EMORY UNIVERSITY SCHOOL OF MEDICINE

Vascular Biology of Stent Restenosis

European Bifurcation Club 2017
Porto, Portugal
October 14th, 2017

Habib Samady MD
Professor of Medicine
Director, Interventional Cardiology, Emory University
Director, Cardiac Catheterization Laboratory Emory University Hospital

EMORY UNIVERSITY SCHOOL OF MEDICINE

Disclosures

EPIC-SEC

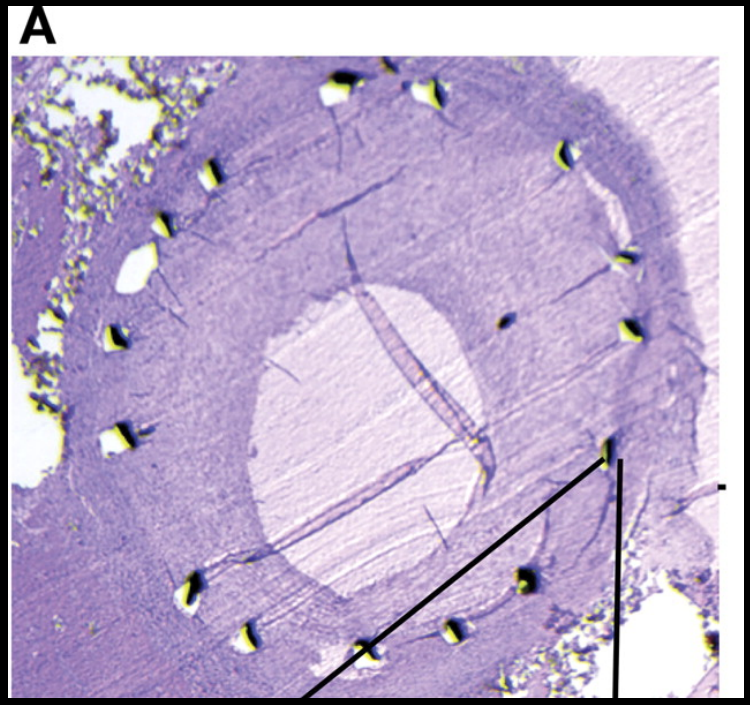
- **Medtronic:** PI SHEAR STENT Trial
- **Abbott Vascular:** PI Restoration Study (Subanalysis of ABSORB III Img.)
- **Gilead:** PI MARINA Trial
- **Volcano Therapeutics:** Research Grants
  Steering Comm ADVISE II and Define PCI
- **St. Jude Medical:** Research Grants
- **American Heart Association:** Mentor Fellowship Awards
- **National Institute of Health:** Co-I NIH ROI/PPG
- **American College of Cardiology:** Deputy Editor, JACC Interventions

Restenosis: POBA to Stent

Mechanisms of POBA Restenosis

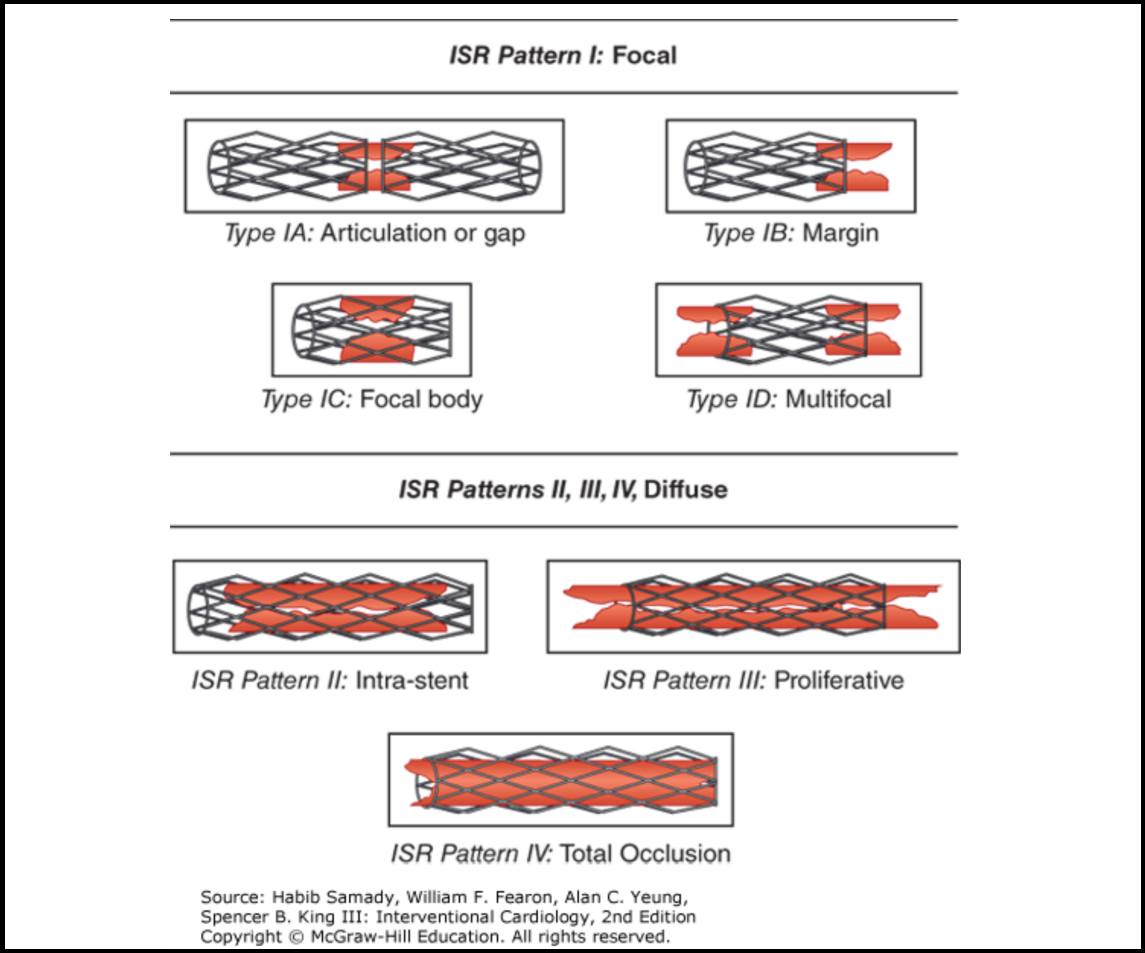
Acute Recoil
Dissection
Constrictive Remodeling

BMS: 20-50% ISR



Clinical Patterns of ISR:

R Mehran et al.

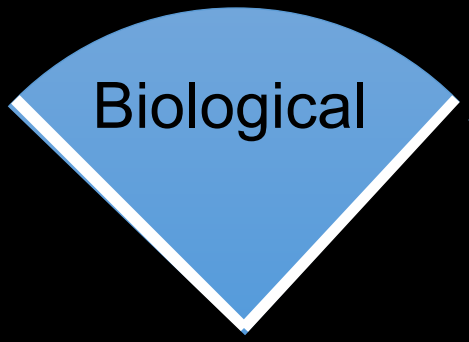


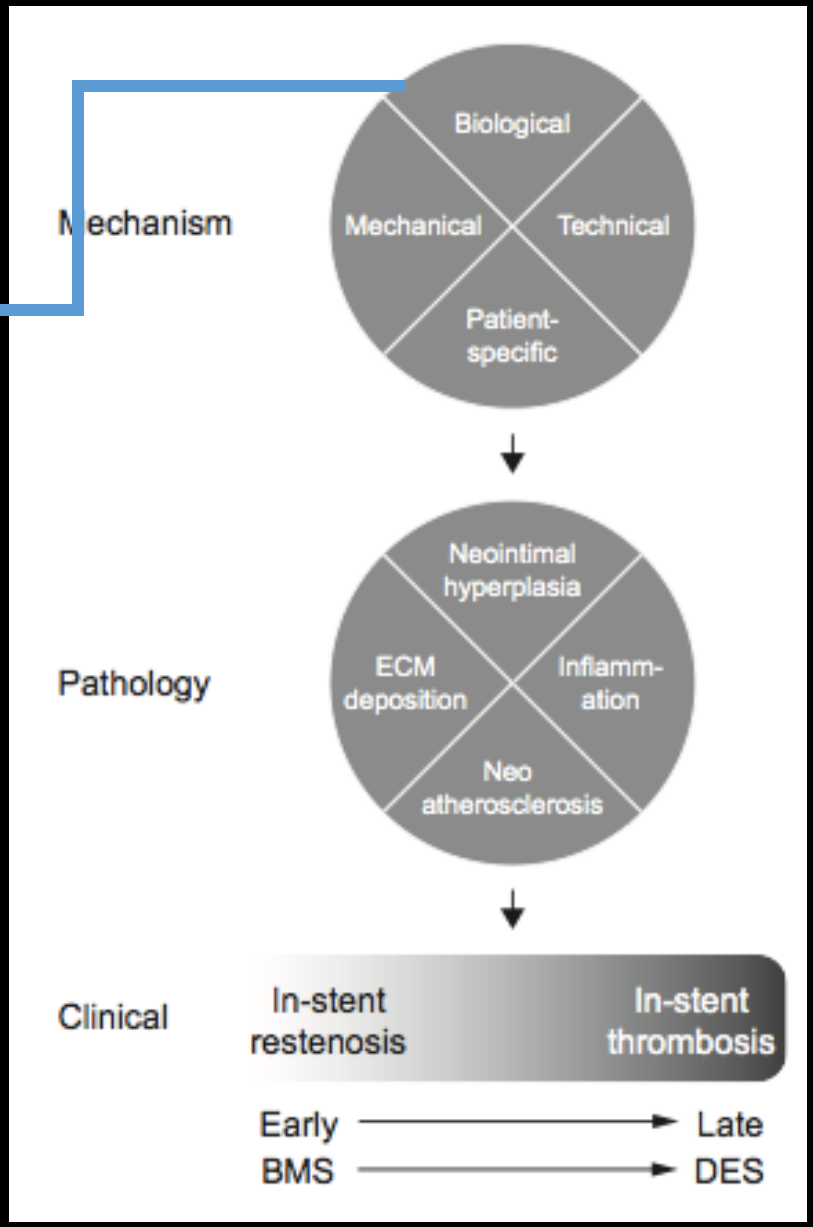
Source: Habib Samady, William F. Fearon, Alan C. Yeung, Spencer B. King III: Interventional Cardiology, 2nd Edition

Source: In-Stent Restenosis, *Interventional Cardiology, 2e*

Citation: Samady H, Fearon WF, Yeung AC, King III SB. *Interventional Cardiology, 2e*; 2017 Available at: http://accesscardiology.mhmedical.com/content.aspx?bookid=1986&sectionid=165115695 Accessed: October 14, 2017

Mechanisms and Pathology of ISR





Vascular Injury
Non-uniform drug delivery

Nakamura et al. Intervent Cardiol Clin 5 (2016) 391–403

Four Components of Arterial Injury After Stenting

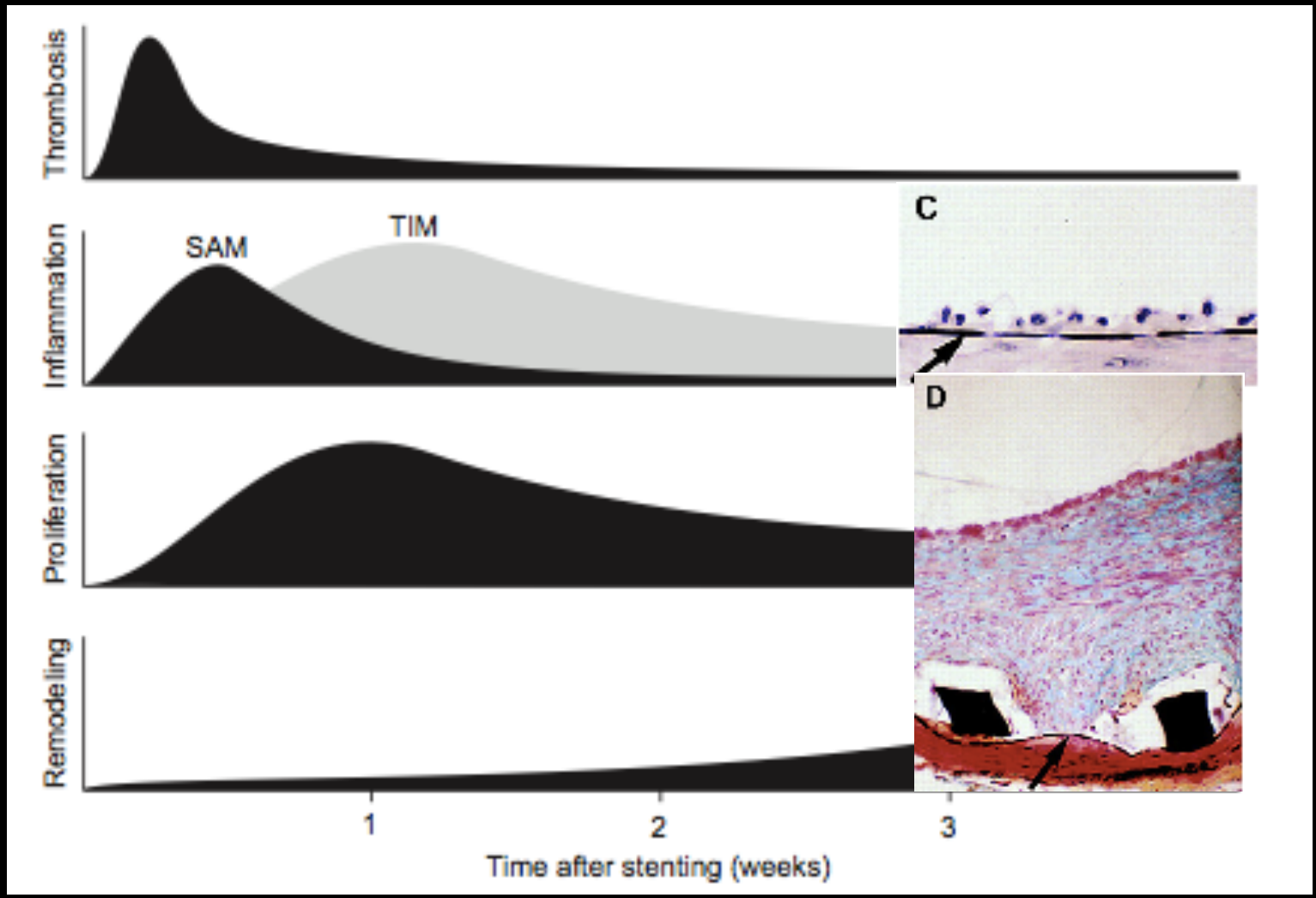
Platelet Rich Thrombosis

Surface adherent Monocytes

Tissue infiltrating monocytes

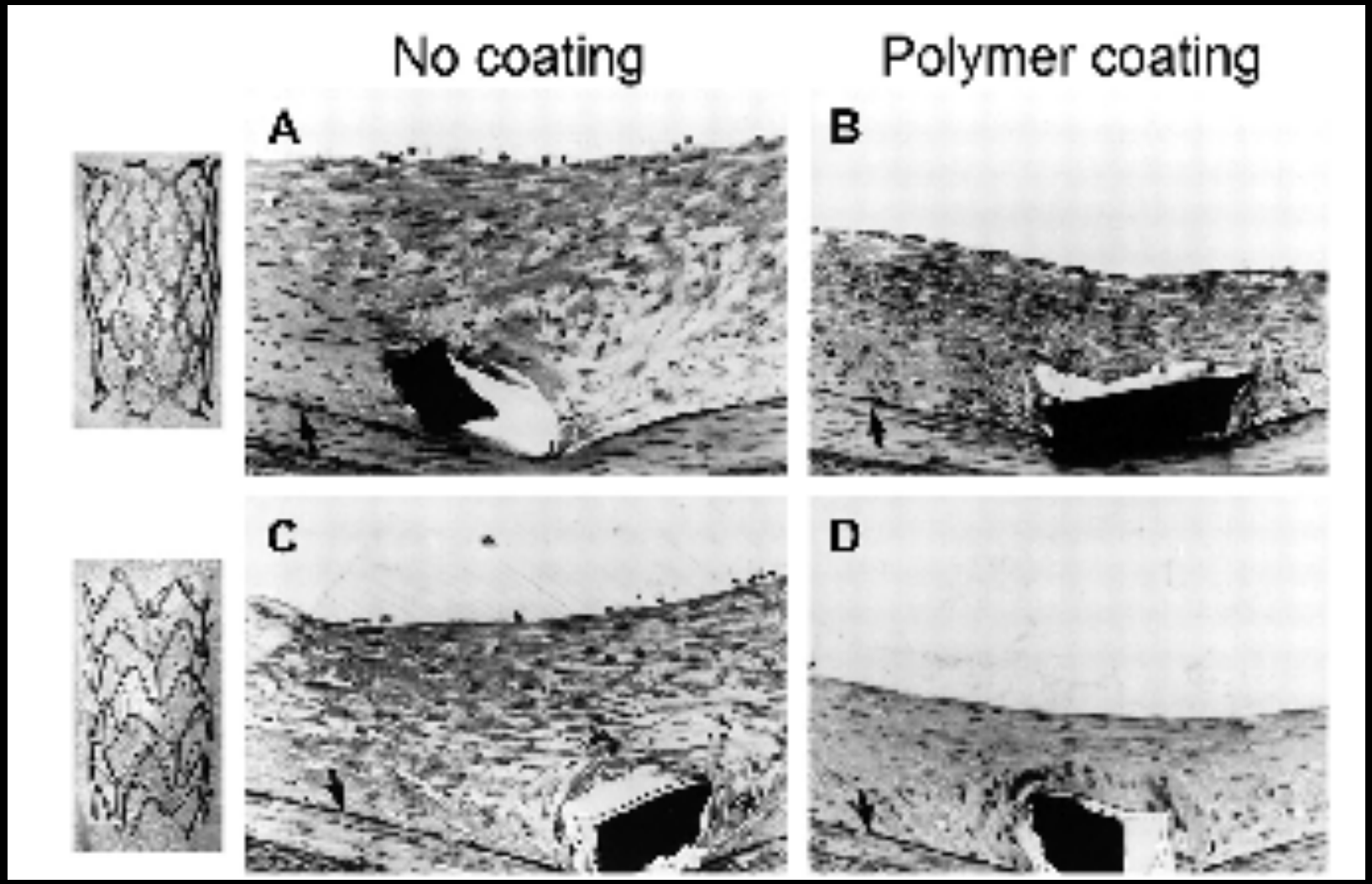
Smooth muscle cell

Extracellular matrix Deposition in adventitia, media and neointima



Edelman et al. AJC 1998:81(7A)

Polymer Coating Suppresses Neointimal Hyperplasia

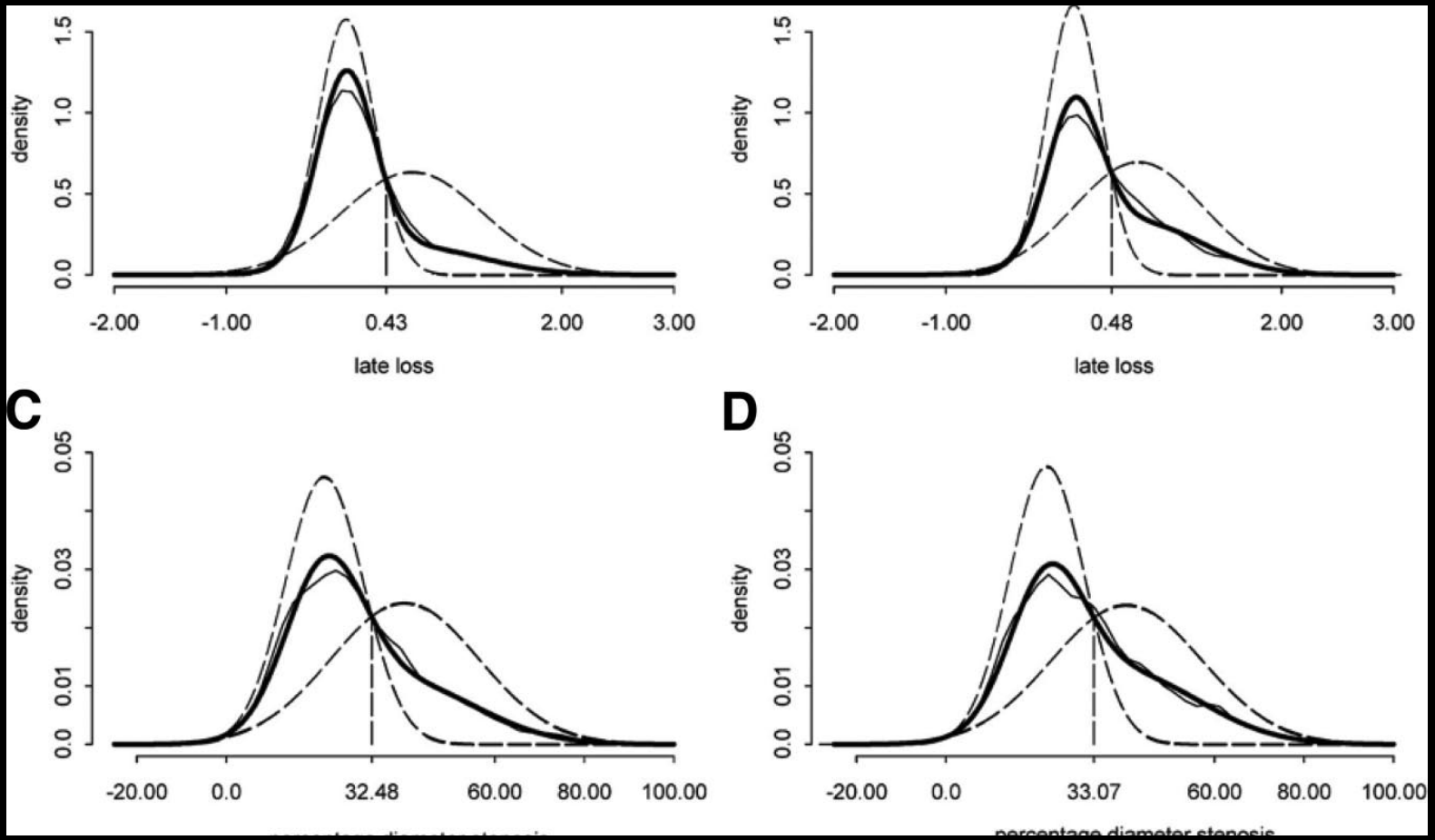


Rogers, C et al. Circulation 1995;91(12):2996 and 2999

Drug Patterns of Neointimal Suppression

Cypher

Taxus



Byrne et al. Heart. 2009;95:1572–1578.

Histology of Neointima: EES vs ZES

Rabbit IliacsModel

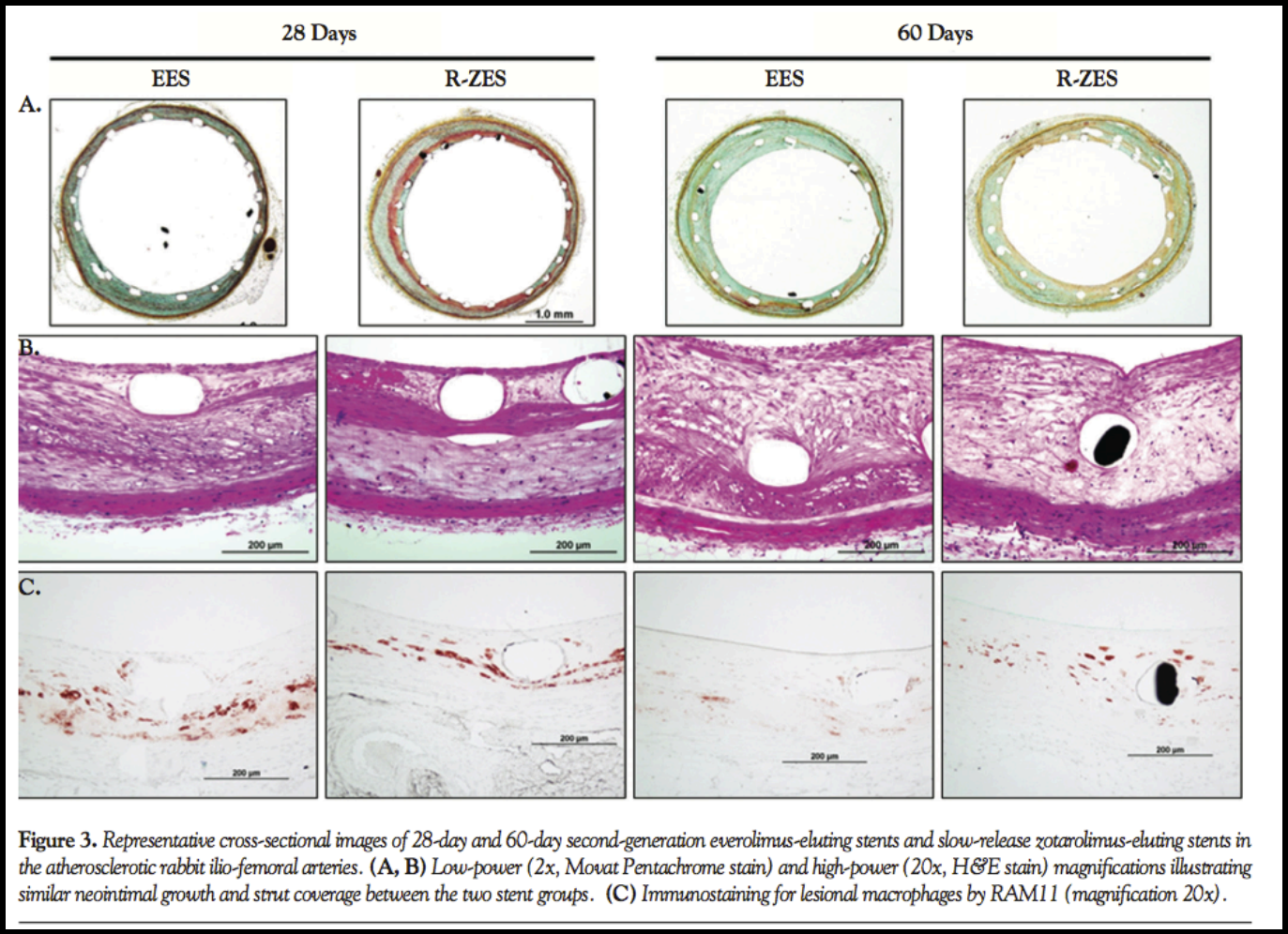
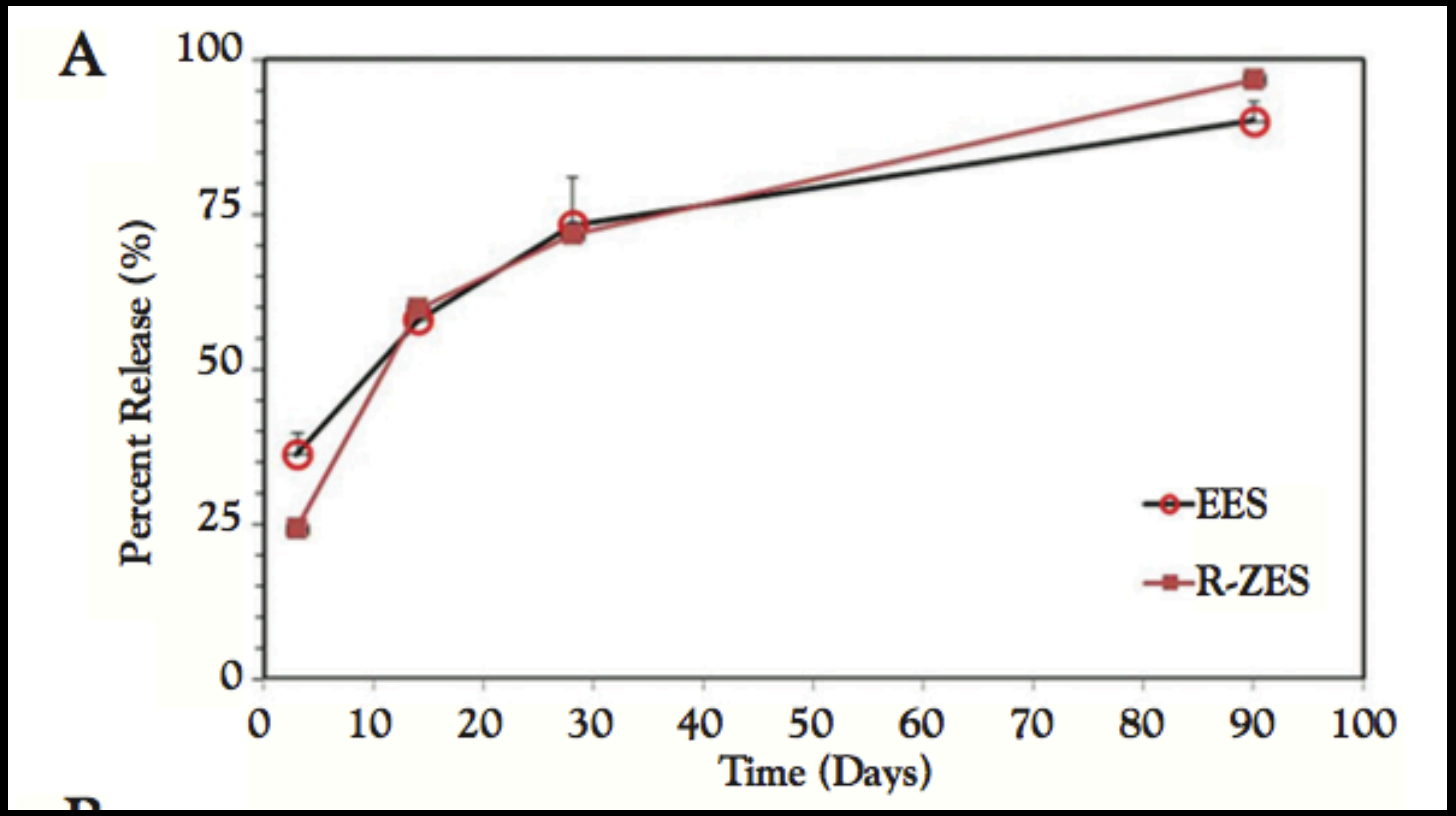


Figure 3. *Representative cross-sectional images of 28-day and 60-day second-generation everolimus-eluting stents and slow-release zotarolimus-eluting stents in the atherosclerotic rabbit ilio-femoral arteries.* **(A, B)** *Low-power (2x, Movat Pentachrome stain) and high-power (20x, H&E stain) magnifications illustrating similar neointimal growth and strut coverage between the two stent groups.* **(C)** *Immunostaining for lesional macrophages by RAM11 (magnification 20x).*

Yazdani, Virmani. JIC 2013

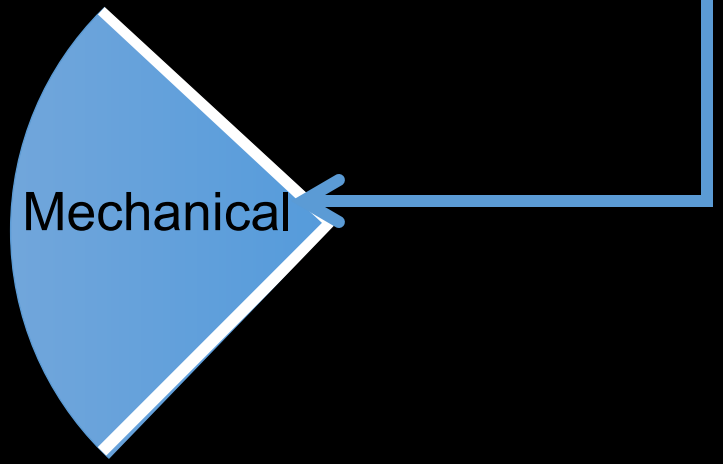
Timing of Drug Release: EES vs ZES

Rabbit Iliacs

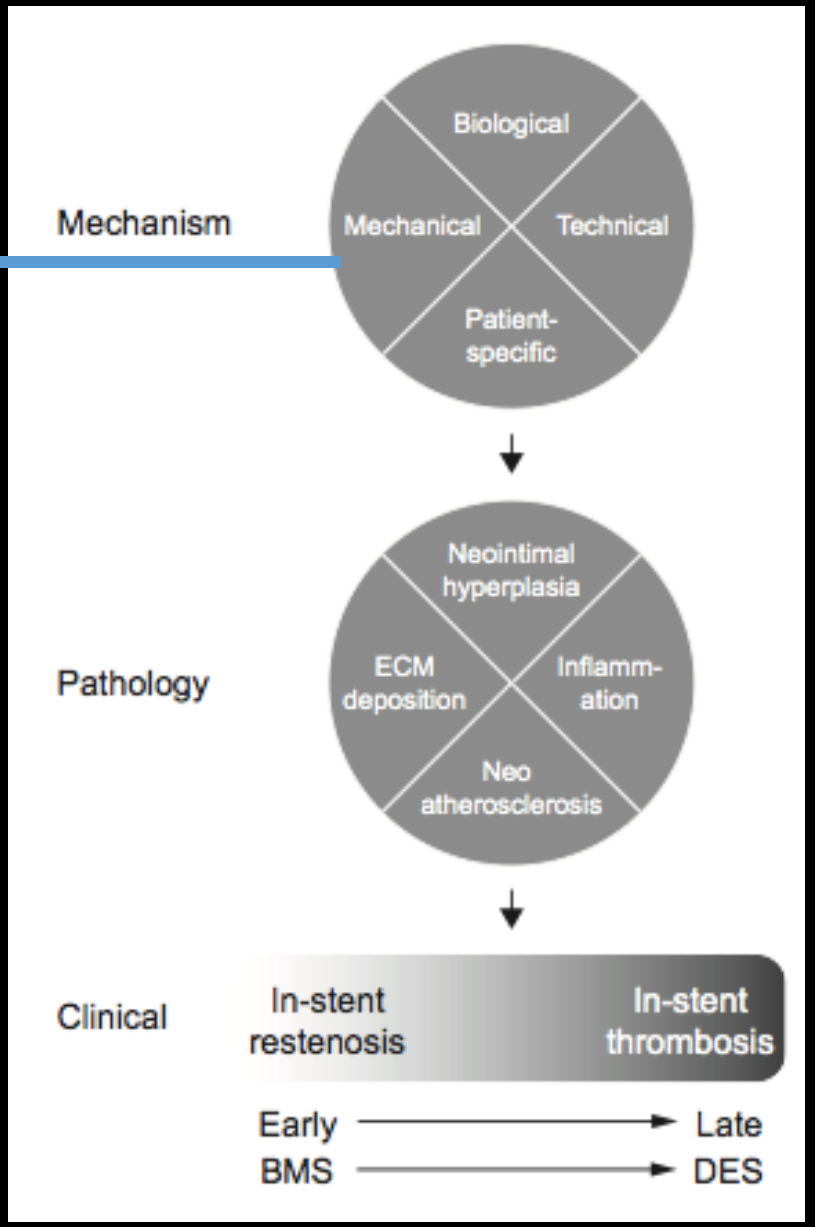


Yazdani, Virmani. JIC 2013

Mechanisms and Pathology of ISR



Vessel size and length
Hemodynamics

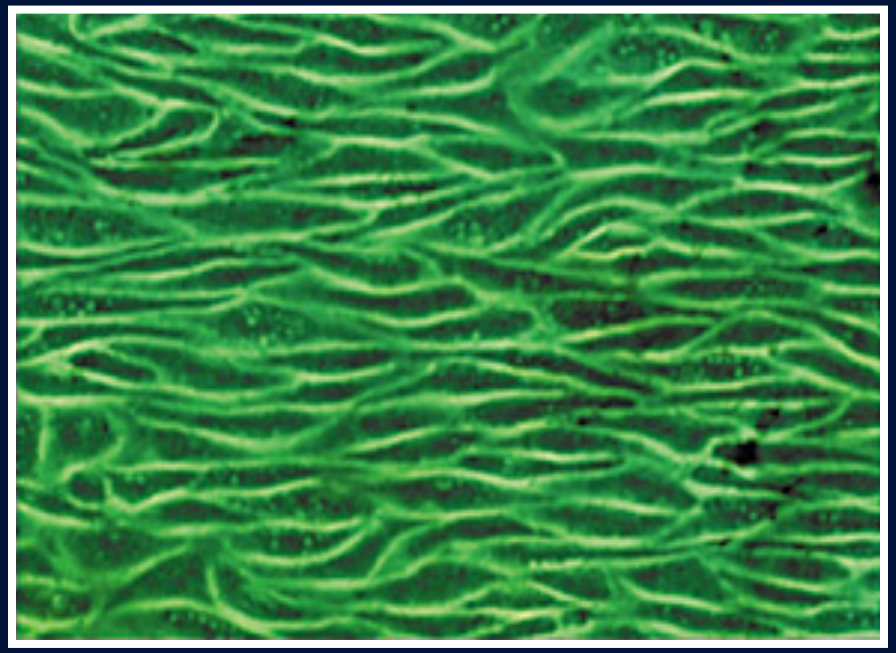


Nakamura et al. Intervent Cardiol Clin 5 (2016) 391–403

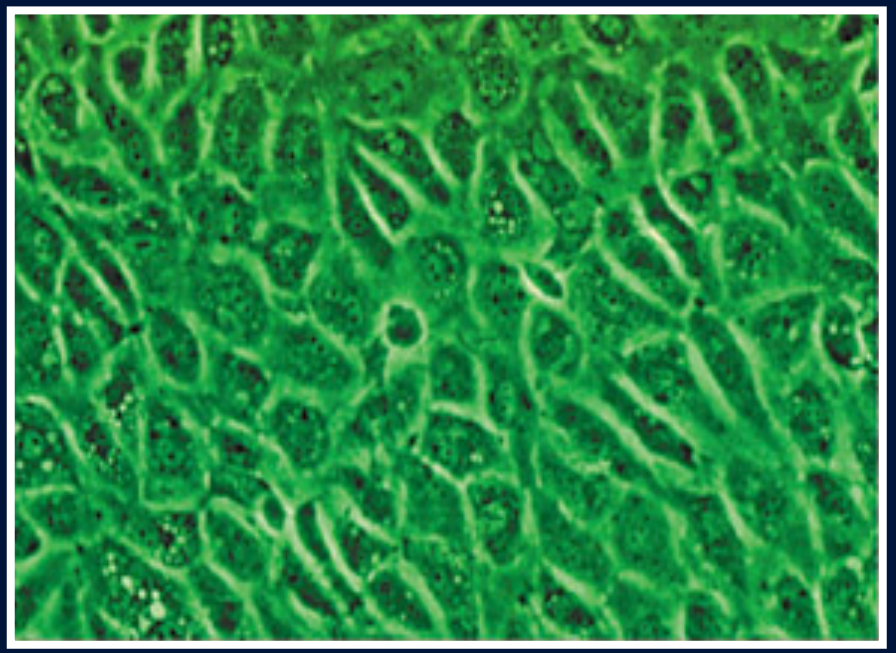
Transformation of Endothelial Cell Morphology by Fluid Shear Stress

Bovine aortic endothelial cells.

Physiologic Arterial Hemodynamic Shear Stress (>15 dynes/cm^2)

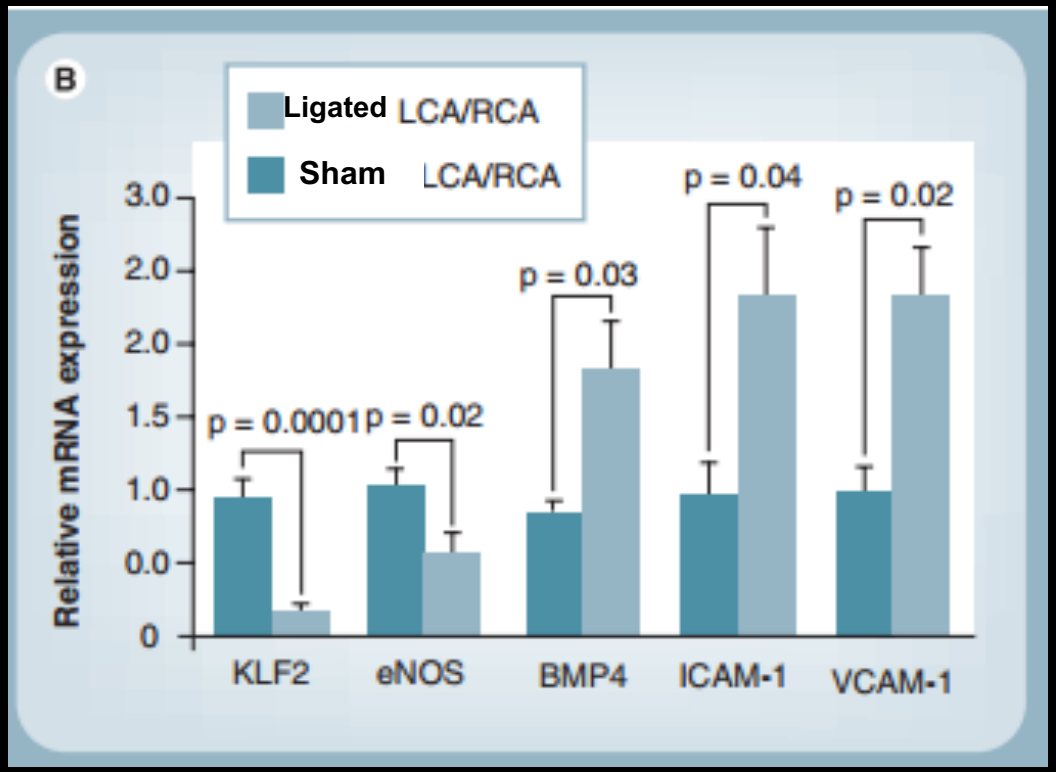


Low Arterial Hemodynamic Shear Stress (0-4 dynes/cm^2)



Molecular Association of low WSS with Plaque Progression

- ApoE-knockout mice
- Partial carotid ligation model
- Intimal RNA in zones of low WSS developed:
  - Upregulation of proatherogenic genes (eg. VCAM-1 and ICAM-1 expression)
  - Downregulation of antiatherogenic genes (e.g., those governing eNOS and KLF-2 expression
- Low WSS regions exhibited endothelial dysfunction and developed rapidly progressive atherosclerosis to advanced lesions within 4weeks



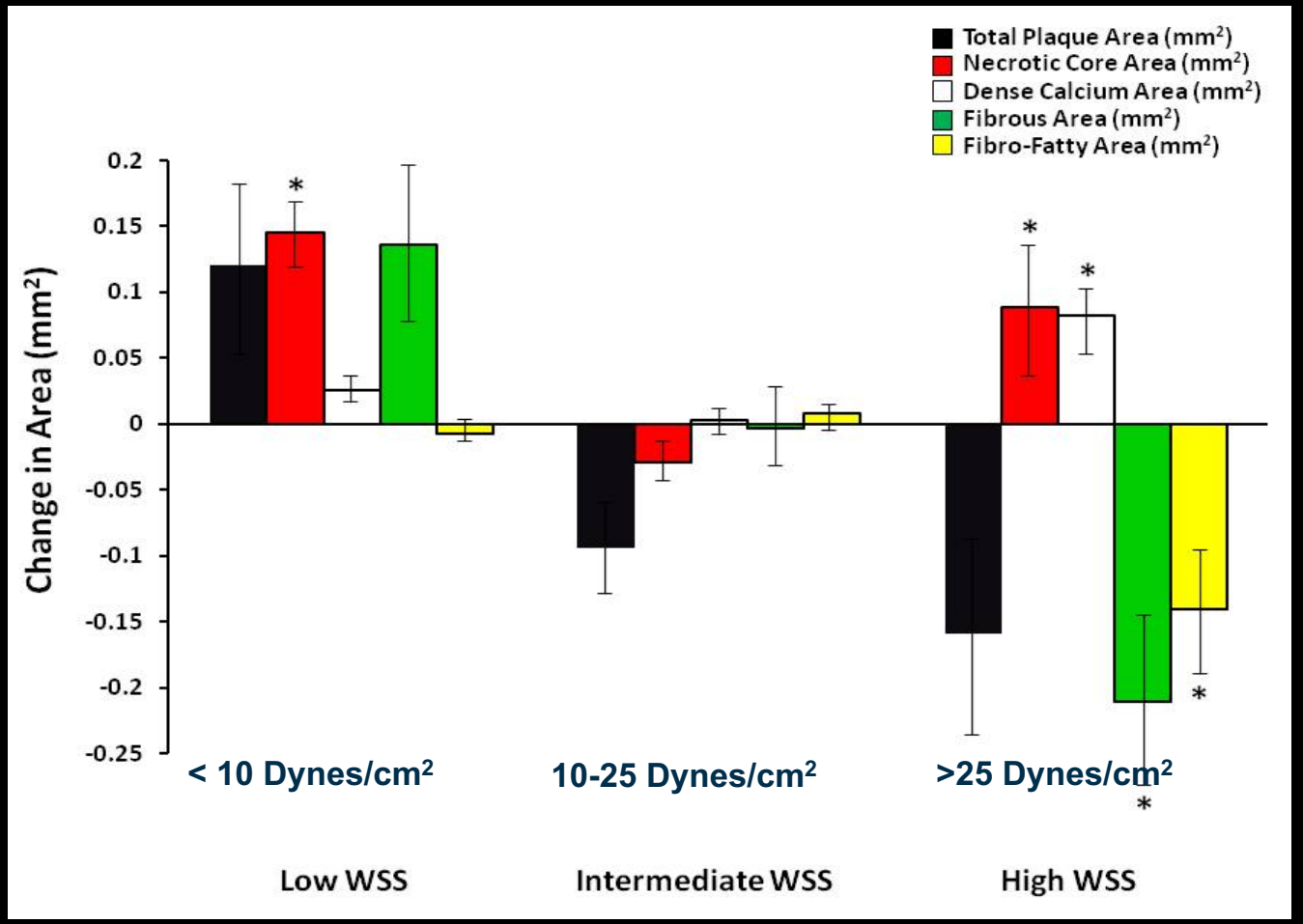
Nam D, Am. J. Physiol. Heart Circ. Physiol. 2009; 297, H1535–H1543.

High WSS and Plaque Progression

Change in Plaque Composition in Low, Intermediate, and High WSS Segments

Patients with Moderate/Non-Obstructive CAD

N=20
6 months f/u
High Dose Statin Tx



Circulation. 2011 Aug 16;124(7):779-88.

In-Stent Neoatherosclerosis

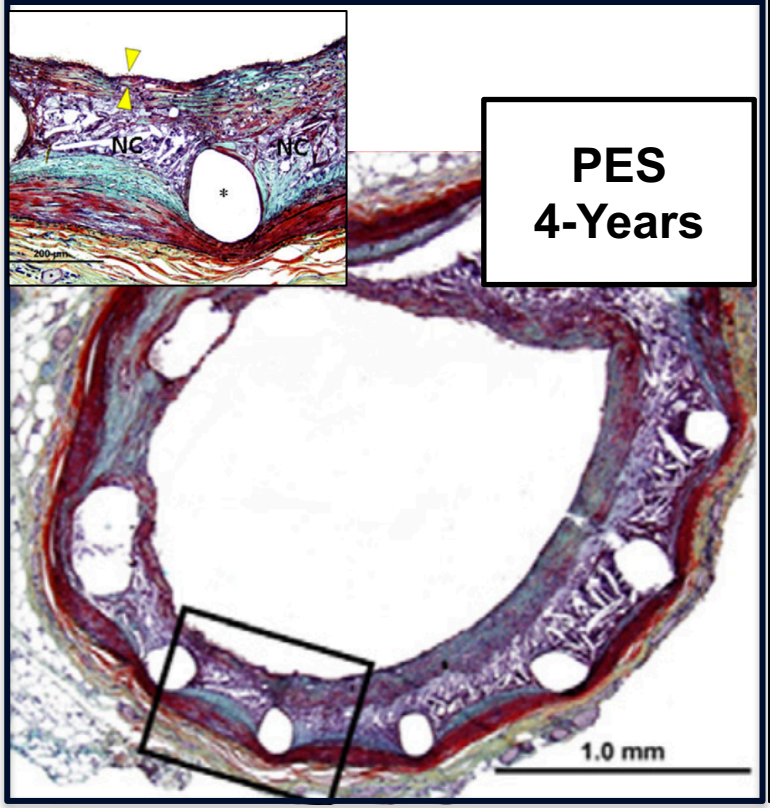
A Final Common Pathway of Late Stent Failure

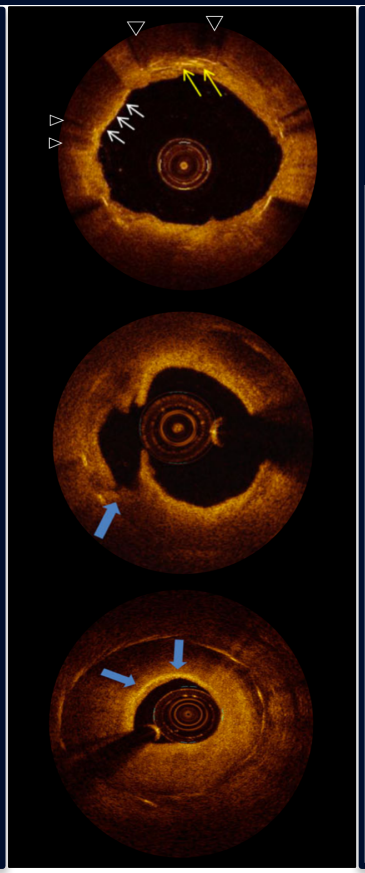
Seung-Jung Park, MD, PhD,* Soo-Jin Kang, MD, PhD,* Renu Virmani, MD,†
Masataka Nakano, MD,† Yasunori Ueda, MD‡

Seoul, South Korea; Gaithersburg, Maryland; and Osaka, Japan

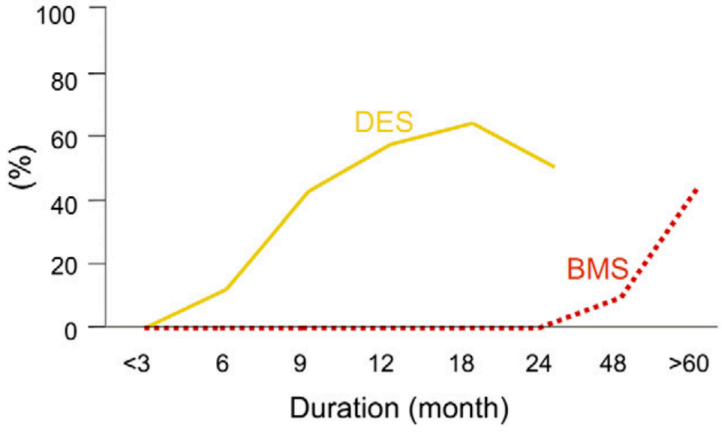
In-stent neoatherosclerosis is an important substrate for both ISR and LST, especially in the extended phase.

Histological findings of neoatherosclerosis



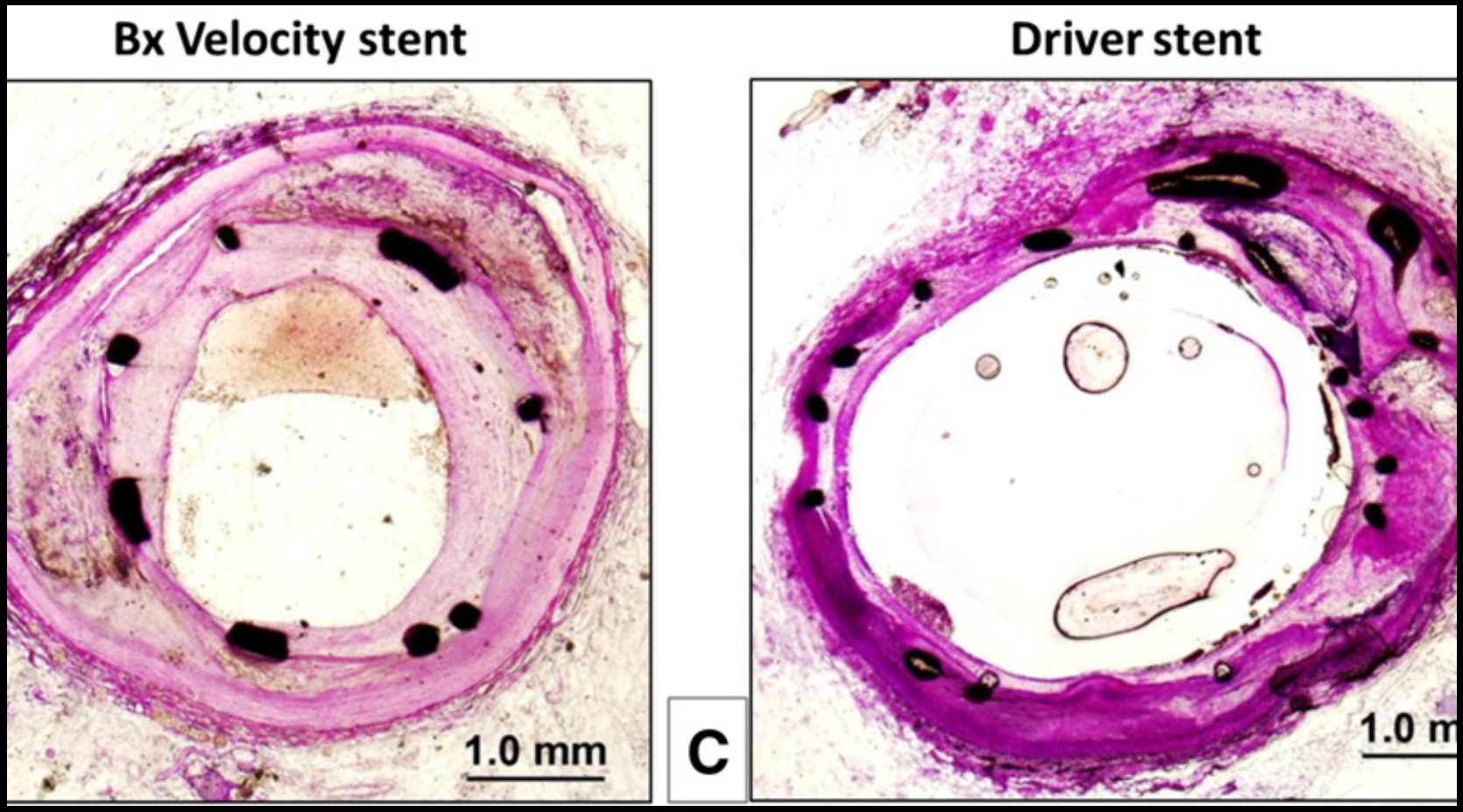


The atherosclerotic change in SES is seen in 40% of cases by 9-m; in the BMS, the atherosclerotic change does not begin to appear until 2-y



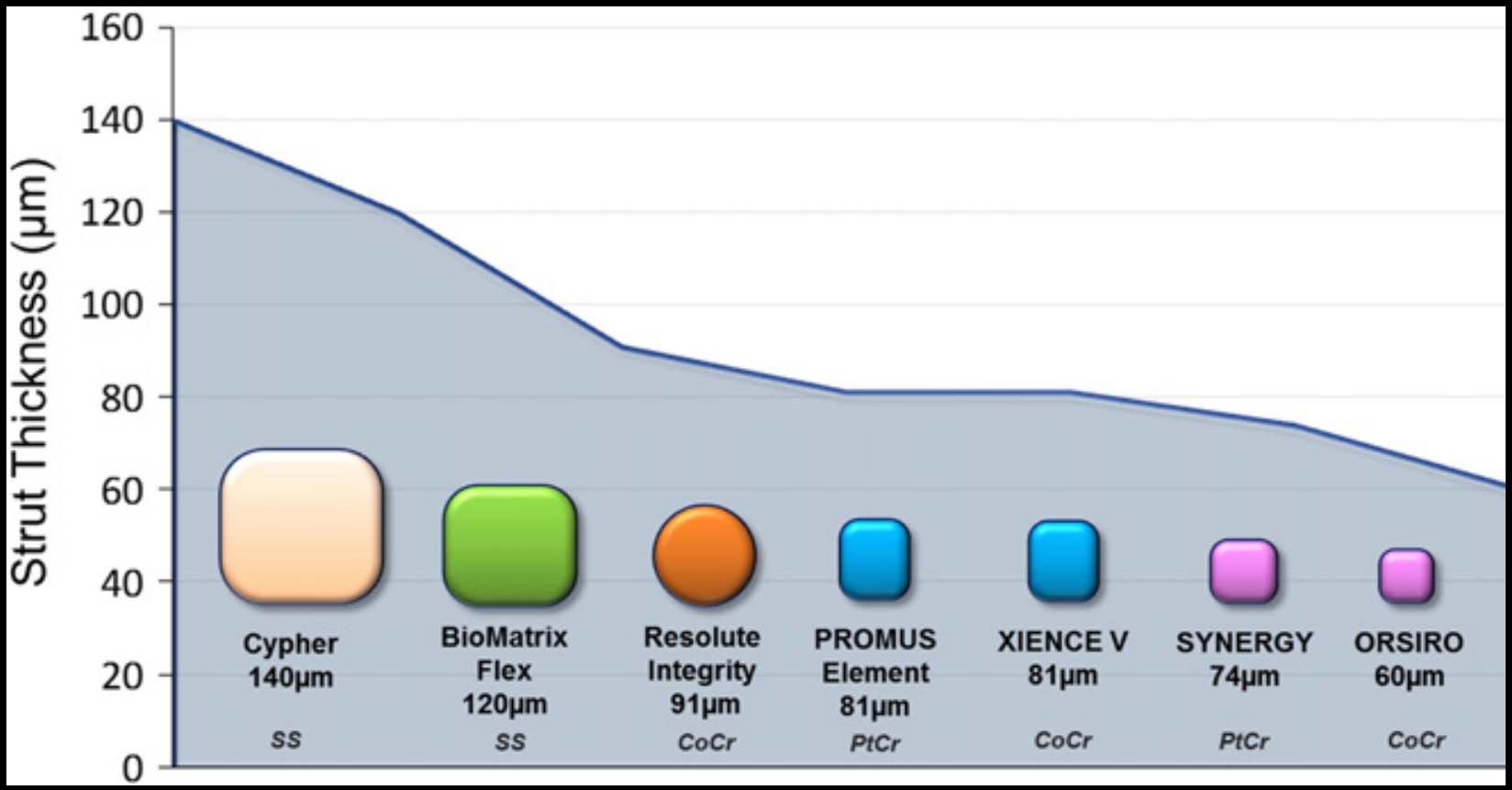
J Am Coll Cardiol. 2012 Jun 5;59(23):2051-7

Strut Thickness and NIH



Foin et al. International Journal of Cardiology 177 (2014) 800–808

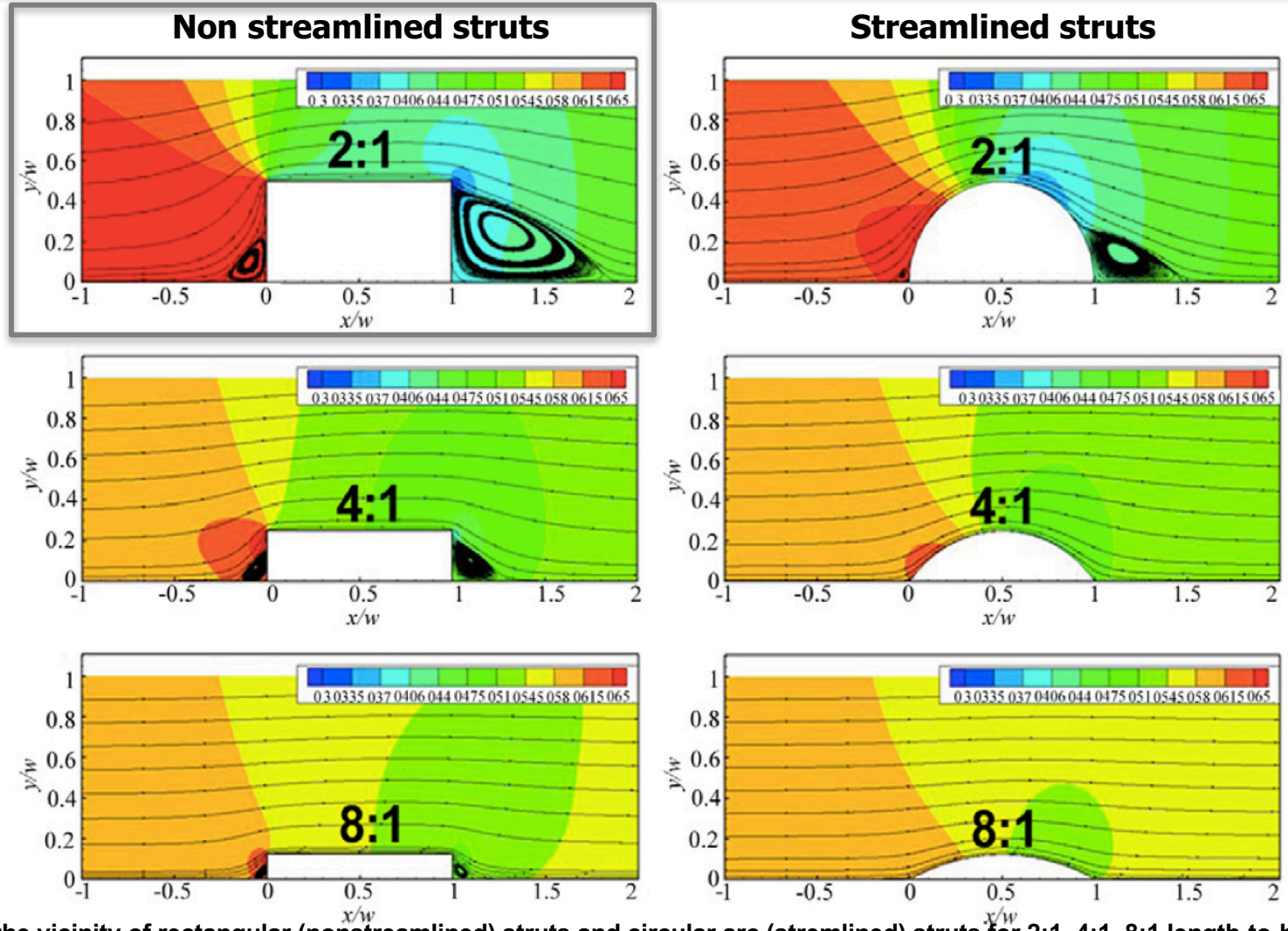
Strut Thickness Getting Thinner



Foin et al. International Journal of Cardiology 177 (2014) 800–808

Hemodynamically Driven Stent Strut Design

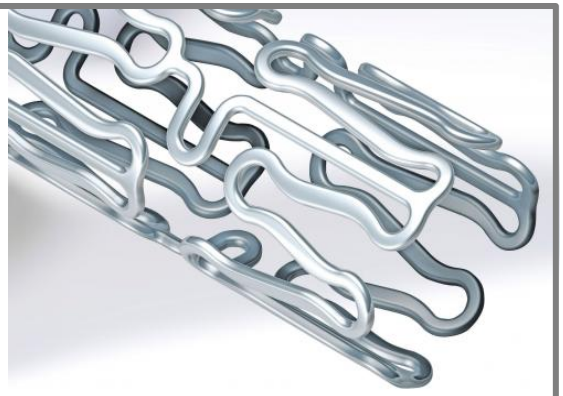
JUAN M. JIMÉNEZ[1] and PETER F. DAVIES[1,2,3]



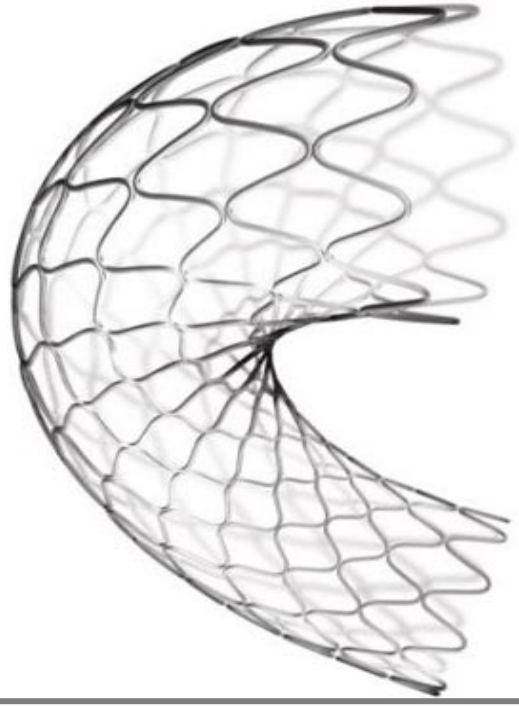
Streamlines at the vicinity of rectangular (nonstreamlined) struts and circular arc (stremlined) struts for 2:1, 4:1, 8:1 length-to-height ratios. Recirculation zones occur in rectangular struts of all aspect ratios but only in thick circular-shaped struts with a 2:1 length-to-height ratio

Shear-Stent Platform Profiles

- **XIENCE Xpedition® Everolimus-eluting stent (X-EES) - Abbott Vascular**



- **Resolute Integrity® Zotarolimus-eluting stent (R-ZES) – Medtronic Inc.**
  - **continuous wire that is molded into a sinusoidal wave and wrapped in a helical pattern and** **oints**



Shear Stent Status Update

Shear Stent study Design

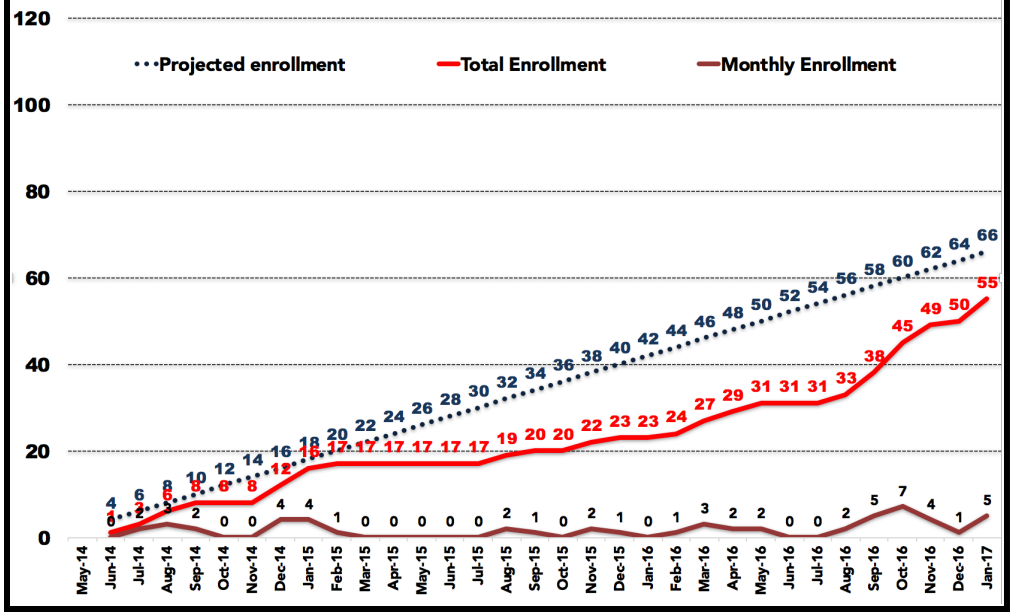
Patients w/ ACS undergoing PCI (n=126)

- Bi-plane Angio
  - Resolute ZES
  - Xience Xpedition EES
    - OCT & IVUS
      - 1 Year
      - Follow-up Bi-plane Angio, OCT, IVUS
    - OCT & IVUS derived CFDs

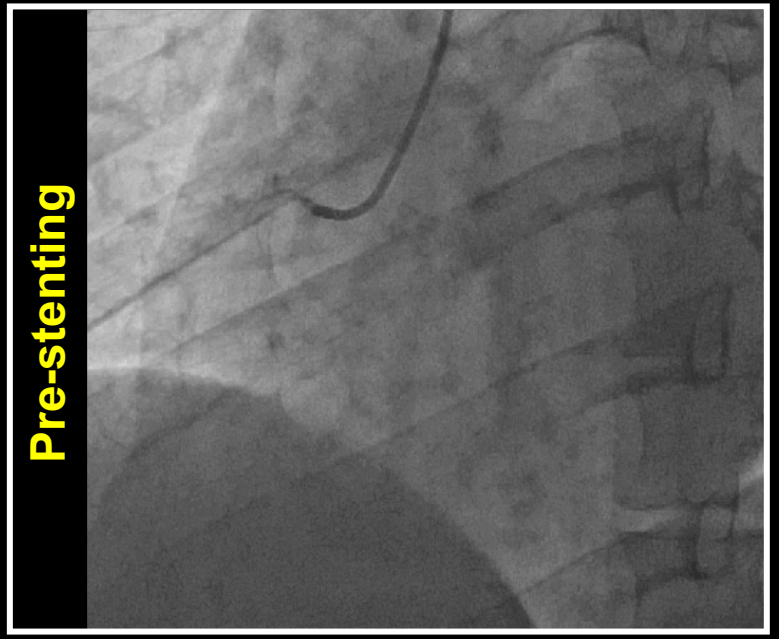
Assessment of Angulation, Re-endothelialization, Neointimal Hyperplasia, Edge restenosis

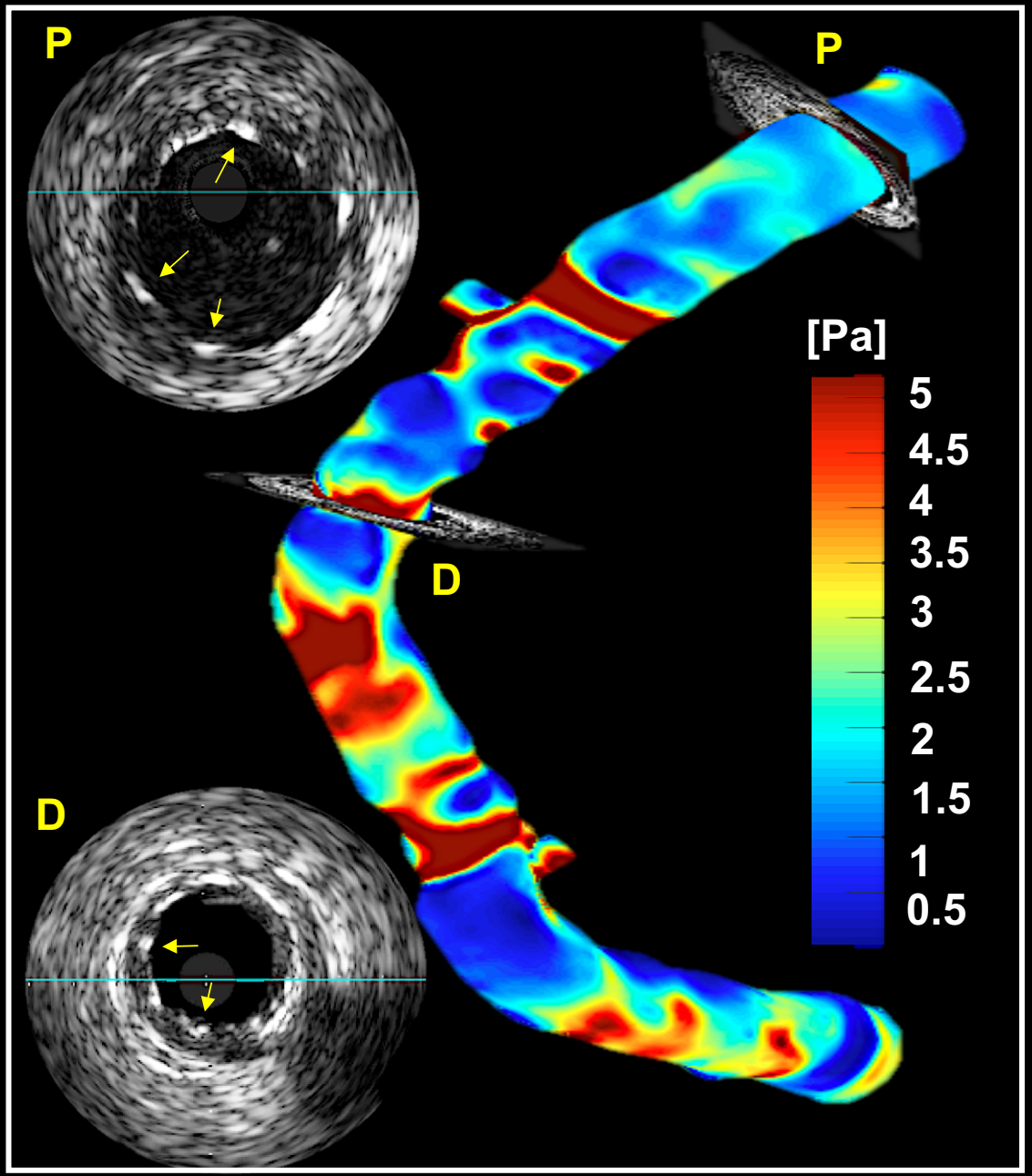
Emory Univ.	Nanjing Univ.	Serbia





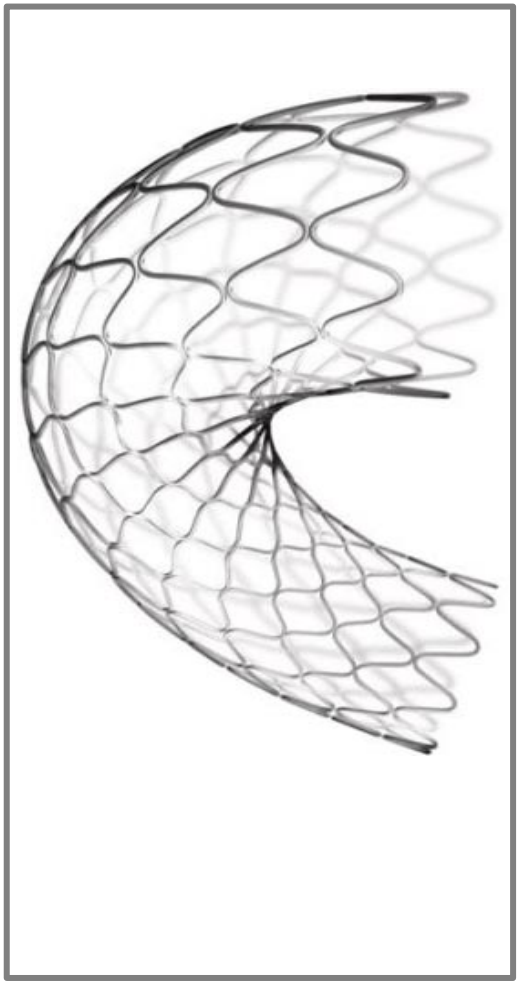
ID: 281-26: 42 year-old male presented with unstable angina.
History of CCS III angina w/ infero-apical ischemia in non-invasive imaging

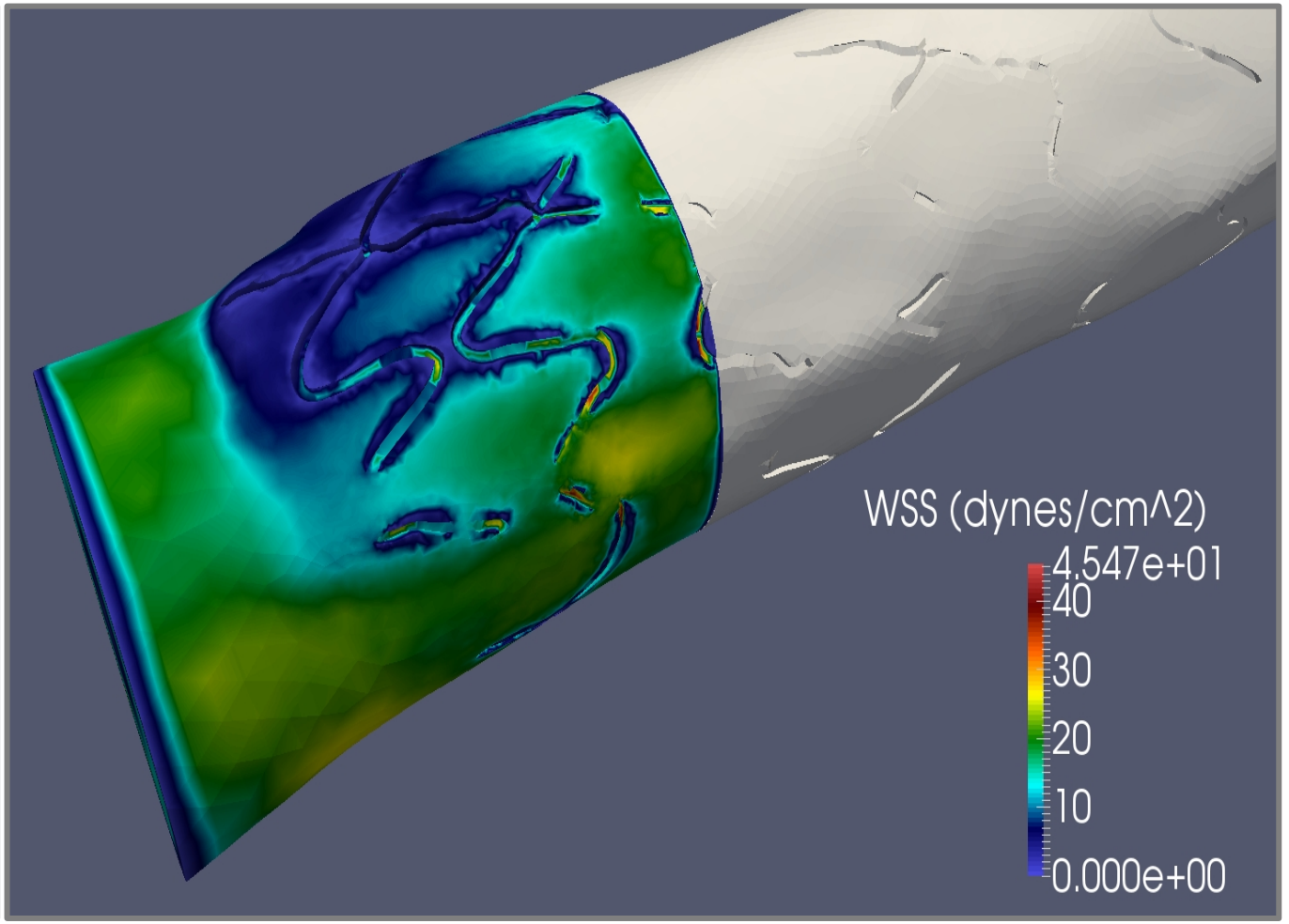




Resolute Integrity®

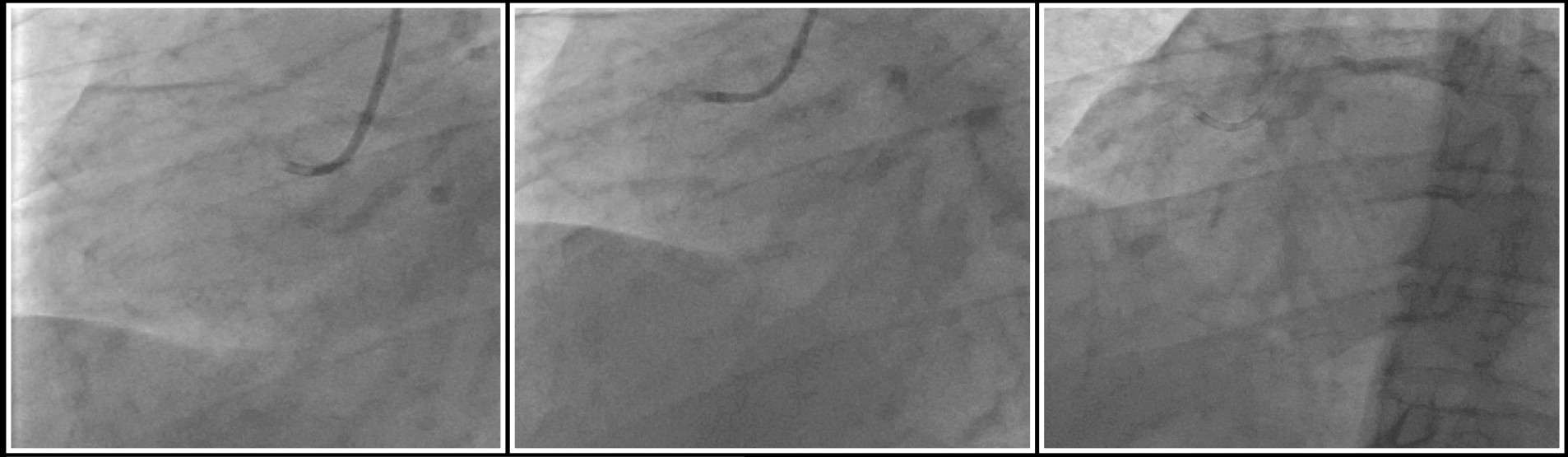
Zotarolimus-eluting stent (R-ZES)



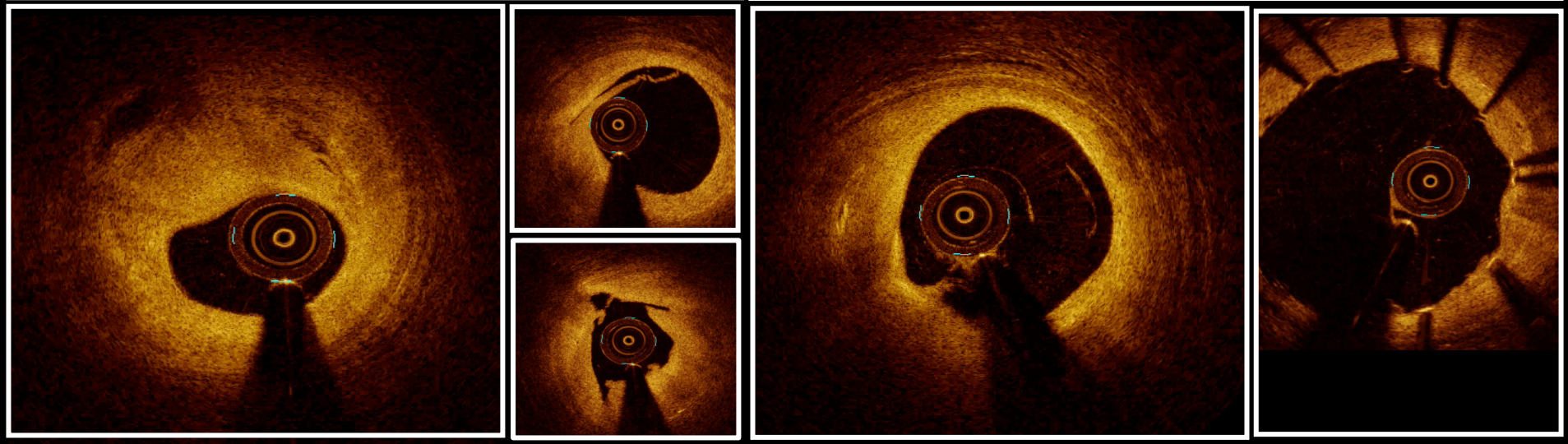


Shear Stent Optical Coherence Tomographic -derived Computational Fluid Dynamics

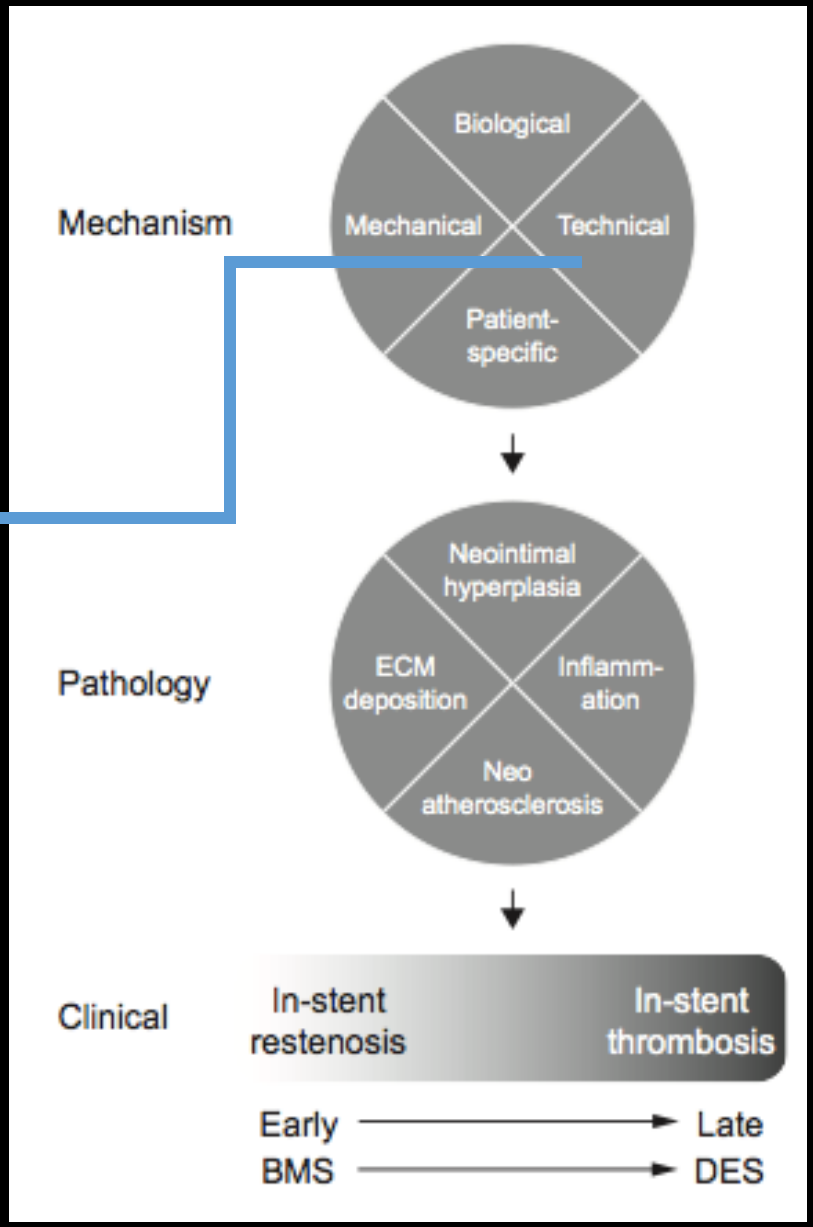
Baseline Procedure after BA	Post-stent Deployment	1Y follow-up



Baseline Procedure after BA	Post-Procedure



Mechanisms and Pathology of ISR

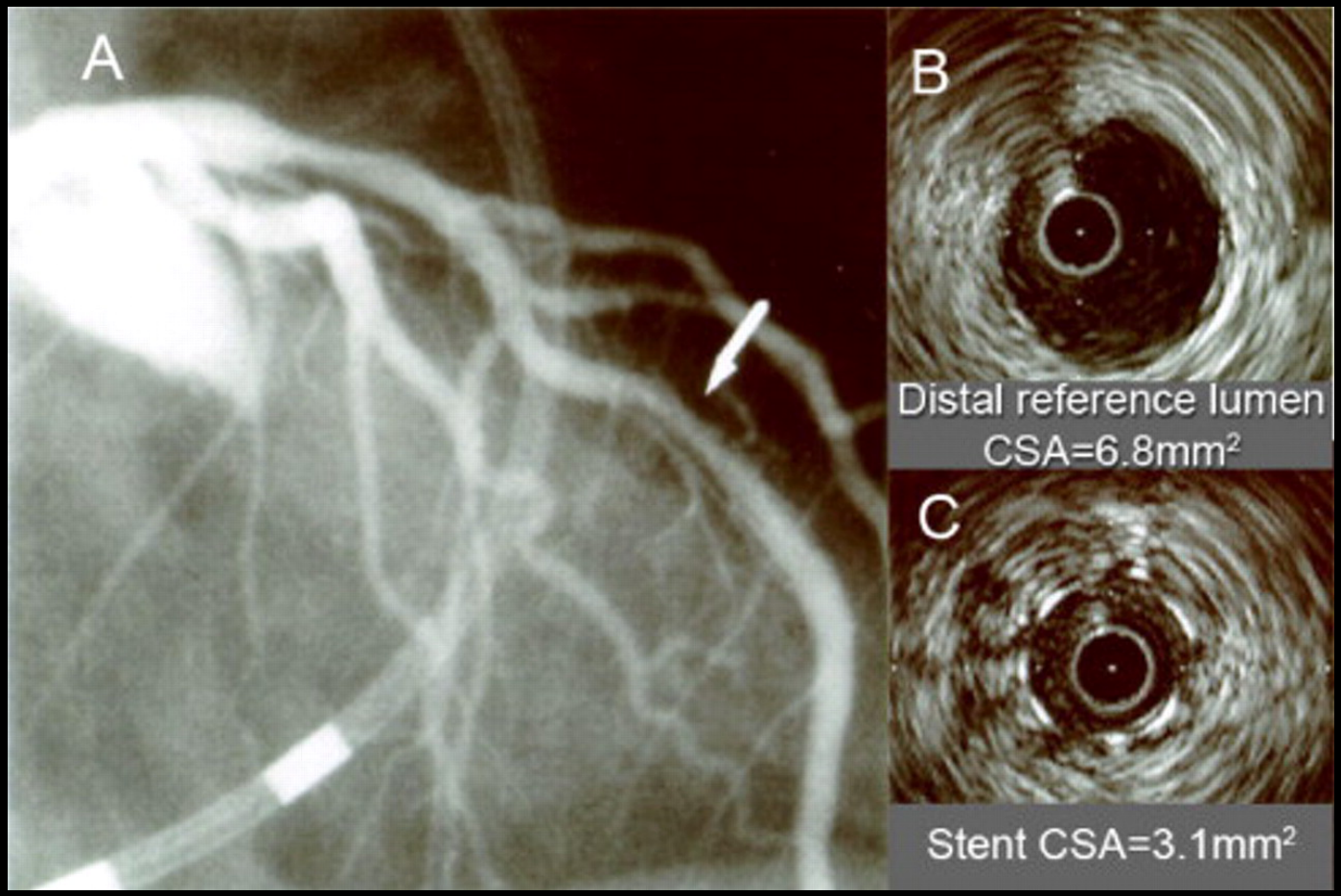


Technical

Under-expansion
Stent Fracture
Barotrauma
Stent gap and overlap
Geographic miss

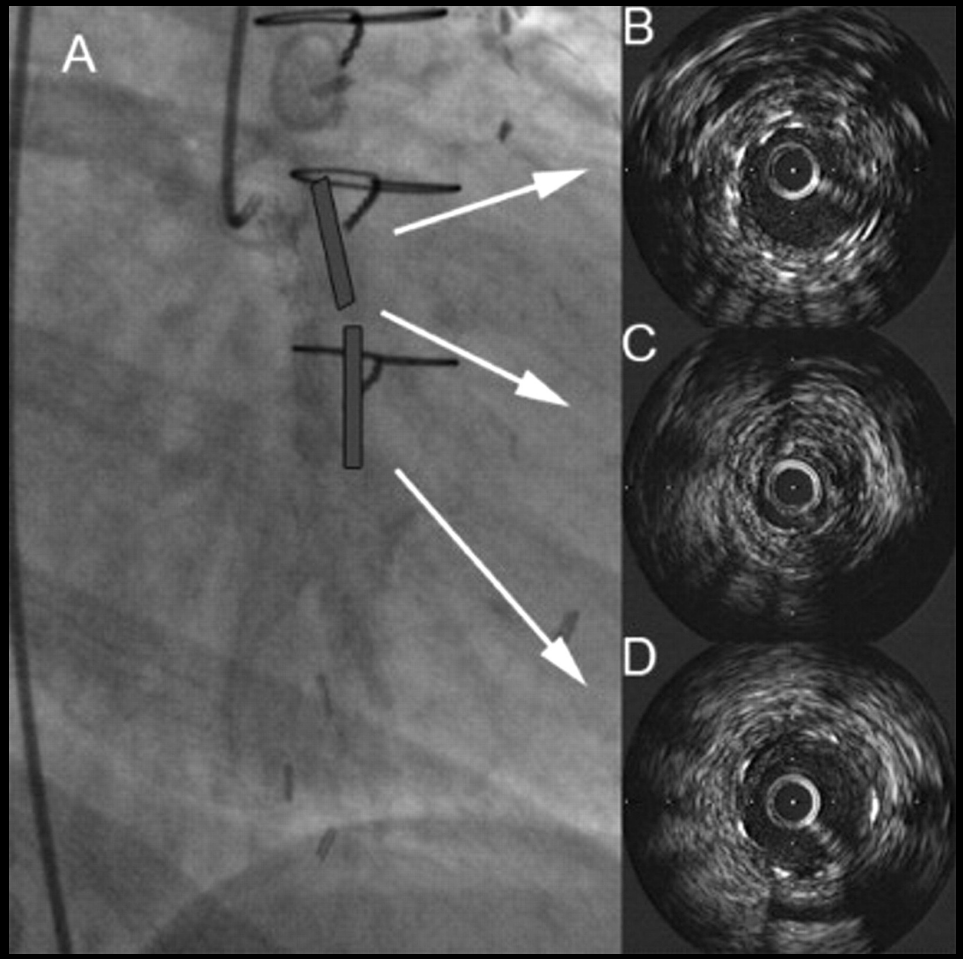
Nakamura et al. Intervent Cardiol Clin 5 (2016) 391–403

Under-expansion and Restenosis



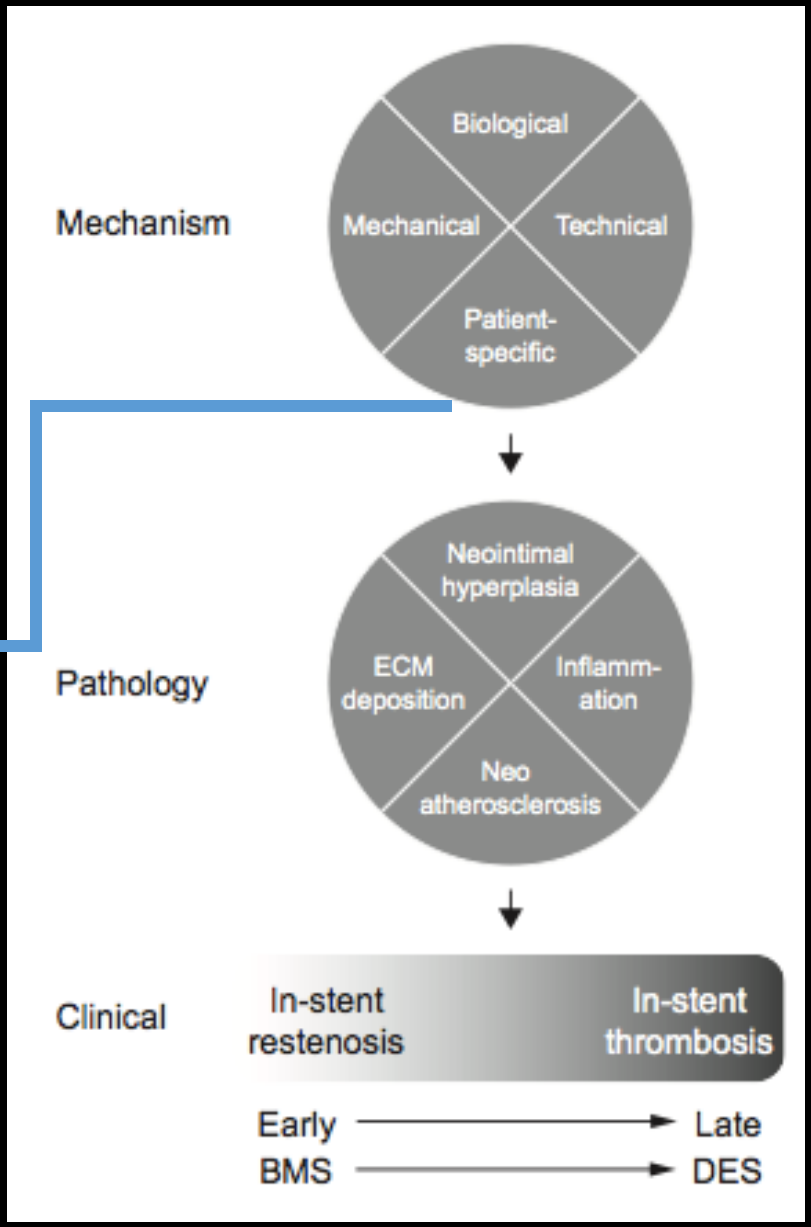
Dangas et al. JACC 2010; 56:1897-1907

Stent Fracture and Restenosis



Dangas et al. JACC 2010; 56:1897-1907

Mechanisms and Pathology of ISR



Patient-specific

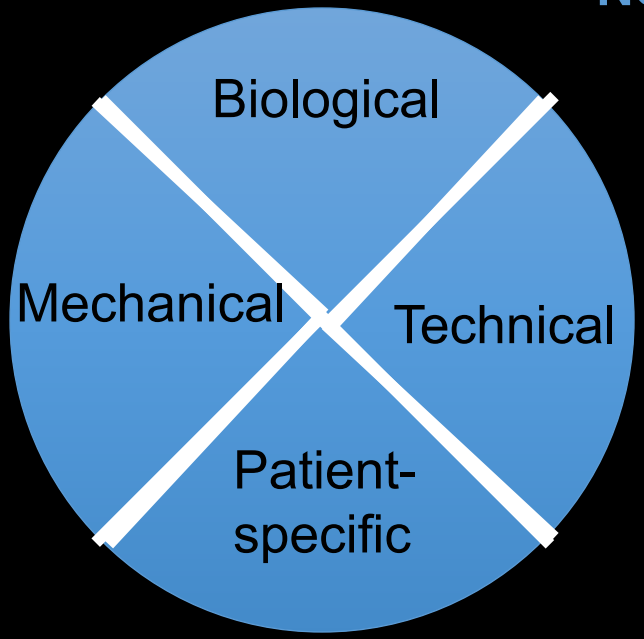
Co-morbidities
Drug resistance
Hypersensitivity

Nakamura et al. Intervent Cardiol Clin 5 (2016) 391–403

Mechanisms and Pathology of ISR

Vascular Injury
Non-uniform drug delivery

Vessel size and length
Hemodynamics/WSS



Under-expansion
Stent Fracture
Barotrauma
Stent gap and overlap
Geographic miss

Co-morbidities
Drug resistance
Hypersensitivity

Nakamura et al. Intervent Cardiol Clin 5 (2016) 391–403