

Erasmus MC



# Vulnerable Plaque Trials Using Surrogate Imaging Markers

**Prof. Patrick W. Serruys MD, PhD**

**Hector M. Garcia-Garcia MD, MSc**

**Yoshinobu Onuma MD**

**Subject: Imaging II: Clinical Implications of Imaging and Physiology Tools**

**Place: Symposium Arena, Level 3**

**5:00 PM ~ 5:12 PM**

# Surrogate markers Definition

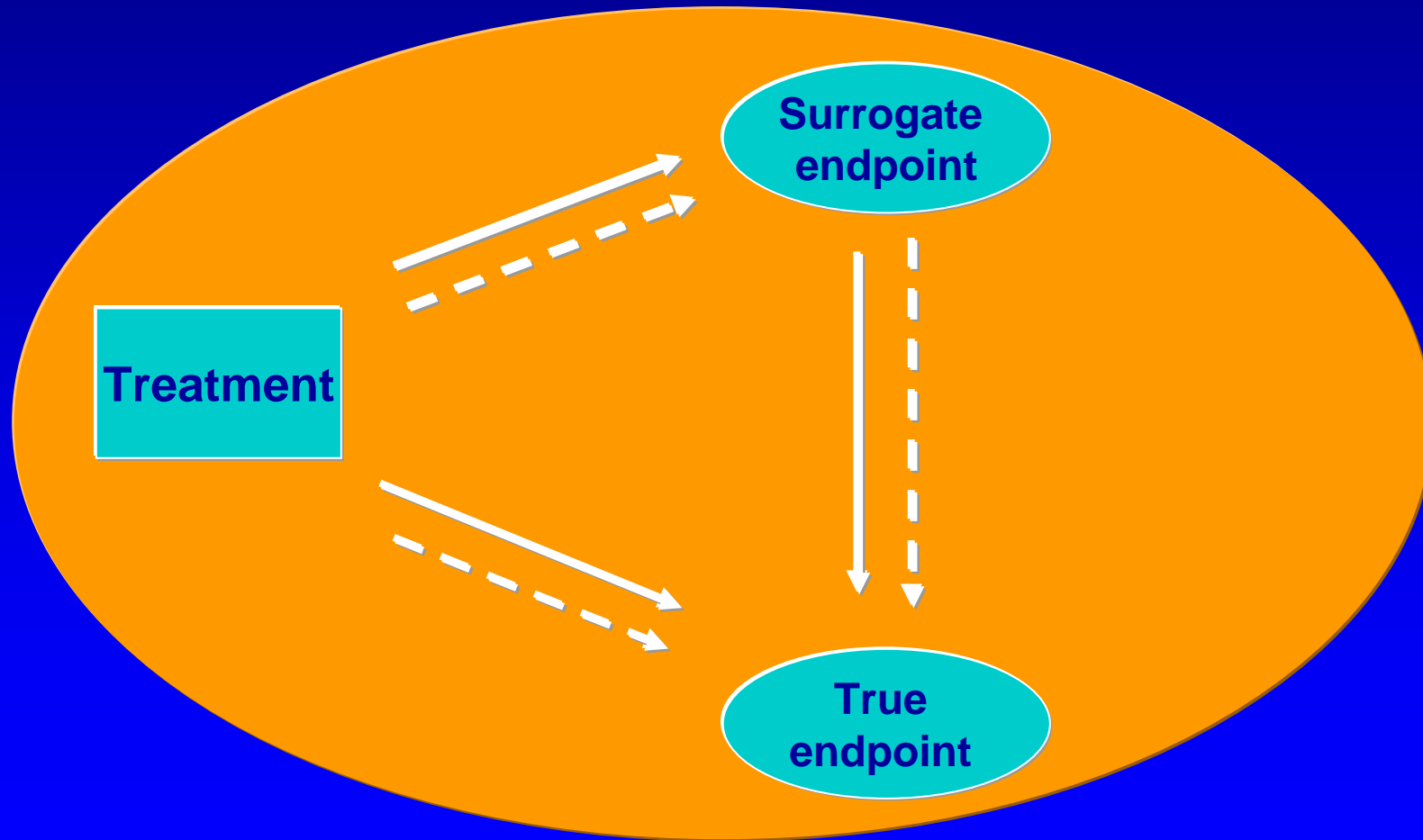
- a clinical/imaging measurement
- statistically associated with a clinical outcome
- with current knowledge is believed to share a causal mechanism with the clinical outcome

# Surrogate markers

## Definition

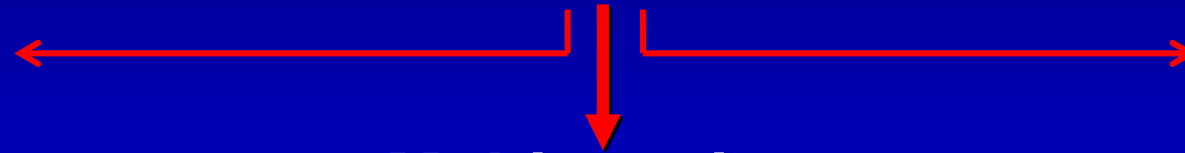
- A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy

# Surrogate markers Definition



# BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population

**7300 pts multicenter**



**Mobile units**

**Coronary Artery Calcium (CAC) score, Carotid Intima-Media Thickness (IMT), atherosclerotic plaque, Ankle Brachial Index (ABI), and presence of Abdominal Aortic Aneurysm (AAA)**

**Biomarkers, RNA expression profiling, and candidate gene analysis or genome wide scanning.**

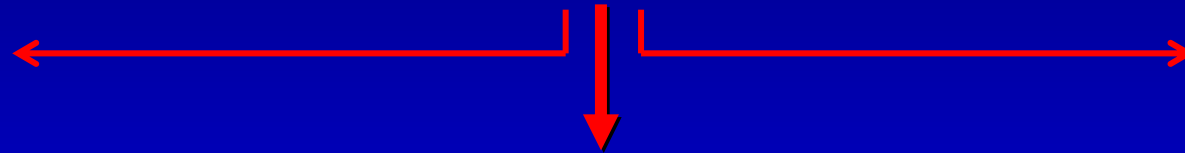
PI: Valentin Fuster, MD, PhD and Erling Falk, MD, PhD

Sponsor: BG Medicine, Inc; AstraZeneca; Abbott; Merck; Philips Medical Systems; Takeda Global Research & Development Center, Inc

# The PREDICTION Trial

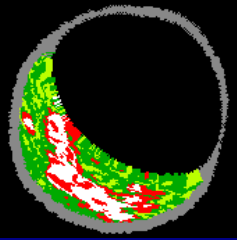
Prediction of Vascular and Clinical Outcomes by Intracoronary Vascular Profiling Study

**500 pts multicenter**

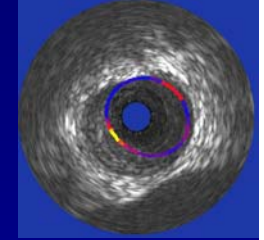


**1-vessel imaging**

**The study will examine abnormalities of coronary blood flow by fusing coronary angiography and intravascular ultrasound.**

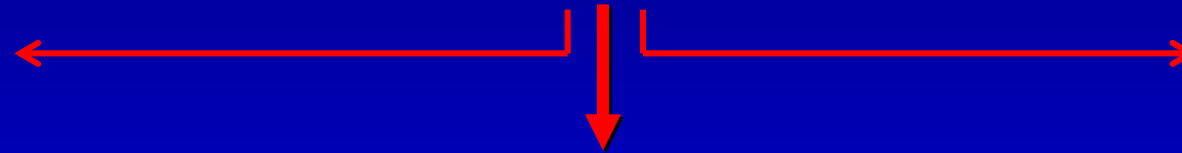


# The PROSPECT Trial



700 pts with ACS

MSCT  
Substudy  
N=50-100

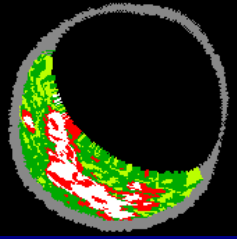


Biomarkers

- Hs CRP
- IL-6
- sCD40L
- MPO
- TNF  $\alpha$
- MMP9
- Lp-PLA2
- others

3-vessel imaging post PCI

Angiography (QCA of entire coronary tree), IVUS,  
**Virtual histology**, Palpography

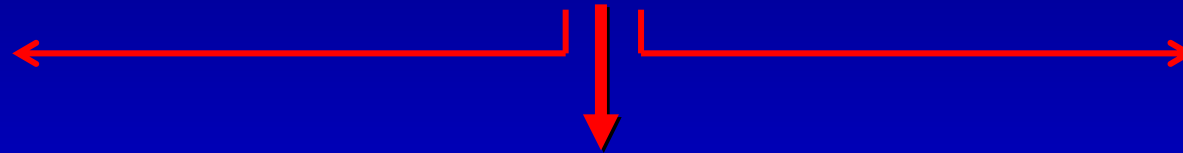


# The ATHEROREMO Study

## 800 pts with ACS/Non-ACS

Thoraxcenter

Several EU  
University  
Hospitals



Biomarkers

- Hs CRP
- IL-6
- sCD40L
- MPO
- TNF  $\alpha$
- MMP9
- Lp-PLA2
- Others....

1-2 vessel imaging post PCI

Angiography (QCA of entire coronary tree), IVUS,  
**Virtual histology**, NIR spectroscopy

PI: Patrick W. Serruys

Sponsor: EU Grant Partner: Volcano



# The Vulnerable Plaque Patient Study

600 pts with ACS/Non-ACS

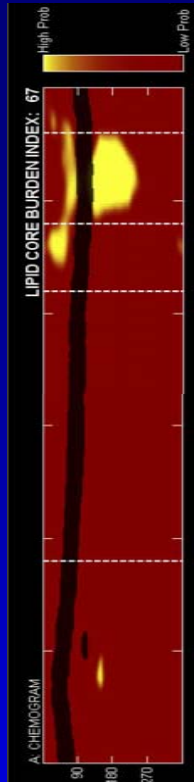
Thoraxcenter

1-2 vessel imaging post PCI

Biomarkers

- Hs CRP
- IL-6
- sCD40L
- MPO
- TNF  $\alpha$
- MMP9
- Lp-PLA2
- Others....

Angiography (QCA of entire coronary tree), IVUS,  
NIR spectroscopy



# In Vivo Assessment of High-Risk Coronary Plaques at Bifurcations With Combined Intravascular Ultrasound and Optical Coherence Tomography

Nieves Gonzalo, MD, Hector M. Garcia-Garcia, MD, MSc, Evelyn Regar, MD, PhD,  
Peter Barlis, MBBS, MPH, Jolanda Wentzel, PhD, Yoshinobu Onuma, MD,  
Jurgen Ligthart, BsC, Patrick W. Serruys, MD, PhD

*Rotterdam, the Netherlands*

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# Some people think that only Little...

JACC: CARDIOVASCULAR IMAGING

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## EDITORIAL COMMENT

### The Vulnerable Plaque “Hypothesis”

Promise, but Little Progress\*

Steven E. Nissen, MD

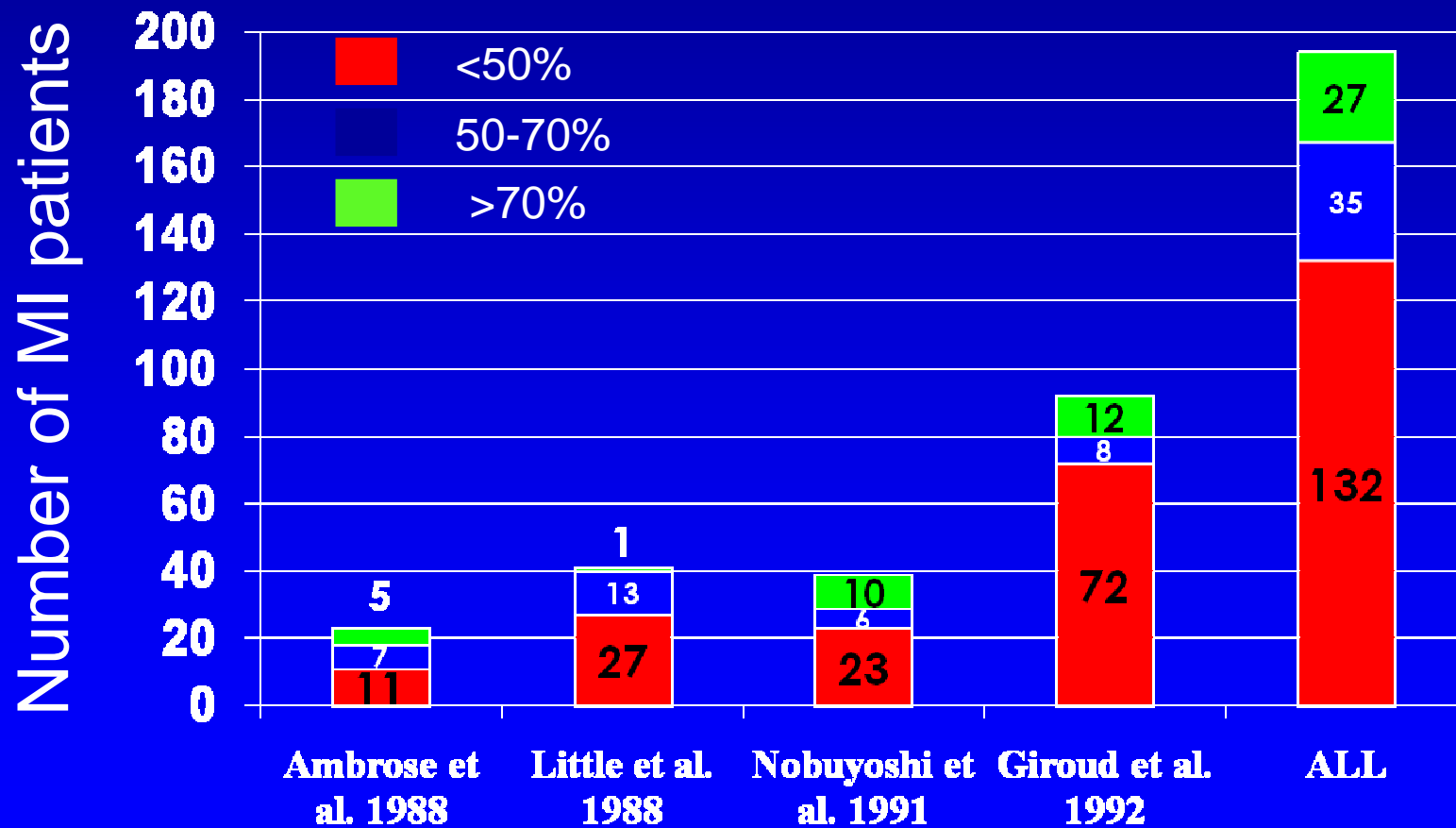
*Cleveland, Ohio*

A PubMed search using the terms “vulnerable plaque” or “high-risk” plaque yields >2,000 references to journal articles published over the past 20 years. Indeed, few concepts in cardiovascular medicine have achieved such intense scientific interest over such a long duration. During this 20-year period, many diagnostic techniques designed to “detect” vulnerable plaques have come and gone. In each case, a flurry of promising “findings” has been followed by a sobering reality check. These include thermography, spectroscopy, palpography, virtual histology, optical coherence tomography, and many more (1–5). A large number of startup companies with “breakthrough” approaches have come and gone, nearly all leaving investors with empty pockets, but no progress. What has gone wrong?

It is time to face reality. Much of the contemporary concept of vulnerable plaque is fundamentally flawed or overly simplistic, and most approaches to detection are poorly conceived. ▮

# Background 1: Acute Myocardial Infarctions Evolve Most Frequently From Plaques With Mild to Moderate Obstruction

**Inclusion criterion: FFR > 0.75**



## Background 2: TICFA, a theoretical precursor of plaque rupture maybe detected invasively by IVUS-VH according to the following criteria:

1. 3 consecutive frames with three characteristics
2. Necrotic core  $\geq 10\%$
3. In direct contact with the lumen
4. Plaque burden  $>40\%$

FIBROTIC

FT

FIBROFATTY

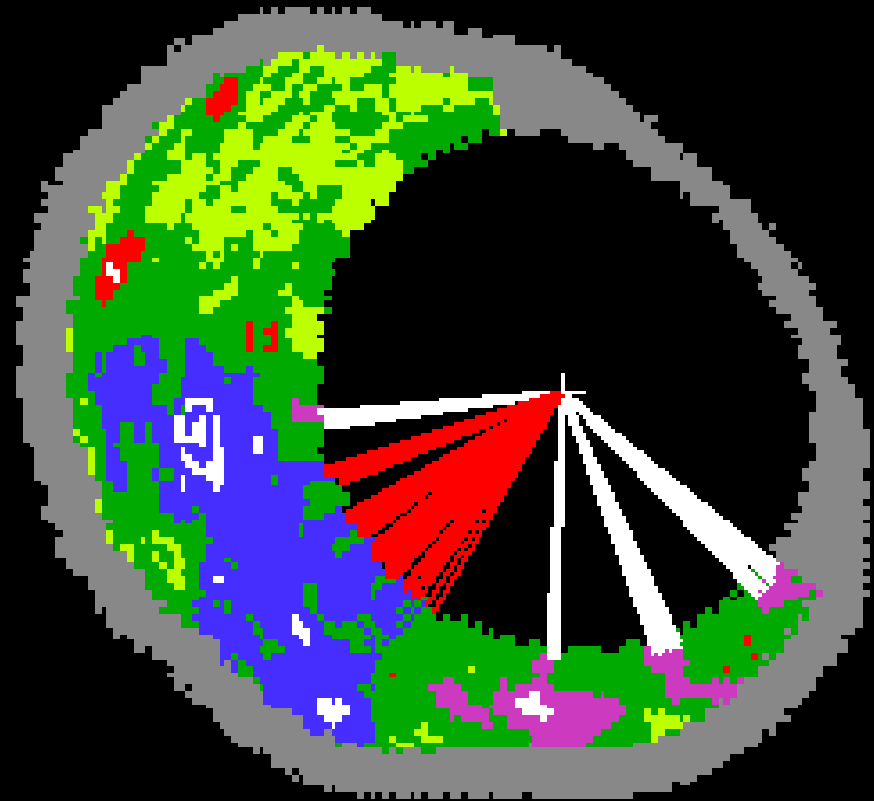
FF

DENSE CALCIUM

DC

NECROTIC CORE

NC



Rodriguez-Granillo GA, Garcia-Garcia HM, Serruys P W. J Am Coll Cardiol 2005;46:2038-42

Garcia-Garcia HM, Serruys PW et al. Eurointervention 2006;2:338-344.

# Background 3: OCT enables to measure accurately fibrous cap thickness, increases accuracy of detecting TCFAs and allows to identify plaque rupture



European Heart Journal  
doi:10.1093/eurheartj/ehh132

CLINICAL RESEARCH

## Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma

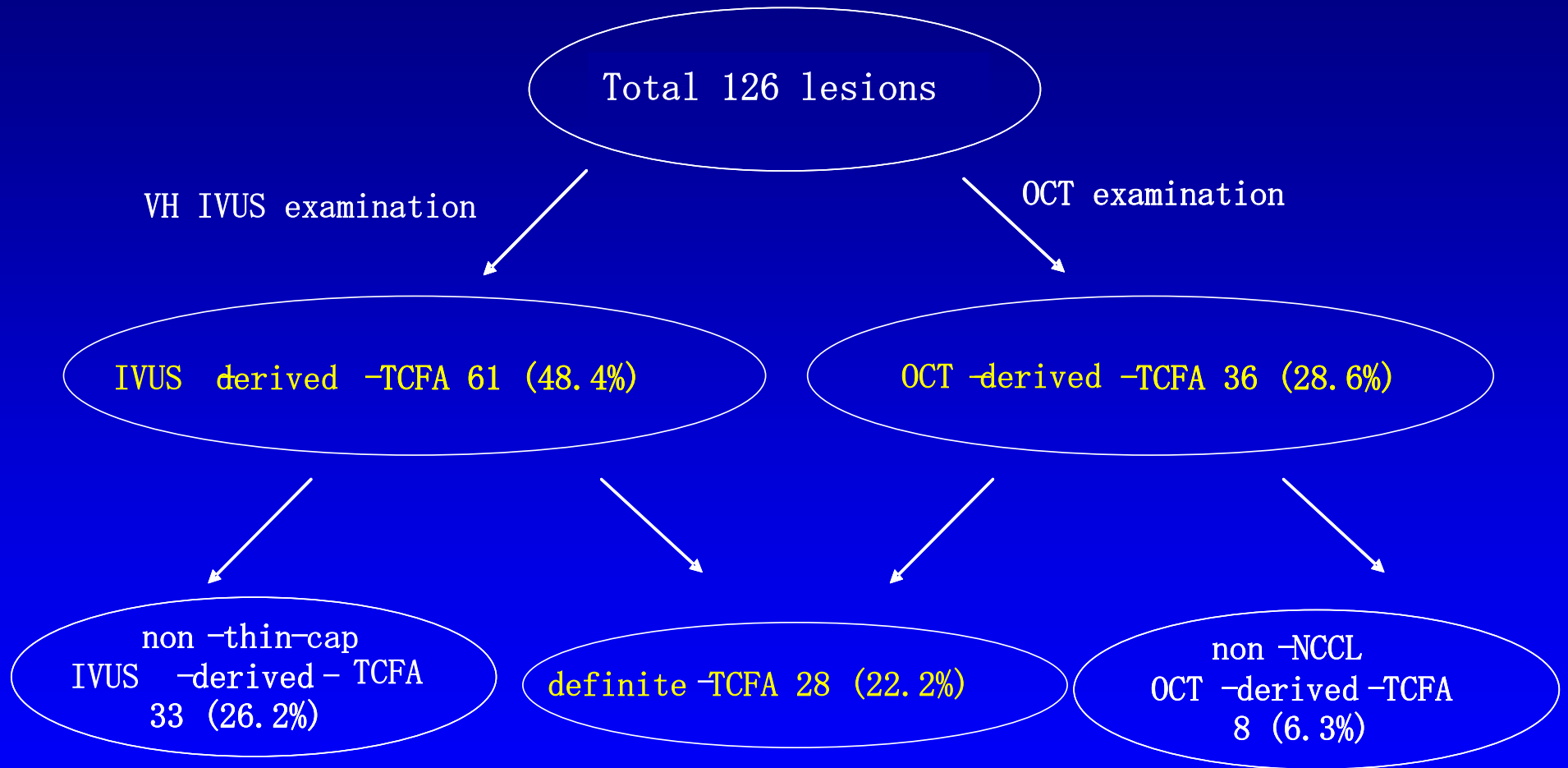
**Takahiro Sawada<sup>1</sup>, Junya Shite<sup>1\*</sup>, Hector M. Garcia-Garcia<sup>2</sup>, Toshiro Shinke<sup>1</sup>, Satoshi Watanabe<sup>1</sup>, Hiromasa Otake<sup>1</sup>, Daisuke Matsumoto<sup>1</sup>, Yusuke Tanino<sup>1</sup>, Daisuke Ogasawara<sup>1</sup>, Hiroyuki Kawamori<sup>1</sup>, Hiroki Kato<sup>1</sup>, Naoki Miyoshi<sup>1</sup>, Mitsuhiro Yokoyama<sup>1</sup>, Patrick W. Serruys<sup>2</sup>, and Ken-ichi Hirata<sup>1</sup>**

<sup>1</sup>Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan; and <sup>2</sup>Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

PB 55.8%; NC 22%

Cap thickness 40 microns

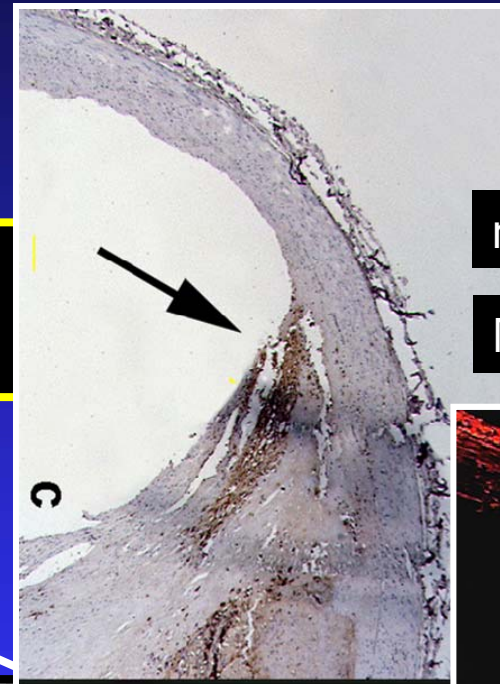
# Background 3: OCT enables to measure accurately fibrous cap thickness, increases accuracy of detecting TCFA and allows to identify plaque rupture



# Background 4: Palpography detects high-strain spot which has been proven to be TICFA associated

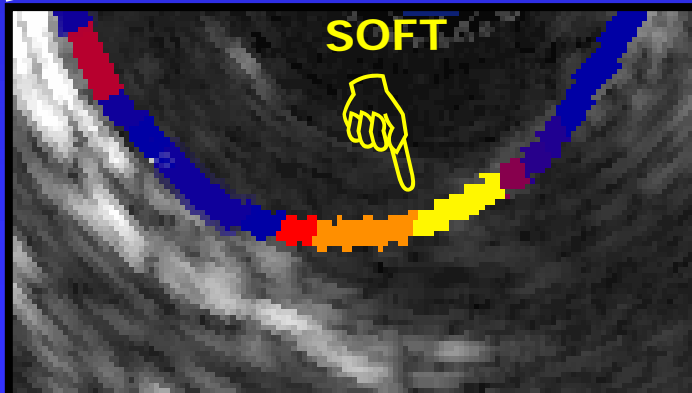
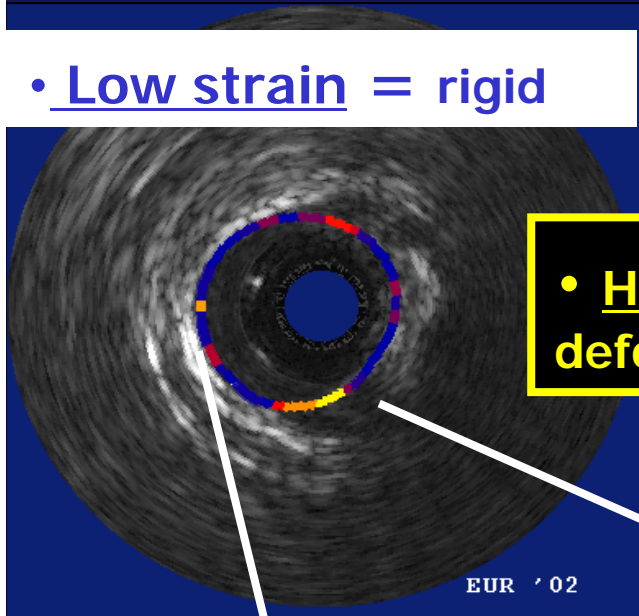
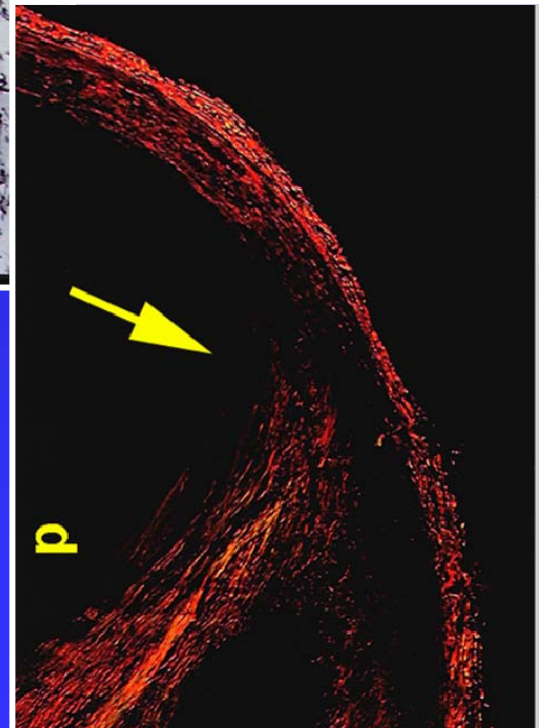
• Low strain = rigid

• High strain = deformable



macrophage

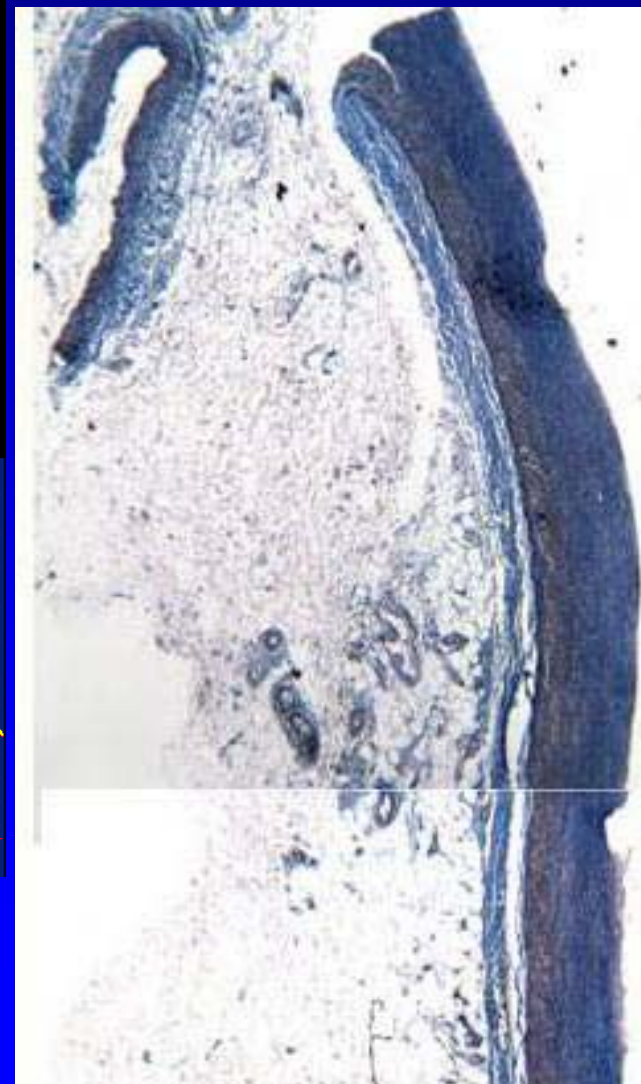
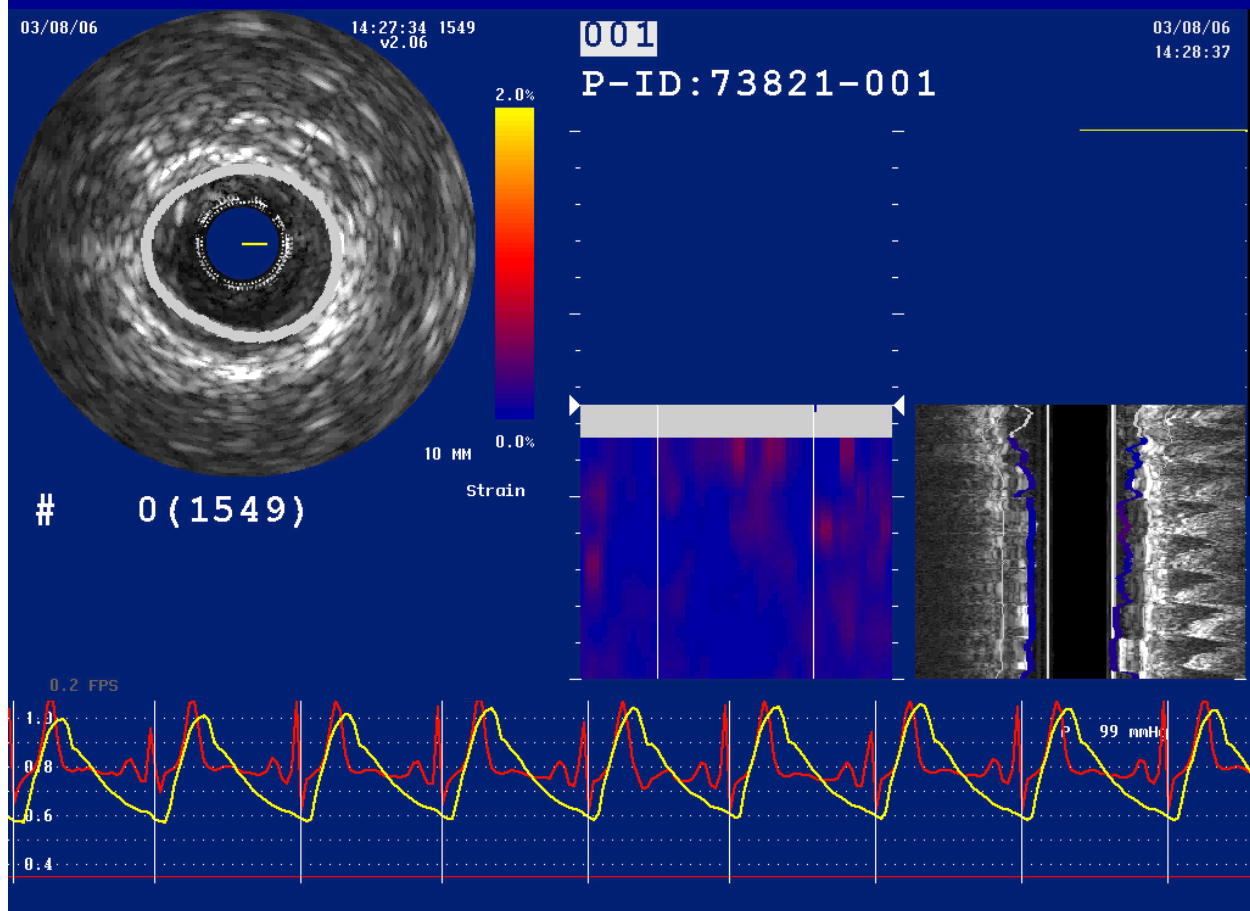
No collagen



Schaar et al. *Circulation*



# Background 4: Palpography detects high-strain spot which has been proven to be TICFA associated



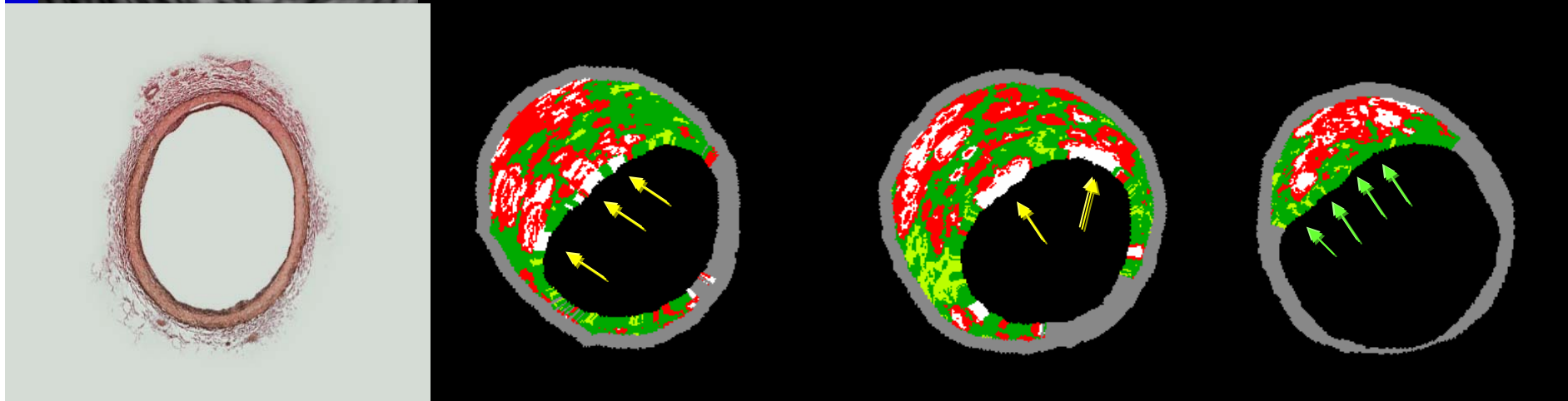
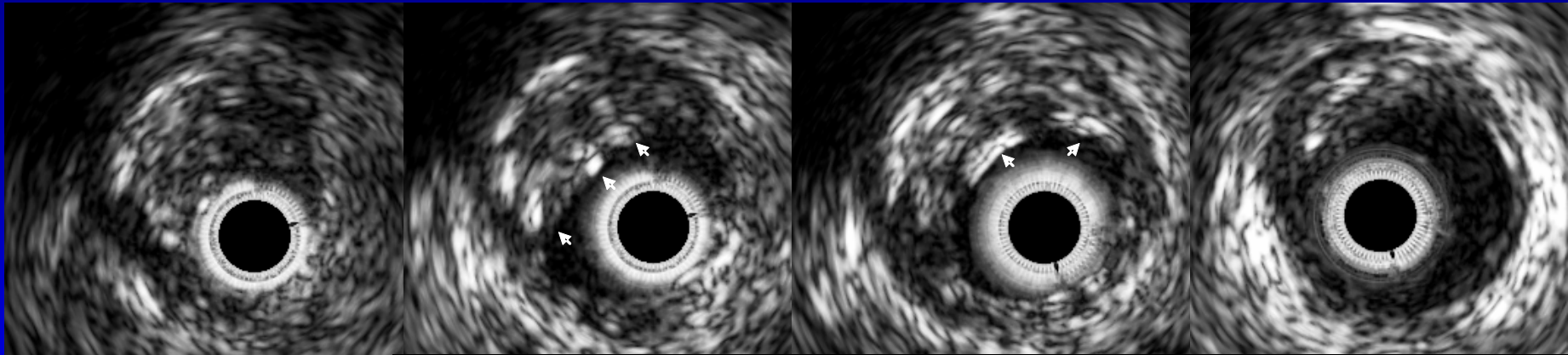
# Background 5: Disappearance of high-strain spot after scaffolding by stent, the Absorb experience and sequestration of the necrotic core by a *de novo* fibrotic cap

Pre-stenting

Post-stenting

6-month

24-month



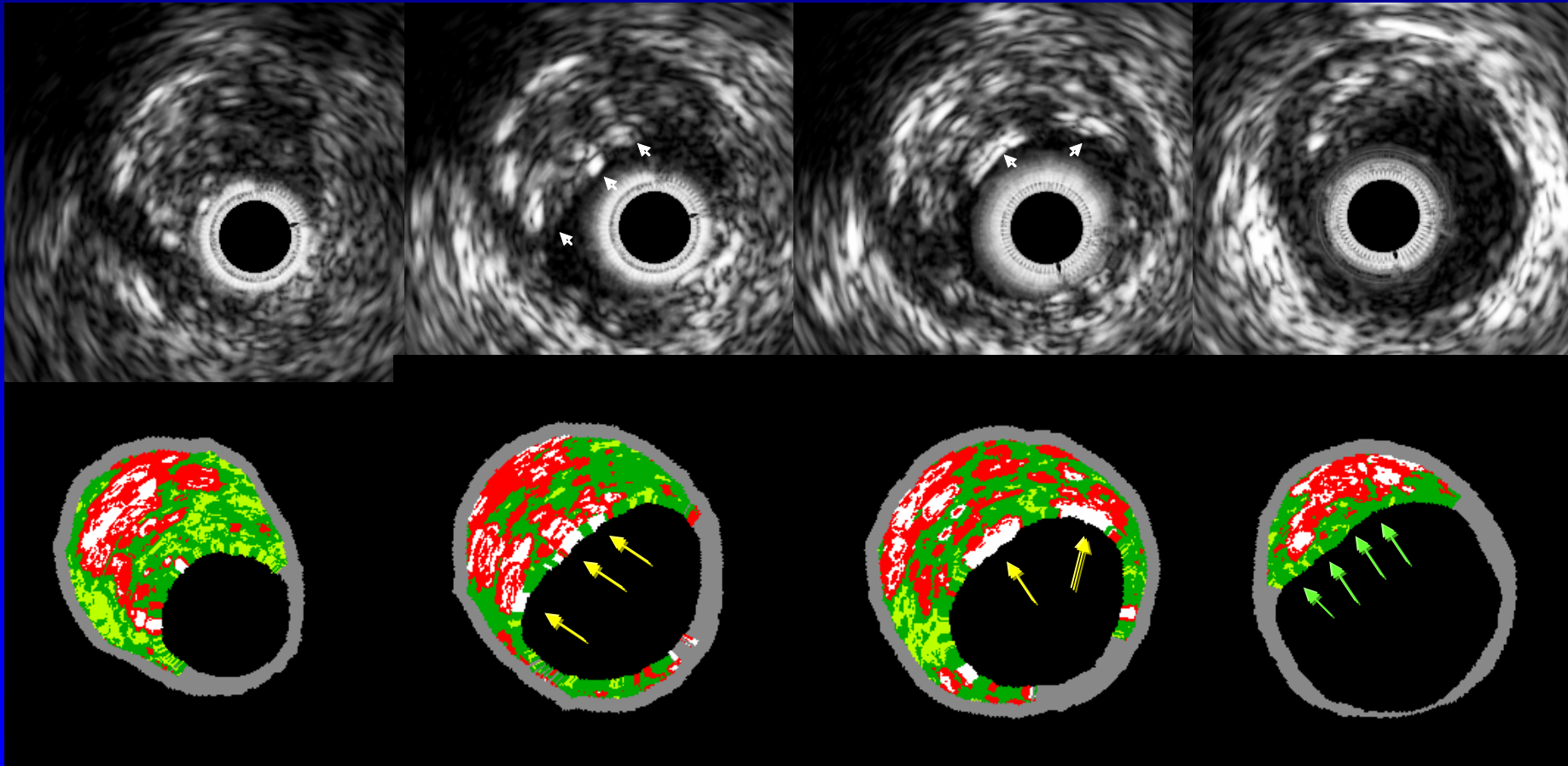
Background 5: Disappearance of high-strain spot after scaffolding by stent, the Absorb experience and **sequestration of the necrotic core by a *de novo* fibrotic cap**

Pre-stenting

Post-stenting

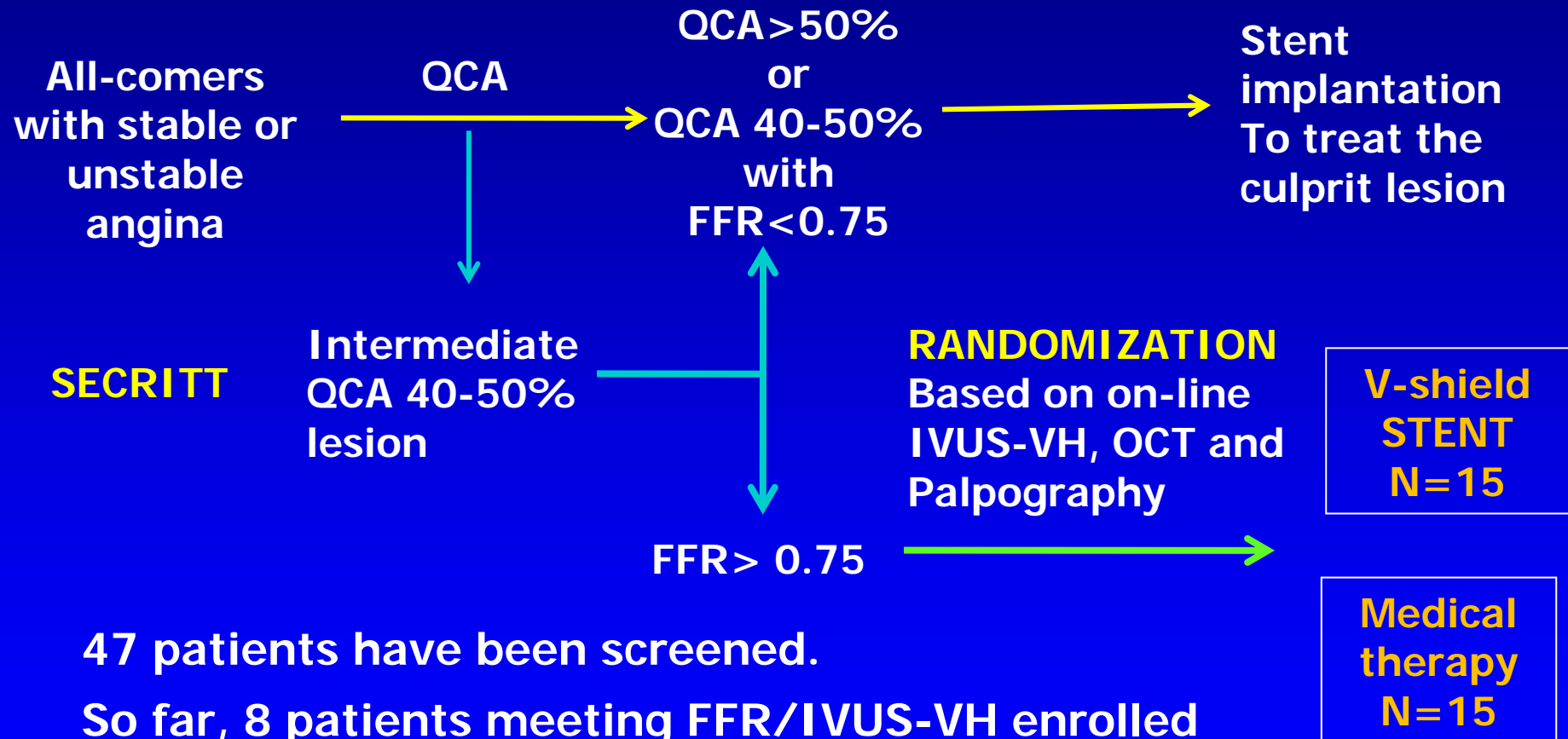
6-month

24-month



# SECRITT Trial I decision algorithm: Randomized trial to detect and treat high-risk plaque

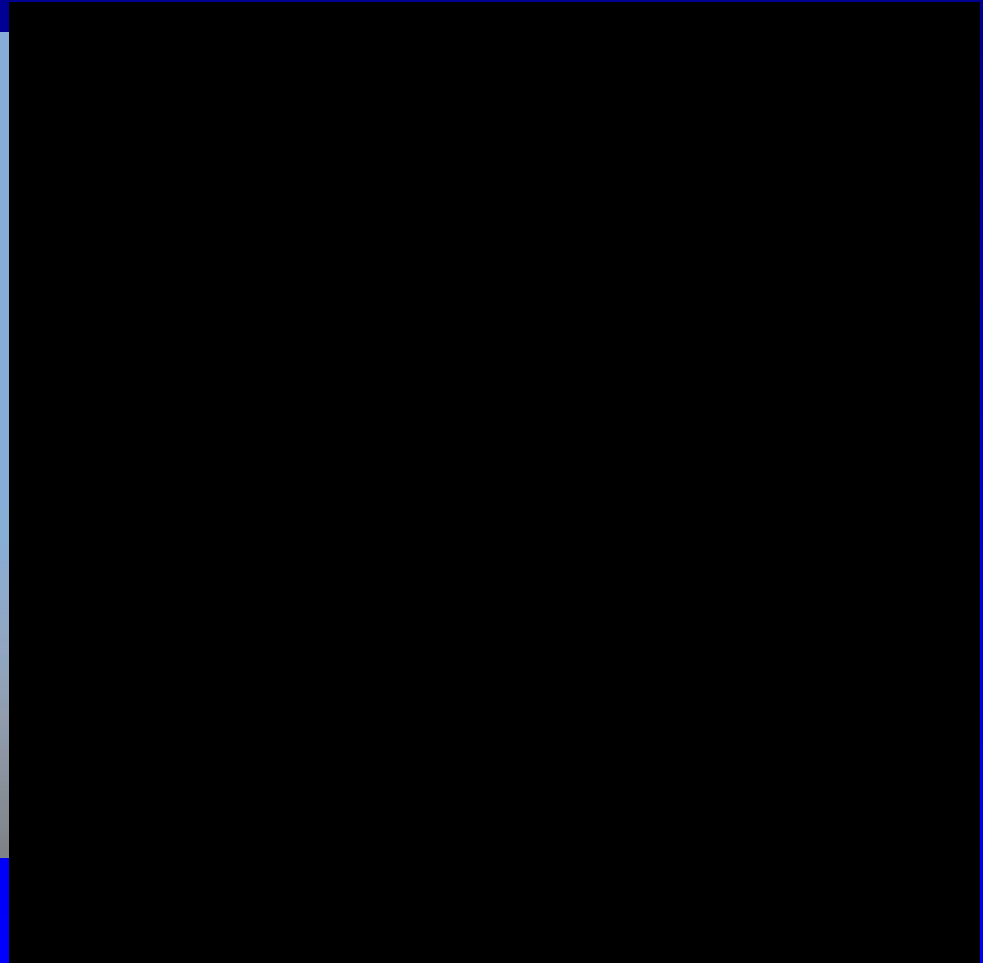
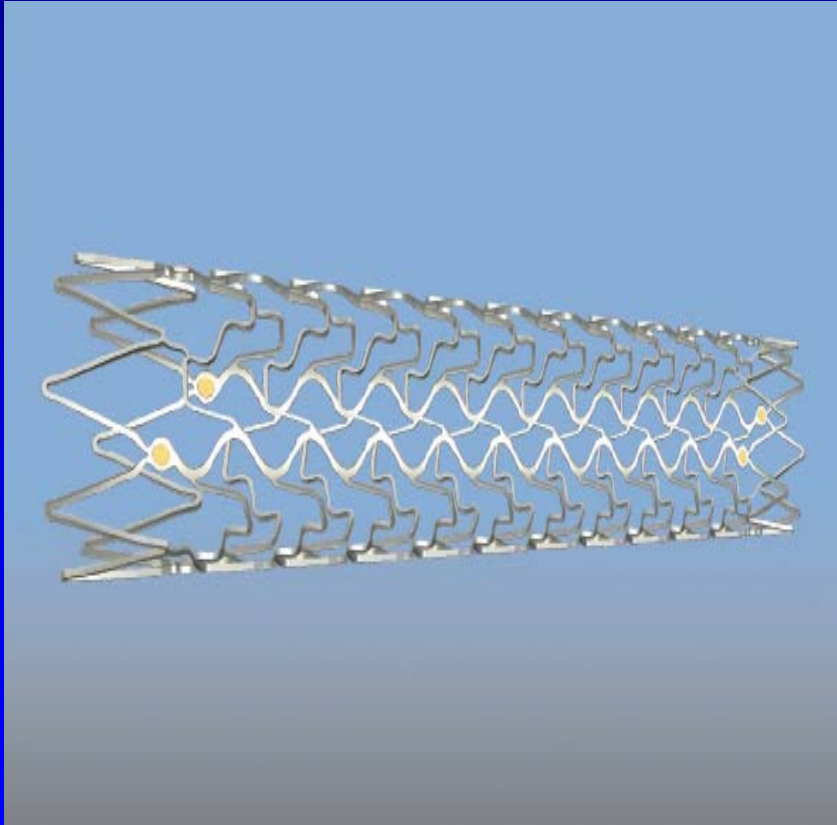
What is done now:



47 patients have been screened.

So far, 8 patients meeting FFR/IVUS-VH enrolled (5 randomized to "Shield" and 3 randomized to control); with one patient crossing over from control to v-shield arm

# V-Shield : Self-expanding Nitinol scaffold with thin struts (56 micron) and 6F compatible



**\*This product is currently under development and is not approved for sale or use.**

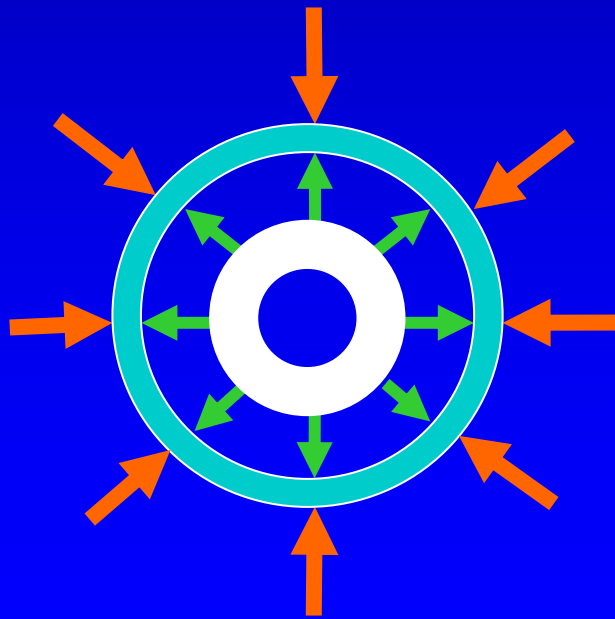
# V-Shield : Self-expanding Shield Forces

■ Radial Resistive Force (RRF) – Force the Shield exerts to resist the recoil of the plaque and vessel wall

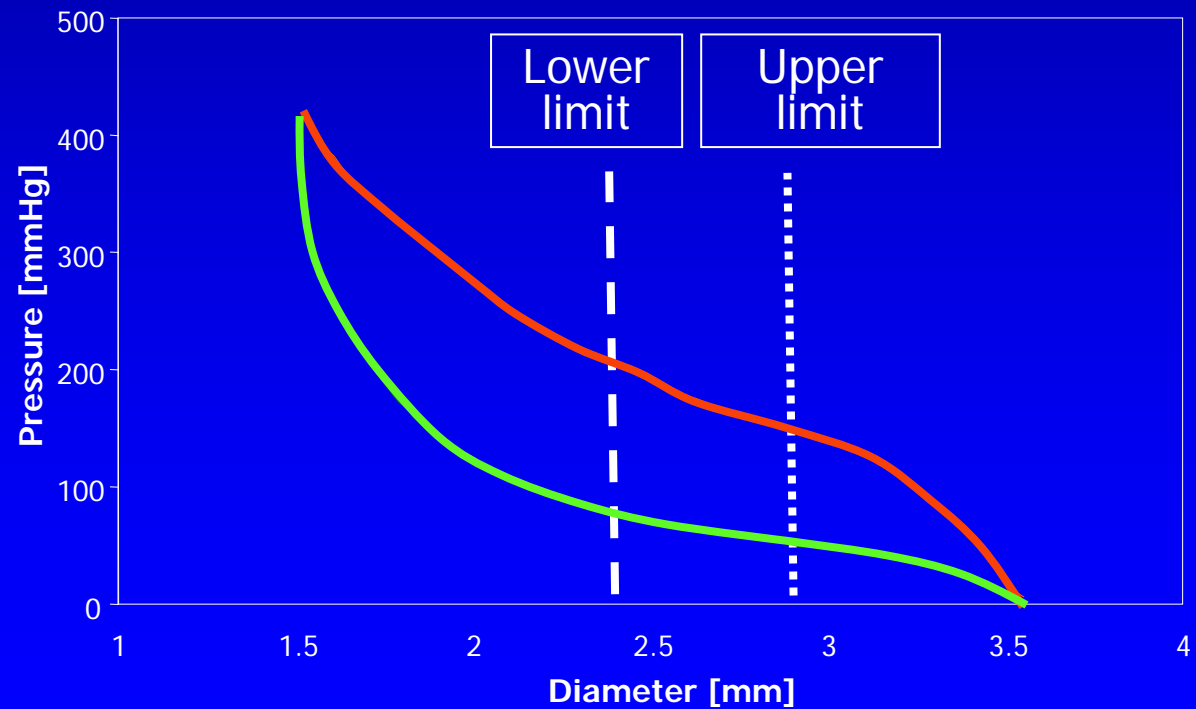
(crush resistance)

■ Chronic Outward Force (COF) - Force the Shield exerts on the plaque and vessel wall

(dilation force)

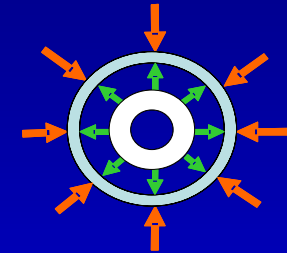
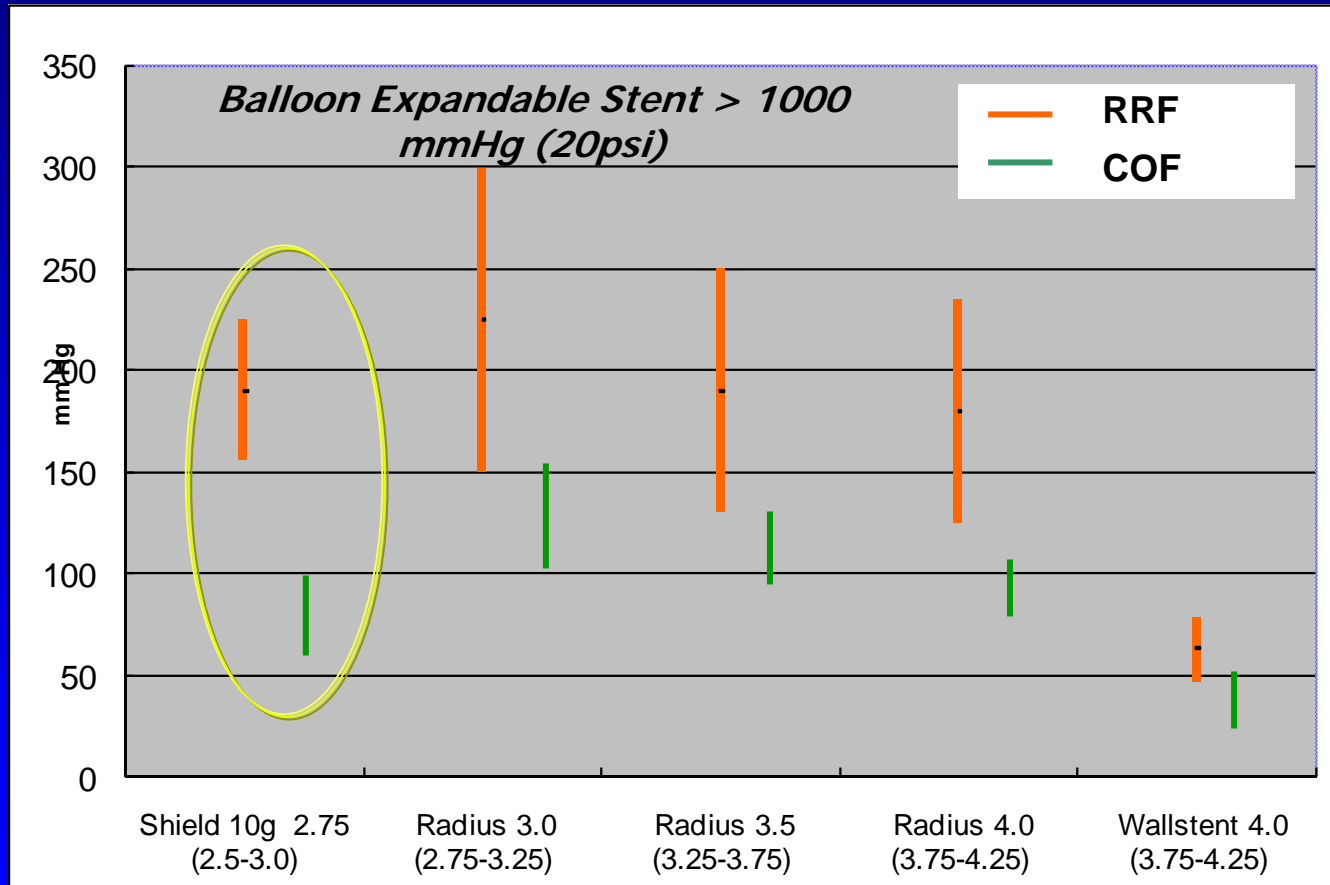


### Radial Stiffness Testing



# V-Shield : RRF & COF

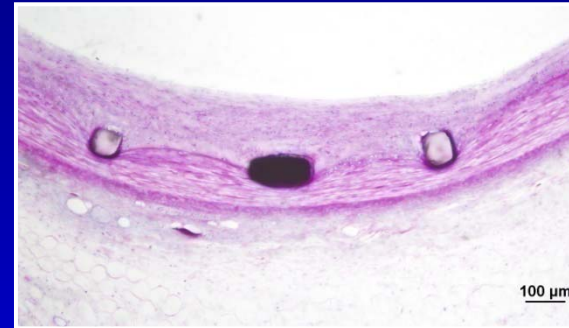
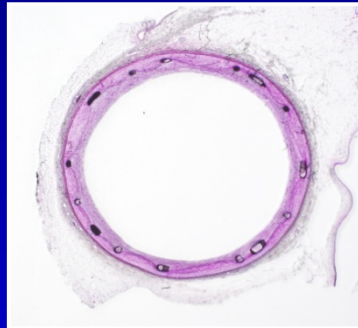
High crush resistance/chronic outward force ratio



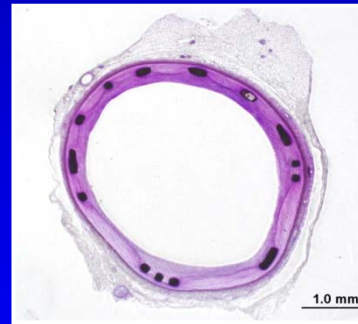
Testing performed on MSI tester May 2007

# V-Shield : Chronic Feasibility Histology

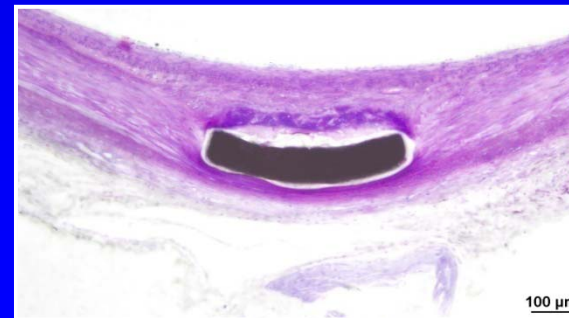
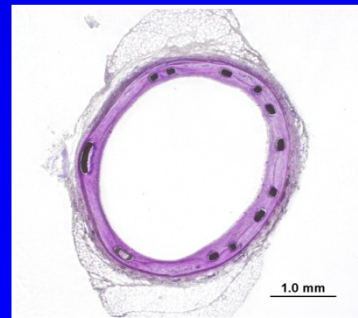
CV18925 107  
RCA mid **Shield**



CV18932 114  
LAD mid **BMS CrCo**



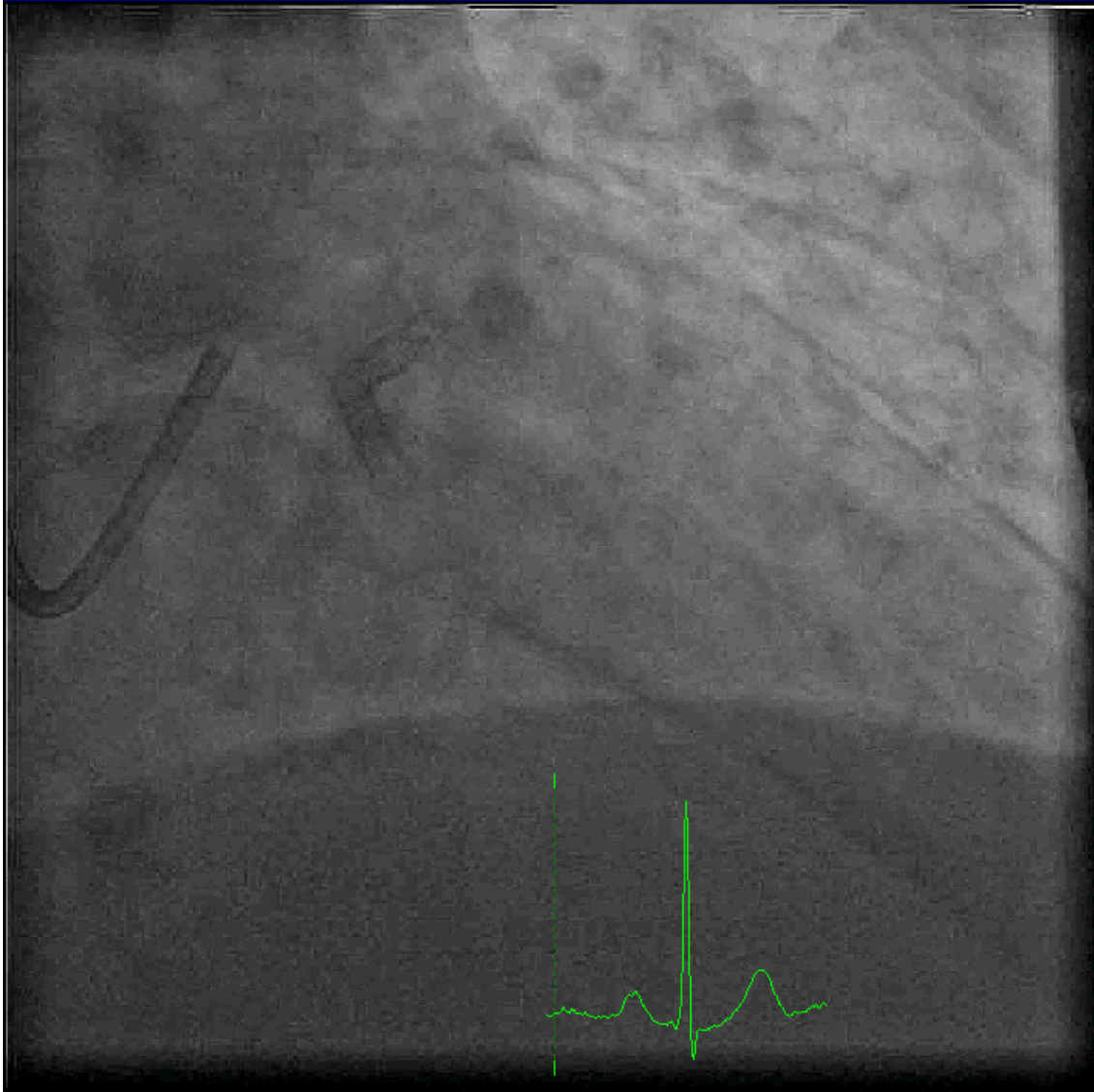
CV18928 110  
RCA mid **DES CrCo**



Granada JF,  
Kaluza GL,  
Kolodgie F,  
Virmani R



# Case 1: History and Initial Angiography



64 year old

class II angina

coronary risk factors:

- past smoking
- high cholesterol
- hypertension

Flow-limiting lesion in  
LCx

Non flow-limiting lesion  
(40% diameter  
stenosis) with FFR of  
0.84 in the LAD

- (Ramcharitar, S et al., 2008 in press)

# Case 1: History and Initial Angiography

64 year old

class II angina

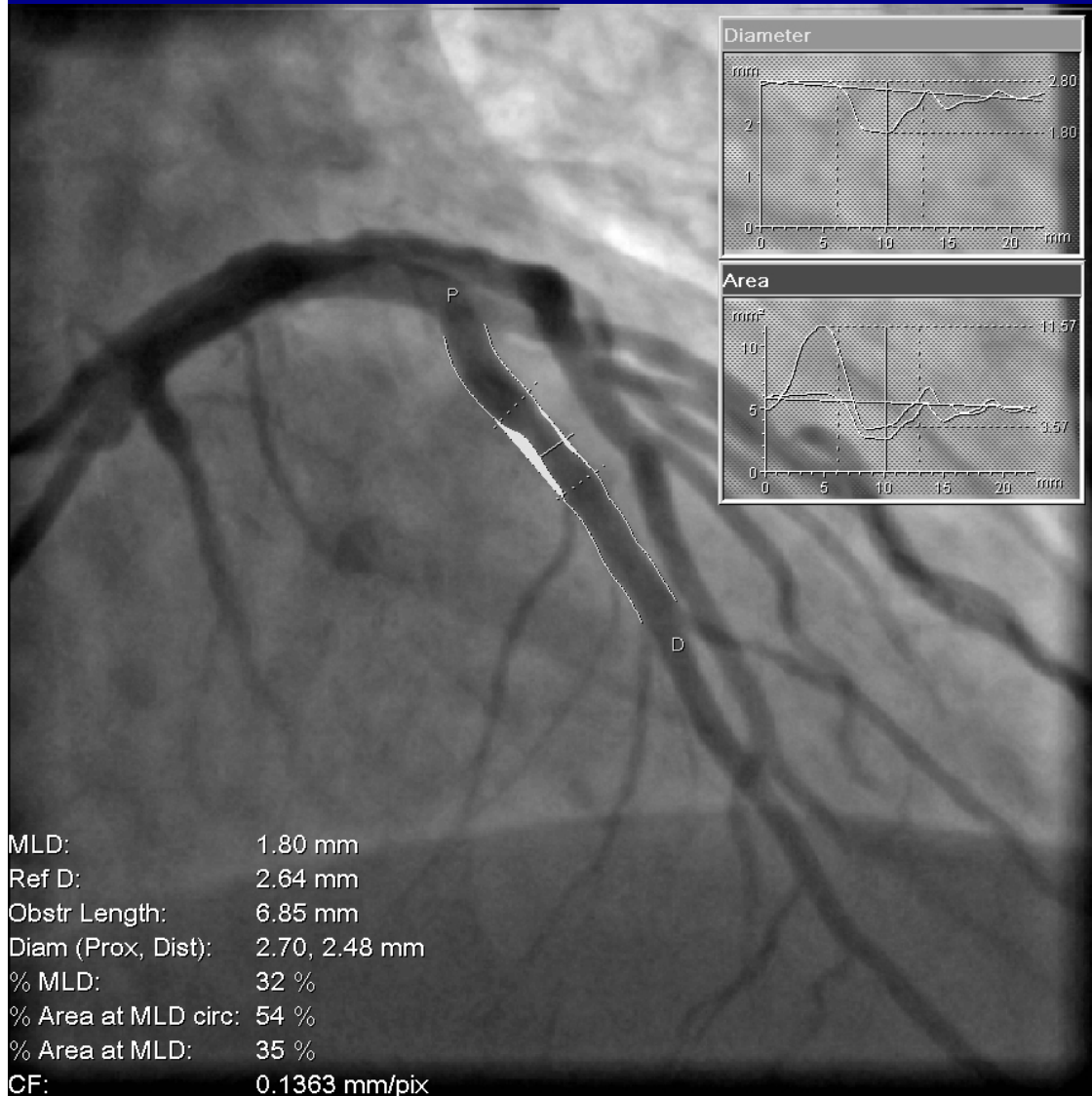
coronary risk factors:

- past smoking
- high cholesterol
- hypertension

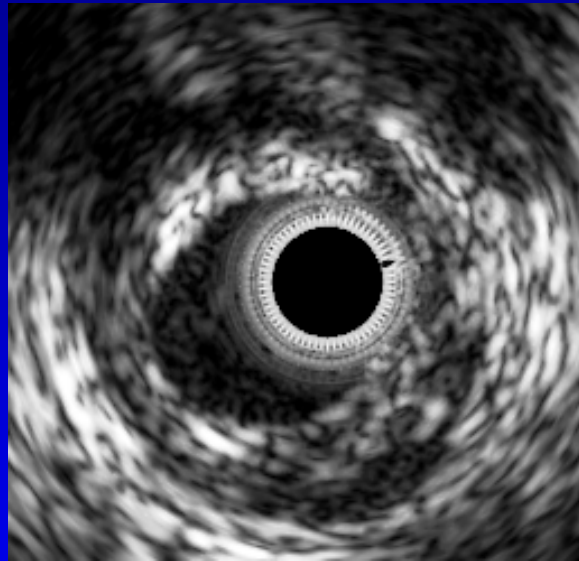
Flow-limiting lesion in LCx

Non flow-limiting lesion (40% diameter stenosis) with FFR of 0.84 in the LAD

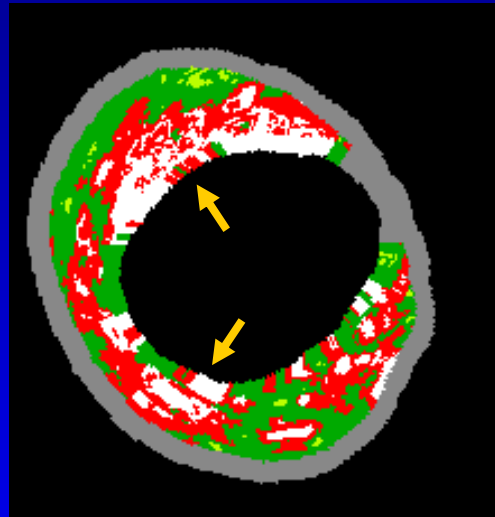
- (Ramcharitar, S et al., 2008 in press)



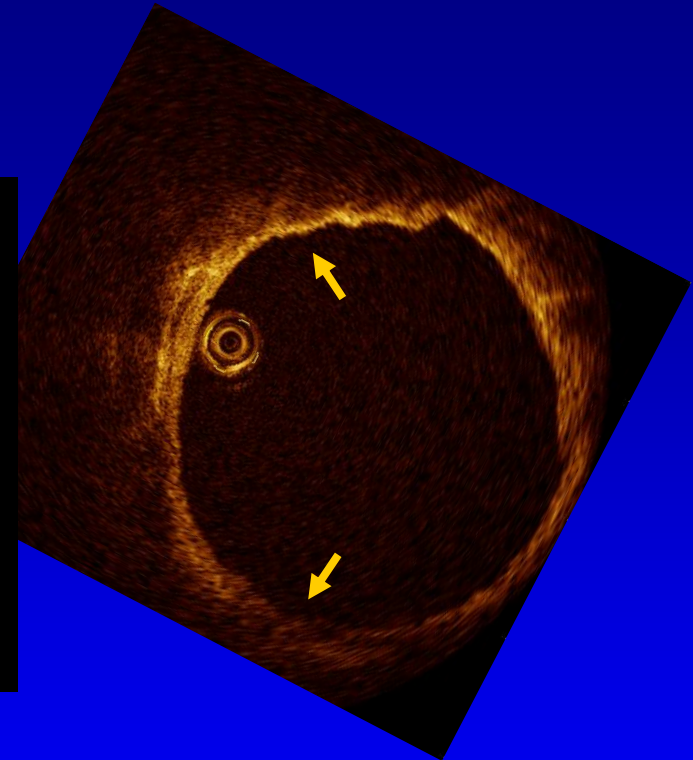
# Case 1: Pre-randomization IVUS, IVUS-VH and OCT



Remodeling Index > 1.05

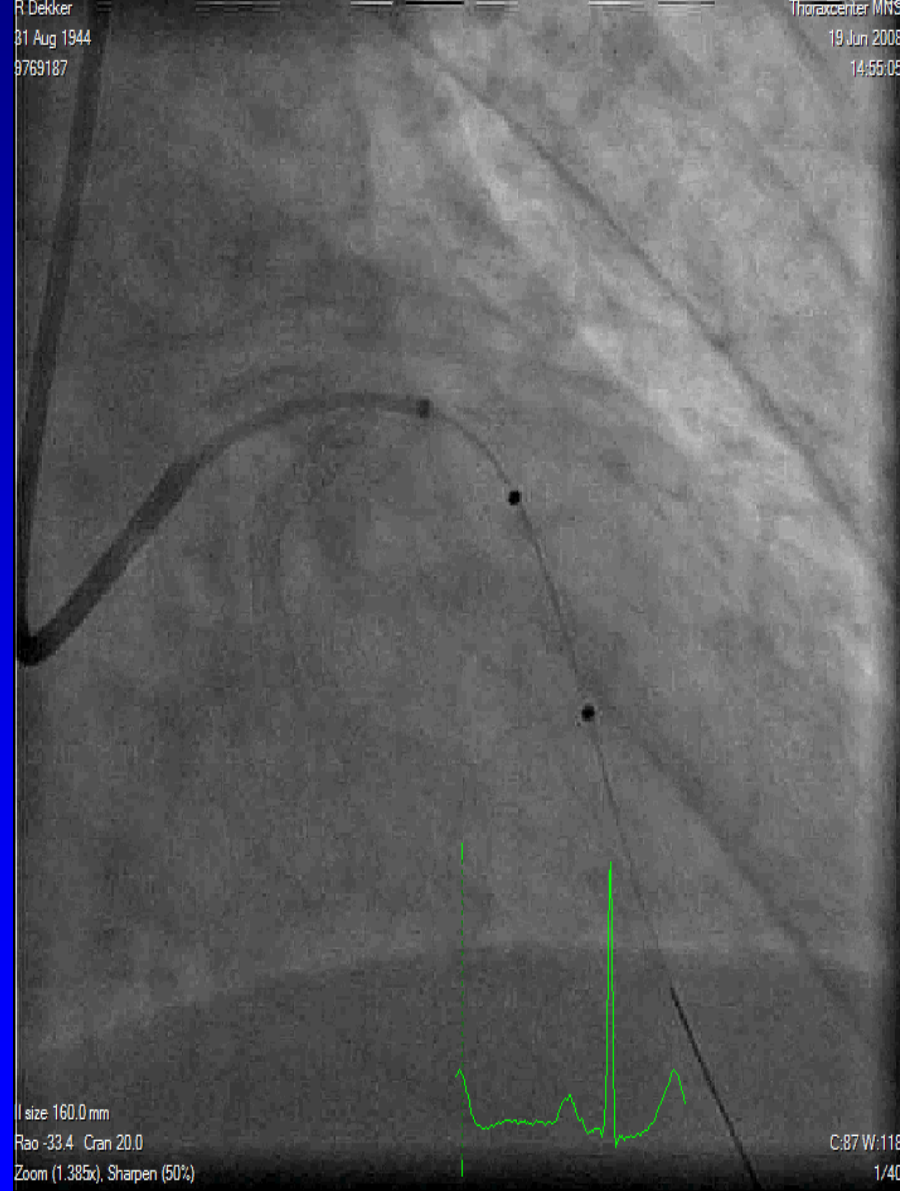


% Plaque Burden Area:  
71%  
Necrotic core % area in  
contact: >10%

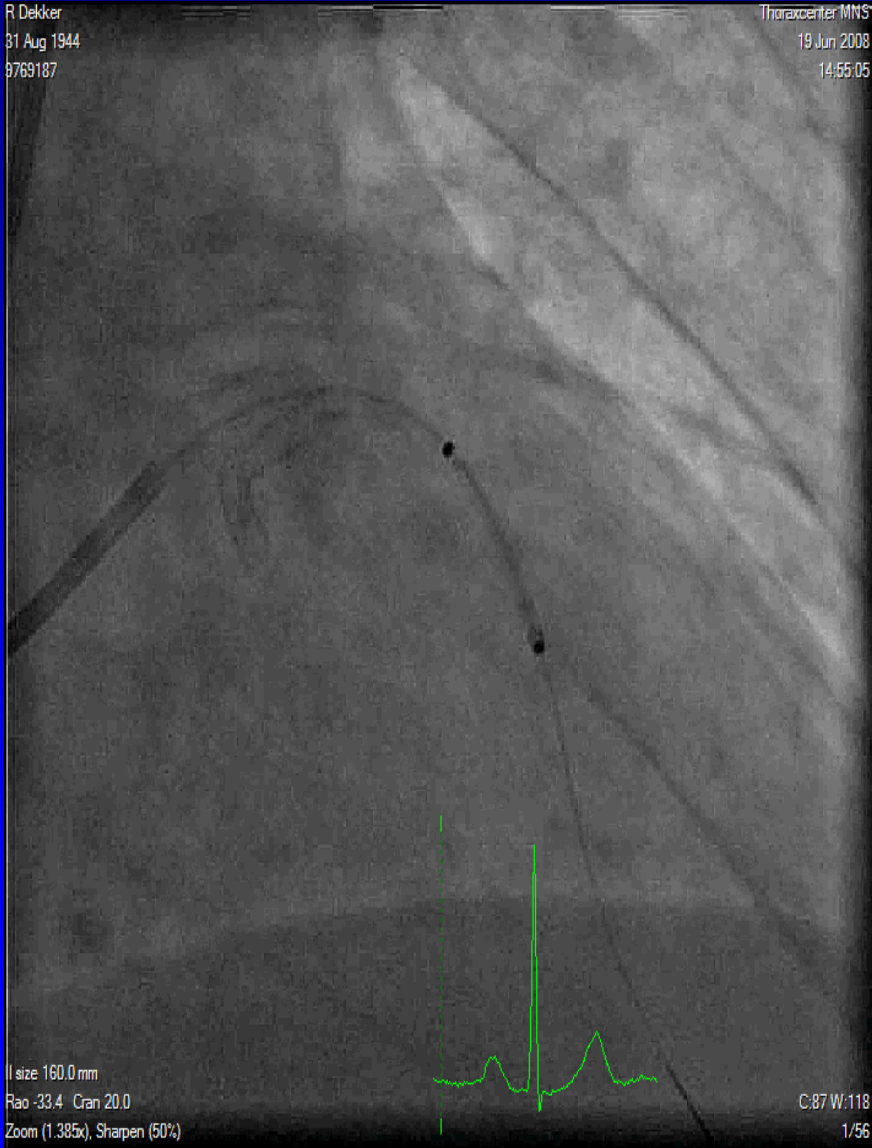
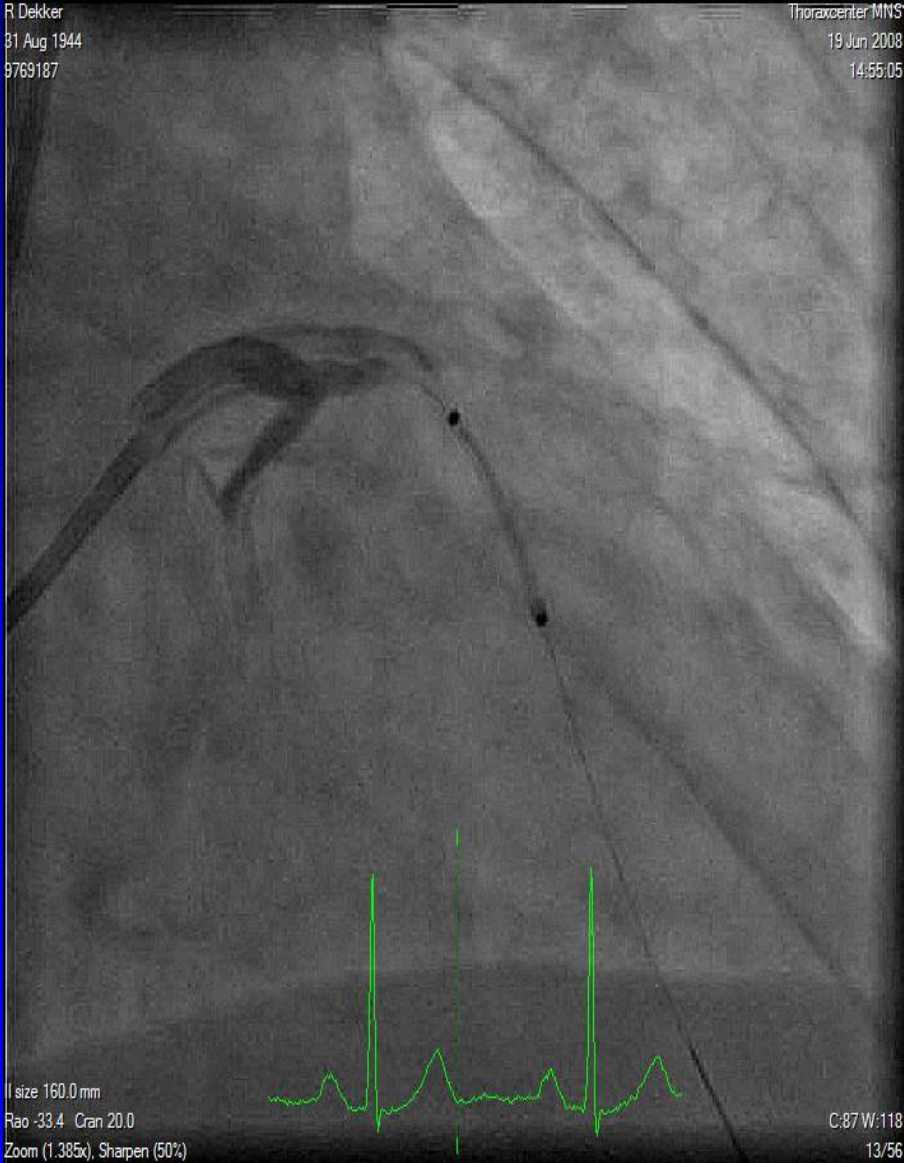


OCT cap: 60 micron;  
no rupture

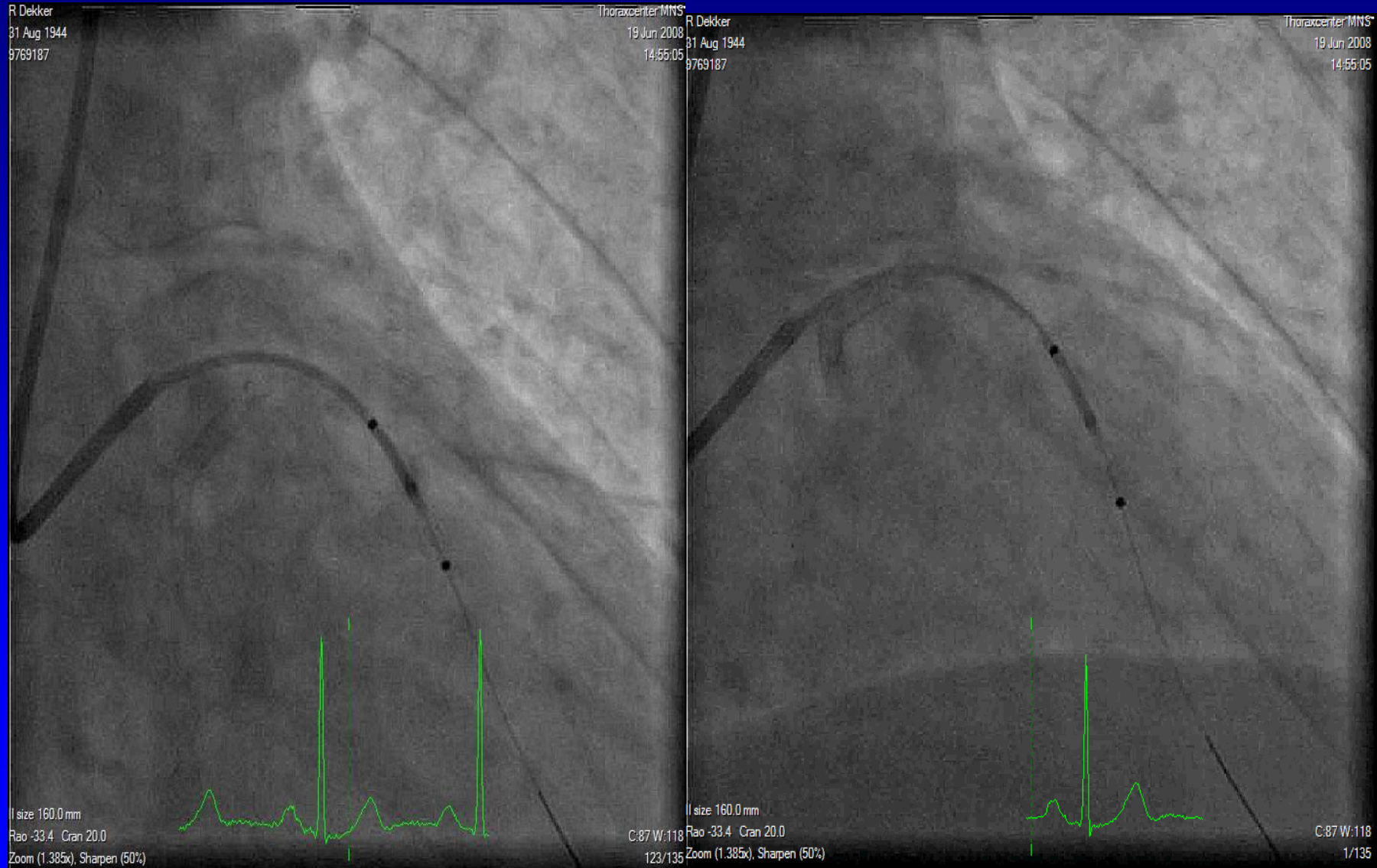
# Case 1: Shield deployment 1



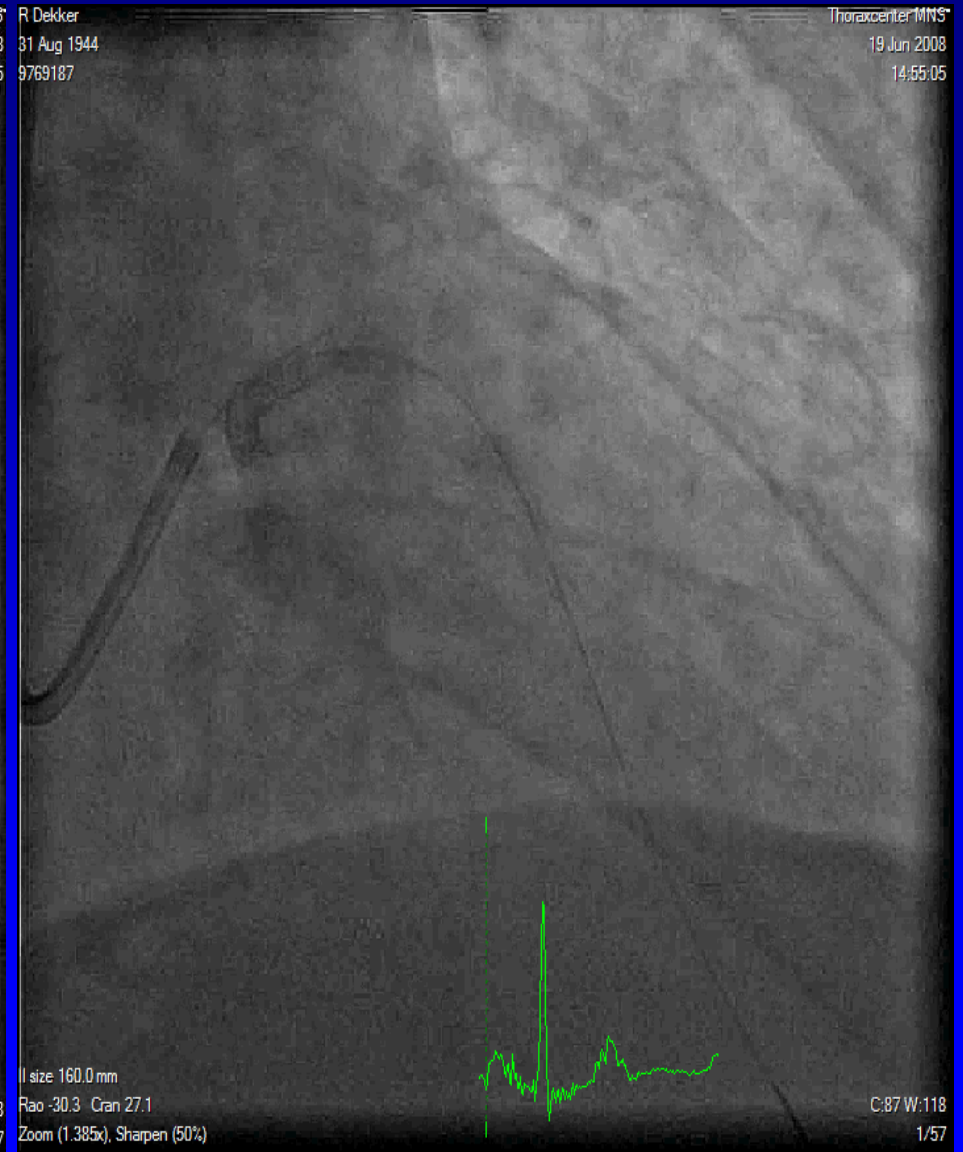
# Case 1: Shield positioning



# Case 1: Shield Unsheathing



# Case 1: Shield post deployment

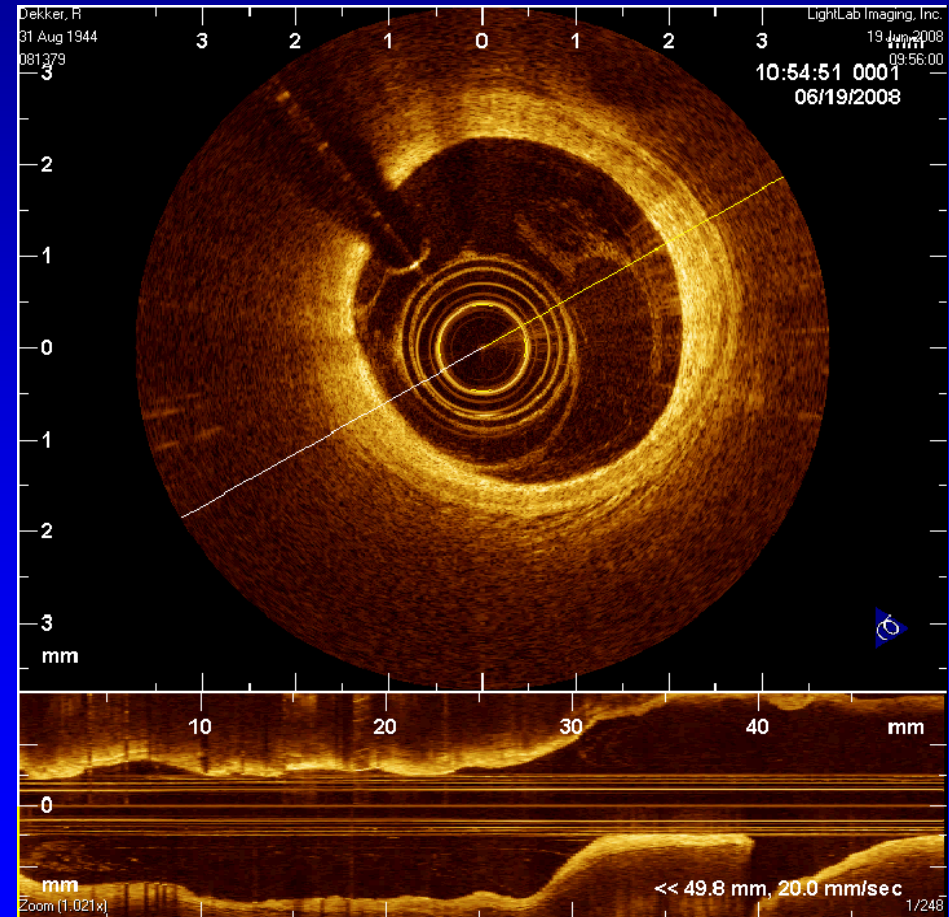
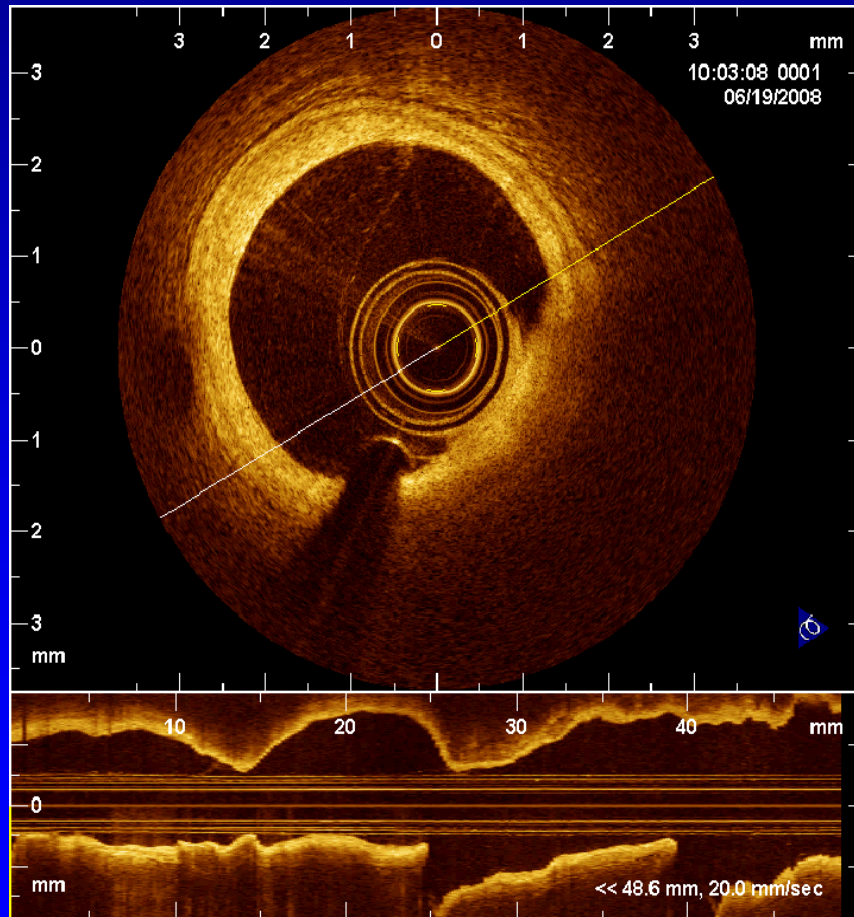


# Case 1: Final angiogram after post dilation at 6 atm

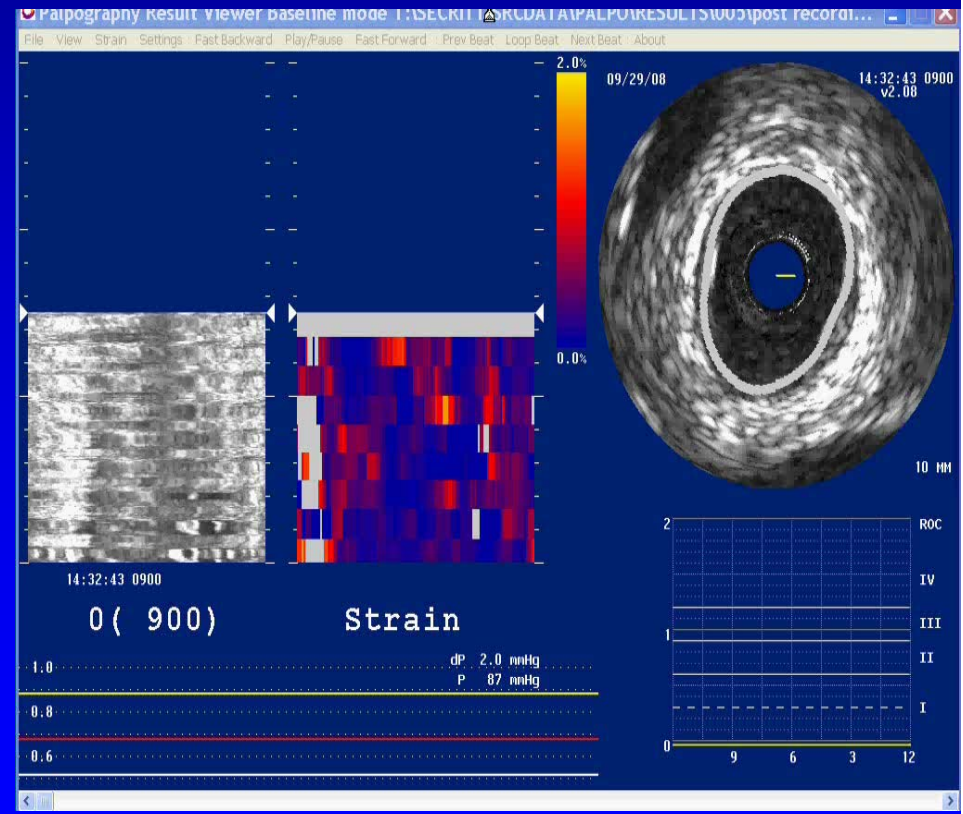
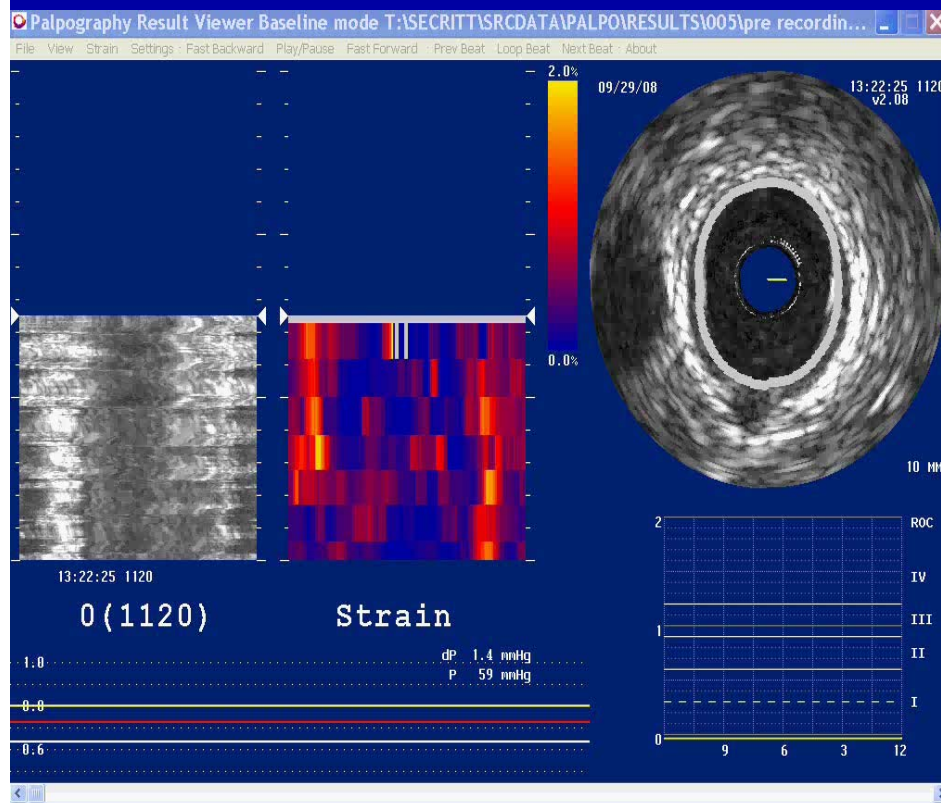




# Case 1. OCT M4 pullbacks pre and post stenting showing enlargement of luminal area with well apposed struts

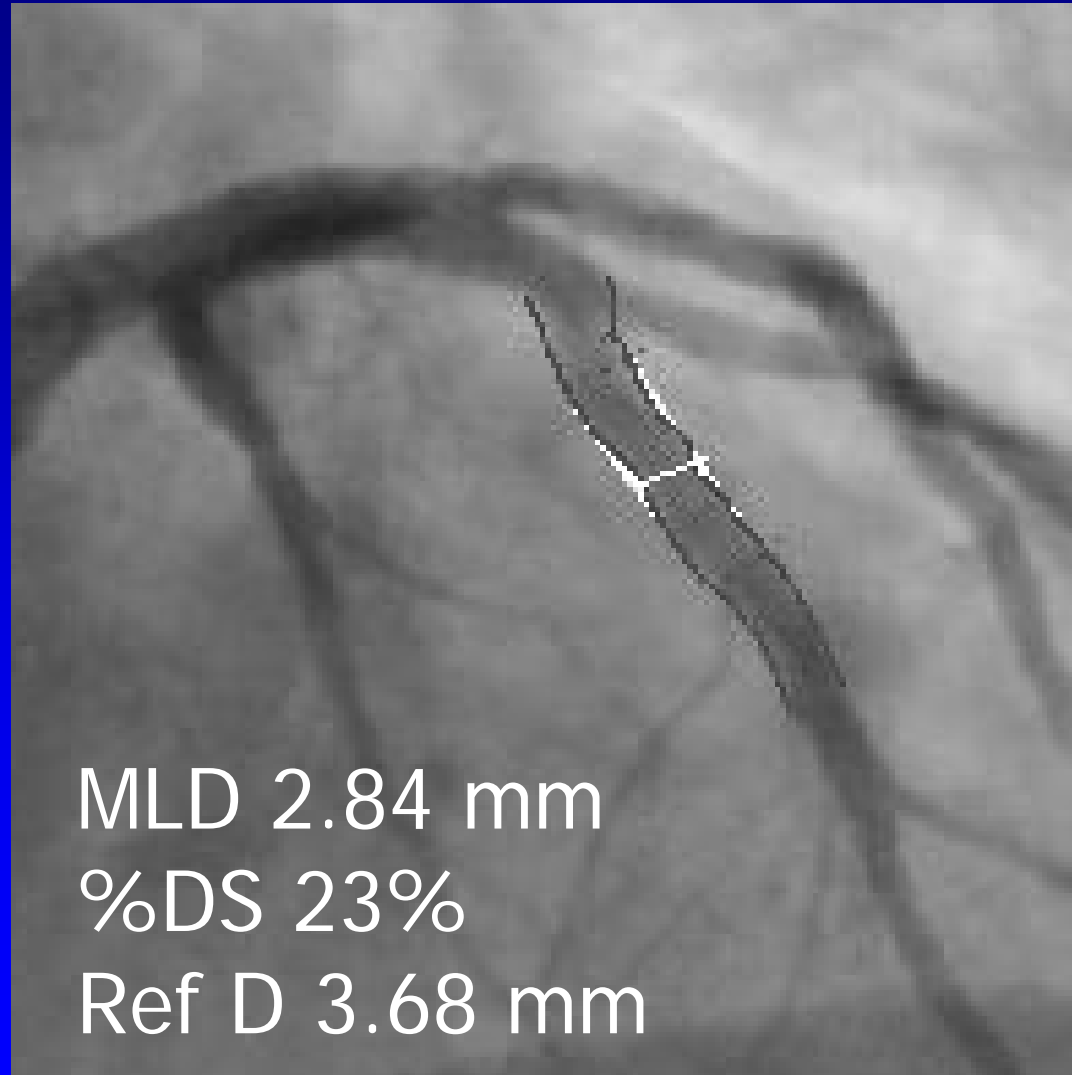


# Carpet view of palpography pre and post shielding



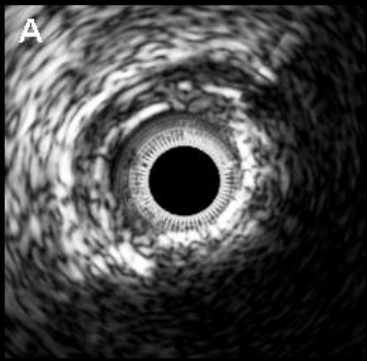
**6 months follow up on the  
first shielded patient**

# QCA at 6 months follow up

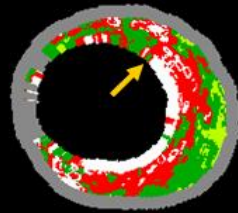


# 6-month FUP IVUS, IVUS-VH and OCT

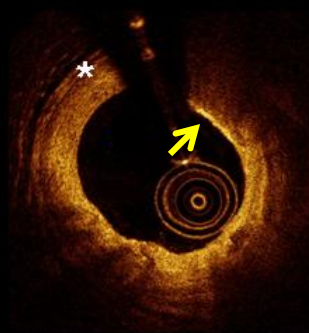
Pre



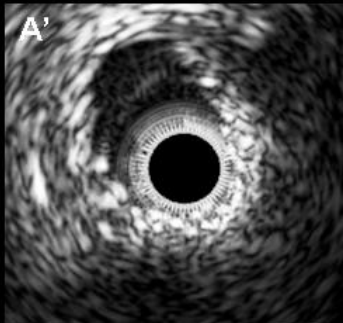
B



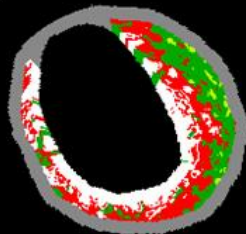
C



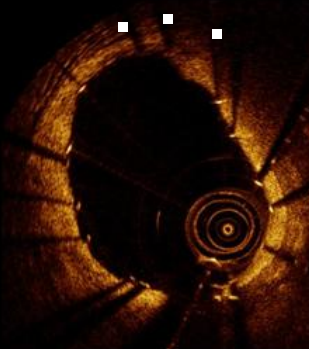
Post



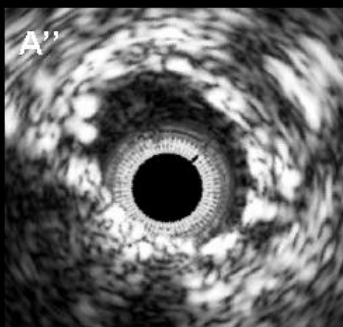
B'



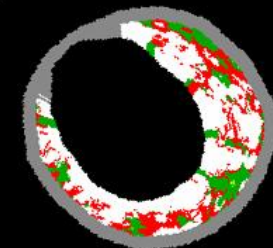
C'



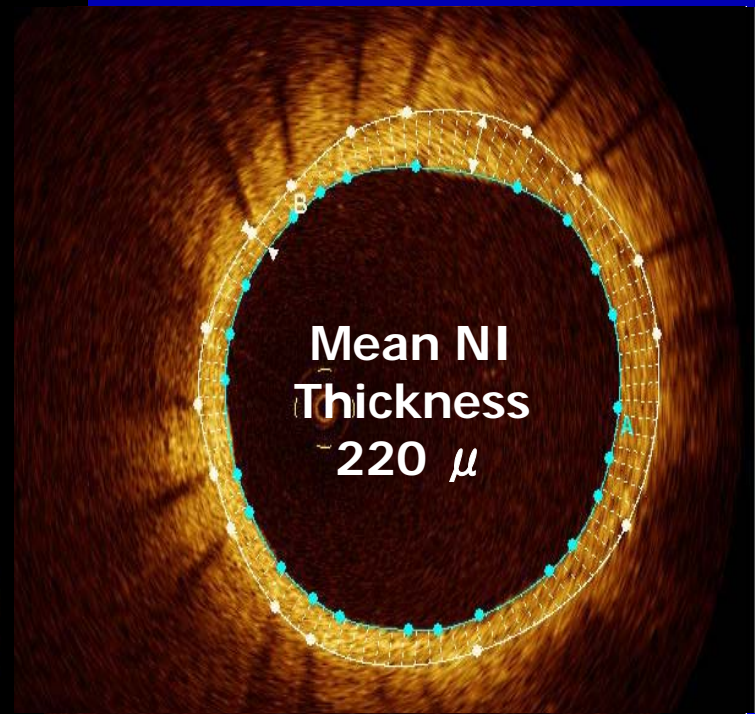
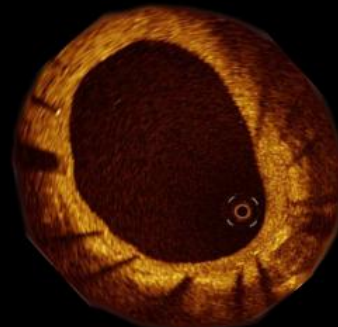
6 months fup



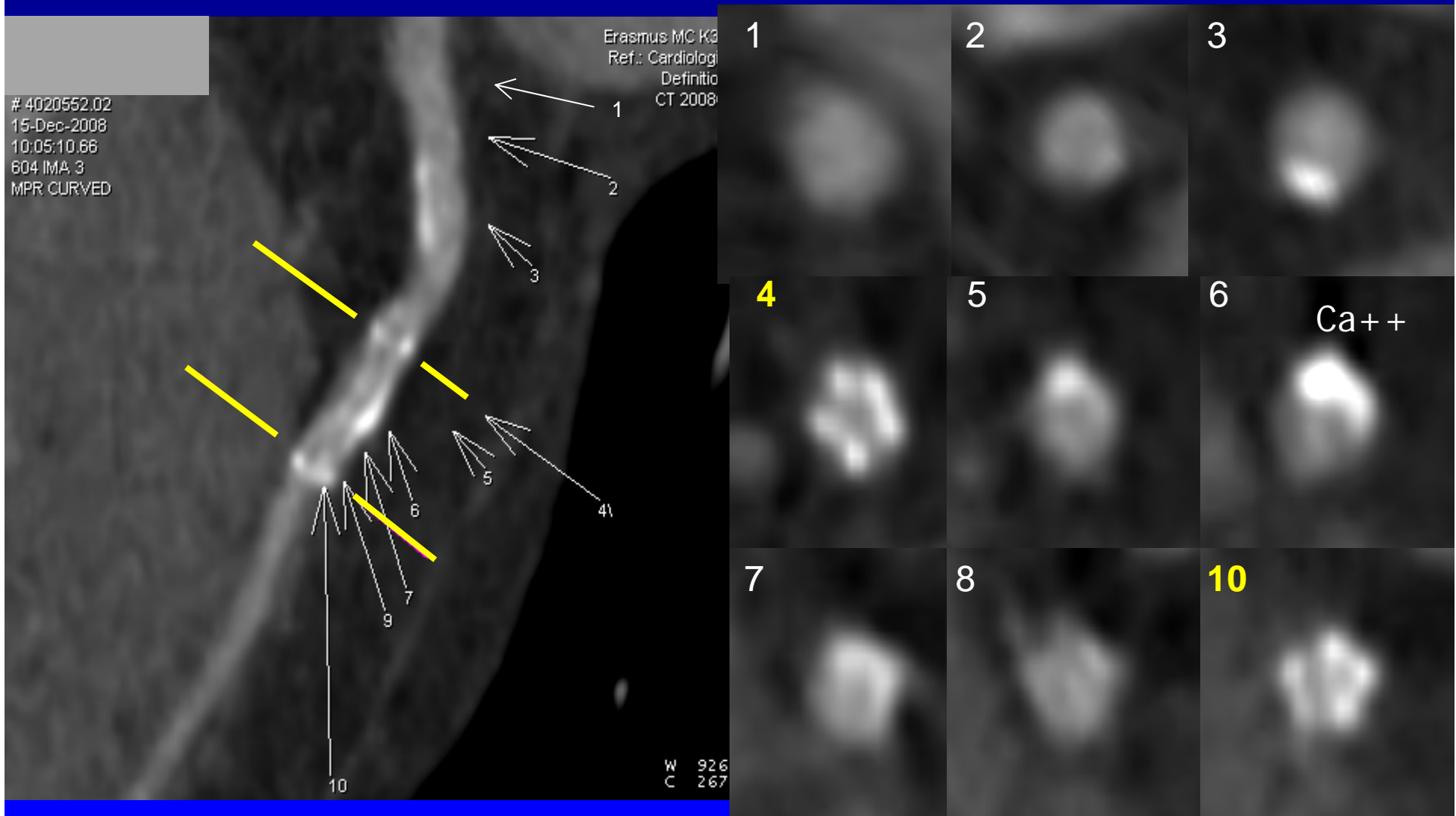
B''



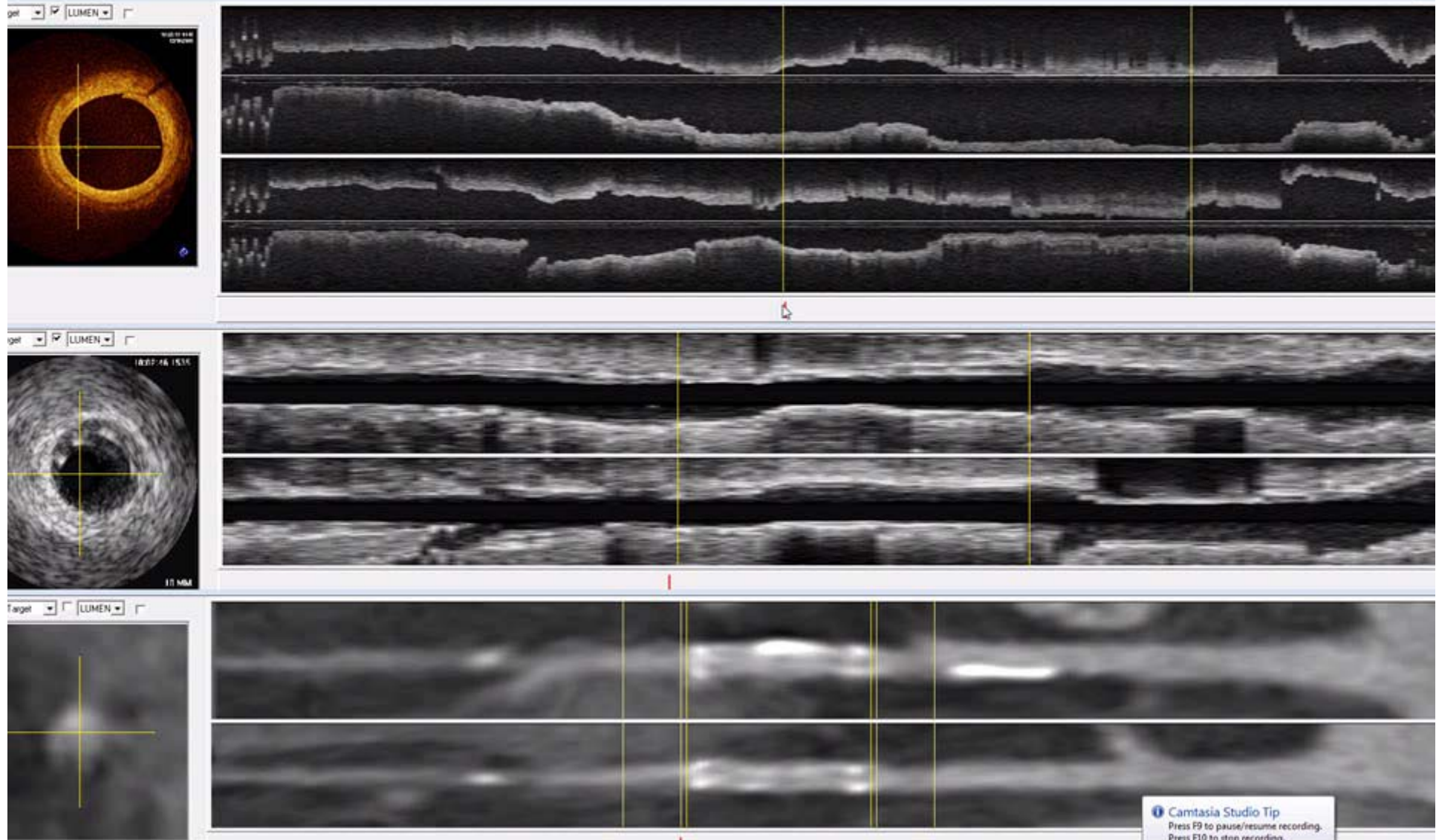
C''



# MSCT – 50 micron nitinol struts make the shield evaluatable non-invasively



# Colocalization of MSCT and OCT within the nitinol shield stent at 6 months post-implantation, showing good stent patency and blooming artefact from distal markers as well as calcification. (Core lab Cardialysis)



# Conclusions

- This is the first trial of localized therapy for vulnerable plaque/TCFA
- The first patient controlled at 6 months shows a thin de Novo neointima cap by OCT
- Stent appears evaluable by non-invasive MSCT
- There have been no adverse events so far in 5 patients shielded