

14<sup>th</sup>

AICT

ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS  
THE OFFICIAL CONGRESS OF APSIC

# What is True Healing and the Importance of Restored Functional Endothelium

NAKAZAWA, G; TOKAI Univ.



Interventional Cardiology  
International Course



SUNRISE lab.

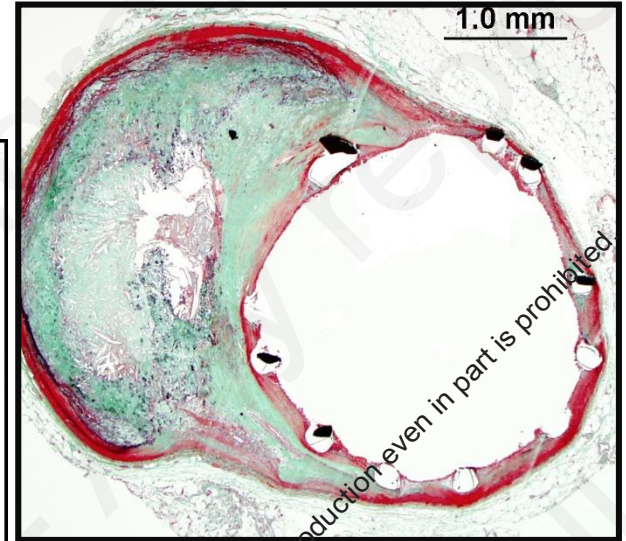
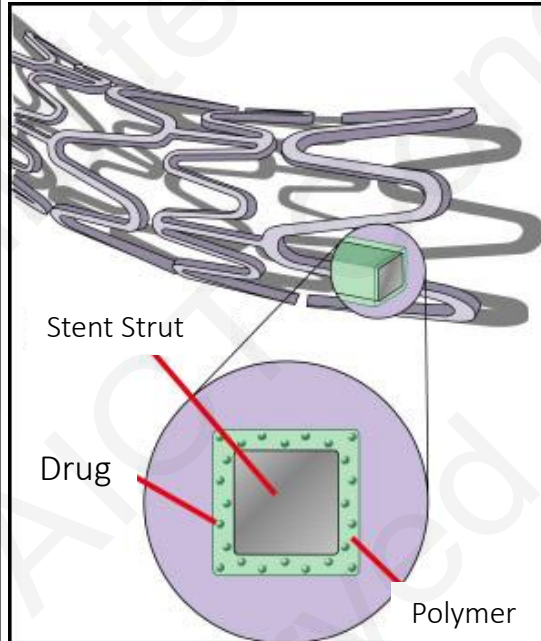
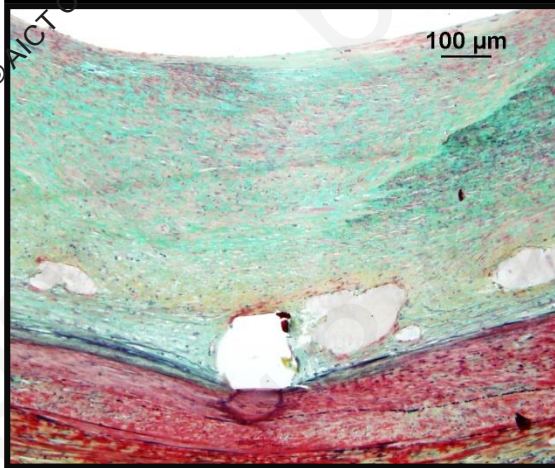
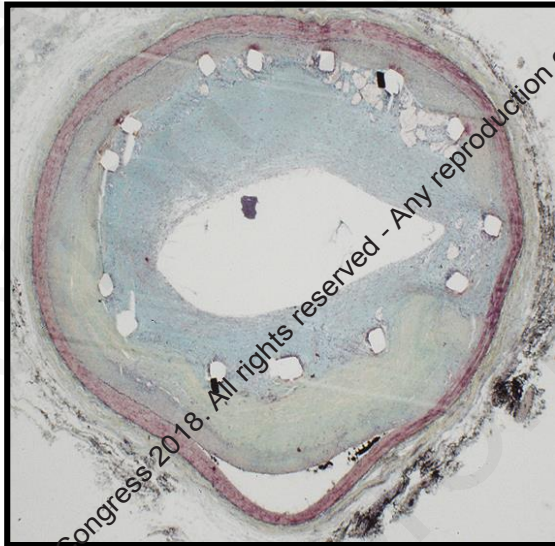


Gaku Nakazawa : None

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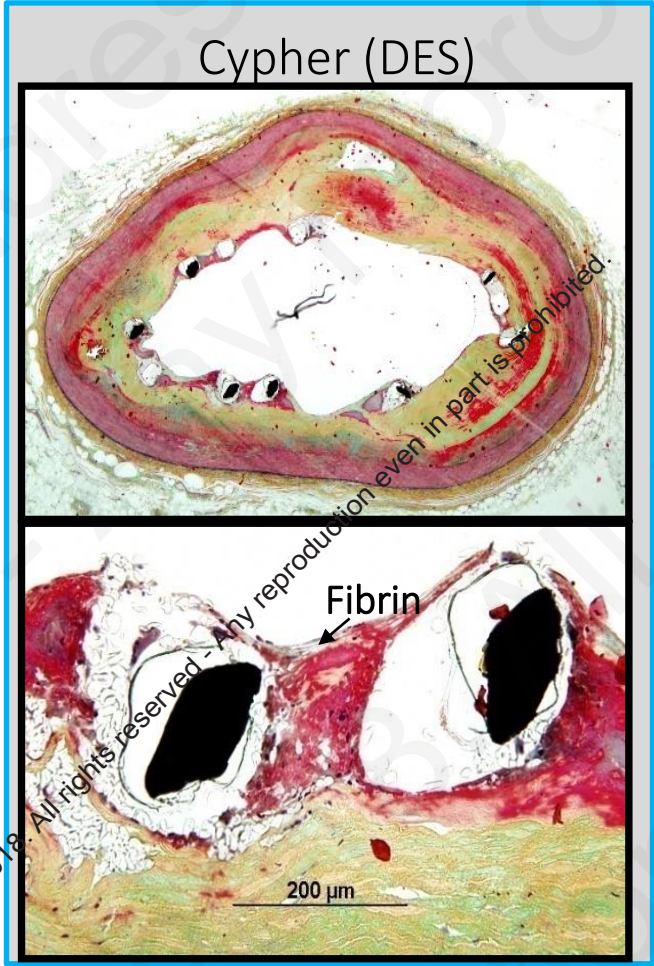
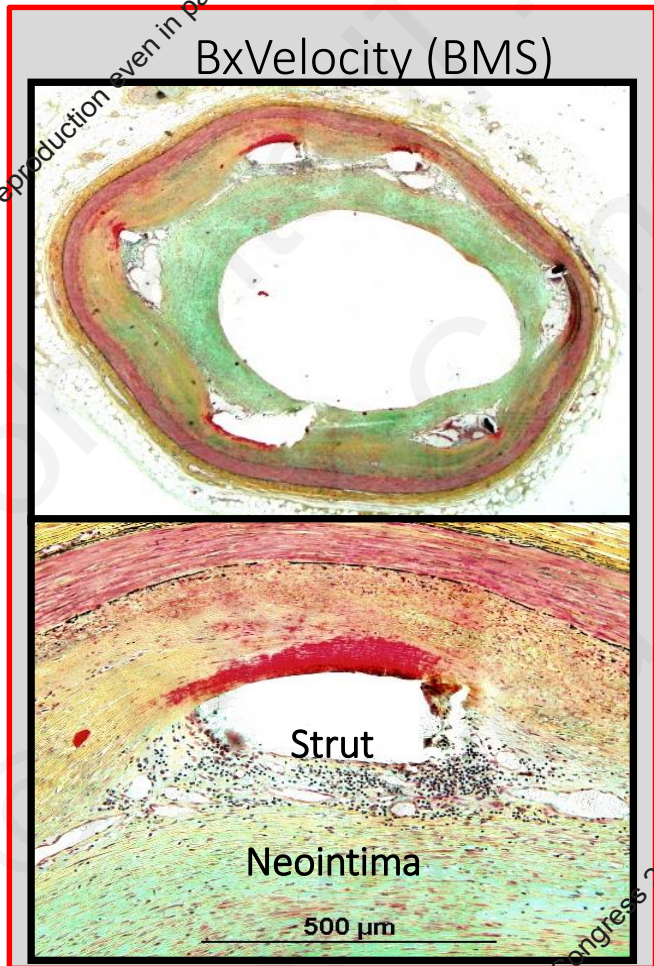
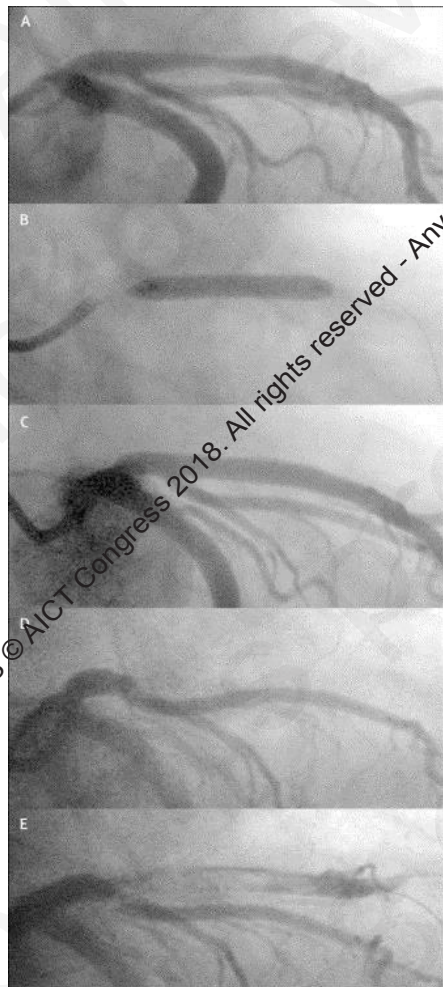
## Reduced Restenosis by DES



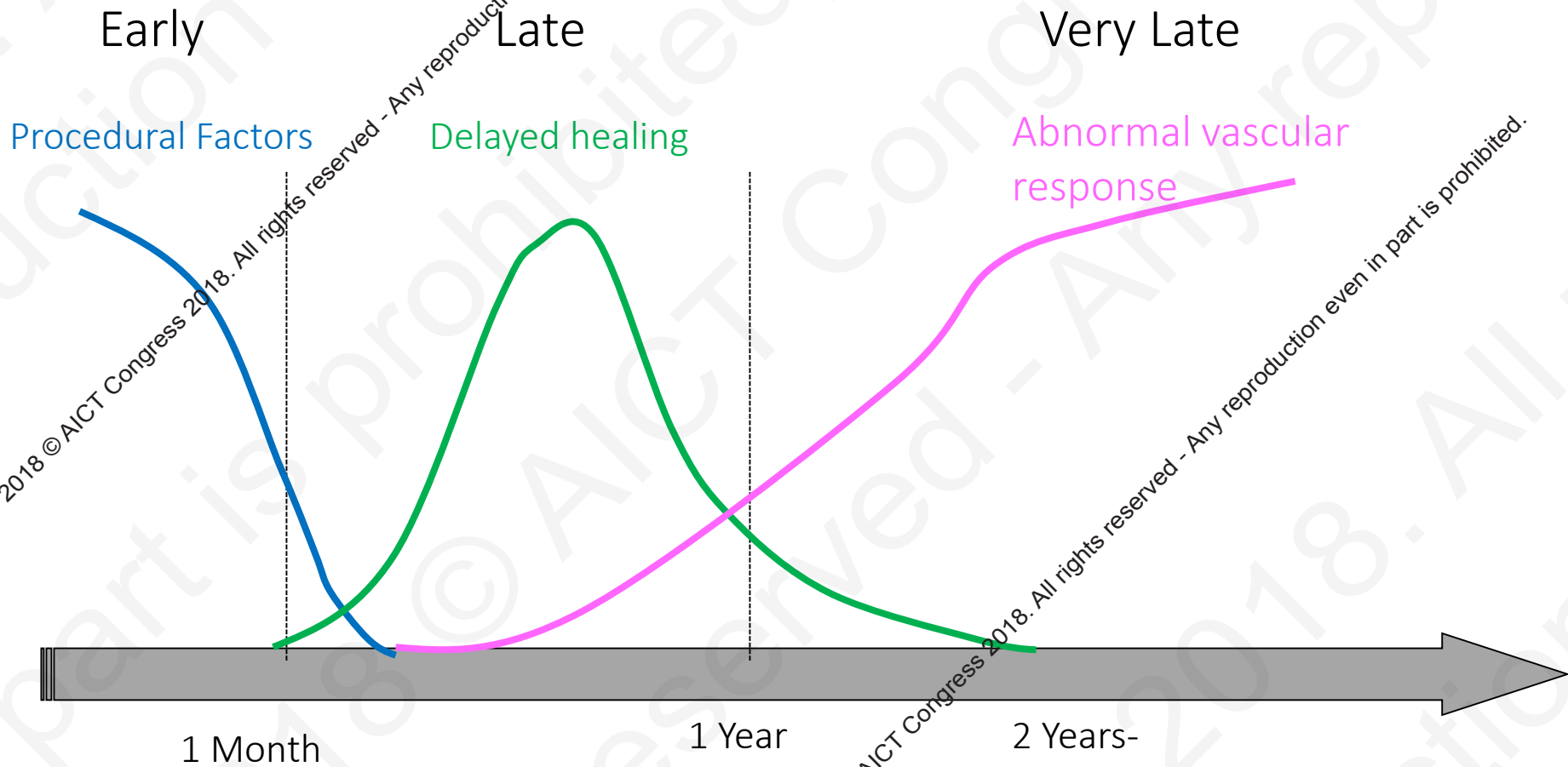


# Delayed Arterial Healing as a cause of LST

McFadden E et al. Lancet 2004



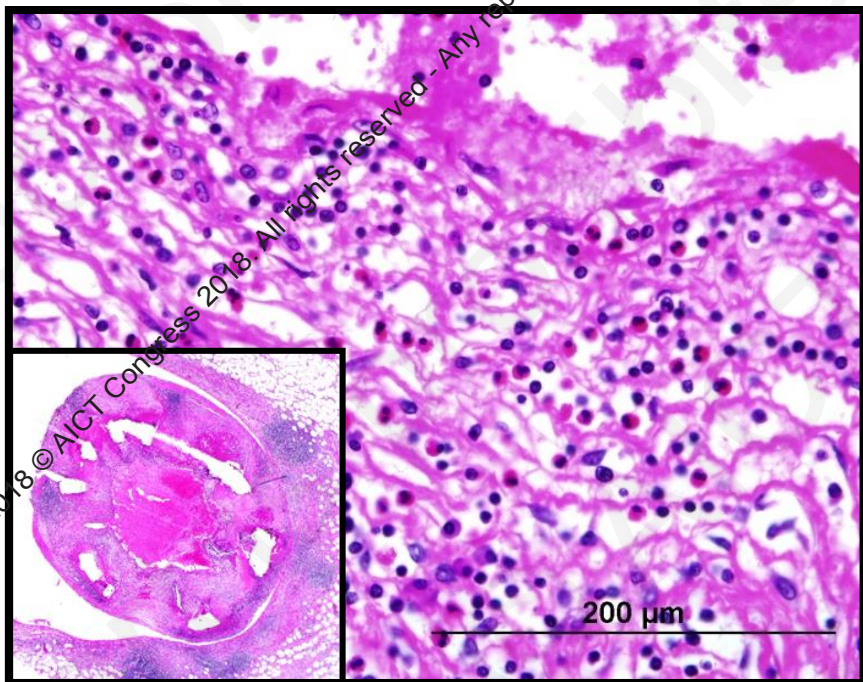
Joner M & Finn AV. J Am Coll Cardiol. 2006;48(1):193-202.





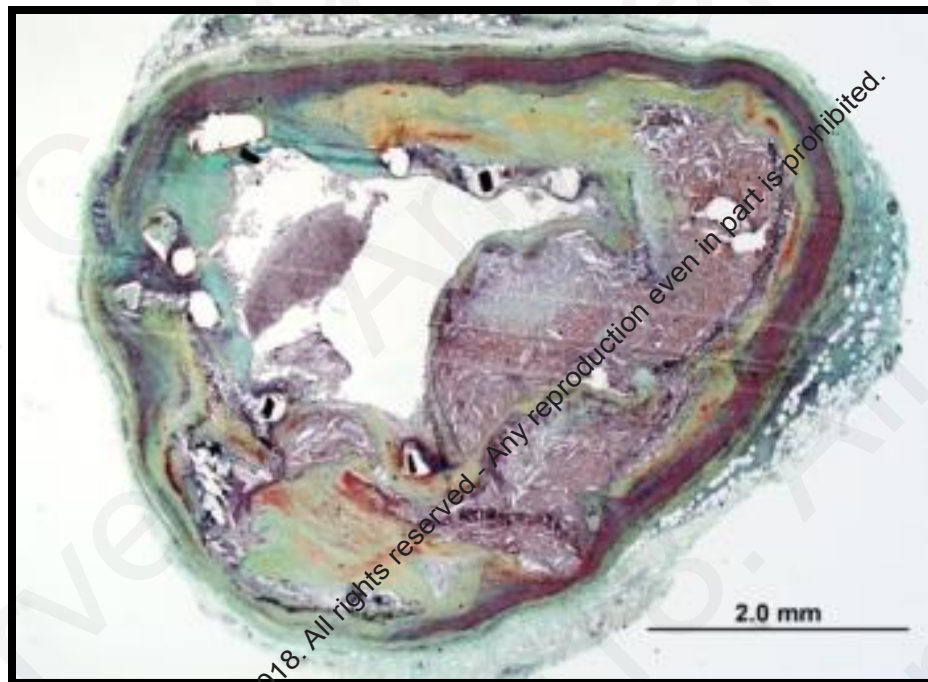
# Abnormal Vascular Response

## Hypersensitivity



Nakazawa, G et al. J Am Coll Cardiol 2011;57(4):390-8

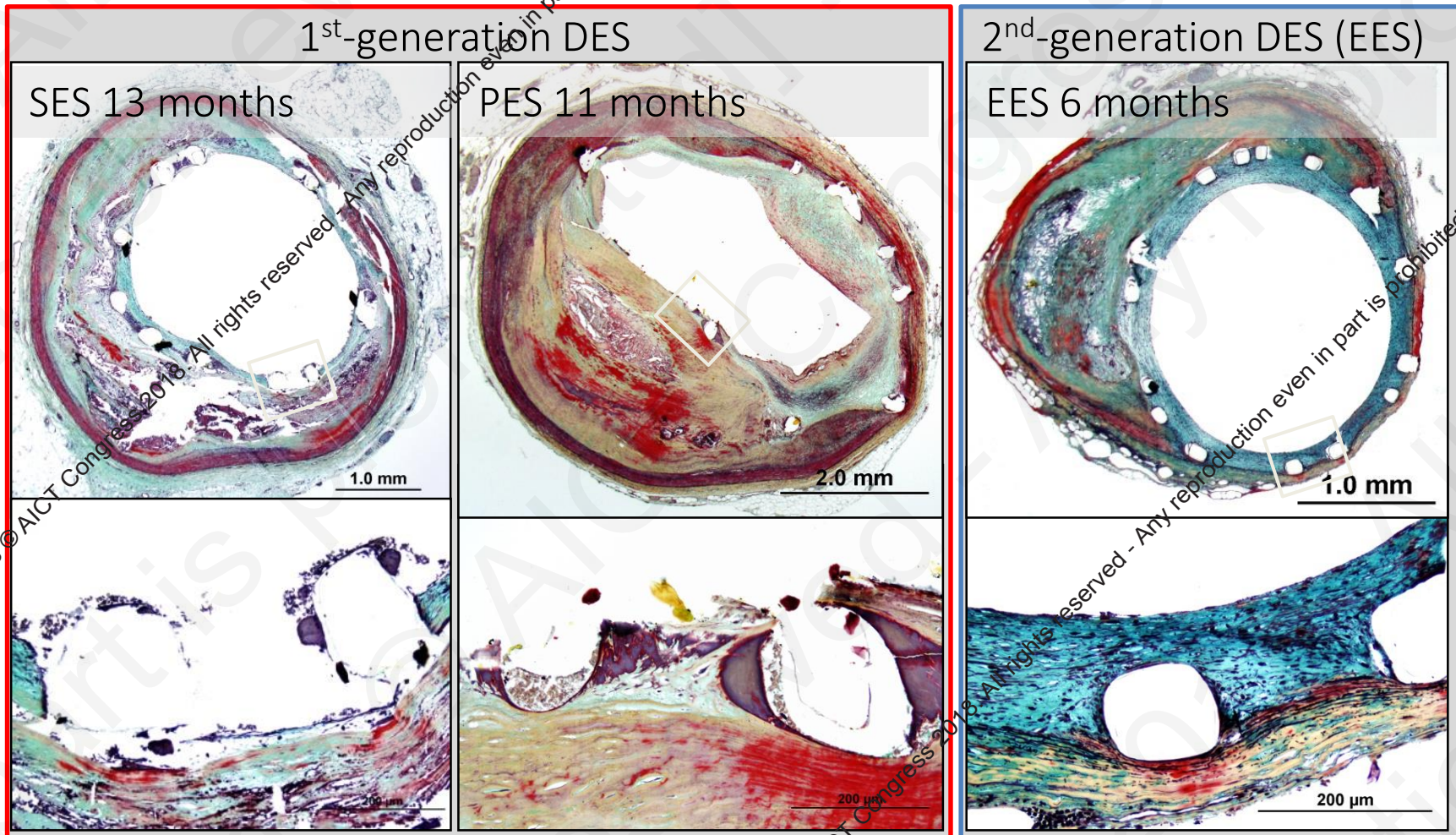
## Neoatherosclerosis



Nakazawa, G & Gotsuka, F et al. J Am Coll Cardiol. 2011;57(11):1314-22.



# Histologic findings in 2<sup>nd</sup> Gen DES at autopsy

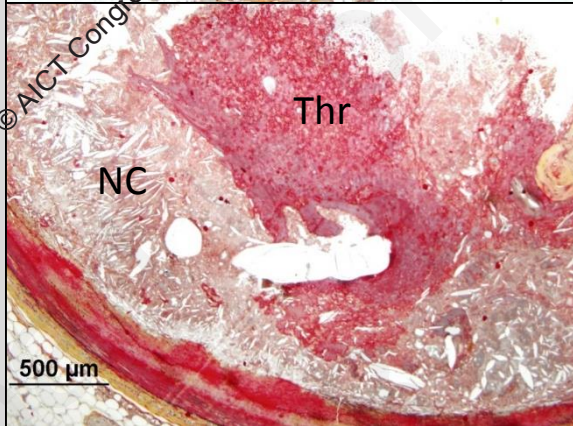
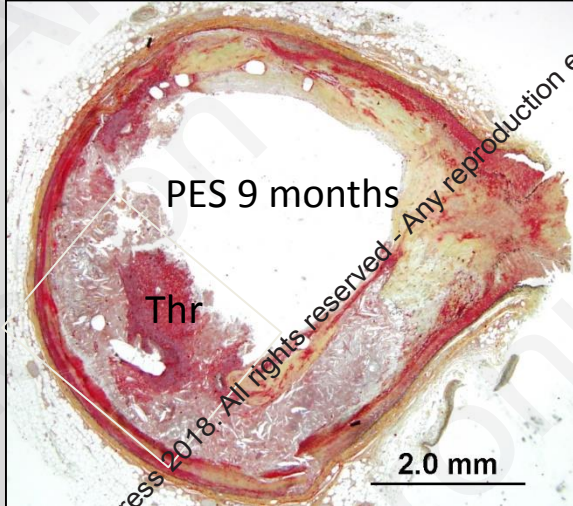


Otsuka F et al. Circulation. 2014;129:211-223



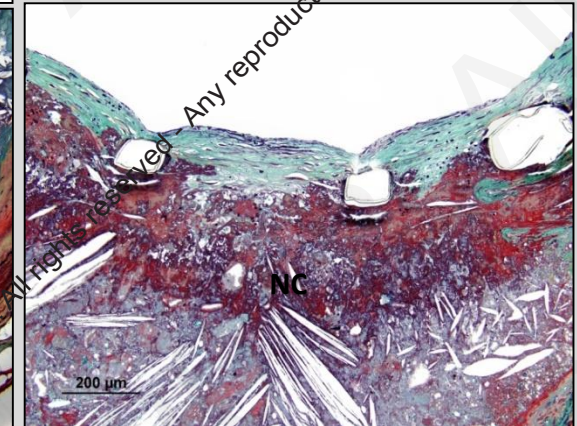
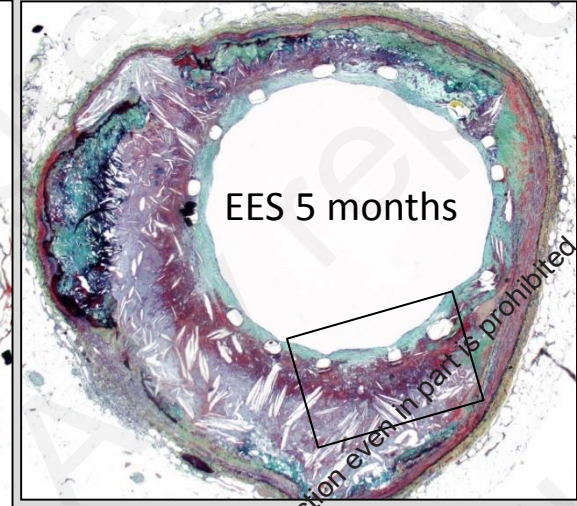
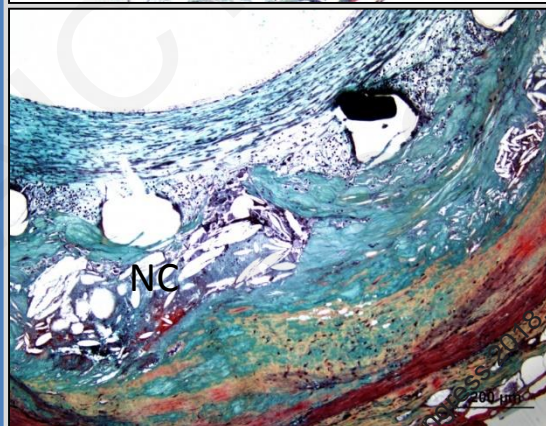
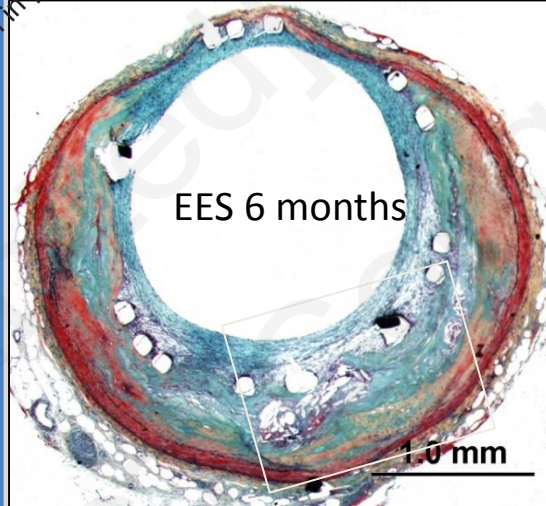
# Delayed Arterial Healing Accelerated in ACS

## 1<sup>st</sup>-generation DES



NC=necrotic core, Thr=thrombus.

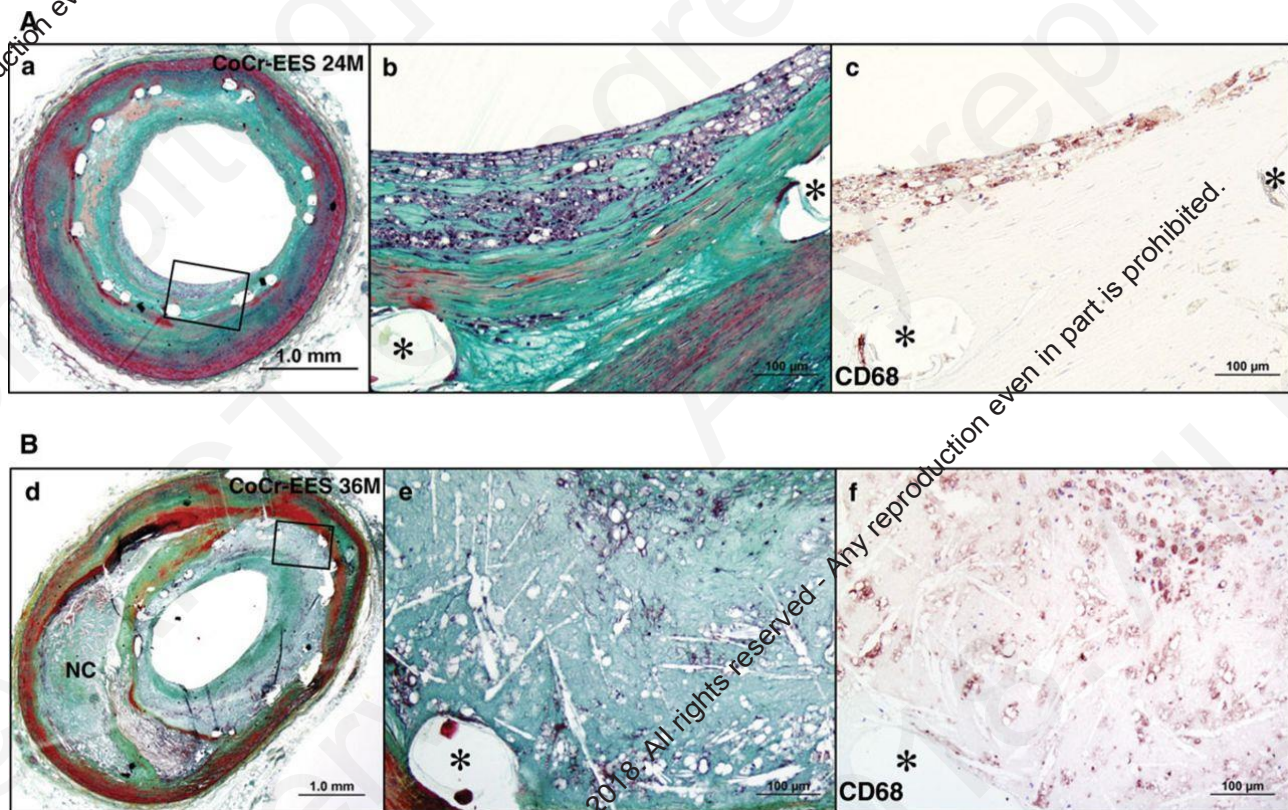
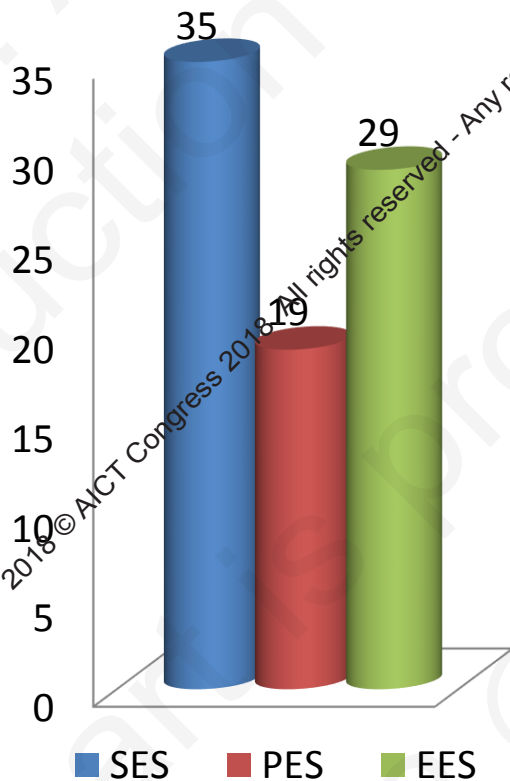
## 2<sup>nd</sup>-generation DES (Everolimus: EES)



Otsuka F et al. Circulation. 2014;129:211-223



# Incidence of Neoatherosclerosis in EES



Otsuka F, et al. Circulation. 2014 Jan 14;129(2):211-23

## Vascular reaction

Endothelial dysfunction

ECM Predominant NI

Chronic inflammation

## Mechanical factor

Lost of Pliability

## Patient factor

Hyperlipidemia

Platelet Activity

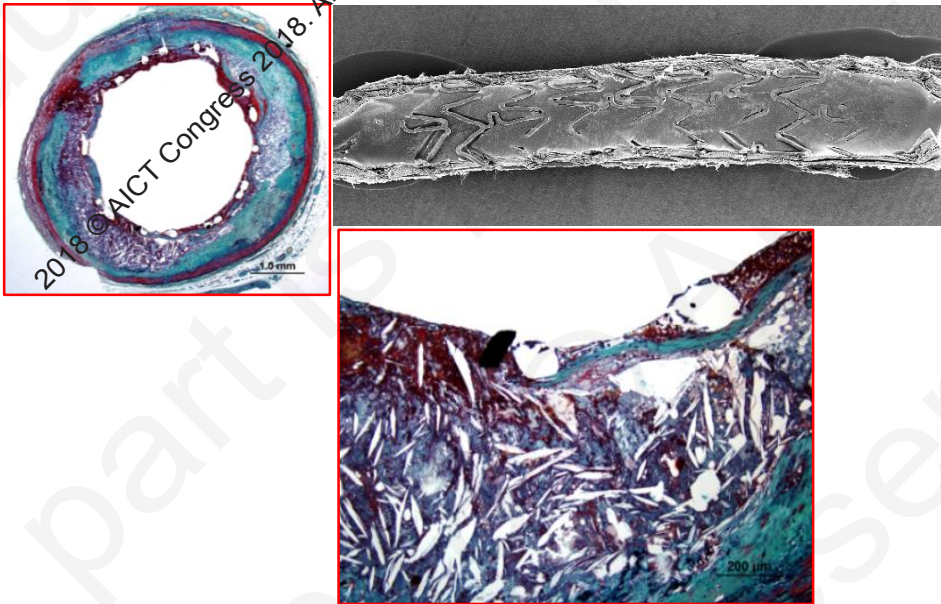
Neoatherosclerosis



# Key objectives about vessel healing that all Interventional Cardiologists should understand

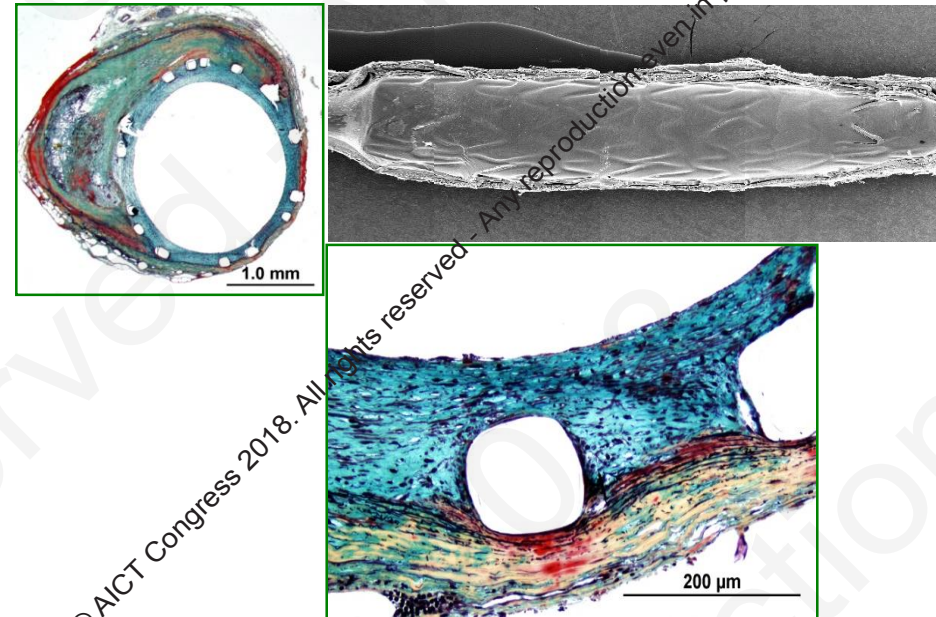
## Delayed Healing

- Peristitut 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



To obtain greater healing...

- Pro-healing approach
- Abluminal Coating
- Biodegradable polymer



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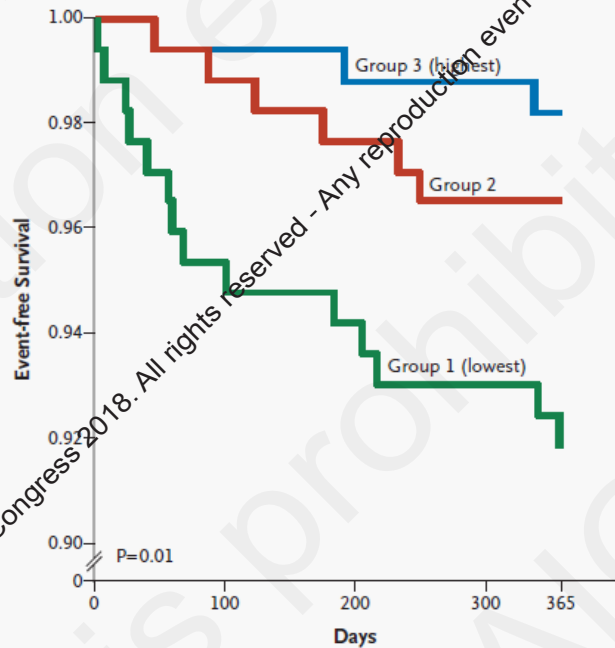


SUNRISE lab.



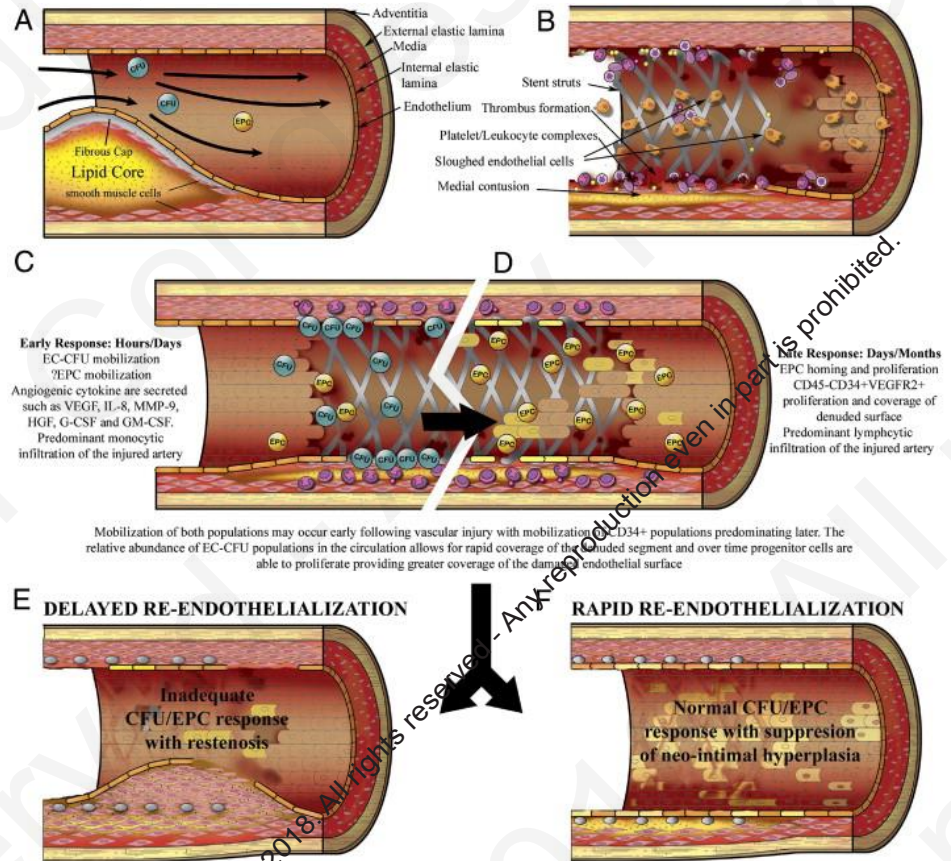


# EPC in Cardiovascular Medicine



No. at Risk	0	100	200	300	365
Group 1	168	160	158	156	77
Group 2	172	170	168	166	83
Group 3	167	166	165	165	82
Total	507	496	491	487	242

Werner, et al. NEJM 353, 10, Sep 8, 2005



Padfield GJ, et al. J Am Coll Cardiol 55, 15, 2010: 1553-1565

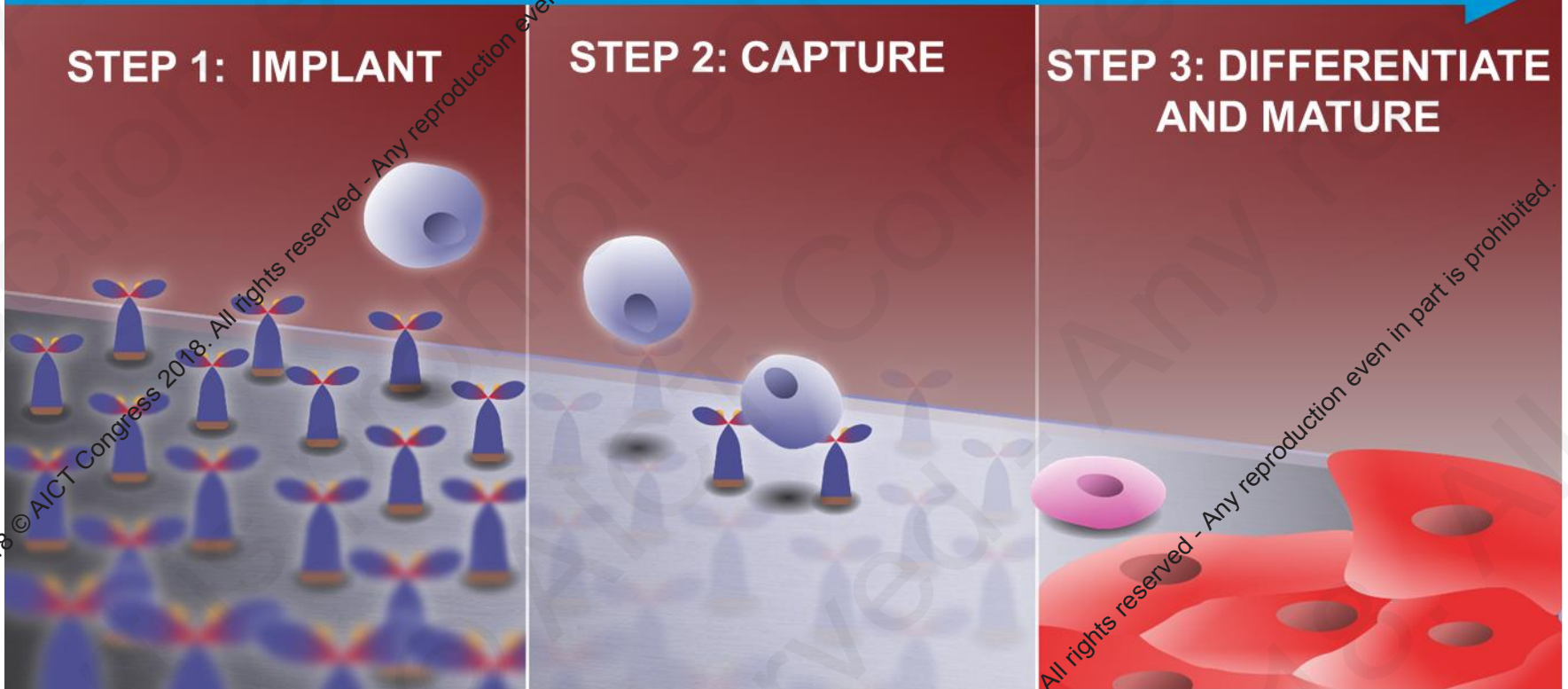
# CD34 antibodies capture circulating EPCs who mature into functional endothelium

Coronary blood flow

## STEP 1: IMPLANT

## STEP 2: CAPTURE

## STEP 3: DIFFERENTIATE AND MATURE



Following implantation, the immobilized CD34 antibodies are exposed to the circulating blood

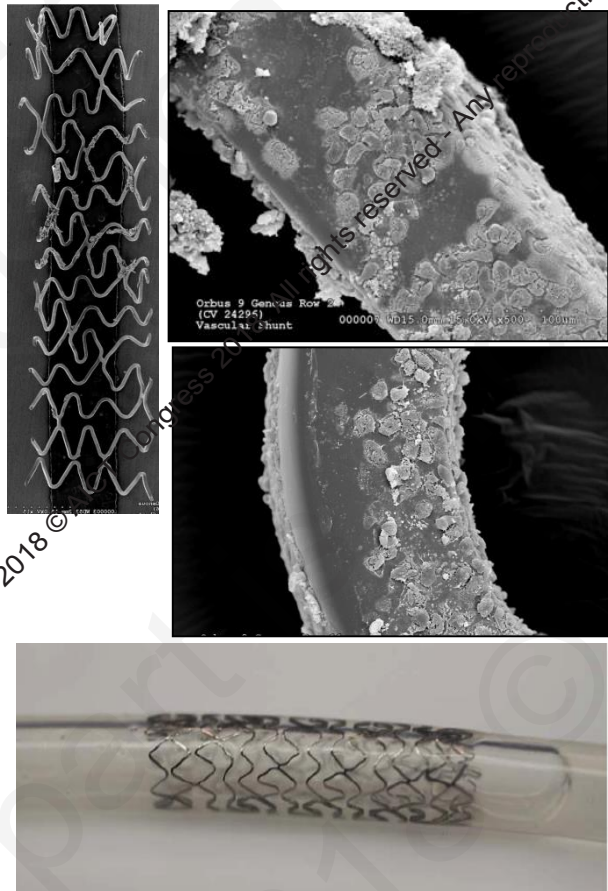
Circulating endothelial progenitor cells (EPC) are captured by antibody

EPCs attach and differentiate into mature endothelial cells; an important step in re-establishing healthy neointima

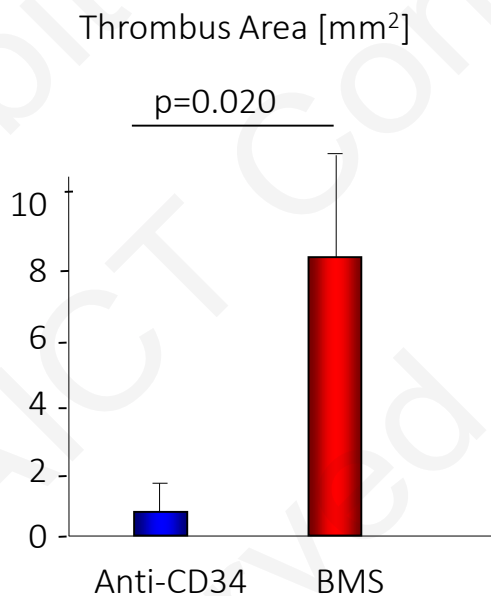


# Scanning Electron Microscopy (SEM) following Shunt Model

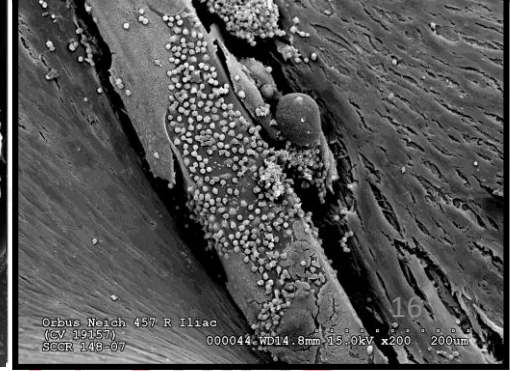
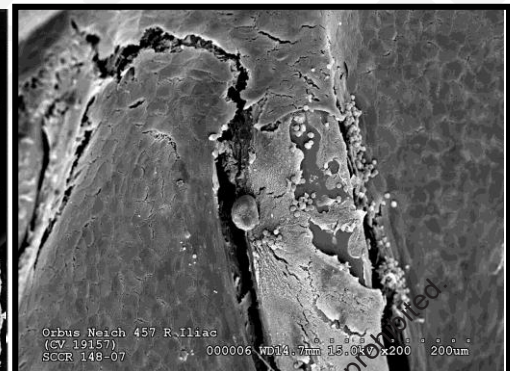
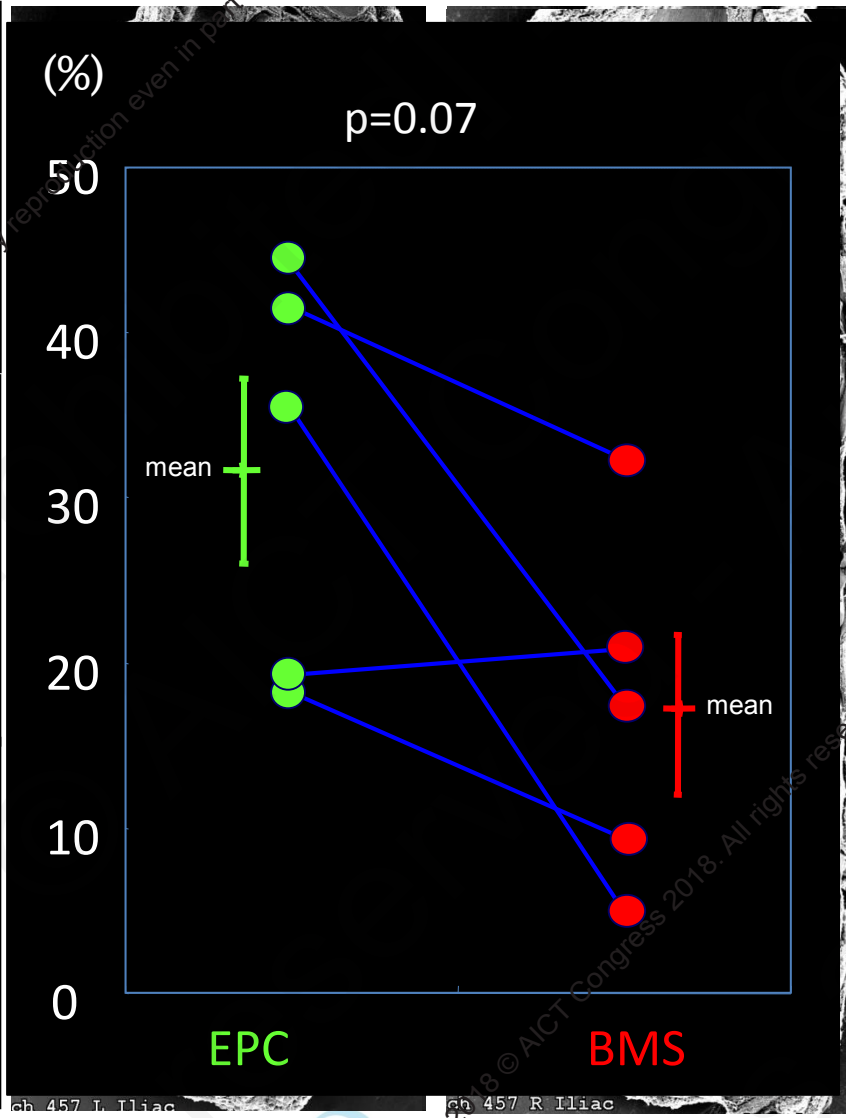
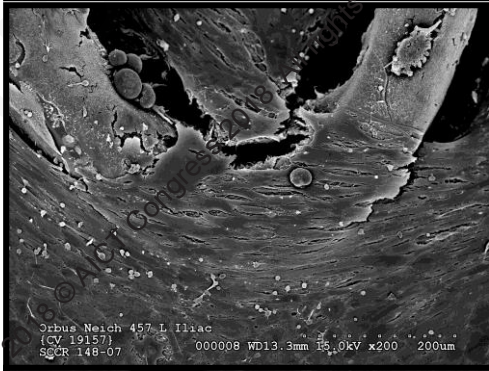
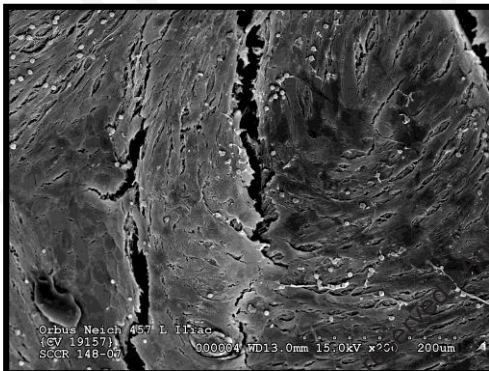
## Anti-CD34+ stent



## Bare Metal Stent



(Rabbit iliac model)  
**EPC Capture**      7-day      **BMS**

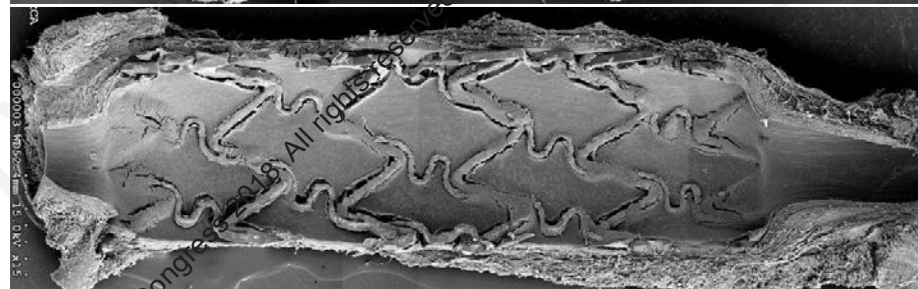
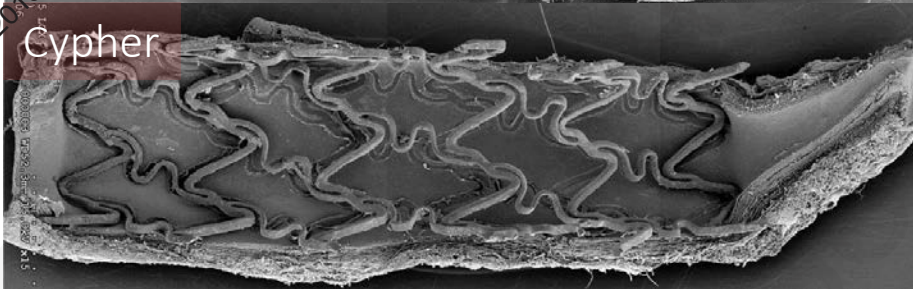
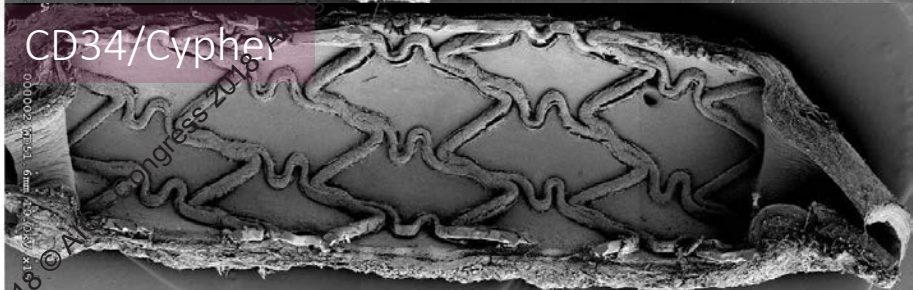
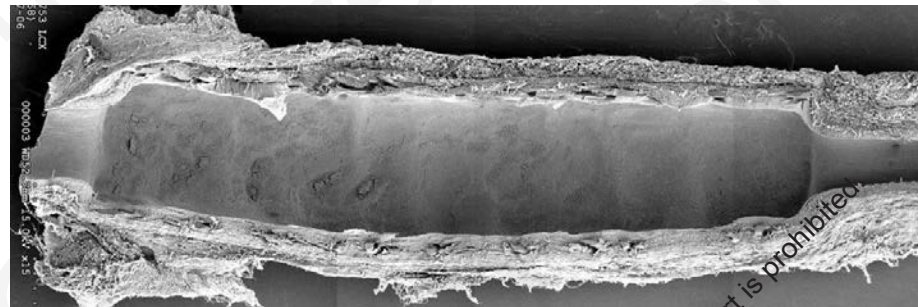
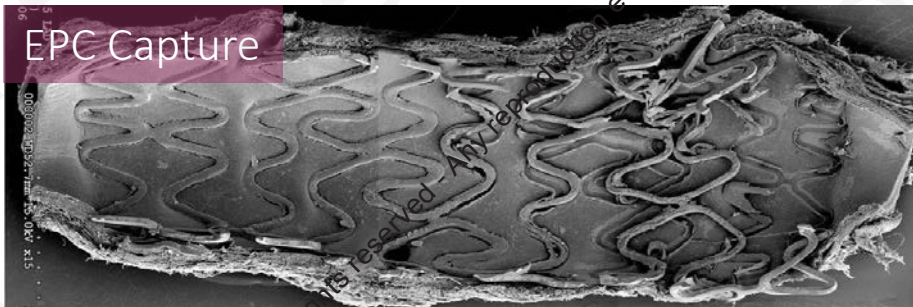




# Endothelial Coverage by SEM in Stented Porcine Coronary Arteries

3 Days

14 Days



Nakazawa G et al. JACC Cardiovasc Interv. 2010 Jan;3(1):68-75.

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# Abluminal Coating

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# Biodegradable Abluminal vs. Uniform Coating

- Test Devices:

- Anti-CD34 Stent + Sirolimus *Abluminal* Coating

- A-Combo (n=18)

- Anti-CD34 Stent + Sirolimus *Uniform* Coating

- C-Combo (n=18)

- Analysis:

- 3 Days: SEM & IMH (n = 6 in each group = 12)

- 14 Days: SEM & IMH (n = 6 in each group = 12)

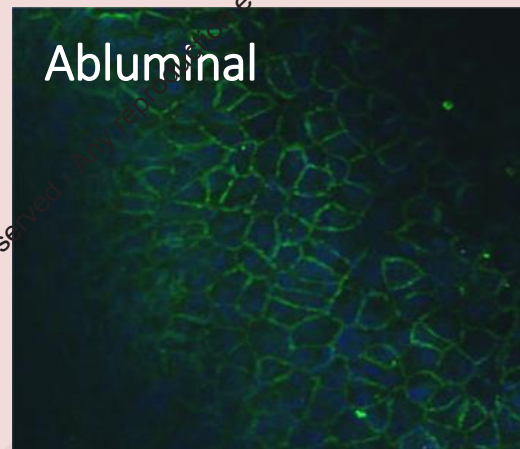
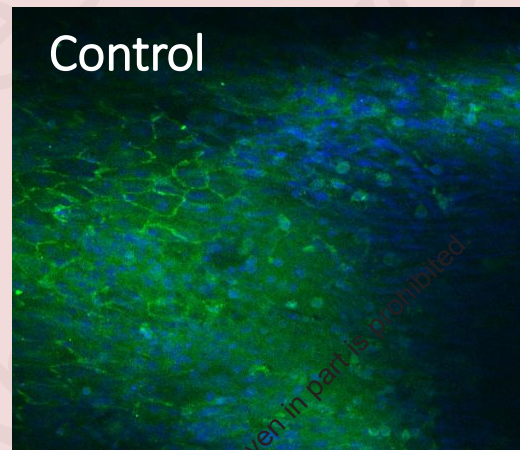
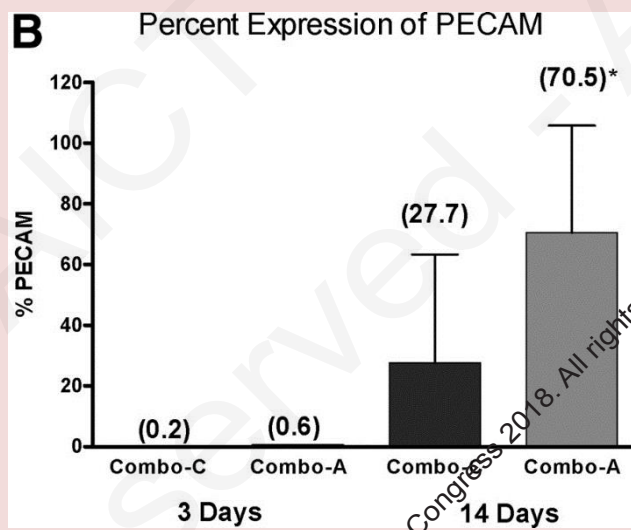
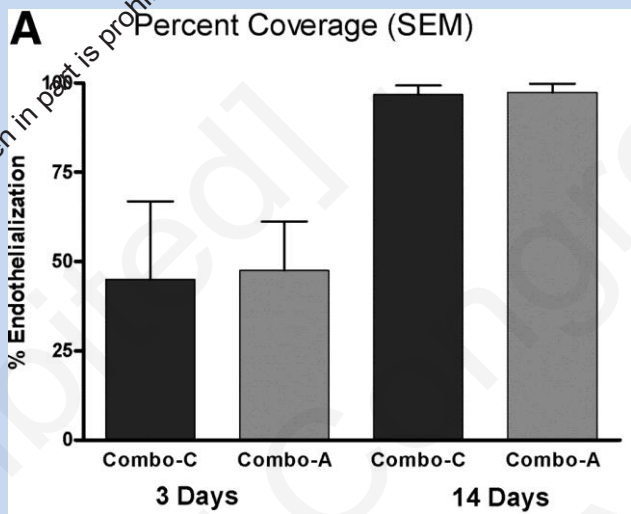
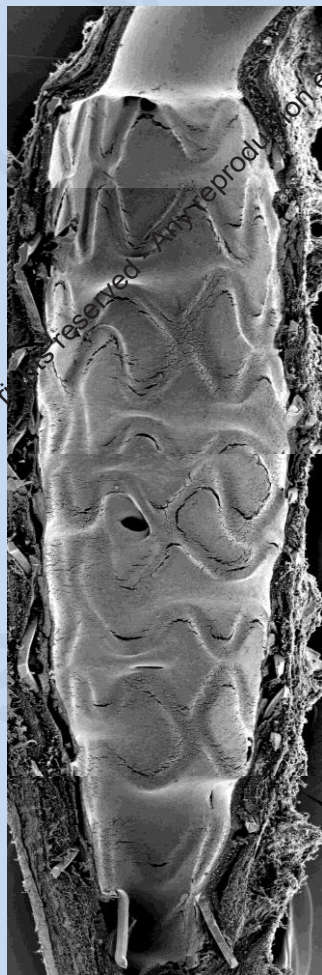
- 28 Days: Light Microscopy (n = 6 in each group = 12)

Granada J F et al. Circ Cardiovasc Interv 2010;3:257-266



Control

Abluminal



Granada J F et al. Circ Cardiovasc Interv 2010;3:257-266

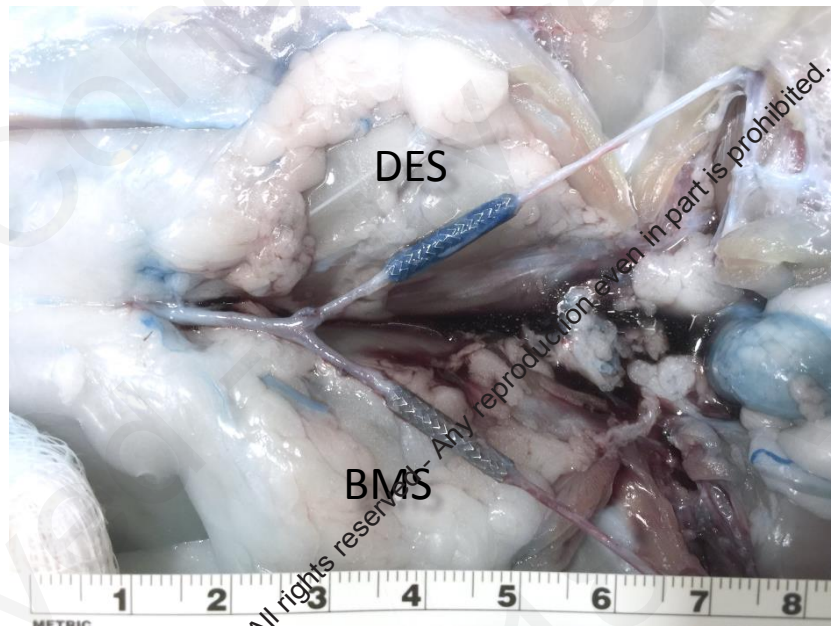


# BMS vs Permanent Polymer DES

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

DES

BMS



"No permeability"

EB-Albumin complex



EB-Albumin complex 70kDa

EB 1kDa

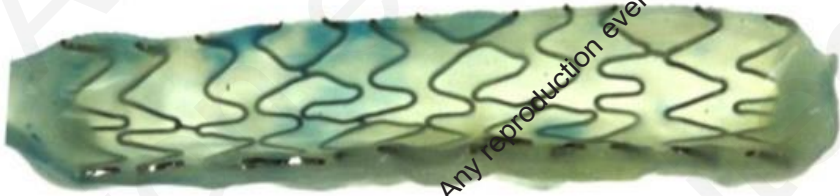
Albumin 69kDa

Endothelium

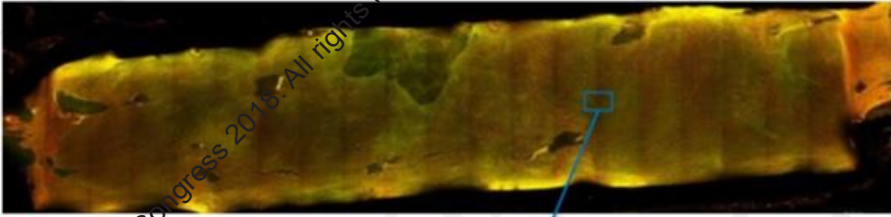
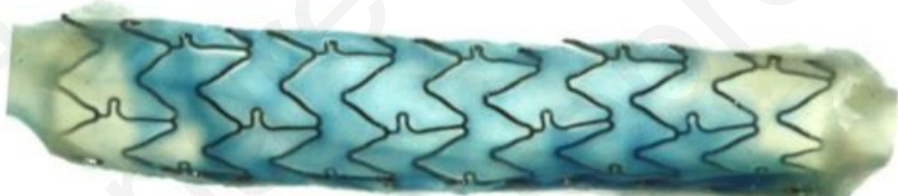
"Permeability"

# Endothelialization: COMBO vs DP-DES (90-day)

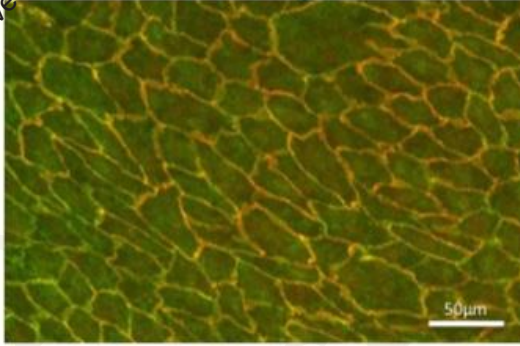
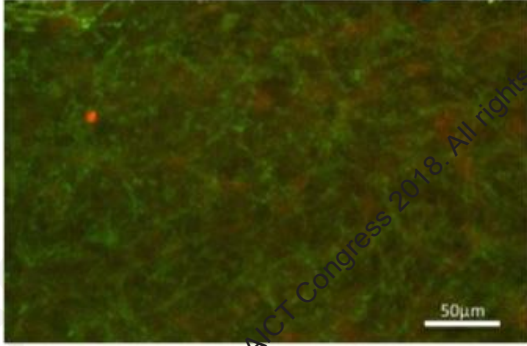
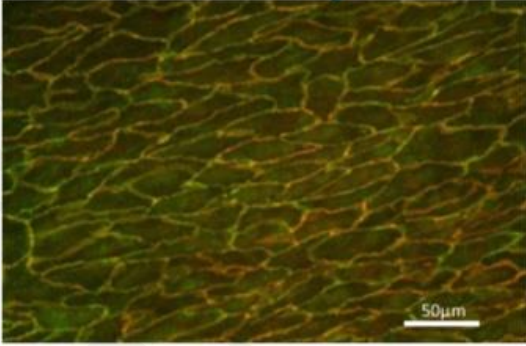
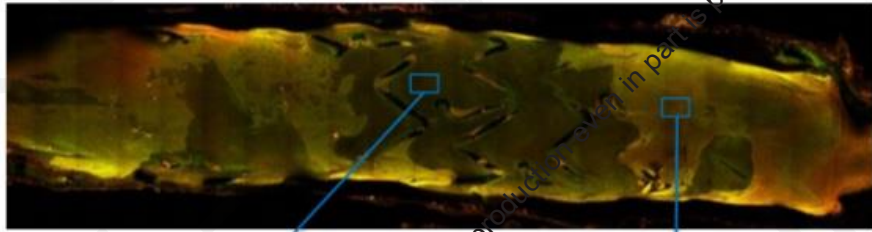
**COMBO**



**DP-DES**



VE-cadherin p120





# Summary

- Delayed or impaired healing is the major cause of stent failure
- True healing is defined by restoration of endothelial function
- Biocompatibility is also important for the long-term safety
- “Combo” showed early healing with higher maturation of endothelium in animal models which indicate the potential benefit of shorter DAPT in this stent

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SUNRISE lab.

