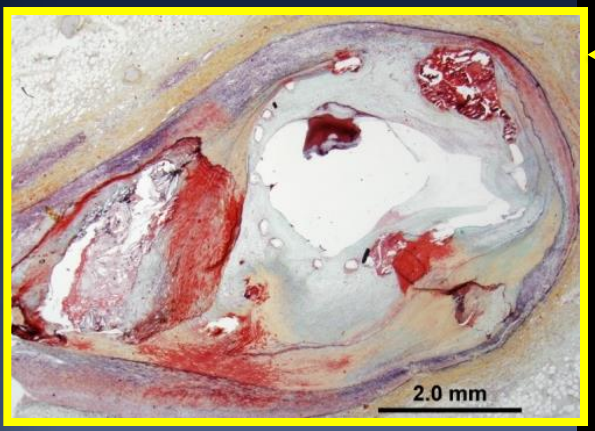


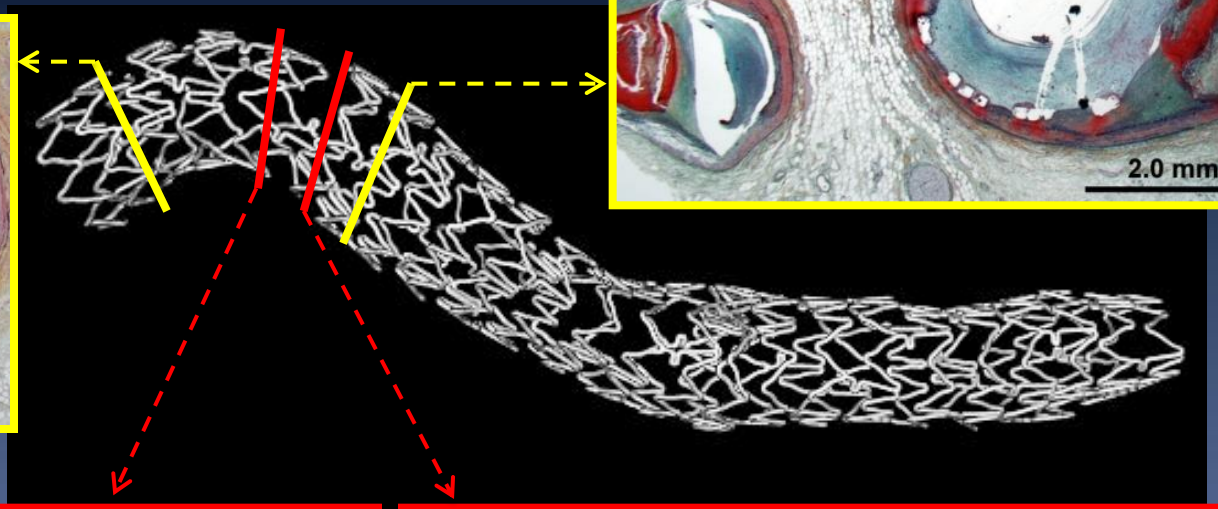


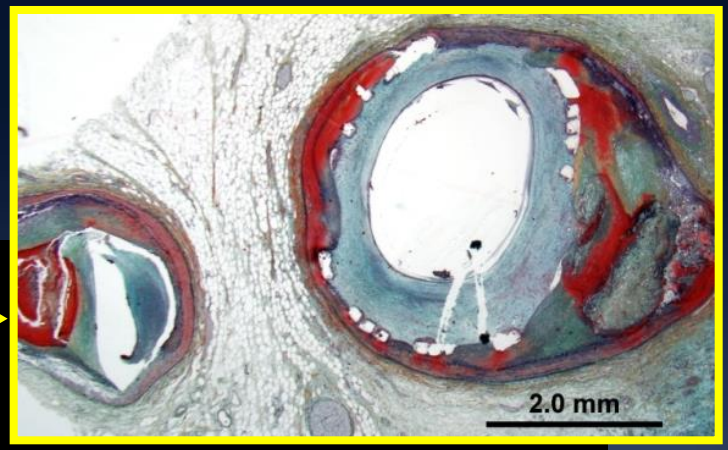
Masataka Nakano et al. Eur Heart J 2013;34:3304-3313

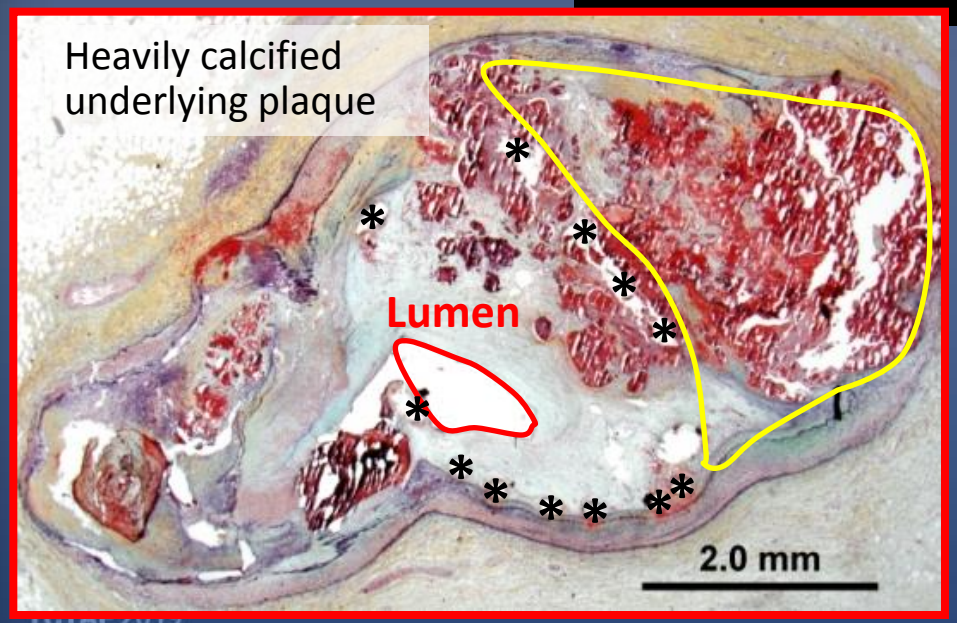
EES Restenosis Associated with Stent Fracture

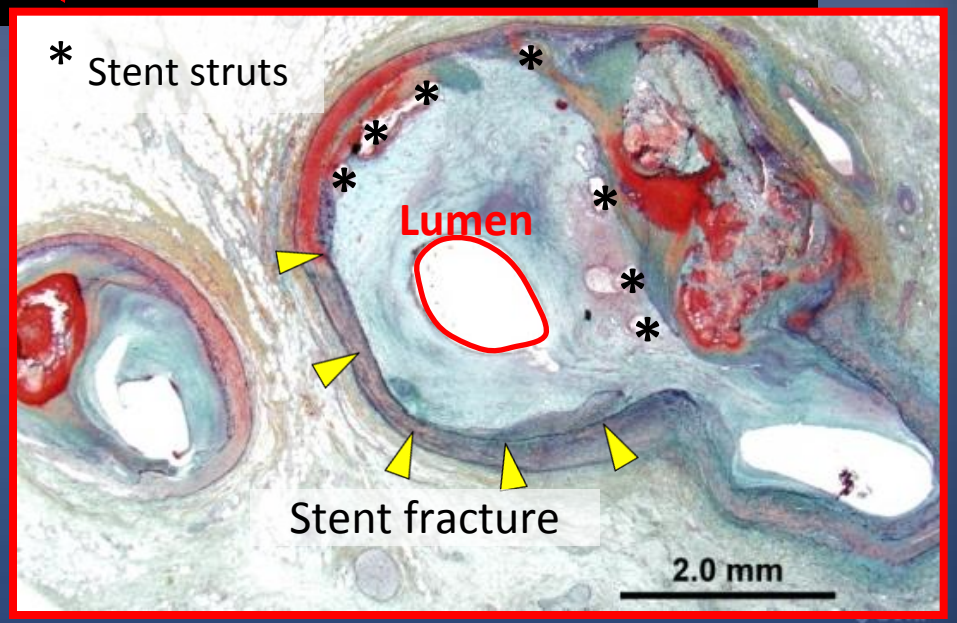
70F, EES implanted in LM to LCX for 6 months











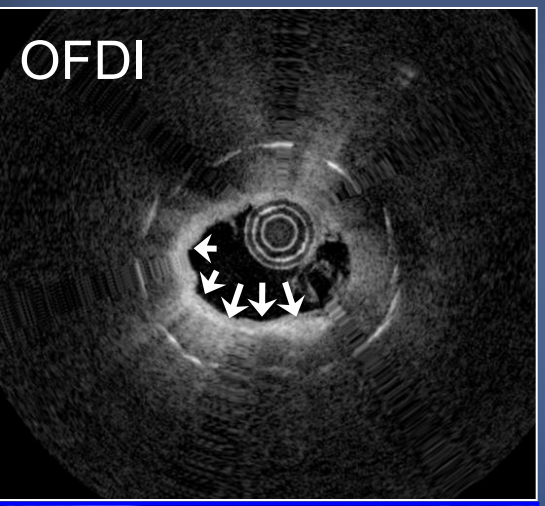
Foerst JR, et al. J Am Coll Cardiol Intv 2012;5:239-42.

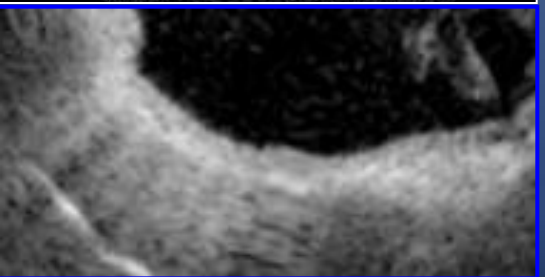
Cause of Late DES Failure; Neoatherosclerosis

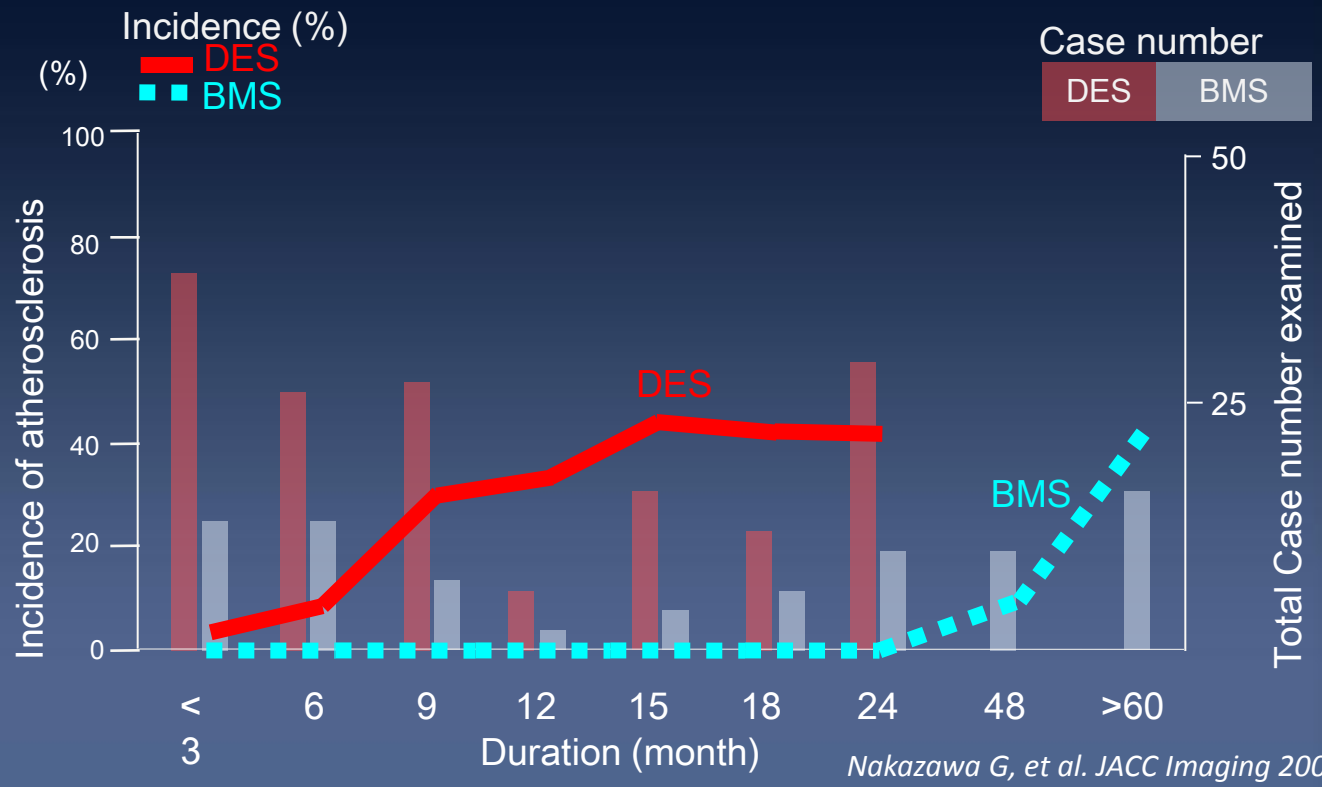
Late vascular complication: Neoatherosclerosis

Definition:
In-stent neo-atherosclerosis is histologically characterized by an accumulation of lipid-laden foamy macrophages with or without necrotic core formation and/or calcification within the neointima.

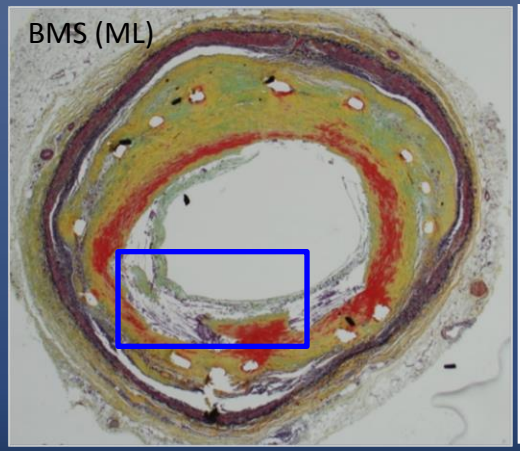
Otsuka et al., Eur Heart J. 2015 May 20. pii: ehv205



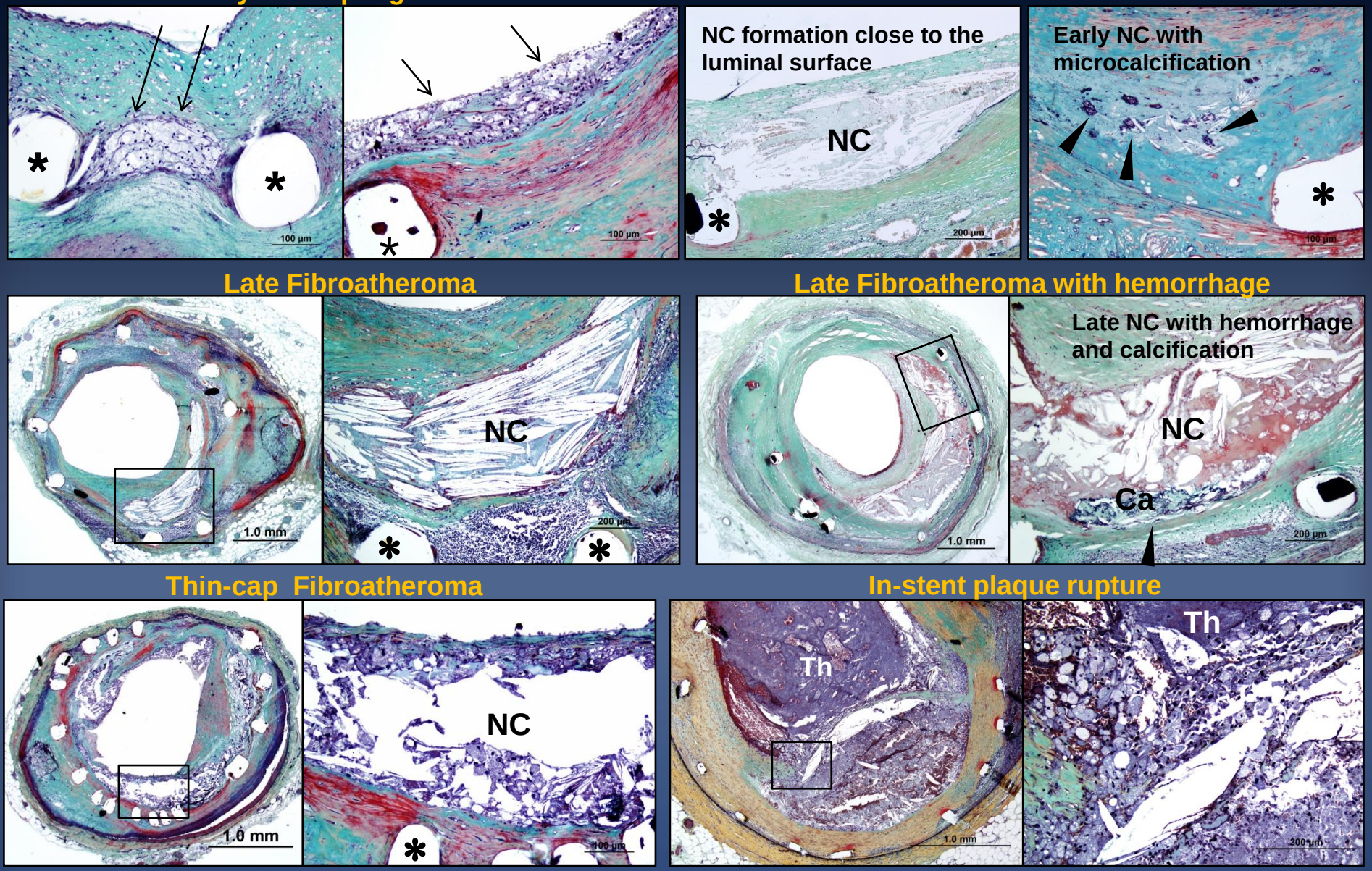




Nakazawa G, et al. JACC Imaging 2009

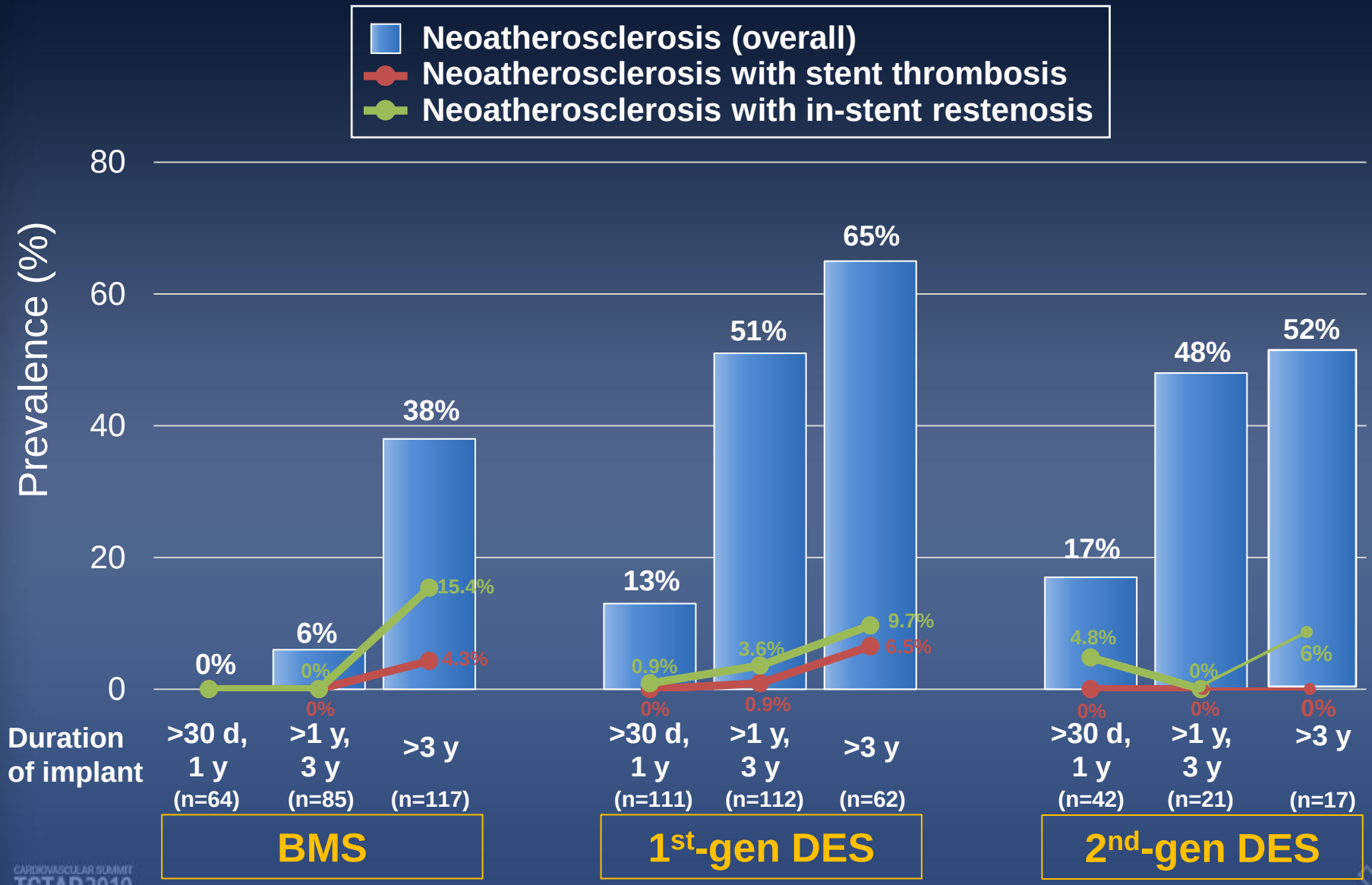


Representative Images Showing Progression of Neoatherosclerosis

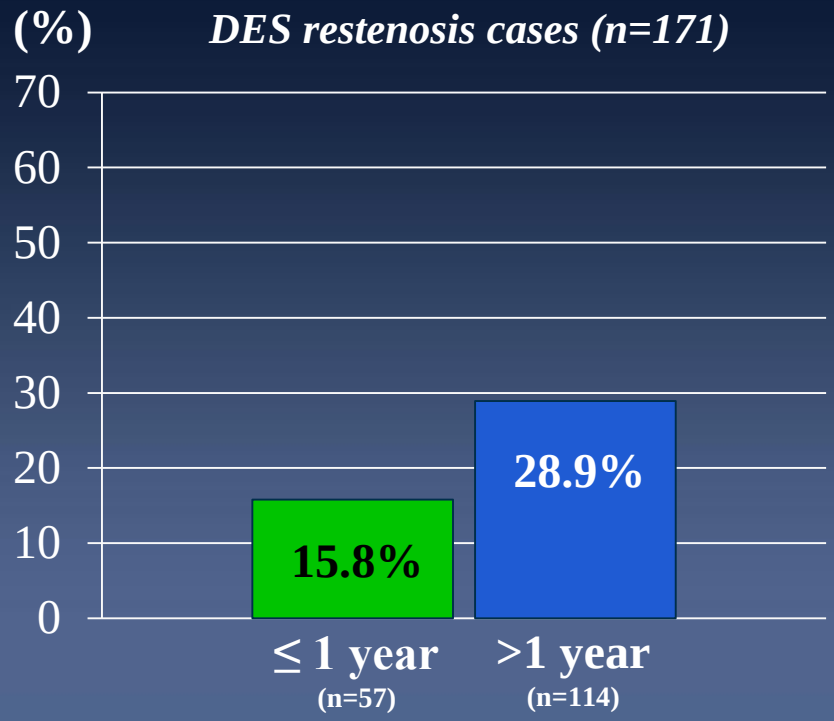


Neoatherosclerosis was defined as the presence of foamy macrophages within the neointima with or without necrotic core and/or calcification.

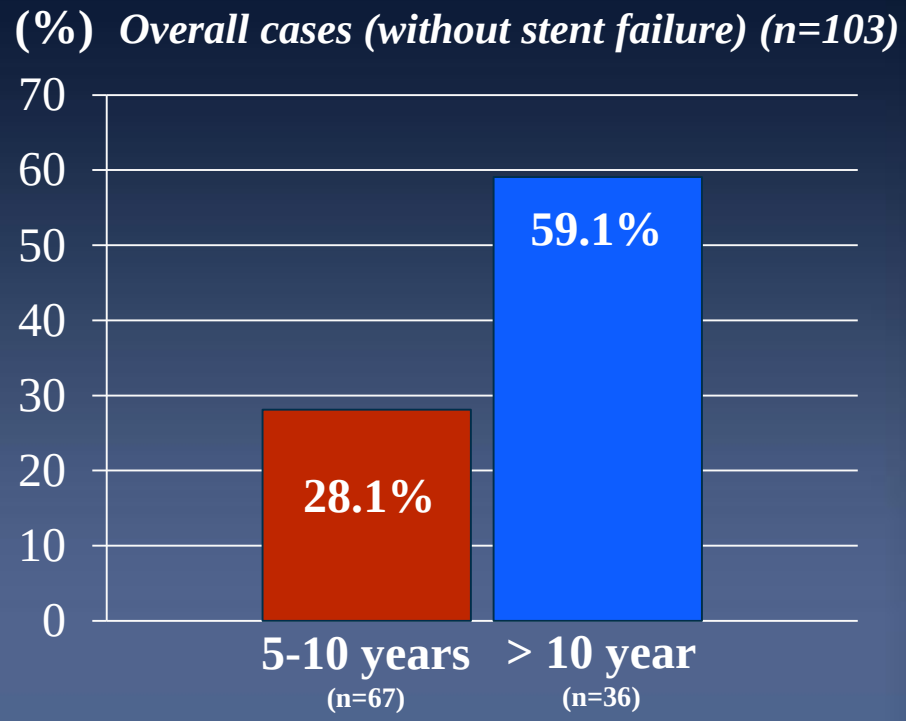
Prevalence of Neoatherosclerosis (Autopsy cases): Overall, in Stent Thrombosis, and Restenosis



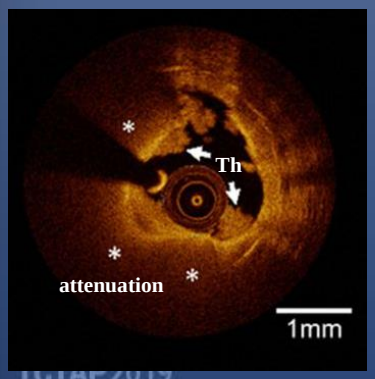
Over-time Clinical Prevalence of Neoatherosclerosis in DES (in vivo OCT analysis)



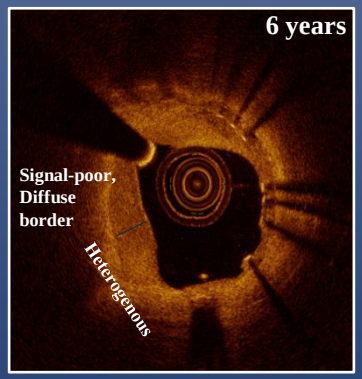
Song L, et al. EuroIntervention. 2017;13:294-302.



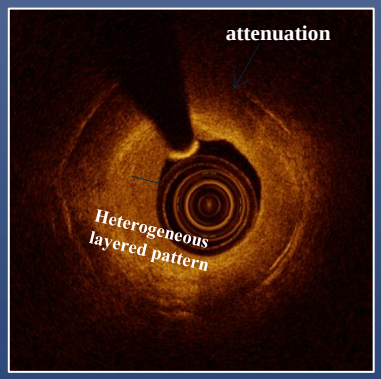
Usui E, et al. EuroIntervention.2018;14:e1316-e1323



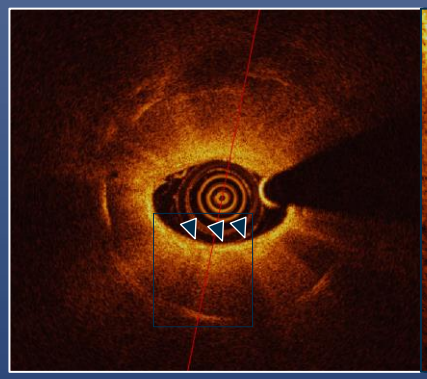
Plaque Rupture



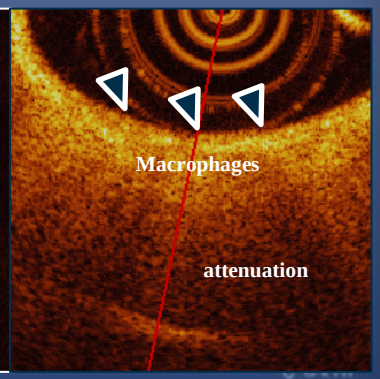
Fibroatheroma



Fibroatheroma

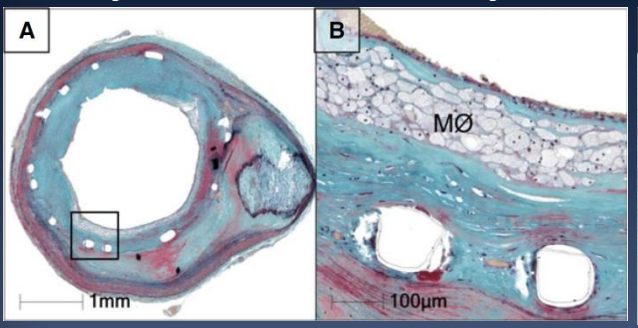


Fatty Streak

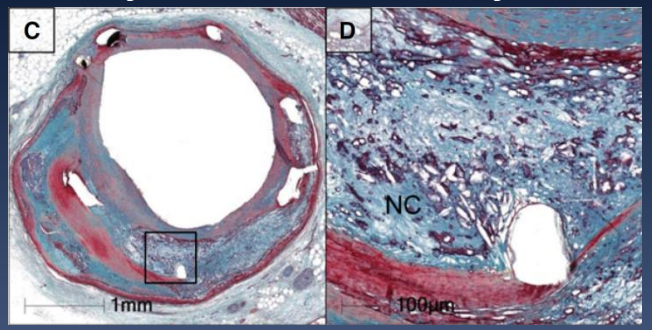


Prevalence and Type of Neoatherosclerosis in very long term (1-5 years)

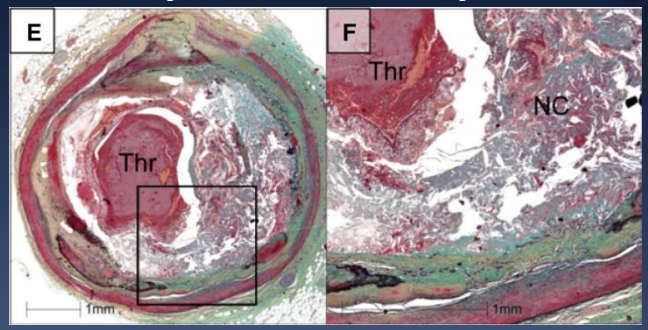
63-y male CoCr-EES 5 years

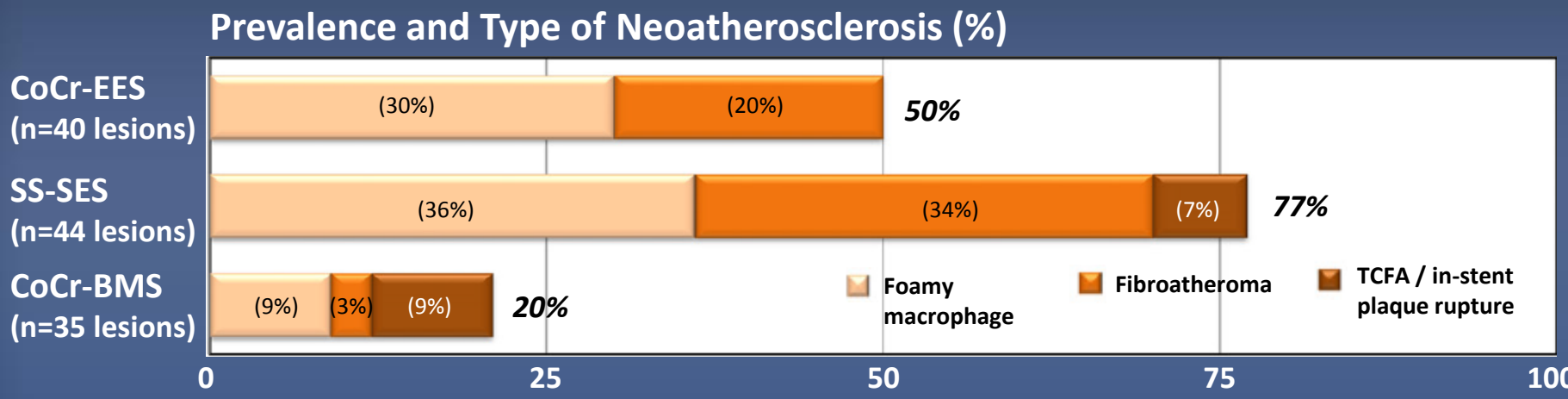


40-y female SS-SES 5 years



56-y male BMS 5 years





	CoCr-EES (n=20 lesions)	SS-SES (n=34 lesions)	CoCr-BMS (n=7 lesions)	P-value for CoCr-EES vs. SS-SES	P-value for CoCr-EES vs. CoCr-BMS
Distribution of neoatherosclerosis	n=20	n=34	n=7	0.74	0.92
Focal	11 (55%)	17 (50%)	4 (57%)		
Diffuse	9 (45%)	17 (50%)	3 (43%)		

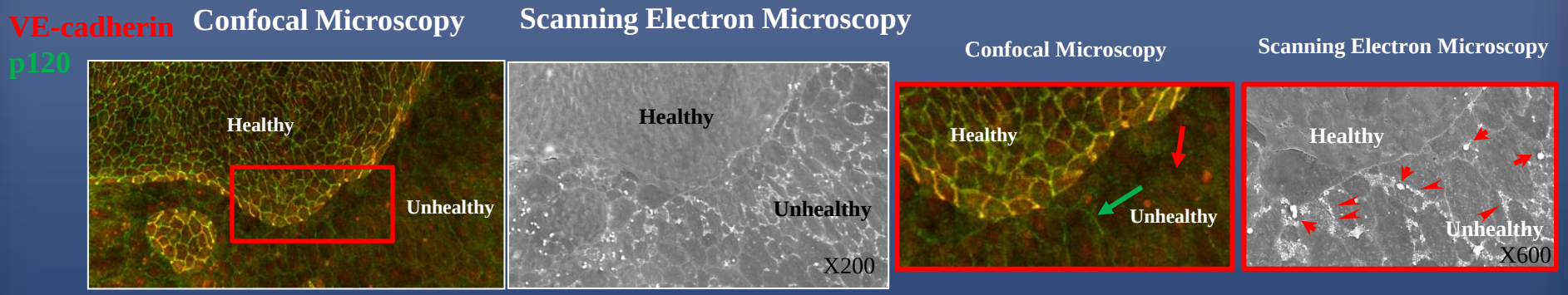
Mori, et al. J Am Heart Assoc. 2017 Nov 17;6(11).

Why neoatherosclerosis is accelerated in DES as compared to BMS?

- Impact of Endothelial Integrity -

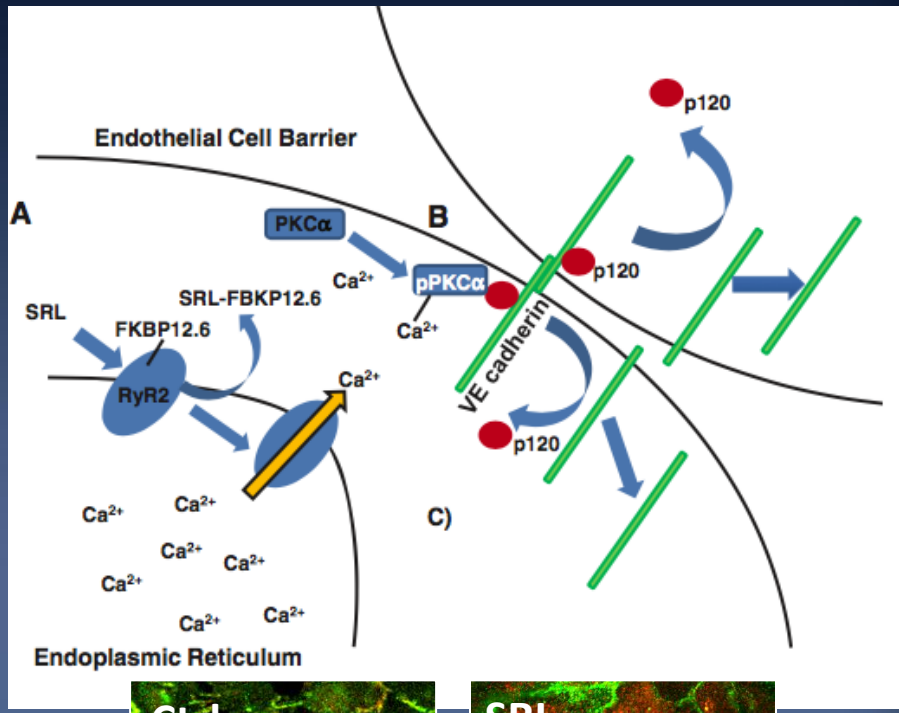
Importance of the Endothelial Barrier Function in Health and Disease

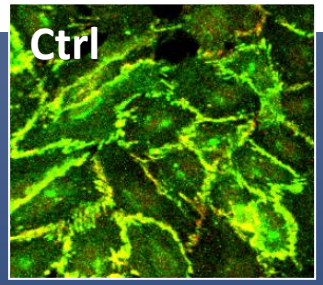
- ✓ The endothelium plays a critical role in vascular homeostasis by providing a solid barrier between blood and vessel wall, secreting substances that influence vascular inflammation, cell migration, and proliferation over the longer term
- ✓ Dysfunction of the endothelium is the initial inciting event in atherogenesis
- ✓ **VE-cadherin** (red arrow) regulates endothelial barrier function via binding to **p120** (green arrow), constructing healthy adherence cell-cell junction
- ✓ Unhealthy endothelium has dysregulation of these two molecules which normally should be expressed together at endothelial cell borders (as yellow)

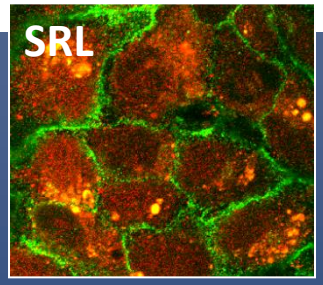


mTOR inhibitors and the endothelium

- ✓ 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



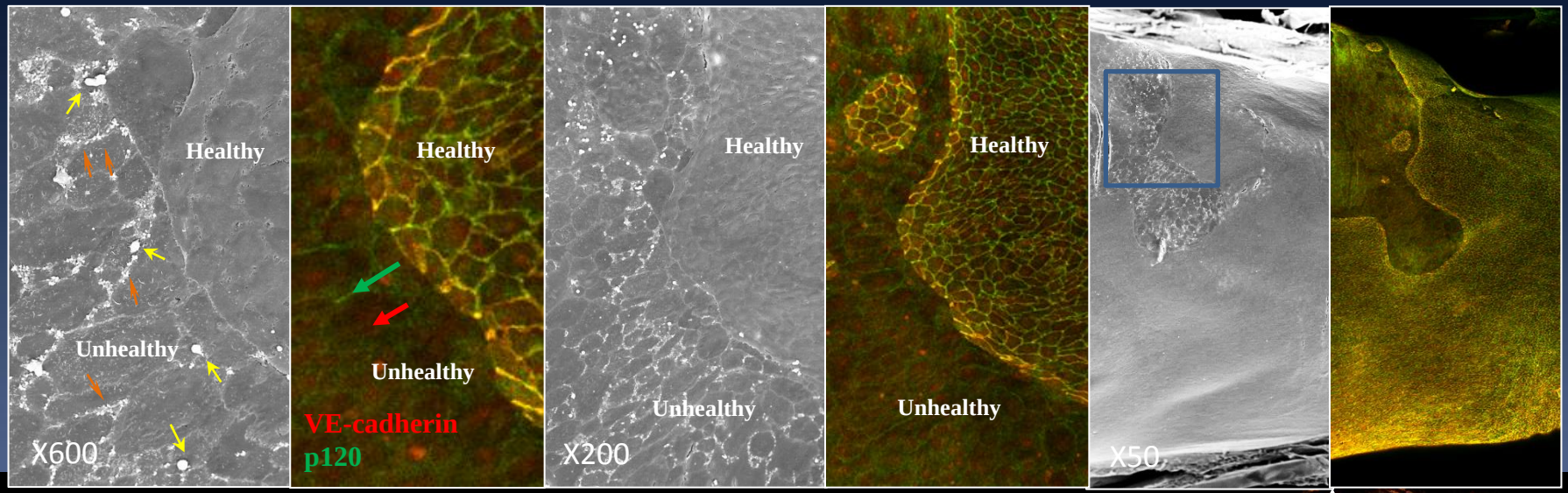


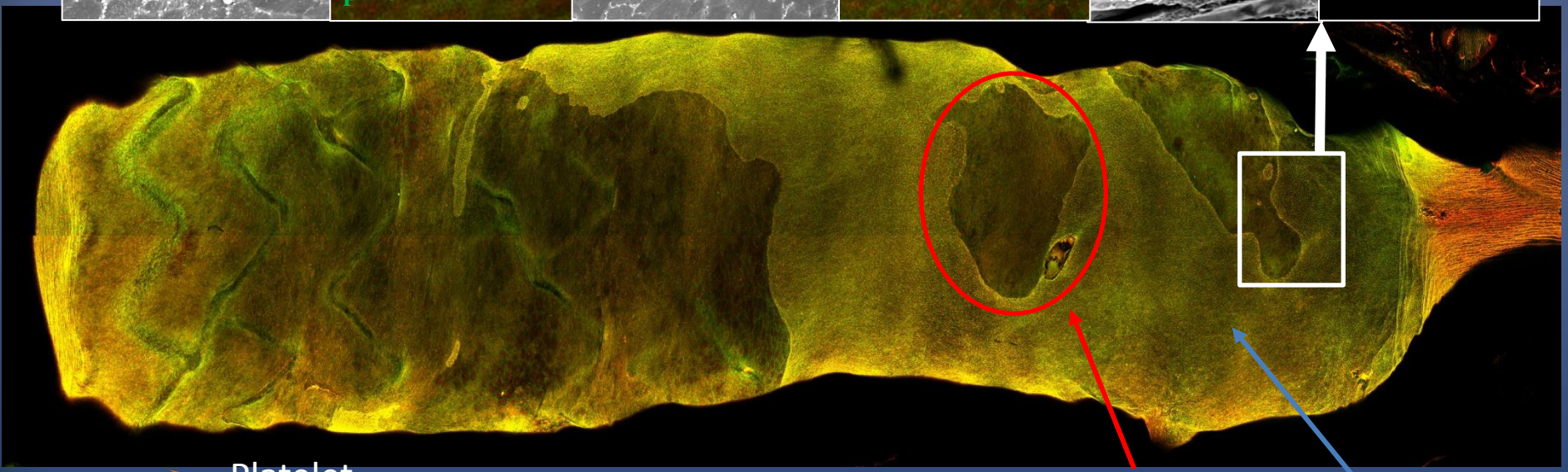


Habib A, at al. Arterioscler Thromb Vasc Biol. 2013;33:2425-31.

VE-CAD Pattern and Monocyte Adhesion

Rabbit Iliac artery stenting model





Platelet

Monocyte

DES (60-day post implant)

Unhealthy

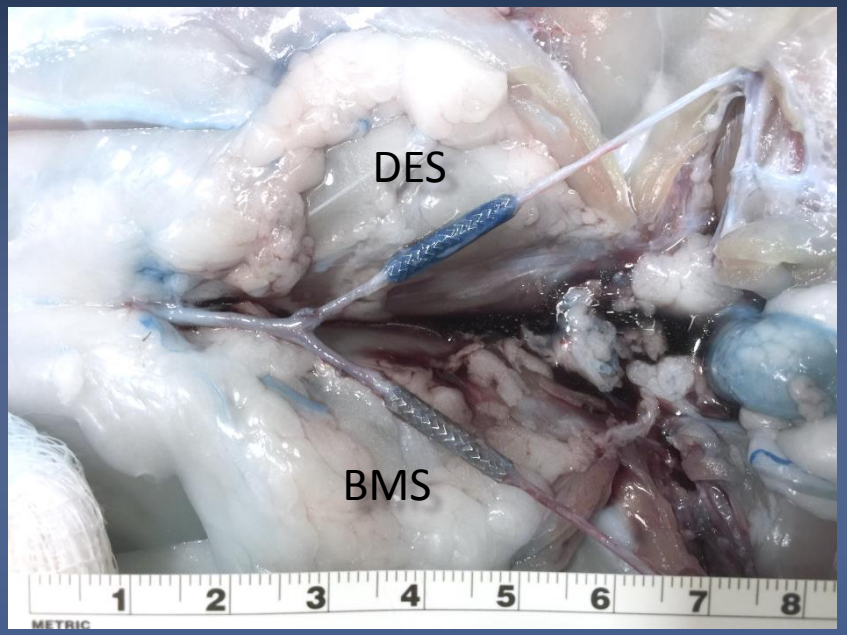
Healthy

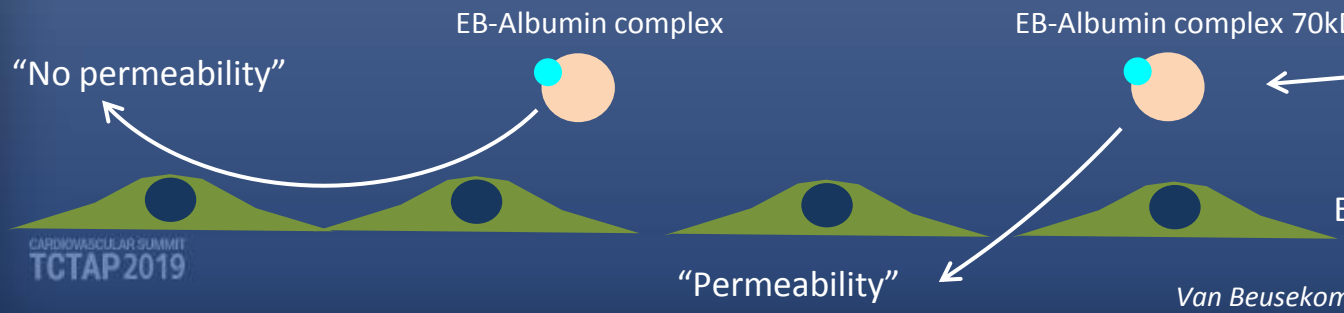
Impaired Endothelial Barrier Function at DES site

Evans Blue Dye analysis

Gross image of the rabbit iliac arteries following Evans Blue (EB) injection prior to sacrifice at **60-days**

DES **BMS**



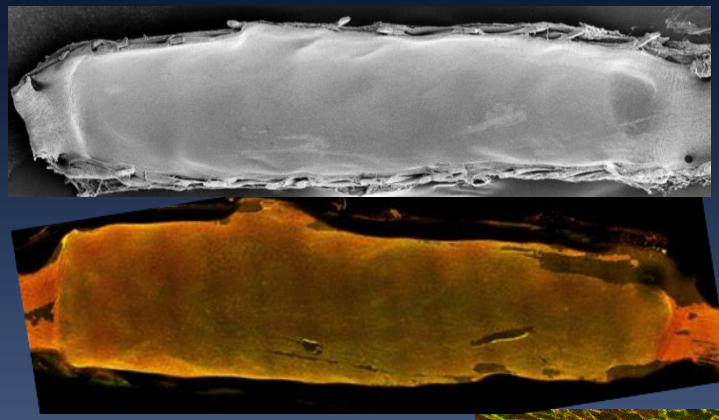


Van Beusekom HM, et al. J Am Coll Cardiol. 1998;32:1109-17.

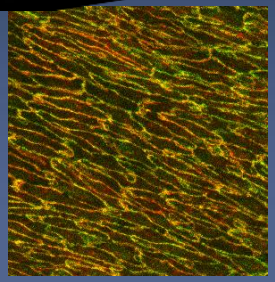
Impaired Endothelial Barrier Function in DES site

VE-Cad/p120 co-localization and cell shape

BMS

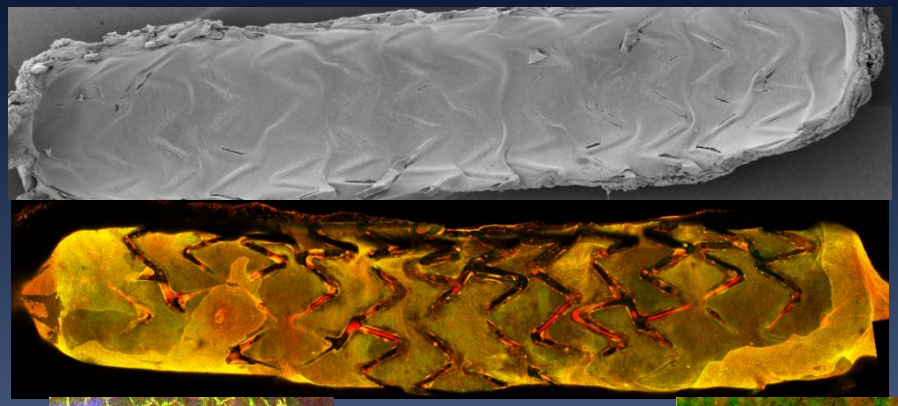


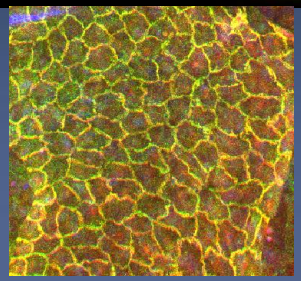
Spindle shape

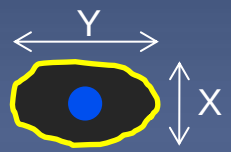


VE-cadherin
p120

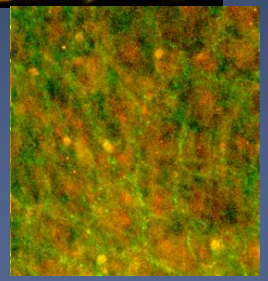
DP-DES





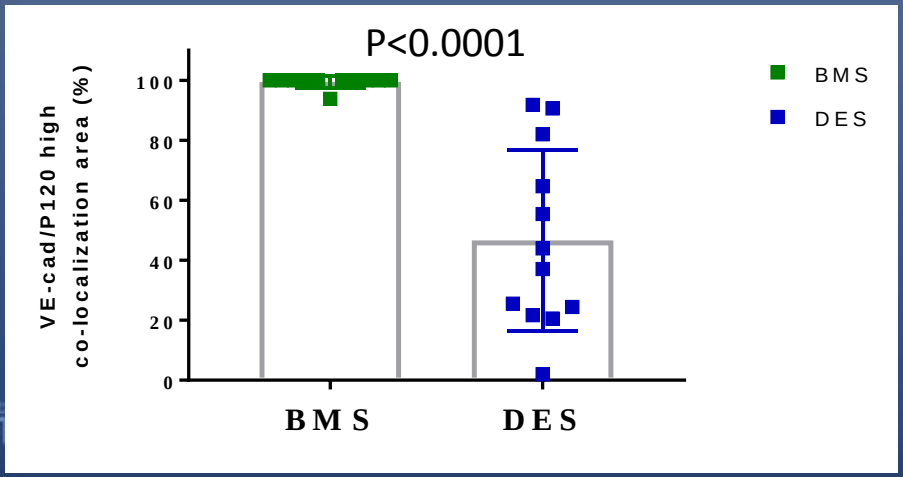


Cobble-stone shape

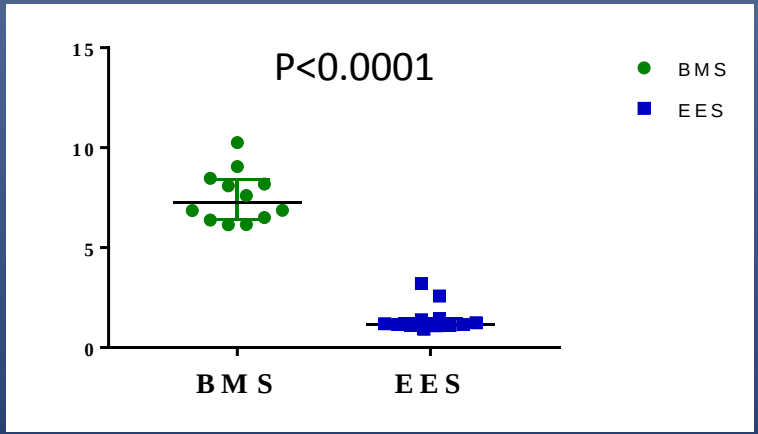


60-day rabbit iliac model

VE-Cad/P120 co-localization



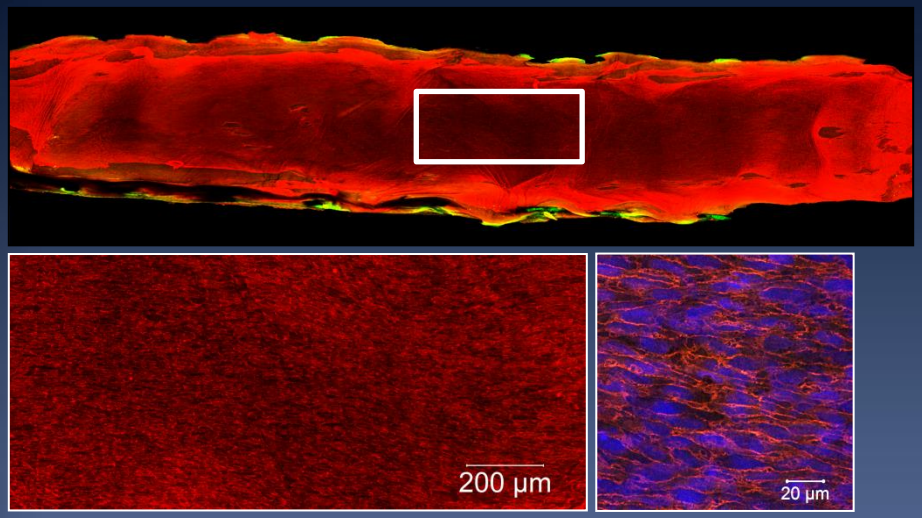
Cell Shape Index



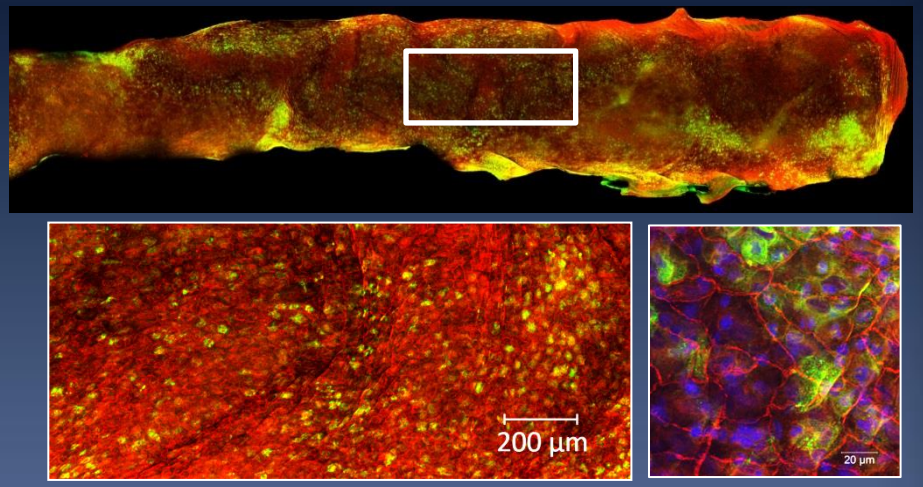
Accelerated Macrophage infiltration at DES site

RAM11 (macrophage marker) and VE-cad

BMS



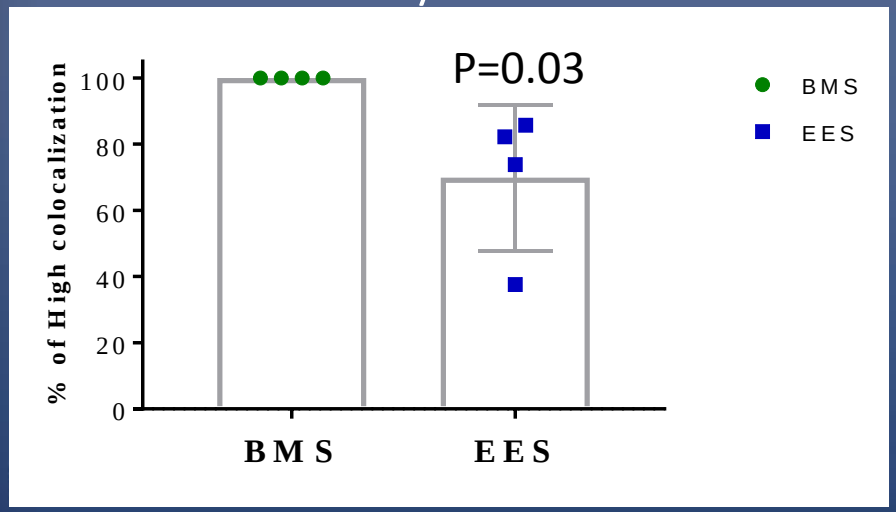
DP-EES



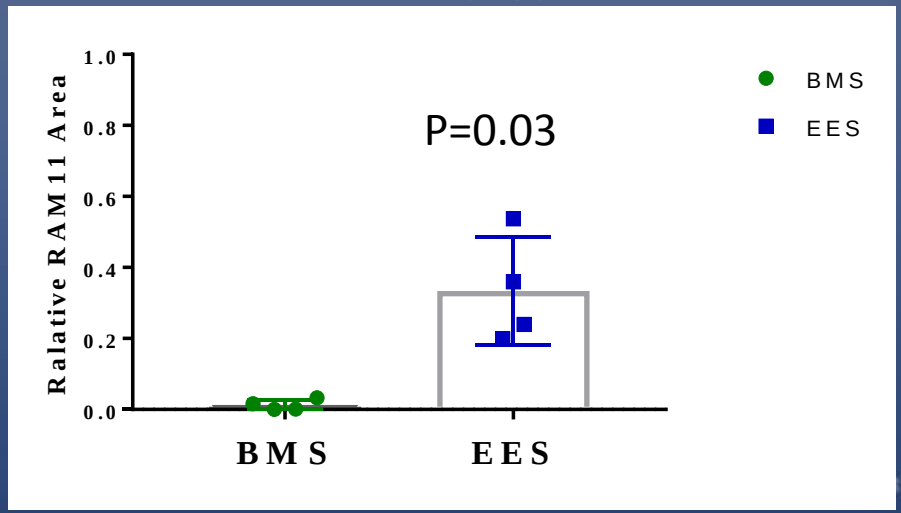
VECAD RAM11 DAPI

130-day atherosclerotic rabbit iliac model

VE-Cad/P120



RAM11 area



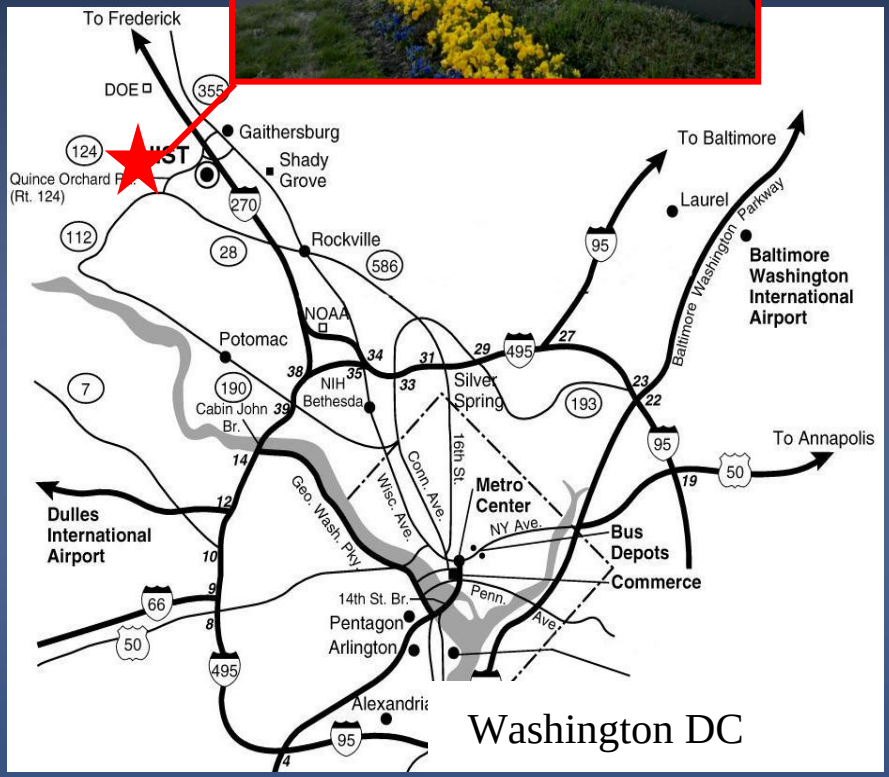
Summary

1) Neointimal hyperplasia is the cause of restenosis in stented arteries.
2) Drugs used on DES mainly inhibit SMC proliferation.
3) The efficacy of DES wanes if the distribution of anti-proliferative drug is uneven (e.g. complex lesion, stent fracture, etc…).
4) Neoatherosclerosis is one of the crucial mechanisms of late stent failure, develops rapidly and more frequently in 1st- and 2nd-generation DES as compared to BMS.
5) The optimal treatment strategy for ISR lesions with underlying neoatherosclerosis remains unstudied.
6) Endothelial barrier dysfunction due to rapamycin analogues loaded in DES is one of the main causes of early development of in-stent neoatherosclerosis.
7) Further technical innovations are needed to achieve better long term outcome after coronary stenting.

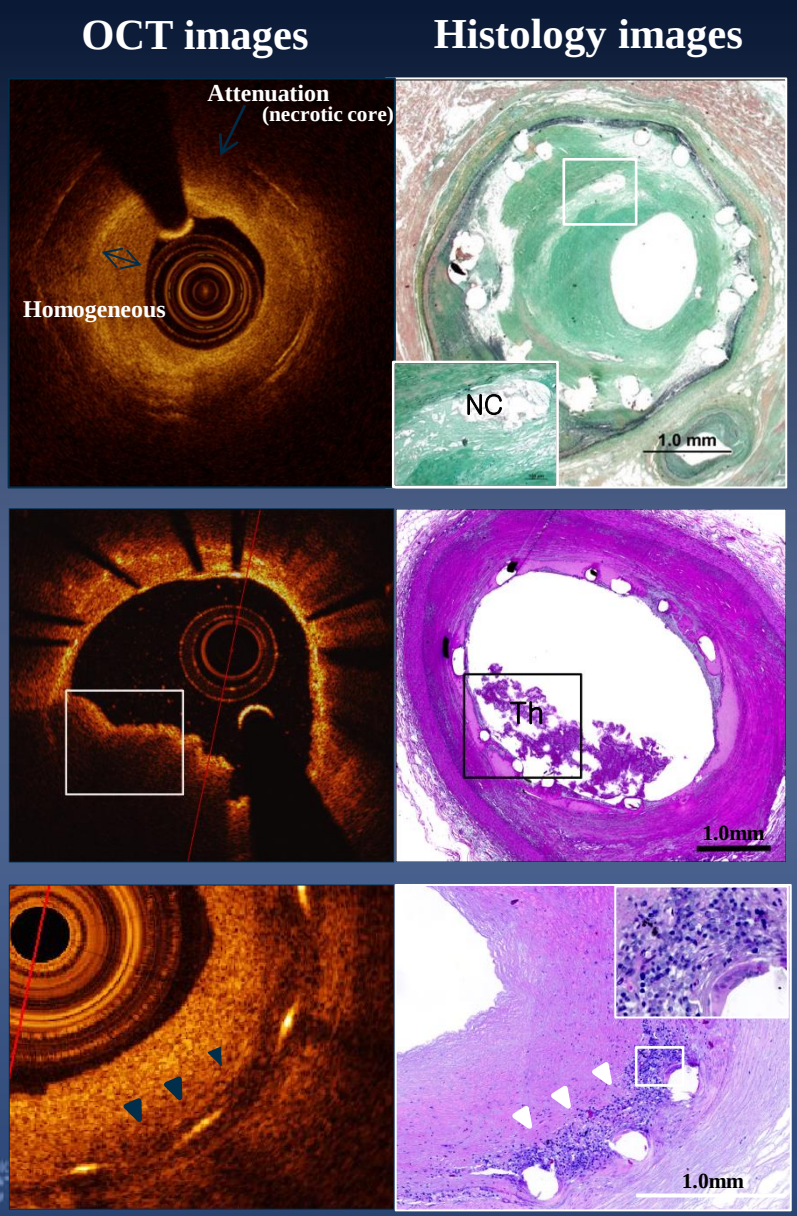
Acknowledgments

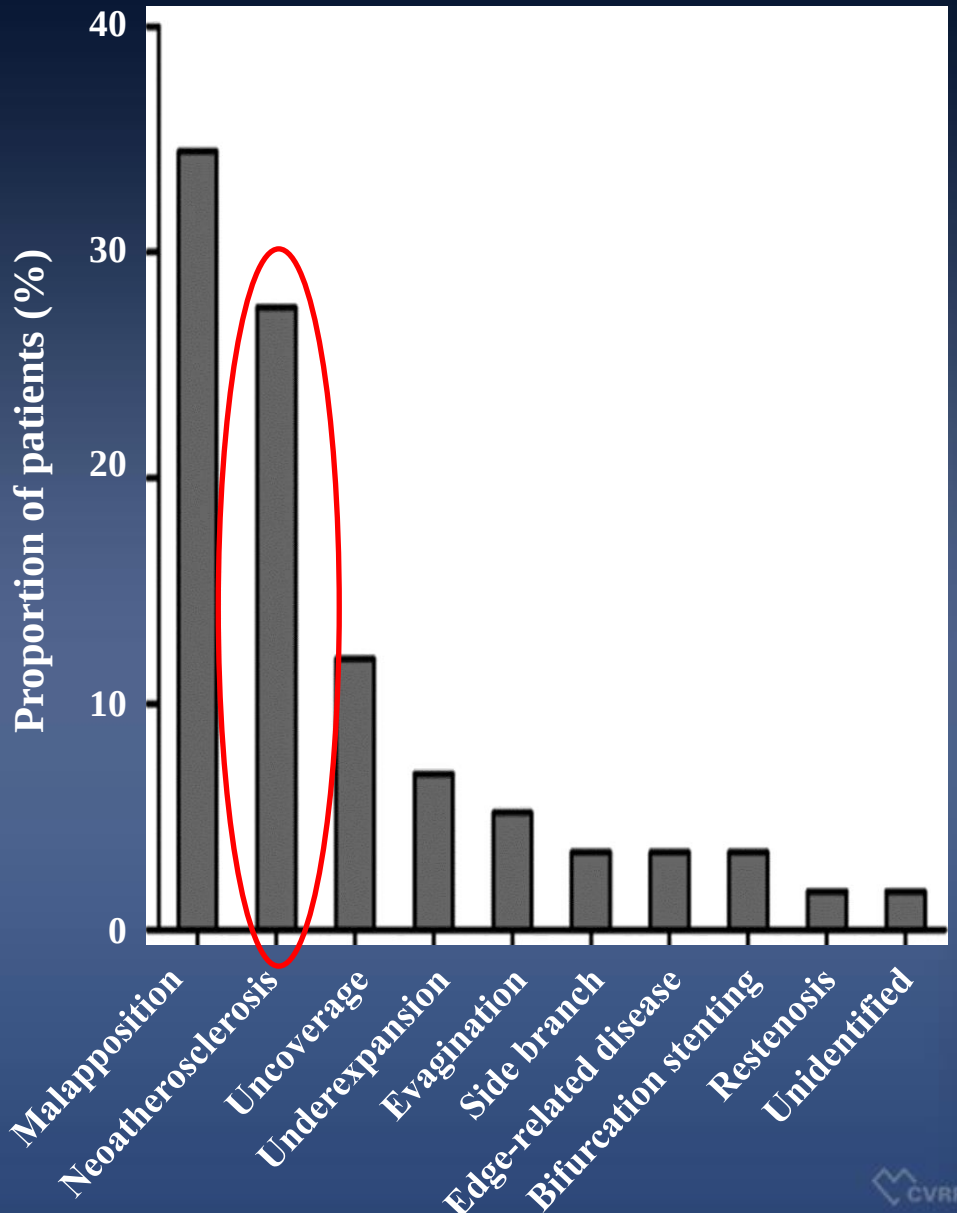
CVPath Institute

Atsushi Sakamoto, MD
Hiroyuki Jinnouchi, MD
Yu Sato, MD
Anne Cornelissen, MD
Salome Kuntz, MD
Liang Guo, PhD
Robert Kutyz, MS
Russ Jones
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Renu Virmani, MD



Causes of Very Late (>1 year) Drug-Eluting Stent Thrombosis: Malapposition and Neoatherosclerosis >60%

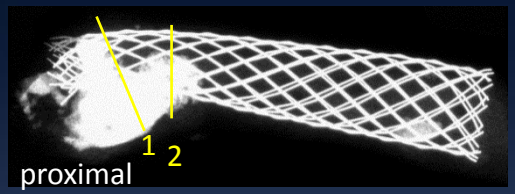


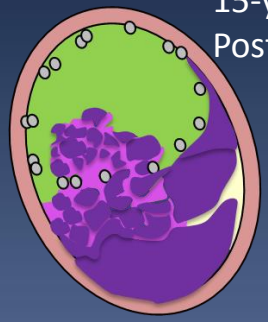


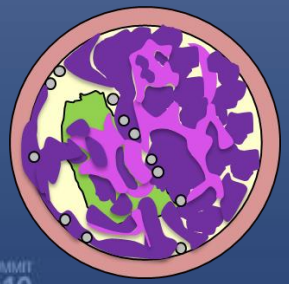
Lutter C, et al. JACC Cardiovasc Interv. 2016;9:2511-2523.

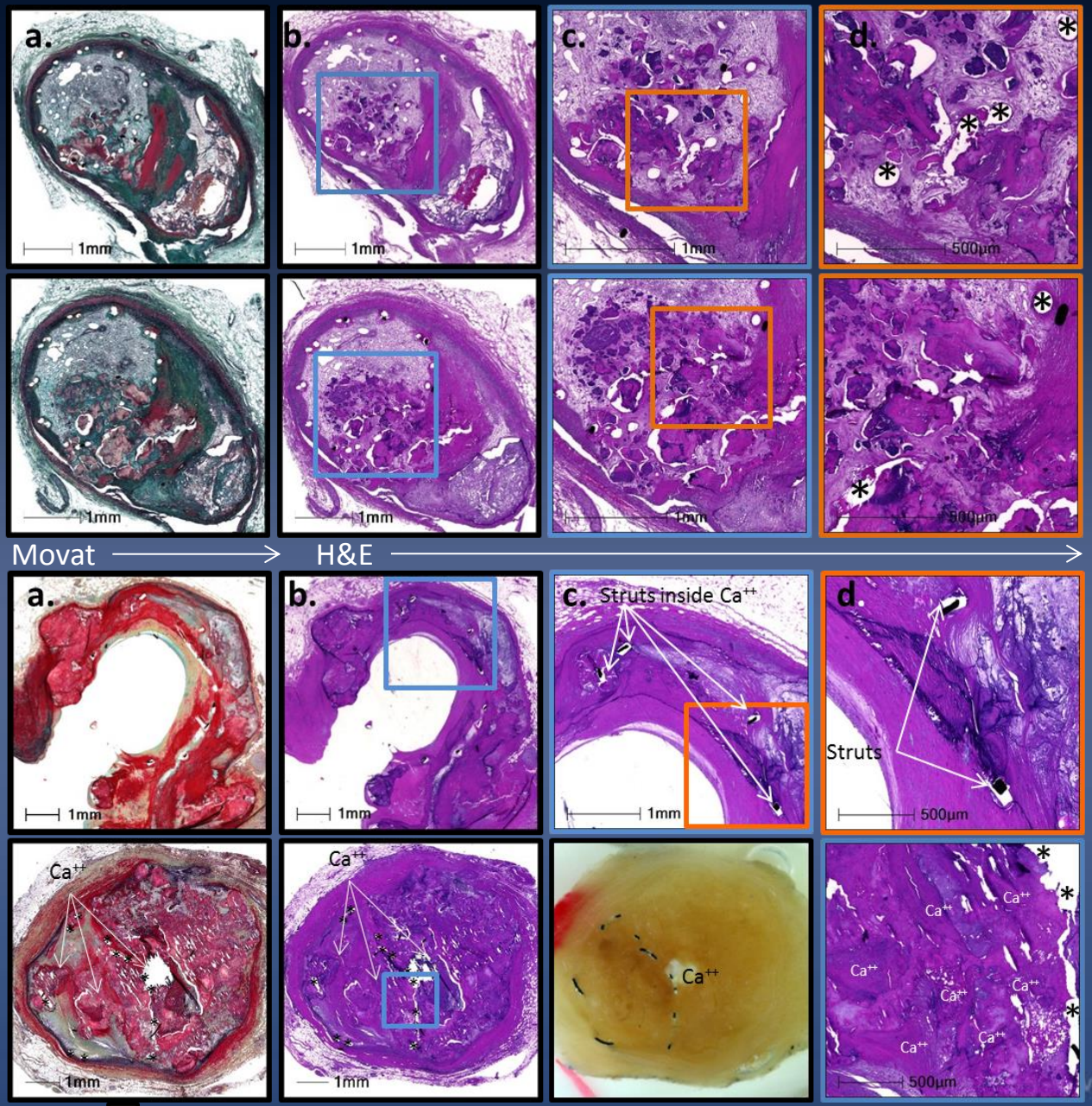
Taniwaki M, et al. Circulation. 2016;133:650-660

In-stent calcified nodule









Ca++ Fibrin Organized thrombus Collagen

Mori H, et al. JACC Cardiovasc Interv. 2016;9:e125-6.