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Does True Vessel Healing Matter?

Roxana Mehran, MD

Professor of Medicine (Cardiology), Health Evidence and Policy
Icahn School of Medicine at Mount Sinai,
Cardiovascular Research Foundation
New York, NY

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Vascular Response to stent implantation

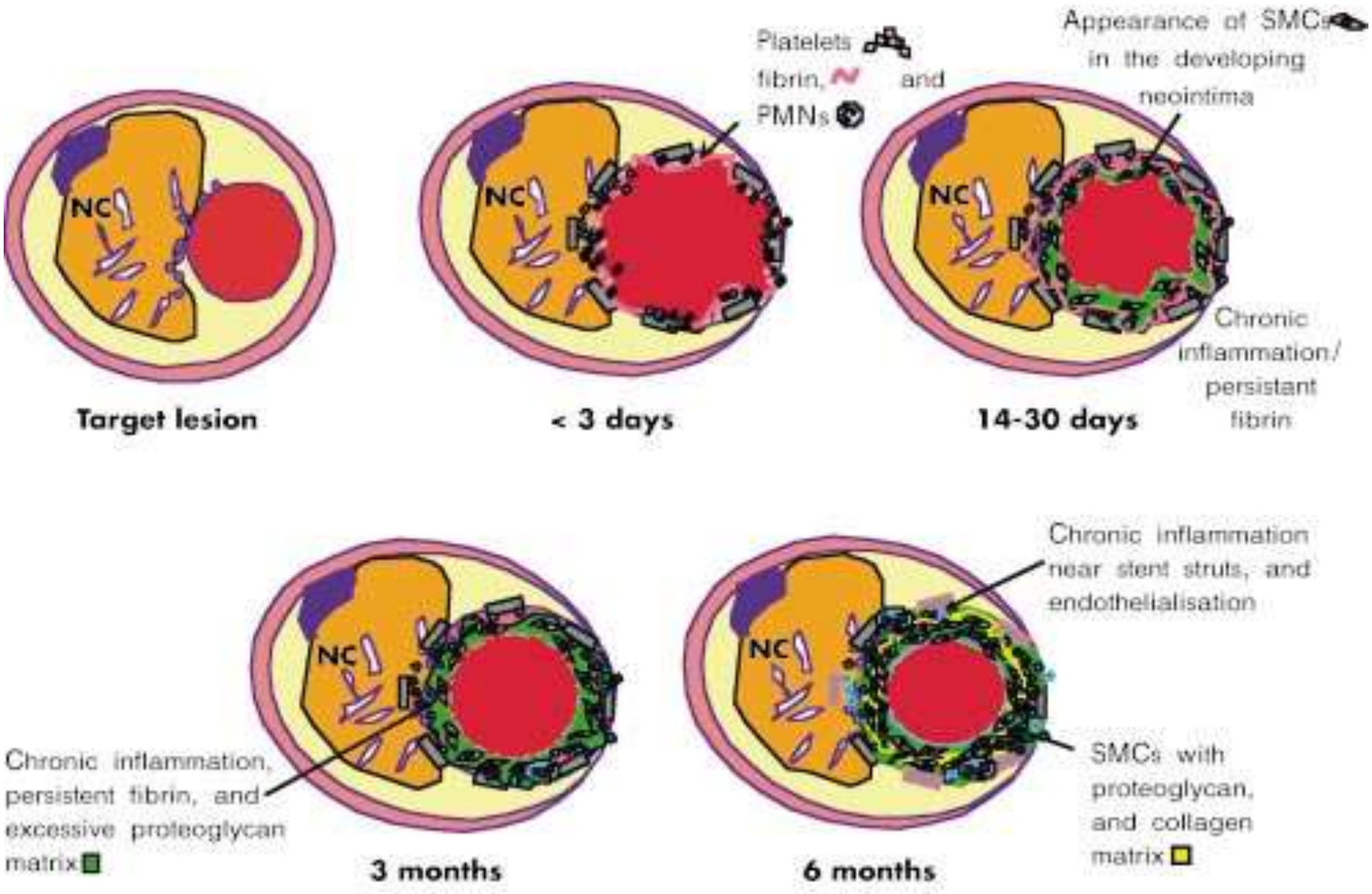

Figure 3 Illustration of the vascular response to a balloon expandable stainless steel stent implanted in an atherosclerotic human coronary artery. NC, necrotic core; PMNs, polymorphonuclear leucocytes; SMCs, smooth muscle cells.

Virmani et al, Heart. 2003 Feb; 89(2): 133–138.

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Adverse Vessel Healing: Cascade of restenosis.

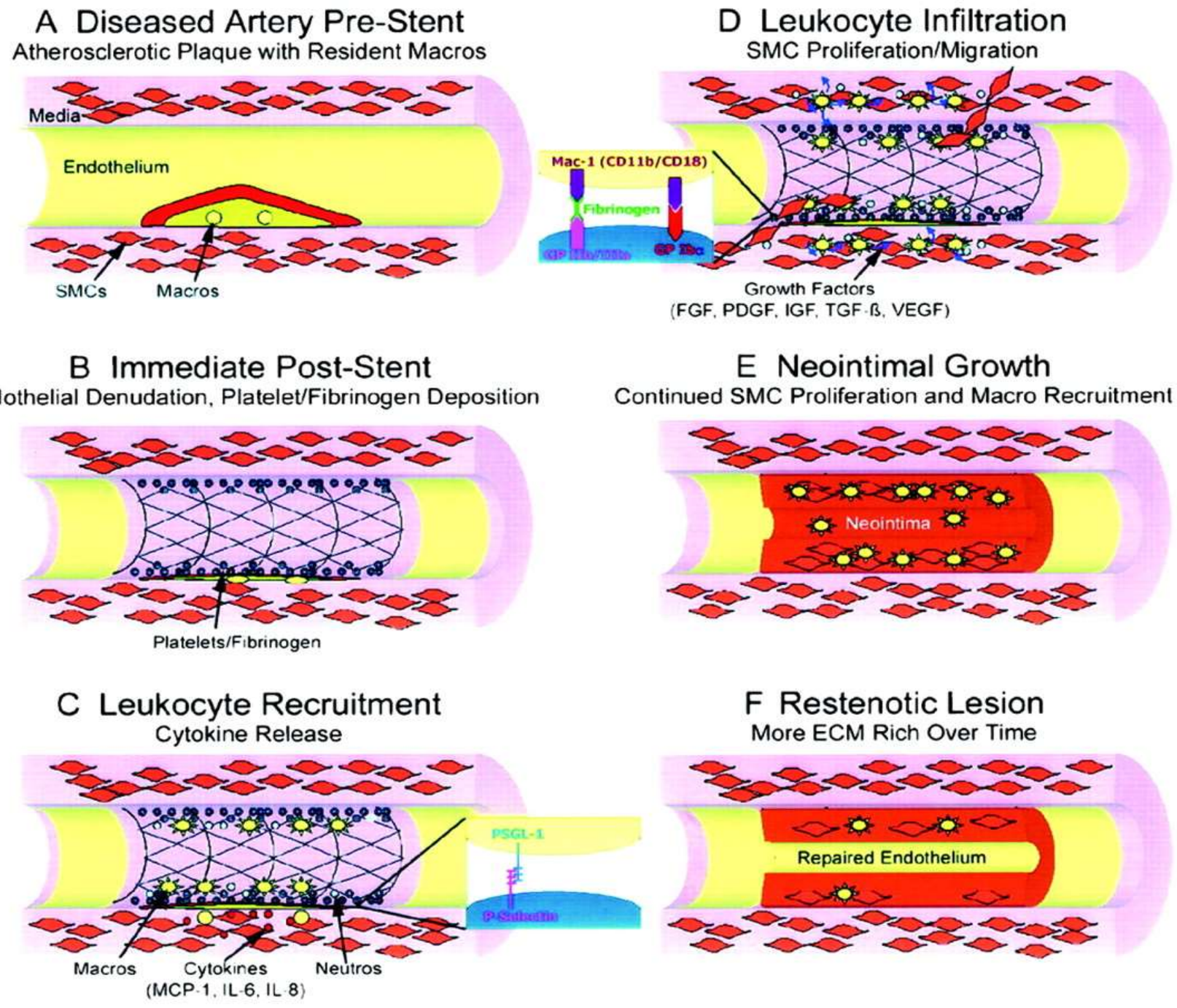

Figure 1. Schematic of an integrated cascade of restenosis. A, Atherosclerotic vessel before intervention. B, Immediate result of stent placement with endothelial denudation and platelet/fibrinogen deposition. C and D, Leukocyte recruitment, infiltration, and SMC proliferation and migration in e days after injury. E, Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment. F, Long-term eeks to months) change from a predominantly cellular to a less cellular and more ECM-rich plaque. Reprinted with permission from Arterioscler Thromb Vasc Biol.11

Marco A. Costa, and Daniel I. Simon Circulation. 2005;111:2257-2273

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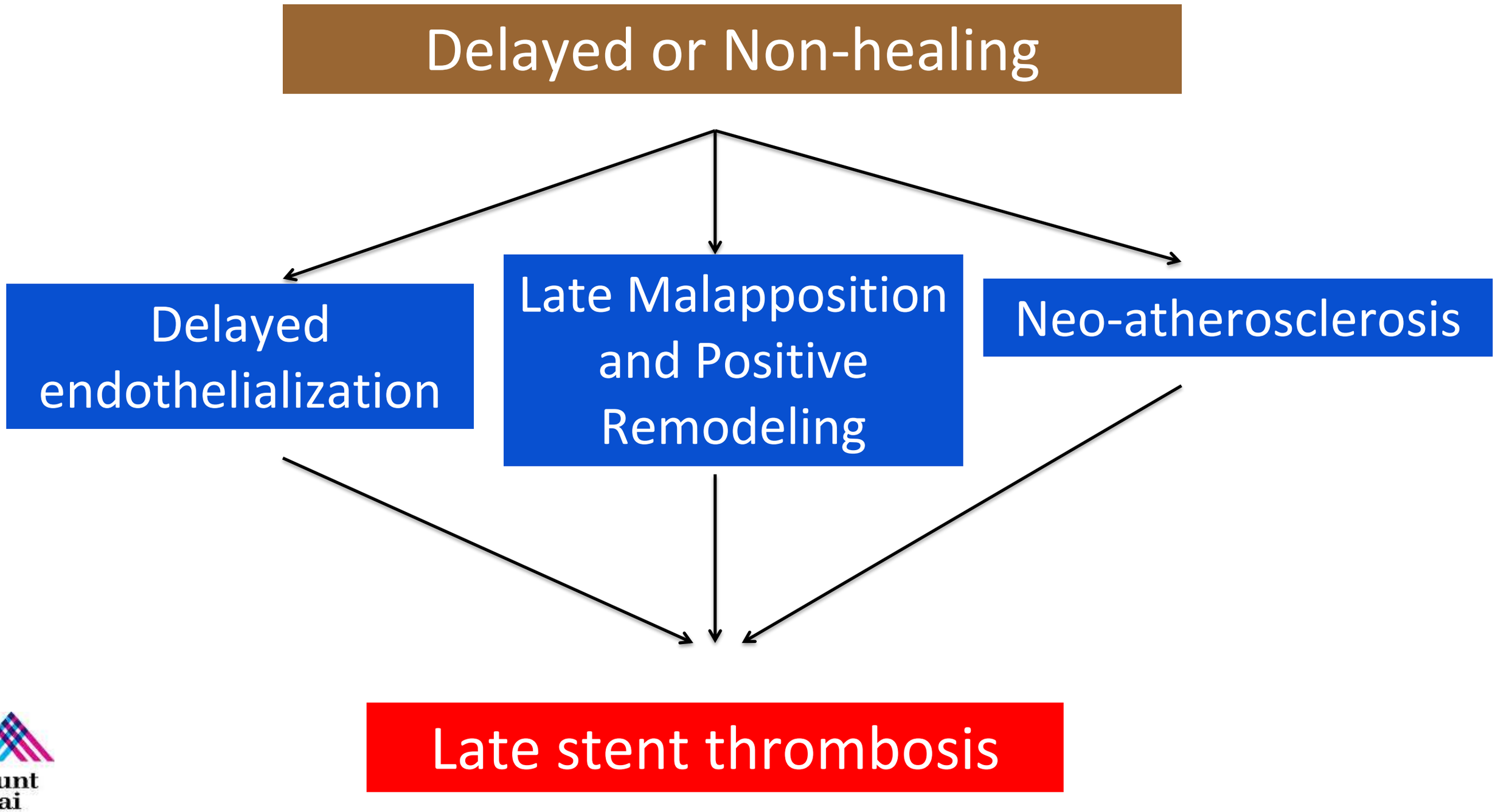
Vessel Non-Healing



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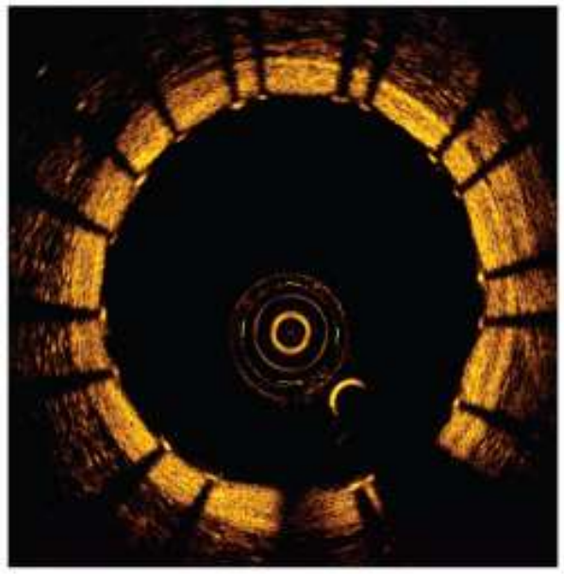
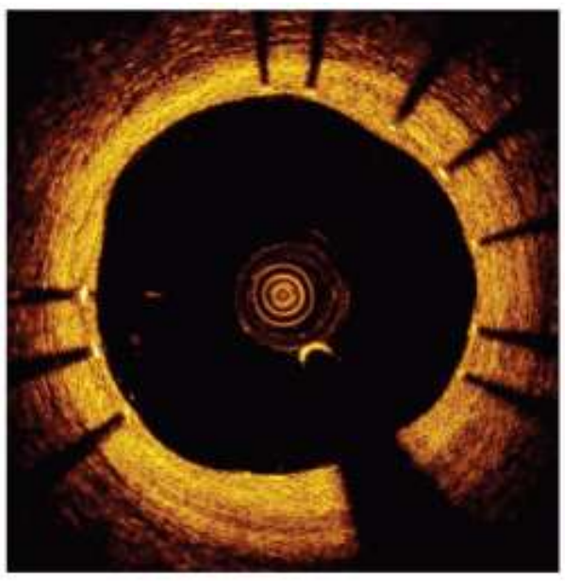
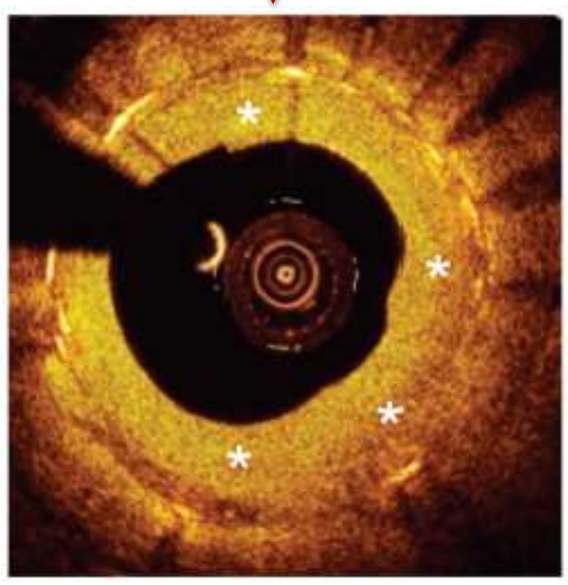
Assessment of Arterial Condition Under OCT



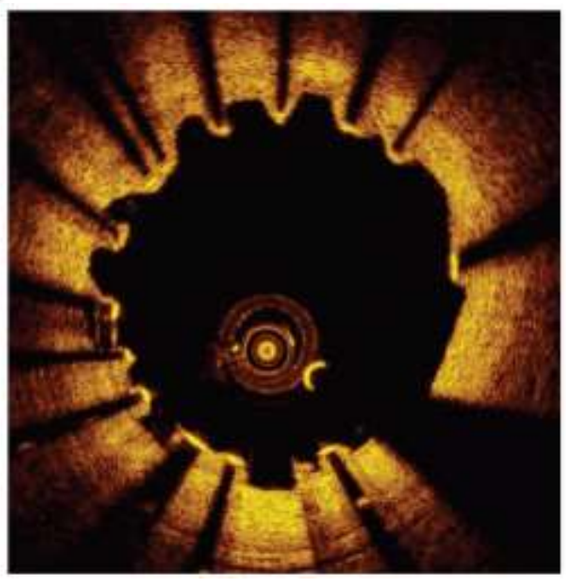
Stent Optimization at Baseline Procedure



Optimal Strut Coverage



Neointimal Proliferation



Non-Healing & Positive Remodeling

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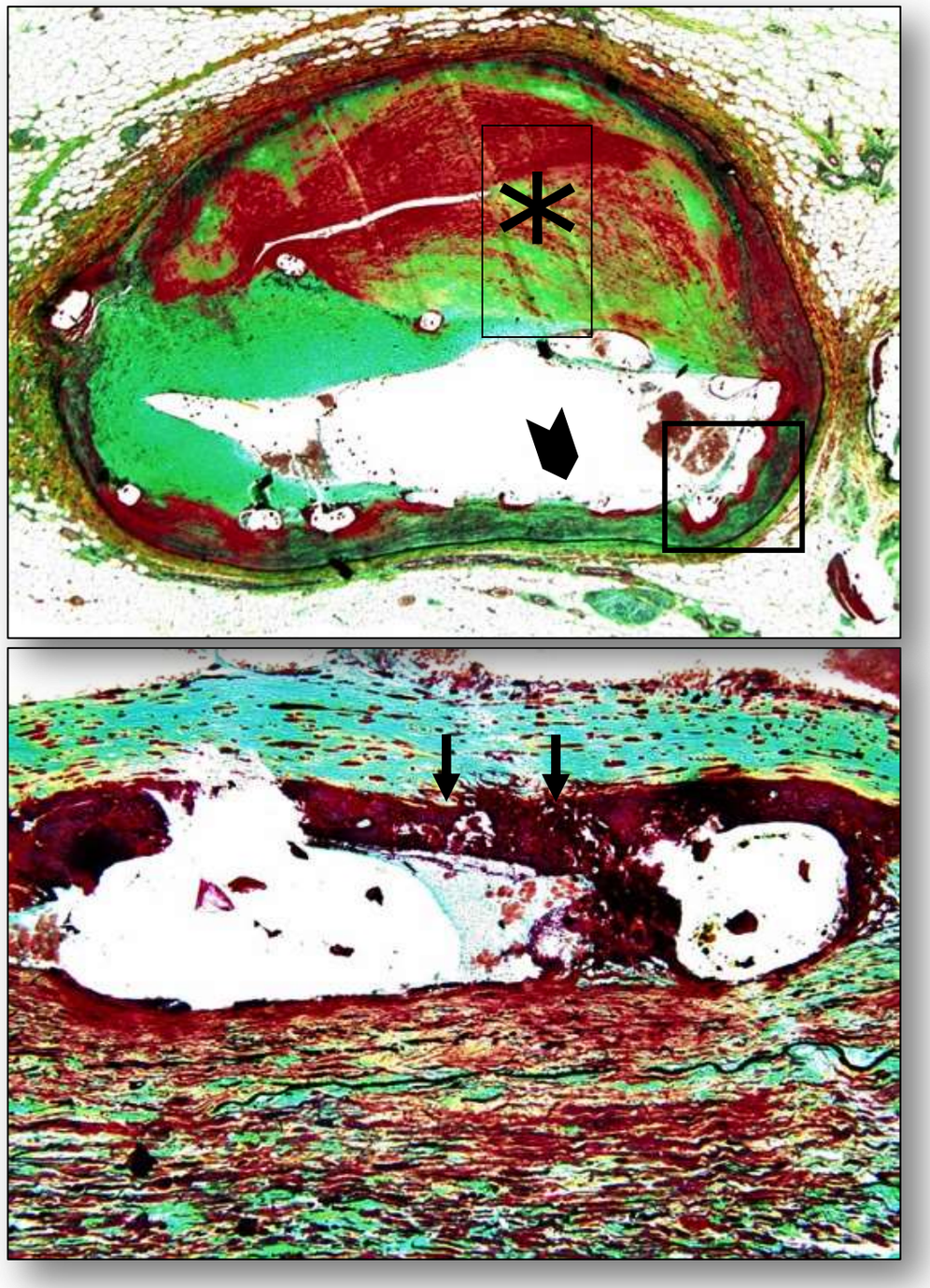
Source: St. Jude Medical ILUMIEN Image Guide

Monitoring of Delayed Arterial Healing (Histology)

- Incomplete Endothelialisation
- Late Fibrin Deposition
- Chronic Inflammation
- Platelet Activation



Joner et al., JACC 2006
Byrne, Joner, Kastrati Minerva Cardioangiol 2009

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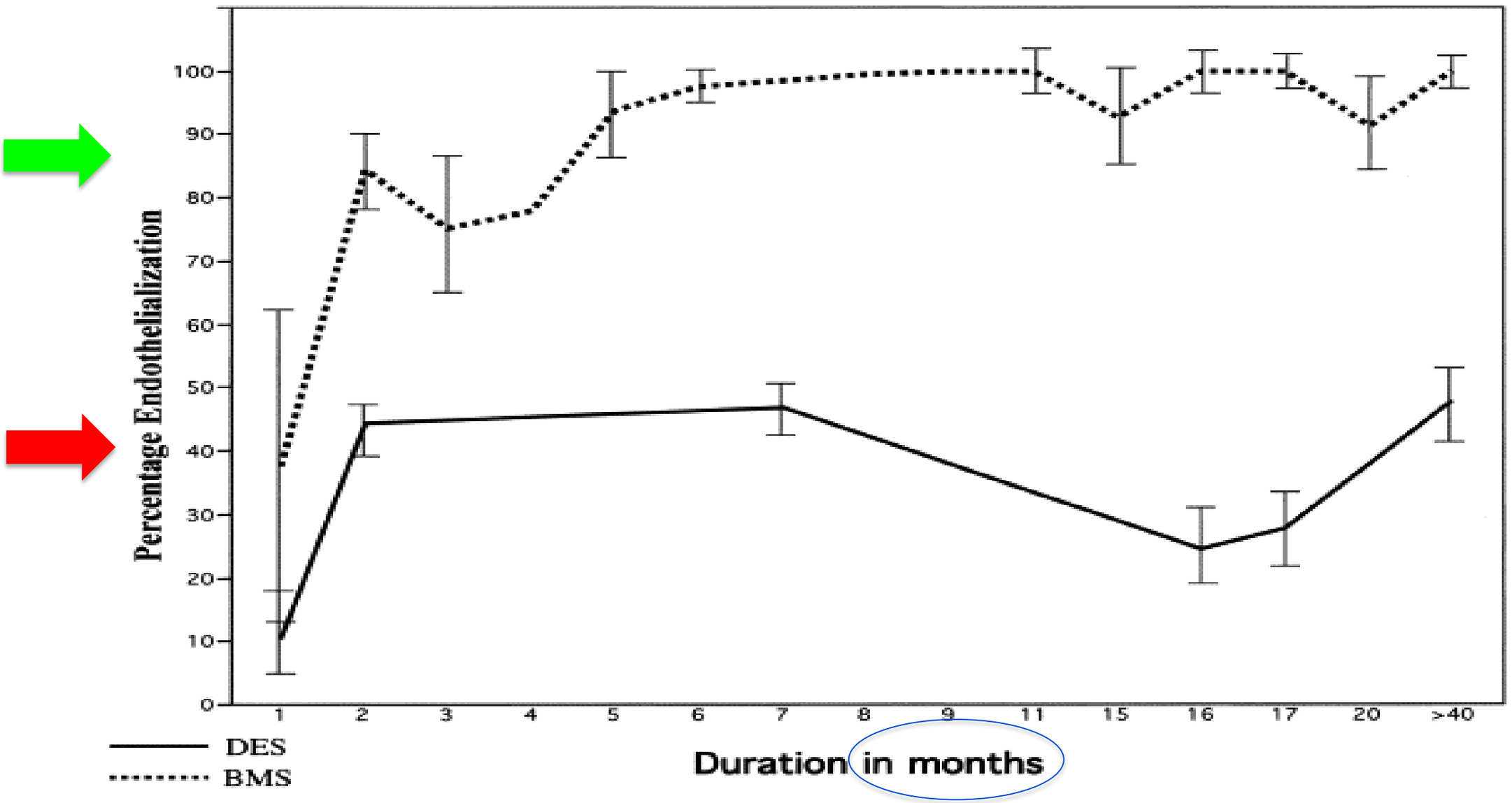
Rate and Degree of Endothelialization in DES Vs BMS



Line chart comparing the percentage of endothelialization in drug-eluting stents (DES) versus bare-metal stents (BMS) as a function of time. Note that DES (solid line) consistently show less endothelialization compared with BMS (dashed line)

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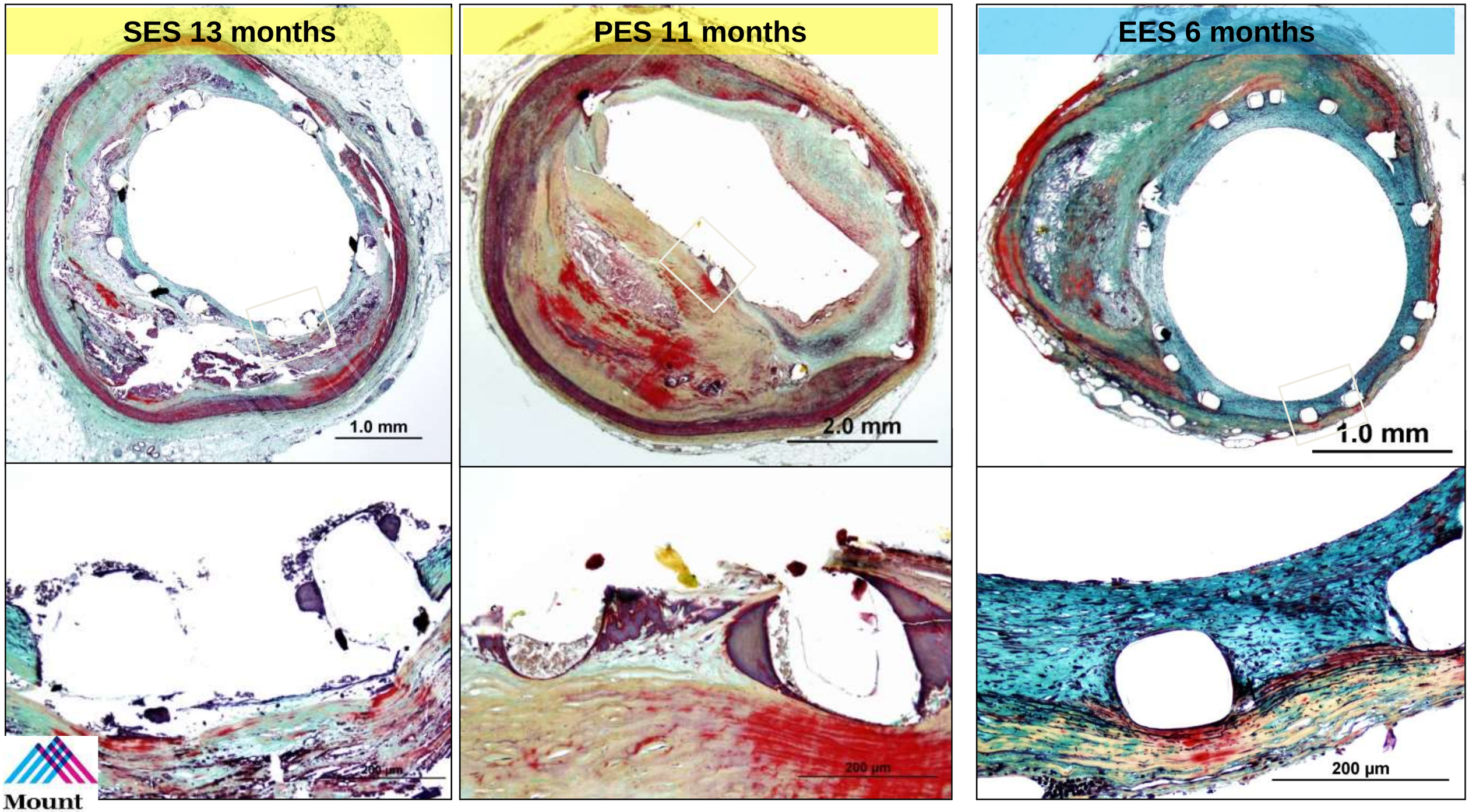
Joner et al, JACC, Volume 48, Issue 1, 2006, 193 – 202, doi 10.1016/j.jacc.2006.03.042

Representative Images of EES vs. SES/PES in Human Coronary Arteries



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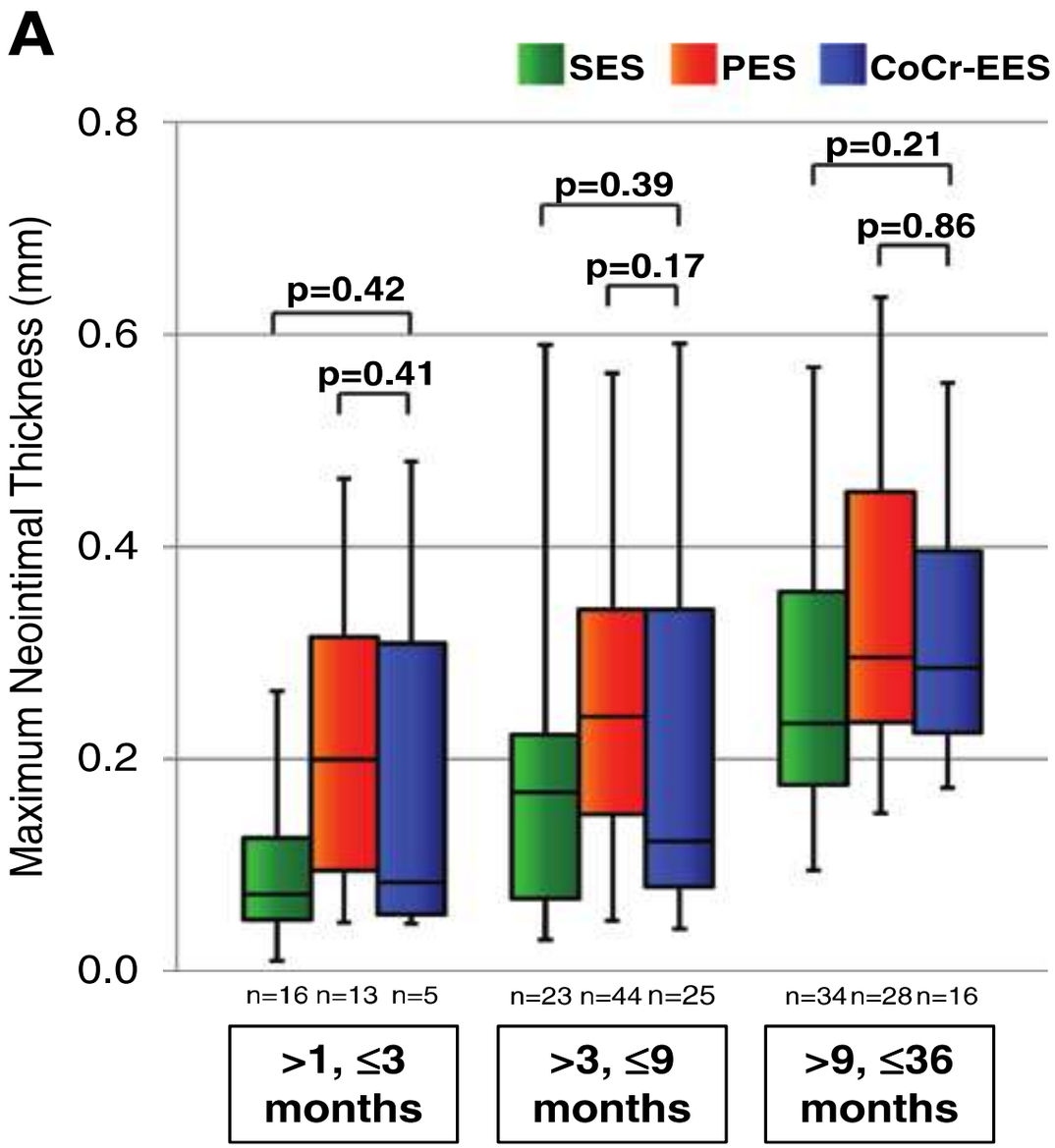
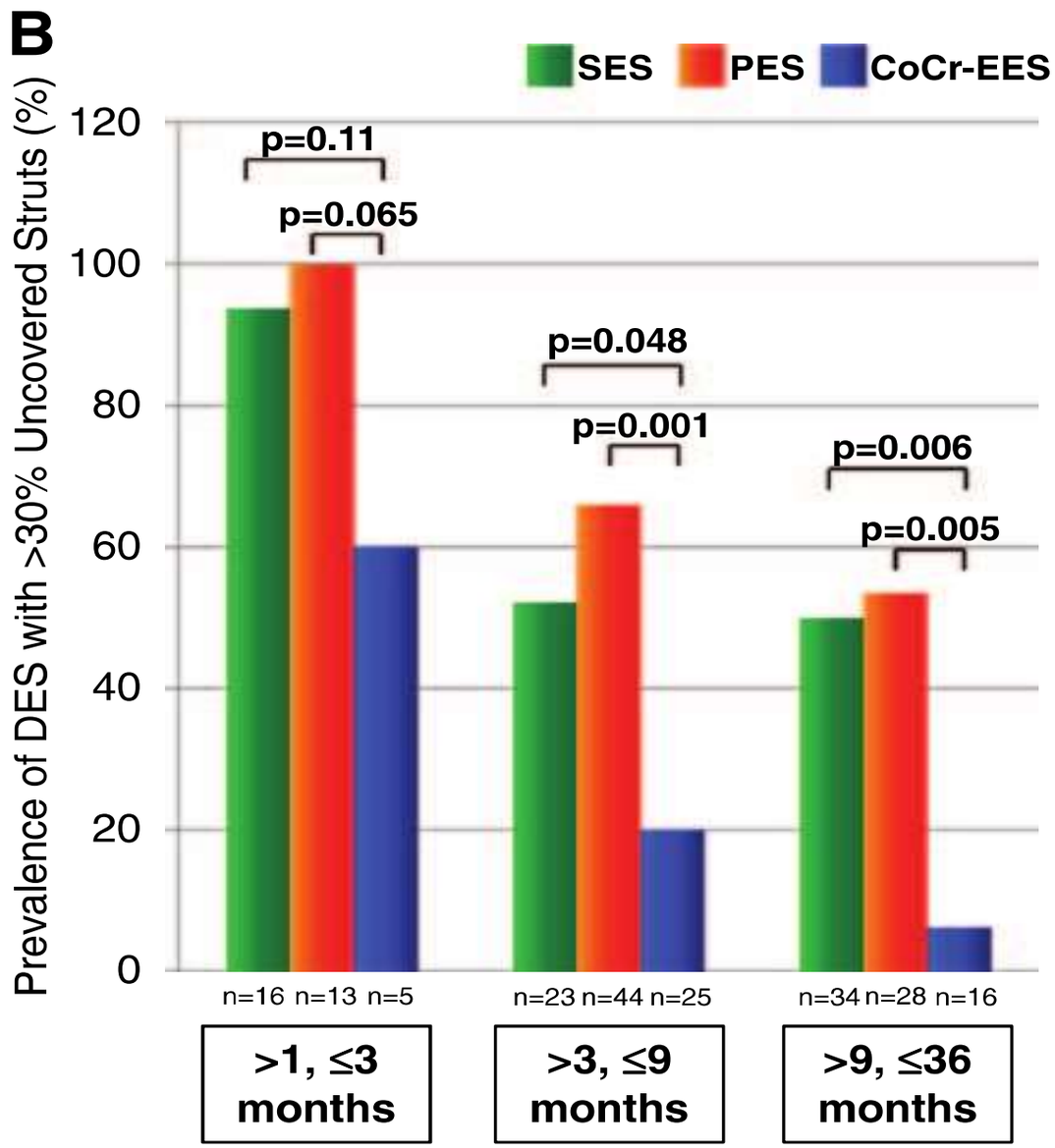
Otsuka F et al. Circulation. 2014;129:211-223

Degree of endothelialization with different DES





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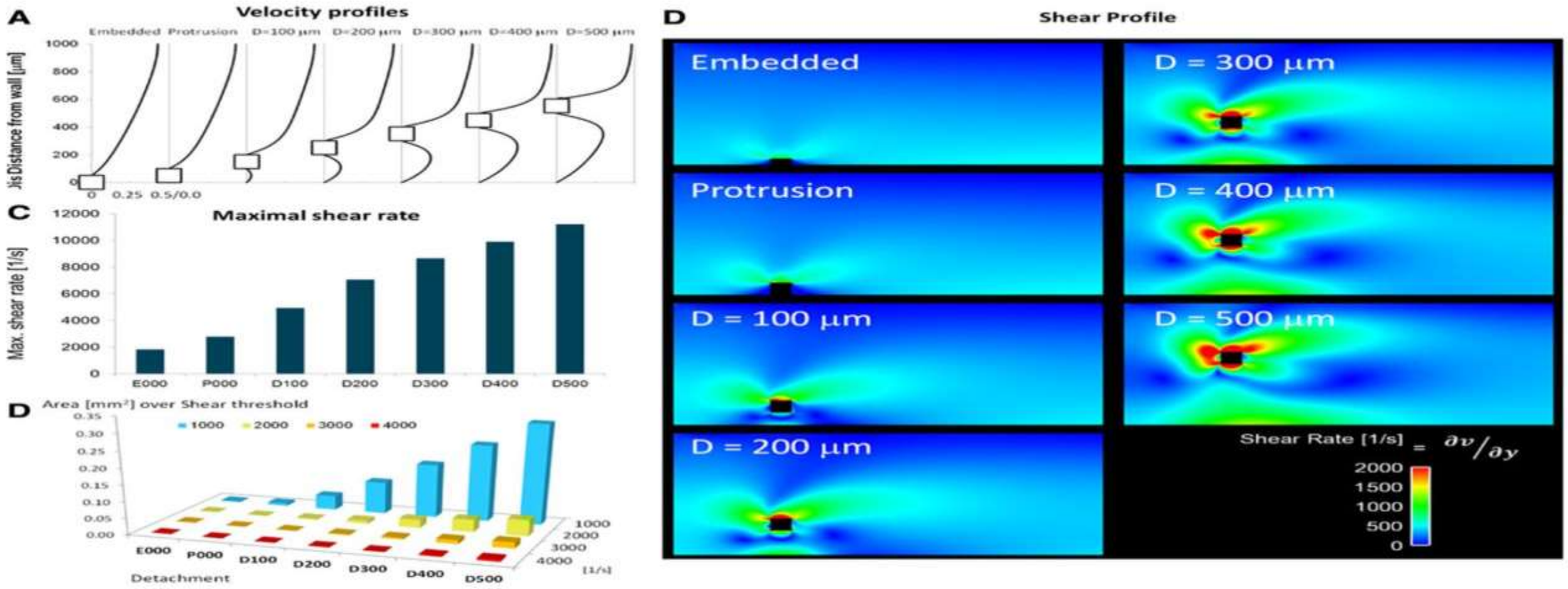
Otsuka F et al. Circulation. 2014;129:211-223

Impact of strut-wall malapposition distance on blood flow velocity profiles (A) and shear rate patterns (B).



Strut apposition	Case	Shear_max [1/s]	Area > shear threshold [mm2]				
			> 500	> 1000	> 2000	> 3000	> 4000
Apposed	E000	1828	0.76	0.00	0.00	0.00	0.00
	P000	2778	0.79	0.01	0.00	0.00	0.00
ISA	D100	4934	0.90	0.04	0.00	0.00	0.00
	D200	7062	1.04	0.10	0.01	0.00	0.00
	D300	8653	1.12	0.16	0.02	0.00	0.00
	D400	9910	1.20	0.23	0.04	0.01	0.00
	D500	11213	1.11	0.31	0.05	0.02	0.01

A, Blood flow velocity profiles for the different cases of strut apposition (embedded and protrusion) and strut malapposition considered in the computational simulation with increasing maximal strut-wall incomplete stent apposition (ISA) distances, ranging from *D*=100 µm up to *D*=500 µm. **B**, Corresponding shear profile in blood flow around stent strut for each cases. High shear rate values (red) correspond to blood flow disturbance with highest velocity gradients. **C**, Absolute maximal shear rate [1/s] and (**D**) area of blood (mm^2) affected by abnormal shear above the preset threshold computed for each cases. E000, embedded; P000, protrusion; D100–D500, malapposition cases with ISA detachment distance ranging from 100 to 500 µm.

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Nicolas Foin et al. Circ Cardiovasc Interv. 2014;7:180-189

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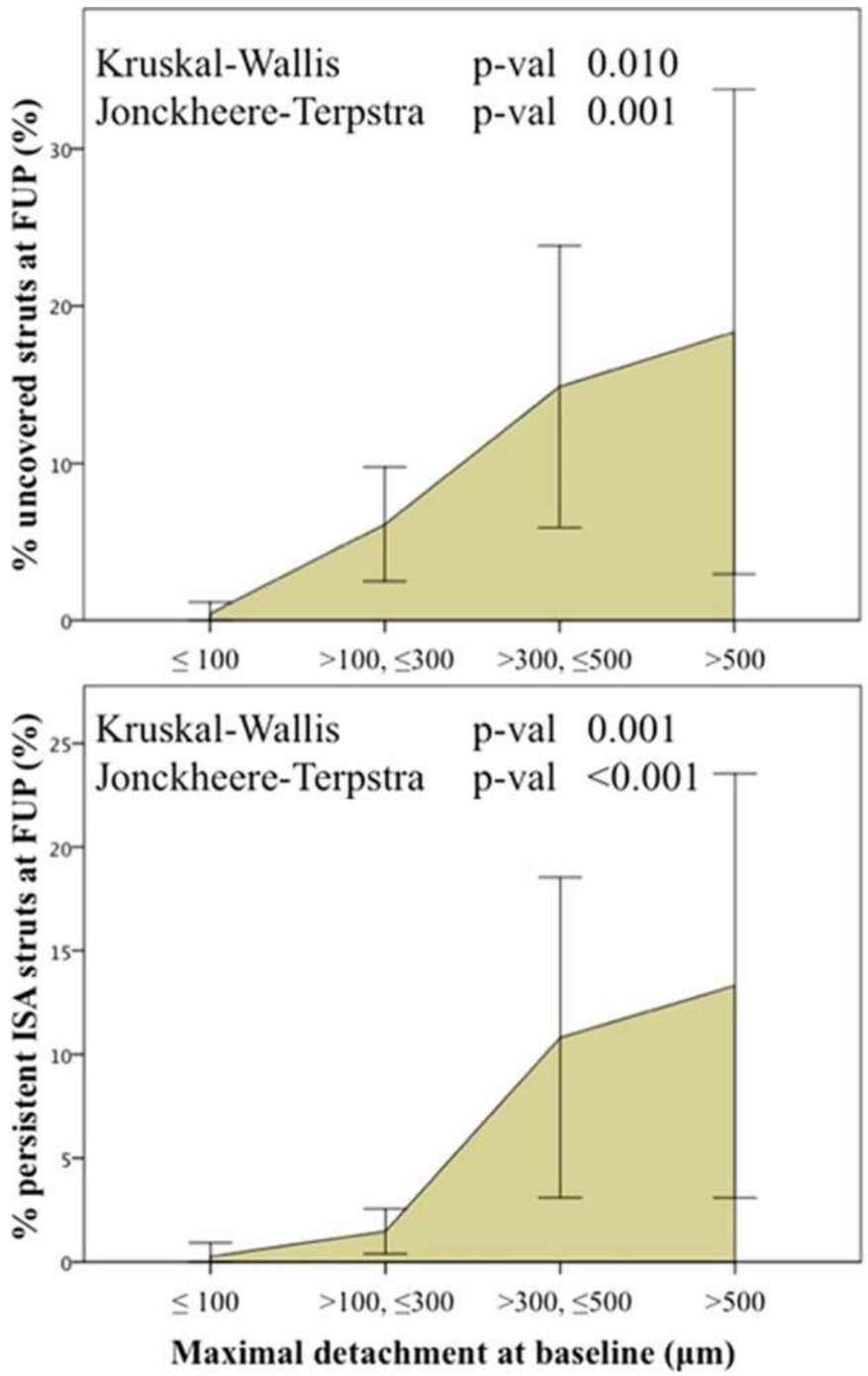
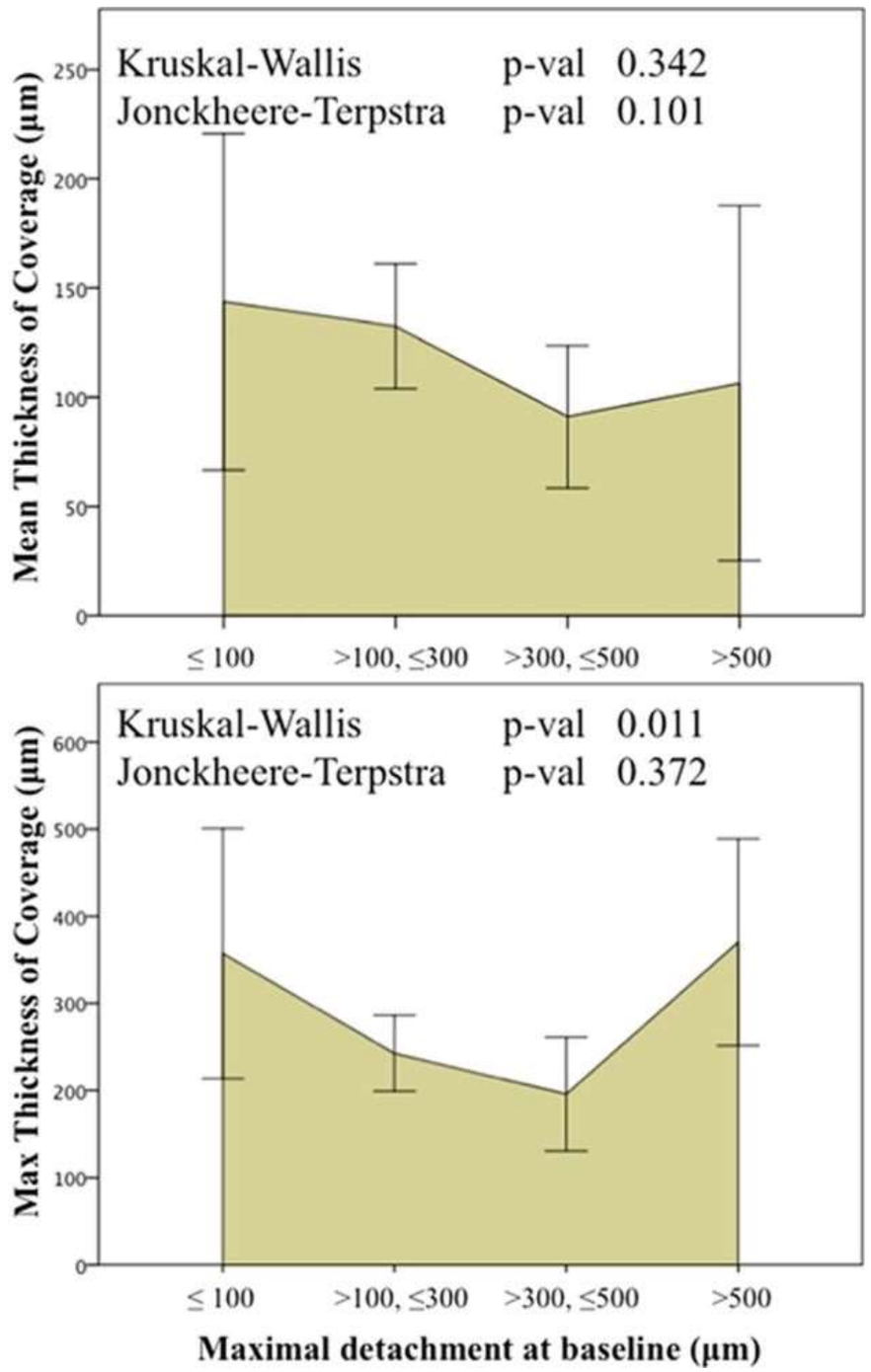
Impact of detachment distance on neointimal coverage in a clinical setting.





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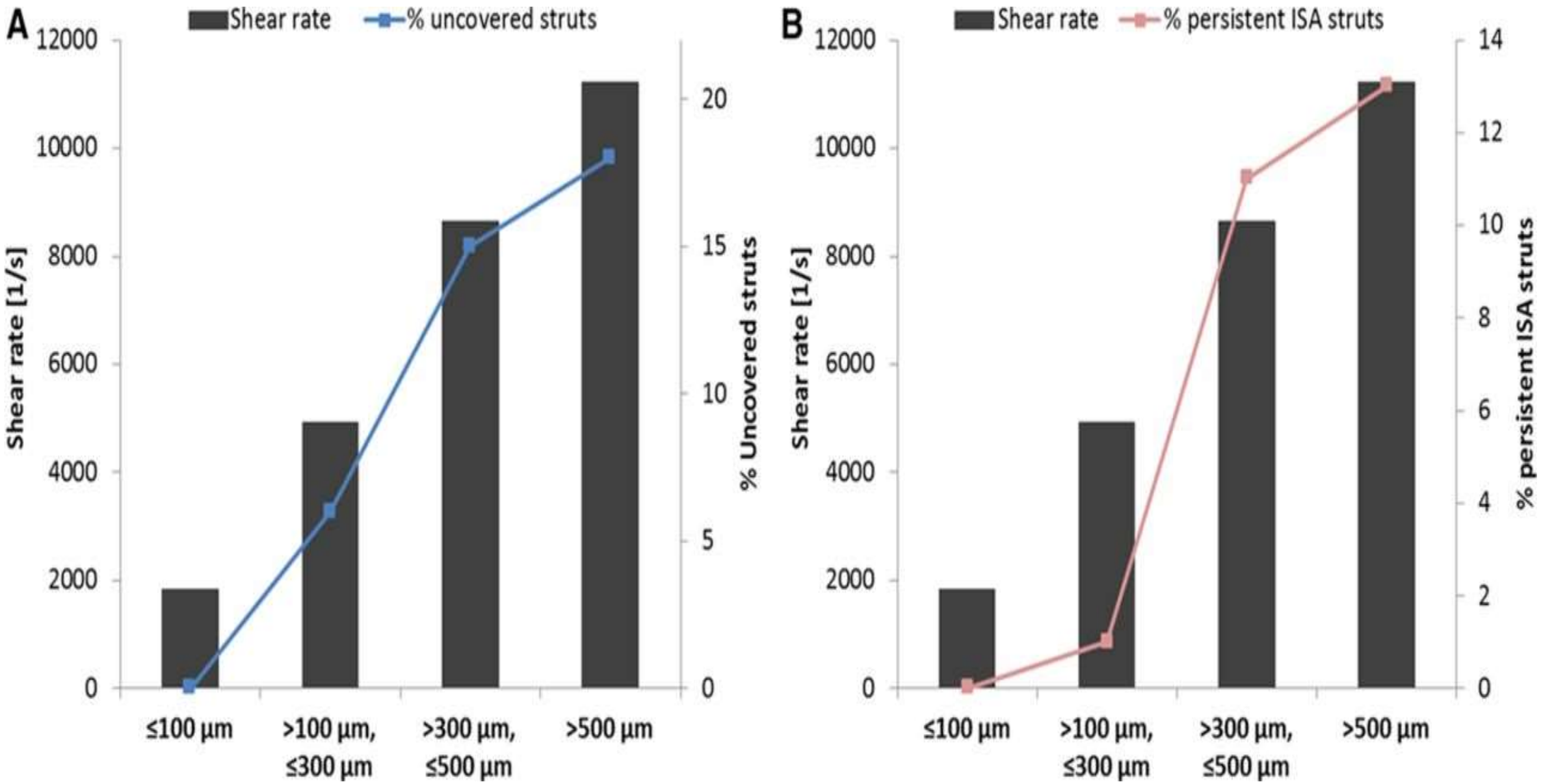
Impact of detachment distance on neointimal coverage in a clinical setting. Mean values of percentage of uncovered struts at follow-up (FUP; primary objective), percentage of persistent malapposed (incomplete stent apposition [ISA]) struts at follow-up, mean and maximal thickness of coverage measured in the ISA segment. Bars, 95% confidence intervals.

Nicolas Foin et al. Circ Cardiovasc Interv. 2014;7:180-189

Correlation between baseline shear rate and mean percentage uncovered strut (A) and percentage persistent incomplete stent apposition (ISA; B) at follow-up in each ISA category.



Correlation between baseline shear rate and mean percentage uncovered strut (**A**) and percentage persistent incomplete stent apposition (ISA; **B**) at follow-up in each ISA category. Baseline shear rate (lower boundary for each ISA category computed in Figure 2) compared with mean percentage of uncovered struts and rate of persistent ISA at follow-up. As shear increases with malapposition distance, so does the rate of uncovered struts (linear regression: r=0.99; P=0.006) and incidence of persistent ISA (linear regression: r=0.92; P=0.04) at follow-up.

Nicolas Foin et al. Circ Cardiovasc Interv. 2014;7:180-189

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Late stent malapposition after DES

- Late acquired stent malapposition occurs in ~12% of cases after DES implantation.

- Predictors of LSM (acquired) are total stent length, primary stenting in acute myocardial infarction, chronic total occlusion lesions

- Acute stent malapposition volume is a predictor of persistent LSM

- The clinical implications of LSM on adverse outcomes are controversial – However, large sized stent malappositions are associated with stent thrombosis

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Hong et al, ***Circulation*. 2006; 113:414-419**
Im et al, ***Circ Cardiovasc Interv*. 2014;7:88-96.**

Association between acute and late persistent stent malapposition

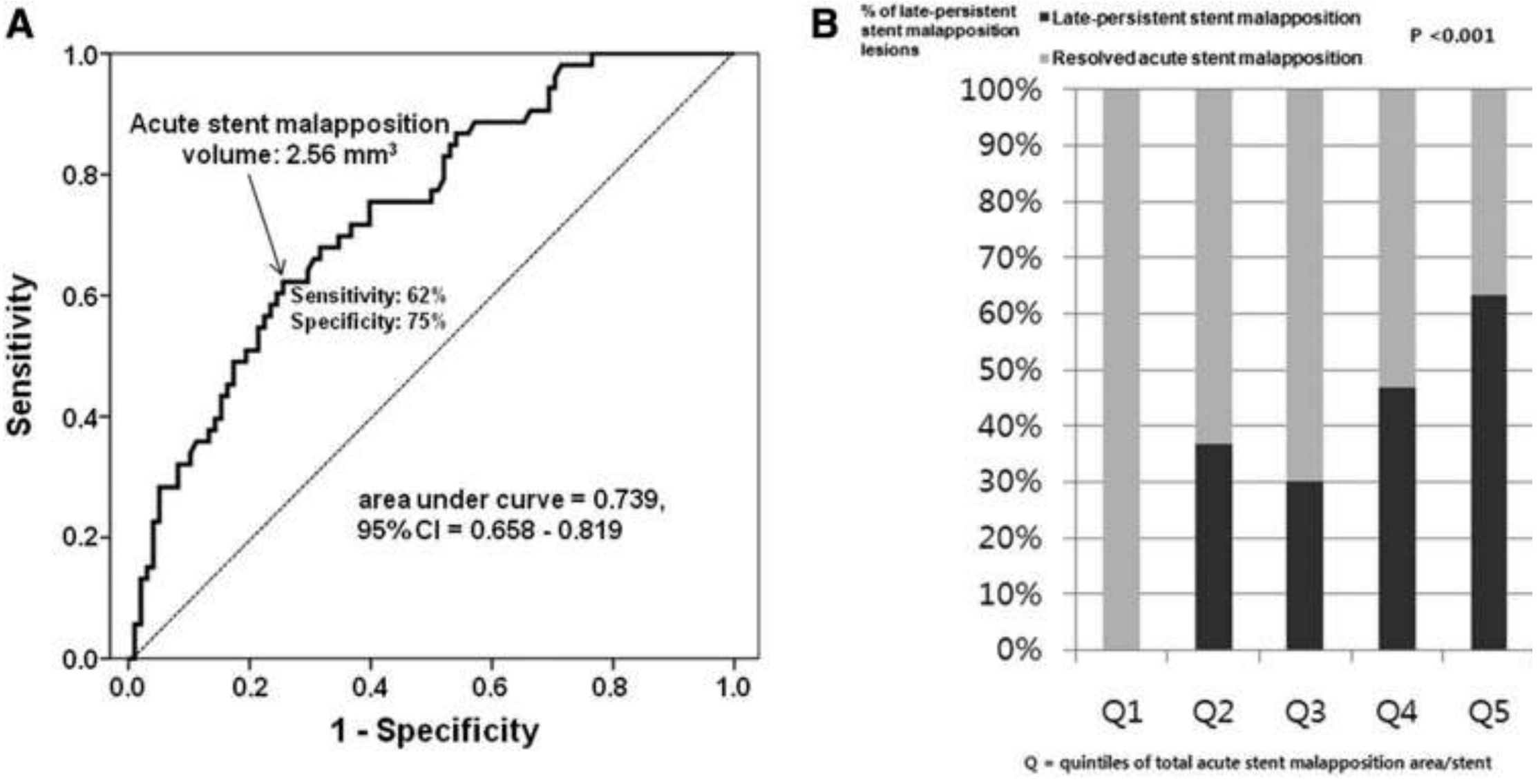

Figure 3. A, Receiver-operating curve demonstrating the best cut-off value for acute stent malapposition volume, which separates late-persistent stent malapposition lesions from resolved acute stent malapposition lesions. **B**, The percentage of late-persistent stent malapposition lesions according to the quintiles of total acute stent malapposition area is shown. CI indicates confidence interval.

Im et al, ***Circ Cardiovasc Interv*. 2014;7:88-96.**

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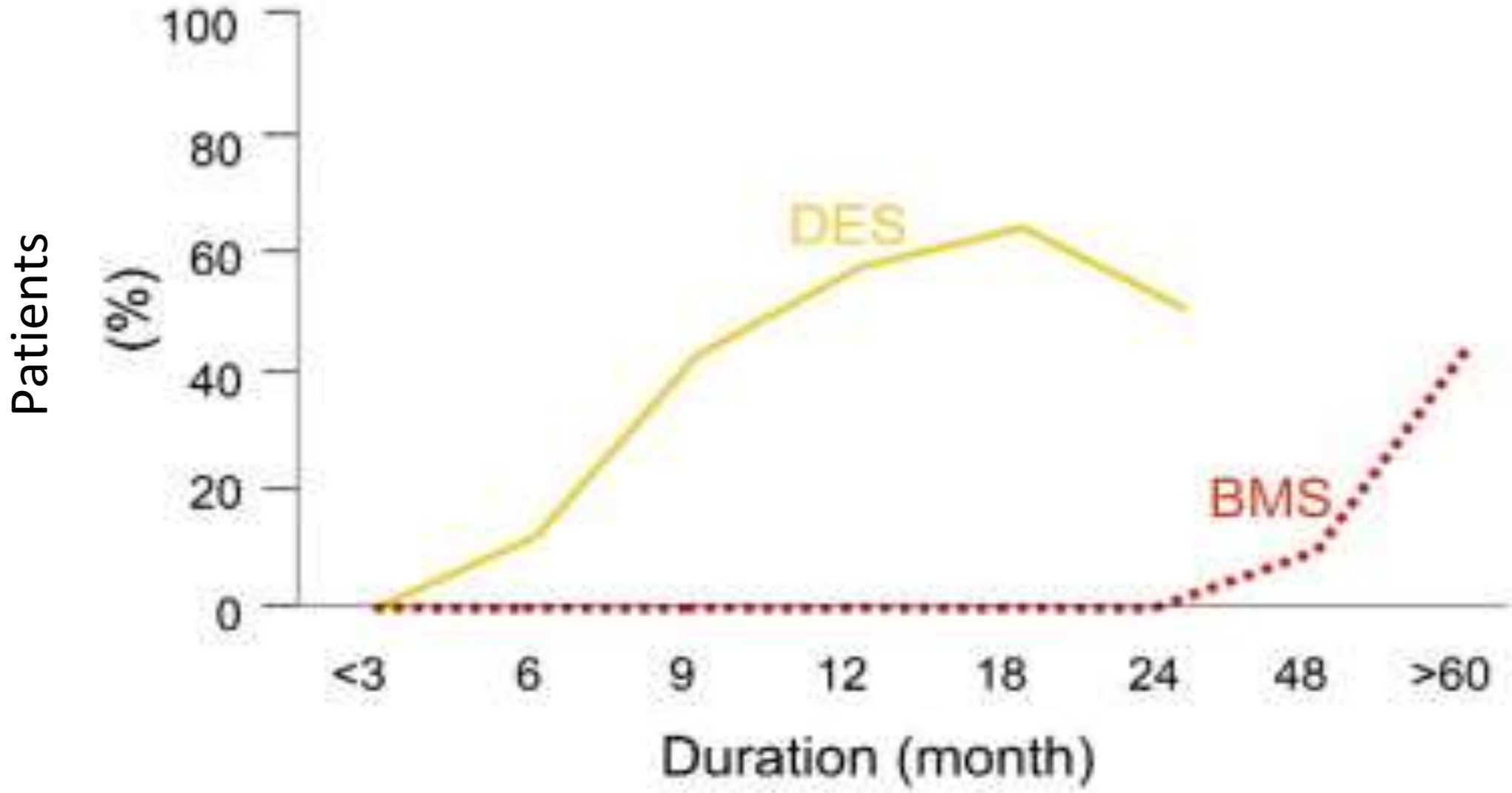
In-Stent Neoatherosclerosis: A Final Common Pathway of Late Stent Failure



Different Time Points of the Neoatherosclerosis: Percentage of patients with atherosclerotic change in drug-eluting stent (DES) versus bare-metal stent (BMS) in relation to duration of implant at autopsy is depicted.

The atherosclerotic change in sirolimus-eluting stents is seen in >40% of cases by 9 months; in the BMS, the atherosclerotic change does not begin to appear until 2 years, and remains a rare finding until 4 years.

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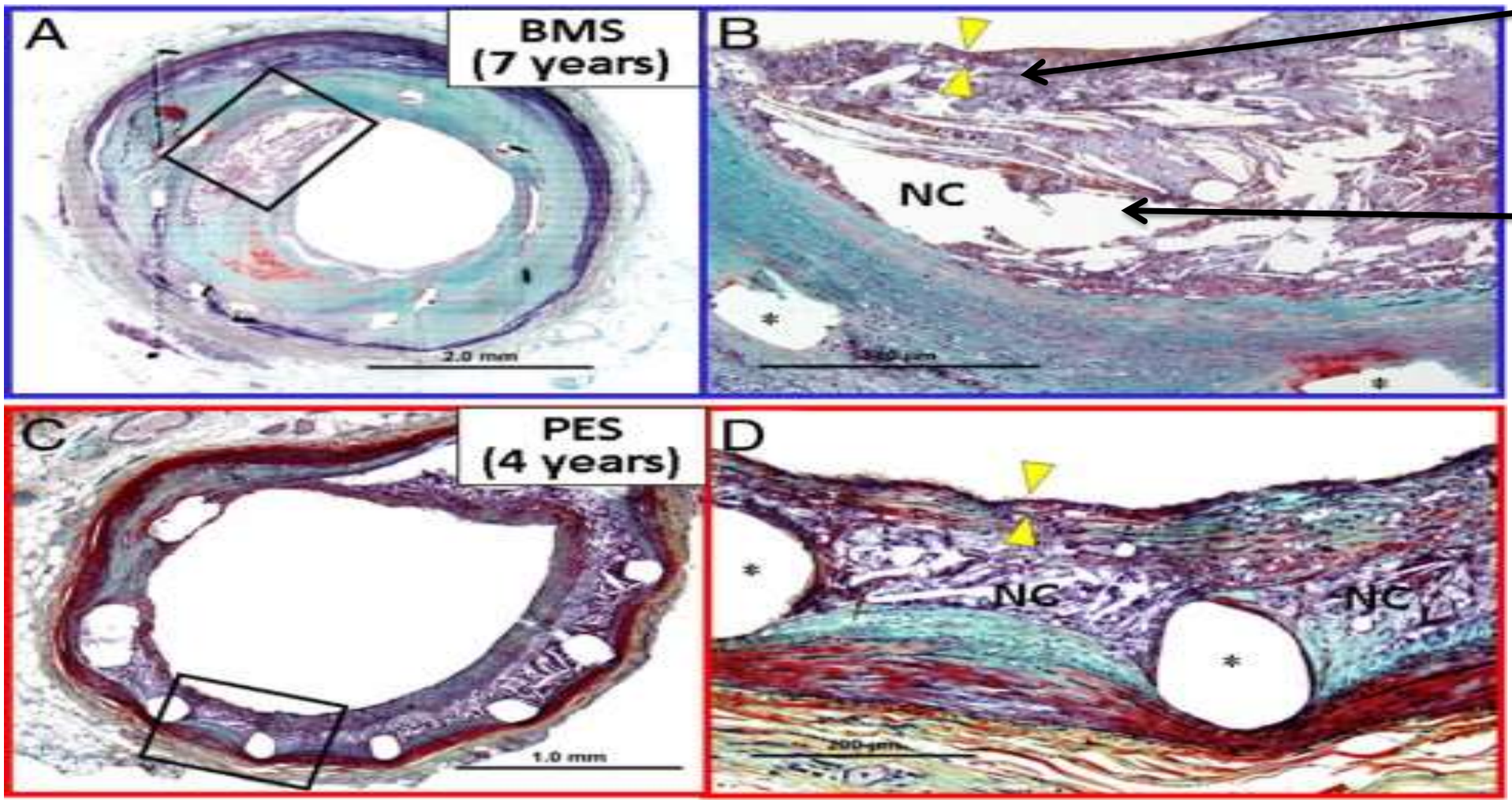
J Am Coll Cardiol. 2012;59(23):2051-2057. doi:10.1016/j.jacc.2011.10.909

In-Stent Neoatherosclerosis



(A) Cross-sectional histology of bare-metal stent (BMS) implanted in the coronary artery for 7 years antemortem

(B) High-power image of the box in A (×100). A large necrotic core (NC) containing cholesterol crystals is identified within the neointima. The fibrous cap overlying the NC is infiltrated by numerous foamy macrophages and is markedly thinned (yellow arrowheads point to thinnest portion), which resembles vulnerable plaque encountered in native coronary arteries. The asterisks represent metal struts.

(C) Cross-sectional histology of paclitaxel-eluting stent (PES) implanted in the coronary artery for 4 years antemortem

(D) High-power image of the box in C (×200). A relatively small NC containing cholesterol crystals is formed around metal struts (asterisk). The fibrous cap is infiltrated by numerous foamy macrophages and is markedly thinned (yellow arrowheads point to thinnest portion).

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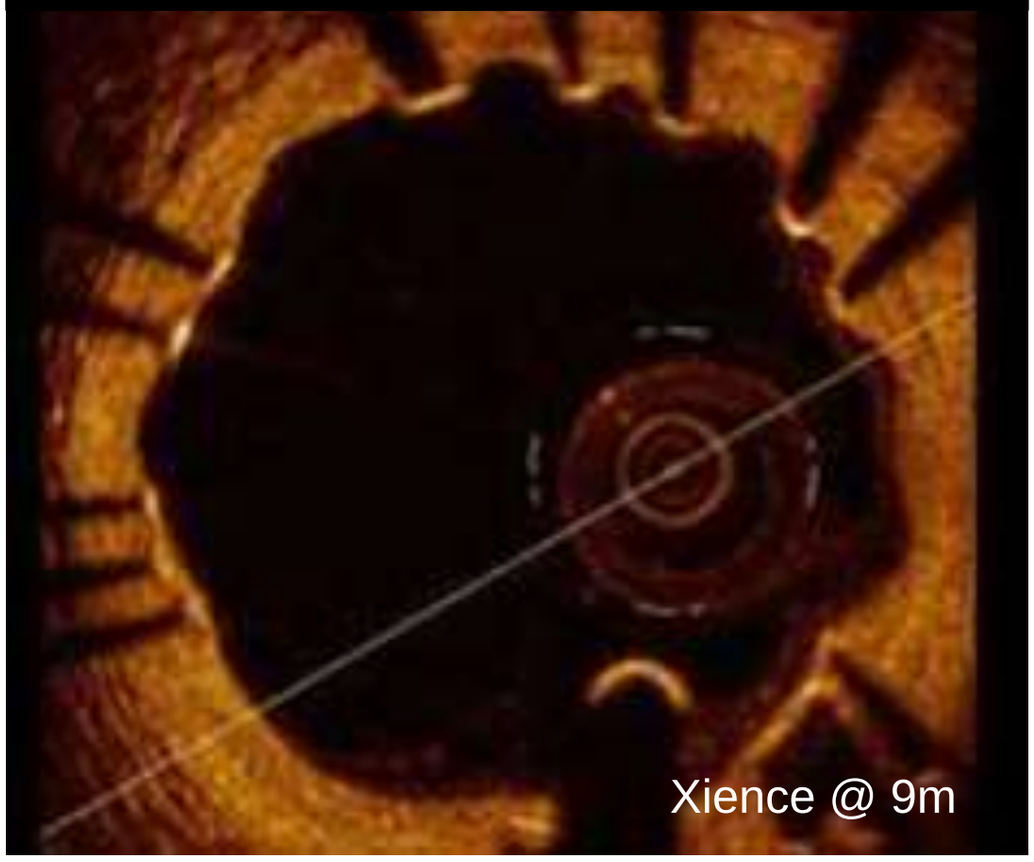
J Am Coll Cardiol. 2012;59(23):2051-2057. doi:10.1016/j.jacc.2011.10.909

Late Stent Thrombosis from Non-Healing

DES at 9 Months



Uncovered Struts

DES at 3 Years

Late Stent Thrombus

What are Key Elements to Proper Vessel Healing?

- Adequate strut coverage to minimize thrombotic risk[1]
- Homogeneity[2] (less peri-strut inflammation and fibrin deposition)
- Stabilized neointima prevents development of neoatherosclerosis[3]
- Functional endothelium to regain normal vasomotor function[4]

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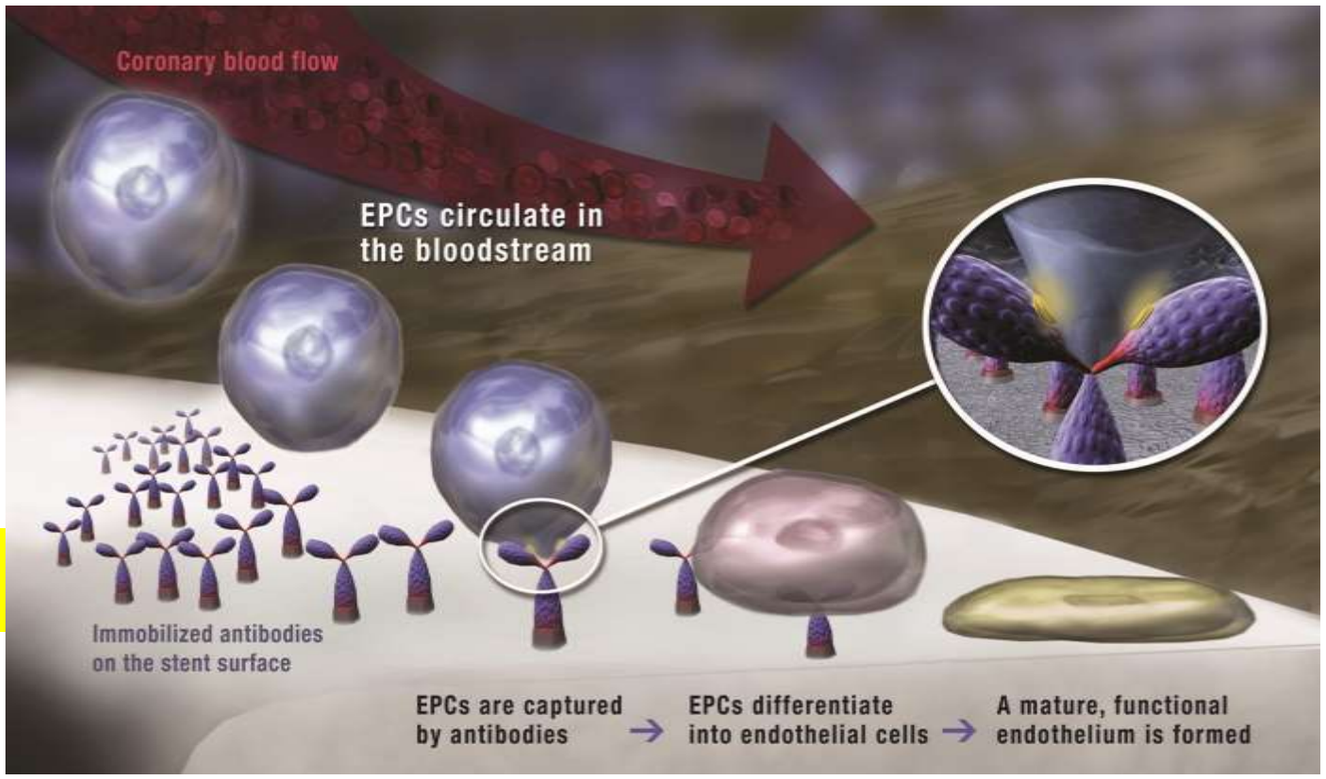
1. Finn et al, Circulation 2007;115:2435-2441
2. Kim et al, Eur Heart Journal – Cardiovascular Imaging (2014) 15, 292–298
3. Virmani et. Al, MINERVA CARDIOANGIOLOGICA Vol.63, No. 1, Feb 2015
4. Doshi et al. BMJ. 2001 Aug 18; 323(7309):352-353

Components of Currently Available DES

Dual Therapy Stent

- Scaffold Platform
- Anti-proliferative Drug
- Polymer (biodegradable) — **90 days**
- EPC Capture (pro-healing) ✓



Luminal EPC Capture

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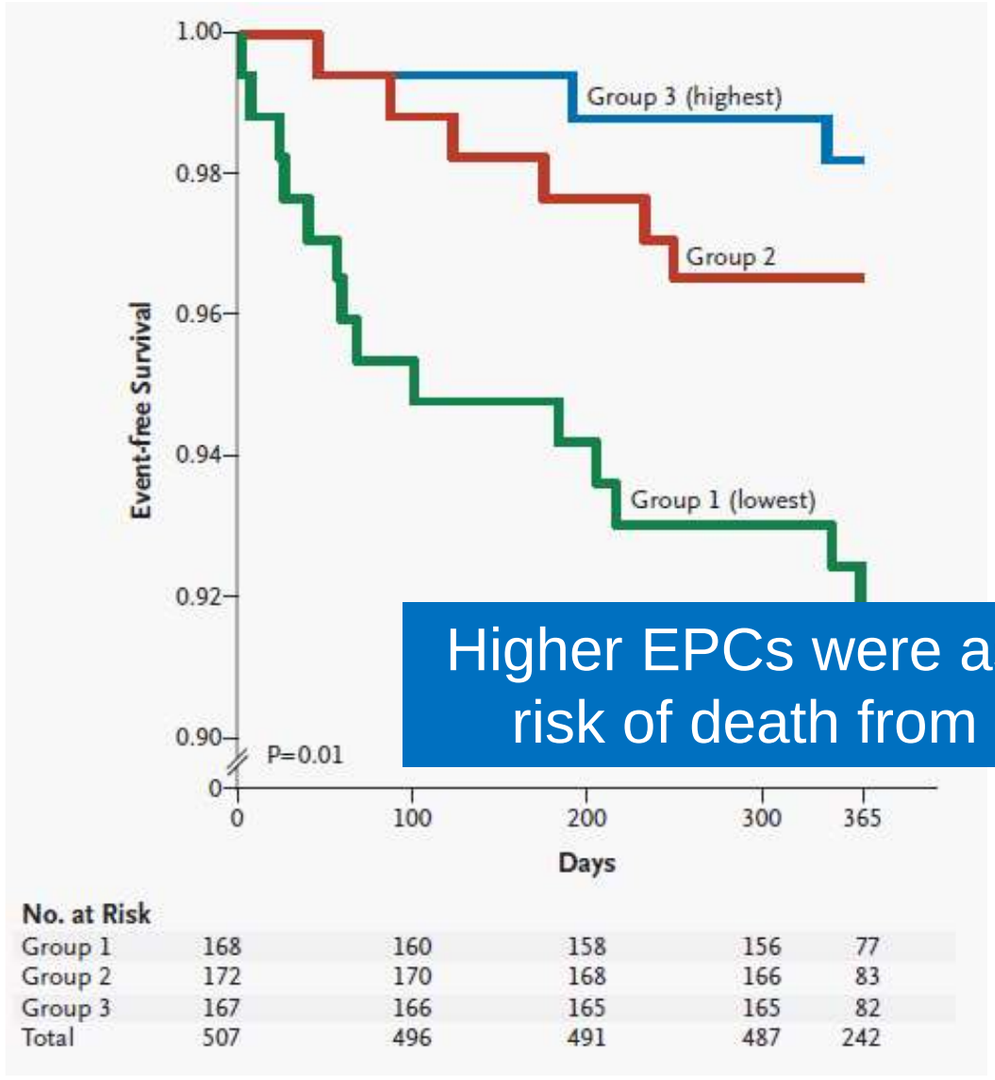
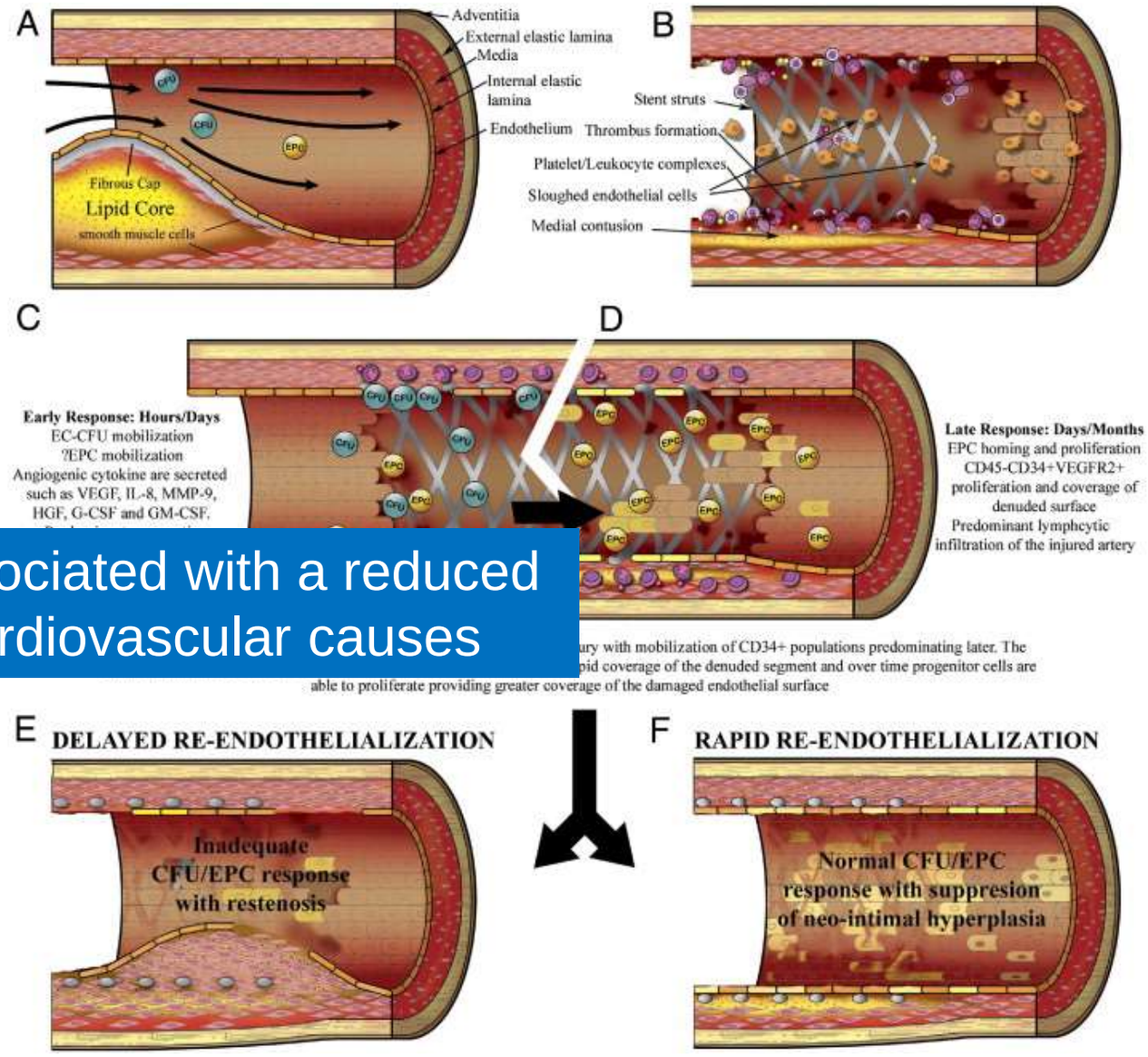
Role of EPC in Cardiovascular Medicine



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



Higher EPCs were associated with a reduced risk of death from cardiovascular causes

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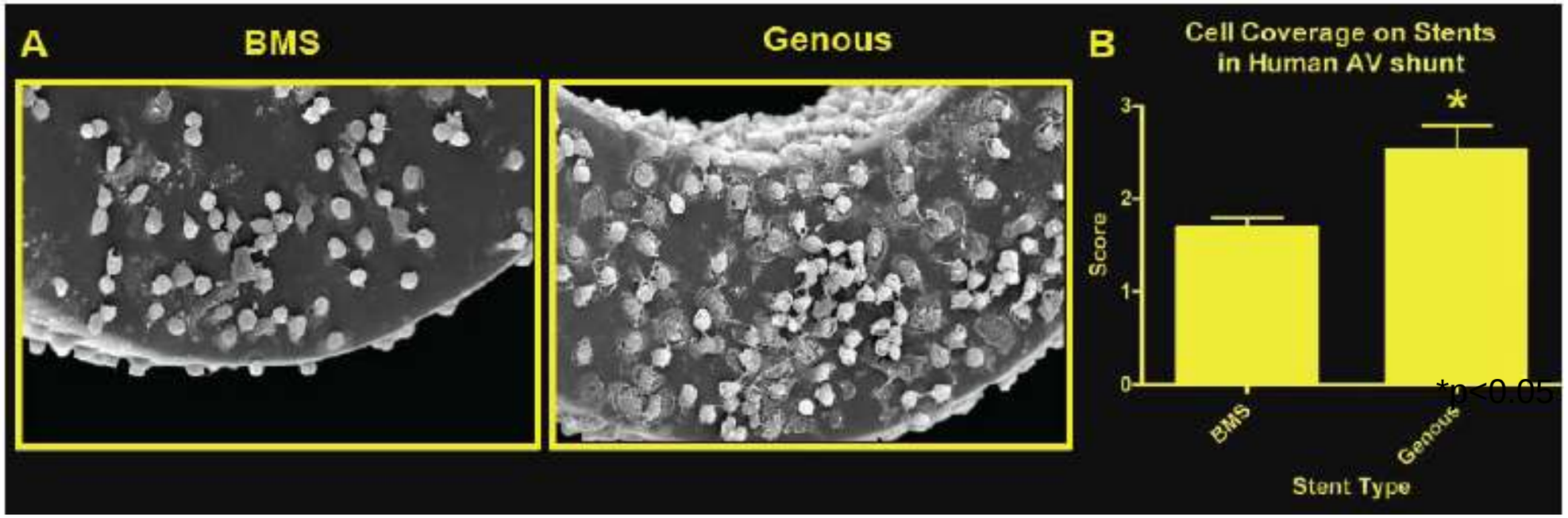
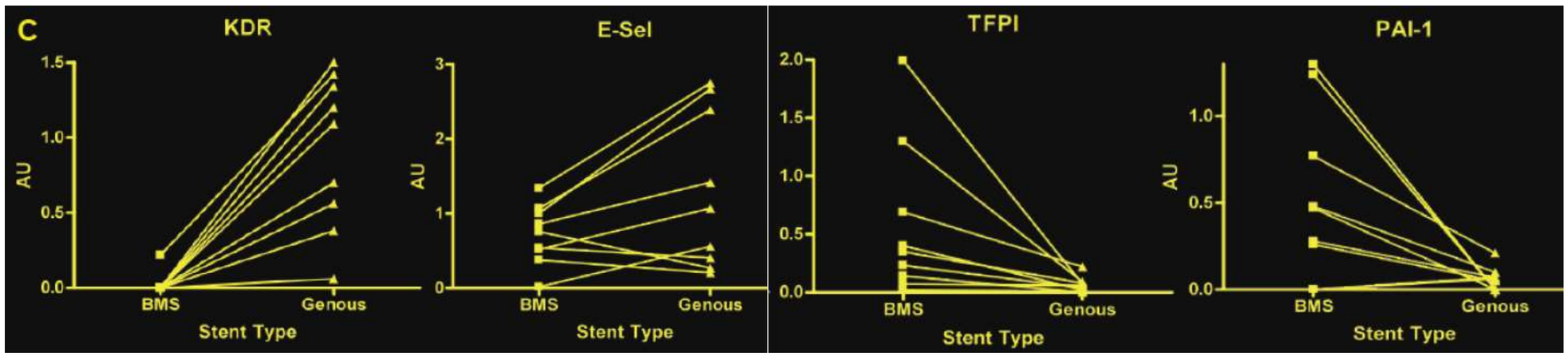
Padfield GJ, et al. J Am Coll Cardiol 55, 15, 2010, 1553 1565

Human AV Shunt (SEM and Molecular Analysis)



Human AV Shunt (Molecular Analysis)



Endothelial Genes

Thrombogenic Genes

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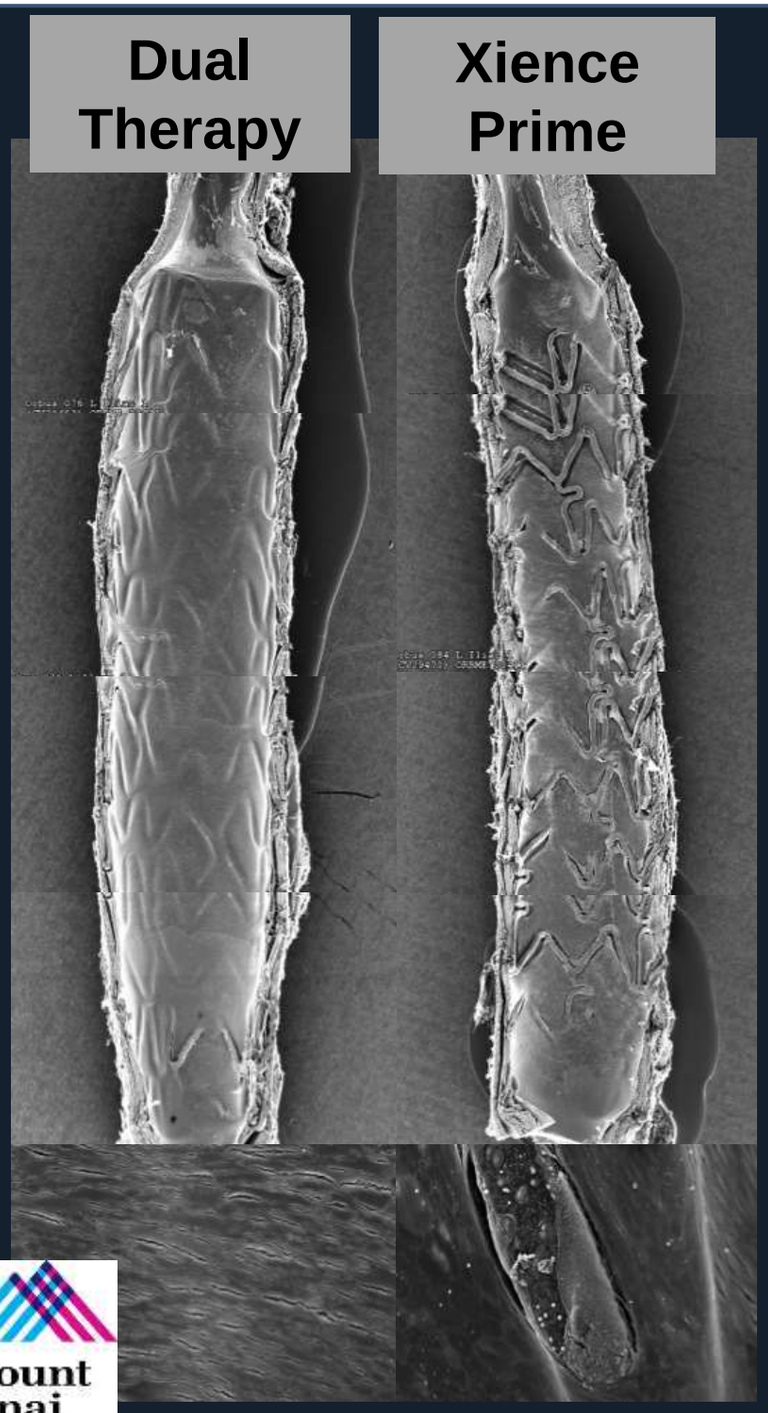
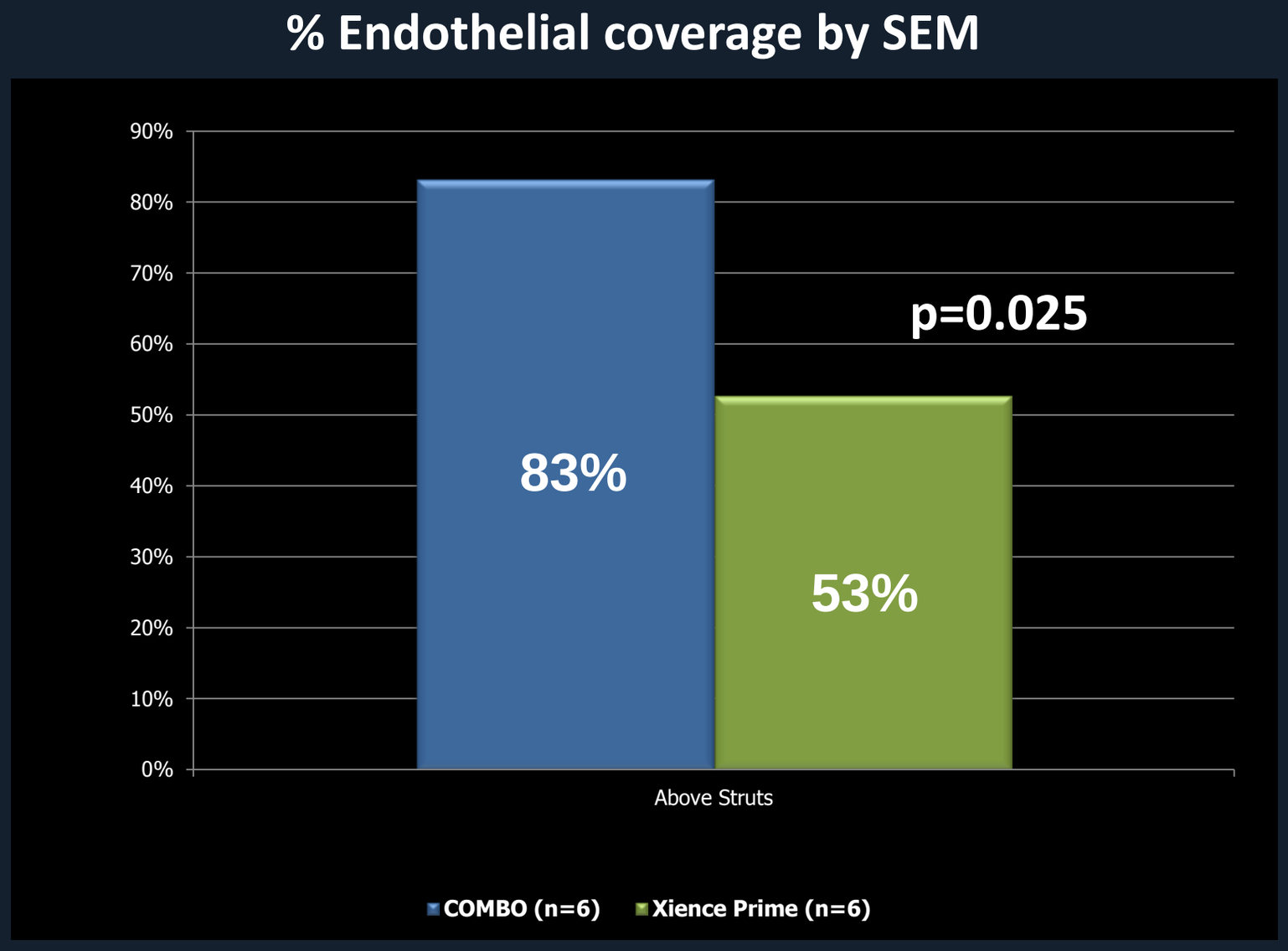
EPC capture enhances endothelialization and less stent thrombosis

Larsen K et al. Eur Heart J 2012; 33 (1): 120-8. PMID: 21733913 DOI: 10.1093/eurheartj/ehr196

SEM at 28 days in an Atherosclerotic Rabbit Model





Values are expressed as median (interquartile range)

M. Joner, EuroPCR 2014

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Clinical Results:
EGO COMBO Trial

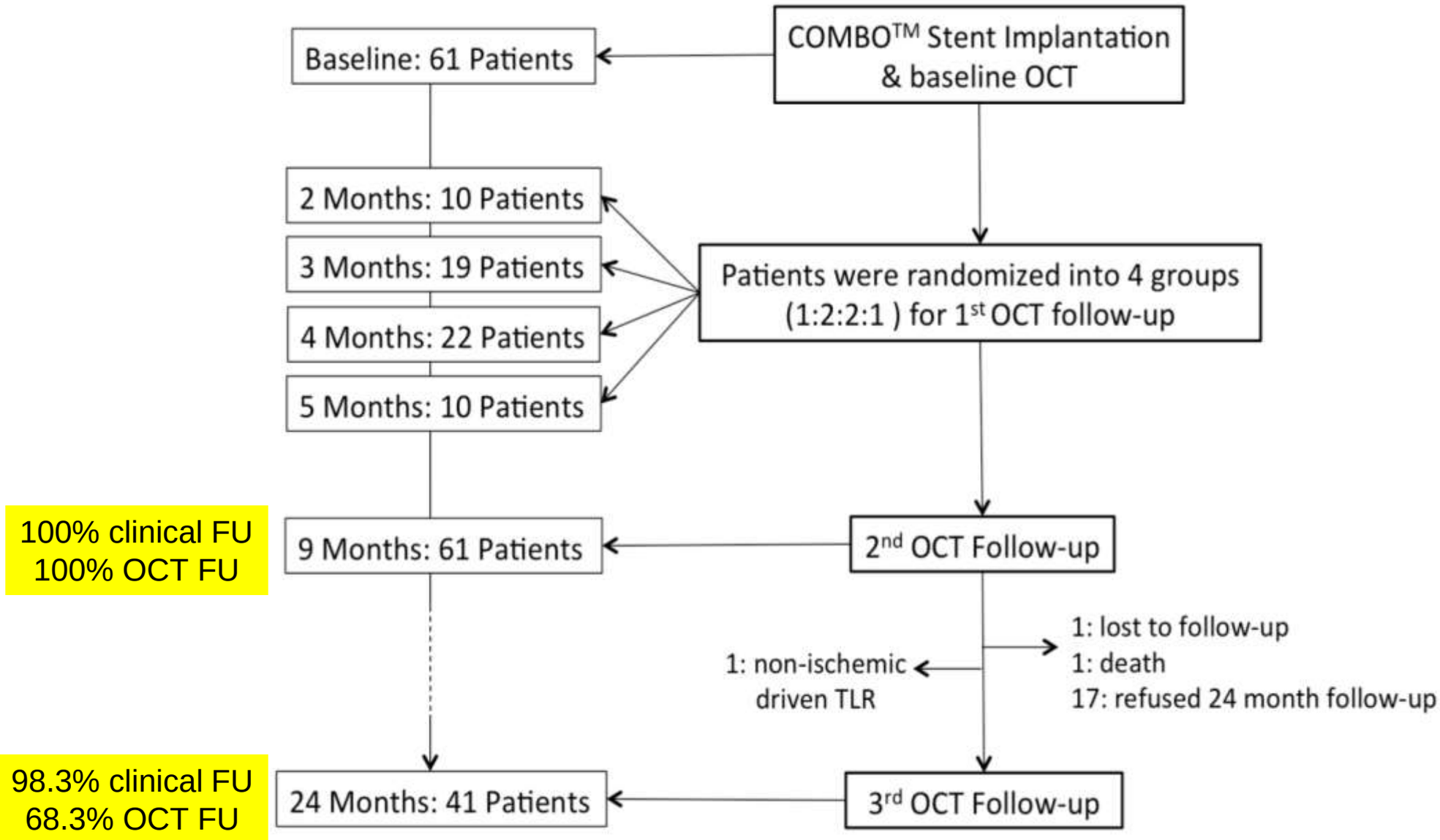
Objective:

- To monitor stent healing with the COMBO Dual Therapy Stent
  - Short term (2-5 months)
  - Long term (9-24 months)
  - Highest resolution equipment available in the clinic: OCT
    - Progression of strut coverage
    - Morphology of the neointima

S Lee, TCT 2014

EGO COMBO Trial Study Design

Patient randomization and OCT follow-up



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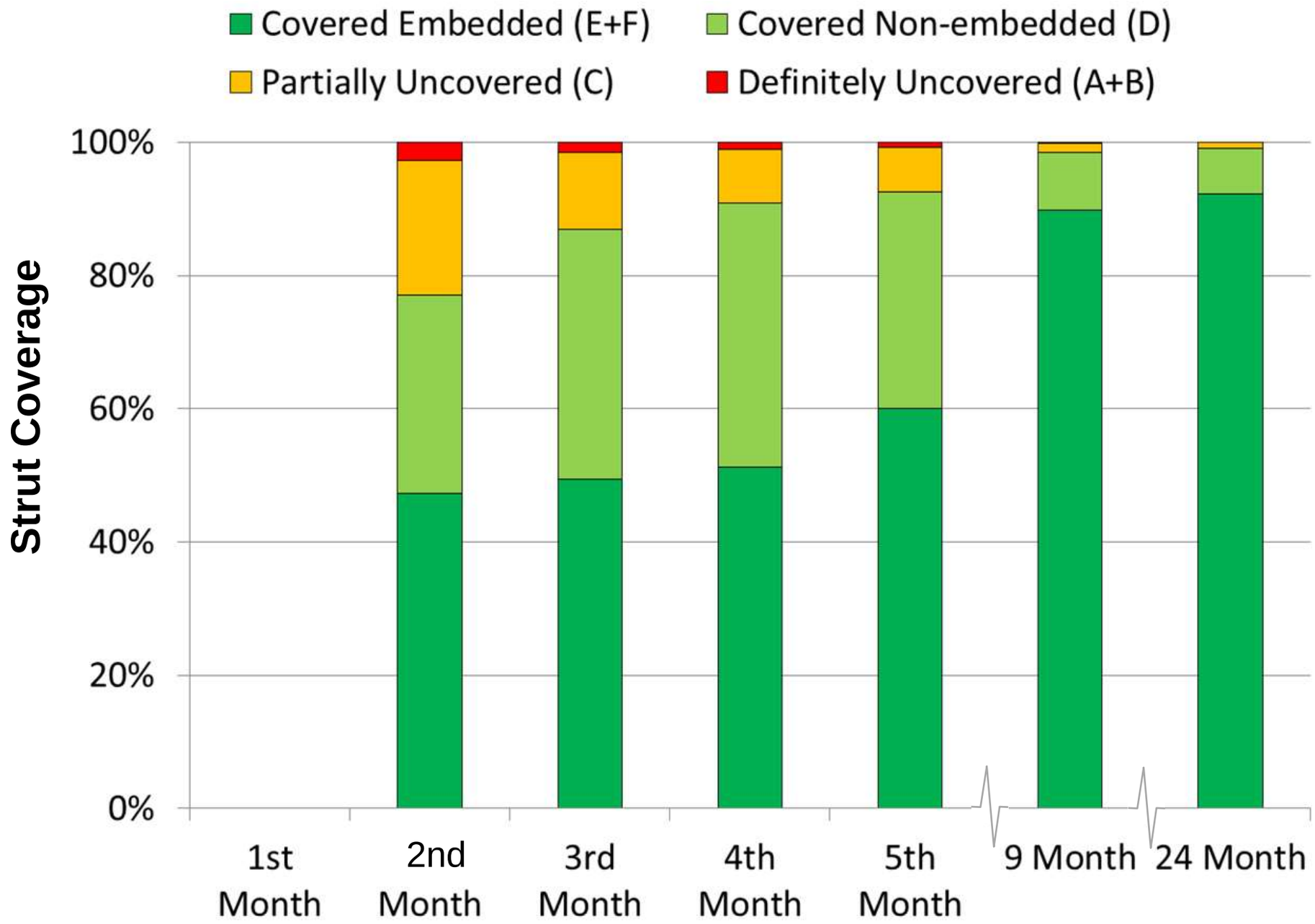
EGO COMBO*

progression of strut coverage with the Combo stent



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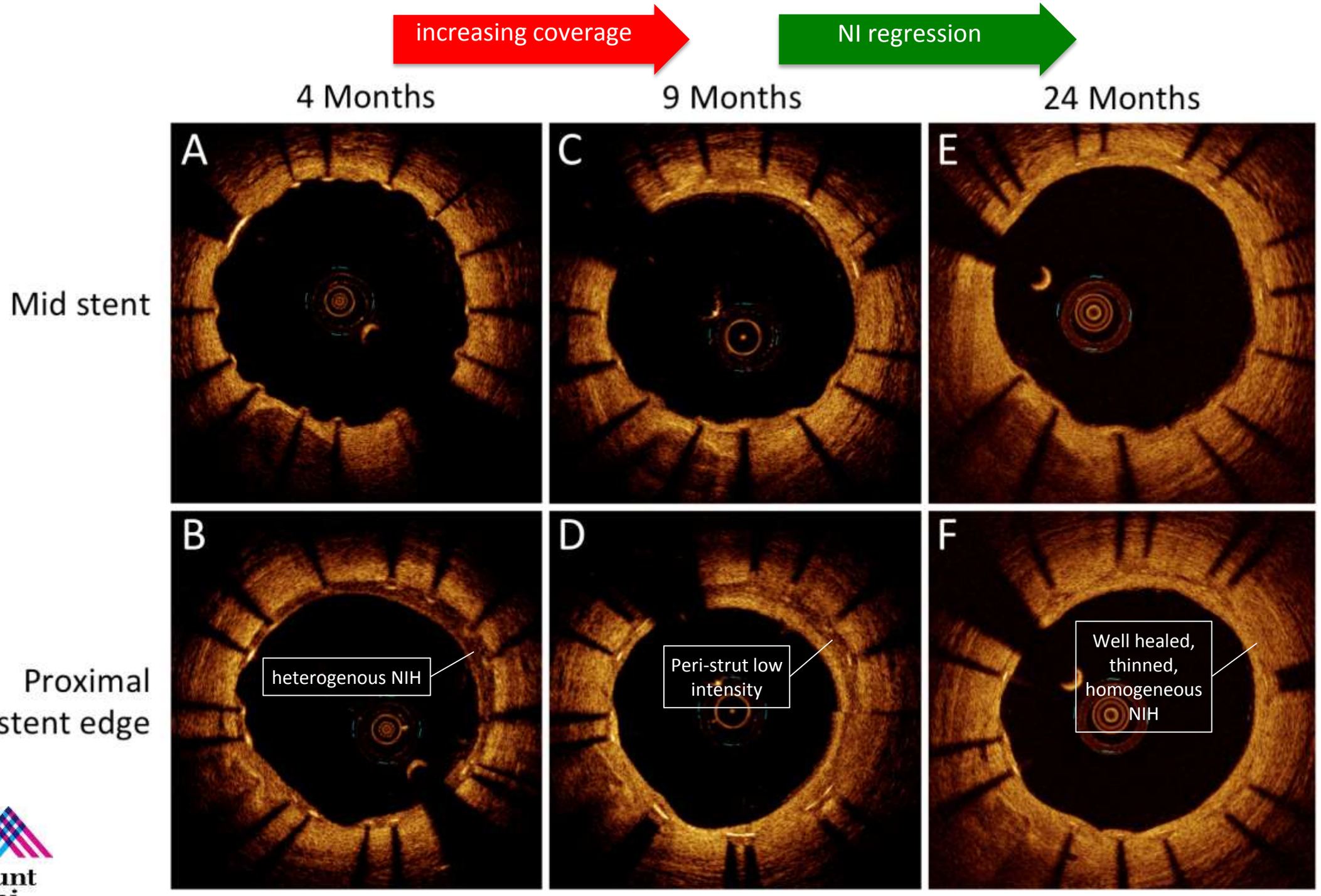
EGO-COMBO

corresponding OCT slices 4 => 9 => 24 months



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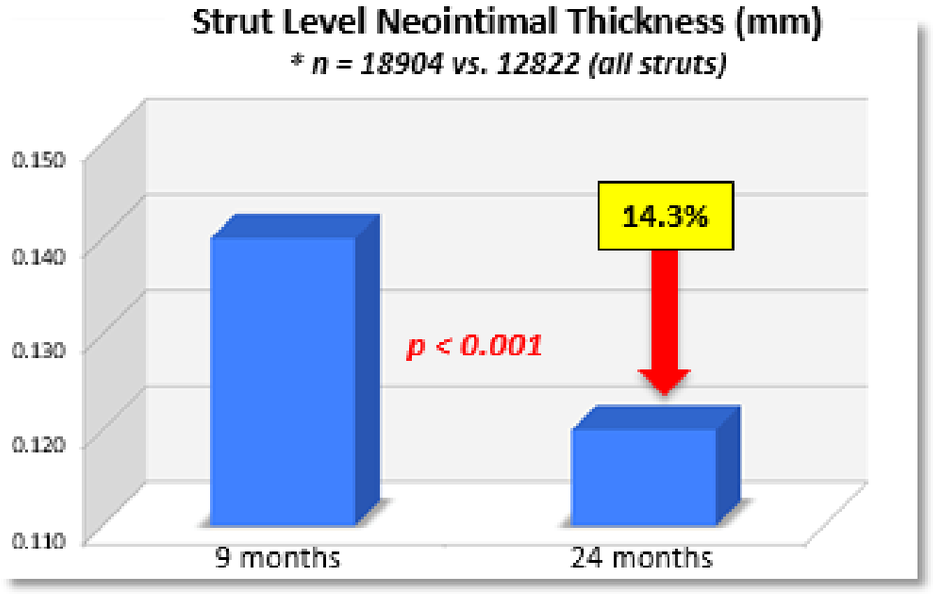
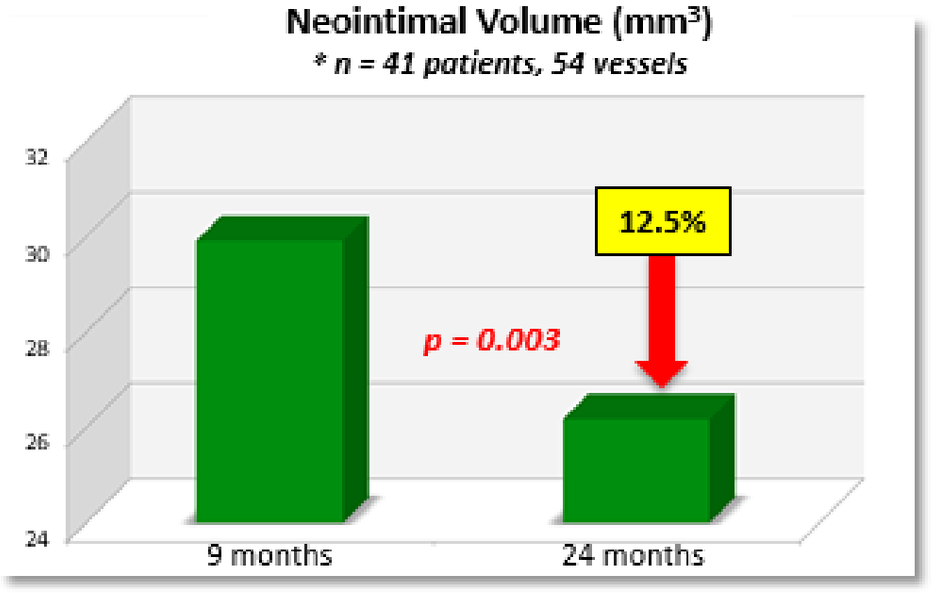
OCT documented neo-intimal regression 9 => 24 month





Increased Lumen Area and decreased Neointimal Area from 9 to 24 months

- Results are consistent with NI maturation and organization
- No neoatherosclerosis

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S Lee, TCT 2014

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EGO-COMBO

Angiographic Results @ 9 months & Clinical Outcomes

QCA: Quantitative Measurements at 9 months (n = 61)		
Category	**Statistic**	**9 Months FU**
Lesions	N	74
Stented Lesion Length (mm)	Mean ± Std.Dev	23.84±7.53
	Median [IQR]	22.92 [18.01,23.06]
In-stent MLD (mm)	Mean ± Std.Dev	2.66±0.43
	Median [IQR]	2.77 [2.36,2.94]
In-Segment (Stent+Edge) DS % - interpolated	Mean ± Std.Dev	16.04±10.13
	Median [IQR]	15.19 [8.27,21.02]
In-Segment (Stent+Edge) Late Lumen Loss (mm)	Mean ± Std.Dev	0.09±0.36
	Median [IQR]	0.10 [-0.09,0.29]
In-stent percent diameter stenosis (%DS) – interpolated RVD	Mean ± Std.Dev	10.93±9.86
	Median [IQR]	8.23 [4.08,16.27]
In-stent Late lumen Loss (mm)	Mean ± Std.Dev	0.23±0.36
	Median [IQR]	0.24 [0.08,0.40]

Clinical Outcome	9 Months FU	3 Years FU
TLR / TVF	1/61 (1.64%)	1/61 (1.64%)
Cardiac Death*	0.0%	1/61 (1.64%)
Stent thrombosis	0.0%	0.0%

* elderly patient died at 22 months from VF after many days of recurrent chest pain without seeking treatment.

Note: Results adjudicated by an independent Core Lab (CRF, New York)

No ST and 1.6% TLR out to 3 years

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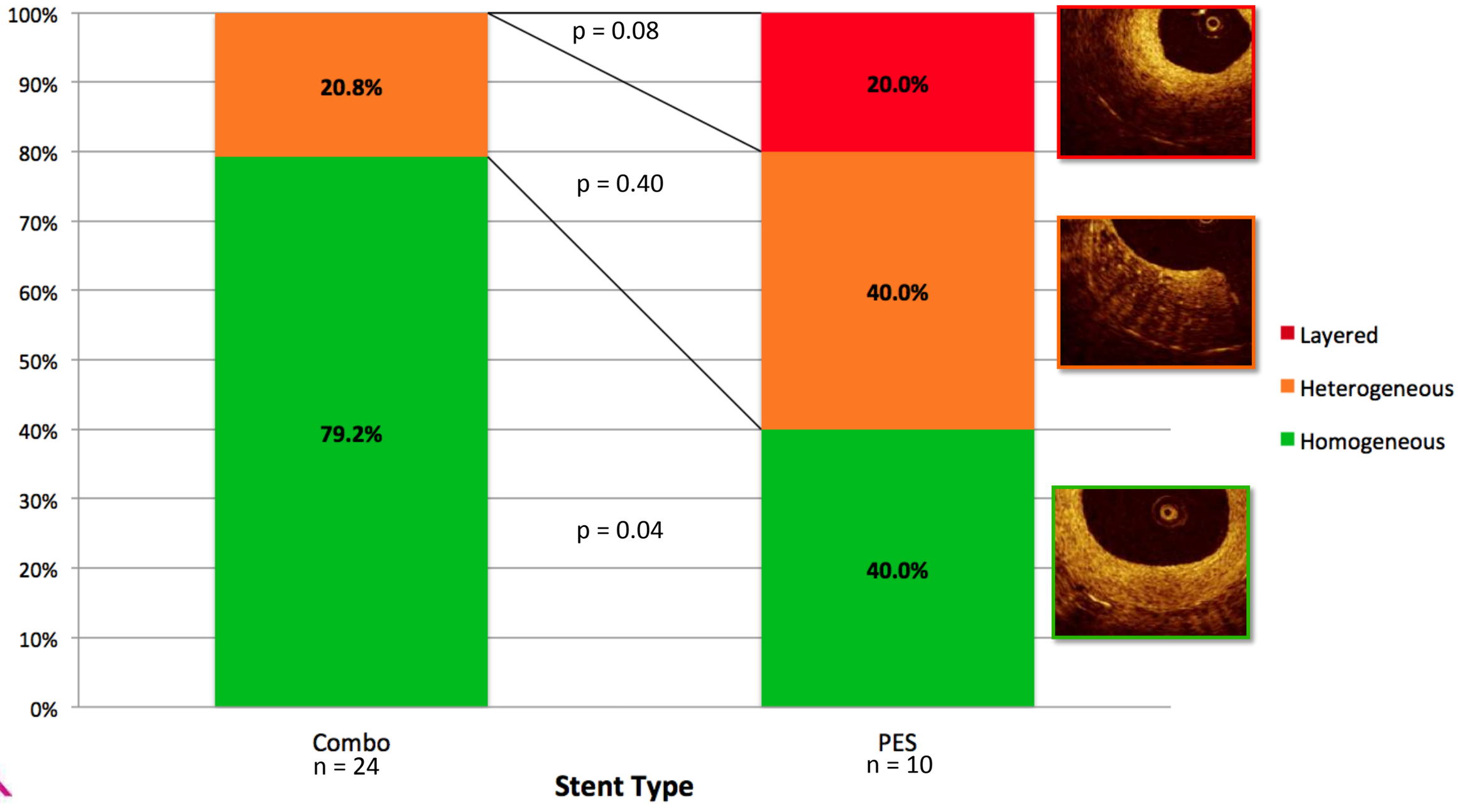
S Lee, TCT 2014

NI Tissue Characterization (OCT)

REMEDEE (9 month FU)

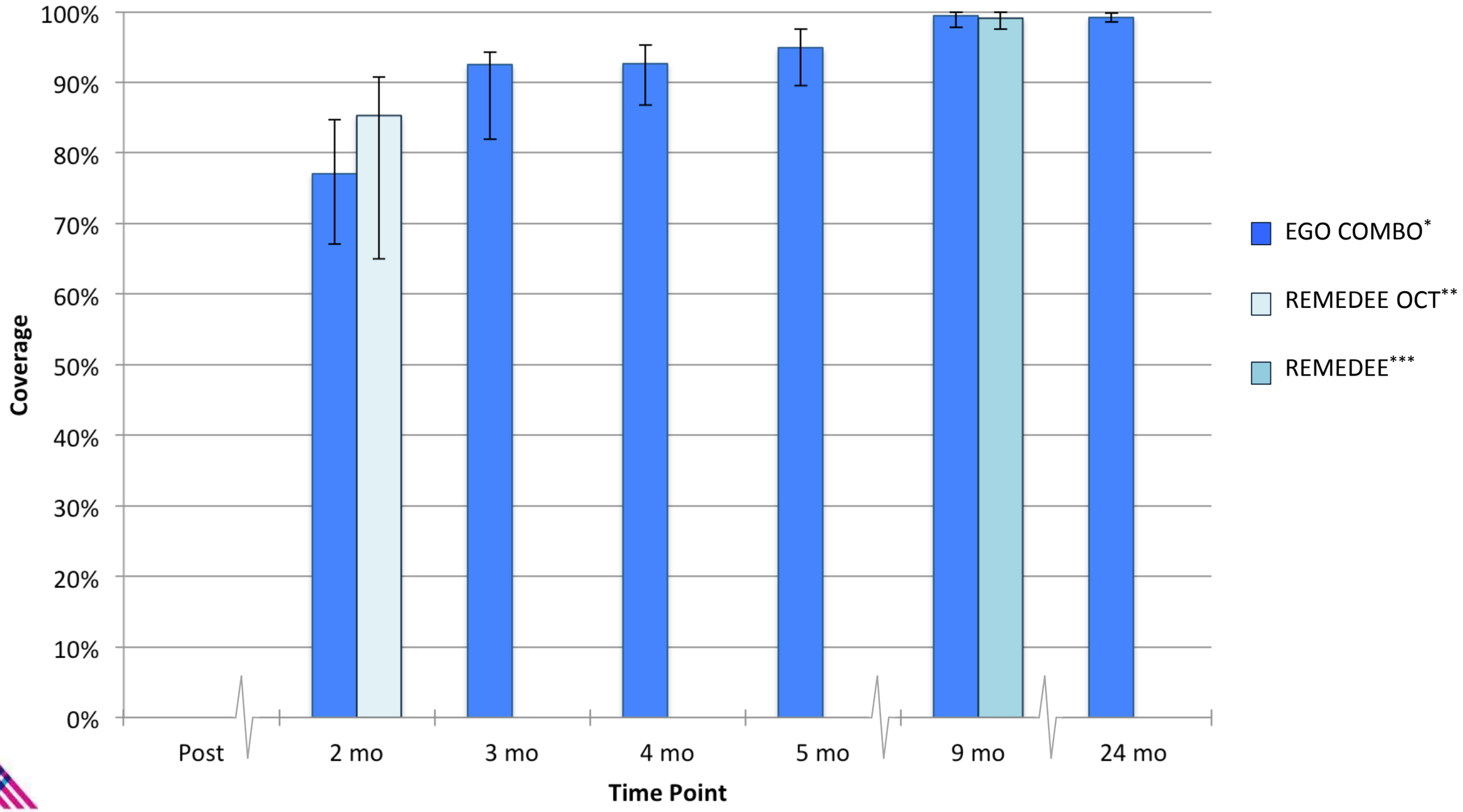


Mount Sinai Heart

M Haude M, EuroPCR 2014

COMBO Strut Coverage % (OCT)

Median & IQR (per patient)

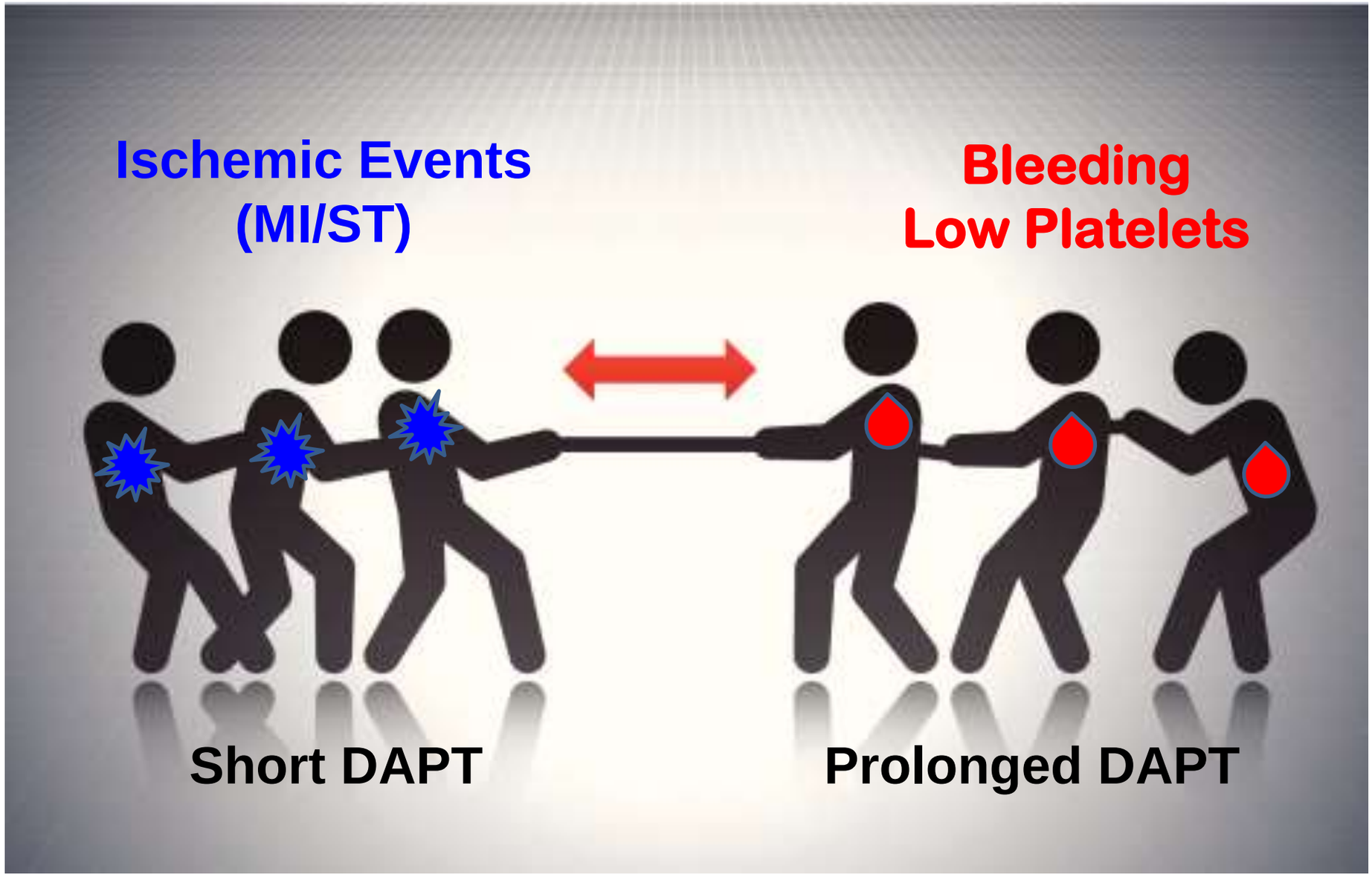


Mount Sinai Heart

* S. Lee, TCTAP 2014
** U. Landmesser, TCT 2012
*** M. Haude, EuroPCR 2012

Are there any other factors of consideration?

1. DAPT: Shorter the better or longer the better?



2. Are we treating the patient or the stent?

Both received a contemporary DES…

Should they be prescribed with the same duration of DAPT?

Mount Sinai Heart

There is no one standard DAPT regimen for all

- **Stable Coronary Artery Disease (SCAD)**
- **STEMI undergoing primary PCI**
- **NSTE-ACS**
- **Pre-surgery PCI**
- **PCI in conjunction with oral anticoagulation**

DAPT After Stenting

Bleeding risk…*per se*….the <u>third</u> DAPT driver

Stable CAD

DAPT for at least 1 month after BMS — **IA**
DAPT for 12 Months after DES (6 months ESC) — **IB**
Shorter DAPT duration (< 6 mos) may be considered after DES in patients at high bleeding risk — **IIa C**

ISAR
SARS
PRODIGY

PRODIGY
EXCELLENT
Meta-analysis

RESET
OPTIMIZE

NSTEMI

DAPT for 12 mos **<u>unless excessive bleeding risk</u>** — **IB/C**

PLATO
TRITON
PCI CURE

STEMI

DAPT for 12 mos **<u>unless excessive bleeding risk</u>** — **IB**

PLATO
TRITON
CURRENT
OASIS 7

Conclusion and Take Home Messages

- DES are associated with delayed healing and require DAPT to prevent stent thrombosis

- Appropriate DAPT duration must be tailored to patient risks as well as stent properties

- Dual Therapy Stent combines Sirolimus and EPC capture for control of neointimal proliferation and promotion of endothelial healing, potentially allowing for less dependence on prolonged DAPT