TRANSCATHETER CARDIOVASCULAR THERAPEUTICS ASIA PACIFIC
ANGIOPLASTY SUMMIT
TCTAP 2012
APRIL 24-27, 2012
SHERATON GRANDE WALKERHILL HOTEL
SEOUL, KOREA
17TH

Usefulness of OCT in Preclinical Study

Kim, Jung-Sun, M.D. Ph D

Division of Cardiology, Severance Cardiovascular Hospital
Yonsei University College of Medicine

I have nothing disclosure to this presentation

Agenda

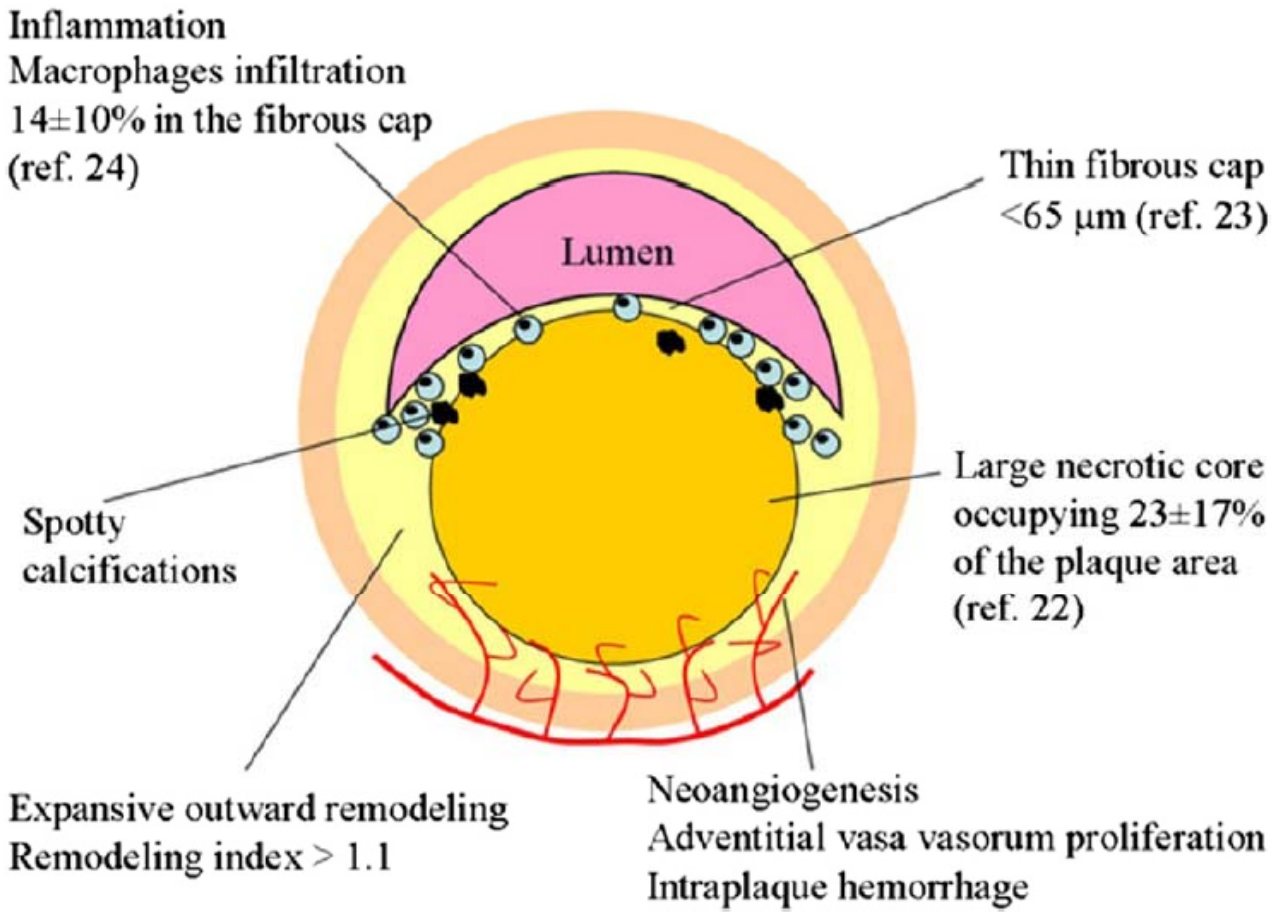
- Development of Animal Model
- New device evaluation

Agenda

- **Development of Animal Model**
- **New device evaluation**

Vulnerable Plaque

Histological Aspect

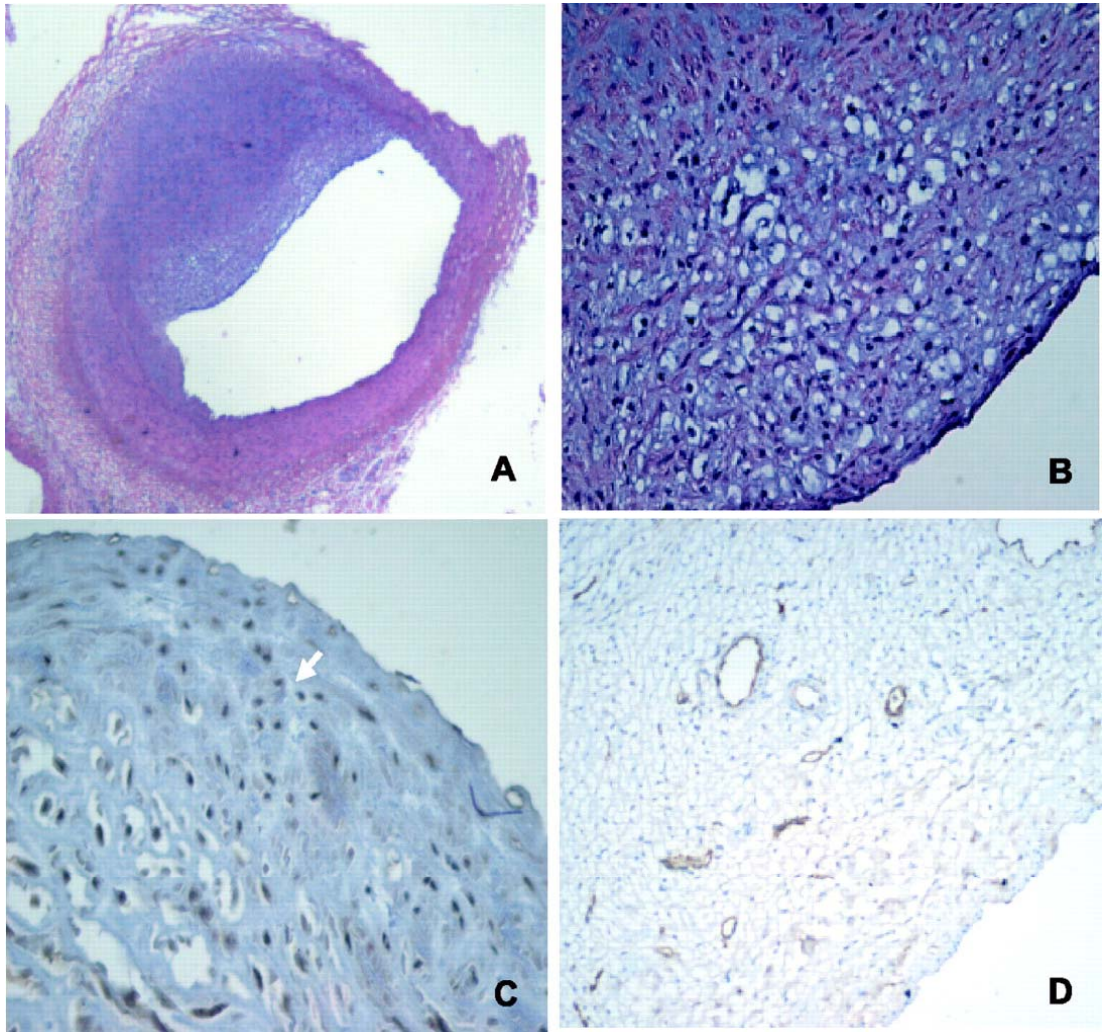


Vancraeynest D, et al. J Am Coll Cardiol 2011;57:1961-79

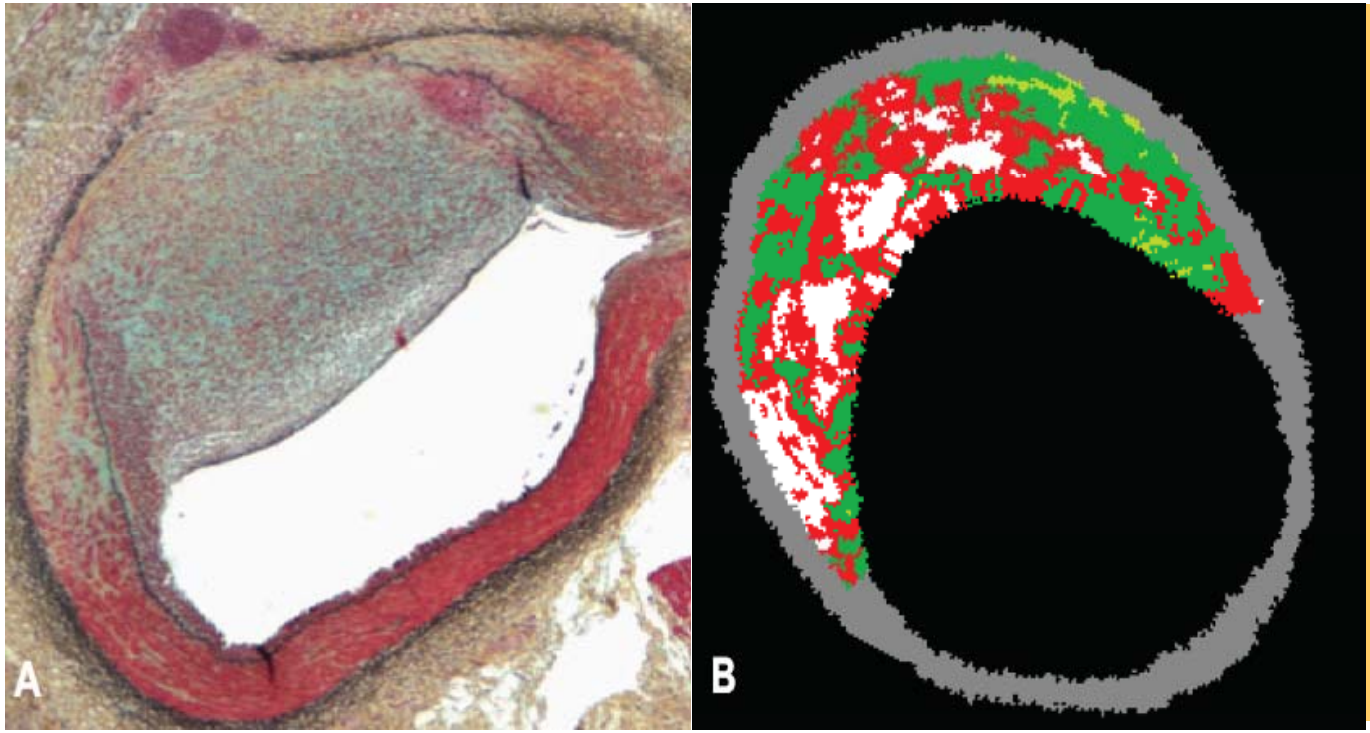
Why We Need a Animal Model with Vulnerable Plaque

- TCFA appear to be the most common type of VP in autopsy study.
- But, the mechanism of plaque rupture and subsequent occlusive thrombus formation is still unclear.
- The need to identify and characterize vulnerable atherosclerotic lesions in human has led to the development of various animal model of plaque vulnerability.

Vascular lesion harvested from the proximal left anterior descending artery 10 weeks after adventitial liposome delivery



Granada JF et al. Arterioscler Thromb Vasc Biol 2007;27:387-393

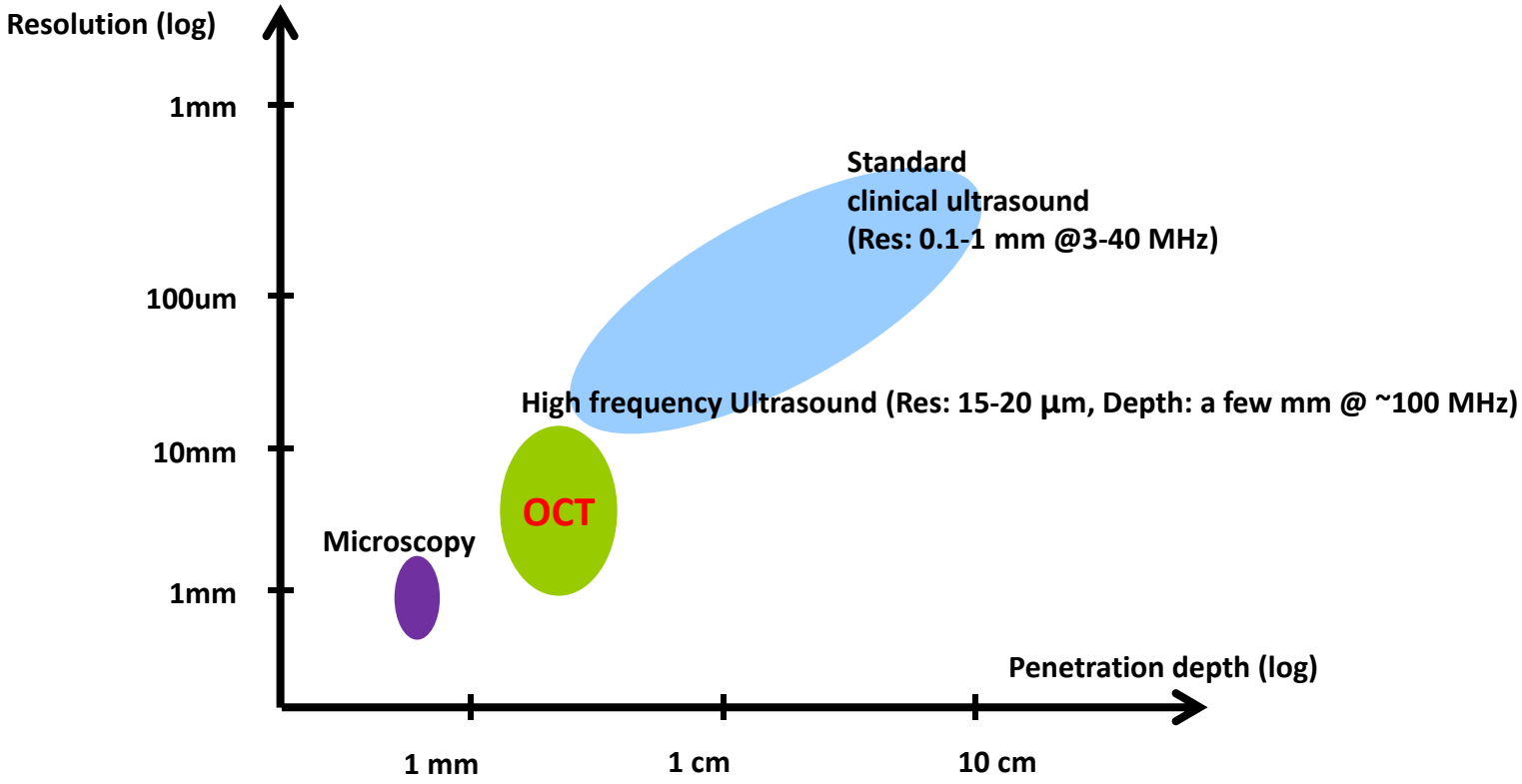


Plaque harvested from the LAD in a pig at 10 weeks of follow-up.
A, Movat pentachrome section (2) showing a fibrolipidic plaque with no evidence of calcification.
B, Corresponding IVUS-VH image acquired in vivo showing significant amount of necrotic core and calcification.

The sensitivity of IVUS-VH for the detection of fibrous, fibro-fatty, and necrotic core tissue was 76.1%, 46%, and 41.1%.

This model is rich in smooth muscle cells/proteoglycans and the lesions lack a necrotic core, calcification, and collagen (type I). Therefore, this model might be more indicative of a restenosis model.

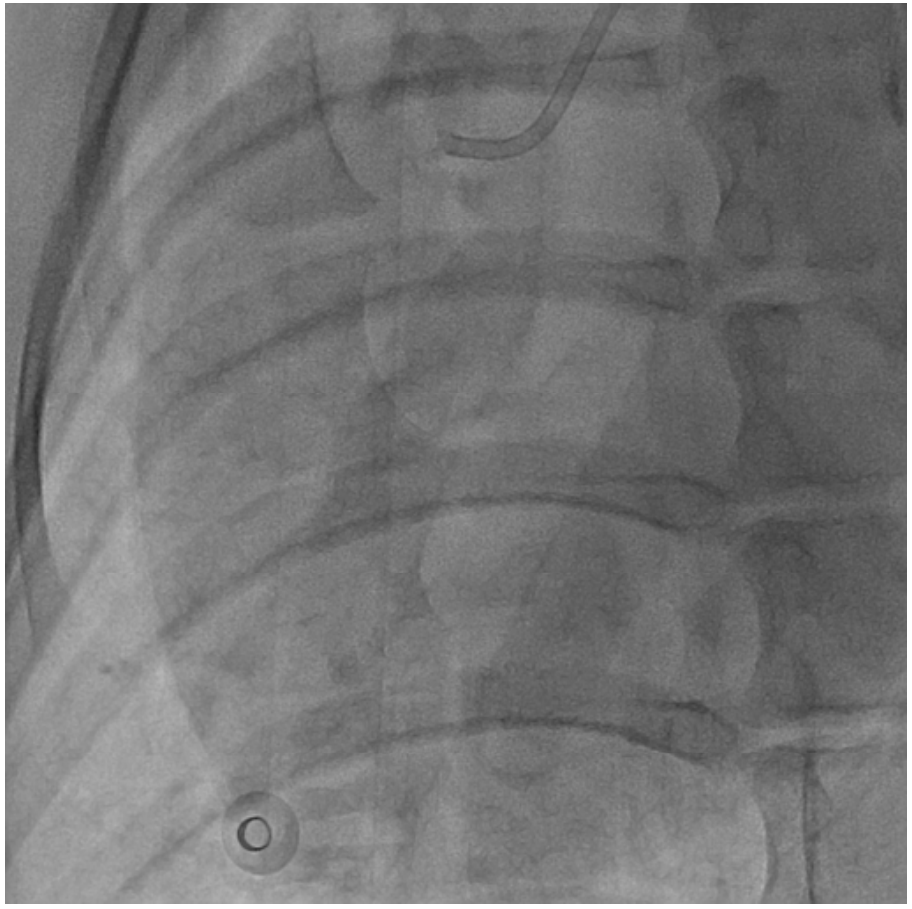
Clinical imaging modalities



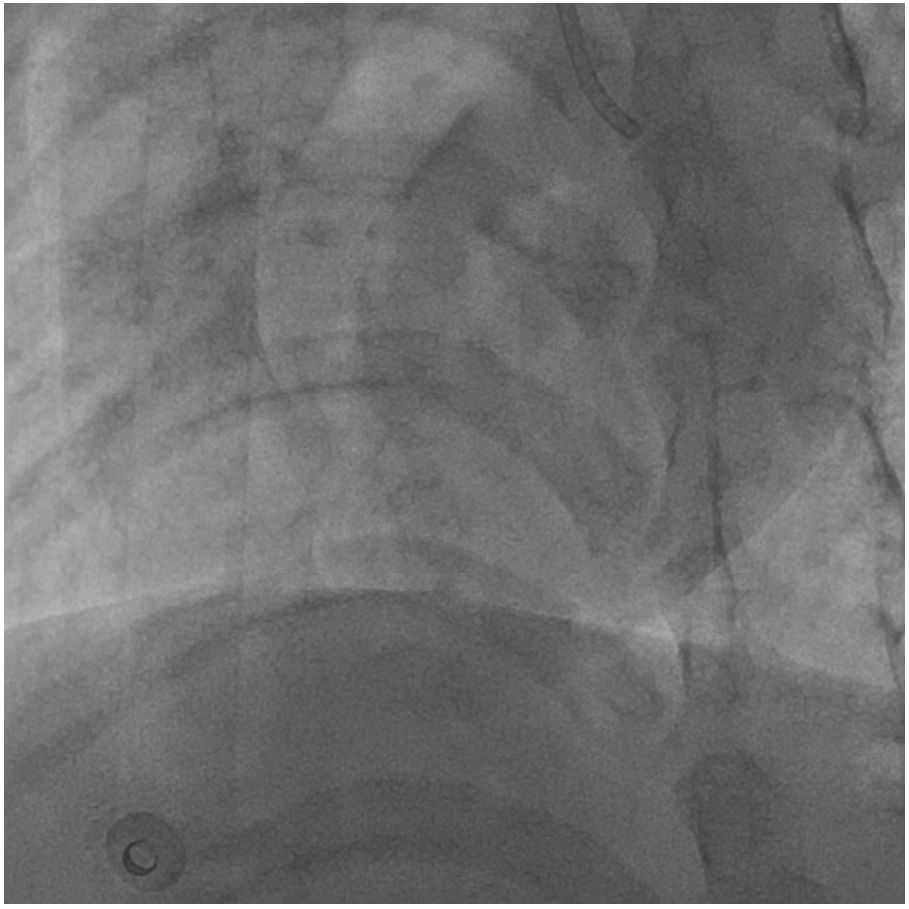
- OCT provides images with resolutions of 10 – 15 µm and depths of 2-3 mm
- Imaging resolution is 10 times better than ultrasound

Swine Model

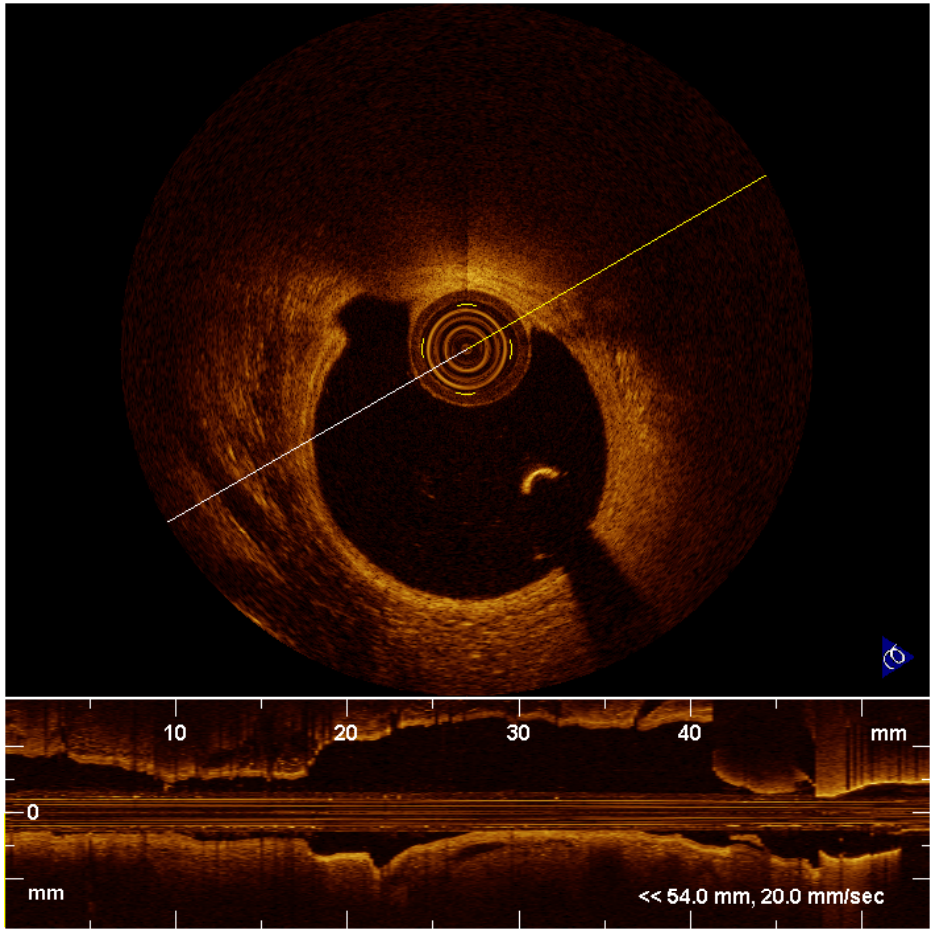
RCA

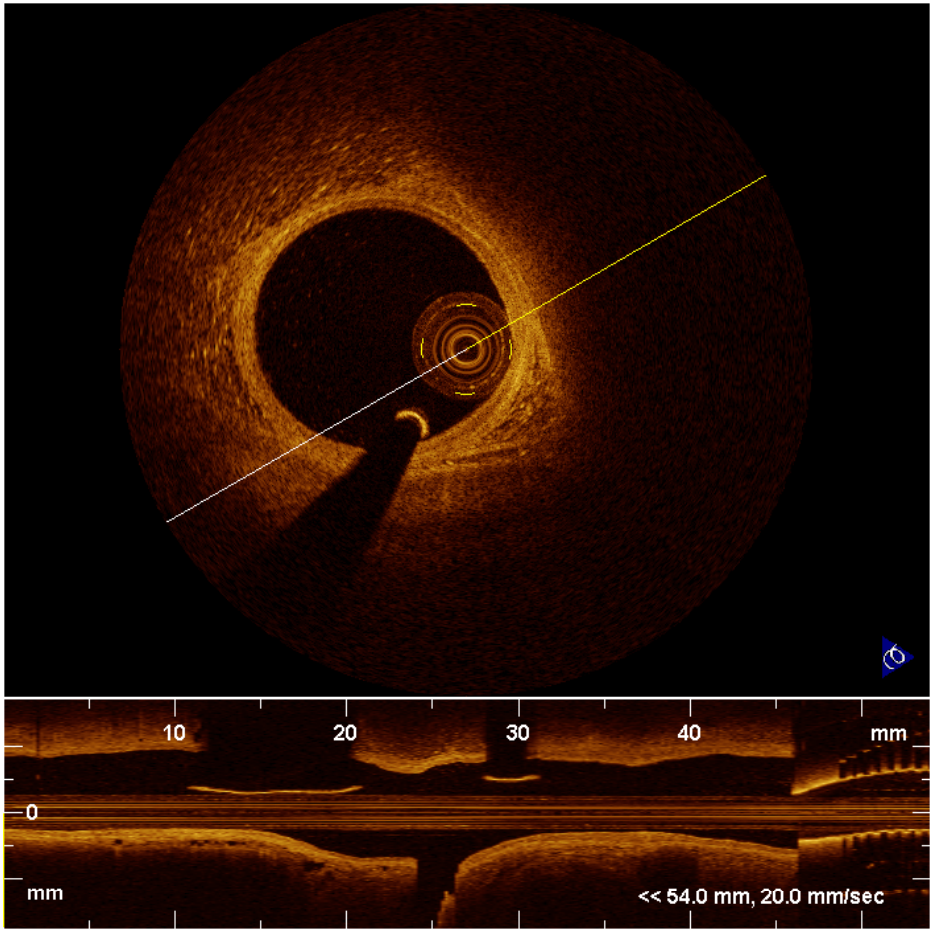


LCA



Vulnerable Plaque Model in Swine Model





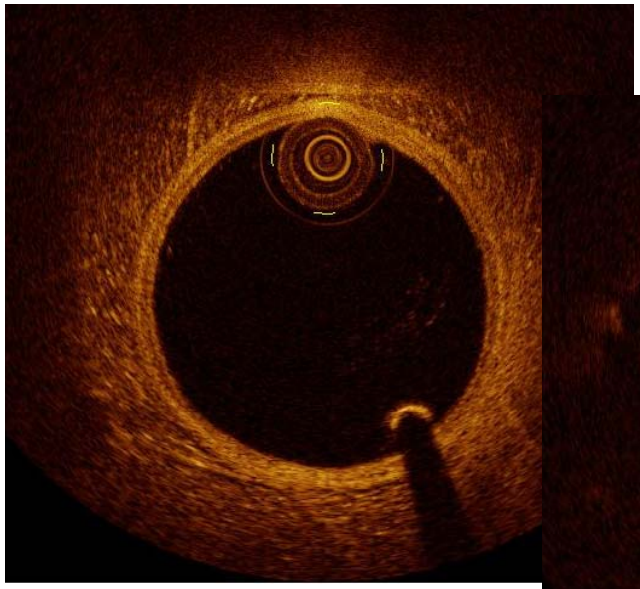
Post-Injection

2 weeks follow-up

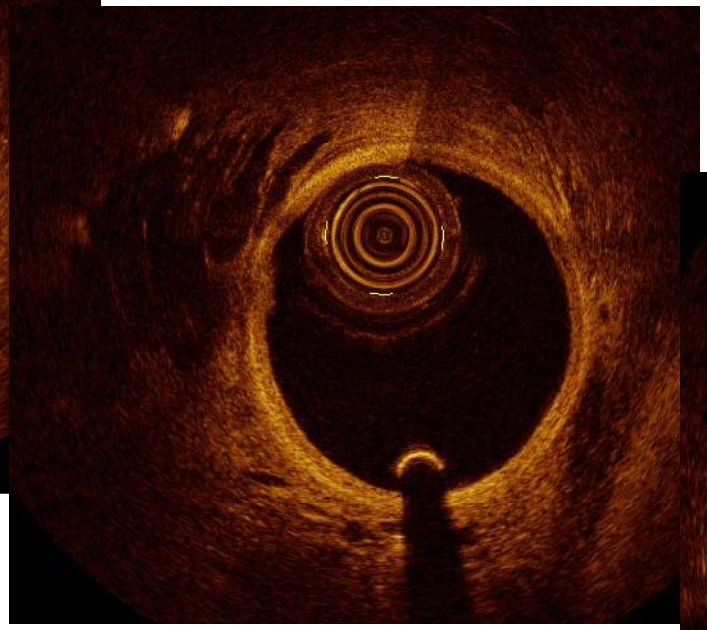
Vulnerable Plaque Model in Swine Model

Preliminary Data

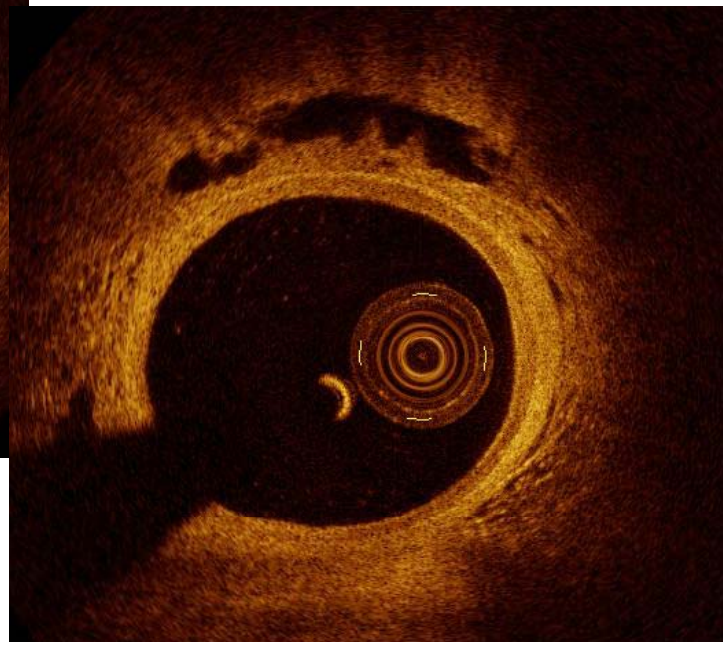
Inject with HMGB1 (RAGE ligand) + cholesterol esters using Mecator catheter



Pre-Injection

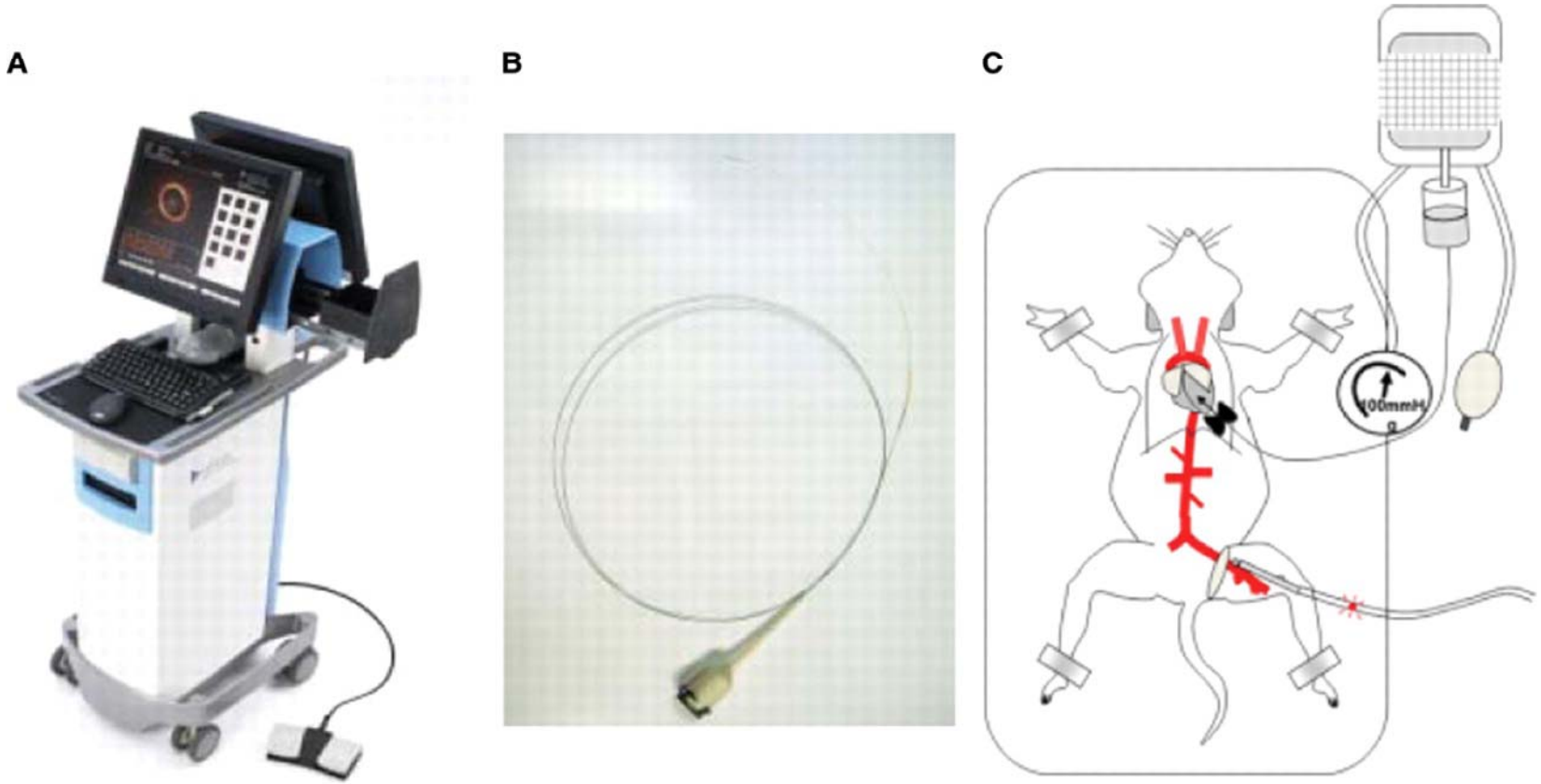


Post-Injection



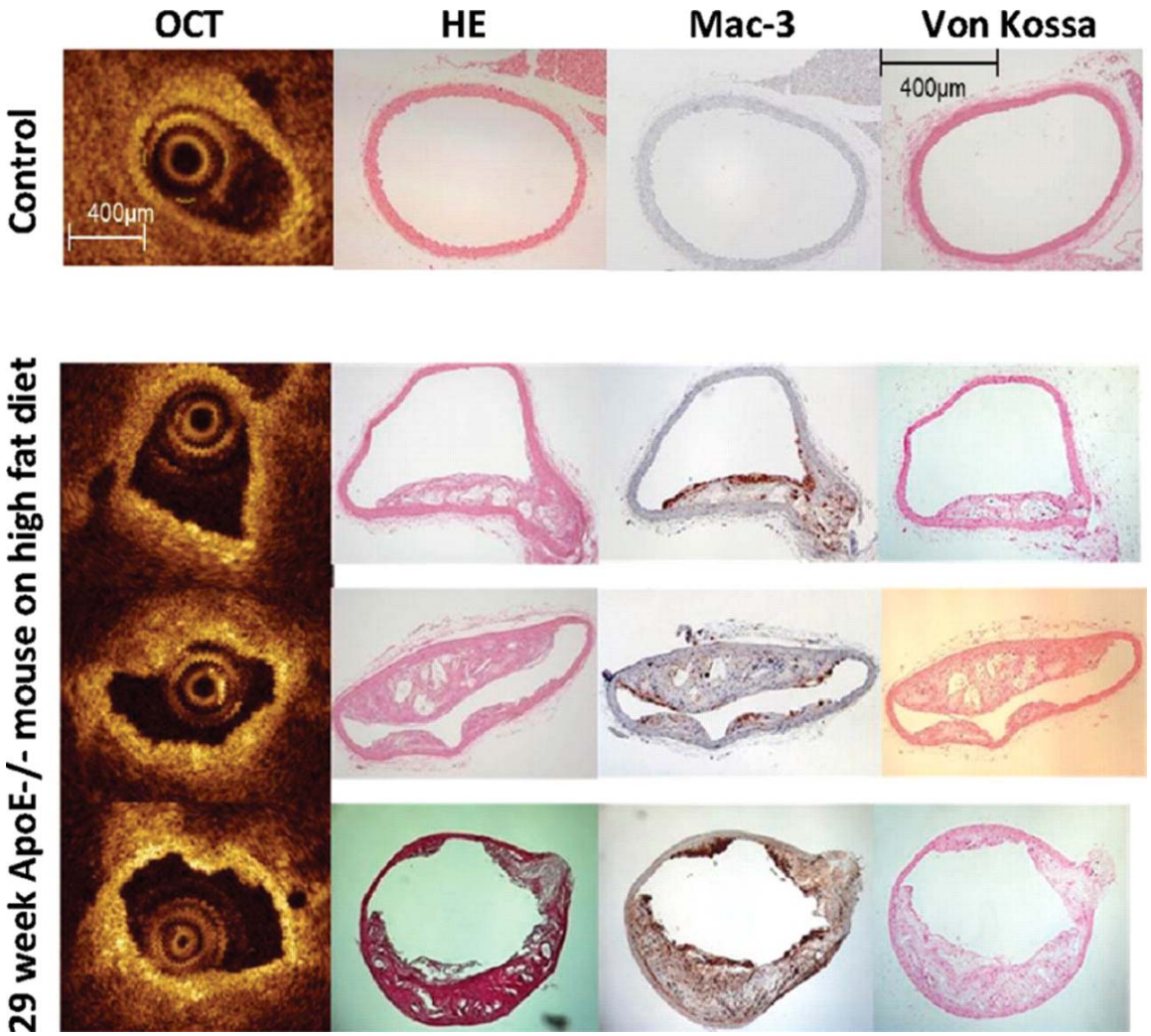
2 weeks follow-up

Intra-aortic OCT in a mouse apolipoprotein E–/– model.



Tahara S et al. Arterioscler Thromb Vasc Biol 2012;32:1150-1157

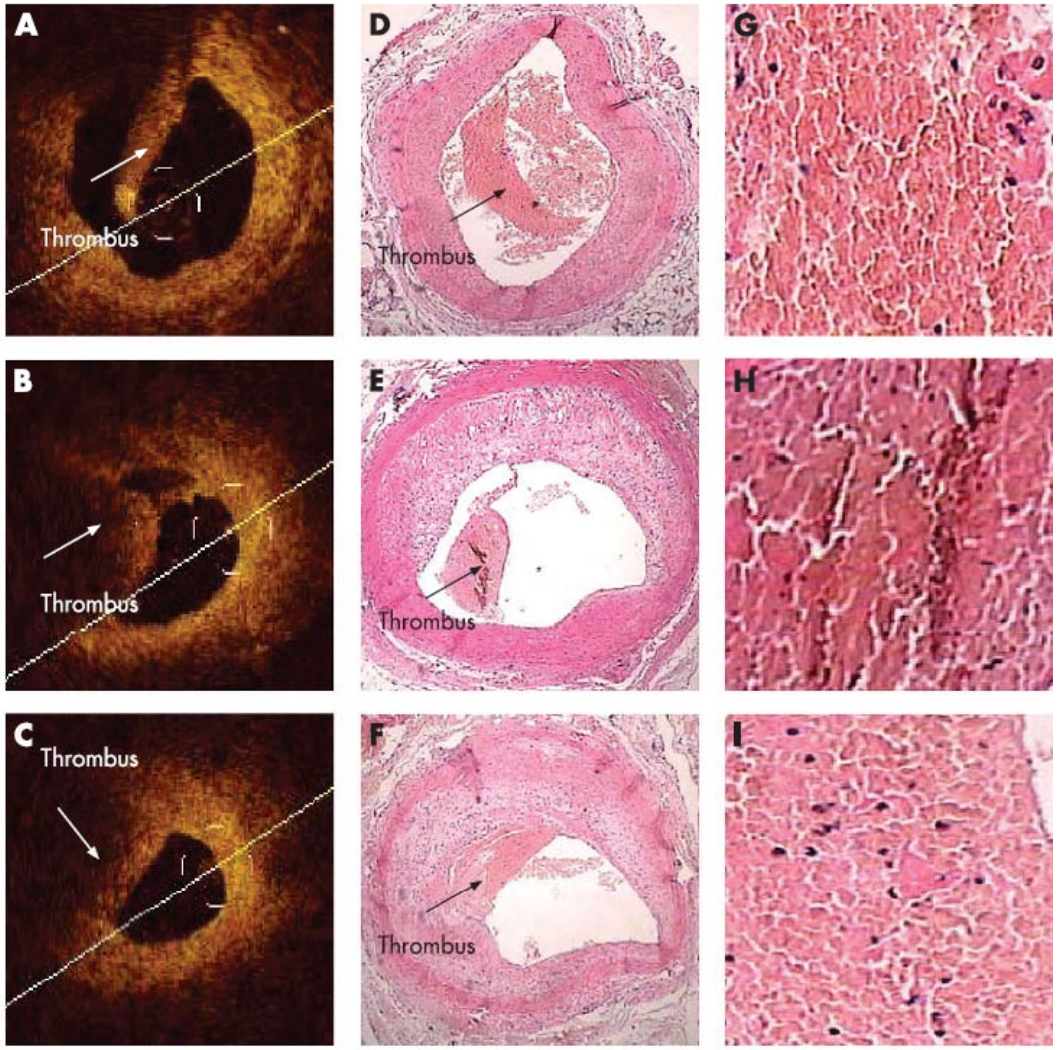
Macrophage accumulation detected by intra-aortic OCT and immunohistochemistry in apolipoprotein E (ApoE)–/– mice.



Tahara S et al. Arterioscler Thromb Vasc Biol 2012;32:1150-1157

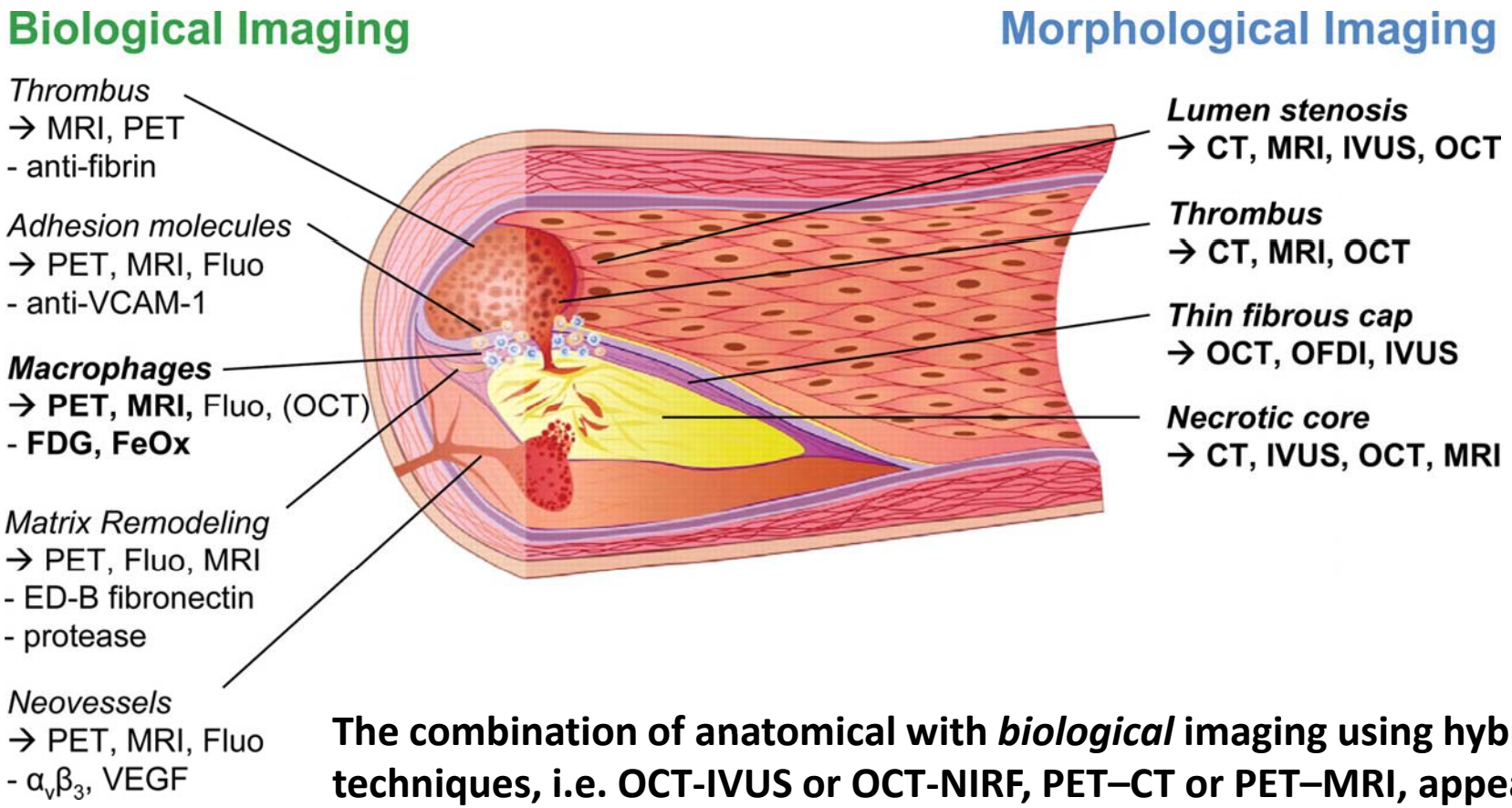
In vivo optical coherence tomography of experimental thrombosis in a rabbit carotid model

Figure 2 Comparative analysis of the histomorphometric and OCT features of carotid artery thrombus presence or absence of thrombus. Correlation between OCT images obtained in vivo and later histological examination of animal model red thrombi. A, B and C show OCT images of the right common carotid artery cross-sections, with each showing a signal-rich mass protruding into the lumen. The corresponding histological sections, D, E and F, confirm the thrombus within the lumen of the common carotid artery at these levels. OCT images of red thrombi are characterised as high-backscattering protrusions with signal-free shadowing (arrows). Red thrombus, which is a cell-rich structure and consists mainly of red blood cells, causes scatter and attenuation of OCT signal intensity from the inner surface of the thrombus to the vessel wall. OCT was able to determine the presence or absence of a thrombus in all arterial segments.



Meng L, et al. Heart 2007;94:777-780

Techniques for Imaging the Unstable Plaque.



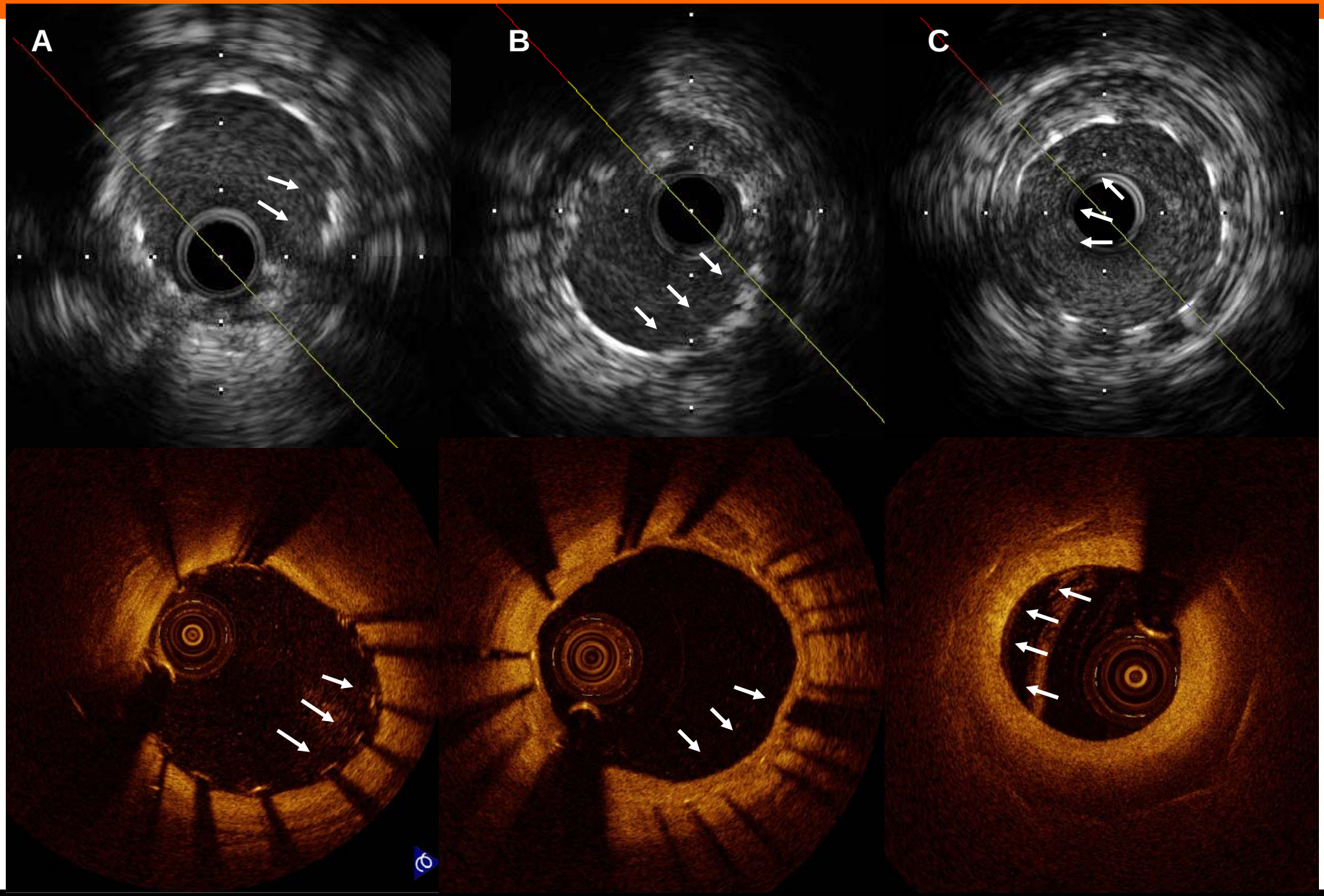
The combination of anatomical with *biological* imaging using hybrid techniques, i.e. OCT-IVUS or OCT-NIRF, PET–CT or PET–MRI, appears to be attractive.

Matter C M et al. Eur Heart J 2009;30:2566-2574

Agenda

- Development of Animal Model
- **New device evaluation**

OCT vs. IVUS



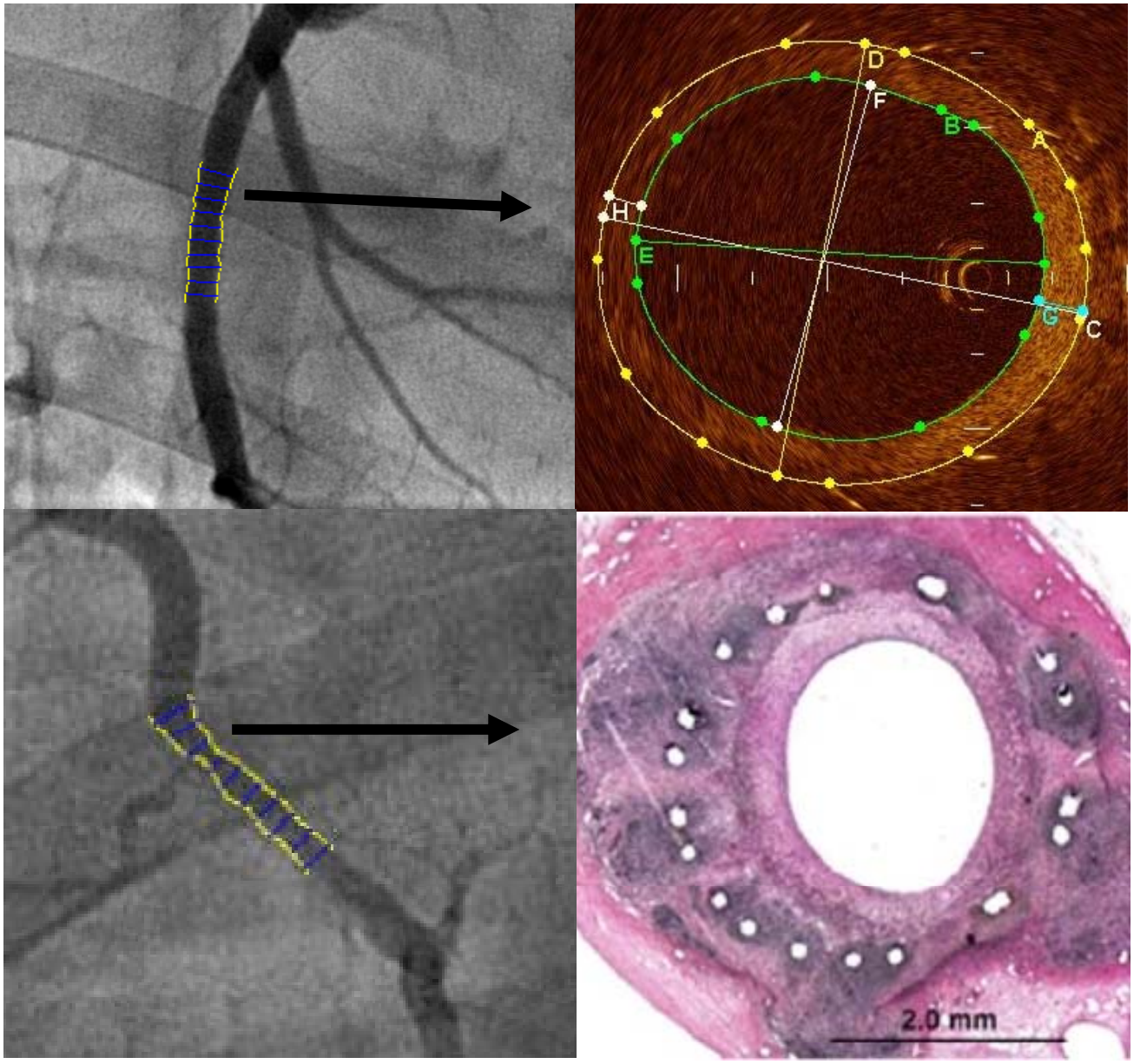
Angiographic Late Loss in DES

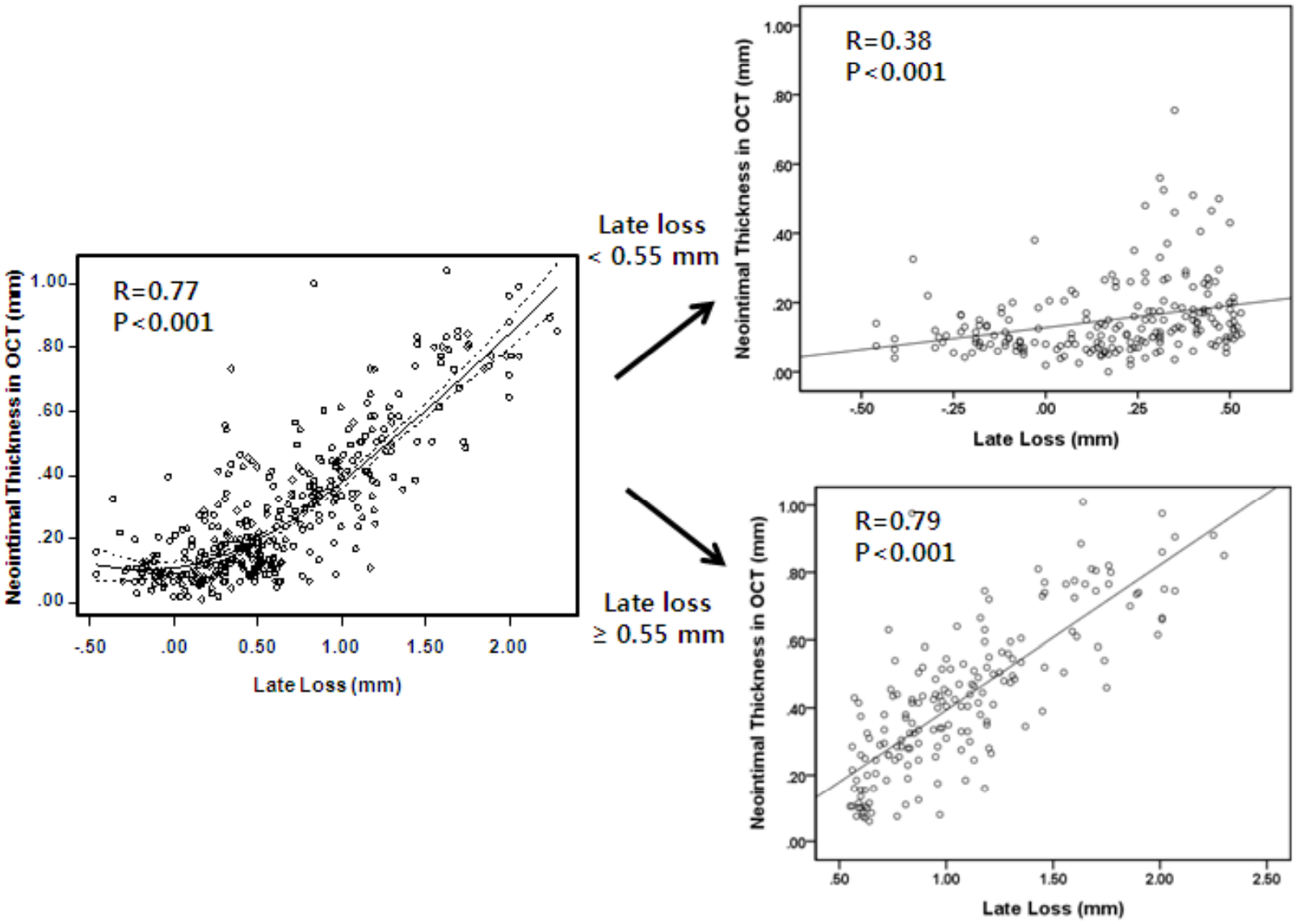
The degree of angiographic LL in DESs < 0.4 mm,

The resolution threshold of angiography : around 0.5 mm

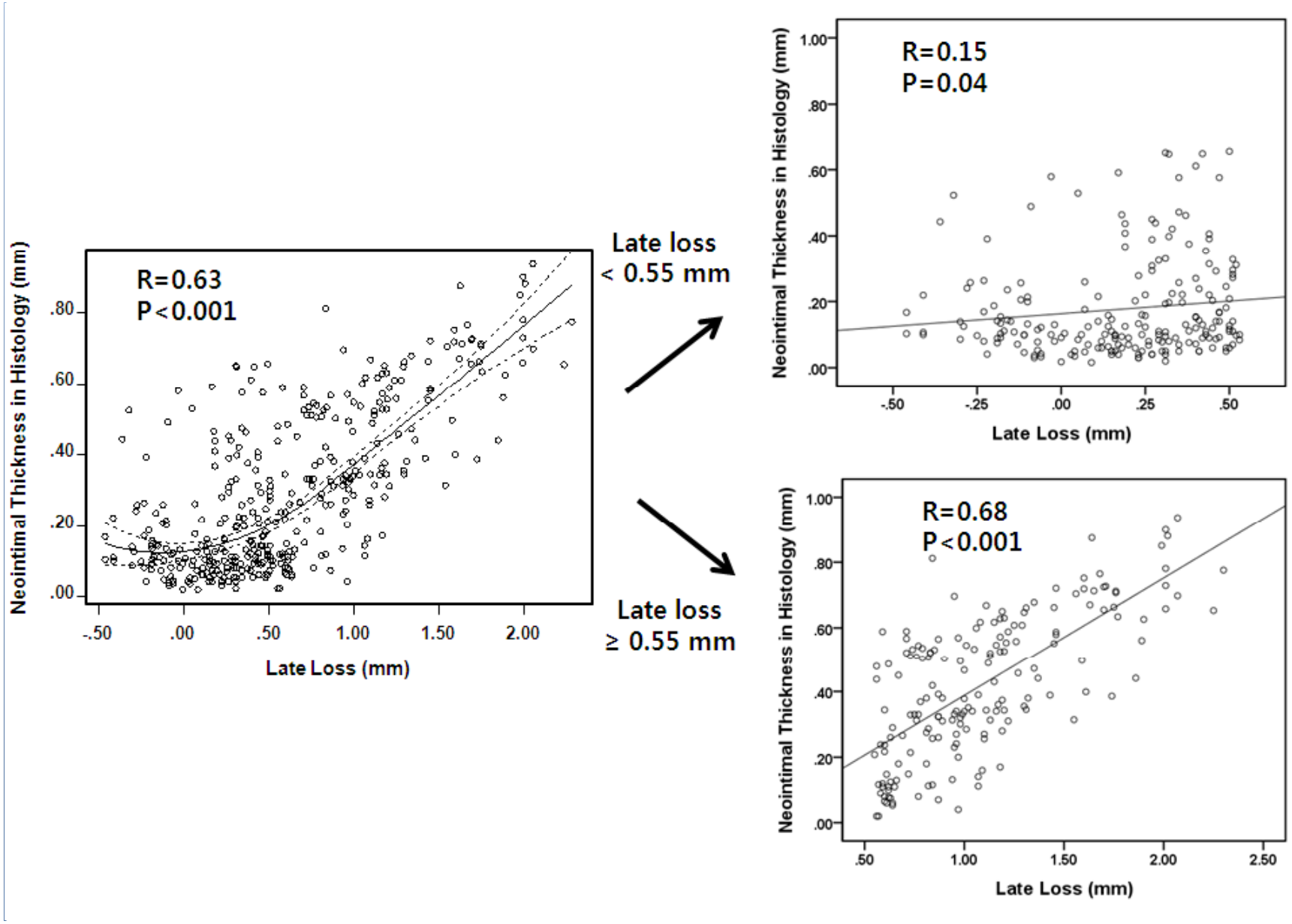
⇩

Evaluate the correlation of angiographic late loss (LL) with the degree of in-stent neointimal proliferation assessed by optical coherence tomography (OCT) and histology

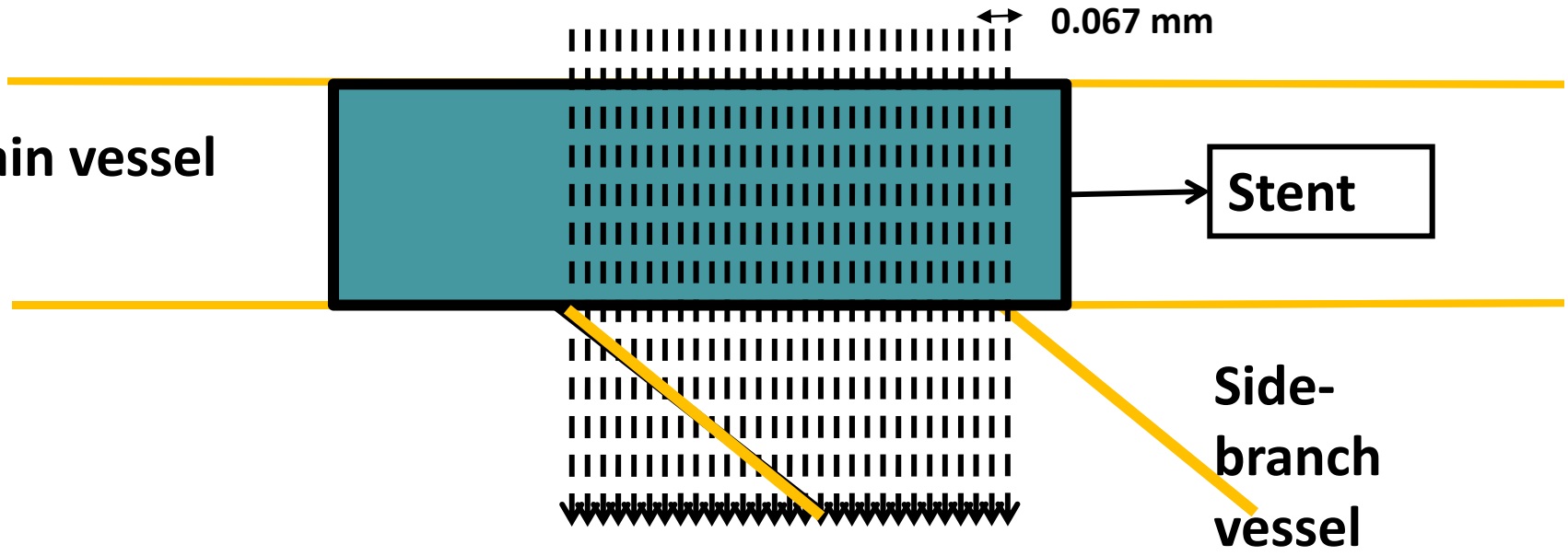

D
F
B
A
H
E
G
C
2.0 mm

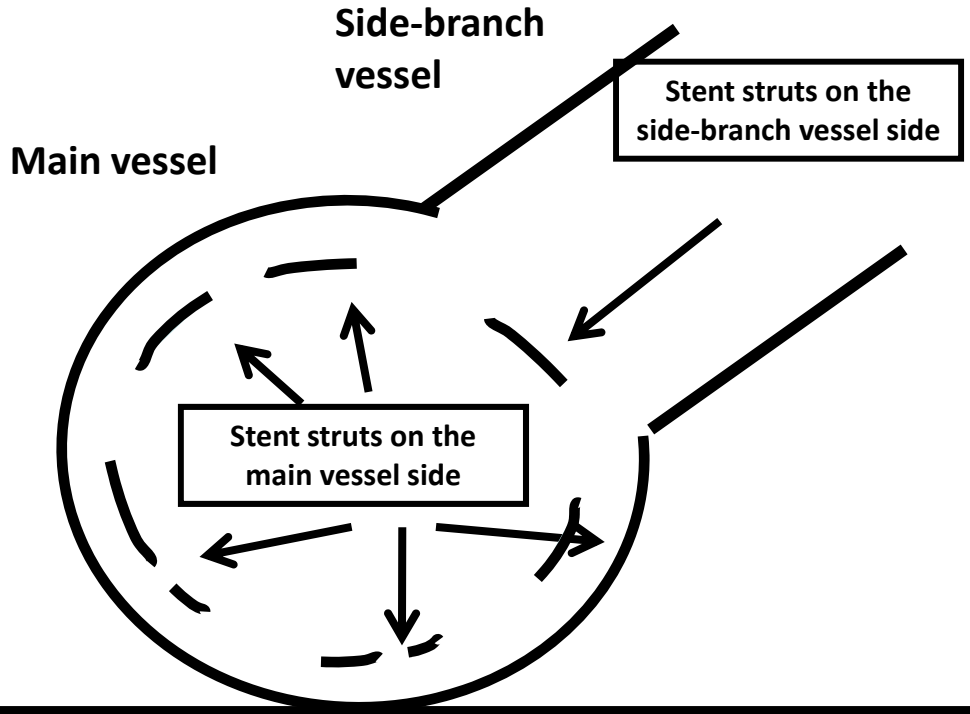


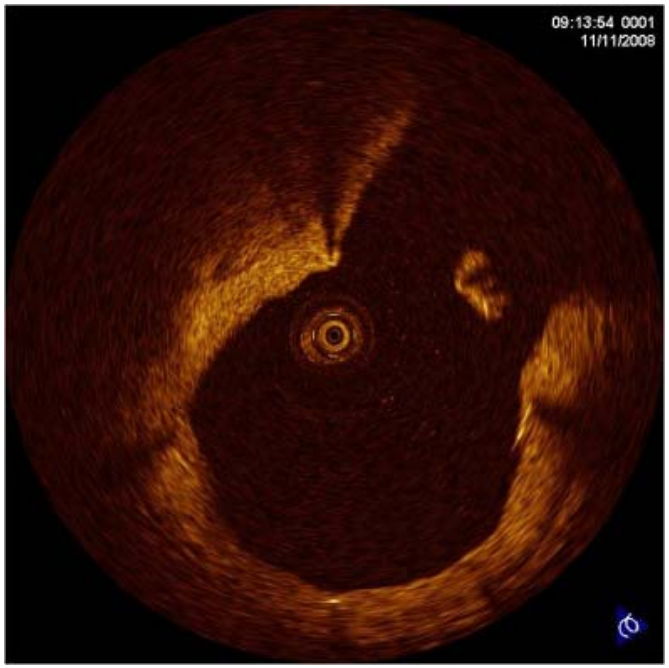
Kim JS, Granada JF, et al. J Am Coll Cardiol Img 2011;4:1002-10



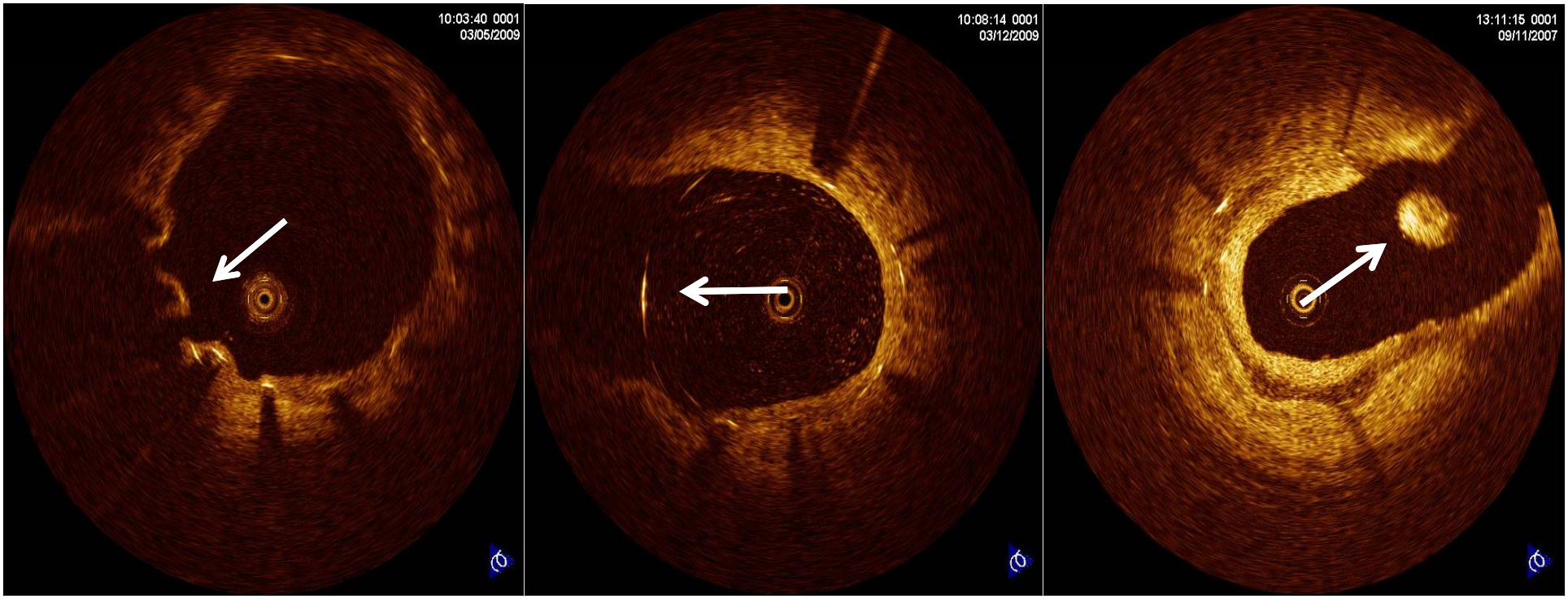
Kim JS, Granada JF, et al. J Am Coll Cardiol Img 2011;4:1002-10


0.067 mm
Main vessel
Stent
Side-
branch
vessel


Side-branch
vessel
Stent struts on the
side-branch vessel side
Main vessel
Stent struts on the
main vessel side

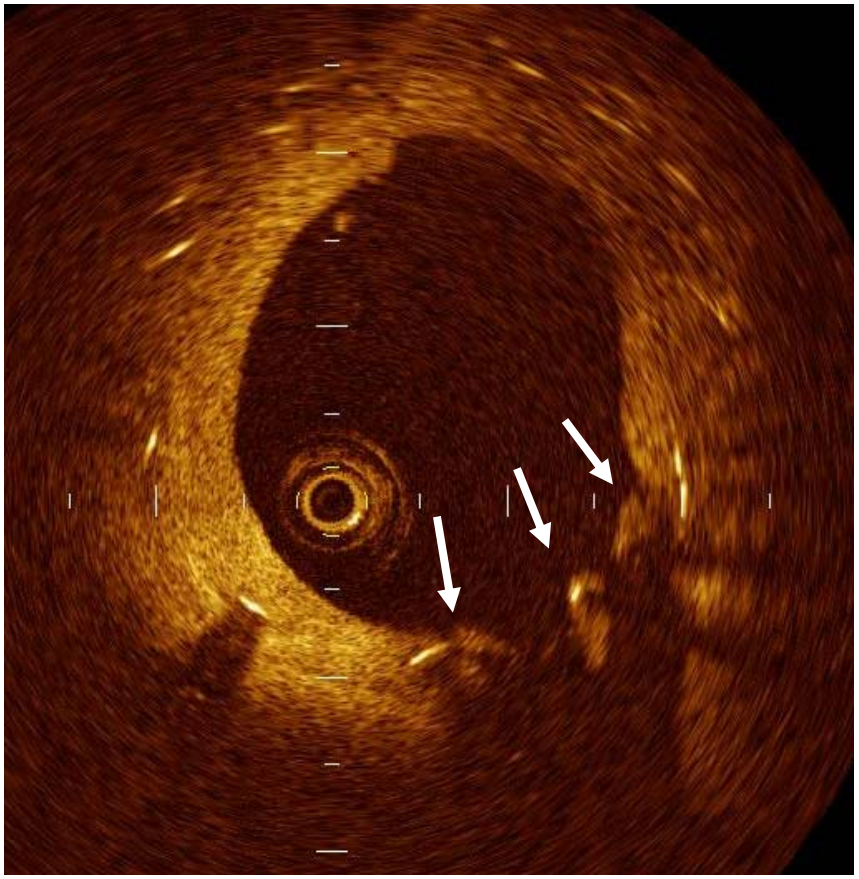

09:13:54 0001
11/11/2008

Comparison of neointimal formation on struts crossing the side-branch

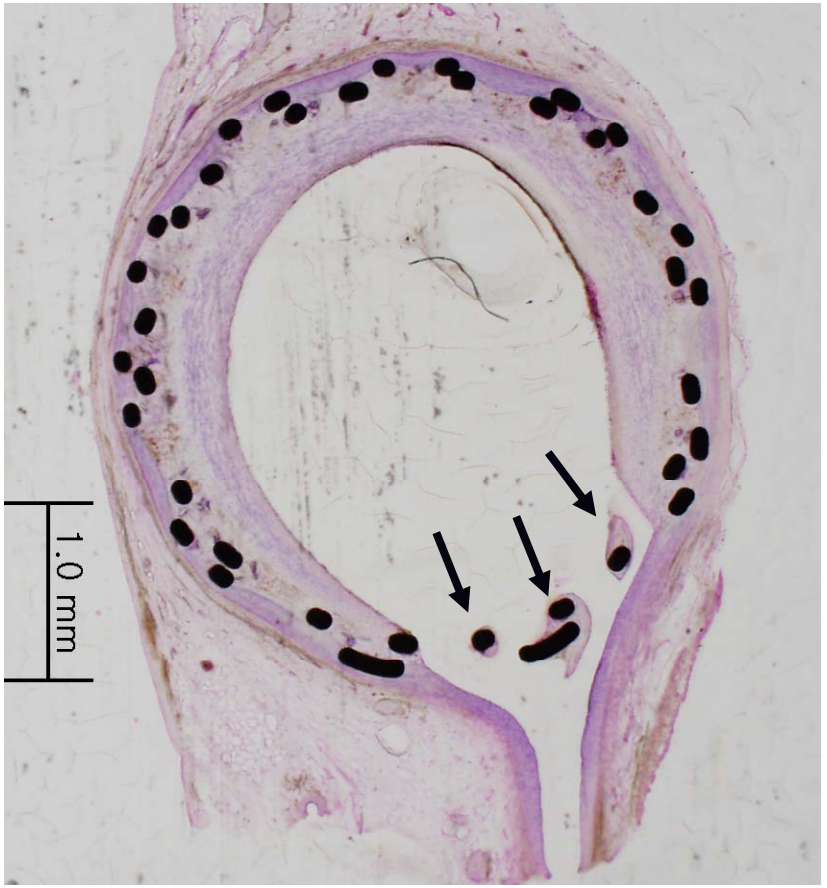


Cypher (SES) **Taxus (PES)** **Endeavor (ZES)**

Her AY, Hong MK, et al. Am J Cardiol 2010;105:1565-9



OCT

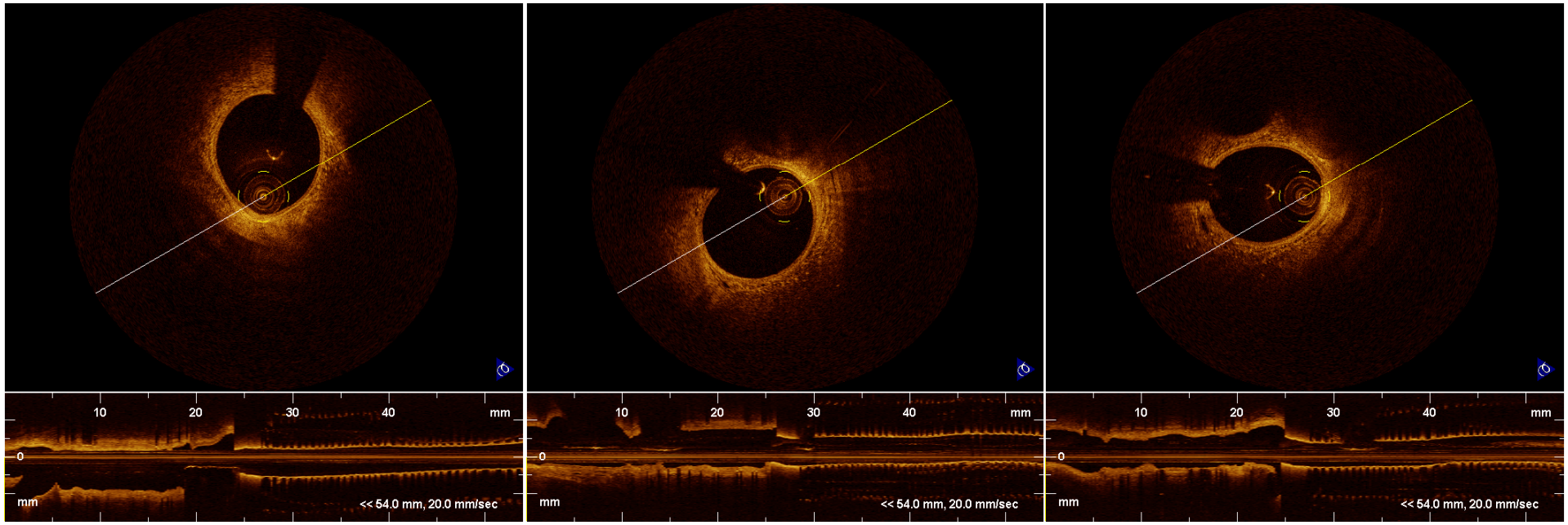


Histology

2 struts are covered with SMC-rich neointima, 1 strut covered with proteoglycan- rich, 1 strut covered with proteoglycan-rich but partially uncovered (bare strut)

Interpreted by CVPath

Evaluation of Flushing Solution



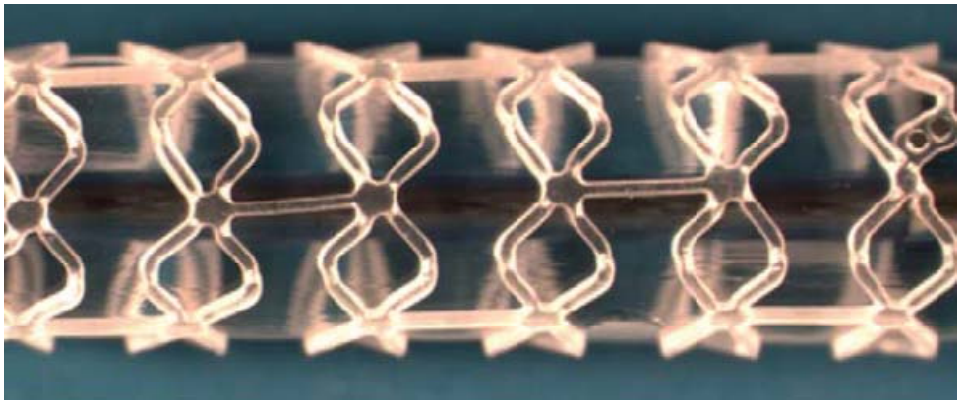
100 % Contrast **50 % Contrast + Dextran** **Dextran**

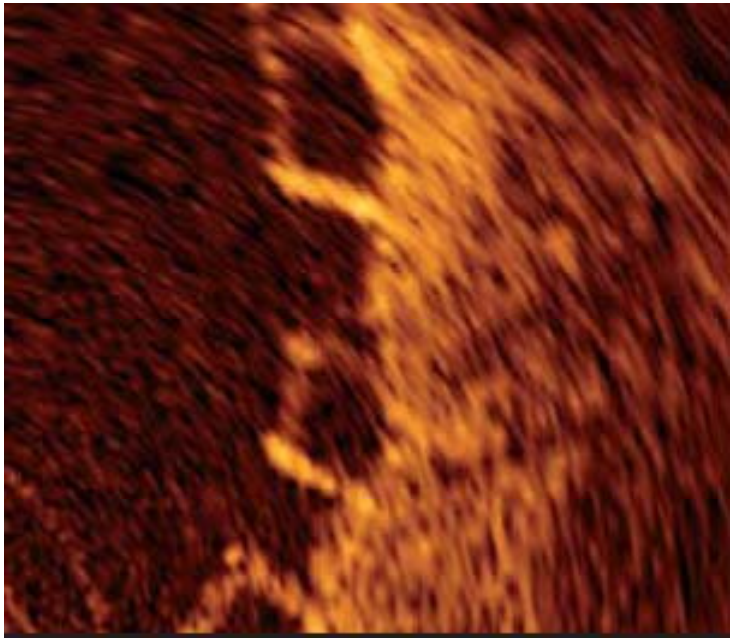
Dextrose Solution

- Dextran or Contrast could cause a renal impairment.
- 10 % DW or 20 % DW

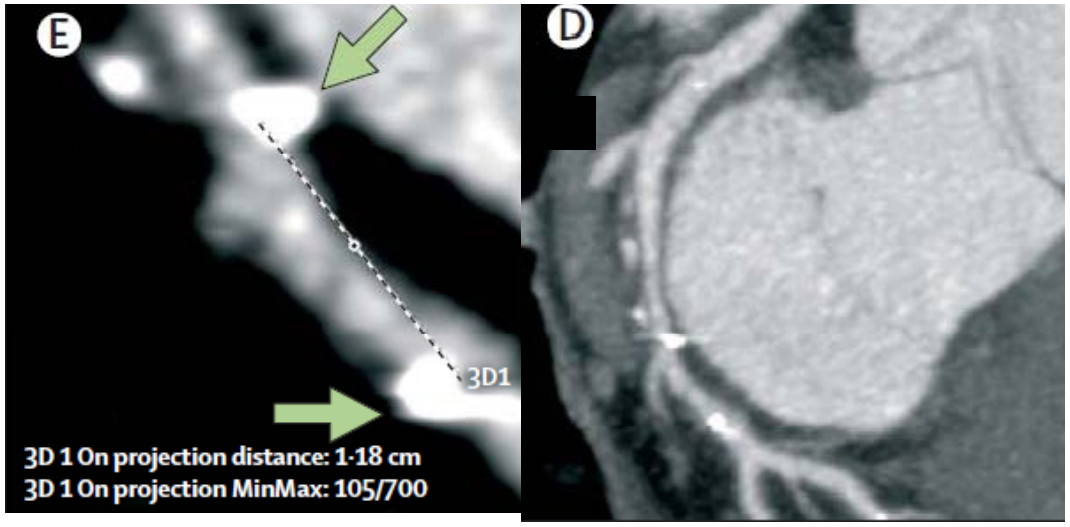
  -> Not clear image and induce frequent PVC's and ST segment change.
- Cannot apply in clinical practice because of safety issue.

Bioabsorbable everolimus eluting stent (BVS)





OCT (Stent strut thickness 150um)

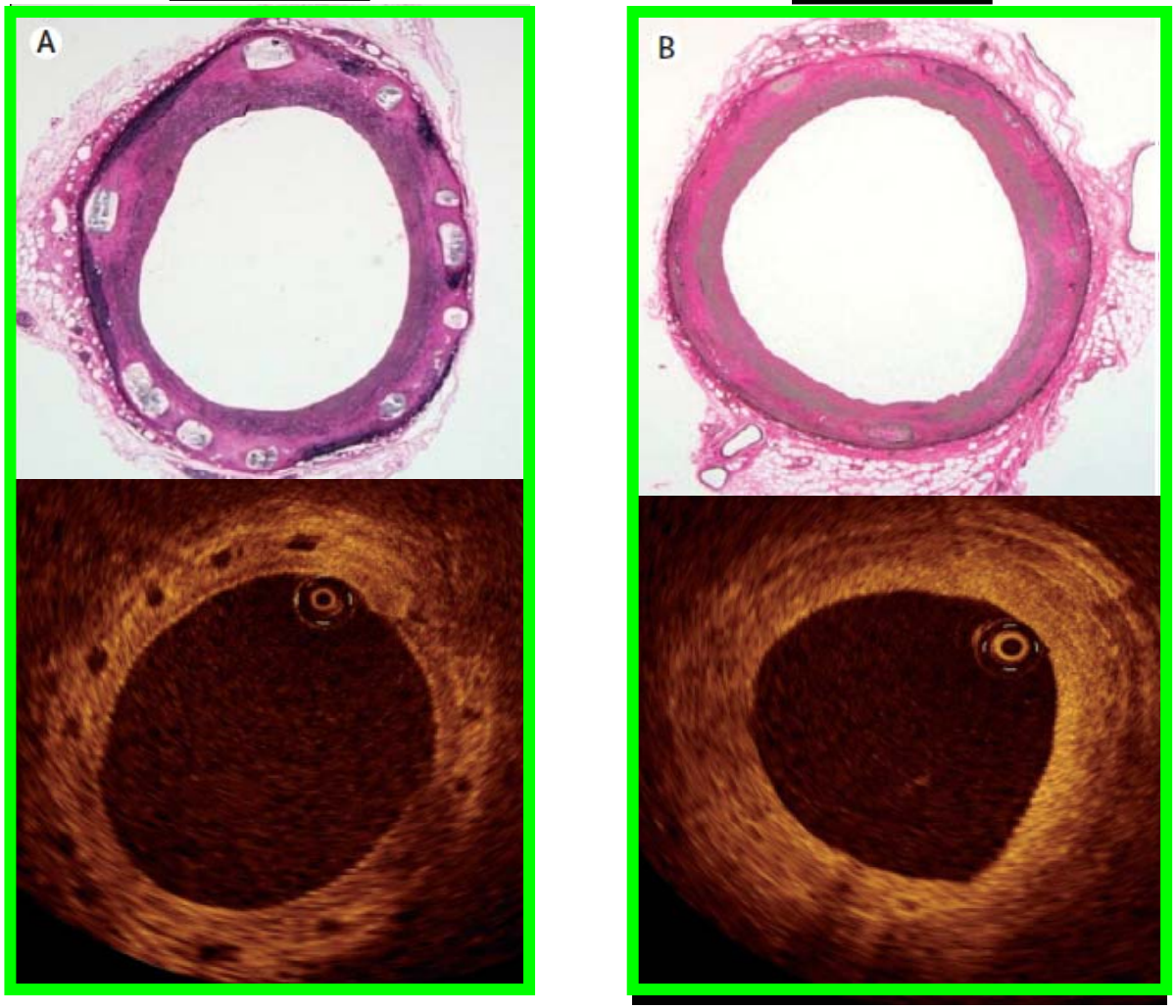


CT delineates easily the contours of the stented vessel because the stent structures are not radio-opaque

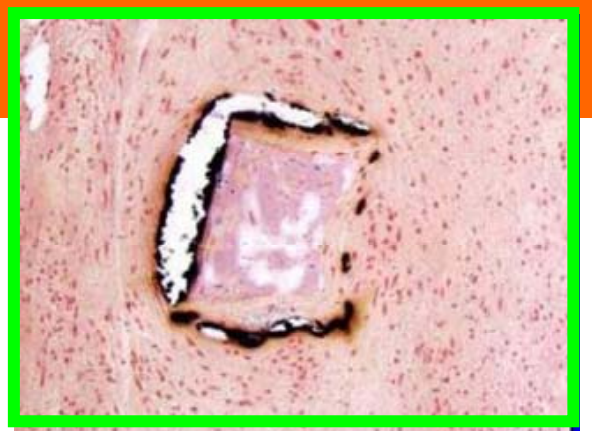
Serruys PW, et al. Lancet 2009;373:897-910

Preclinical porcine studies

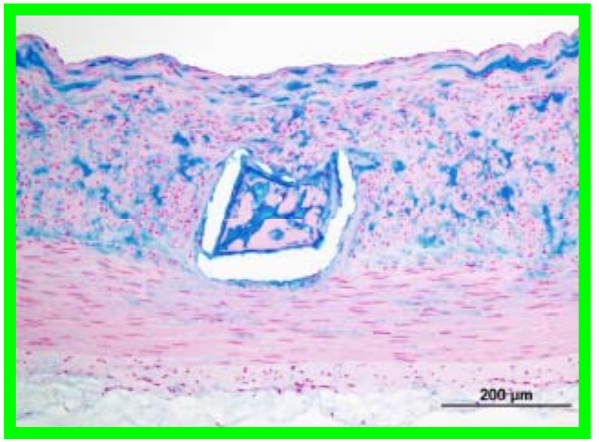
2 years → 3 years



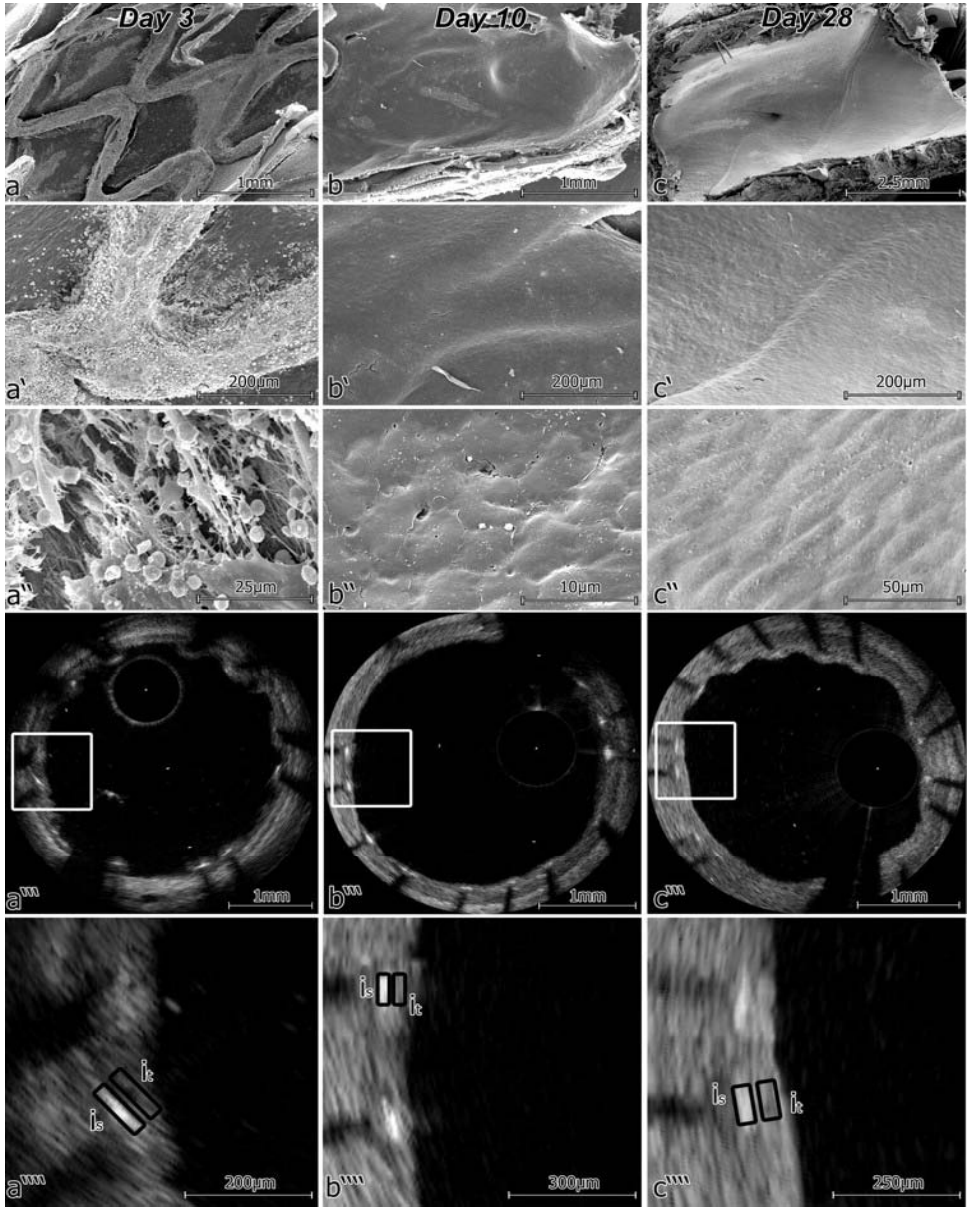
Onuma Y, et al. Circulation 2010;122:2280-300



Von Kossa Stain
Mineralization seen around pre-existing BVS struts. It is typically seen on most DES struts.



Alcian Blue Stain
Proteoglycan encompassing and replacing the pre-existing BVS stent struts



Different characteristics of stent strut coverage at different time points after stent implantation, fibrin- vs. neointima-covered stent struts

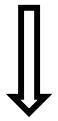
Different characteristics of stent strut coverage at different time points after stent implantation, i.e. fibrin- vs. neointima-covered stent struts. (A) Fibrin at Day 3 in SEM and OFDI, where a low intensity of stent strut coverage can be seen (A‴′); (B) neointima at Day 10 in SEM and OFDI, where stent strut coverage with higher intensity when compared with fibrin can be observed; (C) neointima at Day 28 in SEM and OFDI, where a high intensity of stent strut coverage is present (is, intensity of strut; it, intensity of tissue).

Templin C et al. Eur Heart J 2010

Change of Neotintimal Tissue after Stenting

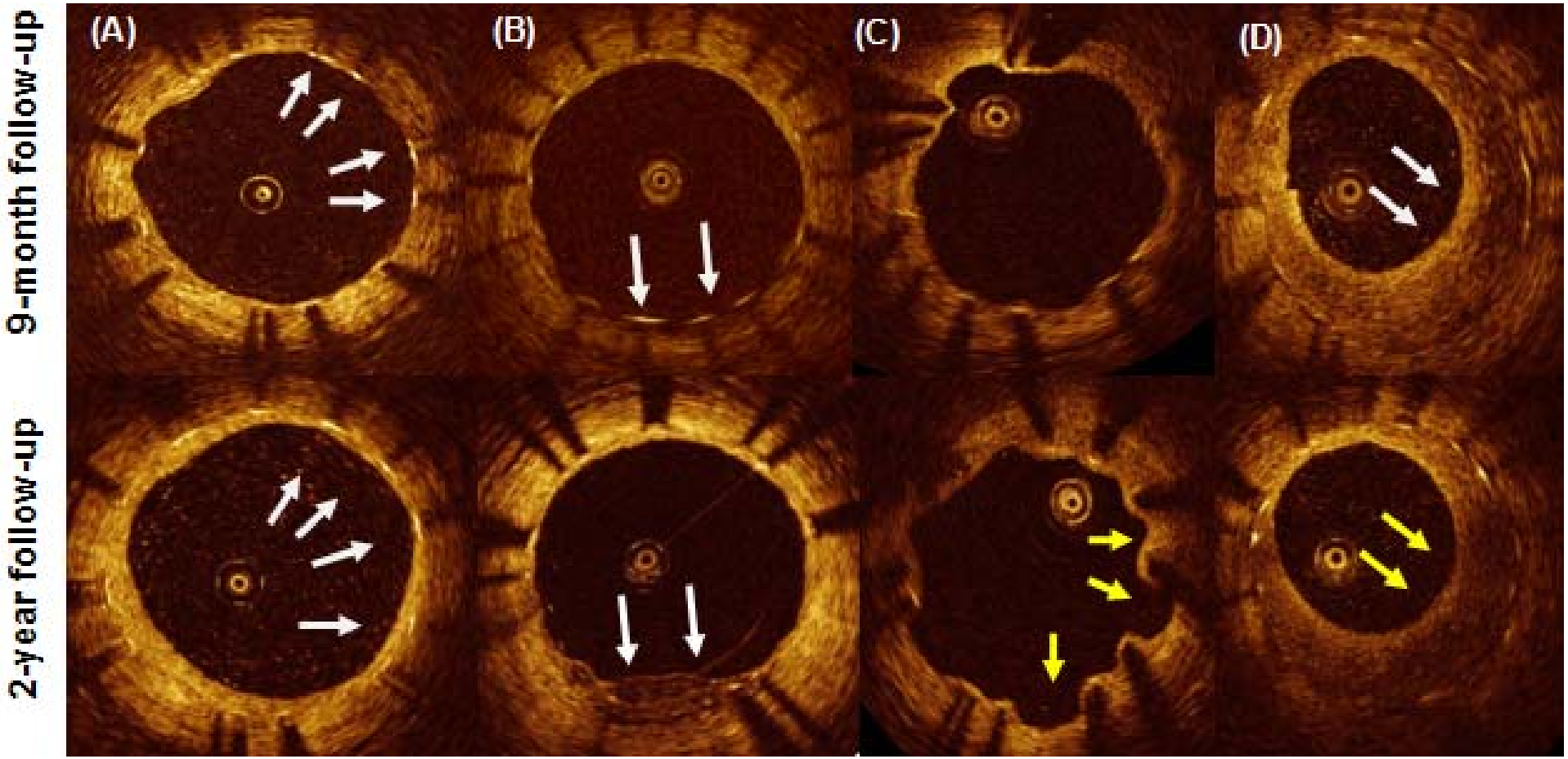
Delayed vascular healing after DES implantation is suggested as a strong predictor among several factors.

In addition, recent studies demonstrated that development of neoatherosclerosis within neointimal tissues could be another cause of stent thrombosis due to neointimal rupture



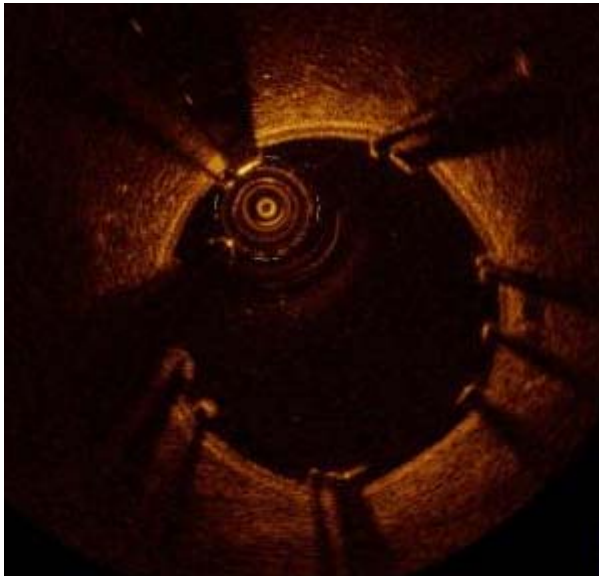
Evaluate different OCT morphological characteristics with different in-stent neointimal tissue types analyzed by histology

Serial follow-up OCT finding

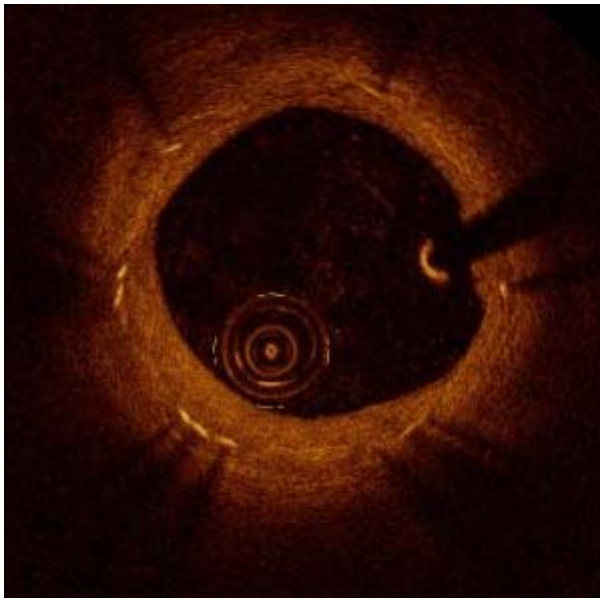


Kim JS, Hong MK, et al. J Am Coll Cardiol Img 2012 in press

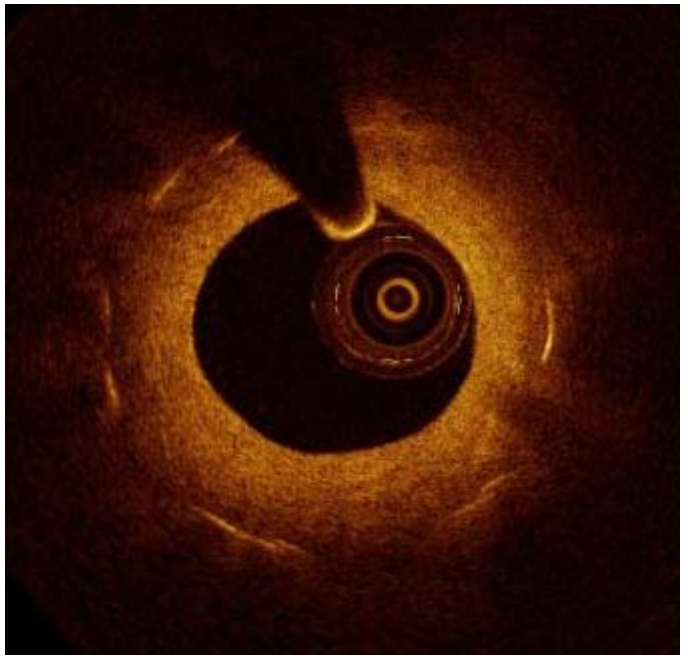
Serial Stent Evaluation



Post Stent



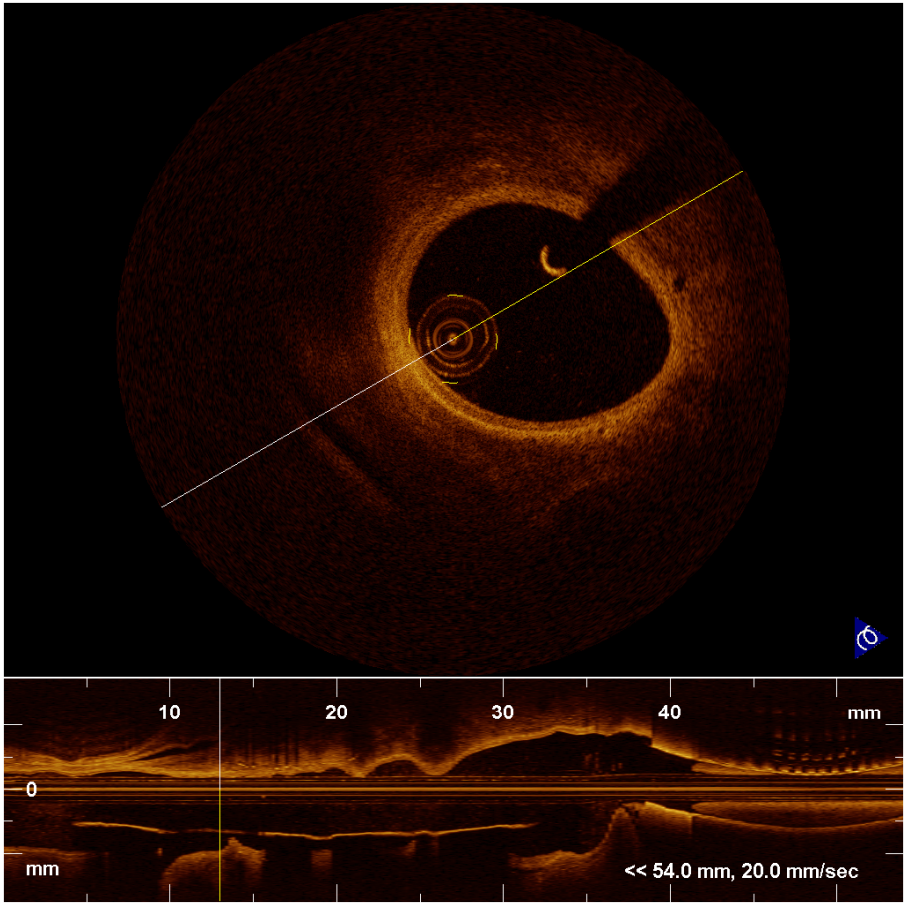
1 month



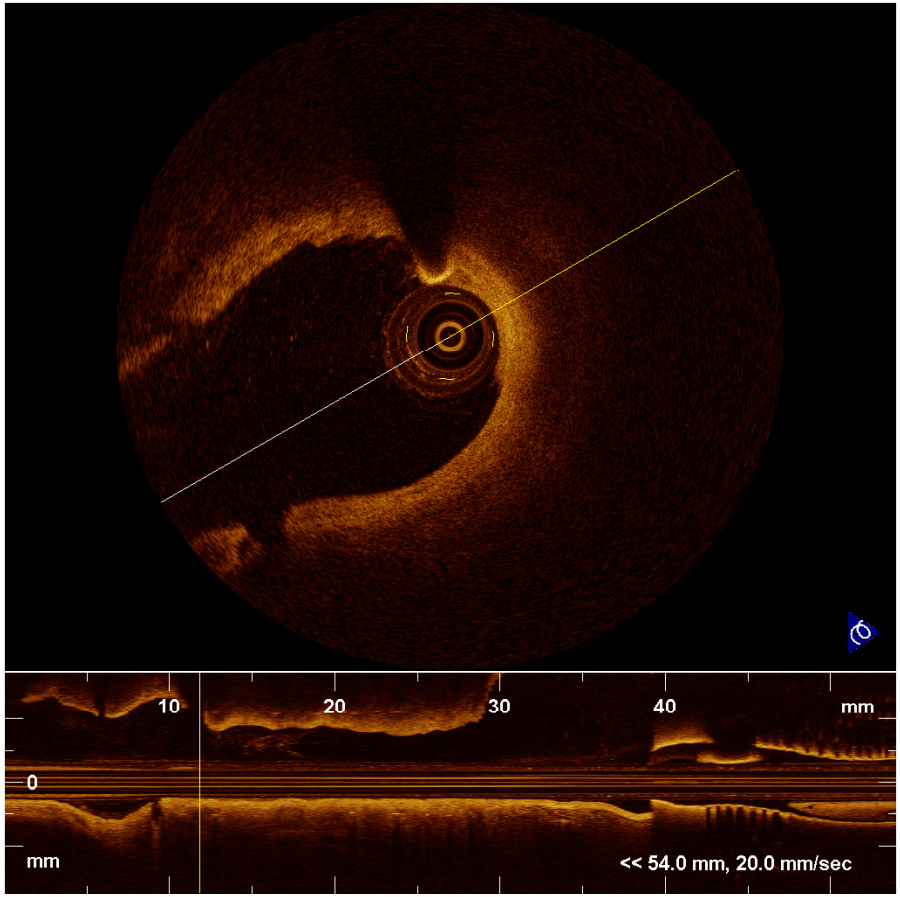
3 months weeks

Waiting for 6 months follow-up

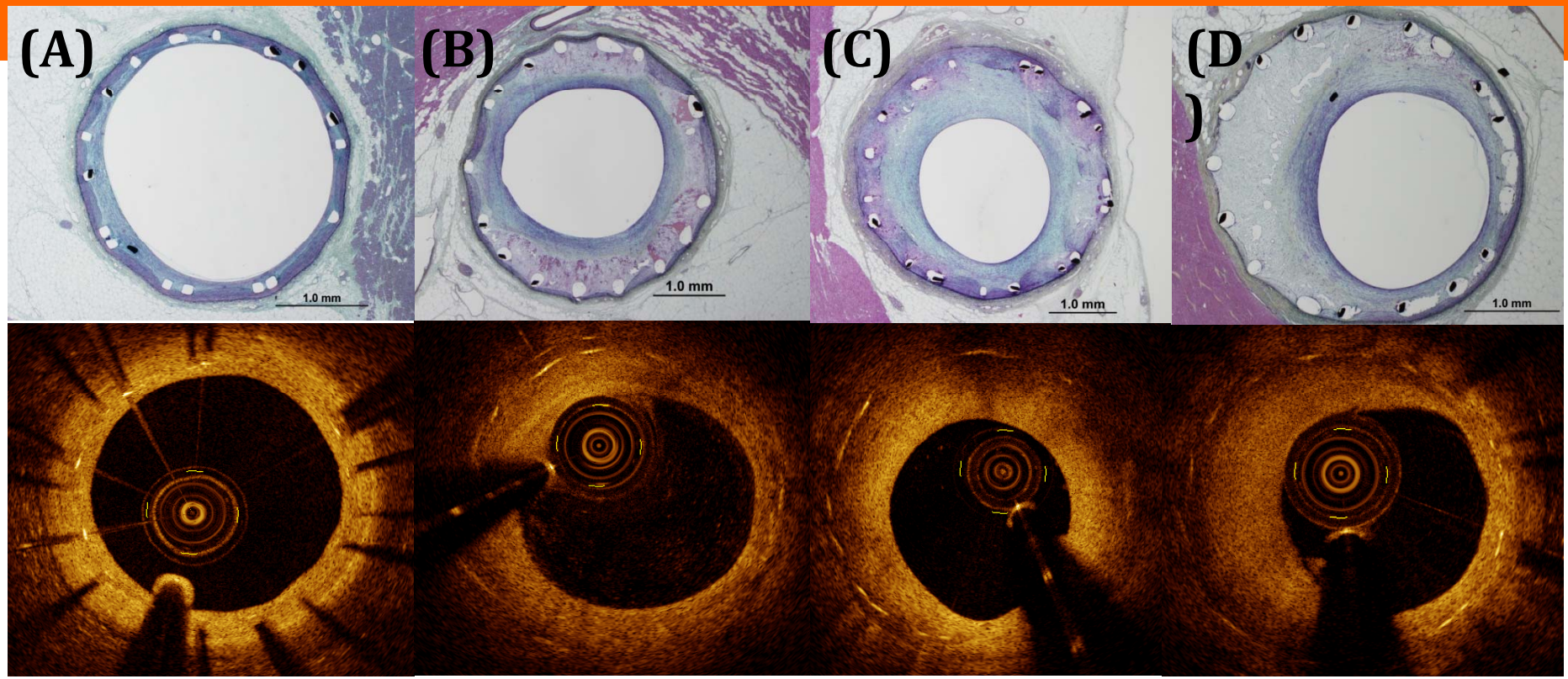
Serial Stent Evaluation



1 Month after stent implantation



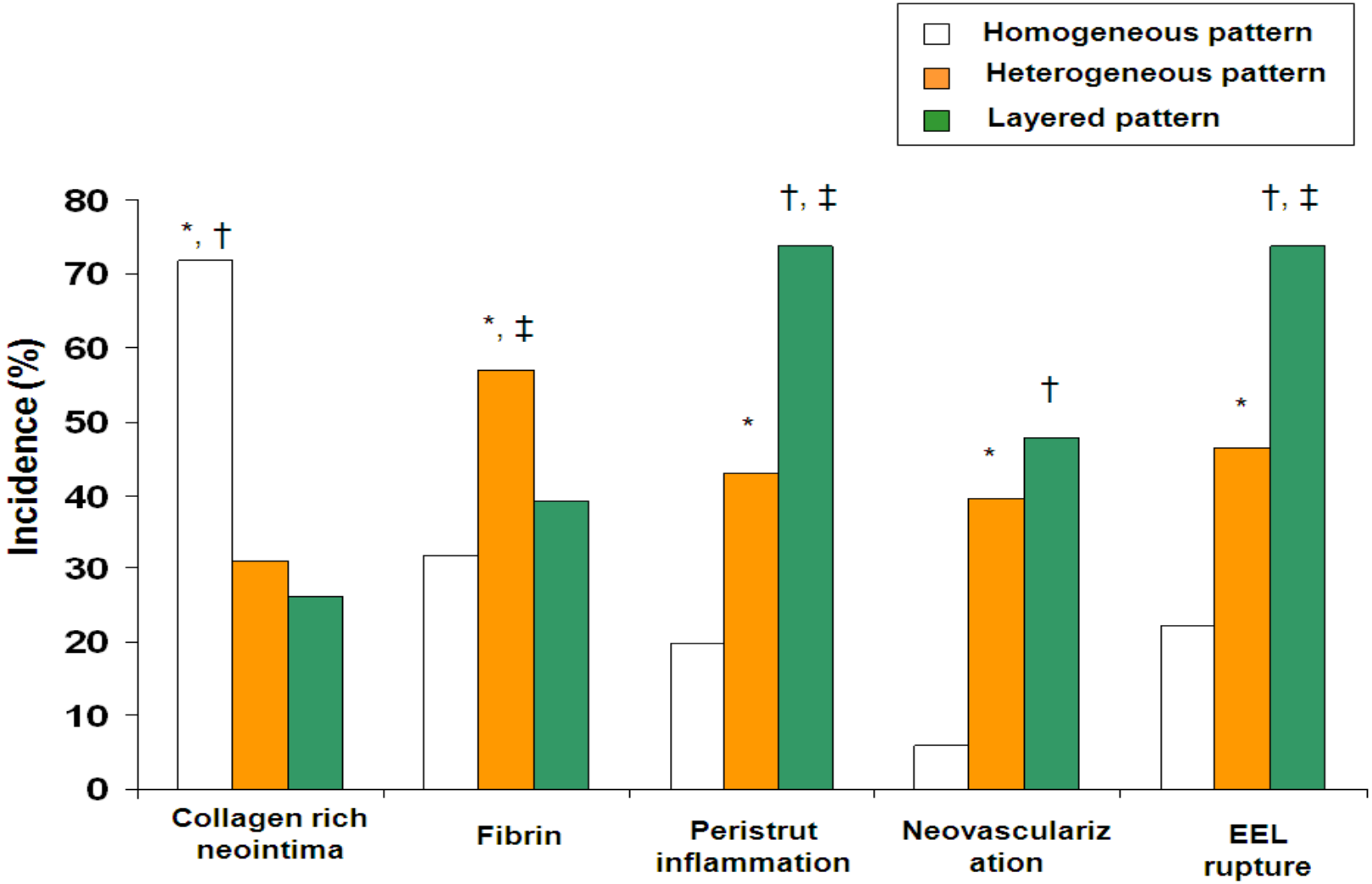
3 Months after stent implantation



Representative images of OCT and histologic sections.

(A) Homogeneous neointimal pattern in OCT has a collagen rich neointima (bluish color) (B) heterogeneous neointimal pattern shows lots of loose connective tissue (grey color) and fibrin (pink color) (C) layered neointimal pattern shows thick neointima, external elastic laminal rupture and peristrut inflammation (D) neovascularization is shown in the middle of neointima.

Kim JS, Granada JF, et al. TCT 2011



Histological evaluation of OCT neointimal pattern.

*: p<0.05 between homogeneous and heterogeneous group, †: p<0.05 between homogeneous and layered group, ‡: p<0.05 between heterogeneous and layered group

Kim JS, Granada JF, et al. TCT 2011

Advantage and Pitfalls

-Intravascular OCT is a high-resolution intravascular imaging modality that can be used to evaluate the surface vascular structure.

- *Limited penetration and scan area – need a hybrid modality.*

Summary

-Intravascular OCT is a high-resolution intravascular imaging modality that can be used to evaluate the surface vascular structure and thin neointimal tissue *in Pre-clinical study.*

-It is useful to evaluate the adequate animal model.

- It is also valuable to assess the efficacy and safety evaluation of newly developed intravascular devices.

Thanks for Your Attentions


TOSHIBA INFX 8000V Cardiac Angiography System

Cardiovascular Product Evaluation Center


Conference Room


Angio Room


Control Room


Echocadiogram Lab


Surgery Zone


Rabbit Cage

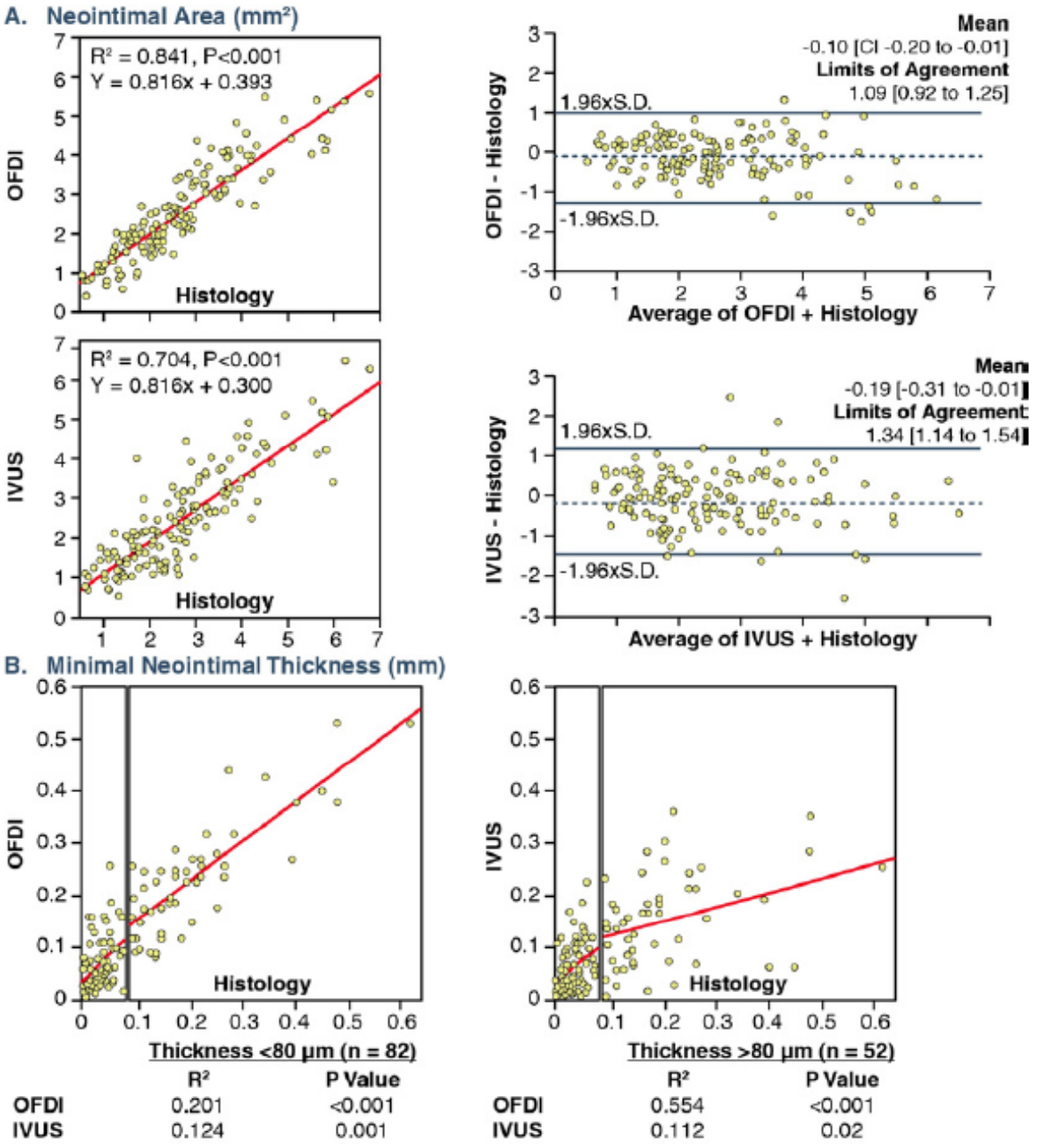
JACC: CARDIOVASCULAR IMAGING
VOL. 5, NO. 1, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.09.015

Ex Vivo Assessment of Vascular Response to Coronary Stents by Optical Frequency Domain Imaging

Masataka Nakano, MD,* Marc Vorpahl, MD,* Fumiyuki Otsuka, MD,*
Masanori Taniwaki, MD,† Saami K. Yazdani, PHD,* Aloke V. Finn, MD,‡
Elena R. Ladich, MD,* Frank D. Kolodgie, PHD,* Renu Virmani, MD*
Gaithersburg, Maryland; Tokyo, Japan; and Atlanta, Georgia

METHODS Fourteen human stented coronary segments with implant duration ≥1 month from 10 hearts acquired at autopsy were interrogated ex vivo by OFDI and intravascular ultrasound (IVUS). Comparison with histology was assessed in 134 pairs of images where the endpoints were to investigate: 1) accuracy of morphological measurements; 2) detection of uncovered struts; and 3) characterization of neointima.

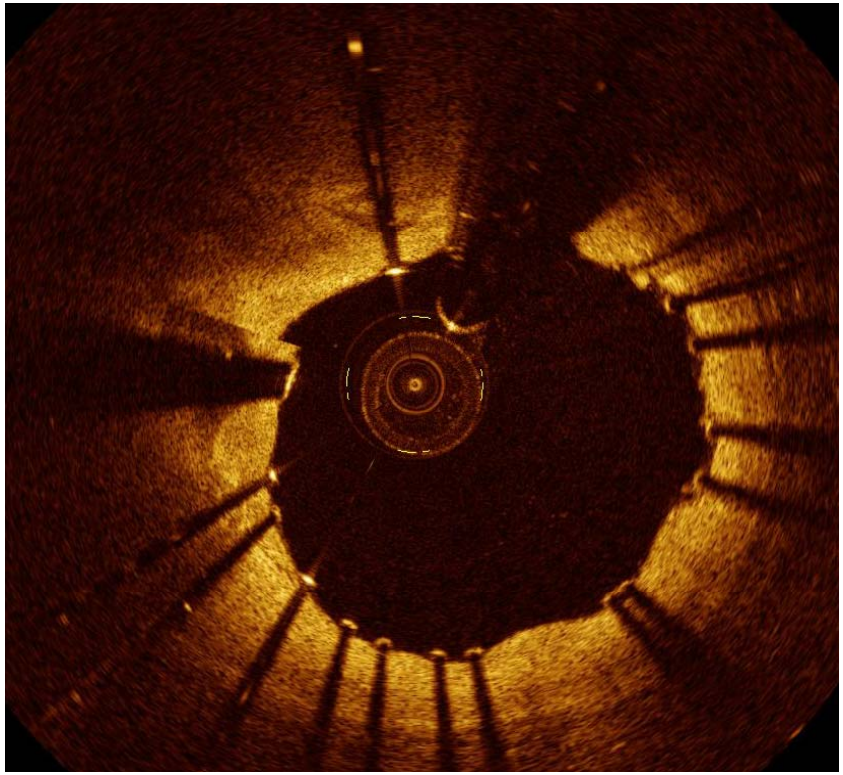


	R²	P Value
OFDI	0.201	<0.001
IVUS	0.124	0.001

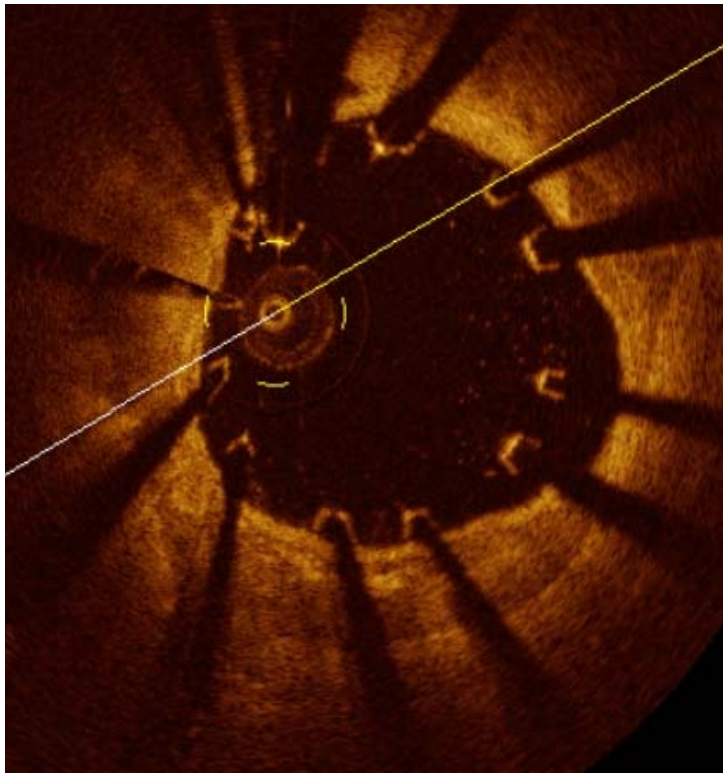
	R²	P Value
OFDI	0.554	<0.001
IVUS	0.112	0.02

Nakano M, et al.
JACC Img 2012

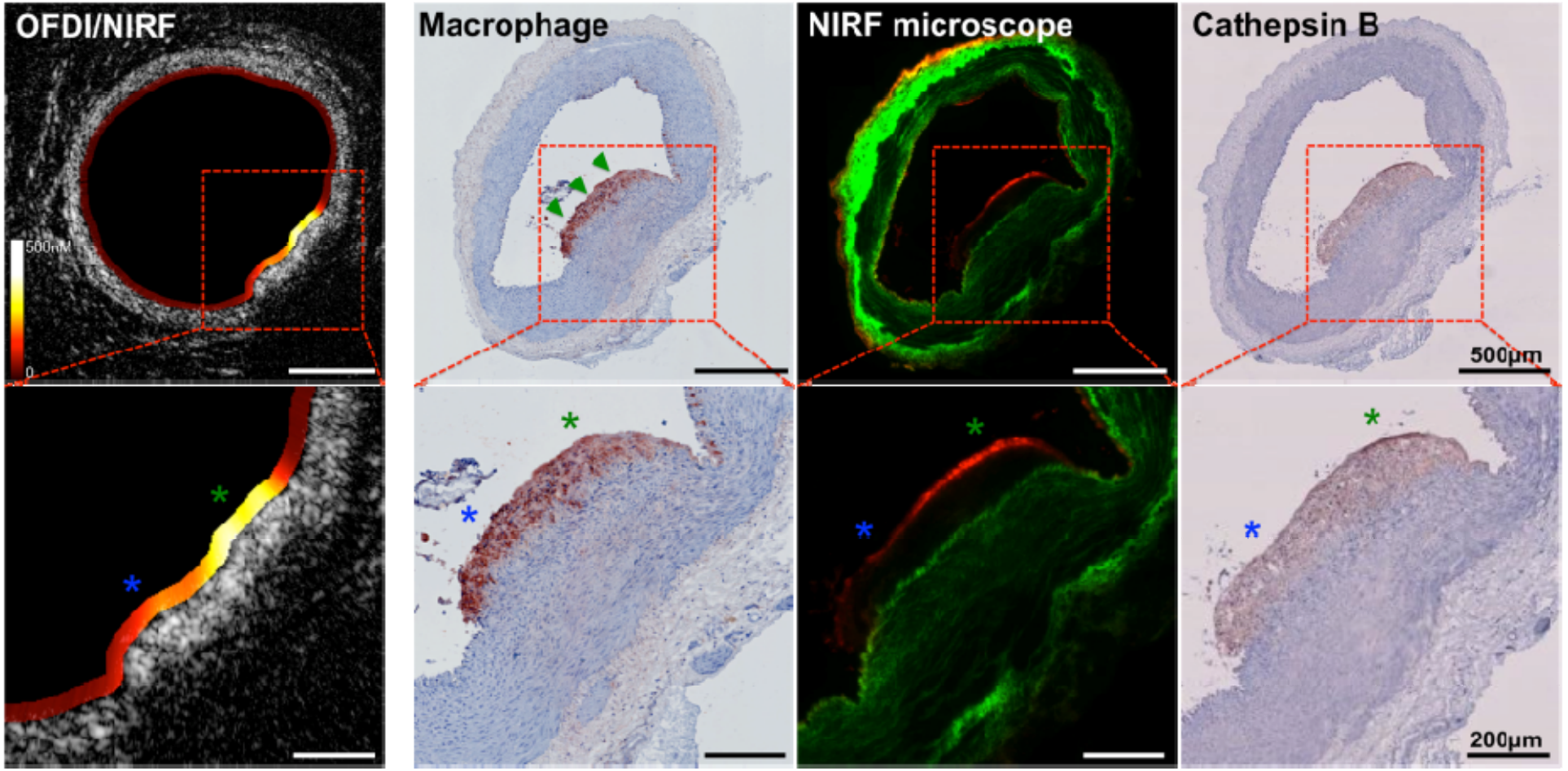
Well Apposed Stent



Malapposed Stent



Atheroma OFDI-NIRF *In Vivo* Imaging



Slide Courtesy of Dr. JW Kim

DES Evaluation of Pre-clinical study

The **recommendation** of **U.S. Food and Drug Administration** for pre-clinical stent data.

- Several time points should be used for the evaluation of DES performance, **the first at 28 days** to observe for neointimal hyperplasia, and at least 1 later time point to examine long-term effects.
- The **later time point (3 or 6 months)** depends on when "healing" and drug release are both complete.

Suzuki, Y. et al. J Am Coll Cardiol Intv 2009;2:373-383